



**Fraunhofer** Institute  
Systems and  
Innovation Research

## **OECD TIP**

# **Case study on biotechnology innovation systems**

## **National Report Germany**

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# **1 Introduction**

## **1.1 Goals**

As the TIP Working Group of the OECD concluded, the development of new policy initiatives asks for a deeper understanding of the sector- and technology-specific properties of innovation systems. Accordingly, the working, structure and dynamics of a sector in developing, producing and selling products and services need to be described. A too general public policy has the danger of misfits; it is not tuned to the specific characteristics of the technological or sectoral innovation system at hand. The development of new policy initiatives that stimulate and support the rapid development in national innovation systems asks for an understanding of the idiosyncratic properties of the system. This project wants to contribute to an understanding of these differences in the national innovation systems by providing a careful analysis of a certain section, pharmaceutical biotechnology, of the biotechnology innovation systems in OECD countries.

Biotechnology has become the driving force of dramatic changes of the innovation process in various sectors. This is illustrated best by the pharmaceutical industry where the traditional chemical paradigm of drug discovery and development is replaced by a new biotechnological paradigm. This has important consequences for the structure and functioning of the pharmaceutical biotechnology innovation system: biotechnology firms and public sector research organisations are becoming key actors generating the new knowledge, tools and substances for the pharmaceutical industry. Regulations, standards, IPR-schemes have to deal with new types of components, and on the demand side new solutions for so far unmet needs are emerging.

The current state of biotechnology differs considerably between countries. A number of factors might be responsible for such differences. In the case of pharmaceutical biotechnology diverse health care systems, product approval regulations and procedures, or demand configurations can generate different feed backs into the R&D process. The growing internationalisation of the pharmaceutical industry may exert increasing competitive pressure on national biotechnology innovation systems. Public R&D promotion might compensate unfavourable demand conditions. Education systems are adapted differently to the changing requirements of the life sciences industry. Public perception of biotechnology developed along different paths. In order to understand the role of these and other forces in shaping the configuration, dynamics, and performance of the various national biotechnology innovation systems, international comparisons are required.

The **general aim** of this project is to fill this gap by elaborating a systematic comparison of biotechnology innovation systems in OECD countries. On the basis of cross-country analyses and an explanation of the national differences, policy conclusions can be drawn as regards the balance between horizontal innovation policies and measures that take into account the more sectoral or technological characteristics of innovation processes.

Given the specific characteristics of national innovation systems in the participating countries and the role public policies can play in the management of innovation processes in order to correct systems imperfections, a set of key questions specific for biotechnology innovations can be formulated.

Starting from the general key question,

*“Can we identify important differences and similarities in the structure and dynamics of national biotech innovation systems of the participating countries which explain the performances of these systems, and what are the policy implications?”*,

the project focuses on more specific questions dealing with four main issues to be investigated: systemic failures and fits, system openness, demand-side factors and systems policies. Although the concept of national innovation systems addresses many research issues we think that these issues are in particular relevant to the biotechnology innovation system.

First, systemic failures can be seen as symptoms of sub-optimal innovation systems and are judged as being a rationale for innovation policy actions, next to other rationales. However, an in-depth investigation of these systemic failures and their implications for policies is lacking so far for biotechnology. The investigation of these systemic characteristics is one of the main goals of the overall research project ‘Case Studies in Innovation’ as formulated by the OECD (DSTI/STP/TIP(2002)1), and therefore is a main issue in this project.

Second, 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, the presence of foreign companies such as major pharmaceutical multinational companies in a country, and international regulative frameworks. This national-international dimension of system openness is especially relevant to national policy-making.

Third, 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

been relatively unattended. What are the effects of these demand side factors on the biotechnology innovation process and how should they be taken into account by the research, business and policy communities? We feel that an investigation of demand side factors and their influence on national innovation systems is needed.

And fourth, a specific objective of the OECD 'Case Studies in Innovation' 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 (DSTI/STP/TIP(2002)1).

In this report the results of the case study on Germany are presented. In parallel, case studies on the Netherlands, Spain, Belgium, Finland, France, Japan and Norway were carried out.

## **1.2 Approach**

The approach and methodology of the national case study of Germany are described in detail in the guidebook for the case study on biotechnology innovation systems from December 2002 which was developed by the biopharmaceutical focus group and is used as common methodological framework (Enzing et al. 2002).

Basically the methodology consists of four interrelated steps:

- (1) Descriptive analysis of the national biotechnology innovation system. In this part the actors (organisations) that are involved in the biopharmaceutical innovation system, their interactions and the framework conditions (institutions) that govern the activities of the various organisations are described.
- (2) Bibliometric and patent analysis. In order to get an overview of the performance of the biopharmaceutical innovation system various indicators are used for measuring the scientific and technological output of the system.
- (3) Company survey on cooperation. For getting additional information on the structure of the biotechnological innovation system a survey was performed asking biotechnology firms which are active in the pharmaceutical area to indicate their cooperation behaviour with other firms and with universities and public sector research organisations.
- (4) Interviews with selected companies, sector experts and demand side actors (e. g. representations of patient organisations and physicians' associations).

In addition to these four basic steps extensive desk research covering existing literature and also analysing available statistical information was carried out.

## 1.3 Country characteristics

### 1.3.1 General information

With a population of 82,259,500 (in 2000) corresponding to 7.3 % of total population of OECD countries Germany is the largest European Union Member State (Statistisches Bundesamt 2002a). The German gross domestic product (GDP) amounted to 2,025 million € in 2000.

The economic environment in Germany in the 1990s has been largely influenced by the German reunification in 1989. Despite of the post-reunification economic problems (reflected in high unemployment rates and structural differences between regions), in the second half of the 1990s Germany has gradually increased its investment in R&D. The total R&D intensity rose from 2.26 % in 1994 to 2.44 % in 2000 (Grupp et al. 2003). This increasing R&D intensity is largely due to R&D investments from the industry sector which increased its contribution during the 1990s and was responsible for 65.7 % of the total R&D investment in 2000 compared to a ratio of 61.4 % in the year 1994. For comparison, at the OECD level in particular Sweden and Finland achieve much higher R&D intensities (Sweden: 3.9 % in 2000, Finland: 3.4 % in 2000), Japan had a ratio of approximately 3.0 % in the year 2000 and the USA, Switzerland and Korea invested approximately 2.7 % of their GDP into R&D. On the other hand, the German R&D intensity is well above the intensity of the other big European countries France and Great Britain (Grupp et al. 2003).

According to the Report on Germany's Technological Performance from 2003 (Grupp et al. 2003) Germany's performance in general can still be considered as well. However, if a differentiation between sectors according to their R&D intensities is made, it turns out that during the years 2001 and 2002 in particular the high-tech industries<sup>1</sup> started to lag behind the most dynamic international developments. This is mainly due to a slump in the IT sector which was responsible for a 10 % cut in production volume of high-tech firms in the year 2002 compared to the year 2001. On the other hand, the medium-tech sector<sup>2</sup>, was still very successful in Germany in particular in securing a very favourable international trade position. However, this is mainly due to the performance of the automotive industry. Other important sectors in this group such as the chemical industry and mechanical engineering experienced a continuous decrease of their international competitiveness. According to Grupp et al. (2003) those indicators describing established structures (such as indicators for external trade and economic structure)

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1 Defined as sectors with an R&D intensity above 8.5 %.

2 Defined as industries investing between 3.5 and 8.5 % of their sales into R&D.

still present a very favourable picture of the German competitiveness. However, other indicators measuring investive activities which are important for a future structural change (such as expenditures on education, R&D and investment into information technology) give a less positive picture of Germany. The report concludes that following a period where industry had a focus on making innovation processes more efficient the time has come now to move again towards expansion in R&D and innovation. The challenge for innovation policy in this context would be not to act procyclic, but rather to use technological and economic potentials as rating scales for designing and implementing innovation support.

### **1.3.2 Main industries**

The main industries in the German economy are motorvehicles with a turnover of 238,251 million € in 2000, followed by electronics and electrical engineering (turnover 257,912 million €), machinery and equipment (turnover 151,760 million €), the chemical industry including pharmaceuticals (turnover 133,993 million €), the food industry (turnover 120,353 million €) and construction (turnover 108,732 million €) (Statistisches Bundesamt 2002b). Similar to other major economies also in Germany the service sector is gaining significance. Between 1991 and 2000 the share of total manufacturing in total gross value added decreased from 36 % to 30 % to the expense of the service sector which grew from 62 % to about 69 % in the same period (BMW 2003).

However, the service sector in Germany remains less important compared to other major economies of the OECD. For example, in the year 1998 its contribution to total gross value added in Germany was 68.2 % compared to 73.7 % in the United States, 72.3 % in France and 70.5 % in Great Britain. On the other hand, total manufacturing is more important in Germany compared to these countries gaining a share of 22.5 % in total gross value added compared to 16.9 % in the United States, 17.9 % in France and 19.3 % in Great Britain (OECD 2001). This structure of the German economy is also reflected in the structure of employment: 33.5 % of total employment in Germany is provided by total manufacturing industries compared to an OECD level of 26.8 % (Statistisches Bundesamt 2002a). In the service industries 63.8 % of all jobs are provided in Germany compared to an OECD ratio of 70.3 %.

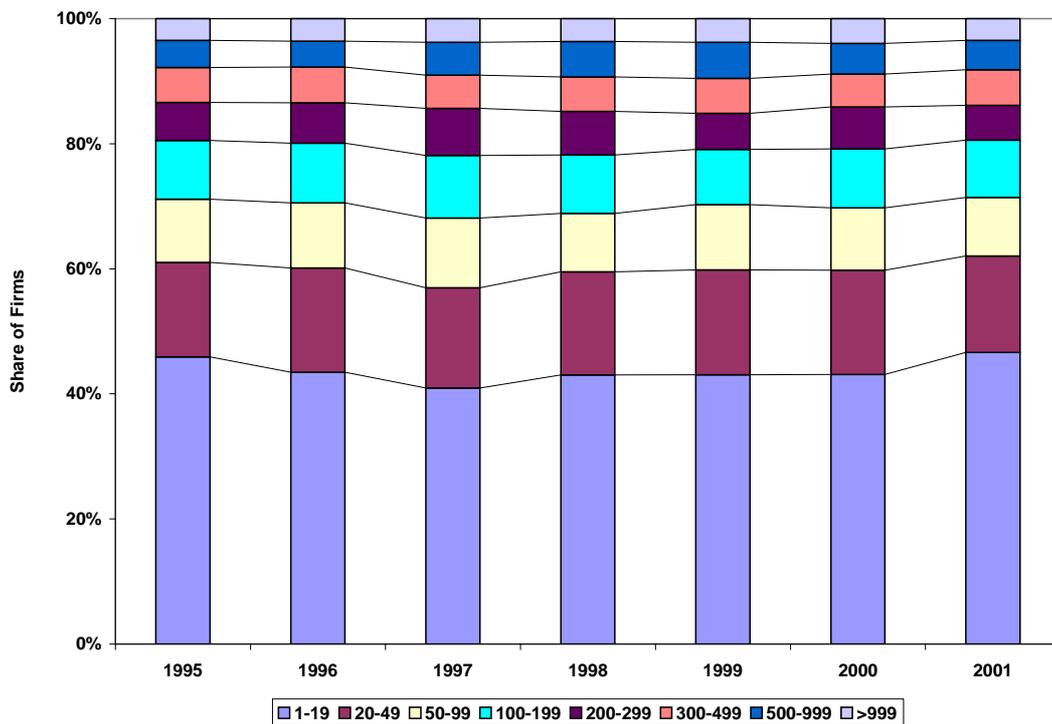
### **1.3.3 The pharmaceutical industry**

The pharmaceutical industry has a long tradition in Germany. About 20 years ago companies like Hoechst and Bayer were leading the list of the top ten pharmaceutical companies of the world (McKinsey & Company 2003). Germany was called once the “pharmacy of the world”. However, since the 1990s the position of the German pharmaceutical industry became weaker, in particular compared to competitors from the United States and Great Britain (Hinze et al.

2001). In 2001, for example, except the French-German company Aventis no German company ranked among the top ten pharmaceutical companies of the world (McKinsey & Company 2003). In the following the present state and the development since the mid 1990s of the sector is analysed using various economic and innovation indicators.

In 2001 there were 577 pharmaceutical firms in Germany (not including pharmacies producing their own pharmaceuticals which sometimes are also counted as members of the pharmaceutical sector). Starting from the middle of the 1990s there had been a slight decrease in the total number of firms until 1997. Since then the number of firms has been increasing continuously. The structure of the sector is dominated by small and medium-sized firms with less than 500 employees. More than 90 % of the firms belong to this category. On the other hand, about 20 firms employ more than 1,000 people. The development of the structure of the pharmaceutical sector in Germany from 1995 to 2001 as shown in figure 1.1, indicates that the sector has been relatively stable during the last seven years.

Figure 1.1: Structure of the pharmaceutical sector in Germany (source: Statistisches Bundesamt 1995 – 2002)



Compared to total manufacturing, medium-sized firms are less important in the pharmaceutical sector which is indicated e. g. by the contribution of these firms to total employment of the sector. While in total manufacturing in the year 2001 57.6 % of all employees were working in medium-sized firms with less than

500 employees, the respective ratio of the pharmaceutical sector was only 27.0 % (Statistisches Bundesamt 2002).

The top ten pharmaceutical firms in Germany ranked by the number of employees in Germany are shown in table 1.1.

Table 1.1: Top ten pharmaceutical firms in Germany (source: VFA 2002)

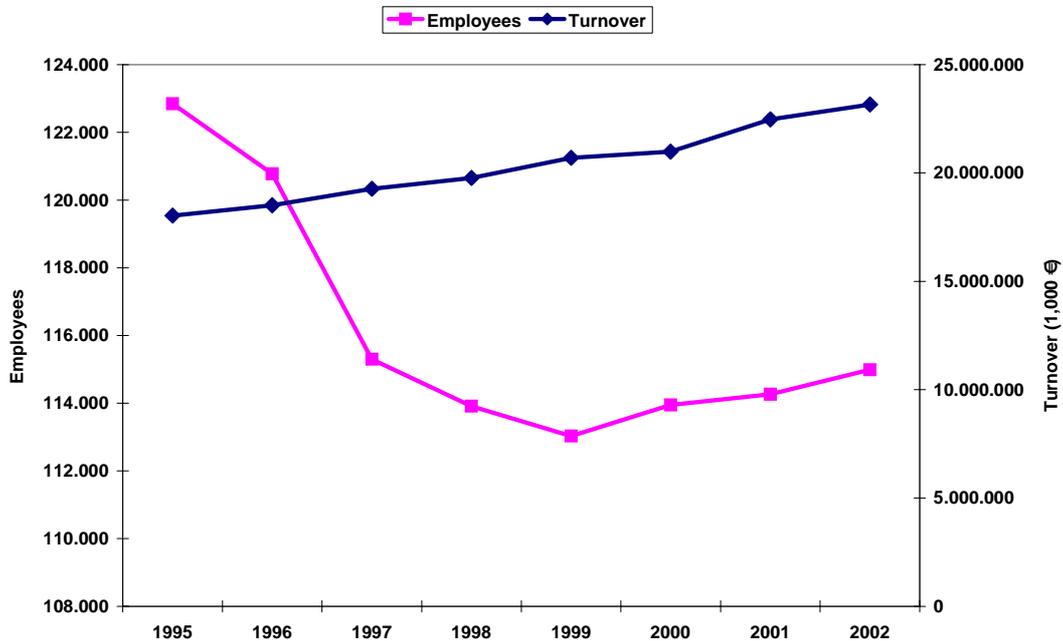
<b>Company</b>	<b>Employees in Germany (2001)</b>
Roche Deutschland Holding	12,100
Schering AG	10,042
Boehringer Ingelheim	8,128
Aventis Pharma AG	7,500
Bayer AG	5,140
Pfizer Deutschland GmbH	4,200
Abbott GmbH & Co. KG	3,500
Merck KGaA	3,328
Altana Pharma GmbH	3,022
GlaxoSmithKline GmbH & Co. KG	2,200

Three of these top ten companies are subsidiaries of foreign pharmaceutical companies (Abbott, Pfizer, GlaxoSmithKline).

