TNO Strategy, Technology and Policy

Schoemakerstraat 97
P.O. Box 6030
2600 JA Delft
Nederland

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www.tno.nl

T +31 (0)15 269 69 00
F +31 (0)15 269 54 60
stb@stb.tno.nl

OECD Case Study on Innovation: The Dutch Pharmaceutical and Food Biotechnology Innovation Systems

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Author(s) C. Enzing, A. van der Giessen, S. Kern

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Summary

Introduction

The Netherlands is a medium-sized European country with a population exceeding 16 million inhabitants in 2002. It has an open economy depending heavily on foreign trade. In 2001, the Dutch gross domestic product (GDP) amounted to 429 billion euros, 71% coming from service activities and 26% from industrial activities. In 2001, the Netherlands showed a positive trade balance with exports equal to 280 billion euros and imports to 257 billion euros. The predominant industrial sectors are food processing, chemicals, petroleum refining, and electrical machinery. The labour force in the Netherlands amounts to 7.2 million people (2000 figures) of which approximately 3% are unemployed. However, since the economic recession the Netherlands has been facing increasing unemployment and inflation figures.

The gross domestic expenditures on R&D (GERD) have shown an increase since the early 1990s. The figure in 2000 was 7.8 billion euros. This means a growth of almost 34% compared to 1994. However, compared to 1999 this is only a growth of 3%. In 2000, the Dutch R&D intensity of 1.94%, in terms of GERD as percentage of GDP, was below the OECD average (2.24%), but above the EU-average (1.88%). The private sector contributes most to the R&D intensity in 2000 as it accounts for 1.11 percentage points of the R&D intensity. However, this is considerably lower than the EU and OECD figures (1.21 and 1.56%). The public sector, i.e. universities and research institutes, accounts for almost 0.84 percentage points of the R&D intensity. Although the R&D intensity of the public sector has significantly decreased since 1993, it is still far above the EU and OECD figures (0.67 % and 0.68%).

National policies

Profile of national biotech innovation policies in the period 1979 - 2004
In the 1980s, creating a strong biotech R&D structure had a high priority in The Netherlands. Two biotech R&D programmes were set up (the Innovation Oriented Research Programme Biotechnology – IOPb, and the Programmatic Industry Related Technology Stimulation on Biotech - PBTS) and industry research was sponsored considerably. After this period of biotech dedicated policies, Dutch technology and innovation policies shifted in the early 1990s from dedicated towards more generic policies. New programmes had a generic character and existing dedicated programmes (IOPb and PBTS) were transformed into generic programmes, open to all technology fields. Commercialisation of biotechnology was a mentioned as a priority in national innovation policies, but this was mainly implemented through the support of national networking activities between academia and industry, initiated by actors in the field.

It was only in 1998 that the Dutch government focused its innovation policies on biotechnology again. The Dutch government, in particular the Ministry of Economic Affairs, felt a certain sense of urgency in stimulating the biotechnology sector after the results of a government-sponsored benchmark had been published. The main conclusion of this benchmark - comparing the Dutch entrepreneurial bioscience industry with six other regions in the world - was that many conditions for growth such as financing and incubator facilities were missing in the Netherlands. In 1999, the Ministry of Economic

Affairs presented the *Life Sciences Action Plan 2000-2004*. The main goal of the BioPartner programme was to establish at least 75 new life science start-ups in the period 2000-2004. The total budget amounted to 45.3 million euros.

In 2000, the Dutch industry and public sector research organisations presented the '*Strategic Action Plan Genomics'* for building a strong research infrastructure in the field of genomics. An advisory committee was assigned to investigate the actual need for such investments and the urgency of public financial support. This Temporary Advisory Committee for the Genomics Knowledge Infrastructure advised the Dutch government to invest heavily in genomics research and infrastructure, thereby following an integrated approach that includes commercialisation and the social and ethical aspects of genomics. Based on this advice, the Dutch government presented in 2001 its view in the policy report '*Genomics Knowledge Infrastructure'*. This resulted in the Netherlands Genomics Initiative (NGI), which is responsible for the execution and management of a national genomics strategy, with a budget of 189 million euros for the period 2002-2007.

In the period 1981-1993, the Dutch government invested more than 178 million euros in biotechnology research, mainly through the IOPb and PBTS programs. Between 1994 and 1998, more than 150 million euros were allocated to biotechnology research through several public instruments and programmes. Additionally, in the same period, charity funds provided 75 to 100 million euros for biotechnology related research (Enzing et al, 1999).

Policy instruments and funding for knowledge base support
The main programmes dedicated to biotechnology research in the period 1994-2004 are ABON, a number of NWO research programmes, and the programmes under the supervisions of NGI. Although the 1990s are very much a period when Dutch innovation policies were mainly characterised by their generic character, a number of Dutch biotechnology companies and public research organisations had been successful in attracting some extra public funds in 1991 for the Association of Biotechnology Centres in the Netherlands (ABON). The goal of ABON was to keep and strengthen the science base created by the IOP Biotechnology. ABON ran until 1999 and had a budget of 15.2 million euros including funding by government.

During the mid 1990s, NWO, the Dutch research council, ran two basic research programmes in the biotechnology field: the 'Structural/functional relation biomolecules' programme (1995-2003) and the 'Computational chemistry of biosystems' programme (1996-2002). They had a budget of respectively 2 million euros and 1.3 million euros. Like most NWO-programs they are response mode programmes that stimulate high quality research.

In 1999 NWO initiated the BioMolecular Informatics (BMI) programme and the Genomics programme. In 2000, the Ministry of Economic Affairs started the Innovation Oriented Research Programme (IOP) Genomics. The IOP genomics will run for eight years; the budget for the first phase (2000-2004) is 20.4 million euros. The IOP Genomics targets strategic and pre-competitive industry-oriented fundamental research at universities and public research institutes.

The NGI started its activities in 2002. NGI is formally responsible for the coordination of all national genomics instruments, including the IOP Genomics and the NWO programs BMI and Genomics. One of the tasks of NGI is to establish genomics Centres

of Excellence that perform high level research in specific fields and have an advanced genomics research infrastructure. The centres also offer education and training and perform research into societal aspects. In 2002, four Genomics Centres of Excellence were selected. In January 2003, NGI started the HORIZON programme that stimulates excellent and visionary fundamental research in genomics and biomolecular informatics. In 2004, two Technology Centres (BioInformatics and Proteomics) and four Innovative Clusters will be set up; they will be financed by additional funds (99 million euros) from the so-called Bsik programme.

Besides these dedicated programmes, biotechnology research groups could also join horizontal science and technology schemes, especially those that targeted themes in the area of human health or food in which biotechnology research is an important element. Most of these schemes were oriented to fundamental research and issued by NWO. Moreover, several R&D supporting schemes targeted the stimulation of industrial R&D and R&D co-operation, e.g. by providing subsidies for R&D projects and tax reductions for employing scientific personnel. Additionally, two horizontal initiatives started in the late 1990s, aiming at improving the general conditions of pharmaceutical research: the Netherlands Federation for Innovative Pharmaceutical Research (FIGON) and the Steering Group Orphan Drugs.

Policy instruments and funding for commercialisation support

In the period 1994-2004 three instruments dealt with the commercialisation of biotechnology: BioPartner, Mibiton and STIGON. BioPartner includes networking instruments, subsidies for formulating business plans, incubators, research facilities support, and risk capital to life science start-ups. The BioPartner programme runs until end 2004. Some of the BioPartner instruments will be integrated into a new public organisation that will stimulate entrepreneurship and technology-based start-ups in general, TechnoPartner. Mibiton started in 1994 with a subsidy of 10.8 million euros from the Ministry of Economic Affairs. It provides financial support for the purchase of high-tech research equipment at universities and public research institutes on the basis of facility sharing with private companies. The Mibiton programme proved especially useful for starting firms. The Support Programme for Innovative Medicine Research and Entrepreneurship in the Netherlands (STIGON) is a scheme that supports (bio)pharmaceutical start-ups based on innovative concepts in medicine research. Its main target group is scientists at universities and public research institutes. The total STIGON budget amounts to 8.8 million euros, including matching funds.

Generic instruments aiming at stimulating commercialisation of technology in general were rather limited in the period 1994-2004. Dreamstart is a public initiative initiated by the Ministry of Economic Affairs targeting high-tech start-ups by providing support in networking activities and facilitating access to information and consulting services. Additionally, the Subsidy Infrastructure TechnoStarters facilitates access for high-tech start-ups to research facilities at universities and research institutions.

Instruments with a socio-economic and/or ethic dimension

Since 1993, five nation-wide public debates have been organised for discussing specific biotechnology issues. The debates focused on topics like genetic modification, genetic research, cloning, xeno-transplantation and the application of biotechnology in food. Furthermore, the NGI has set up the Centre for Society and Genomics with a four-year research and education programme, and has a specific research scheme ‘Social component of genomics research’ (set up by NWO). Additionally, the Genomics

Centres of Excellence are also obliged to include socio-economic and ethical aspects in their research program.

Structure and dynamics of the national biopharmaceutical and food biotechnology innovation systems

Public biopharmaceutical R&D system
Public biopharmaceutical R&D in the Netherlands is mainly performed in graduate research school of universities and in research institutes. In 2003, 18 graduate research schools were (partly) active in biopharmaceutical research. This number has been stable over the last years. Public biopharmaceutical research is also performed by ten public research institutes of which seven target fundamental research and three target applied research. Academic research is mainly funded by the Ministry of Education, Culture and Sciences; a considerable part through the Dutch research council, the Netherlands Genomics Initiative and the Royal Netherlands Academy of Sciences. Applied research and commercialisation is mainly funded by the Ministry of Economic Affairs, mainly through programmes managed by the Senter agency and the BioPartner instruments. The other ministries mainly co-fund these programmes and funding organisations.

Public food biotechnology R&D system
The Wageningen University and Research Centre is one of the most important research centres for Dutch food biotechnology research. There are four graduate schools and five public research institutes active in food biotechnology research. In addition, food biotechnology research is carried out in the Top Institute (Wageningen Centre for Food Sciences) and in the recently set up genomics Centres of Excellence. The funding system is similar to that for biopharmaceutical research. A specific characteristic is the co-operative (pre-competitive) R&D performed by public research institute and universities for the food industry. In addition, large food companies participate in public research programmes and the Top Institute and set up research programmes together with the government.

Biopharmaceutical business system
During the period 1994-2001, the number of pharmaceutical firms fluctuated around 100. The most significant Dutch pharmaceutical firms are Organon and the Pharmaceutical Products Group of the Dutch multinational DSM. The Dutch subsidiary of Solvay Pharmaceuticals is another important player. The majority of the pharmaceutical firms in The Netherlands is a subsidiary of major foreign pharmaceutical companies that have production, logistics and/or research facilities in the Netherlands. The total employment in the Dutch pharmaceutical industry in 2001 was estimated at 15,100 jobs and increased with 3.5% compared to 1994.
The annual investments in pharmaceutical R&D in the Netherlands have increased significantly: from 198 million euros in 1994 to 401 million euros in 2001 (Nefarma, 2003, based on CBS figures). The number of employees in pharmaceutical R&D in the Netherlands also increased considerably: from 2,082 jobs in 1994 to 3,077 in 2001 (CBS, 2003c).

Since 1994, a considerable number of dedicated biopharmaceutical firms has been created. In 1994, only 18 pharmaceutical and fine-chemical firms dedicated to biotechnology existed. In 2001 this amounted to almost 80 firms, representing roughly two thirds of the total population of dedicated biotech firms in the Netherlands (Enzing et al., 2002b). The majority of the dedicated biopharmaceutical firms is specialised in

niche-markets, niche-technologies or specific activities within the pharmaceutical R&D process, such as drug discovery, lead optimisation and drug delivery. Very often, they are supplier of specific technologies or research partner to the traditional pharmaceutical firms and larger (foreign) biopharmaceutical companies. The majority of dedicated biopharmaceutical firms has shown very limited growth in terms of employees. The total employment for the dedicated biopharmaceutical firms in 2001 is estimated at 1,764 jobs. This means an average of less than 23 employees per dedicated biopharmaceutical firm (Enzing et al., 2002b). The R&D intensity of these firms is higher than that of the pharmaceutical firms. In 2001, all dedicated biotechnology firms in the Netherlands, of which the biotech firms in human health form the lion's share, invested almost 73 million euros into R&D (realising a total turnover of 123 million euros) (Enzing et al., 2002b). Moreover, 60% of the total labour force employed by the dedicated biotechnology firms is in research and development (Enzing et al., 2002b).

Some 30 clinical trial organisations, mostly private companies, are active in the Netherlands. They support public research organisations and pharmaceutical companies through developing and monitoring of new clinical trials, performing (parts of) the clinical study, managing clinical data and provisioning statistical support or (co)writing the final clinical study reports. The number of (pre)clinical trials conducted in the Netherlands has been significant since years with 640 studies in 2002. Nevertheless, a decrease in (pre)clinical trials has been occurring since 2000, most considerably in phase II.

Food biotechnology business system

The agrofood industry is one of the main industrial sectors in the Netherlands with a total number of companies in the food industry of 5,090 in 2001. This is a decrease of 17.4% compared to 1994 (CBS/Statline, 2003). Well known Dutch companies are Unilever, Numico, CSM and DSM (ingredients), as well as large dairy companies, such as Firesland Coberco Dairy Foods and Campina/DMV. Most food companies are rather small; in 2001, only 35 companies had more than 500 employees. In 2001, the total employment in the Dutch food industry (including tobacco) amounted to 129,200 full time equivalents (ftes). In 2001, the total value of sales of the food industry was 37.5 billion euros; an increase of 22% compared to 1994. The investments in food R&D (including tobacco) have increased considerably: from 182 million euros in 1994 to 269 million euros in 2001. The employment in R&D in the food industry is estimated at 2,989 ftes in 2001, compared to 2,523 ftes in 1994. In 2000, 174 food companies performed R&D activities and these activities are mainly concentrated in the larger companies (more than 200 employees); they provide 2,742 of the 3,063 R&D ftes in the food industry. The Dutch food industry (including tobacco) invests 0.5% of the total turnover in R&D activities (CBS/Statline, 2003).

Especially the large food and food ingredients companies are active in biotechnology. The number of established food companies that have adopted biotechnology is estimated at approximately 17 companies (Enzing et al., 2002). The number of dedicated food biotechnology firms is very limited. In 2001, 13 dedicated biotechnology companies had activities that were related to the food industry. In 1994, there were four dedicated food biotechnology companies (TNO-STB figures). Dedicated food biotechnology firms develop and produce ingredients for the food industry, are active in bioprocessing, and provide analytical services for determination of compounds, detection of contaminants, and safety control. One company is specialised in clinical research into novel and functional foods. Most of these companies are not solely dedicated to the food industry, but work for other industrial

sectors as well. The R&d intensity of dedicated food biotechnology firms is much higher than the average R&D intensity of the whole food industry. On average 60% of the employees of these firms are performing R&D and for half of these companies more than 80% of their personnel is active in R&D activities. In 2001, the dedicated food companies employed approximately 285 people (TNO-STB figures).

Biopharmaceutical M&A and R&D collaboration

Industry dynamics in the Netherlands caused by mergers and acquisitions have been limited. In 1998, DSM acquired Gist-Brocades, another Dutch multinational and the world's largest supplier of antibiotics and specialist in enzyme and fermentation technologies. In 2000, DSM acquired Catalytica Pharmaceuticals, a US-based company specialised in pharmaceutical intermediates. Akzo Nobel's Organon acquired the Japanese pharmaceutical company Kanebo in 1999 and Covance Biotechnology Services in 2001, and sold its subsidiary Organon Teknika, specialised in in-vitro diagnostics, to the French BioMerieux in 2001.

Considering the dedicated biopharmaceutical firms, only two mergers occurred until 2001. It is only after 2001 that merger and acquisition activities in the Dutch biopharmaceutical industry seem to have intensified: two mergers and three acquisitions occurred until the first half of 2003. R&D collaboration is a widespread phenomenon in the pharmaceutical and biopharmaceutical industries. Approximately 35% of the R&D partners of Dutch firms in the biopharmaceutical innovation system are located in the Netherlands (most are public research organisations), the rest mostly in Europe (31%, most are firms) and the US (21%, most are firms).

Food biotechnology M&A and R&D collaboration

Since 1994, Dutch food companies have been rather active in mergers and acquisitions. Major acquisitions and mergers concerned the take-over of Bestfoods and Slimfast by Unilever in 2000, the take-overs of GNC and Rexall Sundown by Numico in 1999 and 2000, the take-overs by dairy company Melkunie, and the merger of four dairy cooperatives into Friesland Coberco Dairy Foods. Main reasons for these mergers and acquisition are the strategy of focusing on specific product groups with a high gross profit margin and the entry on international markets. The dedicated food biotechnology companies were not involved in mergers and acquisitions in the period 1994-2001.

Food biotechnology R&D collaboration in the food industry is mainly nationally oriented; over 50% of the partners of the food companies in the survey are from the Netherlands. Other partners come from the rest of Europe and the United States. Especially collaborations with small and medium sized companies are a national matter, but collaborations with large firms are more internationally oriented.

Biopharmaceutical demand system

The expenditures on pharmaceutical products in the Netherlands have increased continuously over the last decades. In addition, the growth of the Dutch pharmaceutical expenditures has been stronger than the growth of the total Dutch expenditures on health.

The Dutch market for pharmaceuticals in 2002 consisted for 72.2% of branded (or in-patent) pharmaceuticals, for 18.5% of generic (or out-of-patent) pharmaceuticals, and for 9.4% of parallel imports (Nefarma, 2003). Although the branded pharmaceuticals still dominate the market, the generic pharmaceuticals are increasingly gaining a larger market share (Nefarma, 2003). This development already started during the 1990s due

to the large number of pharmaceutical patents that expired and due to the government policy of stimulating the prescription of generic pharmaceuticals.

The market for pharmaceuticals based on biotechnology is still limited. In 2001, approximately 60 biopharmaceutical products were on the Dutch market with insulin representing the largest share (Nefarma, 2002). The expenditures on biopharmaceuticals are growing annually and have an increasing share in the total expenditures on pharmaceuticals: from 295 million euros in 2001 (8.6% of total pharmaceutical expenditures) to 345 million euros in 2002 (9.2%).

Public health policies

For several years, public health policies in the Netherlands have strongly emphasised cost containment. In particular pharmaceuticals have been subject to cost containment measures such as the setting of maximum price levels, stimulating the prescription of generic pharmaceuticals and tolerating the parallel import of brand name pharmaceuticals. The continuously rising expenditures on health care in the Netherlands and its decreasing quality forced the Dutch government to introduce measures to deregulate the system and place more responsibilities at the level of individual actors within the health care system. The government acknowledged that targeting cost-containment is not the main solution, but that it has to be combined with measures that increase the effectiveness and efficiency of health care in the Netherlands. Therefore, the Dutch government decided in 2000 to commit the central role in the national health care system to the health care insurance companies, forcing them to take a more active role in the reorganisation of the health care system. In addition, the system for determining the tariffs of intramural treatments was replaced by the system of Diagnosis Treatment Combination in 2003. This system entails a specified price for a complete treatment of the patients, covering the entire process from diagnosis and hospitalisation to the discharge from the hospital. The new system still shows many growing pains. The fall of the Dutch government in 2003 has led to considerable delay in the development and implementation of the system. Moreover, it remains unclear how pharmaceutical products will fit into the concept of Diagnosis Treatment Combination and what the consequences will be of the new health care system for new and expensive pharmaceuticals, e.g. biotherapeutics (Nefarma, 2003; BioFarmind, 2002).

Market access of pharmaceutical products

Market access of new pharmaceutical products is mainly covered by international regulations that have been implemented in the Dutch Medicines Act. The Medicines Evaluation Board, the Dutch authority responsible for the evaluation and issuing of market authorisations for pharmaceutical products determines whether or not pharmaceuticals should be made available on prescription or not. In general, two alternative routes exist for authorisation of new pharmaceutical products: the centralised route at the European level by the European Agency for the Evaluation of Medicial Products (EMEA) and the decentralised route at the national level. For pharmaceuticals based on biotechnology only the centralised route at the EMEA is possible.

The promotion of the prescription of generic drugs has been an important element in the Dutch health care policies. However, the concept of generic drugs might prove problematic in the case of biopharmaceuticals (Schellekens and Brouwer, 2002, and Nefarma website). In contrast to the pharmaceuticals that are based on chemical synthesis, no generic copies have been developed and introduced for biopharmaceuticals so far. First of all, this is because most biopharmaceuticals are still

covered by a patent, which makes the development of a generic copy impossible. Second, it is not clear yet which specific requirements the authorities will demand from the dossiers for generic copies of biopharmaceuticals. A complicating factor is that it is extremely difficult to prove that a biogeneric drug has the same properties and effects as the original biopharmaceutical drug. As a consequence, extensive clinical evidence will be necessary, in addition to a study of bio-equivalence, before the registration authorities will declare the new biopharmaceutical as a bio-equivalent copy of the original biopharmaceutical. This leads to very elaborated, lengthy and expensive development processes for biogenerics that are comparable to the development process for a totally new drug. This is relatively new for the development of generic drugs and makes the development of biogenerics less attractive (Schellekens and Brouwer, 2002, and Nefarma website).

Patient organisations

A specific feature of the Dutch biopharmaceutical innovation system is the presence of a large number of patient organisations. At least 400 associations and organisations exist for patients with a specific disease or disorder (Smit, 2003). A number of them is united in umbrella organisations like the Dutch Genetic Alliance (VSOP) and Association for people suffering from chronic diseases and for handicapped people. Generally speaking, patient organisations represent patients' interests by improving awareness and understanding of diseases and disorders. The main activities of patient organisations are to spread information among their members and to communicate with government, public health authorities and welfare services in the political arena (Herxheimer, 2003; VSOP website). Patient organisations try to influence the decision making processes, for example in the case of listing a new but more expensive drug under the public insurance schemes or the stimulation of specific health research areas. Patient organisations also communicate with pharmaceutical companies, especially with the more integrated (bio)pharmaceutical firms.

Food biotechnology demand system

The food industry in general is a rather market-driven industry. In the Netherlands, the food industry introduced hundreds of products every year, mainly driven by ideas that have been put forward by market development departments. The consumer determines the commercial success of these products. The food industry considers the lack of public support for food biotechnology as one of the main barriers in the further development and application of biotechnology in food. Already in the beginning of the 1990s, the industry started a discussion with consumer organisations and other non governmental organisations. These informal consultation processes resulted in several agreements on various issues, e.g. labelling. Nevertheless, the support for biotechnology in food has only decreased since then, especially in the period 1999-2002 (Stichting Consument en Biotechnology, 2003, based on European Commission, 2003b). The industry realises that more work is needed to increase the support of consumers for food biotechnology. The focus on the cost benefits of biotechnology in food has shifted to a focus on consumer benefits, In addition, the food companies increasingly involve scientists, key opinion leaders and health professionals in their innovation processes. According to the industry, a stronger involvement of the demand side in biotechnology innovations will be one of the major challenges for the coming years (Bureau Blaauwberg, 2003).

The market access of new food products based on food biotechnology is strictly regulated by both European and national legislative frameworks. The process for authorisation is a timely and costly process with much insecurity. In 1998, a European

moratorium on the introduction of new GMOs was installed. Since then it has been impossible to introduce products that contain new GMOs. Only in July 2003, new directives on GMO food and feed have been adopted by the Council of Agriculture Ministers of the European Union. The new directives give new guidelines for authorisation and labelling. The European Food Safety Authority will manage the centralised authorisation procedure. This intends to make the authorisation procedure shorter, more transparent and less complex. It is expected that the moratorium will be lifted as soon as the directives are effectuated.

Key drivers and barriers in biopharmaceutical and food biotechnology innovations

Public IPRs and technology transfer

Dutch universities have had technology transfer offices since the late 1970s to support university-industry interaction and provide assistance to researchers in IPR issues. However, their efficacy in commercialising biotechnology is often considered as insufficient (Kern et al., 2003; OECD, 2003). Technology transfer between the Dutch public R&D system and industry is limited, in particular when it concerns patenting and licensing activities (CBS, 2003c). A prominent reason is the lack of a combination of expertise in commercial, legal and specific biotechnological issues. This is aggravated by the limited size and small budgets of most technology transfer offices. A complicating factor in relation is the heterogeneity of the academic IPR system in the Netherlands. Each university is relatively autonomous in developing its own IPR systems and policies.

Small and large firms

Pharmaceutical companies have extensive experiences in activities in the down-stream stages of the innovation process, such as manufacturing, distribution, marketing and regulatory affairs. They are highly experienced in these ‘disciplines’ and can assist small firms on these matters. Pharmaceutical companies are also important clients of small high tech biopharmaceutical firms as they buy the highly specialised scientific and technological knowledge and tools that are too costly to develop internally. From this perspective the very limited number of large integrated pharmaceutical companies in The Netherlands can be considered as a serious problem. Proximity is an issue and as most small firms work in business-to-business markets with larger pharmaceutical firms as their main clients, they have to spend extra efforts and costs in building up relations with clients abroad. Especially for small firms this can have a negative effect on the survival and - in a later stage – on their successful exit strategies.

The relations between large food companies and small dedicated food biotechnology firms show a different picture. The interviews with the large food companies showed that these companies do not really have research collaborations with Dutch dedicated food biotechnology companies, except for clinical trials for functional foods. According to the large firms, an important reason for this is that the dedicated food biotechnology firms lack the expertise and technologies the large firms need. On the other hand, the small firms mention as reason for the limited co-operation their lack of an appropriate track record; they are still too small and too young to be attractive research partners. To open this vicious circle the small firms will need to work on convincing the large companies of their capabilities or search for other options to become more experienced.

Human resources

Knowledge is also acquired by attracting high quality human resources. The availability of and access to qualified human resources is a growing bottleneck to the Dutch biopharmaceutical sector. This not only refers to the limited number of students graduating in life sciences but also to the rapid increase of biotechnology firms world-wide, which leads to a higher demand for skilled labour. In particular small and medium sized firms and public research organisations encounter difficulties as they often are not able to offer the same employment conditions and career opportunities as larger firms can. The areas in which most significant shortages emerge are laboratory support and the scientific disciplines bio-informatics, genetics, genomics and proteomics. For industry it proves especially difficult to attract staff with both scientific and managerial expertise.

Private financing

The Dutch market for private equity is considered mature, increasingly competitive and can be characterised by a large variety and number of private equity houses. Although the overall level of private equity investments has increased over the years, an important share is invested outside the Netherlands. The total amount of venture capital investments in biotechnology in the Netherlands in the years 1999-2000 equaled 56.8 million euros. Compared to the years 1994-1995 when 19.8 million euros were invested this means an increase of more than 186% (Kern et al, 2003). The last few years, providers of private capital have become more reluctant to high-risk investments in biotechnology. Biotechnology companies, including biopharmaceutical and food biotechnology companies, with a business model that is mainly based on investing in R&D, encounter difficulties in raising external financial resources as investors demand income. The first years after the turn of the century are likely to become critical to biotechnology firms in the Netherlands as a substantial gap emerges between public funding in the seed and start-up stages and private venture capital for the follow-up stages (Kern et al., 2003).

Laws and regulations

Generally speaking, both industry and public sector research organisations welcome a sound and strict regulatory framework as it contributes to a higher level of quality and innovativeness of the biotechnology sector (Niaba, 2002). However, the present regulatory framework in the Netherlands causes a number of serious disadvantages in comparison with other countries. Most of these disadvantages concern the timely length of application and decision-making procedures, the lack of transparency and predictability of procedures, and overlapping tasks and evaluation frameworks of the official authorities (Niaba, 2002; BioCollectief en Schenkelaars Biotechnology Consultancy, 2002). Regulatory and legislative issues cause problems in several areas. In particular the legislative framework for food biotechnology is rather complex and strict. Not just the European moratorium on the introduction of new GMOs (installed in 1998), but also the very strict regulation on deliberate release (field trials) has been a serious barrier for food biotechnology companies. The number of field trials has decreased considerably since 1999 and several companies decided to stop their GMO research activities in the Netherlands. Another area of strict and impeding regulation concerns working with animals. Dutch law forbids the application of genetic modification techniques on animals and obtaining a license is only issued if no ethical objections and no unacceptable consequences for the health or well being of animals exist (the so-called ‘No, unless…’-policies). Moreover, ever since its introduction the Dutch government has resisted to the EC directive 98/44/EC on the granting of intellectual property rights on biotechnology.. The directive still has not been implemented at the beginning of 2004, whereas the directive 98/44/EC should have

been implemented on the 30th of July 2000 at latest. This negative attitude isolates the Dutch biotechnology sector within Europe and affects the overall climate for biotechnology in the Netherlands considerably.

Entrepreneurship
In general, the Netherlands is characterised as a country with a lack of entrepreneurial spirit. This hinders considerably the commercialisation of new scientific knowledge, including biotechnology. Scientists are not very willing to leave their academic position and to get fully engaged into business activities (Ernst and Young, 1998).

Systemic imperfections and policy implications

The national case study has revealed various factors that affect the operating of the Dutch biopharmaceutical and food biotechnology innovation systems. This section presents the main systemic imperfections and sketches the implications for public policies. As the Dutch government presented early 2004 the outlines of its policies for stimulating the life sciences sector in the Netherlands (Action Plan Life Sciences 2004-2007), several of the imperfections that have been identified in this study will be addressed by public policies in the period 2004-2007. Additional recommendations are formulated.

Although the Dutch biotechnology science base and education system is of high quality, there is an **imbalance in knowledge production** as there has been strong growth in applied research and in development of technology and hardly in fundamental research. This could ultimately lead to a depletion of the science-driven biotechnology knowledge base and to increasing difficulties for the Dutch research sector and industry in keeping up with international scientific developments. Moreover, present policies are highly focussing on genomics. However, life sciences and biotechnology entail more than genomics and a **post-genomics era** will eventually develop. Finally, the **availability of qualified technical staff and researchers** is increasingly becoming a bottleneck to both the public sector research and industry in general.
Recommendation: Policy measures are necessary to sustain a high-quality fundamental knowledge base in biotechnology. The recently started genomics programme of the Netherlands Genomics Initiative includes strong basic research components and is therefore an important action in this respect. However, it is also necessary to sustain the fundamental knowledge base in other areas relevant to biotechnology. Moreover, future developments need to be explored and monitored. Related to the availability of skilled labour, measures are needed to increase the attractiveness of technical and natural sciences, in particular related to biotechnology. Finally, restrictive regulations to attract talented and experienced foreign human resources need to be removed or simplified. These human resources related problems have already been acknowledged by policy makers in education and S&T policies and actions are being prepared.

There are several systemic failures related to the exploitation and commercialisation of biotechnology. First, there is an **insufficient exploitation of public sector research**, in particular university research. Exploitation of research is not a high priority in most universities and specific infrastructural instruments like technology transfer offices often lack the critical mass and the necessary expertise. Differences between the universities' exploitation policies have evolved. Second, the majority of the scientists that start their own biotechnology firm has a **general lack of managerial skills**. This has a negative impact on the speed of development of many young biopharmaceutical

firms in the Netherlands. Third, the **limited number of major Dutch pharmaceutical firms** pressurises the possibilities for small biopharmaceutical firms in creating a significant home-market with regard to turnover and R&D collaborations. The **lack of track-record of the dedicated food biotechnology companies** makes it difficult to establish **collaborations with large food companies**, needed to build up expertise.
Recommendation: Governmental action is required to improve the priority given to exploitation of research by universities and public sector research organisations. The Action Plan Life Sciences and also the latest Science Budget of the Ministry of Education address explicitly the problem of insufficient exploitation of public sector research. Consequently, new actions aim to improve the quality of business plans and to investigate best-practice concerning organisational and juridical models for valorisation. Moreover, a new measure is being prepared to subsidise the valorisation and exploitation activities at universities (i.e. 'Subsidieregeling Kennisexploitatie'). However, additional governmental action is necessary. First, improved co-ordination of university exploitation policies could increase the sense of urgency felt by university boards and contribute to inter-university learning processes. Second, the inclusion of indicators for valorisation and exploitation in university review procedures could contribute to prioritisation. Third, apart from the financial means a 'Subsidieregeling Kennisexploitatie' will offer, biotechnology transfer offices need a combination of biotechnological, legal and commercial expertise. Finally, activities of national and local government should not only deal with attracting foreign companies to the Netherlands, but also with keeping the Dutch pharmaceutical firms inside the Netherlands.

A systemic failure related to the demand side of the pharmaceutical innovation process is the **large and heterogeneous number of small patient organisations.** Critical mass could be realised through more **co-ordination and interaction** between them. Patient organisations could then have a more active role in the industrial innovation process and in facilitating clinical trails.The **market access for food biotech applications is very restricted**. The new EU directives on GMO food and feed will lead to the abolishment of the moratorium on GMOs, which has been active since 1998. However, there is still much insecurity about the actual procedures included in the new directives. In addition, there is still no harmonised legislation on health claims on food products. More harmonisation and clearer procedures and guidelines will make market access of new food products less complex and insecure. In general, there is a **lack of an appropriate dialogue** between the main stakeholders in biotechnology innovation. Public acceptance for food biotechnology applications is lacking and the public support for these innovations has decreased since 1994. Open and constructive channels of communication are needed for an improved acceptation of biotechnology.
Recommendation: The government should investigate the possibilities of supporting the patients' organisations in realising the necessary internal interaction and co-ordination and should explore how the interaction between patients' organisations and industry through patient-industry networks can be stimulated. The government should strive for more European harmonisation in market access regulation and less complex procedures. Additionally, incentives need to be introduced to stimulate researchers from academia and from biotechnology firms to communicate fairly about their activities, by addressing the benefits as well as the risks.

One very important framework condition that is currently hindering the development of biotechnology in general is the **limited availability and accessibility of risk capital**. This lack of risk capital is especially prominent after the first stages of firm development as a considerable gap exists between the mainly public sources of funding

for the seed and start-up stages and the sources for follow-up financing provided by venture capitalists. A second inappropriate framework condition is the **hindering set of regulations** applied to biotechnology in the Netherlands. A third framework condition that is in particular negatively affecting the biopharmaceutical innovation system is the **set of public health care policies and related measures**. The current and former policies targeting cost-containment are a negative signal for innovative pharmaceutical companies. Also the policy incentives for developing innovative pharmaceuticals in the Netherlands are limited. The last imperfect framework condition is the lack of **interaction and co-ordination among government departments**. Governmental policies in the area of, for example, food, health care and environmental protection and safety have been inconsistent with the aims of innovation and industrial policies in the field of biotechnology on several occasions.