All of the larger pharmaceutical companies shown in table 1.1 are R&D-intensive companies with a focus on developing innovative drugs. In addition, there exists a number of pharmaceutical firms specialised in producing generics. The three largest of these firms are Ratiopharm (2,920 employees in Germany in 2001, source: Hoppenstedt database), Hexal (2,200 employees in Germany in 2002, source: [www.hexal.de](http://www.hexal.de)) and Stada (946 employees in Germany in 2002, source: [www.stada.de](http://www.stada.de)).

Since the middle of the 1990s the turnover of the pharmaceutical sector in Germany increased continuously reaching a volume of 23.2 billion € in 2002 (figure 1.2). During the same period employment first decreased considerably from 123,000 employees in the year 1995 to 113,000 employees in 1999. After 1999 this trend could be reversed and until 2002 a continuous growth at an annual rate between 0.3 to 0.8 % could be observed resulting in almost 115,000 employees in the year 2002.

Figure 1.2: Trends in employment and turnover of the German pharmaceutical industry since 1995 (source: Statistisches Bundesamt 1995 – 2003)



The comparison with other important industry sectors in Germany is presented in figure 1.3. Employment in total manufacturing decreased between 1995 and 1997 and could be stabilised thereafter. The pharmaceutical sector developed similarly as total manufacturing until 1997. However, stabilisation of the sector started later and in the year 2002 the pharmaceutical sector performed better than total manufacturing. The good performance of the pharmaceutical sector during the last four years is in contrast to the chemical industry<sup>3</sup> where the decreasing employment trend could not be stopped until now. The automotive industry obviously performed best among these sectors in terms of increasing employment. However, in the year 2002 this trend stopped.

Turnover of the pharmaceutical sector developed similarly to total manufacturing and to other important industries such as machinery and equipment. In 2002 pharmaceuticals even out-performed most of these industries except the automotive industry which again presented an exceptional performance (figure 1.4).

<sup>3</sup> Data for the chemical industry are without the pharmaceutical subsector.

Figure 1.3: Development of employment in selected industries between 1995 and 2002 (1995 = 100) (source: Statistisches Bundesamt 1995 – 2003)

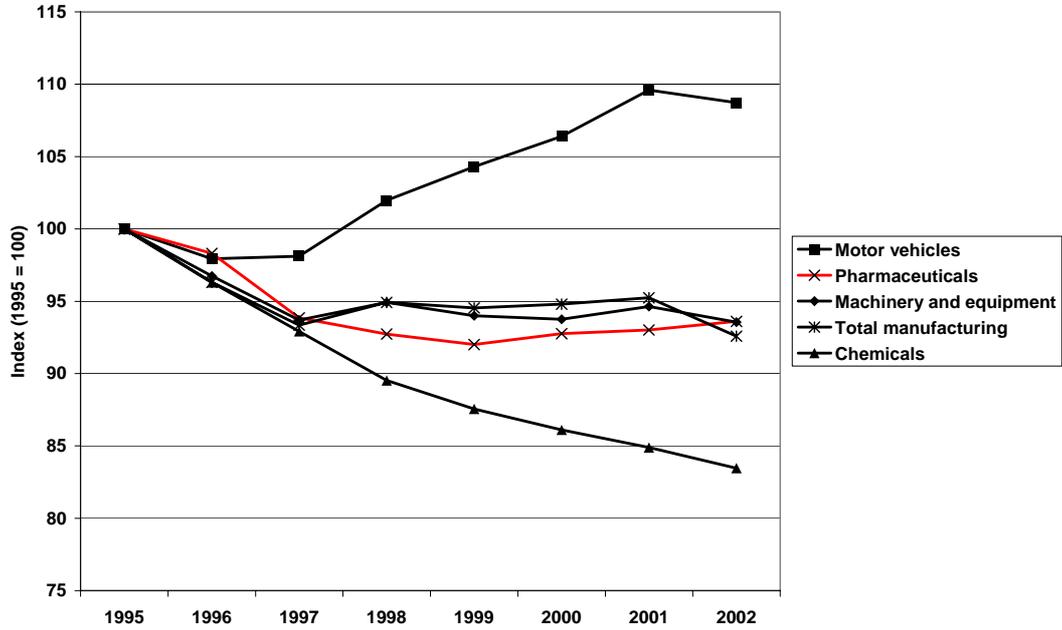
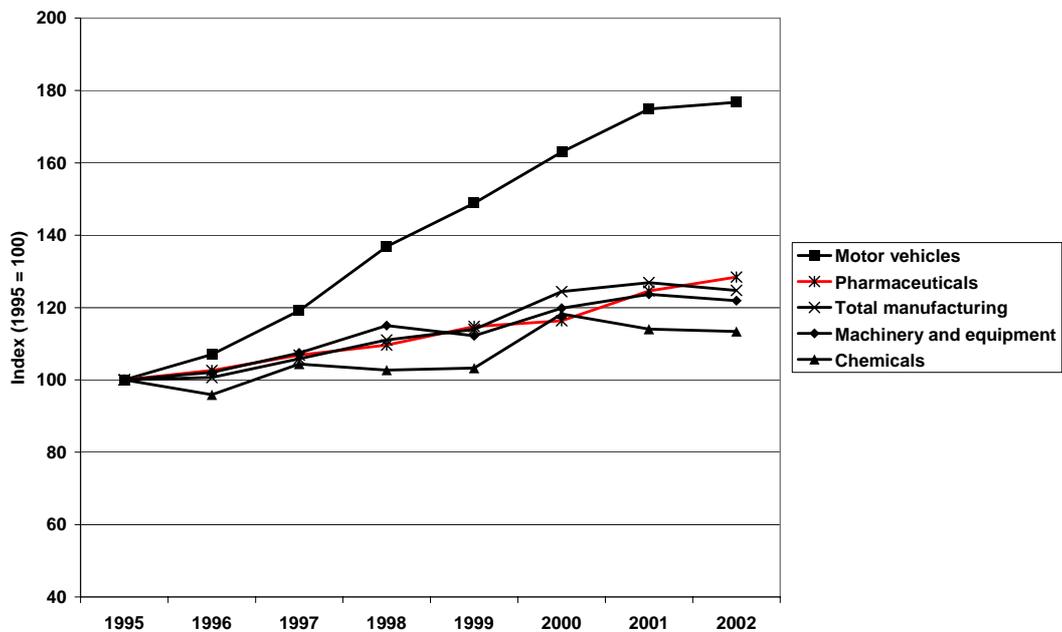


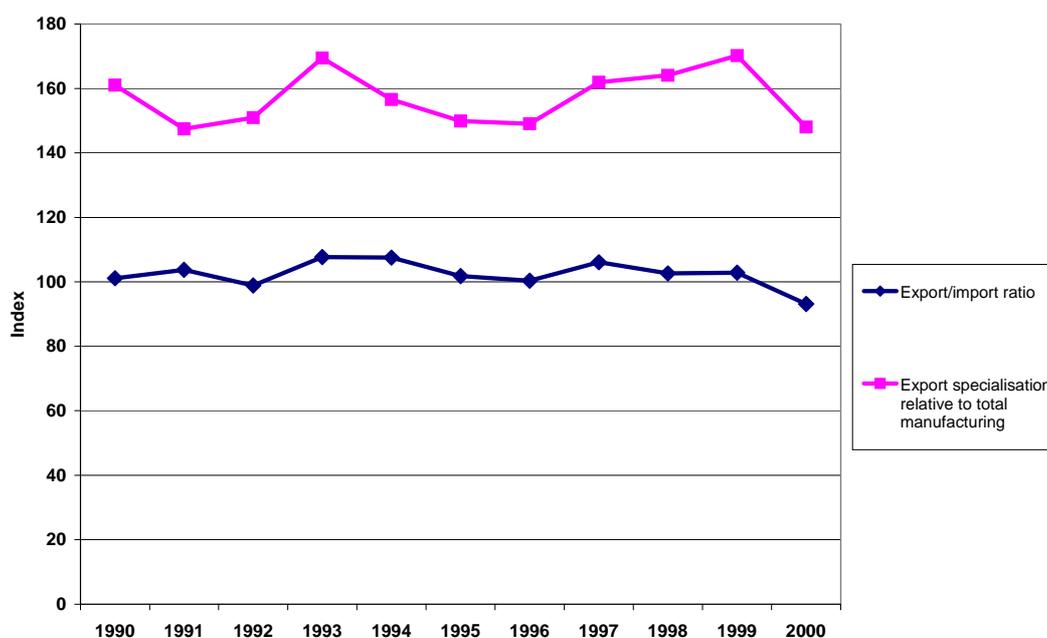
Figure 1.4: Trends in turnover in selected industries between 1995 and 2002 (1995 = 100) (source: Statistisches Bundesamt 1995 – 2003)



Since 1995 also the production volume of the German pharmaceutical industry was growing continuously with the strongest growth rate between the years 2000 and 2001, reaching a volume of 20.2 billion € in 2001 (BPI 2003). The positive development of production in the pharmaceutical industry again indicates that after several periods of low or even negative growth in the beginning of the 1990s the industry seems to recover again.

At a first glance also the trade performance seems to indicate a positive trend. Export-import ratios and export specialisation remained at about the same level between 1999 and 2000 (figure 1.5). However, there seems to be a downwards trend in export performance towards the end of this period which could be interpreted as an early warning signal.

Figure 1.5: Trade performance of the German pharmaceutical industry  
(source: OECD 2002<sup>4</sup>)



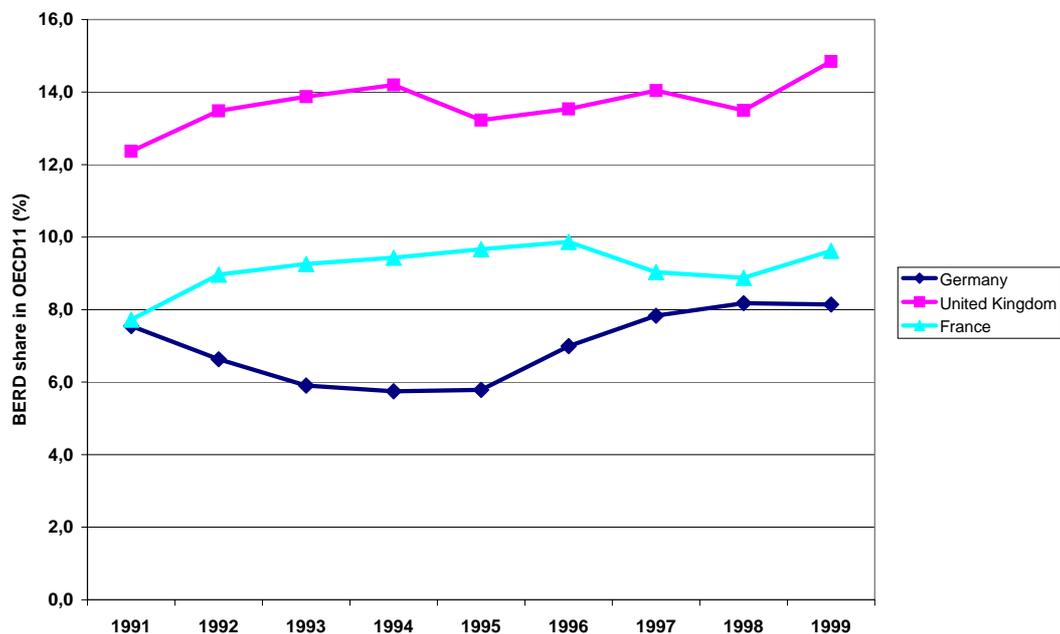
Traditionally the pharmaceutical industry belongs to the most R&D intensive industries. In 1997 approximately 16 % of the personnel of the German pharmaceutical industry was working in R&D (Stifterverband Wissenschaftsstatistik 2000). For member firms of the German association of research-based pharmaceutical companies R&D intensity is even higher reaching a level of approximately 19 % (VFA 2002). Accordingly, R&D expenditures of the

<sup>4</sup> Export specialisation relative to total manufacturing shows the ratio of exports in pharmaceuticals to all exports in manufacturing of a given country related to the same ratio for OECD23. Values above 100 indicate a relative specialisation.

pharmaceutical industry are rather high. In the year 1997 R&D expenditures of German firms reached a share of about 15 % of turnover (17 % for member firms of the German association of research-based pharmaceutical companies). The relative significance of R&D is also indicated by the ratio of R&D expenditure to R&D employees. In the year 1997 this indicator was 150 € in the pharmaceutical industry compared to 117 € of total manufacturing or 119 € for the chemical industry. The automotive industry reached the same level as the pharmaceutical industry (Hinze et al. 2001).

However, in an international comparison the R&D efforts of the German pharmaceutical industry are looking less favourable. Between 1991 and 1995 the share of the business expenditures for R&D of the German pharmaceutical industry in business expenditures for R&D of the total OECD pharmaceutical industry decreased continuously (see figure 1.6). During the same period France and Great Britain could keep or even expand their positions. Since 1995, however, the position of the German industry is improving indicating that there seems to be again a stronger emphasis on R&D.

Figure 1.6: Trends in business expenditures on R&D in Germany, France and Great Britain (source: OECD 2002)

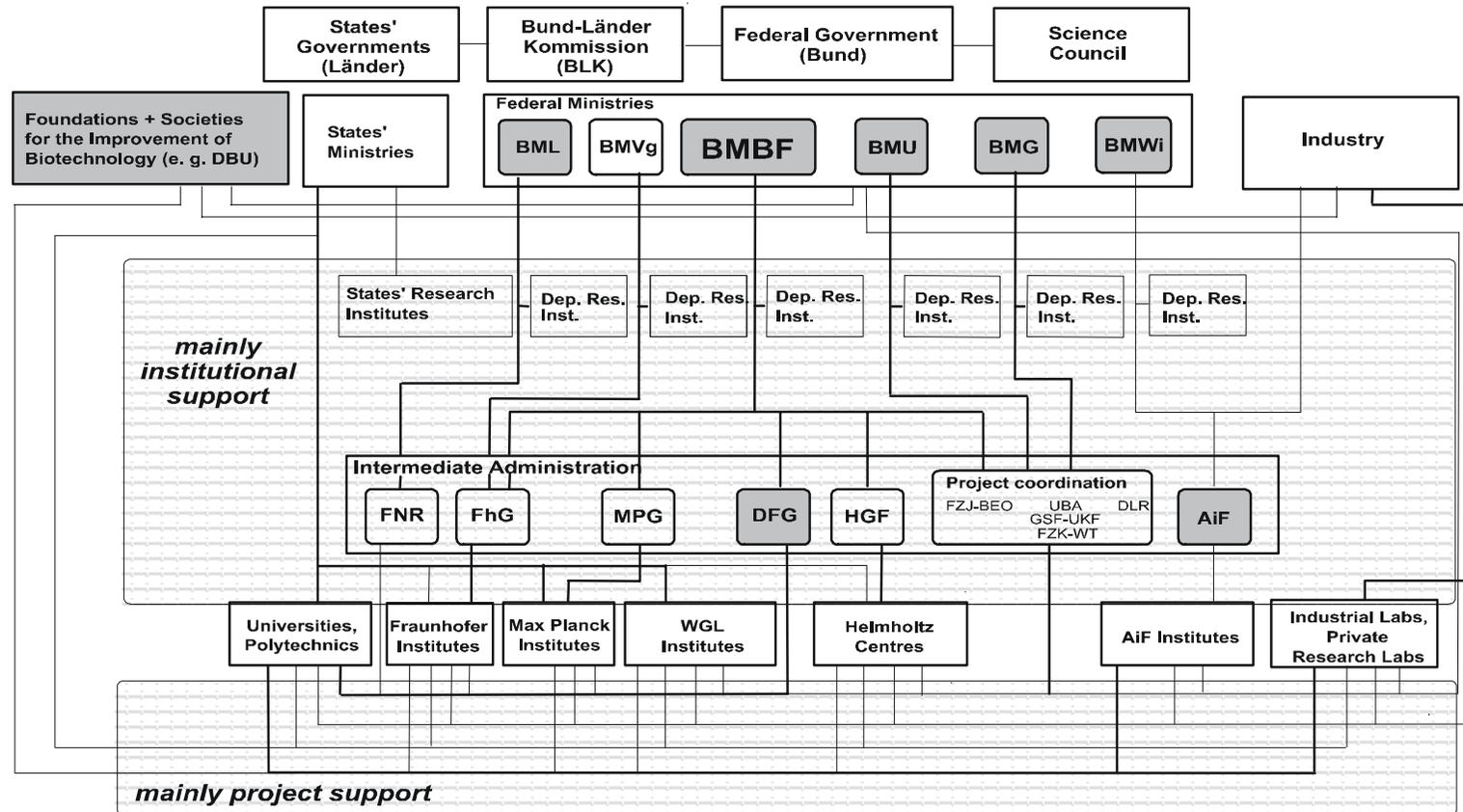


## **2 Overview of national R&D, technology and innovation policies**

### **2.1 Main actors involved in policy-making and policy programme management**

Due to the division of the political responsibility between the federal government and the states, the German system of innovation policy is rather complex and characterised by a large number of actors and ministries involved at the state and federal level. In addition, a broad variety of instruments for supporting innovation and biotechnology has been implemented (Giessler & Reiss 1999). Since 1994 at the national level five federal ministries (education and research; health; environment; food, agriculture and forestry and economics and technology) together with the German Research Foundation (DFG) have been directly or indirectly involved in supporting the development and commercialisation of biotechnology (figure 2.1). In addition, at the state level also various ministries are engaged in supporting biotechnology. Besides these political institutions there exist also foundations and societies for the improvement of biotechnology.

Figure 2.1: Structure of the German R&D system in biotechnology (source: Giessler & Reiss 1999)<sup>5</sup>



<sup>5</sup> Some of the ministries changed their names due to additional/other responsibilities: BML → BMVEL, BMG → BMGS, BMWi → BMWA, BMVEL: Federal Ministry of Consumer Protection, Food and Agriculture; BMVg: Federal Ministry of Defense, BMBF: Federal Ministry of Education and Research; BMU: Federal Ministry of Environment; BMGS: Federal Ministry of Health and Social Security; BMWA: Federal Ministry of Economics and Labour

With respect to the public sector a typical feature of the German R&D landscape is the division of the political responsibilities between the federal government and the “Länder”. The “Länder” are mainly responsible for the educational sector. In consequence they finance the largest part of the university budgets. In addition, the “Länder” support institutes of the different research organisations that are located in the respective state. Some “Länder” have initiated special programmes for biotechnology, providing funding for industry and research organisations. The federal ministries involved in the biotechnology innovation policy system also have a number of departmental research institutes which receive mainly institutional support for conducting research activities which serve the direct needs of the respective ministry in fulfilling their political tasks.

Between the funding organisations and the organisation carrying out research there exists a variety of intermediate organisations leading to quite differentiated decision-making procedures and a complex distribution system of R&D funds. Typical organisations in this system are the so-called project management organisations (PMO, “Projektträger”) which are responsible for the detailed management of nearly all R&D fields supported by the BMBF. In general, the tasks of the PMO include: to support the federal government concerning development, analysis and evaluation of research programmes and concepts, to implement the decisions of the BMBF, to consult the applicants for funding, and to support the preparation of the respective projects, to assess proposals, administrative and financial management of the ongoing projects and the diffusion of results by organising workshops, publications and other activities. Other organisations which are also involved in intermediate R&D management are, for instance, the “Max-Planck-Gesellschaft” (MPG) (Max Planck Society), the “Fraunhofer-Gesellschaft” (FhG) (Fraunhofer Society), the “Arbeitsgemeinschaft industrieller Forschungsvereinigungen Otto von Guericke” (AiF) (Industrial Research Association), the “Hermann von Helmholtz Gemeinschaft deutscher Forschungszentren” (HGF) (Helmholtz Research Centres), the “Wissensgemeinschaft Gottfried Wilhelm Leibniz” (WGL), as well as the “Deutsche Forschungsgemeinschaft” (DFG) (German Research Foundation). With the exception of the DFG, all these organisations are also performing research activities.

The relations between the different funding organisations, the intermediate organisations and the research-performing organisations are indicated in figure 2.1. The lines between related organisations represent financial flows. Concerning funding types the typical feature of the German R&D landscape is the balance between institutional funding and project funding. Figure 2.1 also gives a differentiation of these two funding schemes. The line from the “Länder” to the universities goes down from the upper part of the graph because the support is mainly an institutional one. In addition, a smaller part of the funding of the “Länder” is linked to projects indicated by a thin line coming from below.

## **2.2 Main vertical policies and most important horizontal programmes and instruments<sup>6</sup>**

In the period under consideration in this study (1994-2001) mainly the biotechnology division of the Federal Ministry for Education and Research (BMBF) has been responsible for implementing public funding programmes, explicitly targeting the development and commercialisation of biotechnology. According to the Public Funding Catalogue of the BMBF<sup>7</sup> the share of public funds directed to biotechnology R&D activities amounted in 1994 to 1.9 % of the total R&D expenditures<sup>8</sup>. The share has gradually increased reaching 2.4 % in 1998 and 3.2 % in 2001. Interestingly, industry actors have gained importance in the funding activities of the ministry. In 2000, 23 % of the biotechnology investments of the BMBF were granted to industry (in 1993 this share was 13 %).

### **2.2.1 Policies for knowledge base support**

Horizontal innovation policy instruments play the key role in the support of the biotechnology knowledge base in Germany. Health- and biotechnology-related basic research is mainly funded through mechanisms that do not explicitly target the development of biotechnology. These include institutional support for public research organisations (like universities, Helmholtz Research Centres and Institutes of the Max Planck and Fraunhofer Societies) and the competitive open call system of the German Research Foundation (DFG) to finance public sector research. Through this type of funding the research organisations can preserve their autonomy and accordingly, design and implement their research projects independently from any policy interests and framework programmes of the federal ministries. According to Giessler & Reiss (1999) 75 % of the R&D biotechnology expenditures of the BMBF in the period 1994-1998 run through institutional funding, direct funding to National Research Centres and the project funding of the German Research Foundation (DFG)<sup>9</sup>.

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<sup>6</sup> This section draws on research performed by Fraunhofer ISI within the EU-funded EPOHITE project ([www.epohite.fhg.de](http://www.epohite.fhg.de)).

<sup>7</sup> FöKat (Funding catalogue of the Federal Ministry for Education and Research, September 2002) <http://oas.ip.kp.dlr.de/foekat/foekat/foekat>

<sup>8</sup> This figure includes only the investments classified as biotechnology activities by the BMBF and does not consider expenditures in medical, health and environmental research that may directly support biotechnology research as well. The same accounts all for the shares presented in the paragraph.

<sup>9</sup> These calculations consider the institutional grants from the Biotechnology 2000 programme as horizontal policy instruments since the independence of the research centres in planning research, conducting the projects and choosing their research partners is granted.

Concerning vertical funding activities between 1994 and 2001 biopharmaceutical research was promoted mainly within four framework programmes (table 2.1). The “Biotechnology 2000” framework programme launched in 1990 its successor “Biotechnology Framework Programme” from 2001, the “Health Research 2000 Programme” launched in 1993 and its follow-up activity “Health Research, Scientific Research for the People”. Within these framework programmes several thematically oriented funding initiatives were implemented focussing e. g. on tissue engineering, regenerative medicine, bioinformatics, proteomics, diagnostics, nanobiotechnology and genomic research of microorganisms. Target groups of these initiatives are mainly universities, PSROs and industry (table 2.1).

Table 2.1: Policies for knowledge base support in biopharmaceuticals between 1994 and 2001

<b>Name</b>	<b>Support</b>	<b>Type: horizontal (h), vertical (v)</b>	<b>Target group</b>	<b>Period</b>	<b>Agency</b>
DFG funding	basic research	h	universities, PSRO	continuous	DFG <sup>10</sup>
<i>Biotechnology 2000</i> framework programme	institutional and project funding, linked project, lead projects, networks, education	v	universities, PSRO, industry	1990-2000	BMBF <sup>11</sup>
<i>Biotechnology Framework Programme</i>	institutional and project funding, linked project, lead projects, networks, education	v	universities, PSRO, industry	2001-2005	BMBF
<i>Health Research 2000</i> (framework programme)	research, networks	v	universities, PSRO	1993-2000	BMBF, BMGS <sup>12</sup>
<i>Health Research, Scientific Research for the People</i> (framework programme)	medical research, clinical research,	v,h	universities, PSRO	2000-	BMBF, BMGS
Tissue engineering <sup>13</sup>	see <i>framework programmes</i>	v	see <i>framework programmes</i>	since 2000	BMBF

<sup>10</sup> DFG: German Research Foundation

<sup>11</sup> BMBF: Federal Ministry of Education and Research

<sup>12</sup> BMGS: Federal Ministry of Health and Social Security

<sup>13</sup> Thematic sub-programme within Biotechnology 2000 and the Biotechnology Framework Programme

Name	Support	Type: horizontal (h), vertical (v)	Target group	Period	Agency
Biological replacement of organ functions	see <i>framework programmes</i>	v	see <i>framework programmes</i>	since 2001	BMBF
Bioinformatics <sup>14</sup>	education	v	universities, PSRO	since 2001	BMBF, DFG
Proteomics <sup>15</sup>	see <i>framework programmes</i>	v	see <i>framework programmes</i>	since 2000	BMBF
TSE diagnostics <sup>16</sup>	see <i>framework programmes</i>	v	see <i>framework programmes</i>	since 2001	BMBF
Genomics of microorganisms <sup>17</sup>	see <i>framework programmes</i>	v	see <i>framework programmes</i>	since 2001	BMBF
Nanobiotechnology <sup>18</sup>	see <i>framework programmes</i>	v	see <i>framework programmes</i>	since 2000	BMBF
BioFuture	creation of excellent research groups	v	outstanding young scientists	1988-2000	BMBF
German Human Genome Project	institutional funding, project funding, networks	v	universities, PSRO, industry	1995-2002	BMBF, DFG
National Genome Research Network I	institutional funding, project funding, networks	v	universities, PSRO, industry	2001-2003	BMBF

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<sup>14</sup> Thematic sub-programme within the Biotechnology Framework Programme

<sup>15</sup> Thematic sub-programme within Biotechnology 2000 and the Biotechnology Framework Programme

<sup>16</sup> Thematic sub-programme within the Biotechnology Framework Programme

<sup>17</sup> Thematic sub-programme within the Biotechnology Framework Programme

<sup>18</sup> Thematic sub-programme within the Biotechnology Framework Programme

Special emphasis within these activities was put on collaborative research between universities, PSROs and industry. The “Biotechnology 2000” programme granted about 50 % of its annual budget for project funding (BMFT 1990). To allocate the funding the ministry supported public and industry research units, organising their research projects as “linked” and “lead” projects (*Verbund- und Leitprojekte*). These projects had to be carried out by research consortia that included an industry partner and, most importantly, expected research results of industrial interest.

In 1995 the BMBF together with DFG launched a key initiative for the support of basic research around the human genome – the German Human Genome Project. In 2000 the initiative entered its second phase. Most of the funded projects have been allocated to national research centres (Helmholtz-Centres) and Max Planck Institutes in the form of “linked” projects. A resource centre has been established to gather and coordinate the information and the scientific results of all the projects. Further, companies are very involved and play an important role in the project.

In 2001 the Federal Ministry for Research and Education (BMBF) decided to increase its funding of human genome research substantially by establishing the National Genome Research Network. One main characteristic of the network is its interdisciplinary character, it combines efforts from genome as well as medical research on the genetic basis of diseases.

## 2.2.2 Policies for commercialisation support

Funding measures supporting industrial research and the application and commercialisation of technologies are responsibilities of the Federal Ministry of Economics and Labour (BMWA)<sup>19</sup> (BMW<sub>i</sub>), which reserves funding for industrial research and supports the AiF (German Federation of Industrial Cooperative Research Associations “Otto von Guericke” e.V.) (table 2.2). The AiF has an annual budget of nearly 250 million € of public funds. In 1994 AiF biotechnology project funding amounted to about 35 % of the total AiF project budget (Giessler & Reiss 1999).

In addition to these horizontal funding activities of the BMWA various instruments for technology transfer and support of university spin-offs have been implemented at a federal and regional level<sup>20</sup>. Most of these schemes are generic, however,

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<sup>19</sup> Following the elections of 2002 the BMW<sub>i</sub> changed its name to Federal Ministry of Economics and Labour (BMWA).

<sup>20</sup> These are some of the major initiatives: (1) Establishment of Agencies for Technology Transfer and Innovation Promotion (*Agenturen für Technologietransfer und Innovationsförderung*, ATI), Technology Transfer Centres (TTZ) and AN-Institutes (Technology Transfer Institutes at Universities); (2) the INSTI project launched in 1995 by the Federal Ministry of Education and Research to provide SMEs with access to the scientific-technical information gathered in patent documents and Patent Information Centres (PIZ) were established; (3) Since 1999 and until 2003

biotechnology turned out to be an important sector taking advantage of the various mechanisms.

Specific support for the commercialisation of biotechnology has followed mainly two approaches.

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the Programme INNONET aims at promoting innovative networks and the exchange of R&D staff between business and research institutes; (4) in 1999 the Ministry for Education and Research initiated the InnoRegio competition for the creation of regional clusters of companies, institutions and research institutes in the Eastern states of Germany; (5) since 2001 the initiative “Knowledge creates markets” reserves funding to support the establishment of a professional patent and commercialisation agency. This aims to promote the exploitation of research generated at facilities, which do not have the necessary commercialisation expertise in-house; (6) EXIST – start-ups from science (1998-2001) provide 7.5 million € per year to improve entrepreneurship and knowledge spill-overs from academics to industry.