Recommendation: The Action Plan Life Sciences 2004-2007 announced measures to remove the barriers raised by the lack of risk capital, restrictive regulations and the lack of policy co-ordination. In addition to this, the Dutch government should provide more clarity about the position of innovative but more expensive pharmaceuticals in the health care and reimbursement system. In this respect, it also needs to take into account the benefits that innovative pharmaceuticals provide and how they can contribute to cost-containment on the long term, e.g. by increasing effectiveness and decreasing the necessary time of medical treatments. A more systemic policy approach is needed that combines the objectives of a competitive pharmaceutical industry and of an affordable public health care system. The government should aim for more coordination between the various departments and policies in order to prevent inconsistencies between the biotechnology policies.

Contents

1 Introduction 19
1.1 Background and goal of the OECD-project 19
1.2 Approach 20
1.3 Structure of the report 22
1.4 Country characteristics 22
1.4.1 Size and main industries 22
1.4.2 The pharmaceutical industry 23
1.4.3 The food industry 27

2 Overview of national R&D, technology and innovation policies for biotechnology 32
2.1 Introduction 32
2.2 Main policies and policy making bodies 32
2.3 Biotechnology policy instruments and managing organisations 34
2.3.1 Programme management 34
2.3.2 Policy instruments for knowledge base support 35
2.3.3 Instruments for commercialisation support 39
2.3.4 Instruments with a socio-economic and/or ethic dimension 41

3 Structure, dynamics and performance of the biopharmaceutical and food biotechnology innovation systems 43
3.1 National public R&D system 43
3.1.1 General structure of the public R&D system 43
3.1.2 Public biopharmaceutical R&D system 44
3.1.3 Public system for food biotechnology research 46
3.2 Business system 49
3.2.1 Biopharmaceutical business system 49
3.2.2 Food biotechnology business system 57
3.3 Performance 63
3.3.1 Introduction 63
3.3.2 Scientific performance 63
3.3.3 Training and education 67
3.3.4 Business and innovation performance 68

4 Innovation barriers and drivers – Framework conditions 75
4.1 Introduction 75
4.2 Knowledge sources 75
4.3 Human resources 78
4.4 Risk Capital 79
4.5 Regulations 81
4.6 Entrepreneurship 85

5 Demand Side Factors 86
5.1 Introduction 86
5.2 Market characteristics of the biopharmaceutical system 86
5.2.1 Public insurance schemes, reimbursement and price setting 86
5.2.2 Explosive growth of medicine expenditure 87
5.2.3 Public health policies 88
5.2.4 Regulation of market access 88

5.2.5 Role of patients and their organisations 90
5.3 Market issues in the food biotechnology industry 91
5.3.1 Possible influence of the reimbursement system 91
5.3.2 Regulation of market access 91
5.3.3 Role of consumers and their organisations 92
5.4 Socio-economic and ethical aspects 94

6 Synthesis and conclusions 97
6.1 Systemic imperfections 97
6.1.1 Science base and education 99
6.1.2 Exploitation and commercialisation 99
6.1.3 Demand 102
6.1.4 Framework conditions 102
6.2 System openness 103
6.3 Role of demand 105
6.4 Policy implications 106
6.4.1 Science base and education 107
6.4.2 Exploitation and commercialisation 108
6.4.3 Demand side 109
6.4.4 Framework conditions 110

7 References 112

8 Interviewed persons 118

List of tables and figures

Figures and Tables

Figure 1-1 Size of the Dutch pharmaceutical industry in number of firms 24
Figure 1-2 Employment in the Dutch pharmaceutical industry (in number of jobs) 24
Table 1-1 R&D figures of Dutch pharmaceutical industry 25
Figure 1-3 Production of pharmaceutical materials and products in the Netherlands in € million 26
Table 1-2 Biopharmaceutical expenditures in the Netherlands, in € million 27
Figure 1-4 Agrofood chain 28
Table 1-3 R&D expenditures and R&D employment in the Dutch food industry 29
Figure 1-5 Total value of sales of the food industry in the Netherlands 30
Figure 1-6 Employment in the Dutch food industry in number of jobs 31
Table 2-1 Vertical biotechnology instruments for knowledge base support 1994-2001 37
Table 2-2 Horizontal instruments for biotechnology knowledge base support 1994-2001 38
Table 2-3 Main vertical and horizontal programmes and instruments for biotech commercialisation support 1994-2001 40
Figure 3-1 Public funding system of biopharmaceutical research in the Netherlands ... 44
Table 3-1 Graduate research schools in the field of biopharmaceutical research 45
Table 3-2 Public research institutes carrying out biopharmaceutical research 46
Figure 3-2 Public system of food biotechnology research in the Netherlands 47
Table 3-3 Public research organisations for food biotechnology research 47
Figure 3-3 Size of dedicated biopharmaceutical firms in the Netherlands in number of employees 50
Figure 3-4 M&A activities in the Dutch biopharmaceutical innovation system for 1990-2003 51
Figure 3-5 Nationality of R&D collaboration partners for total human health and per type of partner 52
Figure 3-6 Type of partner of industry and subject of collaboration in human health research 53
Figure 3-7 Nationalities of partners of industry and subject of collaboration in human health research 53
Figure 3-8 Type of partner of industry and subject of collaboration in human health research 54
Table 3-4 Contribution of international co-inventions in biopharmaceuticals 55
Table 3-5 Number of clinical trail studies in the Netherlands 55
Table 3-6 International trade of drugs, medical and pharmaceutical products 56
Figure 3-9 Nationality per type R&D partner in food biotechnology 59
Figure 3-10 Type of partner and subject of collaboration in food biotechnology 60
Figure 3-11 Nationalities of partners and subject of collaboration in food biotechnology 60
Figure 3-12 Type of partner and form of collaboration in food biotechnology 61
Table 3-7 International trade of the Dutch food industry (including tobacco) 62
Table 3-8 Contribution of different author types to biopharmaceutical publications 63
Table 3-9 Number of biopharmaceutical publications 64
Figure 3-13 Biopharmaceutical publications per 1000 researchers 65
Figure 3-14 Biotechnology publications per million capita in 2000 65

Table 3-10 Position of ‘agriculture and food sciences’ in the Dutch research system: the six strongest areas 66
Figure 3-15 Publications growth rate and share in total EU publications 67
Figure 3-16 Patterns of firm creation for dedicated biotechnology companies in the Netherlands and Europe 69
Table 3-11 Turnover, R&D and employment figures for dedicated biotechnology firms in 2001 69
Table 3-12 Initial public offerings by Dutch dedicated biomedical/biopharmaceutical companies 70
Figure 3-17 Biotechnology patenting activities at EPO and USPTO, corrected for size of country 71
Table 3-13 Number of pharmaceutical and biopharmaceutical patent applications (EPO) by Dutch inventors 71
Figure 3-18 Types of inventors and their contributions in biopharmaceutical patent applications (EPO) 72
Table 3-14 Number of biopharmaceutical patent applications (EPO) per million capita 72
Table 3-15 Pharmaceuticals in the pipeline in 2002 73
Table 4-1 Venture capital investments in biotechnology in the Netherlands, PPP in € x1000 80
Table 4-2 Main areas of legislation and regulation for human health and food biotechnology 81
Table 5-1 Dutch expenditures on health and pharmaceuticals 1994-2000, million US $, PPP 87
Table 5-2 Public debates on biotechnology in the Netherlands 94
Table 6-1 Imperfections in the Dutch biopharmaceutical and food biotech innovation system 98

1 Introduction

1.1 Background and goal of the OECD-project

The 'innovation system' concept has gained increasing attention during the past ten years, both from researchers and policy makers. In particular the National Innovation Systems approach has provided a framework for the assessment of the organisation of innovation processes, the innovation performance of countries, and the role of framework conditions, including public policy. The OECD has contributed a great deal to our understanding of the innovation systems approach and its relevance for policy making. The results of OECD studies on innovation systems have been reported in a number of publications, e.g. *National Innovation Systems* (OECD, 1997), *Managing National Innovation Systems* (OECD, 1999a), *Boosting Innovation*: *The Cluster Approach* (1999b), and recently *Dynamising National Innovation Systems* (2002a).

One very important conclusion that can be drawn from the OECD's work on national innovation systems is that too generic public policies can lead to misfits as they are not tuned to the specific characteristics of the technological or sectoral innovation systems at hand. The development of new policies needs to take into account the specific idiosyncratic properties of an innovation system. These properties are to a very large extent caused by the specific characteristics of sectors and technologies that constitute the national system.

This was the reason for the OECD Working Party on Technology and Innovation Policy (TIP) to start in 2002 the project 'Case Studies in Innovation'. Goal of the project is to understand the differences in national innovation systems and to investigate the policy implications following from sectoral differences in innovation systems. The project includes three cases: pharmaceutical biotechnology, knowledge intensive service activities, and energy. The 'Case Study in Biopharmaceutical Innovation'-part of the OECD-project, wants to contribute to an understanding of the differences in national innovation systems by providing an in-depth analysis of the biopharmaceutical part of these systems.

This report presents the analysis of the Dutch biopharmaceutical innovation system. Together with the national reports on the biopharmaceutical innovation systems in Belgium, Finland, France, Germany, Japan, Norway and Spain it will form the basis of a cross country analysis and an explanation of the national differences. On the basis of this the central question of the OECD-project will be addressed.

This question is:
"Can we identify important differences and similarities in the structure and dynamics of national biotech innovation systems of the participating countries which explain the differences in performances of these systems, and what are the policy implications?"

The project focuses on more specific questions dealing with issues that are relevant to biopharmaceutical innovation systems, in particular: systemic imperfections, system openness, demand side factors and systems policies.

Systemic imperfections can be seen as symptoms of sub-optimal innovation systems and are judged as being a rationale for innovation policy actions. However, an in-depth investigation of these systemic imperfections and their implications for policies is so far lacking for biotechnology. The investigation of these systemic characteristics is one of the main goals of the overall research project 'Case Studies in Innovation' and therefore is a main issue in this report.

The concept of national innovation systems implies a definition based on a country's geographical boundaries. However, developments in high technology sectors, in specific in biotechnology, are to an increasing extent realised by international research and business networks as can be found in international R&D co-operations or the presence of foreign pharmaceutical multinational companies. This national-international dimension of system openness is especially relevant to national policy-making.

Demand side factors play a major role in the successful development of new technologies, with biotechnology as the most prominent example. However, in the literature and research on (national) innovation systems demand side factors have received relatively less attention. What are the effects of these demand side factors on the biopharmaceutical innovation process and how should they be taken into account by the research, business and policy communities?

A specific objective of the OECD 'Case Studies in Innovation' project is to draw policy conclusions with regard to the balance between horizontal innovation policies and more customised measures that take into account the specific characteristics of innovation processes in the biomedical/biopharmaceutical innovation system.

As the food industry in the Netherlands is a sector where biotechnology has been widely implemented and has a considerable size larger then the pharmaceutical sector, it was decided also to include the food sector in the study. Unlike for the biopharmaceutical sector, no overall extra data-collection and related analysis could be made. As a result, the food part of this report could be elaborated less extensively. In this report, we speak of biotechnology when issues are related to both the biopharmaceutical and biotech food sectors. Otherwise, we specifically refer to the biopharmaceutical or biotech food sectors.

1.2 Approach

To facilitate comparability across countries, the Biopharmaceutical Focus Group prepared a guidebook that describes the common definitions, approach and methodology to be used for the national case studies (Enzing et al, 2002a.)

This methodology, as implemented in the Dutch case study was as follows:

1. A descriptive analysis of the national biopharmaceutical innovation system on the basis of desk research. This includes a description of the biopharmaceutical innovation chain and the types of actors and organisations involved. Moreover, it serves to describe the main framework conditions that affect the outcomes of the biopharmaceutical innovation process. This first step draws heavily on an extensive literature survey and desk-research.

2. Bibliometric and patent analysis for measuring the national performance. It also serves the identification of the main type of actors and their actual relevance in the biopharmaceutical innovation process. In the case of patent analysis, data are used for patent applications at the European Patent Office. The data collection and calculations are performed by Fraunhofer-ISI by using the OECD Patent database and the Science Citation Index databases in February 2003.

3. Industry survey on R&D co-operation. A questionnaire was sent in February 2003 to 193 Dutch companies that were believed to be active in pharmaceutical and agro-food biotechnology; 107 companies returned the questionnaire. From these 107, 56 are biopharmaceutical companies and 22 are active in food biotechnology[1]. The survey included both dedicated biotechnology firms (high tech companies specialised in biotechnology and active in R&D and in the application in processes/ products and services) and diversified firms (established firms that have integrated biotechnologies in their existing R&D and production activities).

4. Interviews with companies, sector experts and demand side actors in the period March – June 2003. In total, 16 persons were interviewed representing four biopharmaceutical firms and four firms in the food sector, three industry interest groups, one patient organisation and one consumer organisation.

The definition of biotechnology used in the project is the OECD-definition[2] that combines a single and a list-based definition. The single definition describes biotechnology as the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services.

The list based definition is composed of five technologies or processes:

- DNA (the coding): genomics, pharmaco-genetics, gene probes, DNA sequencing/synthesis/amplification, genetic engineering;
- Proteins and molecules (the functional blocks): protein/peptide sequencing/synthesis, lipid/protein engineering, proteomics, hormones and growth factors, cell receptors/signalling/pheromones;
- Cell and tissue culture and engineering: cell/tissue culture, tissue engineering, hybridisation, cellular fusion, vaccine/immune stimulants, embryo manipulation;
- Process biotechnology: bioreactors, fermentation, bio-processing, bioleaching, bio-pulping, bio-bleaching, bio-desulphurisation, bioremediation and biofiltration;
- Sub-cellular organisms: gene therapy, viral vectors.

The biopharmaceutical part of the pharmaceutical system is defined as consisting of those actors and activities of R&D-organisations, companies and others that are involved in or address one or more of the biotechnology activities mentioned in the OECD definition.

[1] In the survey, 'Food' includes food products and food ingredients, but also specialty chemicals, platform technologies and equipment, which have been developed and produced for application in the sector specifically. The agro-part of the agrofood chain is not included in this report.

[2] see OECD document no.: DSTI/EAS/STP/NESTI(2001)3/REV2.

1.3 Structure of the report

This report aims to describe the main actors and their activities, the institutions and framework conditions in the Dutch biopharmaceutical and food biotechnology innovation system, to assess their performance and to draw conclusion that address the questions of the OECD-project.

The structure of this report follows the structure as presented in the Guidebook of the OECD-project. In the last paragraph of this first chapter a number of relevant country characteristics of the Netherlands, including a brief description of the Dutch pharmaceutical and food industry, is given. Chapter 2 presents the main characteristics of Dutch public innovation policies and policy instruments in the field of biotechnology for the period 1994-2001. It also provides information about the main policy making organisations and agencies responsible for the management of national policy instruments. Chapter 3 discusses the structure and performance of the national system, more specific: the public R&D system and the biopharmaceutical and biotech agrofood industries. The assessment of specific framework conditions, and their availability and accessibility, which are judged particular relevant to innovation, are presented in Chapter 4. In Chapter 5, specific elements of the demand side in innovation systems are discussed, i.e. the national health care system, regulation of market access, the role of users and the influence of socio-economic and ethical issues. Finally, in Chapter 6 the main conclusions on systemic imperfections, system openness and the role of demand are drawn. Following from these conclusions, a set of policy implications is presented.

1.4 Country characteristics

1.4.1 Size and main industries[3]

The Netherlands is a medium-sized European country with a population exceeding 16 million inhabitants in 2002. It has an open economy depending heavily on foreign trade. In 2001, the Dutch gross domestic product (GDP) amounted to 429 billion euros, 71% coming from service activities and 26% from industrial activities. In 2001, the Netherlands showed a positive trade balance with exports equal to 280 billion euros and imports to 257 billion euros.

The Dutch economy is characterised by its stable industrial relations, moderate inflation, a sizeable current trading surplus and it plays an important role as European transportation hub. The predominant industrial sectors are food processing, chemicals, petroleum refining, and electrical machinery. The agricultural sector provides important surpluses for the food-processing industry and for exports. However, the agricultural sector is highly mechanised and employs no more than 4% of the total labour force. The labour force in the Netherlands amounts to 7.2 million people (2000 figures) of which approximately 3% are unemployed. For the second half of the 1990s, the Netherlands showed an annual growth rate that nearly averaged 4%; however, the economic growth has considerably slowed down since the millennium.

[3] Sources for this section are: CIA – The World Factbook 2002 (www.odci.gov/publications/factbook) and CBS 2003c

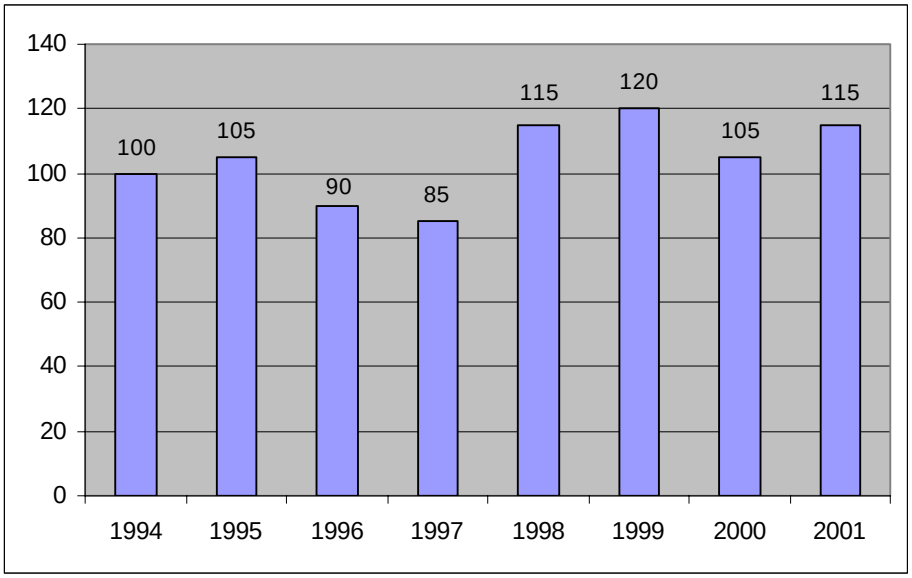
The gross domestic expenditures on R&D (GERD) have shown an increase since the early 1990s. The figure in 2000 was 7.8 billion euros. This means a growth of almost 34% compared to 1994; however, the growth compared to 1999 is only 3%. The Dutch R&D intensity, in terms of GERD as percentage of GDP, has been fluctuating during the past years: 2.04% in 1997; 1.94% in 1998; 2.02% in 1999; and 1.94% in 2000. The Dutch R&D intensity in 2000 was below the OECD average (2.24%) but above the EU-average (1.88%). The private sector contributes most to the R&D intensity in 2000 as it accounts for 1.11 percentage points of the R&D intensity. This is considerably lower than the EU and OECD figures (1.21% and 1.56%). The public sector, i.e. universities and public research organisations, accounts for almost 0.84 percentage points of the R&D intensity. Although the R&D intensity by the public sector has significantly been decreasing since 1993, it is still far above the EU and OECD figures (0.67% and 0.68%).

1.4.2 The pharmaceutical industry

The number of pharmaceutical companies, including producers of pharmaceutical intermediates, amounted to 115 in 2001 (CBS/Statline, 2003). During the period 1994-2001, the number of pharmaceutical firms fluctuated around 100 (figure 1-1). The majority of these companies is a subsidiary of major foreign pharmaceutical companies that have production, logistics and research facilities in the Netherlands.

The most significant Dutch pharmaceutical firms are Organon and the Dutch subsidiary of Solvay Pharmaceuticals[4]. They cover for roughly one third of the total employment in the Dutch pharmaceutical industry. Both companies have major production and R&D facilities in the Netherlands. DSM is another important firm. It is not strictly a pharmaceutical company, but its DSM Pharmaceutical Products Group is specialised in the development and production of chemical and biopharmaceutical intermediates for the pharmaceutical industry and finished dosage forms. DSM is now the world market leader in antibiotics and chiral products.

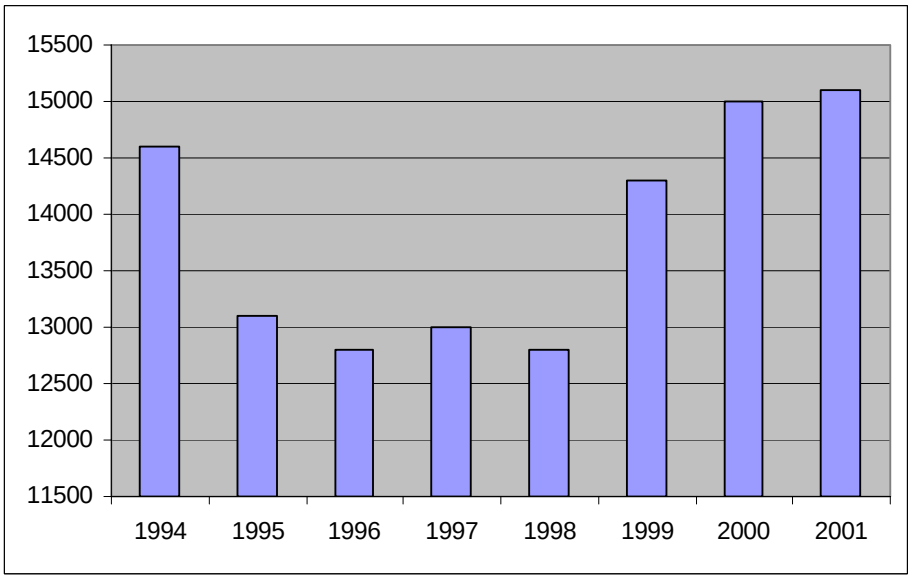
[4] In the early 1980s, the Belgium-based multinational Solvay acquired Philips-Duphar. Since then, it has changed its name into Solvay Duphar and has become part of the pharmaceuticals group of Solvay. It belongs to the European leaders in the production of influenza vaccines.



Source: Central Bureau for Statistics / StatLine database 2003
Figure 1-1 Size of the Dutch pharmaceutical industry in number of firms

Employment

The two largest pharmaceutical companies in the Netherlands, Organon (belonging to the Dutch Akzo Nobel group) and Solvay Pharmaceuticals (belonging to the Belgian Solvay group) employed 3,500 respectively 1,500 employees in 2001 (CPB et al., 2002). The total employment in the Dutch pharmaceutical industry in 2001 was estimated at 15,100 jobs and increased with 3.5% compared to 1994 (figure 1-2).



Source: Nefarma Annual Report 2002, based on CBS figures
Figure 1-2 Employment in the Dutch pharmaceutical industry (in number of jobs)

Research and Development

The pharmaceutical industry invests heavily in R&D. Since 1994, the annual R&D investments by the Dutch pharmaceutical industry have increased significantly, although the latest figures show a relative strong fall (table 1-1). According to the Dutch Organisation of the Research-based Pharmaceutical Industry (Nefarma) at least 8% of its members' global turnover is invested in R&D. For some of its members it even amounts to 15 to 20% (Nefarma, 2002). The number of people employed in pharmaceutical R&D in the Netherlands also increased considerably: from 2,082 jobs in 1994 to 3,077 in 2001 (CBS, 2003c).

Table 1-1 R&D figures of Dutch pharmaceutical industry

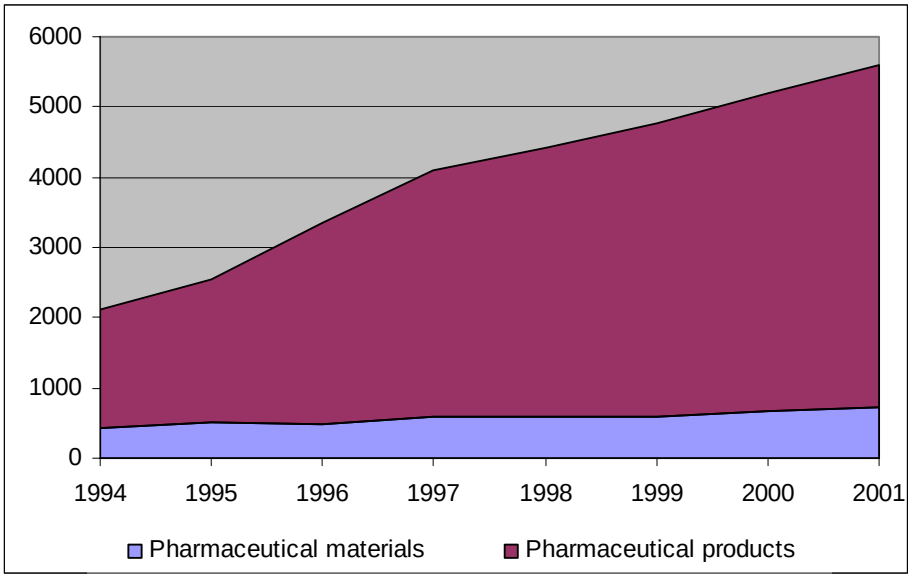
Year	R&D expenditures (€ million)	R&D employment (in number of jobs)
1994	198	2,082
1995	212	2,253
1996	306	2,942
1997	308	2,965
1998	327	2,998
1999	419	3,401
2000	396	2,940
2001	401	3,077

Source: Nefarma 2003, based on CBS figures

The R&D intensity is even higher for the small dedicated biopharmaceutical firms. In 2001, the dedicated biotechnology firms in the Netherlands, of which the biotech firms in human health form the lion's share, invested almost 73 million euros into R&D (realising a total turnover of 123 million euros) (Enzing et al., 2002b). Moreover, 60% of the total labour force employed by the dedicated biotechnology firms is in research and development (Enzing et al., 2002b).

Production

The total production in the Netherlands of pharmaceutical materials and products equalled 5.6 billion euros in 2001 (Nefarma, 2003). This is an increase of more than 165% compared to 1994 (figure 1-3) and an average annual growth rate of 15.3%.



Source: Nefarma Annual Report 2002, based on CBS figures

Figure 1-3 Production of pharmaceutical materials and products in the Netherlands in € million

Market

The Dutch market for pharmaceuticals in 2002 consisted for 72.2% of branded (or in-patent) pharmaceuticals, for 18.5% of generic (or out-of-patent) pharmaceuticals, and for 9.4% of parallel imports (Nefarma, 2003). Although the branded pharmaceuticals still dominate the market, the generic pharmaceuticals increasingly gain market share; it showed a growth rate of more than 35% in 2002 compared to 2001 (Nefarma, 2003). This development already started during the 1990s due to the large number of pharmaceutical patents that expired and due to the government policy of stimulating the prescription of generic pharmaceuticals.

The pharmaceutical market can be divided into approximately 102 smaller sub-markets, in which pharmaceutical companies compete with each other (CPB et al., 2002). These sub-markets often correspond to specific diseases. In the early 1980s, research by Reekie (1981) showed that competition was limited as only a few pharmaceutical companies dominated these sub-markets, resulting in oligopolies. In 73 sub-markets, on average three pharmaceutical companies possessed together over 75% market share. More recent research by the Netherlands Bureau for Economic Policy Analysis (CPB) confirmed these findings for the 50 largest sub-markets in the Netherlands in the period 1994-1999 (CPB et al., 2002). However, this market dominance seems highly temporary, as the market leader changes within every six years in at least one third of these sub-markets (Reekie, 1981; CPB et al., 2002).

The market for pharmaceuticals based on biotechnology is still limited; in 2001 approximately 60 biopharmaceutical products were on the Dutch market (Nefarma, 2002). Insulin is the largest market for biopharmaceuticals in the Netherlands and accounted for almost 90 million euros of pharmaceutical expenses in 2000 and 2001. Nevertheless, the expenditures on biopharmaceuticals are growing annually and have an increasing share in the total expenditures on pharmaceuticals (table 1-2).

Biopharmaceuticals are expected to account for 15 to 20% of the total pharmaceutical expenditures in the Netherlands in the very near future (Nefarma, 2002).

Table 1-2 Biopharmaceutical expenditures in the Netherlands, in € million

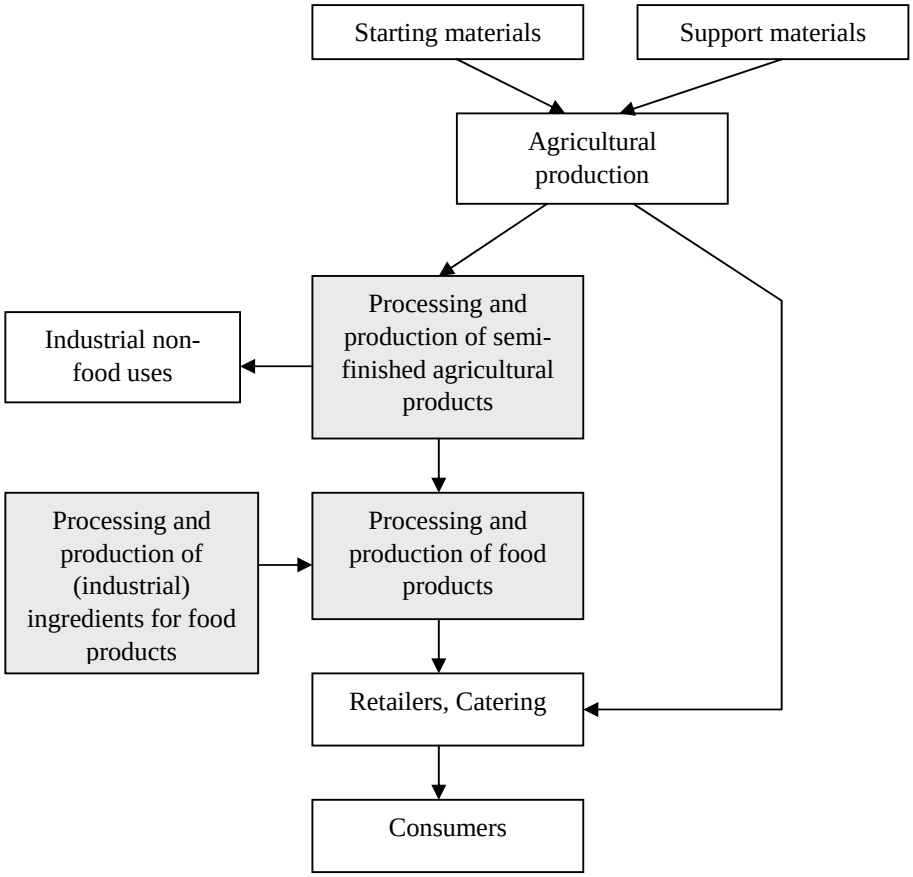
	2001	2002	Growth
Total pharmaceuticals	3,435	3,761	9.5%
Biopharmaceuticals	295	345	16.9%
Share	8.6%	9.2%	

Source: Nefarma website, August 2003

1.4.3 The food industry

The agrofood industry is one of the main industrial sectors in the Netherlands and accounts for approximately 10% of the national GDP (Ministerie van Landbouw, Natuurbeheer en Voedselkwaliteit, 2002). In general, the agrofood industry includes all economic activities related to production, processing and distribution of agrofood products of national and foreign origin. The agrofood chain runs from the suppliers of agricultural inputs to the consumers of agrofood products. Figure 1-4 shows its basic structure. In this report the focus will be on the food industry; the processing, production and distribution of the food products and the production of ingredients for food products. This is shown by the grey-shaded parts of the agrofood chain in figure 1-4.

Most well known Dutch companies in the food industry are Unilever, Numico, CSM, and DSM (ingredients), but there are also large dairy companies like Friesland Coberco Dairy Foods and Campina/DMV. Unilever is one of the largest; it realised a worldwide net turnover of 28.8 billion euros in food products in 2001 (Annual Report 2002). In 2001, it invested 1,178 million euros in research and development of which 210 million euros were spent in the Netherlands (CPB, 2003). Friesland Coberco Dairy Food (FCDF) is one of the largest dairy companies. In 2001, it had a total net turnover of 4.3 billion euros and employed over 12,000 people (website FCDF). In 2002, FCDF invested 16 million euros in corporate research in the Netherlands (CPB, 2003).



Source: TNO-STB, based on Bijman et al.(1994) and Arundel (2000)
Figure 1-4 Agrofood chain

Research and Development

In 2001, the food industry (including tobacco[5]) invested approximately 269 million euros in R&D[6] and this is 47% more than in 1994 (table 1-3). Employment in R&D in the Dutch food industry is estimated at 2,989 full-time equivalents (ftes) in 2001, compared to 2,523 ftes in 1994. In 2000, 174 food companies performed R&D activities and these activities are mainly concentrated in the larger companies; 82 of 174 food companies with R&D have more than 200 employees. Moreover, the same companies also provide 2,742 of the 3,063 R&D ftes in the food industry (CBS/Statline, 2003).

Compared to the pharmaceutical sector, these R&D expenditures are rather small. While the pharmaceutical industry spends about 8% of the total turnover on R&D, in the food sector this is far less. For the whole food industry (including tobacco) approximately 0.5% of the total turnover is spent on R&D (see table 1-3). When the expenditure of R&D in the food industry is related to the added value of this industry, the R&D intensity of the food industry amounts to 2.13% and has the eighth position in

[5] SBI'93 codes D. 15 and 16
[6] R&D expenditures with own employees

the Dutch industry in 2000 (CBS, 2003a). The major part of the R&D expenditures in the food industry is done by large companies with more than 200 employees; in 1999 more than 80% of the total R&D expenditures were made by large food companies (CBS, 2003b).

Table 1-3 R&D expenditures and R&D employment in the Dutch food industry

Year	Total R&D expenditures in € mln	% R&D expenditures / total value of sales	% R&D expenditures/ added value*)	Total jobs in R&D in ftes
1994	182	0.55%	-	2,523
1995	238	0.71%	2.56%	2,875
1996	199	0.57%	2.02%	2,630
1997	197	0.53%	1.82%	2,626
1998	192	0.50%	1.71%	2,636
1999	250	0.67%	2.08%	3,047
2000	258	0.67%	2.13%	3,063
2001	269	0.66%	-	2,989

Source: CBS/Statline 2003, Bedrijfsleven, Algemene overzichten, Research & Development, SBI'93 D.15 + 16, *) CBS Kennis en Economie 1998, 2000, 2002

The R&D intensity of dedicated food biotechnology firms is much higher than the average R&D intensity in the whole food industry. On average, 60% of the employees of these firms are performing R&D and for half of these companies more than 80% of their personnel consist of R&D employees (TNO-STB figures).