Table 2.2 Policies for commercialisation support in biopharmaceuticals between 1994 and 2001

<b>Name</b>	<b>Support</b>	<b>Type: horizontal (h), vertical (v)</b>	<b>Target group</b>	<b>Period</b>	<b>Agency</b>
AIF funding	project funding	h	industry	continuous	BMWA 21
Technology Transfer Agencies	institutional funding	h	intermediate organisations	continuous	States
INSTI	information for commercialisation (e.g. IPR, financing)	h	SME, universities	since 1995	BMBF
InnoNet	innovation networks, linked projects between industry and research, exchange of R&D staff	h	SME, universities, PSRO	1999-2005	BMWA
EXIST	spin-offs from science	h	start-ups	since 1998	BMBF
Gene centres	institutional support, collaboration science-industry	v	universities, PSROs	1982-1995	BMBF
BioChance <sup>22</sup>	funding for high risk projects	v	SME	since 1999	BMBF

<sup>21</sup> BMWA: Federal Ministry of Economics and Labour

<sup>22</sup> Sub-programme within Biotechnology 2000 and the Biotechnology Framework Programme

<b>Name</b>	<b>Support</b>	<b>Type: horizontal (h), vertical (v)</b>	<b>Target group</b>	<b>Period</b>	<b>Agency</b>
BioRegio <sup>23</sup>	regional clusters, institutional and project funding, infrastructures	v	universities, PSRO, industry, intermediate organisations	1995-2001	BMBF
BioProfile <sup>24</sup>	focussing of regional profiles	v	universities, PSRO, industry, intermediate organisations	1999-2006	BMBF
Coordination Centres for Clinical Studies <sup>25</sup>	coordination of clinical studies	v, h	universities, clinics	since 1998	BMBF

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<sup>23</sup> sub-programme within Biotechnology 2000

<sup>24</sup> sub-programme within Biotechnology 2000 and the Biotechnology Framework Programme

<sup>25</sup> within the *Health Research* Framework programme

Firstly, mechanisms were implemented to promote biotechnology research of industry actors. On the one hand, the involvement of industry actors in biotechnology research activities conducted in collaboration with public research organisations was stimulated. The funding of collaborative research has been the major instrument implemented by the Federal Ministry of Education and Research in the pharmaceutical and agro-food sectors. The “Biotechnology 2000” programme gave priority to those “linked” and “target” projects with a large share of industry involvement. Between 1994 and 1998 about 50 % of the “Biotechnology 2000” budget (which added up to about 500 million € for the period 1994 to 1998) were invested in direct project funding with industry involvement (BMFT 1990; Giessler & Reiss 1999). On the other hand, the so-called *Genzentren* (gene centres) were established to improve the access of the industry to scientific and technological capabilities. Between 1982 and 1995 140 million € were invested for this goal. The initiative “BioChance” was issued in 1999 with the goal to further support the commercialisation of biotechnology by providing funding for high-risk projects in biotechnology firms.

Secondly, instruments for commercialisation support of biotechnology included initiatives for cluster formation of research units and industry actors. The “BioRegio” contest (1995-2001) was an important policy instrument implemented within the “Biotechnology 2000” programme. The initiative was designed as a competition where regions presenting the most convincing concept to establish actor networks around specific topics were awarded large amounts of public funding (the three winning regions, Munich, Heidelberg, Rhineland, and the model region Jena altogether received 90 million € of BMBF funding for five years). According to the programme description policy-makers intended to promote and accelerate the transfer of biotechnological know-how into products, processes and services by supporting regional interaction between research units, financing institutions and industry actors. The recent programme “BioProfile” (1999-2006) can be considered as an extension of the “BioRegio” contest, aiming at supporting the development of specific strengths in certain regions.

### **2.2.3 Policies with a socio-economic and/or ethical dimension**

Driven by the public debate and the conflict between scientific, commercial and public interests, the support of activities and institutions concerned with ethical and socio-economic aspects of biotechnology is gradually becoming more important for the policy system.

According to Giessler & Reiss (1999) until the mid 1990s these issues had a minor importance within the funding mechanisms and only approximately 3 % of the budget assigned to the promotion of biotechnology research was invested on projects targeting the socio-economic and ethical dimension of biotechnology.

Examples of initiatives were the participative technology assessment activities co-ordinated by the WZB<sup>26</sup> in Berlin and discourse projects (*Werkstattgespräche* and *Bürgergutachten*) organised by the Academy of Technology Assessment in Baden-Württemberg between 1991 and 1993. In the second half of the 1990s the range of supported activities concerned with socio-economic and ethical issues of biotechnology has broadened. Apart from research projects being funded in fields like biosafety, alternative methods to animal testing or implications of human genome research, policy instruments include discourse activities and institutional measures to improve the public understanding of biotechnology<sup>27</sup>.

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<sup>26</sup> WZB: Wissenschaftszentrum Berlin

<sup>27</sup> These are some of the initiatives launched since 1994: (1) Information and discussion internet platforms launched by the German Federal Ministry Education and Research (BMBF); (2) Public support for the preparation of pedagogic material and activities for school students at regional and federal level; (3) Establishment of the Office for Biotechnology Information (*Informations-Sekretariat Biotechnologie*) supported by the DECHEMA (Association for Technical Chemistry and Biotechnology) and financed by the German Federal Ministry Education and Research (BMBF); (4) Citizens' Conference on Genetic Testing in 2001 in Dresden aiming at involving citizens in the public debate on ethical aspects of genetic research, (5) BMBF-Biotechnology-Days (once-a-year conferences covering the German biotechnology research and commercial developments); (6) Inauguration of the National Ethics Council (2001) as institutional platform for interdisciplinary discourse between the natural sciences, medicine, theology and philosophy, and the social and legal sciences.

### **3 Structure, dynamics and performance of the biopharma/biomedical system**

#### **3.1 National public R&D system**

Germany has a very differentiated system of public R&D organisations doing research with reference to the biopharmaceutical sector. The main actors in this system, as indicated, for example, by their contribution to the scientific output (see section 3.3), are the universities.

At present there are 92 universities in Germany (BMBF 2002). Many of those have science or medical faculties which conduct research with relevance for the biopharmaceutical sector.

In addition to the universities there are different public sector research organisations (PSROs) with individual institutions doing research in the biopharmaceutical sector (table 3.1). Most important is the Max Planck Society where 21 of the 80 institutions are active in the biopharmaceutical sector. The other large umbrella research organisation in Germany is the Fraunhofer Society. However, in this society a much smaller share of institutions (4 out of 57) is devoting their activities to biotechnology. A third important organisation is the Helmholtz Society (HGF) which is the umbrella organisation of large federal research centres in Germany. At present, 15 institutions belong to the society, 5 of those (including the National Biotechnology Research Centre in Braunschweig, the German Cancer Research Centre in Heidelberg or the Max Delbrück Centre in Berlin) are active in biotechnology. Finally, the Leibniz Society (WGL) is an association of state-based research centres where 6 out of 78 institutions are doing research relevant to the biopharmaceutical sector.

Besides these key players some of the departmental research organisations of various federal ministries are active in this system as well as research organisations of the AiF. A special type of institution is the European Molecular Biology Laboratory (EMBL) in Heidelberg which is not only committed to basic biomolecular research, but also to the transfer of research results into industrial applications which is performed in close cooperation with other research organisations, service providers and industry. In addition, the EMBL hosts international training courses in molecular biology.

Table 3.1: Public sector research organisations with a focus on research relevant for the biopharmaceutical sector (source: Hinze et al. 2001, updated)

Name	Location	Organisation
Fraunhofer Institut für Grenzflächen- und Bioverfahrenstechnik (IGB)	Stuttgart	FhG
Fraunhofer Institut für Toxikologie und experimentelle Medizin (ITEM)	Hannover	FhG
Fraunhofer-Institut für Molekularbiologie und angewandte Ökologie (IME)	Schmallenberg-Grafschaft	FhG
Fraunhofer-Institut für Biomedizinische Technik (IBMT)	St. Ingbert	FhG
Friedrich-Miescher-Laboratorien für biologische Arbeitsgruppen der Max-Planck Gesellschaft	Tübingen	MPG
Max-Planck-Institut für Biochemie	Martinsried	MPG
Max-Planck-Institut für Biologie	Tübingen	MPG
Max-Planck-Institut für Biophysik	Frankfurt	MPG
Max-Planck-Institut für Biophysikalische Chemie	Göttingen	MPG
Max-Planck-Institut für Chemie	Mainz	MPG
Max-Planck-Institut für Entwicklungsbiologie	Tübingen	MPG
Max-Planck-Institut für Experimentelle Endokrinologie	Hannover	MPG
Max-Planck-Institut für Experimentelle Medizin	Göttingen	MPG
Max-Planck-Institut für Evolutionäre Anthropologie	Leipzig	MPG
Max-Planck-Institut für Hirnforschung	Frankfurt	MPG
Max-Planck-Institut für Immunbiologie	Freiburg	MPG
Max-Planck-Institut für Infektionsbiologie	Berlin	MPG
Max-Planck-Institut für Medizinische Forschung	Heidelberg	MPG
Max-Planck-Institut für Molekulare Genetik	Berlin	MPG
Max-Planck-Institut für Molekulare Physiologie	Dortmund	MPG
Max-Planck-Institut für molekulare Zellbiologie und Genetik	Dresden	MPG
Max-Planck-Institut für Neurobiologie	Martinsried	MPG
Max-Planck-Institut für Neurologische Forschung	Köln	MPG
Max-Planck-Institut für Neuropsychologische Forschung	Leipzig	MPG
Max-Planck-Institut für Physiologische und Klinische Forschung	Bad Nauheim	MPG
Max-Planck-Institut für Zellbiologie	Ladenburg	MPG
Deutsches Krebsforschungszentrum (DKFZ)	Heidelberg	HGF
Forschungszentrum Jülich (FZJ)	Jülich	HGF
Gesellschaft für Biotechnologische Forschung (GBF)	Braunschweig	HGF
Forschungszentrum für Umwelt und Gesundheit (GSF)	München-Neuherberg	HGF
Max-Delbrück-Zentrum für Molekulare Medizin (MDC)	Berlin-Buch	HGF
Leibniz Institut für Neurobiologie (IfN)	Magdeburg	WGL
Institut für Molekulare Biotechnologie (IMB)	Jena	WGL
Forschungsinstitut für Molekulare Pharmakologie (FMP)	Berlin-Friedrichsfelde	WGL
Deutsches Primatenzentrum (DPZ)	Göttingen	WGL
Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ)	Braunschweig	WGL
European Molecular Biology Laboratory (EMBL)	Heidelberg	supported by 17 countries

## 3.2 Business system

### 3.2.1 Business entry and exit

The key actors of the biopharmaceutical business system are pharmaceutical companies active in biotechnology, specialised biotechnology companies, intermediate supplying companies and clinical trial organisations.

Concerning pharmaceutical companies only a small number of all pharmaceutical companies in Germany can be characterised as large research-based companies<sup>28</sup> that have a core activity in the development and exploitation of biopharmaceutical or biomedical products. Using the criteria of having more than 500 employees and being active in production and/or R&D activities in Germany about 30 biopharmaceutical companies could be identified. All these firms are members of the German association of research-based pharmaceutical firms (VFA).

Specialised biotechnology firms are supplying technology and pre-products to the pharmaceutical industry. Based on the cooperation survey conducted in the beginning of 2003 in Germany (see section 3.2.2), we estimate the number of these firms in the biopharmaceutical sector to about 350.

In principal, several types of firms could be assigned to the category of intermediate supplying companies. First of all, many pharmaceutical firms also produce intermediates for their own use or for sale to other companies. Secondly, also specialised biotechnology firms produce to some extent intermediates for the pharmaceutical industry. These firms are already included in the specialised biotechnology category. Finally, there is a number of companies focussing on specialty chemicals which also produce intermediates for the pharmaceutical industry. About seven large firms of this type could be identified in Germany.

There are several hundred clinical research organisations (CROs) in Germany. However, most of them are small or very small focusing mainly on monitoring activities. Approximately 20 of these organisations can be considered as larger units providing full service for clinical development. Many of these organisations are subsidiaries of international CROs.

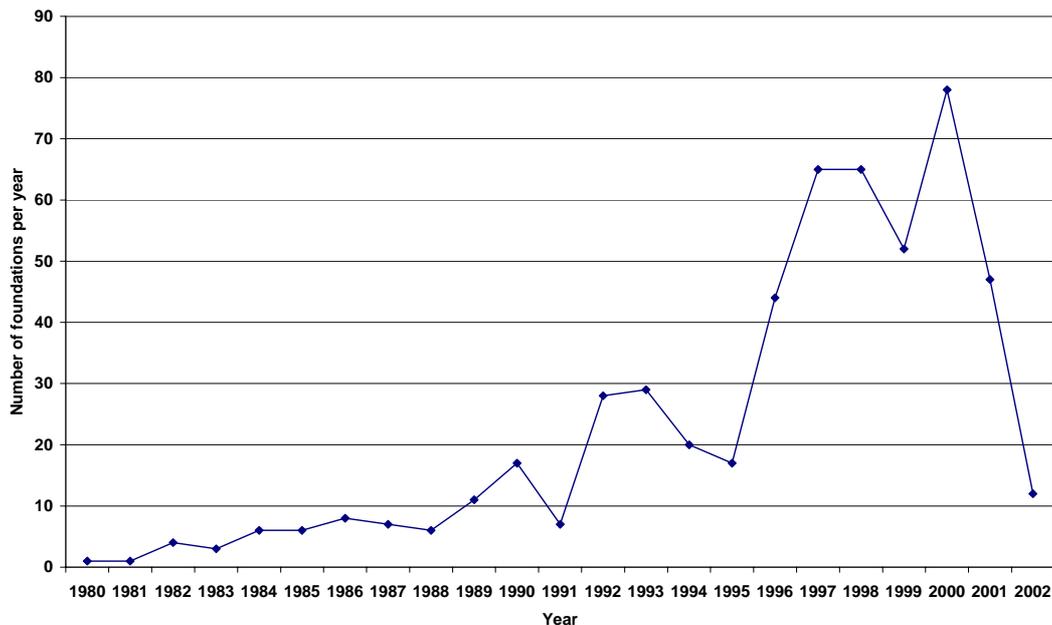
Concerning entry and exit of biotechnology firms specialised in biopharmaceuticals there are no statistical data available for this sub-sector. However, some information is available for the total biotechnology sector which gives a good impression also

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<sup>28</sup> See chapter 1.3.3 on the structure of pharmaceutical industry in Germany.

on the situation in the biopharmaceutical sub-sector, because most of the German biotechnology firms (according to Ernst & Young (2002) about 83 %) are active in biopharmaceuticals. Start-up activities in biotechnology since 1980 are presented in figure 3.1 (ISB 2003).

Figure 3.1 Start-up activities of German biotechnology firms (source: ISB 2003)



A first peak of start-up activity occurred in the beginning of the 1990s soon after the launch of the “Biotechnology 2000” framework programme of the BMFT (and the German reunification). However, it took until the second half of the 1990s before intensive and sustainable founding activities could be observed. The second foundation peak started right after the “BioRegio” contest which was initiated in 1995 by the BMFT. The highest founding rate was achieved in 2000 with almost 80 firms founded in that year. This peak coincided with the excitement on the opportunities of new markets and very high venture capital investments in biotechnology. Since 2001 there was a decline in start-up activities and in 2002 only a few biotech firms were founded. According to the ISB data (ISB 2003) these were in the range of 10 to 15, according to the latest Ernst & Young report about 25 new companies arose in 2002 (Ernst & Young 2003).

Concerning the type of company foundation Woerner & Reiss (2001) found that in the year 1999 the vast majority of biotech firms (59 %) were founded independently. About one third of the new companies arose as spin-offs from public sector research organisations and only about 9 % were spun out from other companies.

Until recently exits of biotech firms were no theme in the discussions in Germany which were dominated by the start-up idea. However, since 2001 there seems to be an increasing number of companies which went bankrupt. According to Ernst & Young (2003) in 2001 6 biotech firms and in 2002 30 biotech firms went out of business. In 2003 until October 18 firms closed<sup>29</sup>. These figures are a little lower than estimates from sector experts which are in the range of 40 to 50 insolvencies in total between 2001 and 2002.

Mergers and acquisitions so far have not been very important in the German biotechnology scene. The Ernst & Young reports (e. g. Ernst & Young 2003) detected 12 mergers and acquisitions in 2000, 8 in 2001 and 4 in 2002. Most of these were acquisitions. Interestingly, in the majority of these cases deals were made with international partners, indicating that securing the presence on international markets might be a major motivation behind such deals.

Summarising the dynamics of the biopharmaceutical system it seems that Germany has reached a steady state in the year 2002 where the rate of company foundations is compensated by company exits via insolvencies or mergers and acquisitions. This indicates that the consolidation process in the German biotechnology industry is gaining momentum. In addition, despite the sharply declining founding activities and also despite problems in public financing the sector still seems to be rather stable and not in a crisis situation.