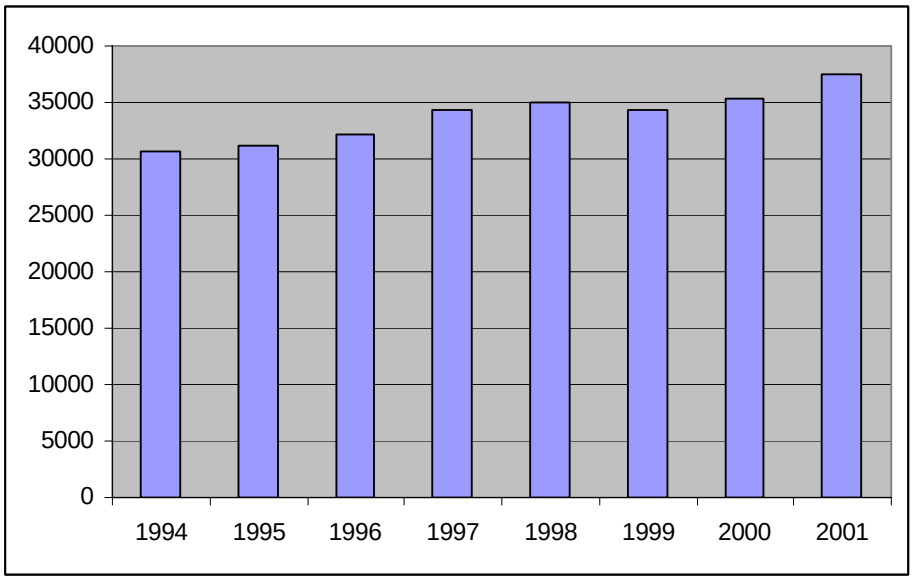
Another characteristic is the co-operative (pre-competitive) R&D performed by public research institutes and universities for the food industry. Especially the co-operatives outsource their research to public or sector financed research institutes (Nationale Raad voor Landbouwkundig Onderzoek - NRLO, 1997[7]). In the past, the co-operative diary industry set up NIZO Food Research, a research institute for carrying out collaborative, pre-competitive research for these companies. Nowadays, the amount of contract research is larger then the co-operatively financed part of its research volume.

Several food companies have located their R&D facilities close to the public research organisations. Recently, Numico Research and Campina Innovation have located their research facilities in Wageningen, and AVEBE is considering it (Enzing et al., 2002b). In Wageningen, the Food Valley initiative was set up by the Regional Development Agency East Netherlands (Ontwikkelingsmaatschappij Oost Nederland NV) and the Foundation Knowledge Town Wageningen (Stichting Kennisstad Wageningen). It aims to promote Wageningen as a top location for R&D and innovation in food, agriculture, life sciences and health. Additionally, a BioPartner Centre was established to attract and support several young food and agrobiotechnology companies.

[7] In 2000 the 'Nationale Raad voor Landbouwkundig Onderzoek' transformed into the 'InnovatieNetwerk Groene Ruimte en Agrocluster'

Employment and sales of the Dutch food industry

The total number of companies in the food industry amounted to 5,090 in 2001; this is a decrease of 17.4% compared to 1994 (CBS/Statline, 2003).[8] Most food companies are rather small; in 2001, about 35 companies had more than 500 employees. Nevertheless, the total turnover of the larger companies is much larger than the total turnover of the smaller firms. In 2001, 3,625 companies with less than 20 employees had a total turnover of 3,252 million euros compared to the total turnover of 8,057 euros of 630 companies with up to 100 employees. In 2001, the total value of the sales of the food industry was 37.5 billion euros and this was an increase of 22% compared to 1994 (figure 1-5).



Source: CBS/Statline 2003

Figure 1-5 Total value of sales of the food industry in the Netherlands

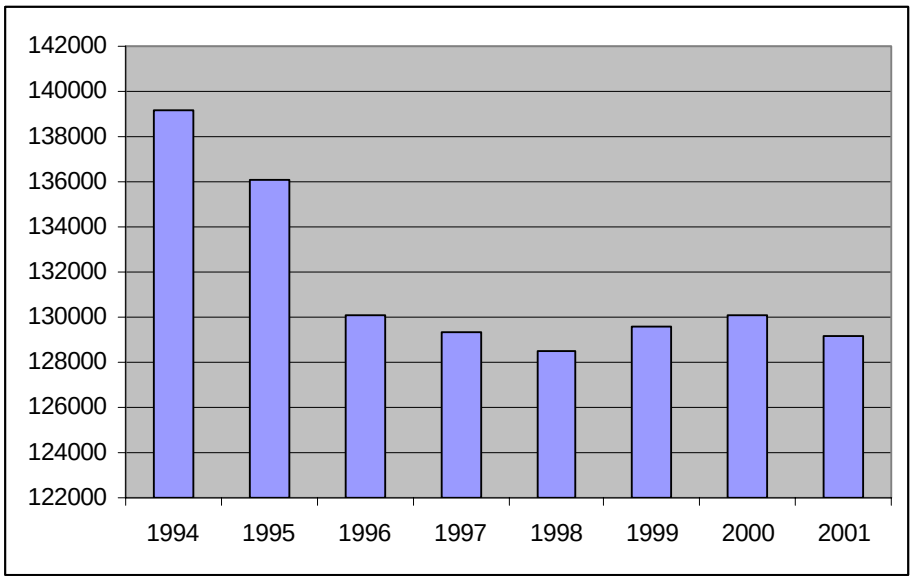
The Dutch food industry (including tobacco) has a relatively high added value. In 2001, the food industry realised an added value of approximately 12 billion euros, an increase of 25.5% compared to 1994 (CBS/Statline, 2003). The food industry contributes for almost 20% to the added value of the total Dutch industry.[9]

About 42 % of the total turnover is exported and one third of the production is based on raw materials from abroad (Raad voor het Landelijk Gebied, 2001 and Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2002). The multinational food companies depend for 46% of their turnover on foreign markets and SMEs export 33% of their total turnover (Raad voor het Landelijk Gebied, 2001).

In 2001, the total employment in the Dutch food industry (including tobacco) amounted to 129,200 full time equivalents (ftes) for employees and decreased with 7.18% compared to 1994 (figure 1-6).

[8] To collect statistics about the food industry, the SBI'93 (Standaard Bedrijfsindeling) code D.15 is used. This code includes all companies that process or produce food products and beverages.

[9] Gross added value, based on basic prices.



Source: CBS/Statline 2003

Figure 1-6 Employment in the Dutch food industry in number of jobs

2 Overview of national R&D, technology and innovation policies for biotechnology

2.1 Introduction

Already since the late 1970s biotechnology has been subject of public innovation policies in the Netherlands. Starting in 1979, the Dutch government initiated over the last 25 year a number of R&D-programmes and set up specialised organisations for the stimulation of biotechnology R&D and its commercialisation. In this chapter, the main policies and policy-making bodies and the main policy instruments of the biopharmaceutical and the food biotechnology part of the Dutch innovation system are presented.

2.2 Main policies and policy making bodies

Biotech innovation policies in the period 1979 - 2004
In general four main stages in Dutch biotechnology innovation policy making can be identified:

- Early 1980s: *reinforcement and strategic orientation of the Dutch biotechnology R&D infrastructure*, by prioritising the creation of a high quality research infrastructure mainly aiming at basic biotechnology research.
- Mid and late 1980s: *enhancement of the biotechnology knowledge transfer* from universities and public research organisations to the biotechnology industry, by prioritising public-private co-operation in basic and applied research activities, networking and technology transfer.
- Mid and late 1990s: *stimulation and reinforcement of a high quality and entrepreneurial biotechnology industry*, by mainly emphasising the commercialisation of biotechnology research results and supporting academic entrepreneurship.
- Early 2000s: recognition of *genomics as a strategic technological area* for economy and society. Through a highly interactive process involving academia, industry and government, an integrated approach for stimulating genomics research, commercialisation and social aspects was formulated.

In the early 1980s two biotech R&D stimulation programmes were started: the Innovation Oriented Research Programme Biotechnology (IOP-b) and the Programmatic Industry Related Technology Stimulation on Biotech (PBTS). After this period of biotechnology dedicated policies, Dutch technology and innovation policies shifted in the early 1990s towards more generic support programmes. Newly set-up programmes had a generic character and existing programmes (such as IOP-b and PBTS) were transformed into generic technology stimulation programmes, open to all technology fields. Commercialisation of biotechnology was a priority in national innovation policy, but was mostly implemented through supporting national networking activities between academia and industry initiated by actors in the field.

It was only in 1998 that the Dutch government focused its innovation policies on biotechnology again. A sense of urgency in stimulating the biotechnology sector was felt by the Dutch government, in particular by the Ministry of Economic Affairs, after

the results of a government-sponsored benchmark had been published. The main conclusion of this benchmark - comparing the Dutch entrepreneurial bioscience industry with six other regions in the world (Ernst & Young, 1998) - was that many conditions for growth such as financing and incubator facilities were missing in the Netherlands. In 1999, the Ministry of Economic Affairs presented the *Life Sciences Action Plan 2000-2004*. It consisted of a number of activities aiming at stimulating start-up activities in the life sciences and especially at improving academic entrepreneurship. The main goal of the programme – BioPartner - was to help establish at least 75 life science start-ups in the period 2000-2004. The total budget amounted to 45.3 million euros.

In 2000, the Dutch industry and public sector research organisations presented the '*Strategic Action Plan Genomics'*, in which they pleaded for reinforcement of the Dutch research infrastructure in the field of genomics. A specific governmental advisory committee was assigned to investigate the actual need for such investments and the urgency of public financial support. The Temporary Advisory Committee for the Genomics Knowledge Infrastructure advised the Dutch government to invest heavily in genomics research and infrastructure, thereby following an integrated approach that includes commercialisation and the social and ethical aspects of genomics. Based on this advice, the Dutch government presented in 2001 its view in the policy report '*Genomics Knowledge Infrastructure'*. This resulted in the Netherlands Genomics Initiative (NGI), which is responsible for the execution and management of a national genomics strategy, with a budget of 189 million euros for the period 2002-2007.

A comparison of the Dutch biotechnology policy-making system with those in other European countries learns that the Dutch system can be characterised as 'concentrated and pluralistic'. It is concentrated because of the many strong interactions between public actors and industry and of the strong co-ordination within the system through a limited number of actors. It is a pluralistic system because of the relative multiplicity of policy players intervening in the policy-making and funding process (Enzing et al., 1999).

Governmental departments involved in biotechnology making
Biotechnology policy making is the primacy of five ministries:

- The Ministry of Economic Affairs
- The Ministry of Education, Culture and Science
- The Ministry of Agriculture, Nature and Food Quality
- The Ministry of Health, Welfare and Sport
- The Ministry of Spatial Planning, Housing and the Environment

The Ministry of Economic Affairs is the main actor in stimulating applied and industrial R&D in the field of biotechnology. It supports industrial biotechnology R&D by a number of public programmes. The Ministry of Economic Affairs is traditionally the largest sponsor of biotechnology stimulation programmes.

The Ministry of Education, Culture and Science is the major co-ordinating and influential body in financing the public basic R&D infrastructure including universities and a large number of public research institutes. The ministry finances public research directly, but also indirectly through the Netherlands Organisation for Scientific Research (NWO) to universities and to a number of research institutes of the Royal

Academy of Sciences (KNAW). The ministry is also responsible for the 'basic funding', i.e. non-targeted funding of TNO.

The Ministry of Agriculture, Nature and Food Quality is the main innovation policy-making body in agriculture and food. The majority of the research funded by the ministry is performed by the research institutes of the Wageningen University and Research Centre (WURC). The ministry firstly prioritised biotechnology research through a specific programme in the period 1986-1992. After 1992, the ministry continued its biotechnology-stimulating activities through the funding of programmes of its research institutes (formulated and decided upon on an annual basis) and by participating in R&D programmes of the Ministry of Economic Affairs. The ministry also plays an important role with respect to the implementation and compliance of biotechnology regulation, especially related to plant and animal biotechnology.

The Ministry of Health, Welfare and Sport supports health-related biotechnology research by annual funding of research programmes of the National Institute of Public Health and Environmental Protection - RIVM (formulated and decided upon on an annual basis). The Ministry of Spatial Planning, Housing and the Environment funds environmental biotechnology research, which is also performed by RIVM. Both ministries also provide annual funding of 'goal oriented' research programmes of institutes of the Dutch Organisation for Applied Scientific Research - TNO.

An institutional characteristic of the Dutch biotechnology policy-making system was (and still is) its segmented structure with respect to the distinctive, separated tasks and responsibilities of the involved ministries. Each ministry has its own vision and set of biotech policies and instruments in the field they are responsible for, like industrial innovation, education and research or environmental protection. Mainly because of the lack of co-ordination, this has led to several inconsistencies in the overall Dutch public policies for biotechnology in the past. The presentation of the 'Integrale Nota Biotechnologie' (INB) in September 2000 by the Dutch government was a turning point in this respect, as a joint vision on biotechnology and its future development was prepared as a co-production by the five ministries. The INB represented the government's vision on biotechnology and sketched the public biotechnology policies for the coming years. The government expressed the aim of exploiting the important opportunities offered by biotechnology, but in a well-considered and conscientious way which implied policy emphasis on creating guarantees for safety, ethical acceptability, transparency in decision-making processes, and freedom of choice for consumers.

2.3 Biotechnology policy instruments and managing organisations

2.3.1 Programme management

The implementation and management of the public programmes and instruments that directly support biotechnology research and its commercialisation is carried out by:

- The Netherlands Organisation for Scientific Research;
- Senter;
- BioPartner;
- Netherlands Genomics Initiative.

The Netherlands Organisation for Scientific Research (NWO) is the central funding and co-ordinating organisation of scientific research at Dutch universities and public research institutes. It has been established by Act of Parliament in 1988. Its prime mission is to promote the quality of scientific research and to support new developments, mainly by allocating funds through its research councils. The annual budget is approximately 450 million euros. The Ministry of Education, Culture and Science provides the bulk of this budget, though other ministries contribute as well. Since 1982, NWO has considerably contributed to the increase of basic and applied research activities in biotechnology. In the period 1982-1992, NWO spent approximately 16 million euros on biotechnology research. In addition, the Technology Foundation (STW), which is an independent council within NWO, financed academic biotechnology research with a total budget of 19 million euros during the period 1984-1992 (Kern and Enzing, 2002).

Senter, an agency under the Ministry of Economic Affairs, is responsible for the execution of grant schemes in the field of technology, energy, environment, exports and international partnerships. In 2002, Senter provided financial support of almost 1.3 billion euros through subsidies, credits, and fiscal instruments and programmes. Senter mainly manages programmes initiated by the Ministry of Economic Affairs; in 2002 this accounted for more than 500 million euros of the total budget of Senter in 2002.

BioPartner – a set of five interlinked organisations and their instruments - is responsible for the implementation and execution of the 'Life Sciences Action Plan 2000-2004'. BioPartner's task is to contribute to an improved entrepreneurial climate for life sciences by providing start-ups with financing, information, facilities, and advice. The total budget for the Life Sciences Action Plan 2000-2004 is 45.3 million euros.

The Netherlands Genomics Initiative (NGI) was established in 2001 as the national organisation responsible for the execution, management and co-ordination of all the initiatives and programmes in the field of genomics. It has been installed as a task force within NWO. It aims at making the Netherlands the leading player in the field of genomics within five years. The NGI has been allocated a budget of 189 million euros. It initiates new genomics programmes and is responsible for genomics programmes that had already been started and directed by Senter and NWO.

2.3.2 Policy instruments for knowledge base support

Building and sustaining an excellent biotechnology knowledge base has been one of the main priorities in the Dutch science and technology policies. As was mentioned above, in the early 1980s a few dedicated biotechnology - vertical[10] - policy instruments (such as R&D programmes and facilities support) were set up. However, a period followed in which generic science and technology policy instruments were favoured. Only at the end of the century new dedicated biotech programmes were launched again in the Netherlands. This paragraph describes in more detail the vertical and horizontal policy instruments used by the Dutch government in the period 1994-2001 in order to

[10] Vertical biotechnology policies concern those public programmes and instruments that directly target the biotechnology knowledge base, commercialisation of biotechnology and/or framework conditions for the development of biotechnology. Horizontal policies concern general public programmes and instruments that affect biotechnology, although they have not been designed specifically for biotechnology.

stimulate biotech R&D and support the creation of a strong national biotech knowledge base.

Vertical instruments

In 1991, the Association of Biotechnology Centres in the Netherlands (ABON) was set up by a number of Dutch biotechnology companies and public research organisations in order to keep and strengthen the science base created by the IOP Biotechnology. ABON consisted of five biotechnology graduate research schools: Biotechnological Sciences Delft-Leiden (BSDL), Groningen Biomolecular Sciences and Biotechnology Institute (GBB), Food Technology, Agrobiotechnology, Nutrition, and Health Sciences (VLAG), Experimental Plant Sciences (EPS), and BioCentrum Amsterdam. ABON coordinated the strategic, industrially relevant research and its total budget amounted to 15.2 million euros. This budget was provided by the universities and by the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, and the Ministry of Agriculture, Nature and Food Quality. The Dutch Industrial and Agricultural Biotechnology Association (NIABA) was involved in the decision making on the research programmes. ABON ran until 1999 (Enzing, 2000a).

During the mid 1990s, two other biotech dedicated programmes were running: the 'Structural/functional relation biomolecules' programme (1995-2003) and the 'Computational chemistry of biosystems' programme (1996-2002), both from NWO. They had a budget of respectively 2 million euros and 1.3 million euros. Both programmes targeted academic research.

In 1999, NWO initiated the BioMolecular Informatics programme and the Genomics programme. Both are response mode programmes that stimulate high quality research in both fields. In 2000 the IOP Genomics was set up. The IOP Genomics will run for eight years; the budget for the first phase (2000-2004) is 20.4 million euros. The executing agency is Senter. Since 2002, the IOP Genomics has formally been running under the responsibility of NGI, which is responsible for managing all national genomics instruments. The programme targets strategic and pre-competitive industry-oriented fundamental research at universities and public research institutes. Industry has therefore been highly involved in the design process of the programme.
The four central research themes of the IOP Genomics are:

- Pathogenesis of chronic and old age disease;
- Functionality, quality and safety of food production;
- Understanding biomolecular processes (e.g. signal transduction, metabolic pathways);
- Genomics technologies (both equipment related and experimental laboratory technologies).

NGI started its activities in 2002. It is responsible for implementing the national genomics strategy. One of the initiatives in this strategy is to establish genomics Centres of Excellence. In these centres research in specific fields is concentrated and supported by state-of-the-art research facilities. The centres will also develop educational and training activities and research into societal aspects. In 2002, four genomics Centres of Excellence were selected: the Cancer Genomics Centre (CGC), the Centre for Medical Systems Genomics (CMSG), the Centre for Biosystems Genomics (CBSG) and the Kluyver Centre for Genomics of Industrial Fermentation (Kluyver Centre).

NGI started the HORIZON programme in January 2003. This programme aims at stimulating excellent and visionary fundamental research in genomics and biomolecular informatics. Genomics researchers (from young to more established scientists) are invited to come up with innovative, fresh and breakthrough ideas that could potentially result in ground-breaking research topics. In 2004, two Technology Centres (BioInformatics and Proteomics) and four Innovative Clusters will be set up.

Table 2-1 provides an overview of the dedicated biotechnology support programmes that ran in the period 1994-2001 and after.

Table 2-1 Vertical biotechnology instruments for knowledge base support 1994-2001

Vertical programmes and instruments					
Name	**Support**	**Target group**	**Budget (€ million)**	**Period**	**Agency**
Netherlands Genomics Initiative (New instruments: Genomics Centres of Excellence, Technology Centres, Innovative Clusters, HORIZON; Including NWO Genomics, NWO Biomolecular Informatics, NWO Social component of genomics Research IOP Genomics)	Fundamental research, technical facilities, innovative application oriented research, socio/ethical research	Universities, research institutes	189 (+ 99 Bsik*)	2002-2007	NGI
Research programme Structural/functional relation biomolecules	Fundamental research	Universities	2	1995-2003	NWO
Research programme Computational chemistry of biosystems	Fundamental research	Universities	1.34	1996-2002	NWO
Research programme Gene-Environment Interactions	Fundamental research	Universities	2.7	1997-2003	NWO
ABON	Fundamental Research	Universities	15.2	1991-1999	-

*): Bsik: Besluit Subsidies Investeringen Kennisinfrastructuur.

Horizontal instruments

Until the national genomics strategy was implemented in 2002, biotechnology research had been stimulated to a large extent through horizontal science and technology schemes. Several of these schemes targeted in particular the stimulation of industrial R&D and R&D co-operation, e.g. by providing subsidies for R&D projects and tax

reductions for employing scientific personnel. Table 2-2 provides an overview of the national horizontal programmes and instruments in the period 1994-2001 and beyond.

Table 2-2 Horizontal instruments for biotechnology knowledge base support 1994-2001

Horizontal programmes and instruments					
Name	**Support**	**Target group**	**Budget (€ million)**	**Period**	**Agency**
Stimulation programme for innovative pharmaceutical research – STIGO	Fundamental and industry oriented research	Universities (in collaboration with industry)	4.5	1998-2003	NWO
Research programme 'Food and chronical diseases'	Fundamental research	Universities	5.22	1997-2002	NOW
Research programme 'Alternatives for animal experiments'	Fundamental and applied research	Universities	6.4	2000-2004	NWO
Research programme 'Infectious diseases and vaccines'	Fundamental research	Universities	n.a.	2001-n.a.	NWO
Research programme 'Tissue engineering'	Fundamental research	Universities	n.a.	n.a.	NWO
Research programme 'Nutritious food'	Fundamental research	Universities	8.17	2000-2006	NWO
Research programme 'Combinatorial chemistry'	Fundamental research	Universities	3.4	2001-2008	NWO
IOP Industrial Proteins	Strategic, pre-competitive and industry oriented research	Universities and research institutions	7.3	1992-2001	Senter
Technological development projects – TOP	Industrial R&D	Industry	24	Annually	Senter
Research and Development Promotion Act – WBSO	Industrial R&D	Industry and self-employed researchers	368	Annually	Senter
Economy, Ecology and Technology – EET	Co-operative industrial R&D	Industry (universities/research institutions only	54.2	Annually	Senter

		as partners)			
Technological Co-operation – TS	Co-operative industrial R&D	Industry (universities/research institutions only as partners)	n.a.	n.a.	Senter

Two horizontal instruments that started in the late 1990s aim at improving the conditions of pharmaceutical research. The Netherlands Federation for Innovative Pharmaceutical Research (FIGON) is a platform that aims at supporting existing initiatives in pharmaceutical research and at identifying new scientific developments. Representatives from both industry and science participate in FIGON. It is sponsored by NWO and the Dutch Organisation for the Research-based Pharmaceutical Industry, Nefarma.

In 2001, the Ministry of Health, Welfare and Sport initiated the Steering Group Orphan Drugs. It aims to stimulate the development of orphan drugs, to improve the conditions for patients suffering from rare diseases, and in particular to intensify the information supply about rare diseases. Its target groups include individual patients, patient organisations, general practitioners, medical experts, researchers, pharmaceutical companies, and health insurance companies. The steering group will run for four years and has a budget of 0.44 million euros.

2.3.3 Instruments for commercialisation support

Commercialisation of research has been a central theme in Dutch innovation policies since the early 1990s. Quite often, commercialisation goals were in an indirect way incorporated in research support schemes (by stimulating co-operative research of industry and universities). It lasted until the late 1990s before an instrument was initiated to stimulate the commercialisation of biotechnology R&D.

In 1999, the Dutch Ministry of Economic Affairs launched the 'Life Sciences Action Plan 2000-2004' with BioPartner as executing agency. BioPartner was expected to stimulate (academic) entrepreneurship and in particular to support the creation of 75 life sciences start-ups in the period 2000-2004.

To do so, BioPartner was given five instruments:
- BioPartner Network, which provides a central point of contact for entrepreneurs in the life sciences and facilitates networking;
- BioPartner First Stage Grant, which provides subsidies for supporting researchers to translate their knowledge into viable business plans;
- BioPartner Centers, which offer accommodation and infrastructure to starting life sciences companies;
- BioPartner Facilities Support, which enables start-ups to use research equipment and facilities in collaboration with universities or research organisations;
- BioPartner Start-up Ventures, which provides risk capital to life science start-ups.

The Life Sciences Action Plan runs until 2004 and – some of - the BioPartner organisations (each responsible for one of the five instruments) will probably merge into a new public organisation that will stimulate entrepreneurship and technology-based start-ups in general, TechnoPartner.

Mibiton started in 1994 with a subsidy of 10.8 million euros from the Ministry of Economic Affairs. It provides financial support for the purchase of high tech research equipment at universities and public research institutes on the basis of facility sharing with private companies. The companies have to pay commercial fees for the use of the research facilities; this created the so-called revolving fund. The Mibiton programme proved especially useful for starting firms. At present, Mibiton provides financial support with the Mibiton+ programme, the successor of the initial fund of 1994. The Mibiton Foundation is also responsible for the management of the BioPartner Facilities Support scheme.

The Support Programme for Innovative Medicine Research and Entrepreneurship in the Netherlands (STIGON) is a scheme that supports (bio)pharmaceutical start-ups based on innovative concepts in medicine research. Its main target group is scientists at universities and public research institutes. STIGON provides financial support for performing feasibility studies of the translation of academic research results into a viable business concept. Moreover, it provides financial support for building a first prototype of a new product or technology. STIGON sponsors projects up to a maximum of 70% of the total costs. The other 30% have to be matched by the involved universities or research institutes. The total STIGON budget amounts to 8.8 million euros, including matching funds.

Table 2-3 shows the main vertical and horizontal programmes and instruments for commercialisation support in the period 1994-2001 and after.

Table 2-3 Main vertical and horizontal programmes and instruments for biotech commercialisation support 1994-2001

Vertical programmes and instruments					
Name	**Support**	**Target group**	**Budget (€ million)**	**Period**	**Agency**
Support programme for Innovative Medicine Research and Entrepreneurship in the Netherlands – *STIGON*	Academic entrepreneur-ship, business development	Researchers from universities and research institutions	8.8	2000-2004	NWO
Mibiton	Facility sharing	Industry, universities and public research institutes	Revolving fund	Since 1994	Mibiton
BioPartner First Stage Grant	Business development	Life Sciences entrepreneurs and start-ups	11.34	2000-2004	BioPartner
BioPartner Centres (6 centres)	Housing, services and infrastructure	Life Sciences entrepreneurs and start-ups	2.3	2000-2004	BioPartner
BioPartner Network	Networking and information	Life Sciences entrepreneurs and start-ups	n.a.	2000-2004	BioPartner
BioPartner Start-up	Venture	Life Sciences	10.5	2000-	BioPartner

Ventures	capital	entrepreneurs and start-ups		2004	
BioPartner Facilities Support	Research facilities	Start-ups (together with universities and research organisations)	1.4 annually	2000-2004	Mibiton / BioPartner
Horizontal programmes and instruments					
Dreamstart	Networking, information and consulting	High-tech start-ups	n.a.	n.a.	Ministry of Economic Affairs
Subsidy Infrastructure Technostarters – *SIT*	Access for high-tech start-ups to research facilities at universities and research institutions	Universities, research institutions and institutions for higher education	45	n.a.	Senter

2.3.4 Instruments with a socio-economic and/or ethic dimension

During the 1970s, an increasing resistance to science and technology emerged on a world-wide scale as they were no longer seen as the main catalysts for social welfare and well-being, but rather serving economic and military progress at the expense of society and nature. In order to counter this increasing resistance, the early emphasis of the Dutch public policies was on educating the public through providing information on the consequences, both positive and negative, of new scientific and technological developments. To that end, in the mid 1980s two organisations were set up: the Netherlands Organisation for Technology Assessment - NOTA (later renamed into Rathenau Institute) for investigating the technological consequences for society and Publieksvoorlichting Wetenchap en Technologie - PWT (later re-named into: Stichting WeTeN) for the diffusion of information about science and technology into society.
In 1990, the Foundation Consumer and Biotechnology (C&B) was established and supported by the Ministry of Agriculture, Nature and Food Quality and later also by the National Consumers Association. The main purpose of this foundation was to inform consumers and consumer organisations about biotechnology and to operate as a partner in discussions between consumer organisations, the government and the industry.

In the 1990s, the Dutch public policies shifted its focus from education to consultation of the public and the creation of a constructive dialogue with the public. Since 1993, five nation-wide public debates have been organised for discussing specific biotechnology issues. The first public debate was on the desirability and consequences of genetic modification, in particular concerning animals. Other debates focused on the future developments of genetic research (‘Forecasting genetic research’), the cloning of animals and humans (‘Clones and cloning’), xenotransplantation (‘Xenotransplantation and medical biotechnology’) and the application of biotechnology in food (‘Food and Genes’).

One of the main strategic goals of the Netherlands Genomics Initiative (NGI) set up in 2002 is to stimulate research on and communication about the social aspects of genomics. It has three different instruments to serve this goal. First, a new institute is currently being set-up: the Centre for Society and Genomics (CSG). It will perform a four-year research programme, especially on the communication with the public, and it will be responsible for education on this subject. Second, the research programme 'Social Component of Genomics Research' specifically targets scientific research on the socio-economic and ethical dimensions of genomics. It has a budget of 9.3 million euros for the period 2002-2007. Finally, the Genomics Centres of Excellence are contracted to include the socio-economic and ethical aspects of genomics in their research programme.

3 Structure, dynamics and performance of the biopharmaceutical and food biotechnology innovation systems

3.1 National public R&D system

3.1.1 General structure of the public R&D system

Universities accounted for over 67% of all public R&D activities in 2000 in the Netherlands, representing 2,278 million euros (CBS, 2003c). Moreover, 15,699 scientific employees were working full time on research at universities in 2000 (CBS, 2003c).

The universities receive funding through three so-called 'flow of funds':

1. The 'first flow of funds'. The direct funding of universities by the Ministry of Education, Culture and Sciences on the basis of students numbers. Universities are relatively autonomous in allocating the funding over the research areas.
2. The 'second flow of funds'. The financial support provided by the Ministry of Education, Culture and Sciences and channelled through the Royal Academy of Sciences (KNAW) and the research councils of the Netherlands Organisation for Scientific Research (NWO) to universities and KNAW research institutes.
3. The 'third flow of funds'. Funding generated through contract research and education activities. Such funds include projects for industry and foundations/charities, but also research funded by national and EU research programmes.

University research is to a large extent organised into graduate research schools in which university research groups can participate. Research schools receive their accreditation from the KNAW and have a combined mission of performing research in a specific scientific discipline and training of high-skilled researchers. In 2003, 109 different research schools exist, covering all areas of scientific research (website KNAW,).

Public research institutes accounted for approximately one third of all public sector research expenditures in 2000 in the Netherlands, i.e. 1,078 million euros (CBS, 2003c). They employed over 14,200 researchers in 2000 (CBS, 2003c). The most significant public research institutes in the Netherlands are the 18 institutes of the Netherlands Organisation for Applied Research (TNO), the five Large Technological Institutes (GTIs), the seven research institutes of the Wageningen University and Research Centre (WURC) and the National Institute of Public Health and the Environment (RIVM). These public research institutes were founded as not-for-profit organisations under Dutch law, most of them before World War II. They perform mainly applied research. Their funding is a combination of contract research for industry, government and other organisations and government subsidies, consisting of block funding and targeted funding.

In addition, there are several academic research institutes, including 10 NWO institutes and 19 KNAW institutes.

In 2000, these universities and public research institutes accounted for 43% of all R&D expenses in the Netherlands, whereas the average for all OECD countries amounted to 30% (CBS, 2003c).

3.1.2 Public biopharmaceutical R&D system

The Dutch public R&D infrastructure for biopharmaceutical and biomedical research is rather diversified (Enzing, 2000b). Many scientific disciplines provide together the basis for biopharmaceutical research: biochemistry, molecular genetics, microbiology, cytology, immunology, virology, pharmacology, clinical chemistry, cell biology, histology, biophysics, etc.

Figure 3-1 shows the public organisations involved in performing and funding biopharmaceutical research.

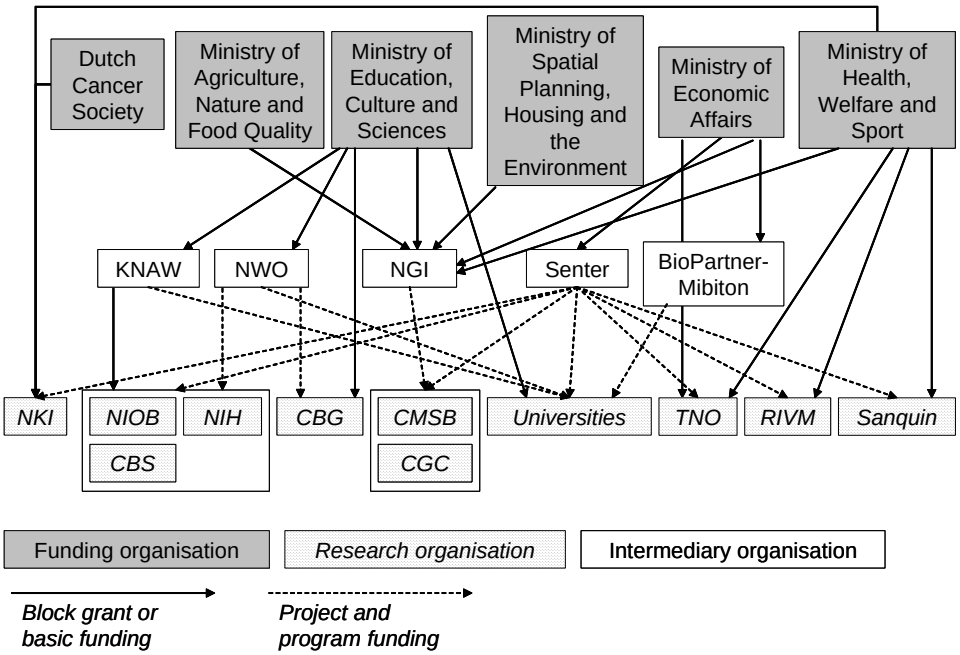


Figure 3-1 Public funding system of biopharmaceutical research in the Netherlands

Universities

In 2003, 18 graduate research schools covered (partly) biopharmaceutical research (see table 3-1). This number has been stable over the last years. Four research schools fully focus on biotechnology: the Groningen Biomolecular Sciences and Biotechnology Institute (GBB), the Groningen University Institute for Drug Exploration (GUIDE), the Leiden/Amsterdam Centre for Drug Research (LACDR) and the Medical Genetics Centre Southwest Netherlands (MGC).

Table 3-1 Graduate research schools in the field of biopharmaceutical research

Graduate Research School	Participating universities *
Dedicated biotech	
Groningen Biomolecular Sciences and Biotechnology Institute (GBB)	RUG
Leiden/Amsterdam Institute for Drug Research (LACDR)	UL and VU
Medical Genetic Centre Southwest Netherlands (MGC)	EUR and UL
Groningen University Institute for Drug Exploration (GUIDE)	RUG
Considerable biotech focus	
Integrated Biomedical Engineering for restoration of human function (IMBE)	KUN, TUD, RUG, UL, UM and UT
Institute of Cellular Signalling (ICS)	KUN
Amsterdam/Leiden Institute for Immunology (ALIFI)	UL, UvA and VU
Oncology Graduate School Amsterdam (OOA)	UvA and VU
Infection and Immunity (I&I)	UU
Research school of Developmental Biology (RSDB)	UU
Limited biotech focus	
Bijvoet graduate school for Biomolecular Chemistry (BIJVOET)	UU
Graduate school of Biomembranes (CBLE)	UU
Graduate school Neurosciences Amsterdam (NEURO)	UvA and VU
Behavioural and Cognitive Neurosciences	RUG
Cardiovascular research school Maastricht/Amsterdam (CARMA)	UM and VU
Molecular medicine: pathophysiology of growth and differentiation (MMPDG)	EUR
Graduate school Metabolism and Nutrition (MENU)	EUR, UM, UU and UvA
Reproduction, endocrinology and metabolism (DENOVEM)	KUN, UU and VU

* KUN: Catholic University of Nijmegen; EUR: Erasmus University Rotterdam; TUD: Delft University of Technology; RUG: University of Groningen; UL: Leiden University; UU: Utrecht University; UM: University of Maastricht; UvA: University of Amsterdam; VU: Free University of Amsterdam; UT: University of Twente

Public research institutes

Eight public research institutes are performing biopharmaceutical research in the Netherlands (table 3-2). The Netherlands Cancer Institute (NKI) is an integrated centre for cancer, including a clinic, a radiotherapy unit, a large research centre, and clinical research facilities. NKI receives funding from the Ministry of Health, Welfare and Sport and the charity organisation Dutch Cancer Society (the 'Koningin Wilhelmina Fonds'). The Sanquin Blood Supply Foundation is the not-for-profit organisation responsible for the blood banks in the Netherlands. It has research programmes on blood transfusion medicine, diagnostics and blood-related diseases like AIDS. The National Institute of Public Health and the Environment (RIVM) applies biotechnology in diagnostics research and development and the development of vaccines. The biopharmaceutical research at The Netherlands Organisation for Scientific Applied Research (TNO) compasses many areas, but especially cardiovascular research.

In 1994, the Dutch government installed a public programme to support the establishment of top level research centres (Technologische Topinstituten-TTI's). The

centre for Biomedical Genetics, in which research groups from the universities of Amsterdam (UvA), Leiden (RUL), Rotterdam (EUR) and Utrecht (UU) work together, is such a Top Institute.

Table 3-2 Public research institutes carrying out biopharmaceutical research

Public research institute	Type of research
Centre for Biomedical Genetics – CBG	Fundamental
The Netherlands Cancer Institute – NKI	Fundamental
Sanquin Blood Supply Foundation	Applied
Fungal Biodiversity Centre – CBS (KNAW institute)	Fundamental
Netherlands Institute for Developmental Biology – NIOB (KNAW Institute)	Fundamental
Netherlands Institute for Brain Research – NIH (KNAW Institute)	Fundamental
Netherlands Organisation for Scientific Applied Research – TNO	Applied
National Institute of Public Health and the Environment - RIVM	Applied

Two of the four Genomics Centres of Excellence, set up by the Netherlands Genomics Initiative (NGI) are active in the field of health related research:

- *The Cancer Genomics Centre's* (CGC) primary objective is to obtain a complete picture of the genetic changes that turn a cell into a tumour cell. In CGC, research groups from two universities and two research institutes co-operate.
- *The Centre for Medical Systems Genomics* (CMSG) focuses its activities on the improvement of the diagnosis, treatment and prevention of common diseases, like Alzheimer, cardiovascular diseases, diabetes and rheumatism. The CMSG includes research groups from three universities and one research institute.

3.1.3 Public system for food biotechnology research

Food research in the Netherlands is concentrated in and around Wageningen. Wageningen University and Research Centre (WURC) is one of the most important research centres for the Dutch food biotechnology research, but there are also other relevant groups that are specialised in food biotechnology. The large food companies (like Unilever, Numico, DSM and the dairy industry) participate in public research programmes and top institutes, set up research programmes together with the government, and outsource research to public research organisations.
Food research traditionally can be characterised by its applied - but increasingly becoming more fundamental – character and by the large number of disciplines involved. Figure 3-2 shows the food research system.

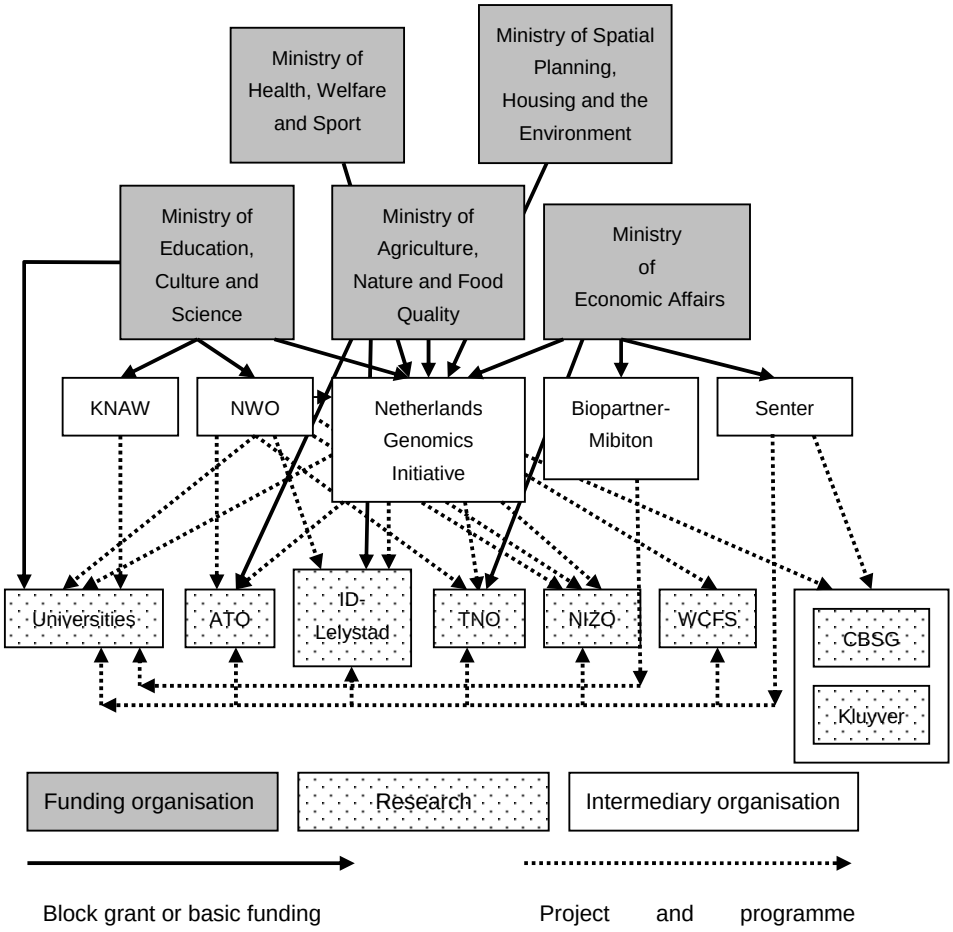


Figure 3-2 Public system of food biotechnology research in the Netherlands

Universities

Research groups in eight universities are active in the food biotechnology. In 2003, there are four graduate research schools active in food biotechnology (table 3-3). Since 1994, there have been no changes in the number of research schools.

Table 3-3 Public research organisations for food biotechnology research[11]

Research School	**Participating organisations***	**Research themes**
BioCentrum Amsterdam	UvA, VU	Dynamics of the living cell Micro-organisms and crops
Biotechnological Sciences Delft Leiden (BSDL)	TUD, UL, WU	Industrial biotechnology Biocatalysis Metabolic Engineering & Fermentation Technology Bioprocess Biotechnology

[11] This table only includes food-biotechnology related research schools. Research schools that are active in agrobiotechnology are the research school Experimental Plant Sciences, the Wageningen Institute for Animal Sciences, and the Graduate School of Animal Health.

Research School	Participating organisations*	Research themes
Groningen Bimolecular Sciences and Biotechnology Institute (GBB)	RUG	Biomolecular structure & function Protein & biomolecular engineering & catalysis Cellular processes, regulation & biotechnological applications
Food Technology, Agrobiotechnology, Nutrition, and Health Sciences (VLAG)	WU, UM, UU, KUN, ATO, RIKILT, NIZO, RIVM, TNO Food & Nutrition Research	Nutrition & Health Food technology & Foods Food Biotechnology & Agrobiotechnology

* KUN: Catholic University of Nijmegen; RUG: University of Groningen; TUD: Delft University of Technology; UL: Leiden University; UM: University of Maastricht; UU: Utrecht University; UvA: University of Amsterdam; VU: Free University of Amsterdam; WU: Wageningen University.
Source: Website KNAW: http://www.knaw.nl/cfdata/ecos/ecos.cfm?var=L#leden; websites universities

Public research institutes

Five public research institutes carry out research in the field of food biotechnology. The Institute for Agrotechnological Research (ATO) is part of the Wageningen University & Research Centre (WURC). Research at ATO focuses on agrotechnology and industrial production chains, food and food processing, and nutrition and health. Another Wageningen based research institute is the Institute of Food Safety (RIKILT is the Dutch abbreviation). RIKILT's research focuses on quality and safety control, supply chain management, and the interaction between nutrition and health. The Institute for Animal Research ID-Lelystad is also part of WURC and includes animal genomics research[12]. TNO-Nutrition and Food Research is based in Zeist and is one of the largest TNO institutes with more then 500 researchers. Its research focuses on quality and safety of food products and ingredients, product and process innovation, and nutrition and health.

The Dutch Centre for Dairy Research (NIZO food research) is a private R&D institute, specialised in research for the dairy and dairy-related food industry. Research at NIZO mainly covers the fields of microbiology, process technology and biopolymer technology.

The Wageningen Centre for Food Sciences (WCFS) is a Top Institute in the field of food research. WCFS started in 1997 and includes research groups from four research organisations (TNO Nutrition and Food Research, NIZO Food Research, NUTRIM and Wageningen University and Research Centre). The Dutch food industry (Unilever, DSM, AVEBE, CSM, Cosun, and the Netherlands Dairy Industry Organisation) is heavily involved in WCFS and also partly finances the research. WCFS's research themes are nutrition and health, structure and functionality, and microbial functionality and safety.

The Netherlands Genomics Initiative (NGI) has set up two genomics Centres of Excellence which carry out research that also covers food related genomics research:

[12] Since June 2003, ID-Lelystad has been collaborating with three other research organisations (Research Institute of Animal Husbandry, Netherlands Institute for Fisheries Research, and Department of Animal Sciences of Wageningen University) in the Animal Sciences Group, which is part of the WURC.

- *The Centre for Biosystems Genomics* (CBSG) focuses on plant biotechnology and aims to develop sustainable traits of plants (main crops are tomato and potato) influenced by multiple genetic and environmental factors. The CBSG consists of four universities and 15 industrial parties;
- *The Kluyver Centre for Genomics of Industrial Fermentation* (Kluyver Centre) is active in industrial fermentation research and focuses on micro-organisms like yeast and bacteria. The research at the Kluyver Centre is highly relevant for the Dutch fermentation industry in food, pharmaceuticals and fine chemicals. The Kluyver Centre includes five universities, four research institutes and 12 industrial partners.

3.2 Business system

3.2.1 Biopharmaceutical business system

The key actors in the Dutch biopharmaceutical business system are pharmaceutical companies active in biotechnology (including intermediate supplying firms), dedicated biotech firms[13] and clinical trial companies.

The number of pharmaceutical companies in the Netherlands amounted to 115 in 2001 (see Chapter 1). Limited by, in particular, the availability of proper statistics, it proves rather difficult to assess the number of pharmaceutical firms (including intermediate supplying firms) that have adopted biotechnology in their R&D and production processes since 1994. Recent research gives an estimate of approximately 10 pharmaceutical firms located in the Netherlands and carrying out biotechnology research in 2002 (Enzing et al, 2002b).

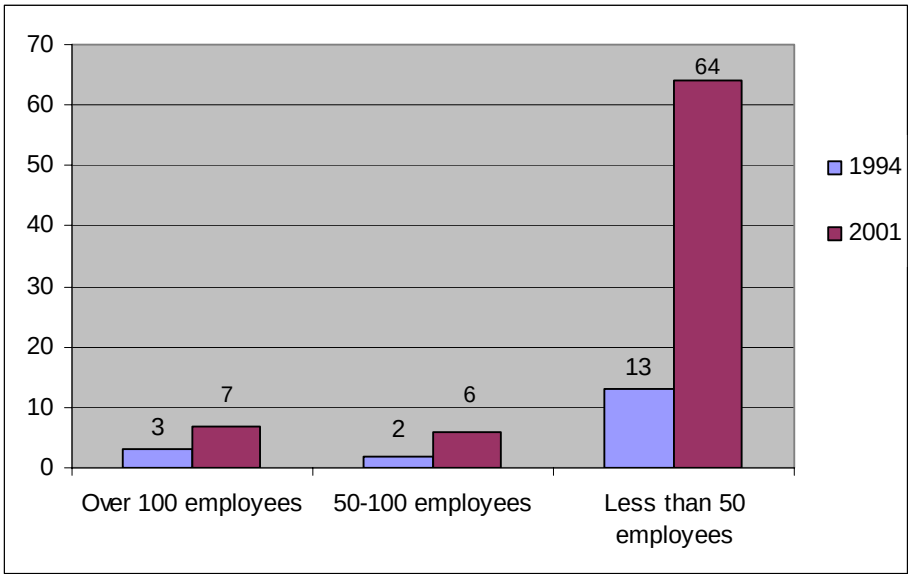
In 2001, the number of dedicated biopharmaceutical firms was almost 80, representing roughly two thirds of the total population of dedicated biotechnology firms in the Netherlands (Enzing et al., 2002b). The majority of the dedicated biopharmaceutical firms is specialised in niche-markets, niche-technologies or specific activities within the pharmaceutical R&D process, such as drug discovery, lead optimisation and drug delivery. Very often, they are supplier of specific technologies or research partner to the traditional pharmaceutical firms and larger (foreign) biopharmaceutical companies. Most dedicated biotechnology firms lack the size and financial resources for developing into fully integrated biopharmaceutical companies, although some have strong ambitions and plans for such a development. So far, only a few, often larger, firms in the Netherlands actually cover the whole process of research to production and marketing of new (bio-) pharmaceuticals.

A relatively large number of clinical trial organisations is active in the Netherlands. Although exact figures are lacking, we estimated the number of clinical trial organisations in 2003 at approximately 30. These organisations, mostly private companies, support research organisations and pharmaceutical companies in performing clinical research. Such support consists for example of initiating and monitoring new clinical trials, performing (parts of) the clinical study, the management of clinical data and provision of statistical support, or (co)writing the final clinical study reports. The presence of such clinical research support organisations seems to be an important reason for foreign pharmaceutical firms to conduct R&D activities in the Netherlands.

[13] Dedicated companies are high tech companies specialised in biotechnology. They are active in R&D and the application of biotechnology in processes/ products and services.

3.2.1.1 Entry and exit, including mergers and acquisitions

Since 1994, a considerable number of dedicated biopharmaceutical firms has been created. In 1994, only 18 pharmaceutical and fine-chemical firms dedicated to biotechnology existed; in 2001 this amounted to almost 80. This growth could point at the potential of the Dutch life sciences sector. However, the majority of dedicated biopharmaceutical firms has shown very limited growth figures in terms of employees (figure 3-3). The total employment for the dedicated biopharmaceutical firms in 2001 is estimated at 1,764 jobs. This means an average of less than 23 employees per dedicated biopharmaceutical firm. Nevertheless, the 1,764 jobs still represent 73% of the estimated employment of the total life sciences sector in the Netherlands (Enzing et al., 2002b).



Source: TNO-STB

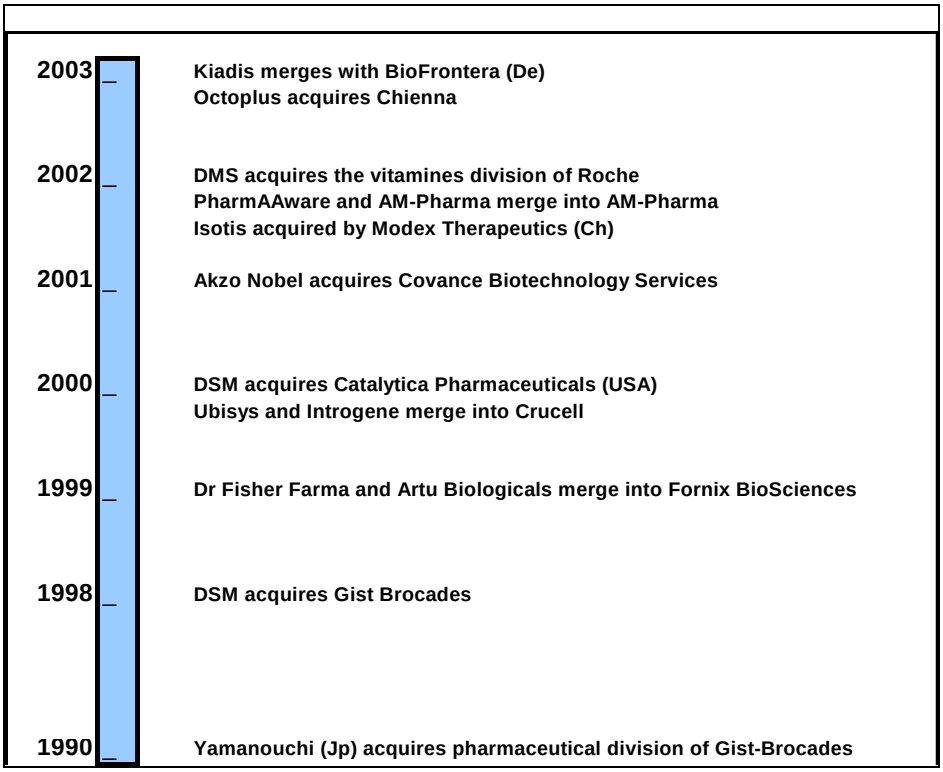
Figure 3-3 Size of dedicated biopharmaceutical firms in the Netherlands in number of employees

Industry dynamics in the Netherlands caused by mergers and acquisitions have been limited (figure 3-4). The Dutch multinationals DSM and AKZO Nobel have been the most active firms when considering the diversified firms. In 1998, DSM acquired Gist-Brocades, another Dutch multinational and the world's largest supplier of antibiotics and specialist in enzyme and fermentation technologies. In 2000, DSM acquired Catalytica Pharmaceuticals, a US-based company specialised in pharmaceutical intermediates. Akzo Nobel's Organon acquired the Japanese pharmaceutical company Kanebo in 1999. Next, Akzo Nobel acquired Covance Biotechnology Services in 2001 and assimilated it with its existing biotechnology activities into DioSynth Biotechnology. Moreover, Akzo Nobel sold its subsidiary Organon Teknika, specialised in in-vitro diagnostics, to the French BioMerieux in 2001.

If we consider the dedicated biopharmaceutical firms, only two relevant mergers occurred. First, Fornix BioSciences was created in 1999 as a result of a 'reversed take-over' of Dr. Fisher Farma BV by Artu Biologicals NV. Second, the biotechnology companies U-bisys and Introgene merged into Crucell NV in 2000. Crucell and Fornix

BioSciences are two of the four Dutch biotechnology companies that are listed at international stock markets.

It is only after 2001 that merger and acquisition activities in the Dutch biopharmaceutical industry seem to have intensified: two mergers and three acquisitions occurred until the first half of 2003.



Source: TNO-STB

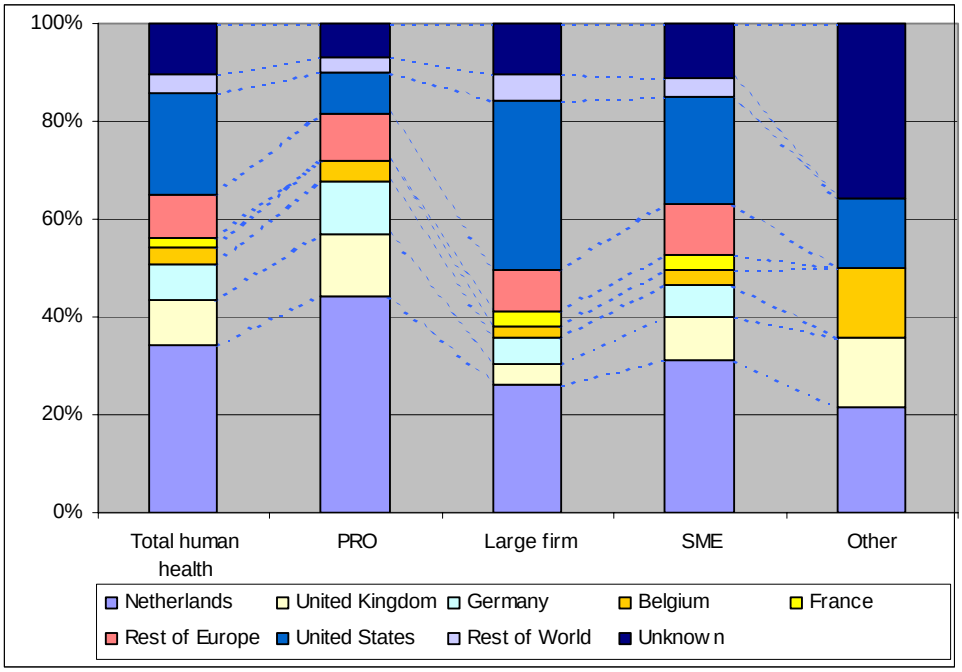
Figure 3-4 M&A activities in the Dutch biopharmaceutical innovation system for 1990-2003

3.2.1.2 R&D co-operation

Some 56 firms active in human health biotechnology filled in the survey on R&D collaboration of the Dutch biotechnology industry. The results of the survey show that approximately 35% of the partners to these 56 firms are located in the Netherlands (figure 3-5). The rest of Europe accounts for 31% of all partners[14] and the US for almost 21%. These findings seem to contradict the conclusions of another recent report on R&D collaboration that argues that Dutch firms active in biotechnology are not able to find appropriate R&D partners within the Netherlands (De Man and Duysters, 2003). This could be explained by the fact that our survey includes both industry-industry and industry-public sector collaboration, whereas De Man and Duysters only included industry-industry R&D collaboration. Indeed, when considering the different categories of R&D partners, our survey shows that especially R&D partners in the public sector originate from the Netherlands: almost 45% (figure 3-5). Small and medium sized firms

[14] The most prominent European countries in this context are the United Kingdom, Germany and Belgium.

and in particular large firms with whom the Dutch firms collaborate are to a large extent coming from outside the Netherlands.

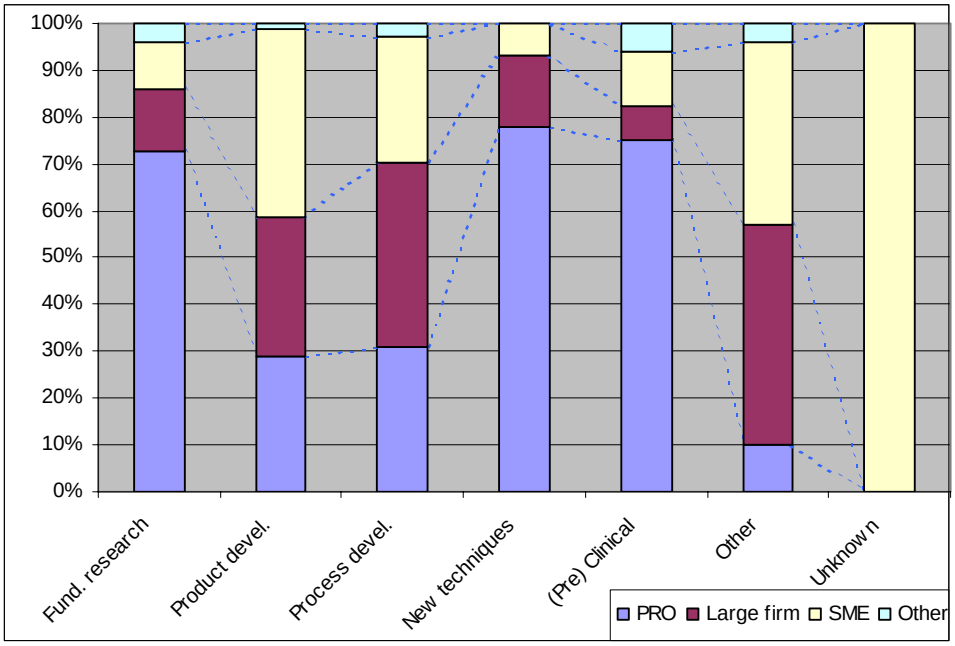


Source: TNO-STB

Figure 3-5 Nationality of R&D collaboration partners for total human health and per type of partner

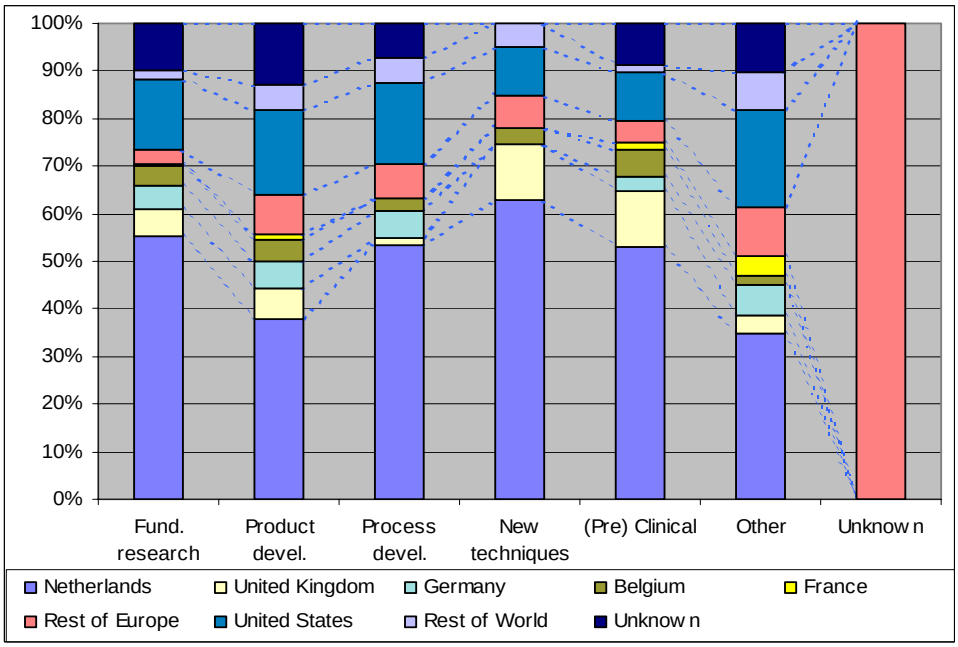
The most common subjects of R&D collaboration in human health biotechnology are 'new product development' and 'fundamental scientific research'. Most collaborative basic research is carried out with universities and public research institutes (figure 3-6). Universities and public research institutes are also the preferred partners in the joint development of new (research-) techniques and (pre-) clinical research. The joint development of a new product or process is mostly carried out with industrial partners; SMEs are more often involved in new product development and large firms more often in new process development. For each subject matter of R&D collaboration, most partners originate from the Netherlands, followed by the United States (figure 3-7).

Companies mostly collaborate with universities and public research organisation through 'collaborative R&D projects', in which all participants carry out research activities and are involved in the formulation and support of the project (figure 3-8). Another popular form of collaborating with the public research sector is 'research financing', in which the firm supports the research activities at the university or research institute with only limited involvement in the design and execution of the project. A very small share of the R&D collaborations with universities and public research organisations are licensing agreements. Collaborative R&D projects and licensing agreements are very common forms of R&D collaborations with other industrial partners.



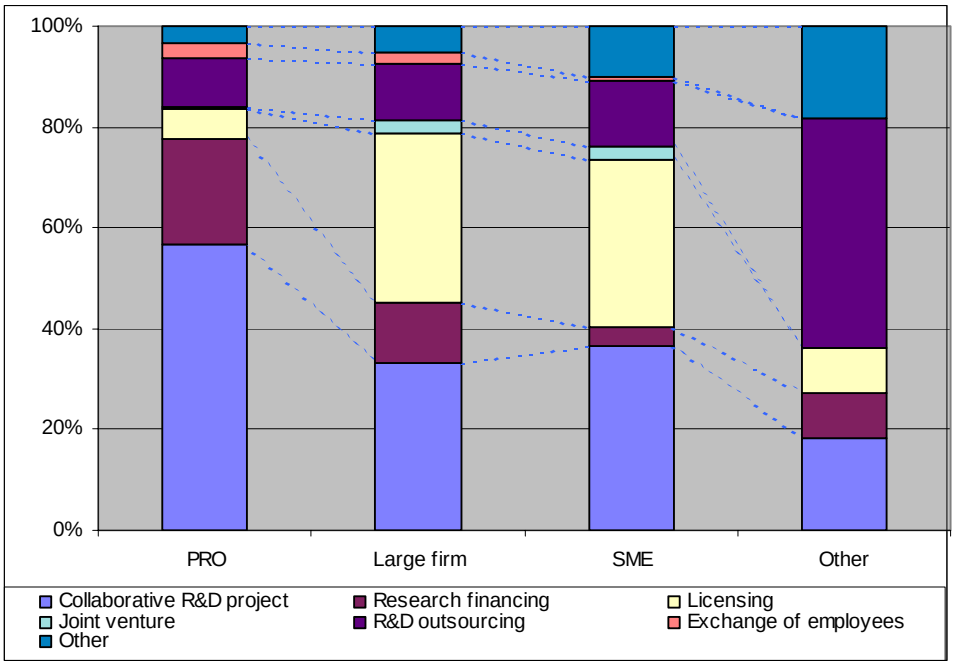
Source: TNO-STB

Figure 3-6 Type of partner of industry and subject of collaboration in human health research



Source: TNO-STB

Figure 3-7 Nationalities of partners of industry and subject of collaboration in human health research



Source: TNO-STB

Figure 3-8 Type of partner of industry and subject of collaboration in human health research

A recent study on the effectiveness of biotech innovation policies in The Netherlands shows that collaboration in R&D is important for both biotechnology research organisations and firms. Approximately one third of the R&D activities by the biotechnology sector are performed in collaboration with external partners (public and private). Main reason for co-operating with academia is their expertise in fundamental research, which is complementary to the expertise of the firms. Fundamental scientific knowledge may also be used to underpin the scientific basis for the firms' products and the scientific reputation of the research organisations may prove to be very supportive in e.g. fund raising, product launches or strategic alliances. An important reason to collaborate with other firms is the joint development and marketing of in-house technologies. Collaborations are also judged as rather tight user-supplier relationships in which the partners are the lead users or preferred suppliers (Kern et al, 2003).

3.2.1.3 Internationalisation of the Dutch biopharmaceutical business system

The Dutch biopharmaceutical industry is very much part of an international system and is also influenced by international developments.

In this section we discuss:

- The high level of internationalisation of R&D processes in this industry;
- The activities of foreign firms in the Netherlands;
- International trade of pharmaceutical products.

International legislation and regulations also have a considerable impact on the pharmaceutical and biopharmaceutical industries. These will be discussed in Chapter 4.

Internationalisation of R&D

The knowledge and skills for biopharmaceutical R&D are distributed among highly specialised firms and research organisations all over the world. Previously, we already discussed the significance of foreign partners (most US, UK and Germany) in collaborative R&D activities by Dutch firms in biotechnology.

The relatively large share of co-inventions with foreign partners in the total number of biopharmaceutical inventions (table 3-4) also shows the international dimension of research in this sector. The share of Dutch biopharmaceutical patents co-invented with an international partner of all Dutch biopharmaceutical patents has been between 25 and 40% since 1994.

Table 3-4 Contribution of international co-inventions in biopharmaceuticals

	1994	1995	1996	1997	1998	1999	2000
Total Dutch biopharmaceutical patents	58	77	99	104	136	150	154
Total biopharmaceutical co-patents with Dutch inventor	23	30	28	26	52	39	44
Share %	39.6	38.9	28.3	25	38.2	26	28.9

Source: OECD, Patent Database, February 2003

The Netherlands has always been an attractive location to perform pharmaceutical R&D, due to the high quality and highly diversified research system in the field of human health. This research system, in combination with a very well organised patient documentation and favourable regulations, has proved to be rather attractive especially for conducting pre-clinical and clinical research (table 3-5). Nevertheless, the number of clinical trials has been decreasing since 2000, most considerably in phase II. Possible reasons for this are the introduction of the new EC-directive for Good Clinical Practice and the introduction of stricter regulations for medical research involving human subjects (the WMO-act) and for clinical research involving several different research centres (so-called multicentre research).

Table 3-5 Number of clinical trail studies in the Netherlands

Year	Phase I	Phase II	Phase III	Phase IV	Total
2000	141	168	287	85	781
2001	121	157	227	88	656
2002	96	165	192	108	640

Source: CCMO, 2003

Foreign firms in the Netherlands

The majority of the pharmaceutical firms active in the Netherlands is a subsidiary of foreign pharmaceutical groups. Figures are lacking, but indicative is the members list of Nefarma, the Dutch association of the research-based pharmaceutical industry. Approximately 95% of all Nefarma members are companies that are (part of) foreign pharmaceutical multinationals.

In 1994, four foreign biotech firms in this field were located in the Netherlands: Amgen (R&D, logistics, marketing & sales), Serono (mainly marketing & sales and distribution), Genzyme (R&D) and Centocor (production). They represented more than 22% of the entire population of dedicated biopharmaceutical firms in the Netherlands in 1994. Since then, only three new foreign dedicated biotech firms in this field have started activities in the Netherlands: Genencor International in 1996 (R&D, sales & marketing), Biogen in 1997 (production, packaging, distribution and marketing & sales) and Genmab in 2000 (R&D). As a consequence of the strong increase in biotechnology start-ups in the Netherlands, the foreign firms represented less than 10% of the total number of dedicated biopharmaceutical firms in 2001. However, they are rather important to the Dutch dedicated biopharmaceutical industry and biotechnology in general, as they provided almost 1,000 jobs in 2001, of which more than 200 in R&D[15].