### **3.2.2 R&D cooperations**

In order to obtain a detailed picture of the cooperation behaviour of German biotech firms active in the biopharmaceutical sector, a written survey of about 600 firms was carried out in spring 2003. 223 responses were obtained corresponding to a response rate of 37 %, 126 questionnaires (21 %) could be used for the analysis of cooperation networks.

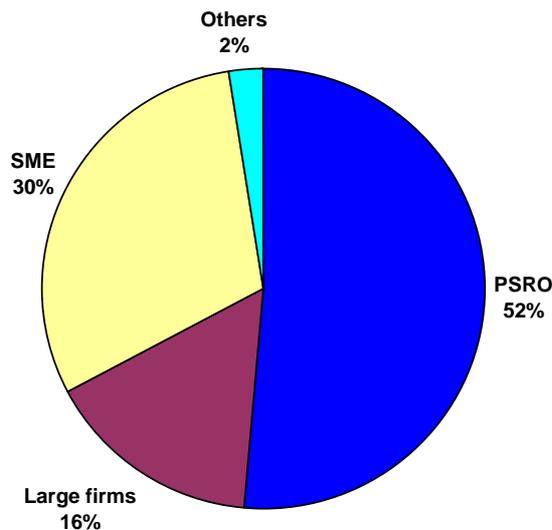
On average, the surveyed companies have 6 cooperation partners, whereas small firms with less than 20 employees have less cooperation partners, medium-sized firms with 21 to 100 employees seem to have a higher number of cooperations. Firms with more than 500 employees have on average more than 10 cooperations. The average duration of cooperations is between 2.5 and 3 years. Cooperations with public sector research organisations (PSROs) and large enterprises seem to last slightly longer than cooperations with small and medium-sized enterprises. The most important cooperation partners for the biotech firms are public sector research organisations which make 52 % of all partners (figure 3.2).

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<sup>29</sup> The figures for 2002 and 2003 are updates to the German Ernst & Young report (Ernst & Young 2003), which were given at the "Biotechnologietage" on October 20-21, 2003 in Leipzig.

Cooperations with other biotechnology firms also play an important role comprising roughly 30 % of all partners. This seems to indicate that there exist intensive cooperation networks among small and medium-sized biotech firms. Finally cooperations with large enterprises account for 16 % of all partners.

Figure 3.2: Type of cooperation partners of biotech firms (source: cooperation survey by Fraunhofer ISI 2003)



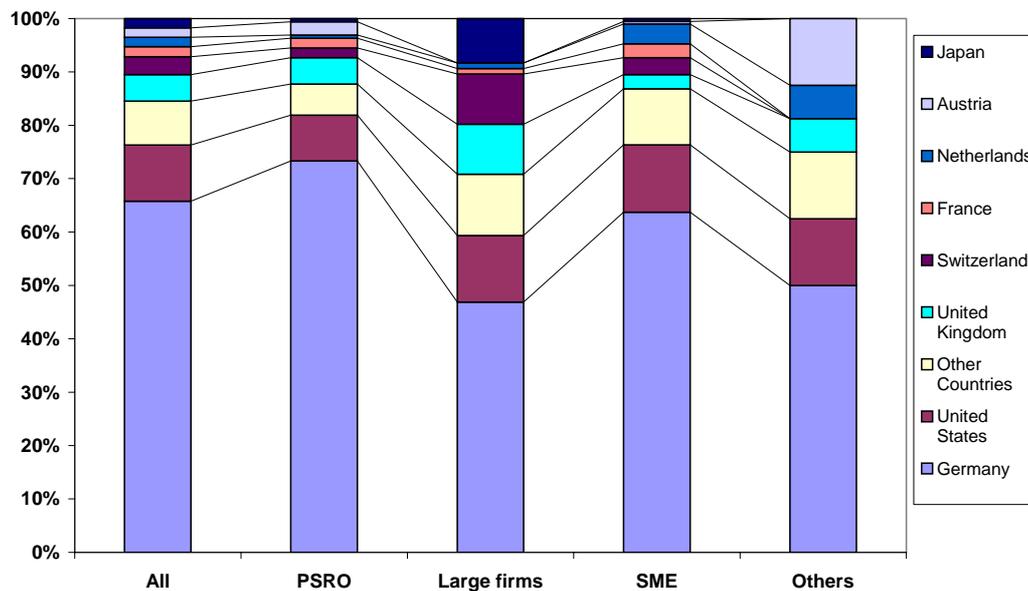
The analysis of the location of cooperation partners indicates that two thirds of all cooperations are made with domestic partners, while one third is done in internationally. Among the international cooperation partners the United States followed by Great Britain and Switzerland are most important. Surprisingly, France does not belong to the important cooperating countries even though it is a direct neighbour of Germany.

If we differentiate the location of cooperation partners by type of cooperation partner, it turns out that cooperations with PSROs are mainly domestic, while cooperations with large firms are mainly international (figure 3.3). In terms of the relation domestic to international partners cooperations with small and medium-sizes are in-between cooperations with PSROs and large firms. International large firms as cooperation partners are mainly located in the United States, Great Britain, Switzerland and Japan, reflecting basically the main locations of global pharmaceutical firms. Concerning cooperations with other biotech firms it is interesting to note that firms from Great Britain are not very important as

cooperation partners, even though Great Britain has the largest number of biotechnology firms in Europe.

The analysis of the location of cooperation partners allows the following conclusions: biotech firms in Germany active in biopharmaceutical sector are mainly using the domestic knowledge base as provided by national PSROs for their innovation activities. This underlines the importance of a well-performing public sector research landscape for the commercial development of biotechnology. Concerning inter-firm cooperations the international cooperation partners – large firms as well as small and medium-sized biotech firms – are located mainly in the United States, indicating that these actors from the United States seem to acknowledge biotech firms from Germany as interesting partners for cooperations<sup>30</sup>. Since the biotech industry in the United States is by far most advanced in the world, this cooperation pattern could also be interpreted as an indication for the growing maturity of the German biotech sector.

Figure 3.3: Location of cooperation partners of German biotech firms (source: cooperation survey by Fraunhofer ISI 2003)

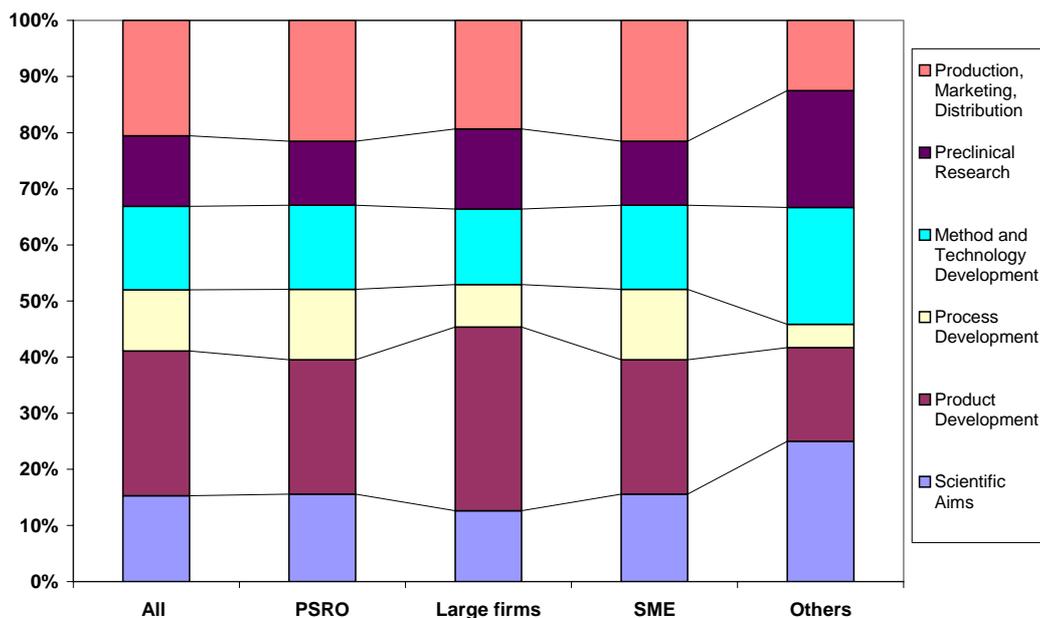


The most important aims of cooperations are product development and production, marketing and distribution contributing. Together about 54 % of the cooperations focus on those aims (figure 3.4). Obviously, product- and market-oriented activities play an important role in cooperations of biotechnology firms. If we differentiate

<sup>30</sup> In order to confirm this interpretation, similar data on the cooperation behaviour of US American biotechnology and pharmaceutical firms would be required. Presently such data is not available.

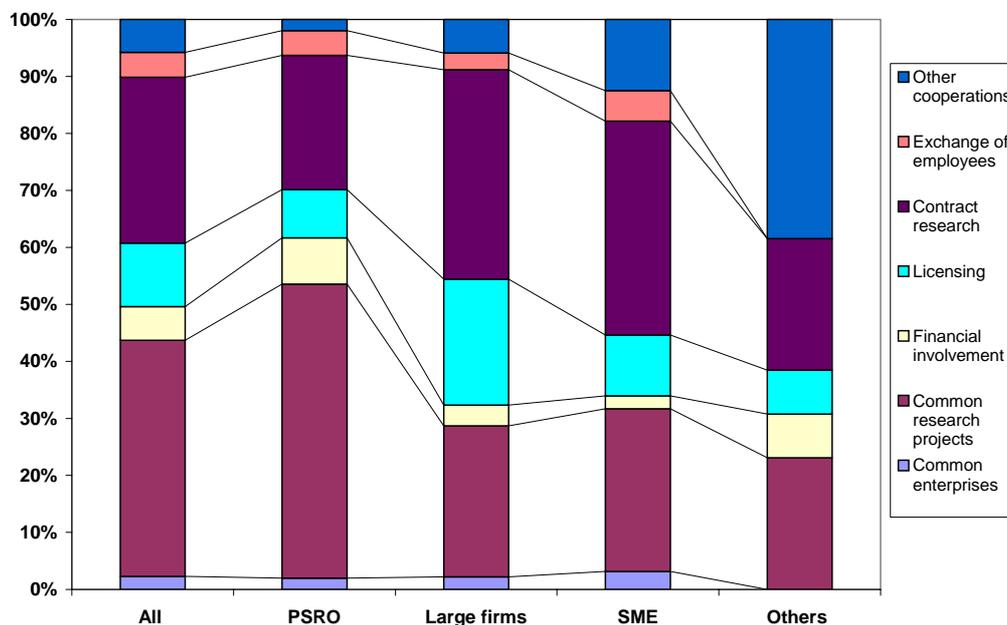
the aims by cooperation partners, there are strong similarities between partners from public sector research organisations and small and medium-sized biotech firms. This seems to indicate that from the perspective of the cooperating firm both types of partners – public sector research organisations and other small and medium-sized biotech firms – are similarly suited to meet the same aims. Accordingly, it is interesting to speculate whether biotechnology firms are partly also performing similar types of activities in the biotechnology innovation context. Such a notion would be supported by the view of many observers that biotech firms are playing an important role as research and development factories. Concerning cooperations with large enterprises product- and market-oriented activities play a stronger role compared to all partners. Large enterprises, therefore, seem to be the preferred partners of biotech firms for their product development activities.

Figure 3.4: Goals of cooperations by type of cooperation partner (source: cooperation survey by Fraunhofer ISI 2003)



Cooperations are most frequently done in the form of common research projects and contract research (figure 3.5). The exchange of employees, financial involvement and the setting-up of common enterprises are less important forms of cooperations. Licensing agreements are an important cooperation type for cooperations with large enterprises, they are less important in cooperations with other biotech firms and public research organisations.

Figure 3.5: Form of cooperations by cooperation partner (source: cooperation survey by Fraunhofer ISI 2003)



### 3.2.3 International dimension of the system

Traditionally the pharmaceutical industry in Germany has a strong export orientation as indicated, for example, by the high export-import ratios discussed in section 1.3.3. The external trade performance also indicates that the industry has gained a favourable international competitive position. But not only pharmaceutical firms but also biotech SME who are active in this sector exhibit a strong international orientation. This is indicated, for example, by an analysis of their main markets which shows that between 50 % and 60 % of the firms have their main markets abroad (Woerner & Reiss 2001).

As another indication for the international dimension of the system the presence of multinational pharmaceutical firms in Germany could be taken. Among the top 30 research-based pharmaceutical firms which are member firms of the German association of research-based pharmaceutical firms (VFA) about two thirds are subsidiaries of multinational enterprises.

The cooperation survey discussed in section 3.2.2 reveals that in the case of cooperations with large firms more than 50 % of the cooperations are made with international partners, in the case of small and medium-sized cooperation partners the international share is slightly below 50 %. A focus of the international orientation of this sector are the United States in terms of markets but also in terms of cooperations and location of parent companies of German subsidiaries.

During the performance analysis which is described in more detail in section 3.3 also co-inventions of German actors which were filed as patents together with inventors from other countries were analysed, indicating that in the period 1994 to 2000 between 24 % and 32 % of all biopharmaceutical patents from Germany were the result of co-inventions. Looking at the nationality of the various co-inventors again the United States show up as the most important country<sup>31</sup>.

All in all, the available indicators point to a rather strong international orientation of the sector.

### **3.3 Performance**

In order to analyse the performance of the German biopharmaceutical innovation system, we used bibliometric indicators as a measure for the output of the research system, patent indicators as a measure for the technological output and the number of new drugs in different stages of the drug pipeline indicating the state of commercial development.

An overview of the development of publication activities in biopharmaceuticals in Germany compared to other participating countries in this case study is given in figure 3.6.

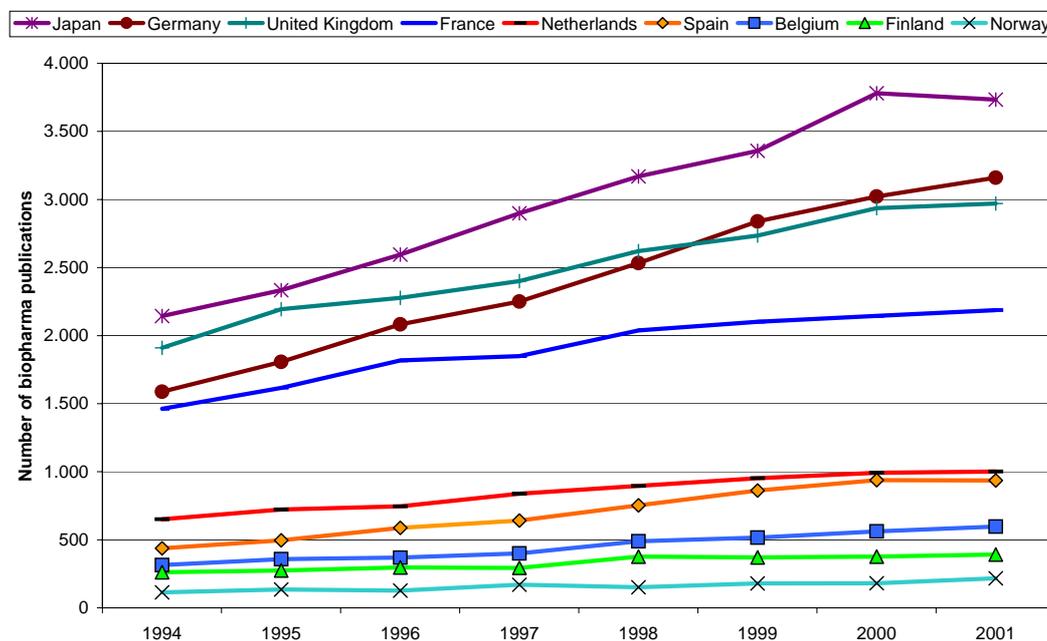
Similar as in other participating countries the publication volume in pharmaceutical biotechnology from Germany increased considerably between 1994 and 2001. The annual average growth rate in this period for Germany was 10.3 % compared to an OECD rate of 7.0 %. The specific growth dynamics of the sectors is indicated by the fact that total growth of all publications over this period took place at a rate of only 3.8 % in Germany compared to 1.9 % at the OECD level. In consequence, the share of biopharmaceutical publications in all publications grew from 3 % in 1994/95 to 5 % in 1999/2000. At the OECD level we observe the same rates.

According to the specialisation indicator RLA (Revealed Literature Advantage), the focus on biopharma-relevant topics among all German publications is about average, which means that the share of biopharma-related publications is about the same in Germany as it is worldwide. Comparing the two periods 1994/95 and 1999/2000 hardly any change can be found.

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<sup>31</sup> Source: OECD Patent Database, February 2003.

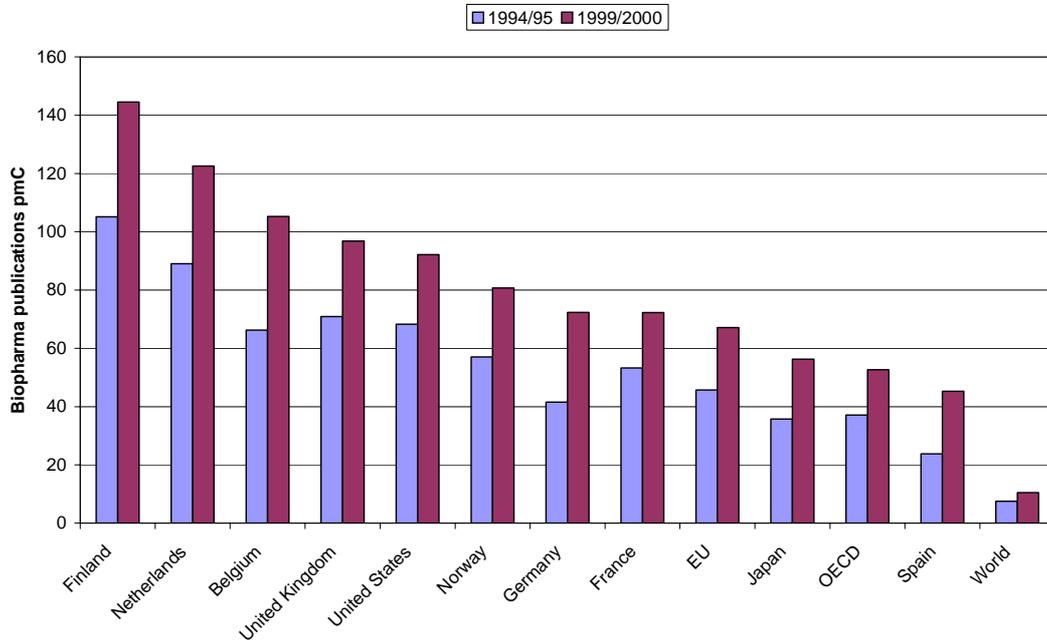
Figure 3.6: Publications in pharmaceutical biotechnology for selected OECD countries over time (source: SCI<sup>32</sup> via host STN, searches and calculations Fraunhofer ISI)



In order to measure the relative performance of Germany in terms of scientific output in the biopharmaceutical sector, two additional indicators are presented in the following. Firstly, in order to compensate for different country sizes, biopharmaceutical publications are related to population figures. The resulting indicator (biopharmaceutical publications per million capita) puts the smaller countries, Finland, the Netherlands and Belgium, in a leading position among the participating countries (figure 3.7). According to the 1999/2000 rankings these countries are followed by the United Kingdom, the United States and Norway. Germany follows on the seventh place with its relative performance slightly above the European average. However, comparing the situation between the middle of the 1990s and the end of the 1990s the German position has improved slightly.

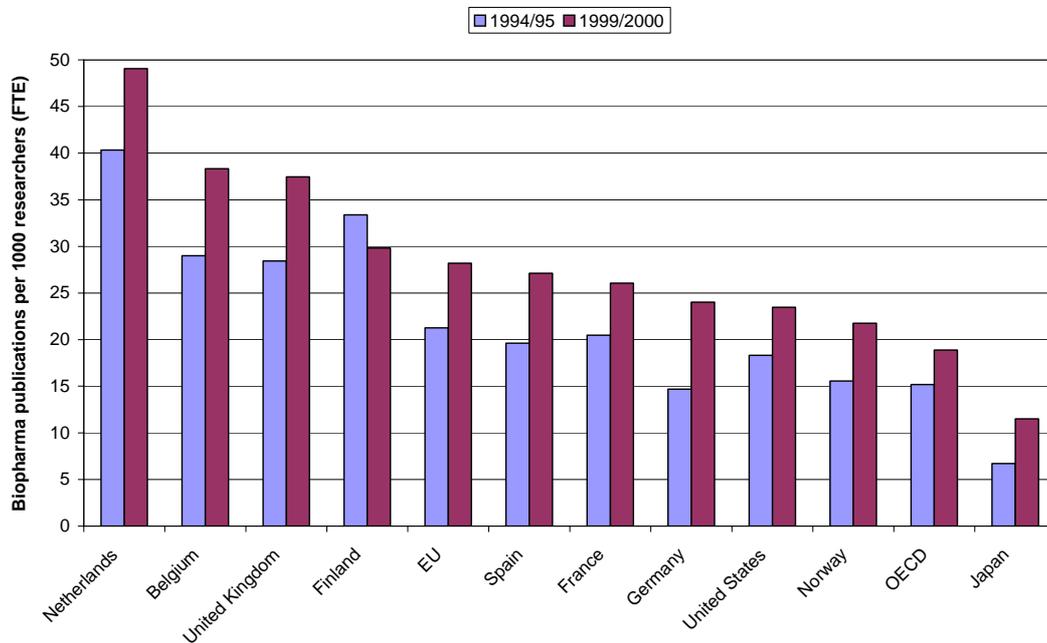
<sup>32</sup> Science Citation Index

Figure 3.7: Biopharmaceutical publications per capita (source: SCI via host STN, searches and calculations Fraunhofer ISI) (pmC: per million capita)



Secondly, publication volumes are related to the number of researchers. Thus, an indication for the efficiency of the research system in terms of scientific output is obtained. Unfortunately, statistical data on the number of researchers in the biopharmaceutical subsector or even in the pharmaceutical sector is not available. Hence, publications had to be related to the total number of researchers in Germany. Therefore, the following data should be interpreted with some caution because they can be influenced by different national specialisations. The number of biopharmaceutical publications per thousand researchers from Germany increased from 15 in the period 1994/1995 to 24 in the period 1999/2000, which could indicate a growing efficiency of the research system in this period, although – as mentioned above – a changing specialisation pattern in a sense that the ratio of researchers active in the different sectors changed during this period could not be ruled out. Compared to the participating countries Germany could improve its position within the OECD slightly, and e. g. outstripped the USA. However, the German publication efficiency in biopharmaceuticals is still way below other countries such as the Netherlands, Belgium or Great Britain. Likewise the German performance is slightly below the European average (figure 3.8).

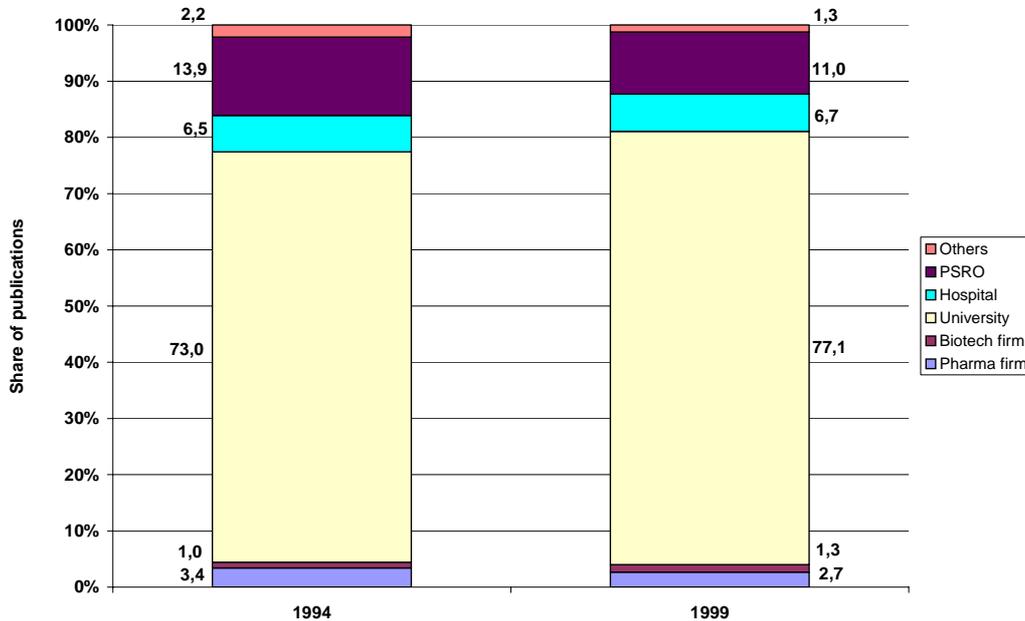
Figure 3.8: Biopharmaceutical publications related to the number of researches per country (source: SCI via host STN, searches and calculations Fraunhofer ISI) (FTE: full time equivalents)



In order to get deeper insight into the performance of the biopharmaceutical innovation system in terms of scientific output, we also analysed which actor types contributed to which extent to the total publication output. As shown in figure 3.9 by far the most publications came from universities with a share of 73 % of all publications in 1994. This ratio increased to more than 77 % in 1999. Public sector research organisations are the second important contributor to the scientific output, however, their contribution decreased slightly between the two periods. Interestingly, also industry is involved in generating publications in this sector. Pharmaceutical firms and biotechnology firms together contribute about 4 % to the total publication volume. Between the two periods biotechnology firms could increase their share slightly.

In conclusion, the bibliometric data indicate that Germany could increase its scientific output, while its specialisation in the biopharmaceutical sector remained rather stable during the 1990s. The increase was mainly driven by publication activities of universities which are by far the most important actors in this system in terms of scientific output and which could increase their contribution to the overall publication volume during this period. Interestingly, also industry is contributing to the scientific output with a growing trend for biotechnology firms. Considering the relative scientific output Germany seems to be less effective than other European countries. However, this notion should be taken with some caution because the required sector-specific data on numbers of researchers are not available.

Figure 3.9: Contribution of different actor types to publications in the biopharmaceutical sector (source: SCI via host STN, searches and calculations Fraunhofer ISI)

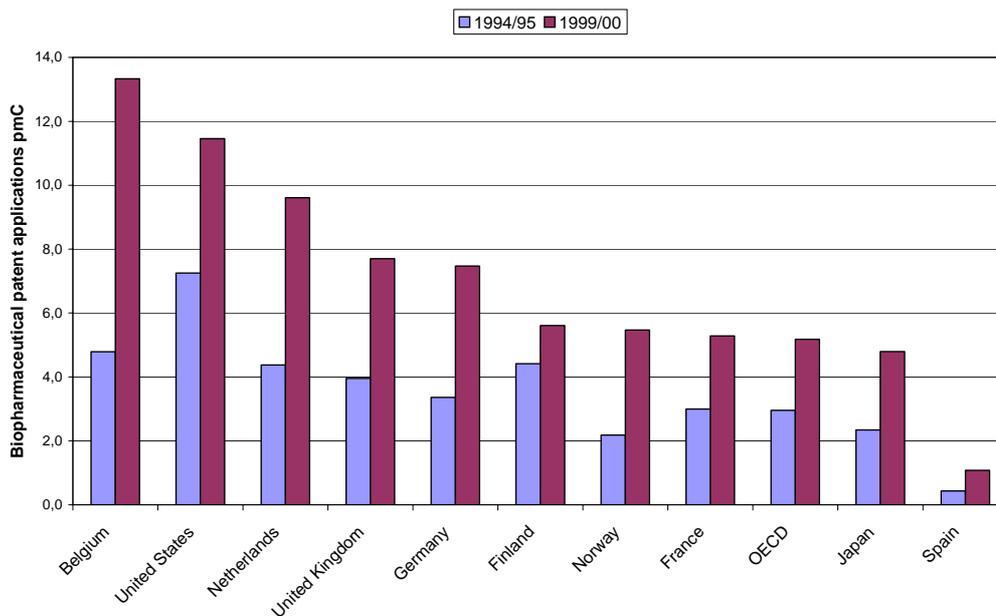


In addition to the bibliometric analysis we also analysed the output of the research and education system in terms of numbers of health graduates at the master and the doctoral level. In 1999 22,490 students passed their master in health sciences. For comparison in the United Kingdom in the same year 45,248 students passed this degree (OECD Health Data 2003). At the doctoral level in 2001 8,339 doctorates in the health sector were counted in Germany which is by far the highest number of all participating countries. For comparison, in the United Kingdom 2,001, in Spain 1,295 or in the Netherlands 668 health PhDs were awarded in that year. Germany also achieves the highest share of health PhDs in all PhDs. In 2001 about one third of all PhDs were granted in the health sector (OECD Education Database 2003). In life sciences Germany also awarded a large number of PhDs in 2001 (2,045). However, with a share of 8.2 % in all PhDs Germany is well below the United Kingdom (15.2 %), France (15.9 %) or Belgium (26.0 %), indicating a lower specialisation of Germany in life sciences education at the PhD level.

The analysis of patent applications in the biopharmaceutical sector shows that Germany could increase its absolute patent volume between 1994/95 and 1999/2000 considerably from 274 patents per year to 620 patents per year. The specific patenting activity measured as number of patents per million capita also increased during this period from 3.4 to 7.5. This ratio is above the OECD average, however, other countries participating in this case study such as Belgium, the Netherlands and Great Britain achieve higher specific patenting rates in the latest period (figure 3.10). We also found an increasing specialisation of Germany on the biopharmaceutical sector as measured by an increasing RPA (Revealed Patent

Advantage) value during the period under consideration. However, indicator values still show tightly below average patenting activities in biopharmaceuticals.

Figure 3.10: Biopharmaceutical patent applications per million capita (pmC) for the periods 1994/95 and 1999/2000 (source: OECD Patent Database 2003, OECD Quarterly Labour Force Statistics 2003, calculations Fraunhofer ISI)



Similar to publication activities also in the case of patent applications the contribution of different actors of the innovation system was analysed (figure 3.11).

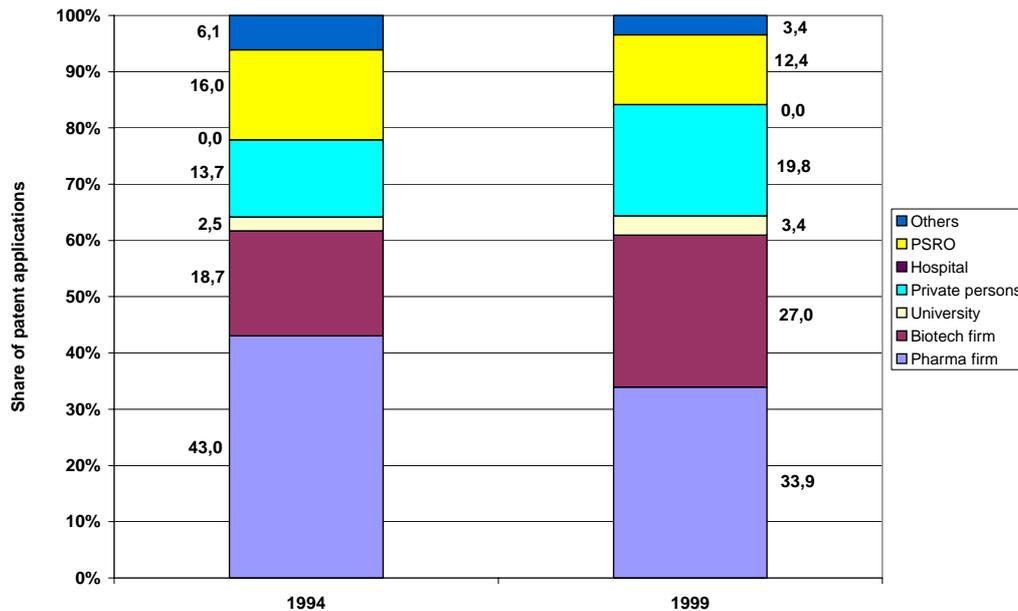
Not surprisingly, in 1994 the most important patent applicants were pharmaceutical firms followed by biotech firms and public sector research organisations. However, in 1999 pharmaceutical firms lost considerably their impact indicated by a change of contribution to patenting from 43 % to 34 %. At the same time biotech firms and universities<sup>33</sup> are gaining importance.