International trade

The Netherlands has a longstanding tradition as trading nation. The total national trade surplus amounted to approximately 23 billion euros in 2001 and it is therefore an important contributor to the Dutch economic performance (CBS, 2001). The international trade of medical and pharmaceutical products regularly leads to substantial surpluses on the national balance of trade (table 3-6). Moreover, the value of imported and exported medical and pharmaceutical products increased in the period 1994-2001 with 155%, respectively 170%.

For many years, the market in the Netherlands for parallel imported drugs[16] has been increasing (Nefarma, 2003). The fact that the general price level of drugs in the Netherlands has been higher compared to other European countries has made it attractive for some wholesalers to import brand name drugs. However, in the late 1990s, the price level of drugs in the Netherlands stabilised and reached a level lower than the EU average (Nefarma, 2003). This has led to stagnation in the growth of the market for parallel imported drugs and made parallel export rather than import more attractive.

Table 3-6 International trade of drugs, medical and pharmaceutical products

Year	Import value (€ million)	Export value (€ million)	Export balance (€ million)
1994	2,332	2,459	137
1995	2,832	3,121	289
1996	2,978	3,033	56
1997	3,327	3,477	150
1998	3,817	4,026	210
1999	4,277	4,402	125
2000	4,839	5,498	659
2001	5,955	6,639	684

Source: Nefarma, 2003 based on CBS figures

[15] Centocor is the major contributor with 700 employees of which 100 in R&D.

[16] Parallel imported drugs are brand name drugs, also called innovator or patented drugs, which are being imported from a country where the drug is marketed at a lower price that in the importing country. Parallel import mostly occurs without the permission of the owner of the patented drug.

3.2.2 Food biotechnology business system

The key actors in the Dutch food biotechnology business system are the large diversified food companies, the small dedicated food biotechnology firms and the so-called following companies.

Especially the large food and food ingredients companies are active in biotechnology. They have integrated biotechnology in their R&D and/or production processes. Due to the limited availability of proper statistics it is rather difficult to assess the number of food products and food ingredients companies that have integrated biotechnology. However, in a recent study the number of established agrofood companies that have adopted biotechnology is estimated at approximately 17 companies (Enzing et al., 2002).

The number of dedicated food biotechnology firms is very limited. In 2001, 13 dedicated biotechnology companies had activities that (also) related to the food industry. They develop and produce ingredients for the food industry, they are active in bioprocessing, and they provide analytical services for determination of compounds, detection of contaminants, and safety control. One company is specialised in clinical research into novel and functional foods. Only a few companies are solely dedicated to the food industry, most of them also work for companies in other industrial sectors. In 2001, these 13 companies had approximately 285 employees.

Following food biotechnology companies do not carry out food biotechnology R&D themselves, but they use food biotechnology knowledge that is developed by others. Examples of this type of firms are companies that are active in the dairy industry, provide bakery supplies, and produce ethylalcohol by fermentation, wine, malt and beer. In 2002, the total number of following food biotechnology companies was estimated at approximately 226 firms (Enzing et al., 2002b).

3.2.2.1 Business entry and exit, including mergers and acquisitions

Since 1994, Dutch food companies have been rather active in mergers and acquisitions. A general reason for mergers and acquisitions in the food sector is the strategy of focusing on specific product groups with a high gross profit margin. Unilever, for example, has announced its new strategy in 2000 (The Path to Growth) and decided to focus on fewer, but stronger brands to accelerate growth. Unilever will decrease the number of brands from 1,600 in 2000 to 400 in 2004 (website Unilever). On the one hand this results in heavy restructuring, on the other hand Unilever has also acquired several strategic brands and companies. Major acquisitions in 2000 were Bestfoods for 23.6 billion euros in order to achieve a strategic position in the food service market and Slimfast, which improves Unilever's position in specialised diet food products (website Unilever). Numico[17] did some major take-overs in 1999 and 2000, when it decided to buy respectively General Nutrition Companies and Rexall Sundown (for 1.8 billion US dollars). These take-overs were intended to strengthen Numico's position in the specialised food (food supplements, clinical food and infant food) and vitamins markets. However in 2003, due to disappointing results, Numico decided to sell Rexall Sundown at a loss and to leave the market for vitamins and minerals (website Numico).

[17] Before 1998 Koninklijke Numico was called Koninklijke NV Verenigde Bedrijven Nutricia

The dairy industry has consolidated heavily since the beginning of the 1990s. Moreover, the dairy industry, which has always been a national industry, has become a more internationalised sector with dairy companies that can be considered as true multinational companies. Two large dairy cooperatives, Melkunie and Campina, merged in 1989 into Campina[18] and since then it has acquired several national and foreign dairy companies (website Campina). Friesland Coberco Dairy Foods (FCDF) was established in 1997 after a merger of four dairy cooperatives. Like Unilever, FCDF decided to decrease the number of brands and to focus on specific products groups, such as dairy products and fruit juices (website FCDF).

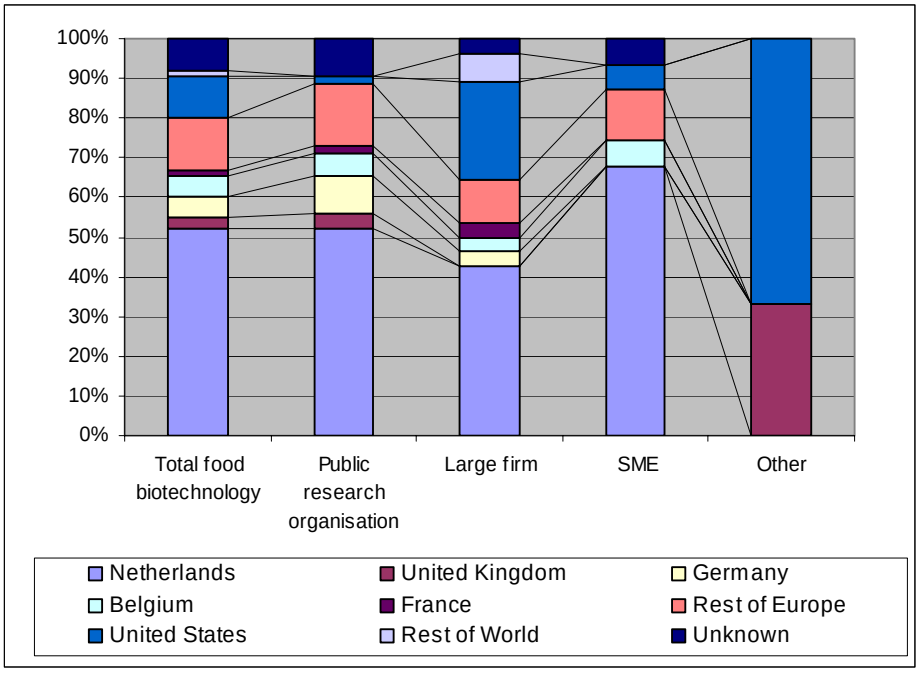
With respect to the business entry of dedicated food biotechnology firms, four of the 13 companies in 2001 already existed in 1994. In 2002 and 2003, no new dedicated food biotechnology companies were established.

3.2.2.2 R&D co-operation

The co-operation survey shows that over 50% of the partners of the 22 food firms that have participated in the survey are from the Netherlands. Almost 28% of the partners come from the rest of Europe, mostly from Germany, Belgium and the United Kingdom. The United States accounts for approximately 10%. These results show that - compared to the Human Health sector - Dutch food biotechnology firms are more likely to collaborate with other Dutch firms and public research organisations than with foreign partners (figure 3-9).

When considering the categories of R&D partners, the survey also shows that in each category the national partners have the largest share (figure 3-9); especially partners in the category ‘small and medium sized enterprises’. About 45% of the total number of foreign partners in the category ‘large firm’ originates from the US, while Germany is a popular European country for collaboration with public research organisations. Partners from the United Kingdom can only be found in the category ‘public research organisations’.

[18] Until 2001 Campina was named CampinaMelkunie

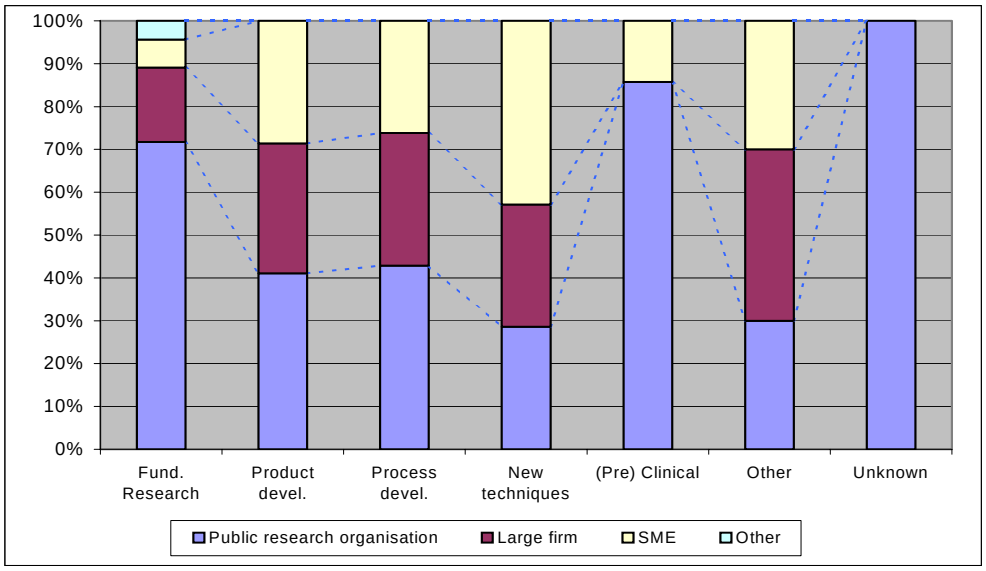


Source: TNO-STB

Figure 3-9 Nationality per type R&D partner in food biotechnology

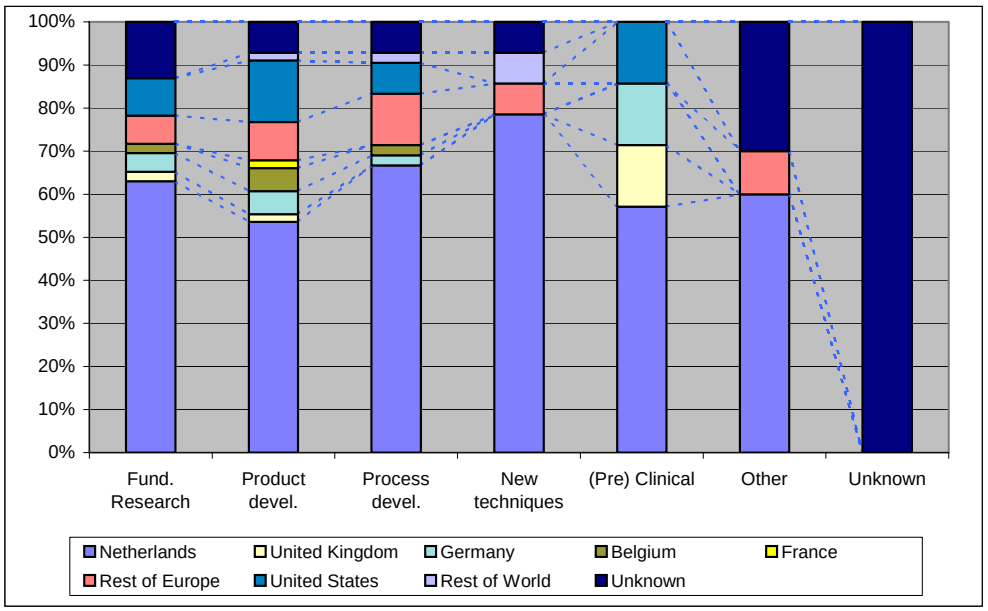
'New product development', 'new process development', and 'fundamental scientific research' are the most common subjects of collaboration. Collaborative fundamental research is mainly (over 70%) carried out with universities and public research organisations (figure 3-10). Companies co-operate mainly with public research organisations in '(pre) clinical research' and with small and medium enterprises in 'development of new techniques'. Especially large firms are preferred partners in the case of 'joint product and process development'.

More than 50% of the partners originate from the Netherlands (figure 3-11). Partners from United Kingdom and Germany are mainly involved in joint '(pre) clinical research', while Belgian partners are mainly involved in 'process and product development' and 'fundamental scientific research'. In the case of joint product development, the most prominent foreign partners originate from the United States.



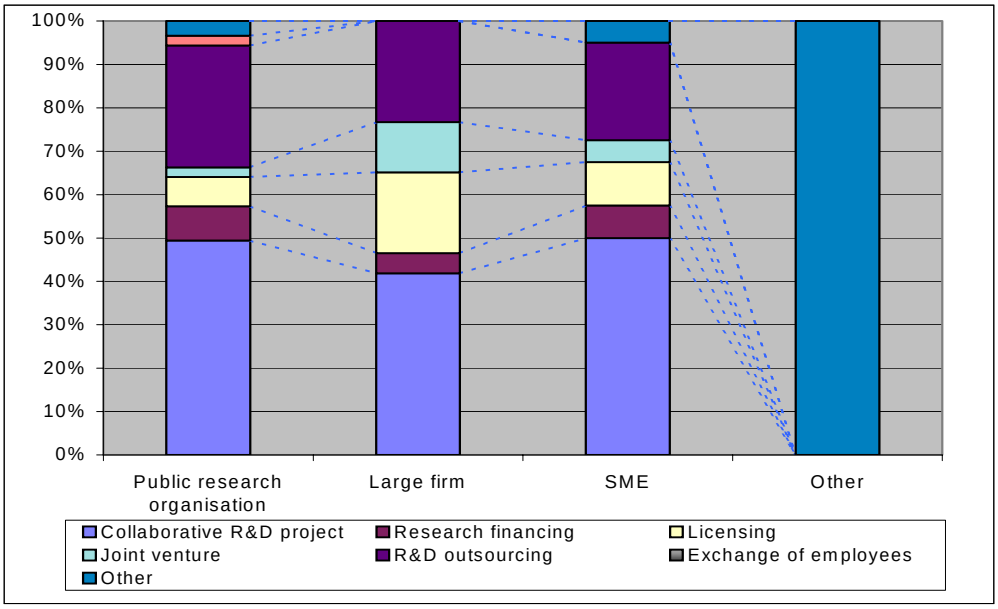
Source: TNO-STB

Figure 3-10 Type of partner and subject of collaboration in food biotechnology



Source: TNO-STB

Figure 3-11 Nationalities of partners and subject of collaboration in food biotechnology



Source: TNO-STB

Figure 3-12 Type of partner and form of collaboration in food biotechnology

'Collaborative R&D projects' are the preferred form for collaborations with both public research organisations and industrial partners (figure 3-12). Companies outsource their R&D often to academia and 'license out' to large firms. 'Exchange of employees'– only a few cases – takes place with public research organisations.

3.2.2.3 International characteristics of the Dutch food industry

Internationalisation of R&D

As mentioned above, over 50% of the R&D partners of the Dutch food companies active in biotechnology originate from the Netherlands. Compared to the biopharmaceutical companies, Dutch food biotechnology companies collaborate more with national partners than with foreign partners. Especially food companies that focus on one product group (e.g. CSM) and/or one product chain (mainly cooperatives) have concentrated their R&D activities in the Netherlands and have strong relationships with national research organisations (NRLO, 1997). On the other hand, food companies that focus on more product groups and/or more functions in the product chain (e.g. Unilever) locate their R&D activities where their main markets are or where the conditions for R&D are most attractive. Therefore, their R&D orientation is more international. They have R&D in the Netherlands, but they also have large R&D centres abroad. A NRLO-study also shows that internationalised production leads to internationalised R&D and that, although a large part of the research will be located in the Netherlands, R&D activities will increasingly be relocated or outsourced abroad. This could imply that the traditional strong relationship between the Dutch food industry and the national research organisations could become less strong, and that the Dutch research organisations will only be one of the potential research partners instead of the preferred partner.

International trade and foreign direct investments

One third of the Dutch production of food products is based on imported products (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2002). Important export products are meat and meat products, frozen potatoes and potato products, and dairy products. Almost 40% of the Dutch agricultural production is not processed by the Dutch food industry (NRLO, 1997). The Netherlands is - after the United States and France - the third largest exporter of agricultural products and the second largest exporter of processed food products and beverages in the world (NRLO, 1997; Netherlands Foreign Investment Agency, 1998).

The export value of the Dutch food industry (including tobacco) is more than twice as large as the import value and this leads to a large trade surplus (table 3-7). In the period 1995-2001, the import value increased with 18.47%, while the export value increased with 24.3% in the same period. In 2001, the Dutch food industry accounted for almost 5% of the total Dutch import value, while its contribution to the total export value amounted to approximately 10% (CBS, 2003a).

Table 3-7 International trade of the Dutch food industry (including tobacco)

Year	Import value (€ million)	Export value (€ million)	Trade balance (€ million)
1995	10,353	21,861	11,508
1996	10,602	22,293	11,691
1997	11,397	23,656	12,259
1998	11,564	24,111	12,547
1999	11,017	23,909	12,892
2000	11,659	25,513	13,854
2001	12,265	27,163	14,898

Source: CBS, 2003a: 'Waarderingen' (Validations)

The strong international dimension of the Dutch food industry can also be illustrated by the size of direct foreign investments. In 1994, nearly five billion euros were invested in the Dutch food industry by foreign investors. In 2001, this has increased with 220% to almost 16 billion euros. The Dutch food industry has invested twice these amounts in foreign companies; in 1994 they invested almost 11 billion euros abroad and in 2001 this amounted to a bit more than 32 billion euros (De Nederlandse Bank, 2003). In 2001, the food industry contributed for about 5% of the total direct foreign investments in the Netherlands, while its share in the total direct foreign investments from the Netherlands reached almost 9%.

Foreign food firms in the Netherlands

The strategic location of the Netherlands in Europe and the extensive logistics infrastructure - but also to gain a position on the Dutch market - has attracted foreign multinational food firms to the Netherlands. Most of these firms have manufacturing and distribution operations in the Netherlands, while others have only located their distribution activities in the Netherlands. Examples of major foreign food firms are General Mills, Heinz, Nestlé, Mars and Leaf. At the same time, Dutch food firms have expanded their activities to the rest of the world and merged with foreign companies in multinational food companies, like Unilever (British/Dutch) and Sara Lee/Douwe Egberts (American/Dutch).

Although the Dutch food industry includes many foreign firms, only one foreign dedicated food biotechnology companies was settled in the Netherlands in 2001 (in 1994 none).

3.3 Performance

3.3.1 Introduction

In this section, we investigate the scientific and commercial performance of the Dutch biopharmaceutical and food biotechnology sectors. Scientific performance is mainly assessed by using bibliometric analysis of scientific publications in pharmaceutical biotechnology. In addition, data on education, training of skilled labour and valorisation of research results are used[19]. Commercial performance is assessed by using data on firm creation, turnover, employment and patenting activities. The countries that are included in the tables and figures in this section are those participating in this OECD-project and some other important countries.

3.3.2 Scientific performance

3.3.2.1 Biopharmaceutical research system

The Dutch biomedical and pharmaceutical research system can be characterised as relatively large and diversified into many scientific disciplines. Peer reviews have generally evaluated the research system as of high quality (Enzing, 2000b).

Table 3-8 shows the contribution of the actors in the R&D system to pharmaceutical publications in 1994 and 1999. The major contributors are universities, as could have been expected. Moreover, their share has increased. The same holds true for the contribution of biotechnology firms and hospitals. The declining share of the public research institutes is remarkable.

Table 3-8 Contribution of different author types to biopharmaceutical publications

Type of organisation	1994	1999
Pharmaceutical firm	1.6 %	1.5 %
Biotechnology firm	0.6 %	1.1 %
University, including academic hospital	76.5 %	79 %
Hospital	7.8 %	8.5 %
Public research institutes	8.3 %	5.8 %
Other	5.2 %	4.1 %
Total	100 %	100 %

Source: SCI via STN, searches and calculations: Fraunhofer ISI

The Dutch biopharmaceutical research output in terms of scientific publications increased from 651 in 1994 to 1,001 in 2001 (table 3-9). The annual increase of approximately 7% is comparable to the growth rates of the United Kingdom and the

[19] The OECD Health Data publications also provide data for the output of the education system; however, these were not available for the Netherlands. Other countries participating in this OECD project have included these data.

United States, but is below the average growth rates of a considerable number of other countries, the world and OECD. We can conclude that countries that have been behind the Netherlands are catching up.

Table 3-9 Number of biopharmaceutical publications

	1994	1996	1998	2000	2001	Growth 1994-2000
World	20,282	24,574	28,145	32,646	33,273	8%
OECD	19,190	23,067	26,368	30,321	30,733	8%
United States	8,658	10,217	11,316	12,971	13,192	7%
EU	7,986	9,850	11,355	12,896	13,024	8%
Japan	2,143	2,594	3,169	3,780	3,733	10%
Germany	1,588	2,082	2,533	3,022	3,160	11%
United Kingdom	1,910	2,277	2,621	2,936	2,970	7%
Canada	889	1,093	1,210	1,421	1,453	8%
Netherlands	**651**	**745**	**895**	**992**	**1001**	**7%**
Spain	438	587	753	938	936	14%
Australia	511	596	723	813	851	8%
Belgium	314	369	489	562	596	10%
Finland	262	296	377	377	392	6%
Norway	114	127	152	181	217	8%

Source: SCI via STN, searches and calculations: Fraunhofer ISI

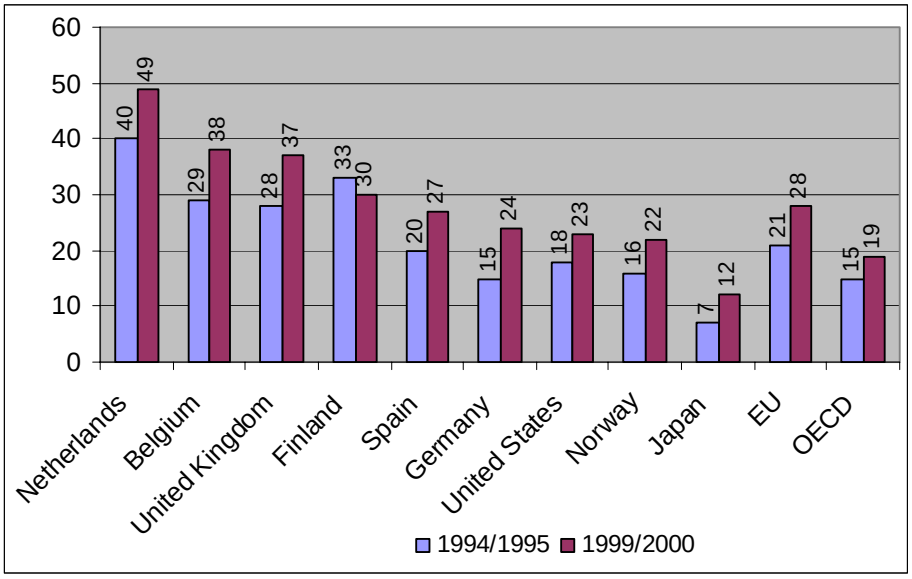
This is confirmed by recent findings of the EPOHITE-project, a comparative study on biotechnology performance and policy effectiveness in 14 EU Member States (Reiss et al, 2003). The Dutch national EPOHITE study included the growth rates of Dutch publications in biotechnology (i.e. not only human health biotechnology) over the periods 1995/1996 and 1999/2000. The number of Dutch biotechnology publications increased considerably during this period with almost 26%, but was far below the EU growth rate of 45.4%. Accordingly, the share of Dutch biotechnology publications in the total number of EU biotechnology publications decreased from 7.7% in 1995/1996 to 6.7% in 1999/2000. Except for industrial biotechnology, this trend was reported for all biotechnology fields, including diagnostics and therapeutics (Kern at al, 2003).

Nevertheless, the Dutch performance is much better when relative figures are presented that take into account the number of researchers and country size. With 40 biopharmaceutical publications per 1,000 researchers in the period 1994/1995 and 49 in the period 1999/2000, the Netherlands is far ahead of most European countries and also the United States and Japan (figure 3-13).

The Biotechnology Innovation Scoreboard 2003[20] of the European Commission includes another relative indicator for biotechnology (all fields): the number of all biotechnology publications per million capita (figure 3-14). Again, the Netherlands belongs to the best performing countries in Europe with 138 biotechnology publications

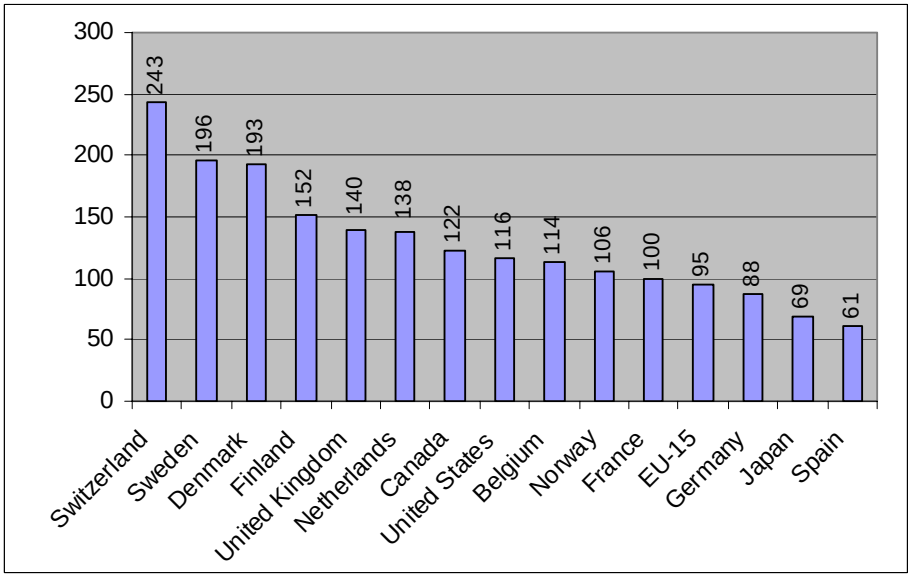
[20] The Biotechnology Innovation Scoreboard is one of the thematic scoreboards complementing the European Innovation Scoreboard for the Trend Chart on Innovation, commissioned by the European Commission.

per million capita in 2000. In addition, the Netherlands performs better than the United States, Canada and Japan.



Source: SCI via STN, data on researchers (fte): OECD (2002) Main Science and Technology Indicators, searches and calculations: Fraunhofer ISI

Figure 3-13 Biopharmaceutical publications per 1000 researchers



Source: European Commission, 2003c

Figure 3-14 Biotechnology publications per million capita in 2000

The EPOHITE study highlighted another issue in the Dutch biotechnology science base. It showed that the majority of the Dutch biotechnology publications concerned the first

stages of innovation, i.e. fundamental and applied research[21]. However, it was also found that in the period from 1995/1996 to 1999/2000, the number of Dutch publications concerning fundamental research hardly increased (+3 %), whereas the strongest increases were to be found in publications concerning applied research (+35 %) and experimental and technology development (+31%). The EU growth rate in fundamental publications was considerably higher, i.e. +45 %. Accordingly, there was a sharp decrease of the Dutch contribution to all European fundamental biotechnology publications: from 7.8 % in 1995/1996 to 5.6 % in 1999/2000.

The limited growth of fundamental publications by Dutch authors is a point for concern as biotechnology is strongly based on scientific developments and also drives a science-based commercial sector. Together with the trend shown in Dutch public policies to stimulate commercialisation of public research and co-operation between industry and academia, applied research and technology development will out-number fundamental research. This may lead to the stimulation of the biotechnology business sector in the short term, but in the long term this could lead to a depletion of the biotechnology knowledge pool and an increasing inability to keep up with scientific developments (Kern et al., 2003).

3.3.2.2 Food biotechnology research system

Research by the 'Nederlands Observatorium van Wetenschap en Technologie' (NOWT) (2001) pointed out that 'agriculture and food sciences' has the strongest position in the Dutch research system (table 3-10). This position is based on high impact scores and on a strong degree of specialisation. This study also showed that especially public research institutes perform agricultural and food research, followed by universities.

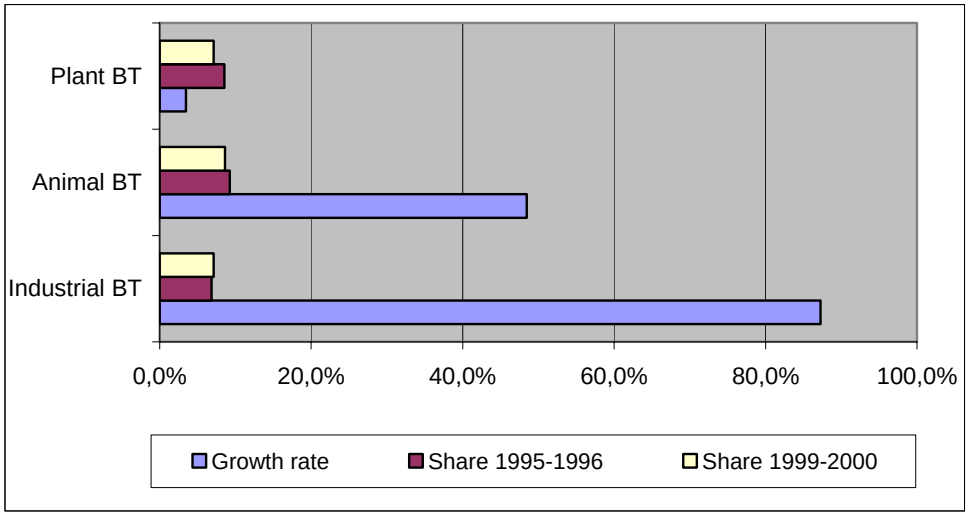
Table 3-10 Position of 'agriculture and food sciences' in the Dutch research system: the six strongest areas

Research discipline	Share of discipline in Dutch publication output	Degree of specialisation of the Netherlands in western Europe*)	Global scientific citation-impact**)	
			Total	In top - 1%
Agriculture and food sciences	4.8%	++	0	++
Biology	4.3%	+	+	+
Environment sciences	2.2%	++	+	0
Chemical technology	0.9%	+	++	++
Civil Engineering	0.5%	+	++	++
ICT sciences	0.3%	++	+	++

*) Share of Dutch publications in a discipline compared to the share of this discipline in all publications of the EU-15, Switzerland and Norway.
**) Global citations impact with regard to all publications in the discipline, and with regard to the top-1% most cited publications.
Source: NOWT, 2001, based on table 3.5, page 50.

[21] Four different stages were used to classify scientific biotechnology publications: fundamental research, applied research, experimental development and technology development. This classification has been developed by the National Science Foundation and CHI Research.

The Dutch case study for the EPOHITE-project presented the performance of the Dutch knowledge base in biotechnology, using bibliometric indicators. The study included some food research related fields: 'plant biotechnology', 'animal biotechnology' and 'industrial biotechnology' (figure 3-15). During the period 1995/1996–1999/2000, the number of Dutch publications considerably increased in the fields of industrial biotechnology (over 85 %) and animal biotechnology (over 45 %). The number of plant biotechnology publications only slightly increased with less than 3.5% in the same period. The strong growth of publications in industrial biotechnology also resulted in a somewhat larger Dutch share in the total number of industrial biotechnology publications in the EU (from 6.8 % to 7.1 %). A decrease of the Dutch share in the total number of publications in the EU was especially to be found in the field of plant biotechnology: from 8.5 % to 7.1 % (Kern et al., 2003).



Source: Kern et al., 2003; based on bibliometric research by Fraunhofer ISI using ISI data
Figure 3-15 Publications growth rate and share in total EU publications

3.3.3 Training and education

Collection of quantitative data on education and training in the Netherlands merely takes place at a high aggregation level and is therefore not well suited for discussing the performance of biotechnology training system. However, some information is available at the level of life sciences in general.

A recent study on the Dutch labour market for life sciences reported that the intake of first-year students at higher vocational education institutions was relatively stable during 1996-2000 for all life sciences courses together. However, a strong fall occurred in 2001 and continued in 2002. The intake of first-year students for all life sciences courses at higher vocational education institutes decreased with 27 % in 2002 compared to 1996 (Broersen et al., 2003). An important decrease in the intake of first-year students was reported for 'laboratory techniques'. This decrease amounted to 28 % for secondary vocational education in 1997-2000 and even to 47 % for the period 1996-2002 at institutions for higher vocational education. Moreover, decreases were identified for the higher vocational education courses in 'biotechnology' (7 %) and 'biology' and 'medical laboratory research' (3 %).

The study showed a rather strong increase in the intake of first-year students at universities for food sciences in 2001 compared to 1999 (48 %). However, at the same time the intake of students at higher vocational education institutes for food sciences decreased with 52 % in the period 1996-2002 (Broersen et al., 2003).

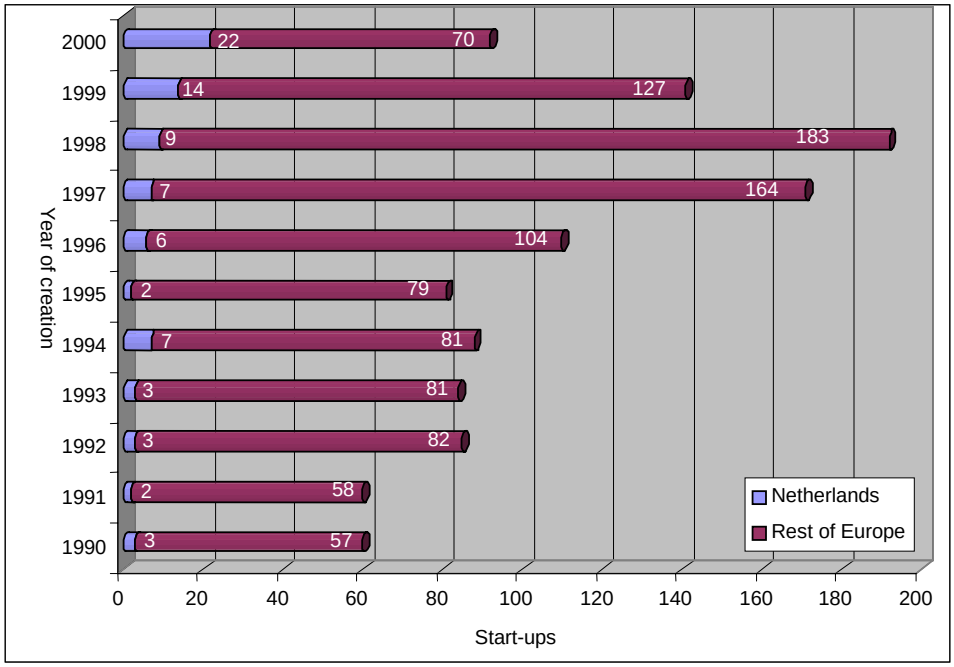
Problems with the intake of first-year students for life sciences education at universities have not been identified. On the contrary, a growth of 22 % was reported for 2001 in comparison with 1999. Nevertheless, the absolute number of first year students remained very low in some disciplines. This seems highly related to the general, negative, attitude of students in the Netherlands towards education in natural, technical or health related disciplines and sciences. Research organisations and firms already have considerable problems in finding qualified employees in particular in the field of bioinformatics. Other areas of concern are genetics, genomics and proteomics. Therefore, it has become common practice to attract foreign employees, mostly Ph.D. and post-doctoral students (Broersen et al., 2003).

In 1998, research in (bio)medical and health sciences at all university faculties and most non-university research institutes was assessed for the period 1992-1996 by an international peer review committee. The committee concluded that biomedical and health sciences research in the Netherlands was of good quality. The committee used a 5-point scale, ranging from ‘poor’ to ‘excellent’. Fifteen percent of the main research themes were rated as excellent, 46 % as good, 36 % as satisfactory and 3% as unsatisfactory. Areas such as ‘cardiovascular research’, ‘oncology and immunology’, and ‘epidemiology and biostatistics’ were considered to be particularly strong. However, some areas have been denoted as weak or less developed, e.g. genetic technology, cell biology and translational research (VSNU and KNAW, 1998).

3.3.4 Business and innovation performance

Although the Netherlands has a strong international reputation when it concerns its science base in biotechnology, it has not succeeded in building up such a reputation for biotechnology business and commercialisation. Approximately 50 biotechnology companies had been started in the Netherlands until mid 1990s, which ranked the Netherlands fifth in Europe. In the consecutive years the number of biotechnology companies increased to 85 in 2000: this is a growth of 70 % compared to 1996. However, this was a much lower growth rate than the European average which amounted to 102 % (Kern and Enzing, 2002).

Another difference in the pattern of firm creation in the Netherlands compared to the rest of Europe is illustrated in figure 3-16. Since the early 1990s, Europe has experienced a period of high growth in the number of biotechnology start-ups until 1998 when a decline started. The Netherlands has rather witnessed a period of stable growth with a very limited number of annual start-ups until 1999 and 2000, when relatively strong increases occurred. However, the growth figures decreased in the consecutive years. The number of start-ups in 2001 and 2002 were respectively 18 and 17 (BioPartner, 2002 and 2003).



Source: Enzing et al., 2002b.

Figure 3-16 Patterns of firm creation for dedicated biotechnology companies in the Netherlands and Europe

3.3.4.1 Biopharmaceutical industry

New firms

A relatively large number of 59 dedicated biotechnology firms was set up in the biomedical and biopharmaceutical areas in the period 1994-2001. The population of biopharmaceutical firms represents by far the lion's share of all dedicated biotechnology firms in the Netherlands. Nevertheless, the majority of the firms has not been able to leave the early phases of firm development yet. Most biopharmaceutical firms employ less than 50 employees and often even less than 25. Most firms still place the emphasis of their activities on research, although many firms are also involved in production activities (Enzing et al., 2002b). Figures on turnover, R&D investments and employment are only available for 2001 and for all dedicated biotechnology firms together (table 3-11).

Table 3-11 Turnover, R&D and employment figures for dedicated biotechnology firms in 2001

Turnover	**€ 122.5 million**
R&D investment	€ 72.9 million
Total employment	2408 jobs (1764 in biopharma)
R&D employment	1445 jobs

Source: Enzing et al., 2002b

IPO's

The number of Dutch dedicated biopharmaceutical firms having performed initial public offerings is very limited (table 3-12): Pharming (Nasdaq Europe in 1998 and Euronext in 1999), Fornix BioSciences[22] (Euronext in 1999), Crucell (Nasdaq and Euronext in 2000) and Isotis (Euronext 2000). Pharming, Crucell and Isotis raised over 270 million euros with their IPOs.

Table 3-12 Initial public offerings by Dutch dedicated biomedical/biopharmaceutical companies

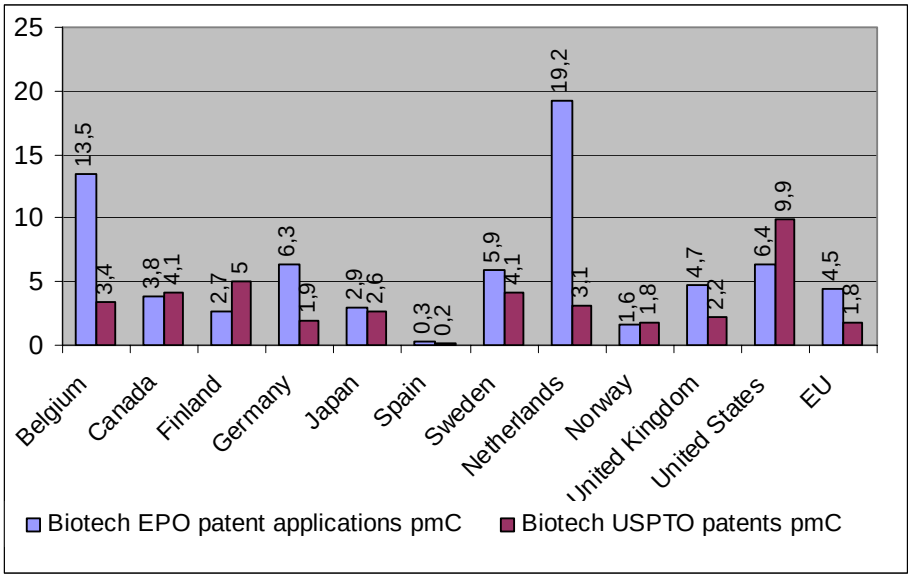
Company	Date and place of listing	Money raised (€ million)
Crucell	Nasdaq and Euronext in 2000	144
Fornix BioSciences	Euronext in 1999	N.a.
Isotis	Euronext in 2000	80
Pharming	Nasdaq in 1998 and Euronext in 1999	52.1

Source: TNO-STB and Ernst & Young

Patenting activities

The Netherlands is performing relatively well in terms of patenting activities. The Biotechnology Innovation Scoreboard 2003 qualified the Dutch patenting in the entire area of biotechnology as a major strength of the Dutch biotechnology innovation system (figure 3-17). The Netherlands ranked first of the countries included in the scoreboard when considering the number of biotechnology patent applications per million capita at the EPO in 2001. Moreover, it ranked 8th in terms of the number of biotechnology patents per million capita registered at the USPTO in 2000. DSM, active in food, intermediates for the pharmaceutical industry and fine chemicals headed in 2001 and in 2002 the list of biotechnology patent applications at the European Patent Office. In 2002 the company applied for 396 patents, of which 237 dealt with biotechnological findings (Bionieuws, 2003).

[22] Fornix BioSciences is the result of a 'reversed takeover' of Dr. Fisher Farma by Artu Biologicals in 1999. Artu Biologicals was already listed at Euronext.



Source: European Commission, 2003c

Figure 3-17 Biotechnology patenting activities at EPO and USPTO, corrected for size of country

The number of pharmaceutical and biopharmaceutical patent applications at the EPO by Dutch inventors has increased steadily over the period 1994-2000 (table 3-13). Nevertheless, the share of pharmaceutical patent applications from all the patent applications by Dutch inventors remains relatively small. In 1994, 4.9% of all applications were pharmaceutical patents; in 2000 this figure was 6.1%. This is considerably below the EU average and OECD average with respectively 6.8% and 9.2% in 1994 and respectively 7.1% and 8.2% in 2000 (OECD Patent database, February 2003).

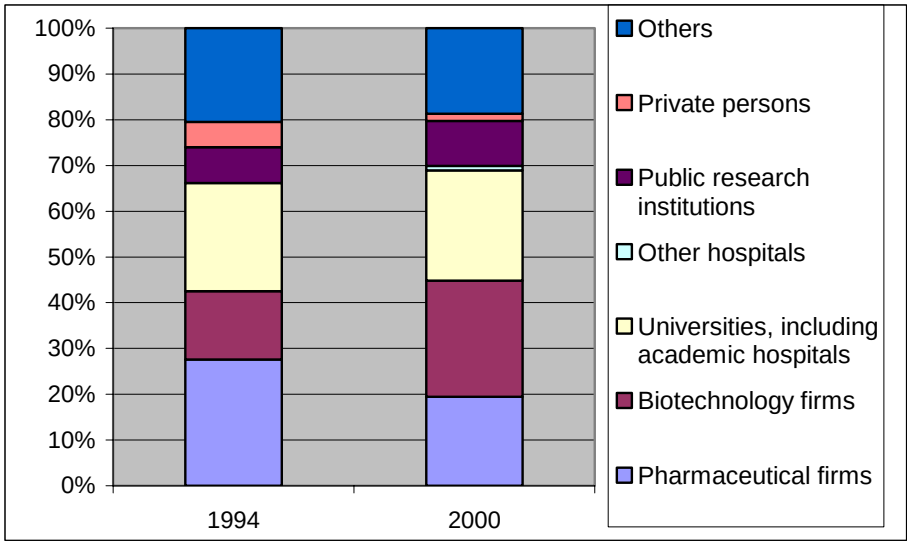
Table 3-13 Number of pharmaceutical and biopharmaceutical patent applications (EPO) by Dutch inventors

Year	Total patents applications	Pharmaceutical applications	Biopharmaceutical applications	Share biopharmaceuticals of pharmaceuticals
1994	1,868	92	58	63%
1995	2,112	106	77	73%
1996	2,601	147	99	67%
1997	2,858	174	104	60%
1998	3,213	213	136	64%
1999	3,599	230	150	65%
2000	4,155	254	154	61%

Source: OECD Patent database, February 2003

Figure 3-18 shows the contribution of actors in the Dutch biopharmaceutical and biomedical innovation system that have applied for biopharmaceutical patents in 1994 and 2000. The data show that the relative contribution of the biotech firms increased

considerably, mostly at the cost of the large pharma firms, of public research institutes and of private persons. The relative contribution of the universities remained more or less the same.



Source: OECD Patent Database (February 2003), identification of actors by TNO-STB.
Figure 3-18 Types of inventors and their contributions in biopharmaceutical patent applications (EPO)

The performance of the Netherlands in terms of pharmaceutical and biopharmaceutical patent applications is considerably higher if the numbers are corrected for the size of the country (table 3-14).

Table 3-14 Number of biopharmaceutical patent applications (EPO) per million capita

Country	Biopharmaceutical patent applications		Biopharmaceutical patent applications pmC	
	1994/1995 (1)	1999/2000 (1)	1994/1995 (1)	1999/2000 (1)
Australia	83	116	4.6	6.1
Belgium	49	137	4.8	13.3
Canada	108	220	3.7	7.2
Finland	23	29	4.4	5.6
Germany	274	620	3.4	7.5
Japan	294	608	2.3	4.8
Netherlands	**68**	**152**	**4.4**	**9.6**
Norway	10	25	2.2	5.5
Spain	17	43	0.4	1.1
United Kingdom	231	456	4.0	7.7
United States	1.899	3.141	7.3	11.5
OECD	3.195	5.779	3.0	5.2

Notes: (1) Average for both years
Source: OECD Patent database February 2003, OECD Quarterly Labour Force Statistics 2003, calculations: Fraunhofer ISI

Drugs in the pipeline

The number of drugs under development by Dutch (bio)pharmaceutical companies can be used as an indicator of the commercial potential of the national pharmaceutical industry. Table 3-15 provides an overview of the number of drugs in the pipeline in 12 different countries for 2002. It shows that the Netherlands is a relatively small player when compared to countries such as the United Stated, the United Kingdom, Japan and Germany. It can be assumed that this is related to the very modest size of the Dutch pharmaceutical industry. It also shows that the majority, i.e. 73%, of the pharmaceuticals in the pipelines of Dutch (bio)pharmaceutical firms has not exceeded the stage of preclinical research yet. This is a relatively large proportion and it means that only a few pharmaceuticals developed by Dutch firms will be introduced on the market in the near future.

Table 3-15 Pharmaceuticals in the pipeline in 2002

Country	Preclinical	Clinics I	Clinics II	Clinics III	Total
United States	2087	389	471	200	3147
United Kingdom	521	114	165	43	843
Japan	226	75	150	42	493
Germany	333	44	81	28	486
France	205	56	78	35	374
Canada	246	34	44	19	343
Austria	88	13	13	2	116
Netherlands	64	7	11	6	88
Belgium	57	9	16	6	88
Spain	31	14	6	7	58
Finland	16	4	5	0	25
Norway	11	5	3	0	19

Source: R&D Focus © 2002 IMS Health Incorporated or its affiliates. All rights reserved.

3.3.4.2 Food biotechnology industry

Compared to the biopharmaceutical sector, the performance in terms of number of dedicated food biotechnology is relatively small; in 2001 there were 13 dedicated food biotechnology firms, of which nine were started in the period 1994-2001. Most of these companies are rather small; 11 of these 13 companies employ less than 25 employees. The emphasis of their activities is mainly on research, sometimes in combination with production, technology development, and contract research.

None of the Dutch dedicated food biotechnology companies performed initial public offerings in the period 1994-2001. The foreign dedicated food biotechnology firm completed its initial public offering in 2000 at the NASDAQ.

Main question is why there are only a few, very small dedicated food biotechnology companies. There could be various reasons, and public opinion could be one of them. Although biotechnology promises various applications of which the food industry could benefit, it meets severe public criticism in most European countries, including the Netherlands. In addition, the European Commission stated in its 'Third European Report on Sciences & Technology Indicators' (2003a) that strong price sensitivity of

food stuffs could imply that biotechnology only makes economic sense when high value added food products are needed in very large quantities, especially early in the food chain.

No detailed figures on patents and patent applications in food biotechnology are available. One publication addresses the subject, it showed that in 1997 the Netherlands had relatively more patents in the food industry (based on USPTO patents) than other countries (NOWT, 2001). This could be explained by the presence of some very large multinational enterprises like Unilever.

4 Innovation barriers and drivers – Framework conditions

4.1 Introduction

Innovative activities of firms and research organisations are to a large extent determined or influenced by so-called framework conditions, e.g. regulations, the general entrepreneurial climate, or the availability and quality of specialised knowledge. They can raise important barriers to innovation or create driving forces that stimulate the innovation process. In this chapter, we discuss those framework conditions that are of particular relevance to emerging high tech sectors such as biotechnology: the sources of knowledge, the availability of human resources, access to risk capital, the presence of an entrepreneurial climate, and the regulatory framework. Most framework conditions concern both human health and food biotechnology; those sector specificities that are relevant will be discussed in more detail.

4.2 Knowledge sources

The innovative capacity of firms relates to the competencies of firms to integrate internal and external knowledge. The Dutch Innovation-survey 1998-2000 (part of the third Community Innovation Survey) identified three main channels or sources for firms to acquire information and knowledge that serve as an input to their innovation processes: firms in the industrial column they operate in, external advisors, and publicly accessible sources (CBS, 2003c). The actors in the industrial column they are part of, is for 96% of the innovating firms the most important source for knowledge and information (CBS, 2003c). Internal sources of the firm itself serves as prime source of knowledge (88%), followed by clients (70%), suppliers (68%), and competitors (63%). Research institutes and universities serve as a source of knowledge for only 31% respectively 22% of the innovating firms. The Innovation Survey reported that less than 3% of the firms considered the knowledge provided by research institutes and universities as ‘very important’ to the firm’s innovation activities.

This seems to be different for the pharmaceutical and biotechnology industry, in particular when it concerns the relevance of the public research sector. Since the 1970s, pharmaceutical firms have been forced to create and sustain new forms of learning processes as radically new knowledge bases emerged in modern biotechnology as well as in other biological and medical areas (McKelvey and Orsenigo, 2001). New biotechnology firms – most university spin-offs – played an important role as they developed the core technologies that were used by the larger pharmaceutical and life sciences companies. The science-driven character of the industry led to new organisational structures for innovation in which new patterns of division of labour emerged in which external partners including public research organisations play an important role (Swann et al., 1998).

Public research as knowledge source

In the Netherlands, the networks between the biotechnology industry and the public R&D system are very dense. These close relations can be found in both the biopharmaceutical and the food biotechnology sectors. The majority of the dedicated biotechnology firms are spin-offs from universities, research institutes and university

hospitals (BioPartner, 2003). Very often strong relations are maintained in the form of joint research projects and staff having jobs at both the spin-off company and the university.

Public research organisations can also be an important knowledge source for companies through their patenting and licensing activities. However, the Dutch Central Bureau for Statistics has recently reported that patenting is not a common activity in Dutch public research organisations (CBS, 2003c). Only 3.7% of all Dutch patent applications at the EPO in 1995-1996 came from these organisations. Moreover, the public research organisations had a share of only 1.5% of all Dutch patents granted by the USPTO in 1995-1996. Finally, only 19% of all university patents were licensed to industry, leaving a considerable pool of knowledge unutilised (CBS, 2003c).

Since the late 1970s, all universities in the Netherlands have technology transfer offices to support university-industry interaction and provide assistance to researchers in IPR issues. However, both university researchers and private firms judge the efficacy of most technology transfer offices to be highly insufficient when it concerns biotechnology. The most important reason is the lack of a combined expertise in commercial, legal and specific technological issues. This is aggravated by the limited size and financial means of most technology transfer offices (Kern et al., 2003; OECD, 2003).

A complicating factor in relation to technology transfer is the heterogeneity of the academic IPR system in the Netherlands. Dutch legislation assigns all intellectual property rights resulting from research activities at public research organisations to the university or research institute. However, each university is relatively autonomous in developing its own IPR systems and policies. This has led to important differences between universities in their attitude towards the exploitation of research through IPRs, including differences in efficiency and effectiveness. Although initiatives have been taken to improve the co-ordination between the academic IPR systems and to ameliorate the exploitation of academic research results, only limited results have been reached yet.

In general, the dedicated biotechnology companies consider the relations with the public research organisations as rather valuable, but they also have some comments. Public research organisations are believed not to consider enough the practical implications of their inventions. They are too much focused on the scientific aspects of their research and they are not able to translate the scientific findings into practical feasible applications. It is also mentioned that public research organisations do not have expertise in exploiting knowledge. Public research organisations lack knowledge of patenting and licensing, and as soon as they are aware of these exploitation possibilities, they tend to overestimate the commercial value of their findings (Interviews; Kern et al., 2003).

The protection and exploitation of research through intellectual property rights and in particular patents is a topical issue at the moment in the Netherlands. New roads to stimulate scientists to become entrepreneurs are explored. However, there remains a long way to go as long as entrepreneurship in science is considered as ‘not-done’ and incentives for working on applied research are lacking (Bureau Blaauwberg, 2003).

Industrial column as knowledge source

Pharmaceutical sector
Pharmaceutical companies can be an important source of knowledge as they have extensive experience in activities in the down-stream stages of the innovation process such as manufacturing, distribution, marketing and regulatory affairs. Pharmaceutical firms are very much experienced in these 'disciplines' and can advice small firms on these matters. In specific regions organisations seek to mediate in this and organise meetings between large and small firms in their region (such as the North Netherlands Development Organisation (NOM), member of BioMedCity-Groningen)

Biopharmaceutical firms can also be important sources for pharmaceutical companies, as the latter can tap highly specialised scientific and technological knowledge that would be too costly to develop internally. The history of the biotech industry has shown that small start-ups play a crucial role in product and technology development. The high number of international alliances and licensing agreements illustrates the international character of the biopharmaceutical innovation system (Jungmittag et al., 2000; Senker et al., 2001).

Dutch interviewees from biopharmaceutical firms acknowledge the international character of the biopharmaceutical innovation system. Nevertheless, they consider the very limited size of the Dutch pharmaceutical industry as a serious problem. Proximity is a factor in biotech research and development. As most small firms work in a business-to-business market with larger pharmaceutical firms as their main clients, they have to spend extra efforts and costs in building up relations with clients abroad. This can be an important barrier; especially to small firms this can have a negative effect on their survival and - in a later stage - successful exit strategies.

Food sector
The relations between large and dedicated companies in the food sector show a rather different pattern compared to the pharmaceutical sector. The large food companies we interviewed do not really have research collaborations with Dutch dedicated food biotechnology companies. Collaborations with small Dutch dedicated firms mostly concern clinical trials for the development of functional foods. According to the large firms, the main reason is that the dedicated food biotechnology companies do not have the knowledge or technologies the large firms need. One large food company mentions that their interaction with dedicated food biotechnology companies is slowly increasing, because their business venture unit actively invests in small dedicated firms (abroad). In this way, the firm can more easily keep up with the latest developments in food biotechnology research. The dedicated food biotechnology firms mention as reason for this limited co-operation their lack of an appropriate track record; they are still too small and too young to be attractive research partners for large food companies.

Important knowledge resources for large food companies are suppliers of food ingredients. Suppliers are involved already in an early stage of product development. New food products may ask for completely new ingredients and food companies develop them in licensing and research collaborations with ingredient supplying companies. Important issues in these agreements are the protection of intellectual capital and the right to exclusivity. The number of collaborations between food products companies and food ingredients suppliers is increasing, mainly because food products companies have sold their own ingredients businesses (interviews).

Clients are a relevant knowledge source for dedicated food biotechnology firms. Providing a service or product to their clients often means collaborating with these clients in the development of the new product or service. The dedicated firm has expertise in the specific technology; while the client has knowledge of the final product, the production process or the logistics. The combined expertise of a dedicated firm and its client is needed to realise a new product, process or service (interviews).

Although there are dense national research networks existing between the Dutch food industry and the public research system, food companies increasingly get involved in international co-operations as they seek for knowledge sources all over the world (interviews). This is also the result of the increased internationalisation of the Dutch food industry; Dutch companies have merged with foreign firms or they have expanded their business activities abroad. According to the NRLO (1997), this international character will lead to loose ties with the Dutch knowledge infrastructure, as Dutch companies will increasingly locate their R&D activities where their market is (see also section 3.2.3.3).

4.3 Human resources

Integration of education and research

In order to improve the attractiveness of a full academic career, the university system was split up in two different phases in the early 1980s. The first phase mainly regards the basic scientific education of the students on the numerous aspects of a specific discipline and leads to a master's degree. The major research component in the first phase is the writing of a thesis based on a student's research in the final year before graduation. The time-span for writing such a thesis is four to six months, depending on the specific scientific discipline. The first phase takes four years for most studies and five years for engineering, mathematics, natural sciences and agriculture. After graduation, students are eligible for the pursuit of a PhD degree through four years of full-time research at university research groups and graduate research schools. With the beginning of the academic year 2002/2003, this system has been restructured. There is a bachelor's phase lasting three years and a master's phase lasting one to two years.

Both Oosterwijk (2003) and Allansdottir et al. (2002) reported that the university education structure in most European countries leads to undergraduate students that are hardly experienced to participate in multidisciplinary scientific research projects teams. Moreover, Allansdotir et al. (2002) stated that this also leads to a slower diffusion of new technologies and research techniques as they are introduced in education to a very limited extent only.

Availability of skilled labour

The percentage of researchers in industry and in academia in the Netherlands is rather low; only Italy has a lower score. The contribution of 'science' and 'engineering' to the total number of Master Graduates is almost the lowest in Europe: 15%. Similar conclusions can be drawn for PhD students (European Commission, 2003a).

The availability of and access to qualified human resources is a growing bottleneck to both the biopharmaceutical and food biotechnology sectors in the Netherlands (Broersen et al, 2003; interviews). This not only refers to the limited number of students

graduating in life sciences but also to the rapid increase of biotechnology firms world-wide, which leads to a higher demand for skilled labour. It proves increasingly difficult for Dutch biotechnology firms and research organisations to attract and retain their employees for a long period.

In particular small and medium sized firms and public research organisations encounter difficulties. The majority of the biotechnology firms in the Netherlands are rather small and in their very early stages of development. Their financial resources are limited and 'business as usual' can best be characterised as fighting for survival. Potential employees, and in particular young graduates, often tend to avoid such a risky and uncertain situation and choose to work for more established biotechnology companies or large firms (interviews). Public research organisations, especially universities encounter difficulties in attracting young researchers as they are considered as an unattractive employer compared to companies, because they are not able to offer attractive working conditions, high salaries and status. Moreover, the career perspectives for young scientists are limited as most of the scientific positions at universities are occupied in the long term.

As stated in section 3.3.3., the areas in which most significant shortages emerge are laboratory support and the scientific disciplines bio-informatics, genetics, genomics and proteomics. For food biotechnology there are also shortages in molecular nutrition and plant biotechnology. Additionally, the industry is increasingly looking for staff with a combined expertise in science and management. Companies do not consider attracting experienced managers without any scientific or technological background as a solution to this recruitment problem. As many biotech researchers are also supposed to carry out an increasing amount of managerial activities, especially within smaller firms, management skills are needed. Some Dutch universities recently added specific courses in management and entrepreneurship to the Masters Programs in life sciences. However, the Dutch Biotech Industry Association considers these measures in the Netherlands as insufficient; they ask for more structural actions (Niaba, 2003).

Human resources increasingly come from abroad. Some firms and research organisations encounter bureaucratic and legal barriers in hiring foreign scientists, especially non-EU citizens. Although the Netherlands has introduced special conditions to support and to ease the hiring of foreign scientists, there is still a need for more explicit policies in the area of mobility of human resources (Enzing et al, 2002b). An additional problem with attracting foreign labour is that the majority returns to their home country within a few years, leading to strong increases in turnover of staff.

4.4 Risk Capital

In the 1990s, the number of Dutch public funds for biotechnology firms was rather limited (Ernst and Young, 1998; Enzing et al, 1999). In order to stimulate the creation of new biotechnology firms, the government installed several instruments. The public policies concerning the creation of new biotechnology firms are described in more detail in Chapter 2. In this section we will further discuss the private financing of biotechnology companies.

After a slow start in the mid 1990s (European Commission, 2003a), the market for private equity is relatively well developed in the Netherlands (Ernst and Young 1998, 2001; EVCA 2001; Kern and Enzing, 2002). It is considered as very mature and

increasingly competitive and it is characterised by a large variety and number of private equity houses. The focus is on the expansion phase and less on seed and start capital (European Commission, 2003a). Although the amount of investments by Dutch equity houses in biotechnology has increased considerably since the late 1990s, an important share seemed to be invested into companies outside the Netherlands. Only 53% of all funds provided by the equity houses, including for biotechnology, were invested in the Netherlands and this reflects an increase of the internationalisation of Dutch private equity houses (EVCA, 2001). The amount of venture capital invested in biotechnology in the Netherlands has increased with more than 186% since the mid 1990s (table 4-1).

Table 4-1 Venture capital investments in biotechnology in the Netherlands, PPP in € x1000

1995-1996	1999-2000	Growth
19,821	56,834	+186.7%

Source: EVCA data

Financial conditions for future growth

Since the latest economic stagnation, providers of private equity have become more reluctant to high-risk investments in biotechnology (interviews). Biotechnology companies with a business model that is mainly based on investing in R&D in order to gain a strong patent position, encounter increasing difficulties in raising external financial resources. Investors demand income, this means activities that already generate substantial operating income or products that can be marketed in the very near future (Kern et al., 2003).

These first years after the turn of the century are likely to become critical to a large number of biotechnology firms in the Netherlands. Most of them are rather young and need extra funds for the next growth stages. The public and private funds available in the Netherlands are considered to be insufficient for realising this growth (interviews; Niaba, 2003). Until the end of 2002, biotechnology companies had relatively few problems in raising seed and start-up capital, but after that date they have encounter difficulties in raising follow-up financing. In the first quarter of 2003 venture capitalists had only invested 2 million euros in Dutch biotech firms, mainly due to the bad financial climate[23].

Most public financial instruments deal with the seed and start-up phases; a substantial gap exists with the availability of venture capital for the follow-up stages (Kern et al., 2003). Many biotechnology firms and industry associations plead for public measures to overcome this gap, for instance by introducing specific funds for the follow-up financing of only a limited number of companies, a national life sciences investment fund, public-private funds, and more incentives for venture capitalists (interviews; Niaba, 2003; Bureau Blaauwberg, 2003). However, others believe that government involvement should be very restrictive, as the shakeout that will take place will ultimately lead to a more attractive and innovative biotechnology industry in the Netherlands (interviews; Bureau Blaauwberg, 2003).

[23] C2W 11 / 7 June 2003 / page 3

Corporate venturing[24] is increasingly gaining popularity among Dutch firms, although it remains rather limited compared with the rest of Europe or the United States. Multinationals like Unilever and Shell, but in particular DSM, have already implemented corporate venturing strategies for supporting their technology portfolios. Public stimulation of corporate venturing could also be a way of improving the general (financial) conditions for an entrepreneurial climate in the Netherlands.

4.5 Regulations

Since the 1980s, the Netherlands has been a front-runner in Europe regarding the development of a national legislative and regulatory framework for biotechnology. However, most of these laws and regulations are now set at the level of the European Commission. Table 4-2 presents the main areas of legislation and regulation for both human health and food biotechnology.

Table 4-2 Main areas of legislation and regulation for human health and food biotechnology

General legislation
Contained use of genetically modified organisms (directive 90/129/EC) and *deliberate release* (directive 90/220/EC and 2001/18/EC), which have been implemented in three sets of national regulations: 'Wet milieubeheer', 'Besluit genetisch gemodificeerde organismen' and 'Regeling ingeperkt gebruik genetisch gemodificeerde organismen'
Biotechnology intellectual property rights (directive 98/44/EC), which has not been translated into national regulations yet
Privacy (directive 2001/20/EC), which has been implemented in the 'Wet bescherming persoonsgegevens'
Research involving humans (directives 2001/83/EC, 2002/98/EC) and *clinical research* (directive 2001/20/EC), which have been implemented in 'Wet medisch-wetenschappelijk onderzoek met mensen' (WMO-act) and 'Wet op bijzondere medische verrichtingen' (WBMV-act); both the WMO-act and the WBMV-act govern issues like xenotransplantation (moratorium), gene therapy and the use of DNA-diagnostics.
Biotechnology with humans (directives 90/219/EC and 90/220/EC) and *animals* (directive 86/609/EEC), which are covered by the national regulations for contained use and deliberate release in combination with the WMO-act, the WBMV-act and the 'Wet op dierproeven' (WOD-act).
Research with embryos, which is covered by the recently introduced law 'Embryowet'; this law regulates the use of embryos for scientific research and breeding of stem cells. Cloning and genetic engineering of embryos is forbidden
Human Health
The authorisation and supervision of medicinal products (directive 2309/93/EEC), which has been implemented in the Netherlands in 1995 in the laws 'Wet op de geneesmiddelenvoorziening' (WOG-act) and 'Wet inzake bloedvoorziening';
Orphan drugs (directive 141/2000/EC), for which no specific national regulations exist
Food
Cartagena Biosafety Protocol, which came into force in September 2003 and regulates the international trade in living GMOs. This biosafety protocol has not been translated into European and national regulations yet. In 2002, the EU proposed new regulation to

[24] With corporate venturing, a larger, more established company takes a (minority) stake in a new or young company.

implement the Cartagena Biosafety Protocol (*Transboundary movement of GMOs-Draft regulation*)
Novel foods (Regulation 258/97; 1139/98; 49/2000; 50/2000), which asks for food safety assessments of foods and food ingredients that have not been used for human consumption in the community. In addition, it arranges the labelling of GM foods, GM maize varieties, GM soy varieties, and of GM additives and flavourings
GM food and feed (Draft regulation), which was adopted by the Council of Agriculture Ministers in July 2003. This legislation regulates the assessment and authorization of GMOs and GM food and feed
Traceability & Labelling (Draft regulation), which was also adopted by the Council of Agriculture Ministers in July 2003. This legislation aims to secure traceability of GMOs in food and feed throughout the whole chain. In addition, this directive regulates the labelling of GMOs, food products and ingredients derived from GMOs
Recommendations to ensure the co-existence of GM and non-GM crops, which were announced by the European Commission in July 2003. These recommendations provide guidelines for Member States to develop measures for co-existence in conformity with EU legislation.
Seeds (draft Amendments Seed Directives), which aims to regulate the marketing and labelling of plant seeds derived from GMOs*,* and to establish conditions and requirements for thresholds for the presence of GM material in non-GM plant varieties
Environmental liability (Draft regulation), which was proposed in January 2002 by the Commission and aims to ensure a system of liability to biodiversity

In particular the legislative framework for food biotechnology is rather complex and has been subject to many discussions and amendments (both nationally and internationally) during the past ten years. Although directives on the contained use and deliberate release of GMOs have been into force since early 1990s, a moratorium on the introduction of new GMOs was installed in the EU in 1998. This moratorium makes it impossible to introduce new GMOs and has been into force until today. However, in July 2003 the Council of Agriculture Ministers adopted the proposals by the European Commission for new directives concerning the traceability and labelling of GMOs and the assessment and authorization of GMO foods and feeds. These new directives address various 'gaps' in the previous directives concerning labelling and authorization. The new legislative framework has two goals: 1) harmonization of environmental, food and feed safety assessments of GMOs, GM seeds and GM food and feed within centralized authorization procedures; and 2) consumer choice through traceability and labelling of GMOs, GM seeds, and GM food and feed, also of GM material in non GM food and feed (Schenkelaars, 2003). It is expected that the moratorium will be lifted as soon as the new directives are put into force (probably before the end of 2003).

Generally speaking, both industry and public sector research organisations welcome a sound and strict regulatory framework as it contributes to an increased quality and innovativeness of the biotechnology sector (Niaba, 2003; Schenkelaars, 2003). However, the present regulatory framework in the Netherlands causes a number of serious disadvantages in comparison with other countries. Most of these disadvantages concern the timely length of application and decision-making procedures, the lack of transparency and predictability of procedures, and overlapping tasks and evaluation frameworks of the official authorities (Niaba, 2003; BioCollectief and Schenkelaars Biotechnology Consultancy, 2002). In particular in the area of biotechnology with animals and intellectual property rights, regulatory and legislative issues cause some problems. For the food biotechnology industry, especially legislations concerning field

trials and health claims are considered as problematic. However, regulation on clinical trials has affected the biotechnology industry rather positively.