In summary, the analysis of the role of different actors in the biopharmaceutical innovation system in terms of their contribution to technological development (as measured by patent applications) indicates, that pharmaceutical firms as the

<sup>33</sup> Germany presents a special case in this respect due to patent legislation, which granted the so-called “professor-privilege”, according to which the university inventor and not the university was the owner of the patent. In the patent statistics these inventors are classified as private persons. Therefore, a realistic picture of the influence of universities is obtained if the figure of private persons is combined with the figure of universities. In 2002 this legislation was amended transferring responsibility for patenting from the inventor to the university which can decide whether it wants to file a patent application or leave it to the inventor. Inventors receive 30 % of the compensation profit.

traditional actors are losing their dominating role while at the same time new actor types, in particular biotech firms and universities, are gaining influence. This implies that the pharmaceutical industry needs to develop strategies to get access to the technological knowledge which is provided by other actors of the system.

Figure 3.11: Contribution of different actor types to patent applications in the biopharmaceutical sector (source: OECD Patent Database 2003, calculations Fraunhofer ISI)

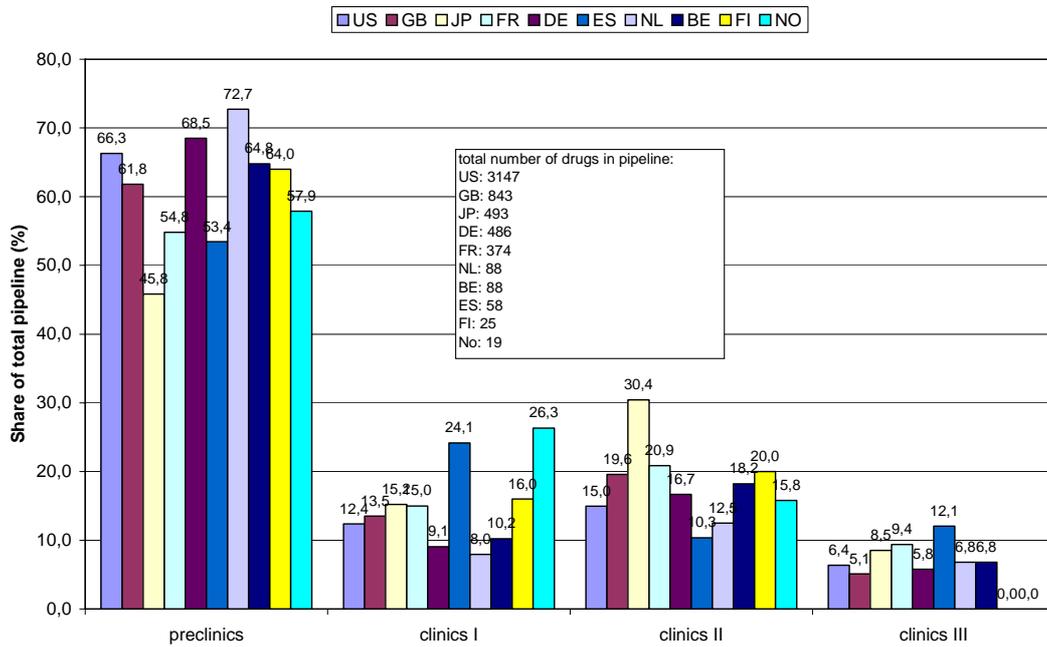


Finally, as an indication for the future commercial performance of the pharmaceutical sector the number of drugs under development in Germany was compared to some other countries. Data for this analysis were provided by the Turku School of Economic and Business Administration based on the IMS database R&D Focus (R&D Focus © 2002 IMS Health Incorporated or its affiliates. All rights reserved. 23 June 2003)<sup>34</sup>. As shown in figure 3.12 there are presently 486 drugs being developed in Germany in pre-clinics and in the clinical stages I to III. The comparison with other countries indicates that in Germany the share of pre-clinical drugs is rather high, while the share of drugs in clinical development is lower. Considering that according to a recent estimate (BioCentury October 6<sup>th</sup>, 2003) the average time period from clinical stage I to market approval is about 7.5 years, the structure of the German drug pipeline seems to indicate that during

<sup>34</sup> The term “drugs developed in Germany” means that the results contain both the drugs that are developed in Germany by a lead company and by a German collaborative partner including agreements for co-development or licensing agreements. This procedure leads to some overestimation of the drugs developed in a country because some drugs might be counted twice: for the lead company and for the co-developer or licensee. Data were retrieved in June 2003 and due to the process of data entering in the database, correspond best to the situation in 2002.

that period the number of new drugs entering the market from Germany might be relatively low compared to other countries. On the other hand, if German companies succeed to bring pre-clinical drugs successful through clinical development, the situation might improve after this transition period.

Figure 3.12: Drugs under development in selected countries. The information corresponds best to the situation in 2002 (source: R&D Focus © 2002 IMS Health Incorporated or its affiliates. All rights reserved. 23 June 2003)



## **4 Innovation barriers/drivers – framework conditions**

### **4.1 Knowledge sources**

In this section knowledge sources will be differentiated into sources contributing to the generation of basic knowledge for the development of biopharmaceuticals and into sources contributing directly to product development.

As an indicator for the first type of knowledge generation publications in biopharmaceuticals can be used as presented in section 3.3. According to figure 3.9 the most important actors for generating knowledge relevant for biopharmaceuticals in Germany are universities and to a lesser extent non-university public sector research organisations. This role of public sector research is also reflected in the scientific partnerships of pharmaceutical firms as measured by co-authorship in scientific publications, assuming that common publications reflect results of common research activities.

Reiss & Hinze (2002) recently performed such an analysis and could show that during the 1990s universities have been by far the most important scientific cooperation partners for the German pharmaceutical industry, being co-authors in 65 % of all co-authored papers. Non-university public research organisations follow on the second place with a share of about 13 % at the end of the 1990s. This analysis also provided some information on the location of scientific cooperation partners of German pharmaceutical firms. In general, an increasing internationalisation of scientific cooperation during the 1990s was found, leading to a decrease of publications co-authored only by German scientists from 44 % at the beginning of the 1990s to 34 % at the end of that decade. Co-authors from other European countries and in particular from the United States displaced German partners supporting the observation of a growing internationalisation of the pharmaceutical industry (see e. g. Jungmittag et al. 2000).

The second issue of knowledge generation concerns the question where firms in the biopharmaceutical sector draw knowledge from which directly feeds into product development. Interviews carried out with large German firms active in biopharmaceuticals during this case study reveal firstly that cooperations are an important source for product-related knowledge. Accordingly, between 15 % and 25 % of the R&D expenditures are spent on external activities. In some companies about one third of the products being developed originates from licensing in.

Concerning the location of cooperation partners the interviewees pointed out that preferred partners presently are biotechnology firms from the United States which seem to be able to provide the required knowledge and products much better compared to European firms. Within Europe biotechnology firms from Britain, France or Germany are preferred partners. Concerning the German situation according to the experience of the interviewees some improvement took place during the last years, in a sense that increasingly more firms from Germany are able to provide suitable know-how.

Results of the interviews also allowed to derive some factors which are important for such cooperations from the perspective of the pharmaceutical industry. Accordingly, the key factor is product orientation of the potential cooperation partner. Product orientation refers not only to specific promising substances for drug development. It also includes validated targets which can be used for the search for new active substances. In this context the term of validation is crucial because quite frequently “would-be cooperation partners” of the pharmaceutical industry do not meet strict validation criteria. According to Drews (2003) a validated target should satisfy the following requirements: firstly, its manipulation should lead to phenotypic changes that are in line with the desired therapeutic effect. Secondly, any such effect should be dose-dependent. Thirdly, the desired phenotypic changes must be inducible in at least one relevant animal model. Fourthly, the way in which the manipulation of a target molecule brings about a particular phenotype should be known.

The second important factor is the market perspective in a sense that the products offered by biotechnology firms should target indications that are interesting for the pharmaceutical company. In addition, they should offer a clear market perspective implying that the biotechnology firm should be able to show in which way markets could be developed for the new products. A third factor is patent protection of products. For the pharmaceutical company it is crucial that the offered substance is already patented or can be patented.

Besides these clear requirements which biotechnology cooperation partners should fulfil from the perspective of the pharmaceutical industry there are also some issues related to the process of cooperation which can form barriers for interaction. On the one hand, in pharmaceutical firms a “not invented here”-attitude still can be found. Traditionally, pharmaceutical firms are used to “big efforts” for developing new drugs, so that there is a certain hesitation to accept that small R&D units which are prevalent in biotechnology firms could also be able to develop interesting products. For these reasons it is important for biotechnology firms to find a sponsor in the pharmaceutical firm who is willing and has the competencies to promote the cooperative activity.

On the other hand, on the side of the biotechnology firm sometimes a type of arrogant attitude is taken, in a sense that the firm tends to overestimate considerably the real value and potential of its products. Such a behaviour might originate from the experience of the biotechnology firm with financing institutions where it seems to be helpful to “oversell” the company. However, when negotiating with pharmaceutical firms an objective and realistic assessment of own strengths is called for.

Even though R&D cooperations are considered as an important source for providing product-related knowledge to the pharmaceutical industry, internal competencies still seem to be much more important for the development of new drugs. According to the interviewed experts from the pharmaceutical industry between 60 % and 90 % of the product developments originate from internal work. An important reason for this situation is the high degree of integration of the internal R&D activities. Integration in this context means that product-oriented networks are established within the firms’ R&D, which combine all the required competencies. Such an integration is considered as a crucial success factor for developing new drugs. External partners frequently are not able to provide this integration because one or more of the needed competencies are missing.

Summing up the analysis of knowledge sources for the development of new products in the biopharmaceutical sector indicates that while the scientific sources are mainly provided by public sector research units including universities, knowledge for product development still originates mainly from internal sources of the pharmaceutical industry. In addition, biotechnology firms are emerging as important contributors to that type of knowledge. In general, an increasing internationalisation and distribution of knowledge sources can be observed.

## **4.2 Human Resources**

Human resources for the biopharmaceutical sector will be discussed from two perspectives: on the one hand the supply with workforce will be discussed, on the other hand the demand situation will be described.

In section 3.3 an overview of the output of the research and education system in terms of health graduates at the master and the doctoral level was given. A more detailed analysis of the development of the labour market for biotechnology in general and biopharmaceuticals in specific was performed recently by Menrad et al. (2003), in a study aiming at analysing the employment potentials of biotechnology. According to this study there was a sharp decrease of the supply with academics in Germany between 1996 and the end of the 1990s. This trend will most likely be reversed until the year 2015 leading to at least the same level of university

graduates (215,000) as in the peak year 1996. If higher transition rates between high schools and universities are assumed, the level of university graduates could be increased until the year 2015 by about 35,000 persons, leading to a total level of about 250,000.

More important than these general trends is the development of the supply by specific disciplines which are relevant for the biopharmaceutical sector. Menrad et al. (2003) present data indicating that the number of graduates in physics, chemistry, medicine, agricultural sciences and forestry will decrease considerably between the peak period of the mid 1990s until 2010. Biology seems to be the only science discipline where an increasing number of graduates could be expected during that period. In parallel to these developments in social sciences and humanities the number of university graduates will increase continuously.

These analyses indicate that the supply with qualified academics in the natural sciences may turn into a bottleneck during the coming ten years. Accordingly, Menrad et al. (2003) argue that the supply with qualified personnel could turn into an important obstacle for the growth of employment in biotechnology.

Considering the demand for qualified personnel in the biopharmaceutical sector, the study of Menrad et al. (2003) shows that the biopharmaceutical sector employs the highest share of academics among those sectors that presently are affected by biotechnology (chemical industry, environmental industries, food-processing industries). During the second half of the 1990s the share of academics in this sector even increased pointing to a growing science intensity of the field. Using data of the so-called "micro-census" which is a representative population survey in Germany, Menrad et al. (2003) also analysed the qualifications of academics who are presently working in the biotechnology industry. Accordingly, the main disciplines are biology and bioengineering, medicine and pharmacy, various engineering sciences, chemistry and chemical engineering, information technology, and also social sciences and economics.

Although, no differentiation was made in this study between biopharmaceuticals and other areas of biotechnology, it seems justified to conclude that the distribution of qualifications confirms the interdisciplinary character of the sector.

From the perspective of the biopharmaceutical industry first of all as indicated in figure 1.2 in chapter 1 a strong increase in employment in the research-intensive pharmaceutical firms could be observed in Germany since 1999. According to the interviewed representatives of pharmaceutical firms, the need for qualified personnel could be met by the German labour market without major problems.

Concerning small and medium-sized biotechnology firms in Germany the recent consolidation period also resulted in some decrease in employment in these firms

(Ernst & Young 2003), so that presently there are no problems in finding qualified academic staff. The situation is a little different with respect to technical staff. Since many of the small biotech firms provide no vocational training for such personnel, they are dependent on the supply by special schools for technicians or by larger firms which train such staff. During the last few years there has been some shortage in these qualifications in Germany, in particular in those regions (such as the surroundings of Munich) where many biotechnology firms were established. Though at present there seem to be no major problems with this type of staff, it could be expected that some shortage might arise during the years to come if the biotechnology industry will turn back into the growth track.

Concerning qualification issues at universities, a recent study of the Boston Consulting Group on the competitiveness of the pharmaceutical industry in Germany (BCG 2001) provides some information on problems with the academic education, which were also confirmed during the interviews with the pharmaceutical industry during this project. At the level of university education from the point of view of the pharmaceutical industry the following problems can be mentioned:

- A rather low orientation of biomedical sciences towards applications.
- Not enough room for students in arranging their study according to their own preferences pointing to lacking flexibility.
- The neglect of management and economic curricula in science study courses.
- Lacking communication skills and capacities for teamwork among students which point to a neglect of such issues during their studies.

At the clinical development level the Boston Consulting Group study (BCG 2001) and company interviews consider patient-oriented clinical research as crucial for the biopharmaceutical industry. In Germany such research activities are not as well developed as in other European countries and in particular as in the United States. Clinical research seems not to be attractive for young scientists in Germany because it is not rated very important for scientific careers. Accordingly, study courses for patient-oriented clinical research are almost completely absent in the German academic universe.

In summary, the analysis of human resources for the biopharmaceutical industry in Germany allows the following conclusions:

- Interdisciplinary skills are crucial for biopharmaceuticals. Interdisciplinarity in this context means that scientists who are specialised in one of the various different disciplines required for biopharmaceuticals also need to develop the capacity to interact with other disciplines.

- Presently there is no shortage in skilled personnel for the biopharmaceutical sector except in some specific areas such as patient-oriented medical research, natural scientists with management and economic know-how, and in general scientists with well-developed communication and team work skills.
- However, scenarios of the future development of the supply of academics in Germany indicate that a shortage in most of the natural sciences and engineering disciplines, which are important for the sector, could be expected.