It is only recently that the government, in particular the Ministry of Economic Affairs, has started to evaluate and investigate the room for improvement of regulations concerning biotechnology. Specific and simple taxation measures for high-technology start-ups and also for investors in high-technology firms could considerably stimulate the entrepreneurial climate (Kern et al., 2003; Ernst and Young, 1998). Moreover, public policies could play a major role in bringing more uniformity in the handling of intellectual property rights at universities and in creating better conditions for the commercial exploitation of academic IPRs. The main initiative in this area has been the start of a consultative platform in 2001 with representatives from industry, universities and other public research organisations, aiming at investigating the possibilities of a nationally co-ordinated IPR policy system for universities. So far, no results have been realised.

Biotechnology with animals

The Dutch law forbids the genetic modification of animals and the application of biotechnology on animals, unless the Minister of Agriculture, Nature and Food Quality issues a license. A license is only issued if no ethical objections exist against the biotechnology activities and if they are considered not to have unacceptable consequences for the health or well being of animals (the so-called 'No, unless…'-policies). Moreover, the Dutch law prescribes two obligatory evaluations by two different authorities, the Dutch Animal Experimentation Committees (DECs) and the Committee for Biotechnology with Animals (CBD). So far, it has proven very difficult and time-consuming for firms and research organisations to obtain the necessary licenses for carrying out biotechnology research involving animals (BioCollectief and Schenkelaars Biotechnology Consultancy., 2002). With this regulation the Dutch government finds itself in a unique position compared to Europe and the United States. In some cases this has led to Dutch biotechnology firms moving some or all of their research activities abroad. It is also expected to have decreased the attractiveness for foreign biotechnology companies to settle their R&D activities in the Netherlands. Although the Dutch regulations for gene therapy, genetic modification of animals and field trials with GMOs were evaluated in 2000 and some changes have been implemented, considerable bottlenecks still exist regarding the length and complexity of administrative procedures and the system of assessment (BioCollectief and Schenkelaars Biotechnology Consultancy, 2002).

Intellectual property rights

The granting of intellectual property rights on biotechnology inventions has been subject to intense political debates ever since the directive 98/44/EC was introduced. The Dutch government has continuously opposed to the EC directive, as it was believed to open the way to patenting the human body or parts thereof and lead to an 'instrumentalisation' of human material. The Dutch government appealed to the European Court of Justice to annul the EC directive; the appeal was dismissed in October 2001. As a consequence, the Dutch government was compelled to effectuate the directive as soon as possible. Nevertheless, the Dutch Parliament adopted six amendments in 2002 that are at odds with the directive. The implementation process got further slowed down by the fall of Dutch government in 2002 and again in 2003. In the summer of 2003, the new IPR law still has not been effectuated, whereas the directive 98/44/EC should have been implemented on the 30th of July 2000 at the latest. This

negative attitude isolates the Dutch biotechnology sector within Europe and affects the overall climate for biotechnology in the Netherlands considerably.

Field trials

In the Netherlands, specific problems concern the regulation on deliberate release, in particular field trials, by the Ministry of Housing, Spatial Planning and Environment. Applications for field trials are arranged by Bureau GGO (GMO Office) and assessed by COGEM (Committee Genetic Modification). In 1999, the minister changed the evaluation criteria, also for previous applications, and decided not to grant the permits for field trials despite a positive advice by COGEM. Moreover, the time needed by the ministry to examine the applications increased from 18 weeks on average in 1996 to 94 weeks on average in 1999 (BioCollectief and Schenkelaars Biotechnology Consultancy, 2002). As a result the number of field trials decreased considerably from 59 in 1999 to 12 in 2001. Moreover, several seed companies like Advanta Seeds, Bejo Zaden, and Syngenta decided to stop their GMO research activities in the Netherlands.[25] Only in 2003 the first permits since several years were granted.

Health claims

An aspect of novel food that has not been settled yet, is the regulation concerning the scientific claims on functional foods. Functional foods aim 'to have beneficial effects on body functions, beyond adequate nutritional effects, that are relevant to improved state of health and well-being and/or reduction or risk (not prevention) of disease' (ILSI Europe, 2003: p5). To communicate these beneficial effects, health-related claims on food-products are used in advertisements and on the packaging of these products. Medicinal claims on food products are prohibited, but health claims (indicating that the food carries a specific health benefit or reduces a risk) are allowed[26]. The basic principle is that claims should be true and not misleading, but the main question is how to ensure this.

International guidelines on food are laid down in the Codex Alimentarius, the food code developed by the FAO and WHO. This code, which has been developed already since the 1960s, is revised several times and the latest revision (in 2003) now also includes definitions and conditions on health claims. However, this codex is not regulation, but a code of conduct which can be translated by the national governments in national guidelines or regulations. At the EU level, there is only EU regulation on dietetic foods, but there is no EU legislative framework for claims on functional foods. At this moment, guidelines on health claims are only implemented and worked out at national levels. In the Netherlands, these claims are verified voluntarily as the Commodities Act (Warenwet) does not include specific rules for health claims. In 1998, the Dutch Nutrition Centre (Voedingscentrum) drew up a code for the use of health claims. This code was formulated with support of regulatory authorities, industry and consumer organisations.[27] Other countries have also developed codes of conduct.

In order to come to a harmonized legislative framework on health claims, the European Commission presented a proposal for regulation on 'Nutrition, Functional and Health Claims Made on Foods' in July 2003. The industry welcomes this initiative, as they will

[25] http://www.projectgroepbiotechnologie.nl/actueel/download/nb13a.html

[26] A medicinal claim states that a food product has the property of treating, preventing or curing human diseases, while a health claim directly or indirectly indicates that consumption of a food product carries a specific health benefit or reduces the risk of a specific health detriment (ILSI Europe, 2003: p.17)

[27] http://www.agriholland.nl/achtergronden/voeding/gezondheidsclaims.html

benefit from one centralized and stringent regulation for health claims on food. Harmonised and stringent regulation will help to enhance consumers' trust, it will streamline the introduction of food products on the European market, and it will exclude 'cowboys' from the market (interviews).

Clinical trials

In the past, the Dutch national regulations and criteria for conducting clinical trials have proven to be less restrictive, compared to many other European countries. The EPOHITE study concluded that it was relatively easy in the Netherlands (and in the United Kingdom), to start with clinical research before having finalised all the pre-clinical studies (Kern et al., 2003). This was believed to be a main reason for the relatively large number of pre-clinical and clinical studies that have been carried out in the Netherlands in the past and the existence of a very large number of contract organisations specialised in clinical research support[28]. Other reasons mentioned are the quality of the Dutch public research system in human health and the highly organised documentation of patient information. Nevertheless, the translation and implementation of the EC directive 2001/20/EC on Good Clinical Practice is expected to level the Dutch situation to the European standards. As a consequence, a decrease in the number of clinical trials being conducted in the Netherlands and a shake-out among the clinical trial support organisations is expected (Kern et al., 2003; interviews).

4.6 Entrepreneurship

"Taking risks and making money is not always looked upon favourably in Holland"(Ernst and Young, 1998). In general, the Netherlands is characterised as a country with a lack of entrepreneurial spirit. This hinders considerably the commercialisation of new scientific knowledge, which is essential for a growing and science-driven high-tech sector such as biotechnology. Many scientists do not seem very willing to leave their academic position and to get fully engaged into business activities and risk social isolation from the academic world (Ernst and Young, 1998). This attitude has led to numerous examples of academics dividing their time in working at the university and in running a company at the same time. Moreover, the average age of the founders of Dutch dedicated biotechnology firms at the time of founding is 41.4 years and the founders have on average 19 years of work experience after education (BioPartner, 2003).

The Dutch government has identified this lack of entrepreneurship in high-tech sectors as an important barrier to innovation. Therefore, a number of programmes have been started. The most relevant for pharmaceutical biotechnology are BioPartner and STIGON that support potential entrepreneurs at universities. Despite the fact that the Dutch government has recognised entrepreneurship as an important issue for its innovation policies, the overall number of initiatives remains limited.

[28] The number of private support organisations in clinical research is estimated at approximately 35 in 2002.

5 Demand Side Factors

5.1 Introduction

In this chapter we discuss the main demand side factors that influence the innovation processes in the biopharmaceutical and the food biotechnology innovation systems. Demand side factors can influence the innovative capacity of firms and research organisations as well as the speed and direction of new developments in biotechnology. These factors differ for the biopharmaceutical and food biotechnology industries. For instance, the national health care system and the regulation of market access are structuring innovation processes in the pharmaceutical sector; in the food sector consumers play a more influential role. Regardless of the field of application, developments in biotechnology have always resulted in strong discussions about the pros and cons of this technology and socio-economic and ethical issues have certainly influenced the further development of biotechnology research and industry.

5.2 Market characteristics of the biopharmaceutical system

5.2.1 Public insurance schemes, reimbursement and price setting

Like in several other European countries, the Dutch health care system is based on a system of public and private insurance schemes (WHO, 1997). First, the Exceptional Medical Expenses Act provides the framework for a compulsory national insurance scheme for all residents in the Netherlands, covering chronic health care risks and catastrophic health expenditures. Second, every resident on an annual income below a yearly-adjusted specified level is compulsorily insured under the Health Insurance Act for normal medical expenses such as general practitioner services, hospital services and dental care. Third, people with an income above the yearly-adjusted specified level can take out private health care insurance.

Under the Health Insurance Act, health insurance companies enter into contracts with health care providers who are paid directly by the insurance companies without financial involvement of the patient. Privately insured patients have to seek reimbursement from their health insurers. In 2003, approximately 50 health insurance companies exist in the Netherlands (Website Zorgverzekaars Nederland).

In the Netherlands only pharmaceuticals prescribed by general practitioners and specialists are reimbursed. Not all pharmaceuticals are eligible for reimbursement. Moreover, the Netherlands operates a co-payment system in which patients are required to meet a part of the costs of their prescribed treatment; only a few pharmaceuticals are reimbursed in full. So-called over-the-counter pharmaceuticals (OTC) are not eligible for reimbursement; they can be bought without prescription. The Dutch government is not able to set prices for pharmaceutical products that are traded and prescribed in the Netherlands; this is the responsibility of the pharmaceutical companies. However, the Dutch government influences the price level by imposing very strict criteria for reimbursement by the public insurance schemes.

Since 1993, the reimbursement of extramural pharmaceuticals has been regulated under the Medicines Reimbursement System (*Geneesmiddelen Vergoeding Systeem* – GVS). Under the GVS, the Minister of Public Health, Welfare and Sports decides, after consultation of the Board for Care Insurers (CVZ), which new pharmaceuticals are admitted to the public insurance schemes and become eligible for reimbursement. Moreover, the Medicines Pricing Act (Wet Geneesmiddelen Prijzen – WGP) gives the Minister of Public Health, Welfare and Sports the authority of setting maximum price levels at which pharmacists are allowed to purchase brand name pharmaceuticals in the Netherlands. The setting of such a maximum price level is based on the average price level for the same active substance in the same therapeutic form in Germany, France, the United Kingdom and Belgium. This system of maximum price-setting has not contributed to the government's aim of cost-containment while retaining the quality of health care, as was hoped for. On the contrary, the maximum price-setting system stimulated a competition in pharmaceuticals merely based on margins rather than on the actual prices, leading to artificial high price levels (Nefarma, 2002).

5.2.2 Explosive growth of medicine expenditure

The expenditures on pharmaceutical products in the Netherlands have continuously been increasing over the last decades. In addition, the growth of the pharmaceutical expenditures has been stronger than the growth of the total expenditures on health (table 5.1).

Table 5-1 Dutch expenditures on health and pharmaceuticals 1994-2000, million US $, PPP

	1994	**1996**	**1998**	**2000**
Total expenditures on health	25166	28233	32036	35766
Total expenditures on pharmaceuticals	2738	3108	3643	4205
Public expenditures on pharmaceuticals	2475	1966	2336	2680
Private expenditures on pharmaceuticals	263	1142	1307	1525
Share of total expenditures on pharmaceuticals from total expenditures on health	10.9%	11%	11.4%	11.8%

Source: OECD Health Data 2002b

The most important reasons for this increase have not been the ageing population or the growth of population, but rather (Gerritsen et al, 2003):

- The introduction of new and more expensive pharmaceuticals;
- The increase in the chronic and preventive use of pharmaceuticals;
- The shift from intramural towards extramural health care;
- Public policies mainly aiming at pharmaceutical pricing instead of efficient prescription and use of pharmaceuticals.

5.2.3 Public health policies

For several years, public health policies in the Netherlands have strongly emphasised cost containment. In particular pharmaceuticals have been subject to cost containment measures, such as the setting of maximum price levels, stimulating the prescription of generic pharmaceuticals and tolerating the parallel import of brand name pharmaceuticals.

The continuously rising expenditures on health care in the Netherlands and its loss of quality forced the Dutch government to introduce measures to deregulate the system and place more responsibilities at the level of individual actors within the health care system. The government acknowledged that targeting cost-containment is not the main solution but has to be combined with measures that increase the effectiveness and efficiency of health care in the Netherlands. Therefore, the Dutch government decided in 2000 to commit the central role in the national health care system to the health care insurance companies, forcing them to take a more active role in the reorganisation of the health care system. In addition, the system for determining the tariffs of intramural treatments has been replaced by the system of Diagnosis Treatment Combination (Diagnose Behandel Combinatie – DBC) in 2003. This system entails a specified price for a complete treatment of the patients, covering the entire process from diagnosis and hospitalisation to the discharge from the hospital.

The new system still shows many growing pains. The fall of the Dutch government in 2003 has led to considerable delay in the development and implementation of the system. Also much obscurity still exists. For instance, it remains unclear how pharmaceutical products will fit into the concept of Diagnosis Treatment Combination and what the consequences will be of the new health care system for new and expensive pharmaceuticals, e.g. biotherapeutics (Nefarma, 2003; BioFarmind, 2003).

As the development of the new health care system remains to be completed, the Dutch government still seems to target pharmaceutical price levels instead of taking a more systematic approach. Mid 2003, the government introduced new measures aiming at reducing the high bonuses and discounts pharmacists receive from wholesalers. In particular, these ‘negative’ price policies by the Dutch government are said to have had and will continue to have a major impact on the willingness of the research oriented (bio)pharmaceutical industry for carrying out R&D in the Netherlands (interviews, Nefarma 2003, EFPIA 2002).

5.2.4 Regulation of market access

Market access of new pharmaceutical products is mainly covered by international regulations that have been implemented in the Dutch Medicines Act (see also Chapter 4). The Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen – CBG) is the Dutch authority responsible for the evaluation and issuing of market authorisations for pharmaceutical products in the Netherlands. CBG also determines whether or not pharmaceuticals should be made available on prescription or not. Pharmaceutical products are evaluated on the basis of criteria that are defined in the Medicines Act; the criteria mainly address efficacy, safety and quality. The CBG carries out the evaluation on the basis of extensive dossiers submitted by the pharmaceutical companies, containing the required information from research studies.

There are two alternative routes for authorisation of the pharmaceutical products:

1. The centralised route or procedure at the European level. This leads to a marketing authorisation that is valid in all member states of the European Union. This centralised procedure is compulsory for market authorisation of all pharmaceuticals based on biotechnology techniques. The procedure starts with the application at the European Agency for the Evaluation of Medicinal Products – EMEA, which was set up in 1995.
2. The decentralised route or procedure. There are two procedures possible: the national procedure and the so-called procedure of mutual recognition. The procedure of mutual recognition entails the recognition of a marketing authorisation provided by a member state of the EU by the other member states. To that end, the member state that issued the first authorisation provides their evaluation report to the other member states. The national procedure is used when the pharmaceutical company desires market authorisation for the Netherlands only or as a starting point for the procedure of mutual recognition.

The Dutch Pharmacovigilance Foundation (LAREB) is responsible for the assessment and registration of adverse reactions of the pharmaceuticals, after market introduction.

It was announced at the formation of the EMEA in 1995 that the procedures governing drug registration would be evaluated and revised every five years. In 2000, the European registration process was revised based on a report by the EMEA. In addition, the European Commission issued a proposal in 2000 for a further rationalisation of the rules and regulations concerning drug registration in order to simplify the complex bureaucratic labyrinth for medicine legislation in Europe. This proposal was welcomed by the pharmaceutical industry and their associations (Nefarma, 2002). However, the actual realisation of the proposal is likely to take a number of years and will imply intensive debates.

As stated in paragraph 5.2.1, the promotion of the prescription of generic drugs has been an important element in the Dutch health policies. However, the concept of generic drugs might prove problematic in the case of biopharmaceuticals (Schellekens and Brouwer, 2002, and Nefarma website). In contrast to the pharmaceuticals that are based on chemical synthesis, no generic copies have been developed and introduced for biopharmaceuticals so far. First, this is because most biopharmaceuticals are still covered by a patent, which makes the development of a generic copy impossible. Second, it is not clear yet which specific requirements the authorities will demand from the dossiers for generic copies of biopharmaceuticals.

A complicating factor is the difficulty to prove that a biogeneric drug has the same properties and effects as the original biopharmaceutical drug. There are hardly any analytical methods available at the moment to fully analyse biopharmaceuticals and to predict their biological effects. As a consequence, extensive clinical evidence will be necessary, in addition to a study of bio-equivalence, before the registration authorities will declare the new biopharmaceutical as a bio-equivalent copy of the original biopharmaceutical. This leads to very elaborated, lengthy and expensive development processes for biogenerics that are comparable to the development process for a totally new drug. This is relatively new for generic drugs and makes the development of biogenerics less attractive (Schellekens and Brouwer, 2002, and Nefarma website).

5.2.5 Role of patients and their organisations

Numerous studies over the last decades have pointed at the importance of users in the process of innovation and new product development (Moors et al, 2002). On the one hand, users in the sense of individuals but also organisations can act as major sources of innovation, as they are often essential in the process of articulating new needs that can subsequently be developed into new innovative products; moreover, they even can act as innovator themselves (see e.g. Von Hippel 1988). On the other hand, users can play a decisive role in the processes of diffusion and adoption of new products or technologies (e.g. Rogers, 1983; Frambach, 1993). This is also true for the Dutch biopharmaceutical innovation system in which two specific categories of users seem relevant: patients often represented by patient organisations, and health care professionals.

Generally speaking, patient organisations represent patients that suffer from a specific disease or disorder. Their aim is to improve awareness and understanding of these diseases and disorders. The main activities of patient organisations are the diffusion of information related to the disease or disorder among their members, and communication with government, public health authorities and welfare services to advocacy the interests of their members in the political arena (Herxheimer, 2003; VSOP website). Patient organisations can influence the lobbying process towards the government, for example in relation to the listing of a new but more expensive drug under the public insurance schemes or the stimulation of specific health research areas.

Patient organisations also interact with pharmaceutical companies. Especially the more integrated (bio)pharmaceutical firms co-operate with patient organisations because:

- Patient organisations can provide important information during the development process of a pharmaceutical product;
- Patient organisations can form an important channel for providing product information to patients, as it is not allowed to advertise drugs directly to patients;
- Patient organisations can pressurise the official authorities responsible for market authorisation of new pharmaceuticals (RGO, 2002; Schellekens and Brouwer, 2002).

At least 400 associations and organisations exist in the Netherlands for patients with a specific disease or disorder (Smit, 2003). A number of them is united in the umbrella organisations of the VSOP (Dutch Genetic Alliance) and CG-Raad (Association for people suffering from chronic diseases and for handicapped people). Almost 60 patient organisations are united in the VSOP and represent approximately 70,000 patients (VSOP website); the CG-Raad consists of more than 130 organisations, which represent 300,000 members (CG-Raad, 2002). In addition, there is the NPCF, the Dutch Patient and Consumer Federation, which represents the more general consumers' interests in the field of health care. The VSOP and CG-Raad are associated to the NPCF together with 15 other organisations.

However, the limited size of the patient organisations and a considerable lack of co-ordination between them reduce the influence they can exert. More co-ordination and co-operation between the umbrella organisations and the individual patient organisations could considerably improve the influence of patients (Smit, 2003). In addition, patient organisations are highly limited in raising funds for their activities. The Dutch government used to finance a substantial part of the organisations' budgets; however, this decreased considerably during the past years. Sponsoring by

pharmaceutical firms could decrease the budget problems of patient organisations. However, patient organisations are often reluctant to (financial) support from pharmaceutical companies, as they are afraid of losing their neutrality and independence. According to Herxheimer (2003) relationships between industry and patient organisations must be uncomplicated and transparent, and not affect the agenda or priorities of the patient organisations.

The relation between the biopharmaceutical industry and health care professionals (medical experts, general practitioners) is very close (Schellekens and Brouwer, 2002). This is to a large extent due to the fact that the introduction of new medicinal products requires extensive education and information of the health care professionals by the pharmaceutical industry. Moreover, market authorisation of new biopharmaceuticals is based on research on a relatively small number of patients; health care professionals are important sources for the necessary additional information that needs to be collected after introduction on the market. Finally, medical experts and health scientists often fulfil the role of advisor to the pharmaceutical or biopharmaceutical firm that is developing a new pharmaceutical product.

5.3 Market issues in the food biotechnology industry

5.3.1 Possible influence of the reimbursement system

The reimbursement system for medicines can, to some extent, also influence the development of functional foods. It is expected that novel food products will be more expensive than the traditional food products. In public discussions on novel food one of the important questions will be who will pay for these new, costly products: the consumers or the insurance companies (Enzing and Van der Giessen, 2003). An example of how the reimbursement system can influence the development of novel foods is the case of gluten free products. Costs for special dietetic food are reimbursed. However, the reimbursement level differs in Europe. In general the reimbursement of costs for dietetic food is much larger in Mediterranean countries than in other European countries. This has resulted in a lower tolerance level for gluten in food products in those Mediterranean countries than in other countries (interviews).

5.3.2 Regulation of market access

Market access of new food products is mainly covered by the Commodities Act (Warenwet), which includes regulations and directives of the European Union. Other important laws concerning food safety and food quality are: the Agriculture Quality Law (Landbouwkwaliteitswet), the Meat Inspection Law (Vleeskeuringswet), the Agrochemicals Law (Bestrijdingsmiddelenwet), the Destruction Law (Destructiewet), the Cattle Law (Veewet), and the Veterinary Medicines Law (Diergeneesmiddelenwet). Other national laws and directives that are related to the introduction of food products on the market concern the best-before-end date, the labelling of contents and amounts of contents, and the packaging of food products. The Commodities Act was established in 1919 and since then this law has been revised several times. The Commodities Act is more or less a framework with some constant propositions, but to which several guidelines, directives and regulations are added. In 1997, the EU Directive on Novel Foods was included in the Commodities Act. It is expected that the new directives on

GMO food and the traceability and labelling of these food products will also be included.

In 2002, the Dutch government decided to establish an independent and centralised agency for safety of foods and consumer products at all stages of the production chain: the Food and Consumer Product Safety Authority (Voedsel- en Warenautoriteit - VWA). VWA is responsible for the inspection and supervision of food products. It has two operating units: the Inspectorate for Health Protection and Veterinary Public Health (Keuringsdienst van Waren) and the National Inspection Service for Livestock and Meat (Rijksdienst voor de Keuring van Vee en Vlees).

A company that is looking for authorization for its new novel food product will need to submit a request (with a complete file) to the authorities of the country EU where the company intends to introduce the novel food products for the first time. In the Netherlands, this is the Ministry of Health, Welfare and Sport. The company will also need to send a copy of this request to the European Commission. The Member State, which received the first request, will asses the safety of the new food product and this assessment and advice will be sent to other Member States for comments. In the Netherlands, the safety assessment is performed by the Committee on the Safety Assessments of Novel Foods, hosted by the Dutch Health Council. After this first assessment a time-consuming process of assessments, comments and decisions by the individual Member States and the European Commission follows. Another route is the route of notification. The route of notification can be followed whenever the new novel food product is equivalent to existing food products. In this case a safety assessment will not be needed; the company only needs to inform the European Commission about the introduction on the market. The latter route will no longer exist as soon as the new directives on GMO food and feed will be put into force.

One of the main purposes of the new directives on GMO food and feed was to come to one central authorization procedure. Safety assessments will no longer be carried out by national authorities, but by a European authority on food safety, the European Food Safety Authority (EFSA). This centralised procedure intends to make the authorisation procedures faster, more transparent and less complex. In principal, the food industry welcomes the establishment of EFSA. The EFSA is still in its start-up phase; it has not been decided upon its information and data requirements and to what extent they will consult advisory bodies of the Member States (Schenkelaars, 2003).

5.3.3 Role of consumers and their organisations

The food industry in general is a rather market-driven industry. In the Netherlands, the food industry introduces hundreds of products every year. Some of these new food products are more science pushed, but most of them originate from ideas that have been put forward by market development. The consumer determines the commercial success of these products: one out of seven introductions disappears very soon from the shelves (Stroeken, 2001).

The food industry considers the lack of public support for food biotechnology as one of the main barriers in the further development and application of biotechnology in food. In the beginning of the 1990s it appeared that, although the first new food products derived from biotechnology could be introduced on the market in the near future, the Dutch public in general, and some non-governmental organisations in specific would

not easily accept these new products. In order to improve this public acceptance the industry tried to start a discussion with consumer organisations and other non-governmental organisations. In 1992, initiated by Unilever, several food companies, consumer associations and other non-governmental organisations started an informal consultation on biotechnology (Informeel Overleg Biotechnologie). This informal consultation existed for several years and resulted in agreements on various issues, e.g. labelling. Additionally, in 1994 an informal consensus group was formed by the Foundation Consumer and Biotechnology (C&B) and the Netherlands' Biotech Industry Association (Niaba) to discuss food labelling. They reached an agreement on voluntary labelling in 1995 (Enzing, 2000b). Although the industry considers the lack of public acceptance as a very important barrier, in 1995 the industry also expected that the public acceptance of biotechnology would have been improved considerably in 2000 (Degenaars and Janszen, 1996).

Contrary to the expectations of the food industry in 1995, the support for biotechnology in food has only decreased since then, especially in the period 1999-2002 (Stichting Consument en Biotechnologie, 2003, based on European Commission, 2003b). The debate on biotechnology in food was again fuelled in November 1996, when transgenic soy was imported to Europe and transported through the Rotterdam harbour. It appeared that a number of food companies did not follow the agreements on voluntary labelling and the protest against the non-labelling policies of these companies increased heavily. In 1999, the biggest retailer of the Netherlands (Albert Heijn, part of Ahold) decided to label the GMO lecithin in their products that contain transgenic soy. This decision has caused food companies to stop using transgenic ingredients and to search for alternative ingredients (Kern en Enzing, 2002). This illustrates also the influential role of retailers in food innovation processes (see also Bijman and Enzing, 1995). Retailers decide whether they will sell the new food products and their decision is based on several issues: will consumers buy these products, do they offer clear benefits to the consumer, and are these new food products safe? Most of all, the retailers want to offer freedom of choice and this is why they aim for origin-labelling (interviews).

Meanwhile, the industry has realised that more work is needed to increase the support of consumers for biotechnology developments in food. The focus on the cost benefits of biotechnology in food has shifted to a focus on consumer benefits. Food companies also increasingly involve scientists, key opinion leaders and health professionals in their innovation processes (interviews). These groups are important because consumers consider them as reliable and trustworthy; they are important intermediaries between consumers and producers. Consumers are involved in a more traditional way; mainly through marketing research and analysis of the preferences of the consumers. Involving consumers more deeply in the food innovation process, which take several years and which are largely unpredictable, is considered as very difficult. Only at a more general level food companies discuss new developments in food with consumer organisations (interviews).

The focus on the demand side of innovations has been an issue in a recent stakeholders' dialogue organised by the Dutch ministry of Economic Affairs. The companies brought forward that they are convinced of the need of a stronger involvement of the demand side in biotechnology innovations. According to the industry, this will be one of the major challenges for the coming years. Communication should no longer focus on technology, research, risks, and safety, but should increasingly pay attention to future

applications and their contributions to social issues. Main issue remains how to enhance this 'demand articulation' (Bureau Blaauwberg, 2003).

5.4 Socio-economic and ethical aspects

Public perception

Since 1991, the European Commission has investigated on a three-year basis the public perception on biotechnology in the European Union (Eurobarometer). The most recent Eurobarometer was carried out in 2002. The Dutch belong to the most knowledgeable and engaged populations in Europe about biotechnology, although, compared to 1999, Sweden and Denmark took over the top position (European Commission, 2003b). In general, the Dutch public supports the various applications in biotechnology, but compared to other European countries, the Dutch public is certainly not the most supportive. The support for medical applications of biotechnology is the strongest and has increased since 1996. However, the Dutch public has a high risk perception and shows relatively low support for transgenic crops and even less when it comes to food (Stichting Consument en Biotechnologie, 2003, based on Eurobarometer 2003). The support for GM crops dropped in the period 1996-1999, but showed a slight increase in 2002 compared to 1999. Contrary to the majority of European countries, the Dutch support for GM food has decreased considerably since 1996.

Socio-economic and ethical issues can have considerable impacts on the development of biotechnology. Almost 40% of the public and private European research organisations have stopped their GMO research during the past four years. In the private sector alone, more than 61% of the research organisations have stopped their GMO research activities. The number of applications for GMO field trials has decreased with 76% since 1998 (Ministerie van Economische Zaken, 2003).

Another result of the last Eurobarometer is the rather weak willingness of the public to participate in public debates (European Commission, 2003b). Has the Dutch public had enough of public debates and consultations? Since the introduction of the recombinant DNA technology (in the mid 1970s), scientists have discussed the ethical, safety and health aspects of biotechnology. Since late 1980s, the general public is also involved in these discussions. Over the years, the public debates expanded from low-profile discussions with a limited number of public and experts to extensive and lengthy debates, which aimed to involve various groups of stakeholders and which included a large set of instruments to actively involve these stakeholders. Table 5.2 gives an overview of the public debates on biotechnology issues in the Netherlands.

Table 5-2 Public debates on biotechnology in the Netherlands

Year	Public debate	Activities
1993	Genetic Modification of Animals	- Publications on genetic modification of animals - Discussion between a lay people panel, an expert panel and the audience
1994-1995	Predictive Genetic Research	- Workshops for scientists and representatives of NGOs - Discussion between a lay people panel, an expert panel and the audience - Extra research by Rathenau Institute
1998-	Clones and Cloning	- Research in present developments in science

Year	Public debate	Activities
1999		- A lay people panel followed the debate - Several consultations - Public opinion survey - International conference on differences and similarities in debates all over the world
1999-2001	Xenotransplantation	- Website for interaction with the general public - Discussions with lay people panels in the regions - National kick-off and closing debates - Website and theatre for students - Public opinion survey
1999-2000	Agrobiodiversity	- Website for interactions about the meaning of agrobiodiversity for the Dutch agriculture
2001	Food and Genes	- Kick-off conference - Websites for interaction with the general public - Discussions with lay people panels in the regions - Involvement of NGOs and schools - Information in popular magazines - Public questions through email, toll-free telephone number, and advertisements in newspapers - Public consultation of experts' visions - Public debates all over the country - Public opinion survey
1998-	Several Internet debates	- BioDebat for students at secondary schools - Biotechfoodforum - Future of Food

Source: Enzing, 2000b; Hanssen et al., 2001; Stichting Consument en Biotechnologie, 2001

Communication and interaction

All stakeholders in the public debate on biotechnology, whether they represent the industry, the scientists or the consumers, agree that the general public should be provided with clear, open and unbiased information. However, there is no agreement on how this should be organised. Consumer organisations demand complete labelling of products, including all the information necessary for consumers to choose. Companies, are more reluctant and have difficulties with how these products should be labelled. The industry realises that it should communicate more than just via the label and tries to provide more information (using their websites, participate in debates). However, consumer organisations point at the 'bias' in this communication. On the other hand, firms and researchers mention that it is very difficult to communicate because of the complexity of the technology. In addition, they complain that interest organisations always stick to their issues and are not willing to think about solutions.

Over the years, the discussions about the development and application of biotechnology in food mainly concerned the use of genetic modification technologies. However, there is a growing consensus about the necessity to inform the public about and involve the public more in new technological developments, but how should this be done? Interviews with researchers in the field show that they are afraid that the discussion and negative emotions concerning genetic modification could cross over to other biotechnologies. The general public could have difficulties to see the differences in new

developments in for instance genomics, DNA chip technologies and genetic modification as all these topics are not easy to understand. The general public simply lacks the knowledge of the specific characteristics of these technologies. The recent food safety crises and the expansion of anti-GMO food lobby to other fields could influence the public opinion on functional foods in a negative way, the interviewees mentioned (Enzing and Van der Giessen, 2003).

Recently, the government concluded that the stakeholders involved in biotechnology development have not succeeded in organising a coherent communication infrastructure. The Ministry of Economic Affairs decided to reconsider its role in biotechnology communication and therefore analysed the communication behaviour of the main stakeholders in biotechnology. One of the main conclusions was that industry, academia and interest organisations have a responsibility and role of their own in communicating with the public, next to governmental initiatives. In addition, the various ministries should intensify their collaboration and develop a coherent communication strategy (Ministerie van Economische Zaken, 2003).

6 Synthesis and conclusions

The previous chapters presented and discussed the Dutch biopharmaceutical and food biotechnology innovation systems (the public research and education system, the industrial system and the demand system) and the institutions and framework conditions. On the basis of this in this chapter the main research questions of the OECD Case Study on Biopharmaceutical and Food Biotechnology Innovation Systems will be addressed. These questions are:

1. What systemic imperfections are responsible for a sub-optimal performance of the pharmaceutical and food biotechnology innovation systems, especially in the business system (see section 6.1)?
2. What elements of framework conditions and horizontal innovation policies are key to foster innovation (see section 6.1)?
3. Is there a relation between the openness of a national system of innovation and its performance, and if so, how open should the system be when performance maximisation is pursued (see section 6.2)?
4. What specific demand side factors influence the biopharmaceutical and food biotechnology innovation processes and what are the effects on the innovation outcomes (see section 6.3)?
5. To what extent and how should innovation policies be customised to the particular needs and features of the biopharmaceutical and food biotechnology innovation systems (see section 6.4)?

6.1 Systemic imperfections

Systemic imperfections can be defined as mismatches between elements in an innovation system (OECD, 1999). They hinder the functioning of an innovation system, reduce the system's overall efficiency and lead to a sub-optimal performance of the system.

The causes for systemic imperfections can be classified into four general categories:
- Missing or inappropriate functions in the system of innovation, e.g. production, diffusion and application of new knowledge, demand articulation, financing of innovation activities, education and training of skilled researchers, etc;
- Missing or inappropriate actors in the system of innovation, e.g. firms and research organisations but also regulatory authorities, users/consumers, funding organisations, etc;
- Missing or inappropriate institutions (institutional rigidities) and framework conditions in the system of innovation, e.g. set of laws and regulations, entrepreneurship, innovative climate, public policies, etc;
- Too much or too little interaction or co-ordination between the elements in the system of innovation.

In this paragraph, the systemic imperfections of the Dutch biopharmaceutical and food biotechnology innovation systems are discussed for the three main subsystems (science base and education, exploitation and commercialisation and demand side) and the framework conditions. Table 6-1 provides an overview.

Table 6-1 Imperfections in the Dutch biopharmaceutical and food biotech innovation system

	Science base and education	**Exploitation and commercialisation**	**Demand side**	**Framework conditions**
Absent / inappropriate functions	Imbalance in knowledge production	Insufficient exploitation of academic research	-	Shortage of risk capital
Absent / inappropriate actors	Shortage of researchers Weakening relations between large food companies and national public research	Limited number of large domestic pharma firms Insufficient relations between large food companies and dedicated food biotech firms Lack of managerial skills	-	-
Absent / inappropriate institutions	-	-	Restricted market access for food biotech applications Lack of public support for food biotech applications	Weak entrepreneurial climate Regulatory barriers Restrictive health care policies
Too much / little interaction and co-ordination	-	Lack of co-ordination of IPR policies of universities	Lack of dialogue between stakeholders Too little co-ordination between fragmented and heterogeneous patient organisations	Too little interaction between ministries

6.1.1 Science base and education

A main feature of the biotechnology industry is its science driven character. As stated in the previous chapters, the Dutch public research system has a good international reputation in the field of biotechnology, human health and agrofood. It has received several positive evaluations and performs rather well in terms of scientific output and impact.

Imbalance in knowledge production

However, analyses of the type of scientific output show that there is an imbalance in knowledge production in The Netherlands. The majority of the Dutch scientific biotechnology publications concern basic research. However, the number of biotechnology publications in basic research did increase hardly during the period 1995/1996 to 1999/2000 (3%); whereas applied research and experimental and technology development have increased rather strong with 35% and 31% in the same period. This shift towards more applied research in the Dutch biotechnology knowledge base could have short-term advantages, e.g. more patents, commercial spin-offs and contracts with industry. However, it could lead to depletion of the biotechnology knowledge base and to difficulties in keeping up with new scientific developments. On the long term this could also have serious consequences for business development in the field.

Shortage of researchers

The availability of qualified technical staff and researchers has become a bottleneck to both public sector research and industry. First of all, the number of students in natural sciences has been decreasing ever since the beginning of the 1990s. The figures for the Netherlands are now one of the lowest in Europe (Third EU S&T Indicators report, 2003). This had its effects on the pharmaceutical and food biotechnology sectors as shortages have emerged in key disciplines as bio-informatics, genomics and proteomics, but also in supporting areas like laboratory techniques. In addition, small firms and universities have difficulties in competing with big industry in contracting skilled researchers due to the more attractive working conditions in larger firms.

Traditional intense relationship between large food companies and national research organisation is weakening

Traditionally, the large food companies have strong relationships with national public research organisations. The large food companies participate in public research programmes and top institutes, set up research programmes together with the government, and outsource a lot of their research to public research organisations. However, due to mergers and acquisitions, the Dutch food companies increasingly become more internationally oriented. R&D facilities are no longer concentrated in the Netherlands, but are based abroad as well. The food companies will also look for research partners outside the home country. This could imply that the traditional strong relation between Dutch large food companies and national research centres will become less intense, and that the Dutch research organisations will only be one of the potential partners instead of the preferred partner. More than ever, only excellent research at Dutch research organisations will attract national and international partners.

6.1.2 Exploitation and commercialisation

The assessment of the commercial performance of the Dutch biopharmaceutical innovation system shows both positive and negative outcomes. The first and perhaps most important positive outcome is the large number of new entrants since 1994. A

second positive feature is the high level of Dutch patenting activity in biotechnology, especially when corrected for country-size. Third, the survey on biotechnology R&D co-operation indicated that Dutch biopharmaceutical firms are involved in a large number of co-operative projects with both national and international partners. This implies that they are actively involved in national and international innovation networks, which is considered as a prerequisite for today's biotechnology innovation trajectories.

Nevertheless, the Netherlands has not witnessed the development of an innovative and prominent biopharmaceutical industry as compared to other countries. The majority of the new entrants have not been able to develop into more mature firms. They remained very small; only a minority has been able to realise structural profits. They are severely limited in intensity and scope of their activities because of their relatively small budgets and the high-burning rates of financial capital to be spent on R&D.

The food biotechnology innovation system gives a very different picture. First, there is only a very limited number of dedicated food biotechnology firms and both in 2002 and 2003 no new firms were established. Only a few of these companies are dedicated to the food industry. Some of these firms have developed into a more mature stage, but none of them has reached an IPO. Second, the survey on biotechnology R&D co-operation showed that food biotechnology companies mainly collaborate with national partners. Traditionally, the Dutch food industry has strong relations with national research centres, but as mentioned before, this could become less intense due to the increased international orientation of large food companies. Third, there is only limited co-operation between the Dutch large food.

Insufficient exploitation of academic research
Considering the fact that many commercial biotech activities have their first start with a new patent, it is generally recognised in The Netherlands that the exploitation of university research through patenting and licensing out, is not highly prioritised. Figures show there is a lack in the licensing of university patents by industry. The institutional support for technology transfer from university research to the private sector such as coaching of young entrepreneurs or mediation in patenting and licensing agreements is insufficient, notwithstanding the growing importance of BioPartner's activities in this. An important cause for this is the absence of the combination of legal, biotechnological and commercial expertise in technology transfer organisations.

Lack of co-ordination in valorisation policies of universities
Dutch universities are relatively autonomous in developing their own policies, there is a large variety in (in some cases underdeveloped and ineffective) academic IPR policies throughout The Netherlands. Co-ordination at the national level is missing, which means that also a platform is missing where universities can learn from each others best practices.

Lack of managerial skills
In many firms, the founder has a scientific background; he/she is not trained in running a company. This lack of managerial skills is not likely to be solved in the near future as the availability of capable staff with both managerial skills and expertise in scientific disciplines and technologies is expected to remain very limited in the life sciences sector.

Business models too much oriented towards R&D

Many biopharmaceutical firms in the Netherlands are heavily focussing on R&D related activities. This is not surprising as the biopharmaceutical sector is highly depending on scientific and technological developments. Moreover, the majority of the Dutch biopharmaceutical firms have been created in the second half of the 1990s or later, implying that efforts have to be made to improve their initial technological base and develop the first applications. Nevertheless, in particular young biopharmaceutical firms have to seek as soon as possible for possibilities to improve their financial position as their budgets are relatively small and their financial burning rates relatively high. Moreover, providers of private risk capital are increasingly reluctant to invest in firms with a high-risk profile. Therefore, young biopharmaceutical firms need to create a business model that integrates R&D related activities with activities aiming at exploiting the firm's knowledge assets on the short term like contract research or licensing out proprietary knowledge. The survey among biopharmaceutical firms performed for this OECD project showed that a large number of Dutch firms are only active in performing R&D; they have no selling activities. This lack in knowledge exploitation and commercialisation could partly be explained by the lack of business skills within these firms. However, also the public promotion programmes for biotechnology start-ups seem to have insufficiently emphasised the importance of business models that integrate both R&D and exploitation/commercialisation activities.

The situation for the dedicated food biotechnology companies is similar to that of the biopharmaceutical firms. The majority of these firms is active in R&D or contract research. Only a few of them are active in production and marketing activities.

Limited number of large domestic pharmaceutical companies

Geographical proximity of large 'integrated' pharmaceutical firms is crucial in particular to young and small firms. Such pharmaceutical firms act as demanding customers for small firms and are an important driver to innovation in their networks (Dahlander and McKelvey, 2003). These large firms have longstanding expertise in the managing of pharmaceutical R&D processes and in downstream activities of the pharmaceutical innovation chain. Dedicated biotechnology firms need this expertise when the start to produce and to market their products.

However, the Netherlands has only two domestic 'integrated' pharmaceutical firms, i.e. Organon and Solvay Pharmaceuticals. They have a considerable share of their global activities in the Netherlands. Despite a few exceptions such as Yamanouchi and Centocor, the largest part of the Dutch (bio)pharmaceutical industry are subsidiaries of foreign pharmaceutical multinationals. These firms have only distinct and relatively small-scale activities in The Netherlands such as packaging and distribution, marketing and sales or clinical research. This implies that the number of near-by clients and co-operation partners and the pool of experienced worked in downstream activities for young high tech firms in this sector remain limited.

Few collaborations between large food companies and dedicated food biotech firms due to lack of track record

Unlike in the pharmaceutical industry, there is not a lack of large domestic companies in the food industry. The majority of the food companies is rather small, but there are several large food and food ingredients companies. Approximately 17 of these companies have adopted biotechnology. Nevertheless, these large food companies do not really have research collaborations with Dutch dedicated food biotechnology

companies. The few partnerships mainly concern clinical trials. According to the large food companies, the dedicated food biotechnology firms lack expertise and technologies the large firms need. The dedicated food biotechnology companies acknowledge the lack of collaborations. According to them, the main reason is that they are too young and too small to be an attractive research partner. They simply lack a track record. In order to build up one, those companies will need to work on convincing the large companies of their capabilities or search for other options to become more experienced.

6.1.3 Demand

In this chapter we have included a separate section (6.3) on the demand side of the biopharmaceutical and food biotechnology innovation systems, dealing with issues that we would recognise also as systemic imperfections. For that reason we will mention them in this paragraph only shortly and refer to section 6.3 for the full text. They are:

- Heterogeneity and fragmentation of patient organisations;
- Lack of dialogue between stakeholders.
- Restricted market access for food biotech applications
- Lack of public support for food biotech applications

6.1.4 Framework conditions

Regulatory barriers

Although regulation for both food biotechnology and pharmaceutical biotechnology is rather complex and strict, it is in particular food biotechnology that is hindered by the existing regulatory framework. Not just the European moratorium on the introduction of new GMOs (installed in 1998), but also the very strict regulation on deliberate release (field trials) has been a serious barrier for food biotechnology companies. The number of field trials has decreased considerably since 1999 and several companies decided to stop their GMO research activities in the Netherlands. Another area of strict and impeding regulation concerns working with animals. The strict regulatory framework causes serious disadvantages, such as the timely length of application and decision-making procedures, the lack of transparency, and overlapping tasks and evaluation frameworks of the official authorities. As a result, industrial research programmes got delayed, licenses were issued too late and some firms even reallocated their R&D activities to other countries. The continuous opposition of the Dutch government to the European directive on biotechnology intellectual property rights, even after the European Court of Justice rejected all Dutch objections to the directive, is another example. This had a negative effect on the image of the Netherlands as an innovative place for companies active in life sciences.

Restrictive public health care policies

This includes a number of systemic imperfections dealing with the Dutch public health care system and public health care policies, which are discussed in more detail in section 6.3.

Shortage of risk capital

Many dedicated biotechnology firms have encountered increasing difficulties in raising financial capital after the start-up phase. Public financial support in the Netherlands has mainly concentrated on the seed and start-up stages and less on the further development stages of these firms. Biotechnology firms therefore have to attract private capital for financing the next stages of business development. However, venture capitalists are

increasingly reluctant to invest in biotechnology firms that are not able to generate a significant turnover yet.

Lack of entrepreneurial spirit
Entrepreneurial spirit is considered as an important omission in the Dutch innovation system as a whole, and also in the biotechnology sector. The BioPartner programme has been designed in order to stimulate and support entrepreneurial scientists to start their own business. However, the non-entrepreneurial attitude is deeply rooted in the Dutch culture and long time nourished by a wealthy national social security system. With France and Italy, The Netherlands occupies the lowest ranks within Europe when it comes to starting one's own company[29].

Co-ordination of government policies
Public policies in biotechnology in the 1990s proved to be inconsistent in several areas as the relevant ministries developed their own policies without proper co-ordination among them. This has led to the situation in which the Ministry of Economic Affairs stimulated the development of a Dutch life sciences sector and some other ministries maintained more restrictive policies. In 2001, the five ministries that are involved in biotechnology policy making presented for the first time a joint outline of future biotechnology policies. In 2003, the Dutch Ministry of Economic Affairs took the lead in addressing again the policy inconsistencies by commissioning an evaluation of biotechnology regulations and by organising a stakeholders meeting on the future development of biotechnology.

6.2 System openness

The openness of a national innovation system contributes positively to the introduction of diversity in the system and the selection of alternatives which are important conditions for successful innovations (Dosi, 1997; Metcalfe, 1994). Moreover, studies have shown a positive relation between the degree of openness of national economies and their international orientation and their performance in patenting (Furman et al., 2001).

In the OECD project, system openness is defined as the extent to which:
- A national innovation system is open to or affected by international factors, such as the presence of foreign firms in the system, co-operation patterns with foreign partners and the international regulatory frameworks governing innovation activities;
- Actors can enter or leave the system; entry and exit dynamics are important for those actors that are directly involved in innovation activities, such as firms and research organisations.

International openness
We would argue that the Dutch biopharmaceutical innovation system has a relatively large degree of 'international openness', for a number of reasons. First, the size of international trade in pharmaceuticals produced in the Netherlands is rather high. Second, many foreign traditional pharmaceutical firms have subsidiaries in the Netherlands. Especially their clinical research activities have contributed considerably to the development of a specialised clinical research sector in the Netherlands over the

[29] Global Entrepreneurship Monitor of EIM (C2W 2 / 31 January 2004).

last decades. Third, the Dutch biopharmaceutical industry has developed an extensive international network through collaborative R&D-projects with foreign partners. Fourth, international regulatory frameworks at European and global level are increasingly governing the Dutch biopharmaceutical innovation system. It removes legal and regulatory differences between countries that could harm international competition and performance. Last but not least, the Dutch economy in general, through its size, its geographical position and its trading activities, is recognised as an open economy; this is reflected in the biopharmaceutical part of the Dutch economy.

The Dutch food industry is highly internationally oriented, when taking into account large import and exports of food products in the Netherlands, and the large direct foreign investments. The strategic location of the Netherlands in Europe has attracted several foreign multinational food companies to the Netherlands. Nevertheless, the food biotechnology innovation system has a lower degree of 'international openness'. The survey showed that over 50% of the R&D partners of the Dutch food biotechnology companies originate from the Netherlands. Compared to the biopharmaceutical firms, Dutch food biotechnology companies do not really have an extensive international network. One reason could be the traditional strong relationship between domestic food companies and national research centres. International acquisitions and mergers lead to increased internationalisation of the Dutch food companies. This could also result in more internationally oriented networks and relocating R&D activities abroad.

Business entry and exit

Since 1994, a growing number of new dedicated biopharmaceutical firms has entered the Dutch biopharmaceutical innovation system. They have contributed to the diversity in the system as they are specialised in specific technologies and product platforms, covering different types of activities in the pharmaceutical innovation process. Moreover, they have contributed to the convergence between pharmaceutical and agrofood sectors, opening a window of opportunity for innovations, e.g. in the area of nutriceuticals and functional foods. The dedicated biopharmaceutical entrants have explicitly influenced the performance of the whole Dutch system as they have been the main contributors to the growth in biopharmaceutical patent applications in the period 1995-1999.

The degree of openness in terms of 'firms leaving the system' seems rather limited. Business exit has hardly occurred since 1994; only very few biopharmaceutical firms went bankrupt, merged with other firms or were acquired by other (large) firms. However, one can expect more exit dynamics in the years to come. Not all biotechnology firms that have been started over the last years – most of them stimulated by the BioPartner programme - are expected to survive. The reasons have been mentioned before: lack of public and private capital, lack of customers in close geographic reach, lack of managerial skills and lack of entrepreneurial spirit, etc.

Since 1994, the increase in the number of dedicated food biotechnology firms has been very limited. In 2002 and 2003 no new dedicated food biotechnology firms have been started. Several agro biotechnology companies working on genetic modification of plants have stopped their activities, mainly because of the difficult regulatory situation in Europe and the Netherlands. Nevertheless, it will not be easy for the dedicated food biotechnology companies to survive. Reasons are similar to those for the biopharmaceutical companies, but also include insecurity concerning the regulatory

framework, the lack of public support for food biotechnology applications, and strict market access regulations.

6.3 Role of demand

Demand side factors can play a significant role in the speed and direction of new technological developments and in the outcomes of industrial innovation processes. Three demand issues seem highly relevant to the functioning of the Dutch biopharmaceutical innovation system. We only mentioned them in section 6.1; this section will present them in more detail.

Dutch health care system and health care policies
The organisation of the Dutch national health care system is an element of the demand system that affects the biopharmaceutical innovation system considerably. It determines to a large extent the maximum price levels of pharmaceuticals, the way they are distributed and marketed and their reimbursement. Like in many other countries, Dutch health care policies have emphasised heavily cost-containment, as the total expenditures on health care, and in particular on pharmaceuticals, increased constantly over the last decades. Most of the measures were targeted at directly influencing the price-level of drugs. Moreover, prescription of generic pharmaceuticals and the parallel import of brand name drugs were stimulated. Recently, the Dutch government has introduced a new system based on decentralisation and deregulation. Cost-containment in this new system is also addressed through improving efficiency and effectiveness in the health care sector as a whole. However, the implementation of the new health care system has been delayed due to political instability in the Netherlands. Also many open ends still exist. One open end is the unclear position of expensive medical treatments in the new reimbursement system. This uncertainty is regarded by industry as highly unfavourable for the development of new (and more expensive) medicines including those based on biotechnology.

Lack of input of patient organisations in the innovation process
The second demand issue deals with the mobilisation and articulation of demand by patients' organisations. Several hundreds of these organisations advocate the patients' interests in The Netherlands. As lobby groups, they are in intensive communication with the government about for instance the reimbursement of new expensive pharmaceuticals or the stimulation of public research for specific diseases. The individual patient organisations, each focussing on one specific disease, are rather small and only have a limited budget as governmental subsidies have been heavily scrutinised over the recent years. This heterogeneity and fragmentation has resulted in an important lack of critical mass and limited financial possibilities. As a consequence, patient organisations have not been able to fully exploit their expertise in the innovation process. On the other hand, the patients organisations are also often not fully recognised by industry as partners that have knowledge to be used as an input in the innovation process and that can help them for instance in recruiting patients for clinical trials. The involvement of patient organisations in the innovation process remains rather limited which is also caused by the reluctance of these organisations in maintaining intense relations with pharmaceutical firms; they have the fear of losing their neutrality and independence.

Restricted market access for food biotech applications
Regulation of market access for new food products is rather complex. Dutch regulation is harmonised with the European system; however, this has not made things less complex. Authorisation is a time-consuming and costly process. In addition, in 1998 a moratorium on new GMOs was installed. This made it impossible to introduce products containing new GMOs on the market. Since then, the European Commission has debated for a long time on new directives on GMO food and feed. Only in July 2003, the new directives for labelling and authorisation were adopted by the Council of Agriculture Ministers. It is expected that the moratorium will be lifted as soon as these new directives are put into force.

Another difficulty in market access for new food products based on biotechnology applications is the lack of clear regulation on health claims. This is especially relevant to functional food products, because these products intend to have beneficial effects on body functions. At the moment, there is no clear regulation on the distinction between health and medical claims. There is no EU legislative framework and harmonisation between the various Member States is lacking. This makes the introduction of functional food products more difficult.

Lack of public support for food biotech applications
The food industry considers the lack of support for food biotechnology as one of the main barriers in the further development and application of biotechnology. Although several initiatives to improve the public acceptance have been started since the beginning of the 1990s, the support for biotechnology in food has only decreased since then. The food industry has realised that more work should be done to increase the support of consumers for food biotechnology. They shifted the focus on the cost benefits of biotechnology to a focus on the consumer benefits.

Lack of open and constructive communication
One very important condition for the successful introduction and implementation of biotechnology in the health and food sectors is the existence of open and constructive communication about biotechnology, its applications, its advantages but also its disadvantages. So far, the current stakeholders in the biotechnology debate, i.e. representatives from industry, science, government and consumers, have not been able to realise effective structures or platforms for open dialogues and communication, as the Dutch government stated late 2003 (Ministry of Economic Affairs, 2003).

6.4 Policy implications

An important goal of the OECD-project ‘Case Studies in Innovation’ is to formulate policy implications resulting from the analysis of national biopharmaceutical innovation systems. One of the underlying reasons is the growing attention for so-called systemic instruments in innovation policies, which enables policy makers to address the relevant aspects of national innovation systems.

In this section policy recommendations addressing the three elements of the innovation system and the framework conditions are formulated. The interviews held in March – June 2003 have been an important input for the identification of systemic failures mentioned in sections 6.1 and 6.3. At the time of drafting this chapter an important number of these failures had been addressed by the Dutch government in the new

Action Plan Life Sciences, published early 2004. The Action Plan Life Sciences (presenting the government's ambitions and aims in the area of life sciences for the period 2004-2007) includes several measures related to the issues of entrepreneurship, growth of young biotech firms, simplification of laws and regulations, renewal of the life sciences knowledge base, international networking and partnerships, and a clear and consistent governmental communication.

For the case study this implied that a number of policy recommendations needed no longer to be made, although some of the measures still need to be designed in detail.

A last remark that has to be made is that it is not always evident that in the case of all systemic imperfections new national intervening public policies are the only or most relevant means by which the identified imperfections should be addressed. In many cases the involved actors have their own responsibilities to realise the changes needed. In these cases, national public policies could have a more supportive role.

6.4.1 Science base and education

The analyses show that the quality of Dutch scientific research in the field of biotechnology is rather good. Concerning the performance in terms of scientific output and impact The Netherlands belongs to the best performing countries.

However, there is an **imbalance in knowledge production** as there is a clear emphasis on applied research. If this trend will continue, this could lead to depletion of the knowledge base and difficulties in keeping up with new scientific developments. Policy measures already have been taken through which the balance between basic and applied research can be redressed. The recently started genomics research programme of the Netherlands Genomics Initiative (NGI) has a strong basic research component. The coming years (the programme will run until 2007) at least 189 million euros will be invested in genomics research and research facilities. In addition, 12 life sciences projects - partly genomics, partly other life sciences area's - with a total budget of 153.9 million euros will start in 2004 (financed by ICES/KIS3 – Bsik).

Although genomics is considered in the National Genomics Programme as a very broad research field, which covers the development and integration of genomics tools in a wide range of scientific disciplines, it should be mentioned that life sciences and biotechnology is more than genomics. A post-genomics era will eventually develop. The Action Plan Life Sciences announces that the Ministry of Economic Affairs will start a new foresight process as a result of which new promising life sciences fields could be identified and selected for funding.

The **availability of qualified technical staff and researchers** has increasingly become a bottleneck to both public sector research and industry. Small firms and universities have increasing difficulties in competing with big industry in attracting skilled researchers. Campaigns have been organised to attract students (some especially addressing women) to the natural and technical science studies. In the field of life sciences several universities and institutions for higher education have started new education programmes or redesigned their programmes in order to become more attractive for students. Most universities also raised the salary for PhD students. It is only now that the first small numbers of graduates in these disciplines enter the labour market.

These problems have been recognised by policy makers in education and S&T policies. The Ministry of Education, Culture and Sciences recently published the 'Nota Kenniswerkers / Deltaplan beta/techniek' (Ministry of Education, Culture and Science) OCW, 2004). The document mentions that on the mid term there will be a shortage of approximately 120,000 'knowledge workers' (kenniswerkers), especially natural scientists and technologists in the Netherlands. The ministry has allocated a budget of 60 million euros and will install a platform. The latter is a group of experts that will advice the minister on how to realise an increase of 15% (in 2007) in the number of students that choose natural science and technical studies and an increase of 15% (to be realised in 2010) of the number of students that finish these studies. Also the complex entrance procedures for knowledge immigrants will be simplified. Together with the Ministry of Economic Affairs the 'Battle for the Brains' study that will benchmark the Netherlands competitive position in attracting foreign knowledge workers will be drafted later in 2004.

6.4.2 Exploitation and commercialisation

The European paradox implying that Europe is strong in science but weak in its commercial exploitation is also true for The Netherlands. A number of systemic failures that contribute to this low level of biotechnology commercialisation will be addressed by new national policies formulated in the Action Plan Life Sciences. It includes a number of new and old instruments for the stimulation of biotechnology business development in the Netherlands.

The Action Plan Life Sciences also addresses the **insufficient exploitation of academic research** and **the lack of managerial skills.** A pilot project will start that has as its main goal to upgrade the quality of the business plans of starting and growing life sciences companies by offering easy accessible experts in the field of general management, financing, marketing strategies and intellectual property rights (budget: 3 million euros to finance the start of the project).

Policy recommendation: In addition, we would recommend introducing measures that stimulate learning processes and knowledge transfer between firms*;* e.g. through instruments that support exchange of knowledge and experiences between large and small firms, so the latter can learn from the large firms' expertise in managerial and downstream business functions skills.

A related issue is the **mediocre quality of the valorisation policies by Dutch universities and public research organisations**. This issue has been identified by the Ministry of Education, Culture and Sciences in its Science Budget 2004. The ministry intents to clarify the rights and responsibilities of universities and public research organisations attached to their tasks of valorisation and exploitation of public sector research. Moreover, it will initiate in 2004 a study on best practices for organisational and juridical valorisation models, in particular related to EU regulations and procedures. In addition, the new TechnoPartner programme will include a measure for subsidising valorisation activities at universities and other public research organisations, i.e. the 'Subsidieregeling Kennisexploitatie'.

Policy recommendation: Despite the current governmental initiatives, a number of issues seem to receive insufficient attention. First, the exploitation of public sector research should be stimulated more intensively. Clear stimuli need to be introduced like the inclusion of IPR indicators in review and evaluation procedures. Second, there is

still a lack of uniformity or co-ordination between public sector valorisation policies. Learning processes for identifying the best valorisation policies and related infrastructures remain very limited. A platform should be created that facilitates the process of mutual learning. Third, government, universities and public research organisations should take into account that successful valorisation of public sector research needs a qualified supportive infrastructure. This means that sufficient financial resources and highly qualified human resources should be allocated to technology transfer and valorisation units. In this regard, the 'Subsidieregeling Kennisexploitatie' is promising although it mainly provides (limited) financial subsidies.

With respect to the **limited number of large domestic pharmaceutical companies,** we acknowledge the activities of regional development agencies in the Netherlands and the economic departments of the Dutch embassies throughout the world to attract foreign firms to The Netherlands. The Netherlands Genomics Initiative has formulated as one of its valorisation goals to attract high tech genomics companies to The Netherlands. The Action Plan Life Sciences also addresses this systemic failure; one of its actions is to stimulate international commercial cooperation and attracting knowledge intensive businesses to The Netherlands. However, one of the major Dutch pharmaceutical firms, Organon, has indicated several times that perhaps the US, as it is their largest market for a number of products, could be a better place to locate their R&D-headquarters.

Policy recommendation: We would recommend to policymakers not only to address the issue of attracting foreign firms, but also the aspect of keeping foreign and domestic firms in The Netherlands.

6.4.3 Demand side

The patients' organisations would benefit considerably if critical mass could be realised through more **co-ordination and interaction** between them. Umbrella organisations such as the VSOP have aimed at increasing such co-ordination and even integration between the patients' organisations, but limited results have been achieved so far. A crucial factor is their financial resources. Public funds have always been the patients' organisations main financial income as they have chosen to keep the private contributions by their members to a minimum level. Also industry would benefit from more co-ordination and interaction as this would strengthen the patient organisations in the process of bringing in their medical and health needs into the industrial innovation process and in facilitating clinical trails.

Policy recommendation: The current worrisome economic perspectives have forced the government to critically investigate the number, scope and size of the public subsidies. Patient organisations have been spared in the most recent evaluations. We would recommend not to initiate new cuts, but to investigate the possibilities of supporting the patients' organisations in realising the necessary internal interaction and co-ordination and to explore how the interaction between patients' organisations and industry through patient-industry networks can be stimulated.

An important explaining factor for the decreasing public acceptance for biotechnology in the Netherlands is the very limited **dialogue** between industry, public research organisations and 'the public'. Research showed that especially university researchers are one of the highest scoring groups that are trusted by the public as information sources for biotechnology (Stichting Consument en Biotechnologie, 2003). Communication and dialogue are also addressed in the Action Plan Life Sciences. The

five ministries involved will set up a communication plan. Activities mentioned that can be included in this plan are to make available 'objective information' on life sciences through a virtual knowledge centre and to start a dialogue between industry, science and consumers.

Policy recommendation: In order to facilitate this process we would recommend including instruments that stimulate researchers to qualify themselves in communication about their research to lay people, including their own personal thoughts and doubts. Additionally, it is recommended to create conditions for discussing the demands and needs in society that can be addressed by life sciences. Initiatives of responsible actors in this could be supported and firms and research organisations could be stimulated to communicate with these actors.

6.4.4 Framework conditions

The Action Plan Life Sciences announces the introduction of a new instrument (Technopartner Seedfaciliteit), which main goal is to attract risk capital from the private market, to increase the number of venture capitalists, and to improve the quality of venture propositions and the management. This instrument will support young companies (it is a generic instrument, not specific for biotech) that have gone through their first growth stages. Through this, the 'financial gap' that start-up companies meet after their first growth phase, can be filled up. The Ministry of Economic Affairs has allocated a budget and seeks for additional funds. In the meanwhile, also other organisations (Biopartner) are developing plans for setting up risk capital funds (on the basis of corporate venturing fund) that address **the lack of risk capital**.

The Action Plan also mentions a number of actions focussing at the simplification and at having a considerable decrease in the number of the **regulations**, including harmonisation of Dutch regulations (such as genetic modification of animals, IPR) with European regulations. The ministries involved have agreed, for instance, upon the need to decrease the period needed for granting permission in The Netherlands to the European average as a maximum. While the former minister of Environment blocked - against the advice of an independent Advisory Council - the permit for field trails with genetically modified plants, the new minister has chosen for the policy of 'Proceed with Caution'. The Rathenau Institute has prepared an advice concerning an 'Integral Ethical Review Framework' for biotechnological developments.

Health care policies and related measures highly influence the development of and demand for innovative pharmaceuticals. In particular the increasing expenditures on pharmaceuticals have led to important changes in the public health care system, mainly aiming at cost-containment. Like in many other countries, the Dutch government has pursued this to a large extent by stimulating the prescription of generic pharmaceuticals, which are much cheaper than new innovative pharmaceuticals, and even by promoting the parallel trade of cheaper in-patent pharmaceuticals. The set of health care policies that target pharmaceuticals have proved to be restrictive and affect in a negative way the innovative performance of the Dutch (bio)pharmaceutical industry. First, the attractiveness of the Dutch market for *introducing* innovative pharmaceuticals is decreasing as the current system puts the prices and market shares of innovative pharmaceuticals increasingly under scrutiny and favours cheaper but less innovative pharmaceuticals. Second, the attractiveness of *developing* innovative but expensive pharmaceuticals is decreasing as the uncertainties of return on innovation investments

on the Dutch market are increasing. So far, the development and implementation of a new health care system in the Netherlands has been slowed down.

Policy recommendations: We acknowledge the necessity of measures that lead to a decrease in costs of health care and in particular pharmaceuticals. However, the proposed measures could affect the Dutch innovation oriented pharmaceutical and biotechnology industry in a negative way. Clear information is needed concerning the future position of innovative but more expensive pharmaceuticals in the Dutch health care and reimbursement system. In this context, we want to stress the importance of taking into account the benefits of innovative pharmaceuticals and how they can contribute to cost-containment in health care on the long term e.g. by increasing effectiveness of treatments resulting in shorter treatment periods.

The **lack of sufficient interaction between government departments,** that was identified during the interview period and before, is increasingly getting attention as can be concluded form the Action Plan Life Sciences. The Action Plan mentions on several occasions the so-called 'Interdepartementale Overleg' between the involved Ministries of Economic Affairs, Agriculture, Environment, Education and Science, Public Health and Justice for reaching an improved policy interaction and co-ordination. For several policy issues (regulation, communication, R&D-investment), some or all ministries are involved in the decision-making.

Policy recommendations: The majority of the co-ordination and interaction issues being tackled by the Action Plan Life Sciences regards the entire area of life sciences, including issues affecting the biopharmaceutical innovation system. However, the co-ordination and integration of the policies aiming at innovation on the one hand and health care on the other hand seems relatively underexposed in the Action Plan. We have seen that the current health care system and related policies can be highly counter effective to the policies that aim at stimulating innovation. A more systemic policy approach is needed that combines the objectives of a competitive pharmaceutical industry and of an affordable public health care system.

Biotech transfer to 'followers'

In this section the systemic imperfections in the Dutch pharmaceutical innovation system are discussed and policy recommendations have been formulated. Given the set of biotechnology policies in the Netherlands we can observe that there is already a balanced mix of instruments that target most of the relevant aspects of the biotechnology innovation system: the creation and sustaining of a competitive biotechnology science base, its exploitation and commercialisation, communication and stakeholders dialogue and the framework conditions.

An instrument that is missing deals with technology transfer to those companies that are not active in biotech R&D, but for whom biotechnology could contribute to cheaper, safer and/or faster production processes. In some other countries this type of instruments have been proved very successful (e.g. BIOWISE programme in the UK).

Policy recommendation: application of new life sciences and technologies in companies that do not perform R&D in this field themselves can lead to new and improved processes and products. The feasibility of a specific instrument that stimulates this should be evaluated.

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- Nefarma: www.nefarma.nl
- Numico: www.numico.com
- Projectgroep Biotechnologie: www.projectgroepbiotechnologie.nl
- Royal Netherlands Academy of Arts and Sciences (KNAW): www.knaw.nl
- Unilever: www.unilever.com
- Vereniging Samenwerkende Ouder- en Patientenorganisaties (VSOP): www.vsop.nl
- Zorgverzekeraars Nederland: www.zn.nl

8 Interviewed persons

Dr. Alkema, Kiadis

F. Balemans, Synthens

A. van Bellen, Stichting Bloedlink Patienten Netwerk

Dr. R. Beudeker, DSM

Dr. A.D. de Boer, Genetwister Technologies B.V.

Dr. M. van der Graaff, Nefarma

Ir. J.G. Hanstede, BioFarmInd

Ir. M.J.B. Jansen, Centraal Bureau Levensmiddelenhandel

Dr. F.W. Janssen, Nederlandse Coeliakie Vereniging

J. de Jong, Synthens

P.W.T.J. Leufkens, AM-Pharma

Dr. R. Oskam, Genzyme Europe

Dr. C. Smit, VSOP

Dr. H. Theunissen, Organon

Dr. F.M.A. Thomassen, Nutriscience

Dr. H. Zevenbergen, Unilever Research and Development