### 4.3 Financing

In this section we will discuss public and private financing of the biopharmaceutical area in Germany. Concerning public funding it is rather difficult to provide a complete inventory of the current amounts of funding for this sector because there are no respective official statistics. However, drawing on the previous EU-funded INVENTORY project (Giessler & Reiss 1999) it is possible to derive some conclusions on public funding for this sector between 1994 to 1998. During this period the most important funding organisations in Germany for biomedical research were the Federal Ministry of Education and Research (BMBF), the Federal Ministry of Health (BMG<sup>35</sup>) and the DFG (see chapter 2). The BMG funded mainly departmental research activities that were application oriented and had the intention to create knowledge related to departmental functions. In addition, the BMG together with the BMBF initiated the programme “Health Research 2000”, which was one of the most important federal funding activities for the biopharmaceutical sector.

The main instruments of the BMBF to support biopharmaceutical research were the programmes “Health Research 2000” and “Biotechnology 2000”. The thematic priorities of BMBF funding in the area included biomedical research, clinical research and also medical technology.

Besides the programmatic activities of the BMBF and the BMG and funding activities of the DFG various state ministries support research relevant for biopharmaceuticals. In particular due to their responsibility for universities, the German “Länder” are important actors in the funding system.

Woerner et al. (2000) estimate the total amount of federal funding for the biopharmaceutical sector during the period 1994 to 1998 at about 1,700 million € corresponding to annual funding of 340 million €

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<sup>35</sup> The BMG has been reorganised recently and now is also responsible for social security. Accordingly, it was renamed into BMGS.

Additional data on public funding related to biopharmaceuticals was provided recently by the Boston Consulting Group (BCG 2001) in its analysis of the competitiveness of Germany in the pharmaceutical sector. Accordingly, in the year 1999 a total amount of 3.43 billion € of public money was spent for biomedical basic research. Unfortunately, no details of the sources for this figure are provided, so that the reasons for the difference between this rather large amount and the annual funding as estimated by Woerner et al. (2000) are difficult to explore. Partly it might be explained by the fact that probably all types of basic medical research were included in the BCG figure.

In the BCG study also an international comparison of public R&D expenditures for biomedical research was made (BCG 2001). Accordingly, in Germany in the year 1999 the per capita expenditures for biomedical research were 42.6 € compared to 43.0 € in the United Kingdom or 54.5 € in the USA and more than 65 € in Sweden and Denmark. The report argues that the relatively low public expenditures for basic biomedical research in Germany are an important reason for the decreasing attractiveness of Germany as a location for biomedical R&D and recommended to increase public spending considerably.

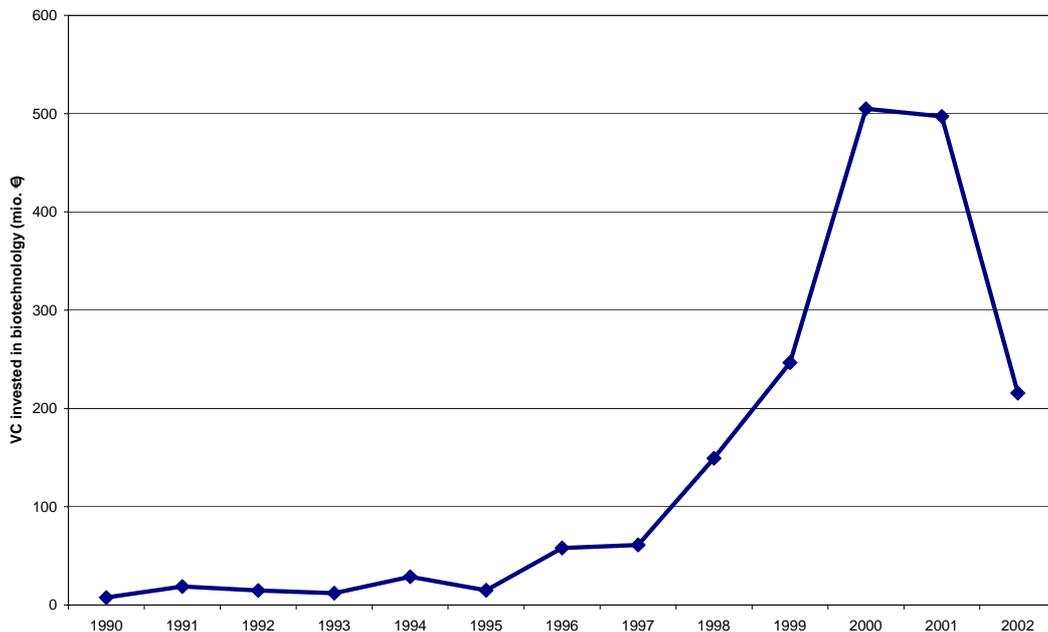
In the interviews with the biopharmaceutical industry another critical feature of public funding was put forward: the time perspective. Since biopharmaceutical research is a long-term activity, it is considered as not very likely that within usual duration of funded projects (about three years) enough scientific output could be generated. Not only in industrial activities but also in public research a certain level of planning security is required, for example, if searching and hiring highly qualified scientists for new projects. Therefore, it is recommended to allow a longer perspective for such projects, however including a clear milestone planning.

Concerning private financing venture capital played a key role for the development of the biopharmaceutical sector in Germany during the last years. In consequence, the recent break-in of the venture capital market changed the business environment considerably. Looking first at the general (not sector-specific) trends in the European venture capital market the year 2002 was characterised by a continuing consolidation. The total amount of venture capital invested dropped from 4,335 million € in the year 2001 to 2,506 million € in the year 2002. The average size of investments decreased from 1.9 million € to 1.4 million €. In addition to this drop in available capital by about 40 %, also structural changes in venture capital investments took place which have important implications for high-tech firms. In particular a strong shift in the stages of investment away from early-stage to late-stage investment can be observed between 2000 and 2002 (EVCA 2003). While in 2000 8.2 % of the venture capital was invested in the seed phase and 26.5 % in the start-up phase, the respective shares dropped to 3.1 % (seed) and 19.3 % (start-up) in the year 2002. All in all, these trends in the venture capital market imply that less

money is available for venture capital financing in general and in particular for early-stage financing.

In biotechnology there was a very strong increase of venture capital financing during the 1990s until the peak years 2000 and 2001 with total investments in biotechnology of about 500 million € per year (figure 4.1).

Figure 4.1: Venture capital invested in biotechnology in Germany between 1990 and 2002 (source: EVCA Yearbooks 1990 to 2003)



In 2002 the amount of invested venture capital in biotechnology dropped to 216 million €. A more detailed look on the development of venture capital investment in biotechnology is given in table 4.1.

Table 4.1 shows first of all, that the decrease of venture capital investments in biotechnology is also reflected in the decreasing share of biotechnology investments related to all investments between 2001 and 2002. However, the share of biotechnology investments in 2002 was still above the share in 1999. In addition, the relative drop was considerably lower compared to the absolute drop. This seems to indicate that the years 2000 and 2001 could be considered as exceptionally good years for venture capital investment in biotechnology, while the year 2002 seems to approach more the normal situation. Further, the biotechnology sector seems to fare better than other sectors as indicated by the rather low relative decrease of investments into the sector. The number of biotechnology companies which received venture capital investment in biotechnology even increased in 2002, reaching with 199 companies an absolute maximum. This indicates on the one hand

that venture capital firms keep their portfolio of biotechnology firms. On the other hand, this also implies that for each individual firm smaller investments are available, leading to more competition for venture capital and accordingly to difficulties for new firms to acquire venture capital investments.

Table 4.1: Venture capital investment in biotechnology in Germany (source: EVCA Yearbooks 1990 to 2003) (n/a: not available)

Year	Amount of biotechnology investment (% of total investment)	Number of biotechnology investments	Number of biotechnology investments (% of total investments)	Number of biotechnology companies	Number of biotechnology companies (% of all companies)
1990	1,4	11	1,8	n/a	n/a
1991	3,2	23	3,2	n/a	n/a
1992	2,3	24	3,5	n/a	n/a
1993	1,9	18	2,7	n/a	n/a
1994	3,6	27	3,6	n/a	n/a
1995	2,3	28	3,7	n/a	n/a
1996	8,3	35	4,6	n/a	n/a
1997	4,6	104	9,6	88	9,2
1998	7,6	135	8,9	80	6,8
1999	7,8	191	9,2	113	7,3
2000	10,6	288	9,6	186	7,9
2001	11,2	256	11,1	174	8,8
2002	8,6	191	11,1	191	11,1

Taken together, the analysis of the venture capital financing situation indicates that it is mainly the general development on the venture capital market which affects biotechnology. Further, biotechnology seems to be more stable in terms of investments received compared to other sectors. The most critical development for biotechnology seems to be the structural shift in venture capital financing away from early-stage financing, resulting in high barriers for new entrants.

Public offerings are an important divestment strategy for venture capital firms. Initial public offerings (IPO) by German firms reached a peak in the year 2000 when ten firms went public. However, since then the stock market window closed almost completely for biotechnology firms. Only one firm filed an IPO in 2001, no offerings were made in 2002 (Ernst & Young 2002). Obviously, going public presently is no option for financing activities of small and medium-sized firms in the biopharmaceutical sector.

## 4.4 Regulations

A large number of regulations is governing the biopharmaceutical sector. A detailed analysis of all these regulations would go far beyond the scope of this study. Therefore, the discussion will focus on a selection of rules that is considered as most important for the biopharmaceutical sector.

Two important general laws which are relevant for the biopharmaceutical sector are the Medical Drug Law (Arzneimittelgesetz) and the Medical Product Law (Medizinproduktegesetz), which form the main regulatory framework for the approval and registration of products of the biopharmaceutical sector. The implementation of these rules creates the framework for market access. Therefore, this issue will be considered in more detail in chapter 5.

For biotechnology-related work the most important law is the Genetic Engineering Act (Gentechnikgesetz) of 1990. By that year Germany was the first industrialised nation to have a specific law governing genetic engineering which was an implementation of the two EU directives for the treatment of genetically modified organisms in closed rooms (90/290/EWG) and for the release and trade of GMOs (90/220/EWG). Soon after the law had been promulgated complaints came up in Germany that due to the costly and time-consuming licensing procedures and stringent requirements prescribed by the law, science and industry in Germany were hindered in their competition with other countries. Against these discussions an amendment of the Genetic Engineering Act was adopted in 1993, aiming at abolishing unreasonable and objectively unjustified restrictions and bureaucratic obstacles. Even though it might be debatable how important the influence of the Genetic Engineering Act on the development of biotechnology in Germany was in practice, nowadays the amendment of the Genetic Engineering Act in 1993 is frequently cited as an important step towards the creation of a wealthy German biotechnology industry. It should be noted, however, that other factors such as the general lack of awareness among industry, science and policy of this key technology in the early years of its development might better explain the late start of commercialisation of biotechnology in Germany (Woerner et al. 2000).

Since 1990 the Embryo Protection Act bans human cloning in Germany. The interpretation and implementation of this law is made difficult because there are still discussions on the exact definition of the embryo and stem cells in the sense of this law. Concerning human stem cells there has been an intensive debate in Germany about the regulation of stem cell research<sup>36</sup>. In April 2002 the German parliament passed a specific stem cell law which bans the import of human embryonic stem cells and allows research on these cells only under strict conditions, permitting

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<sup>36</sup> It should be noted, however, that mainly a few key players had driven the debate.

work only with stem cells created before January 30<sup>th</sup>, 2002 and only if the researcher cannot demonstrate feasible alternatives.

The protection of intellectual property has strong effects on the effective patent life of drugs (which is the number of years remaining in a drug's patent term after the authority approves the drug for market). In Europe (as well as in the USA) patents have a life span of 20 years. After that period other firms may produce medicines on the basis of the same active substance. From the perspective of the biopharmaceutical industry there is a strong interest to keep market exclusivity as long as possible to gain maximum returns on R&D investment. On the other side the institutions reimbursing medical treatments are interested in the development of cheaper generic drugs. According to present law authorities do not register a drug which contains the same active substance as a patented drug for a certain period after market approval. In Germany that period is ten years now. However, in some other country it is much shorter. At a European level recently an amendment of directive 2001/83/EC was passed, harmonising these periods to ten years after the reference medicinal product has been approved with possible extension by one year.

Concerning patenting in biotechnology, the EC directive 98/44 sets the framework for the legal protection of biotechnological inventions. The directive should have been implemented by July 30<sup>th</sup>, 2000. However, only in June 2003 the German government decided to transfer the directive into national law<sup>37</sup>.

Finally, another critical issue related to intellectual property in biopharmaceuticals is the ruling of patent protection in academia. In Germany university patents were traditionally regulated by the "Inventions made by employees Act (ArbNErfG)" that included the so-called "professor-privilege" according to which the university inventor was the owner of the patent. Accordingly, some practitioners argued that research institutions had no incentives to support patent applications.

The discussions on the modification of the regulation concerning IPR for university scientific results started a process of amendment in 2001. The amendment of the ArbNErfG planned to encourage patenting activities in universities, by transferring the responsibility for patent application from the inventor (university researcher) to the institutions and assigning the inventor a participation in the revenues. In 2002 the amendment was approved. Accordingly, since February 2002 all inventions have to be presented to the research institution which has to proof the convenience of applying for intellectual protection. The institution can decide whether it wants to apply for patent protection or leave them to the inventor for application. Inventors receive 30 % of the compensation profits.

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<sup>37</sup> In March 2004 the German parliament startet consultations of the directive.

According to the interviewed experts from industry and research organisations, presently there seem to be no major problems concerning regulations that are relevant for research activities in biopharmaceuticals. Problems can occur, however, in relationship to the implementation of the regulations by the responsible institutions. Bureaucratic procedures may hinder research activities, and most importantly the involvement of different institutions in managing the different regulations without sufficient coordination slows down the overall process and hampers licensing and approval procedures. Concerning the specific regulatory framework for genetic engineering an improvement of the situation in Germany during the 1990s is acknowledged. A strong support for a faster implementation of the biopatent directive was expressed during the interviews. In general, differences between European states in the regulatory framework were perceived as getting smaller. Against this background harmonisation is seen not as much as a European issue, but an issue between Europe and other parts of the world.

As mentioned in the beginning the key regulatory concern, in particular from the perspective of the biopharmaceutical industry, are all those regulations that are related to market access and market attractiveness (see chapter 5).

## **4.5 Entrepreneurship**

In the 1980s and early 1990s a lacking awareness of the commercial potentials of biotechnology among academia (and also among large pharmaceutical firms and politicians) was an important obstacle for the commercial development of this sector (Reiss 1998). This attitude changed considerably during the 1990s not least motivated by the “BioRegio” contest of 1995. Considering and advancing commercialisation of biotechnology became fashionable and founding an own company emerged as a well-acknowledged activity of academics. These changes together with a supportive financial environment resulted in the tremendous start-up dynamics in Germany as shown in figure 3.1.

However, there were also some draw-backs associated with the discovery of entrepreneurship in German academia. Scientist entrepreneurs normally did not have the opportunity to acquire the management and economic skills which are required for leading a start-up to a successful growing company. Some start-ups realised this danger rather early and integrated skilled management staff from the beginning or in some cases company foundation was a joint activity of scientists and managers. Others tended to neglect the management dimension of their business and put too much emphasis and trust into the science push as a driving force for firm development. This too narrow science focus of the new generation of entrepreneurs has its roots in university education where entrepreneurship and

business know-how is still not established widely in science study courses (see section 4.2).

Another dimension of entrepreneurship relates to large research networks which have been established in Germany e. g. in genomics. According to interviewees from the pharmaceutical industry, the idea of entrepreneurship, in a sense that also commercial applications play an important role, in such research networks is not developed well enough. It is argued that only few commercially interesting patents resulted e. g. from the German Human Genome Project.

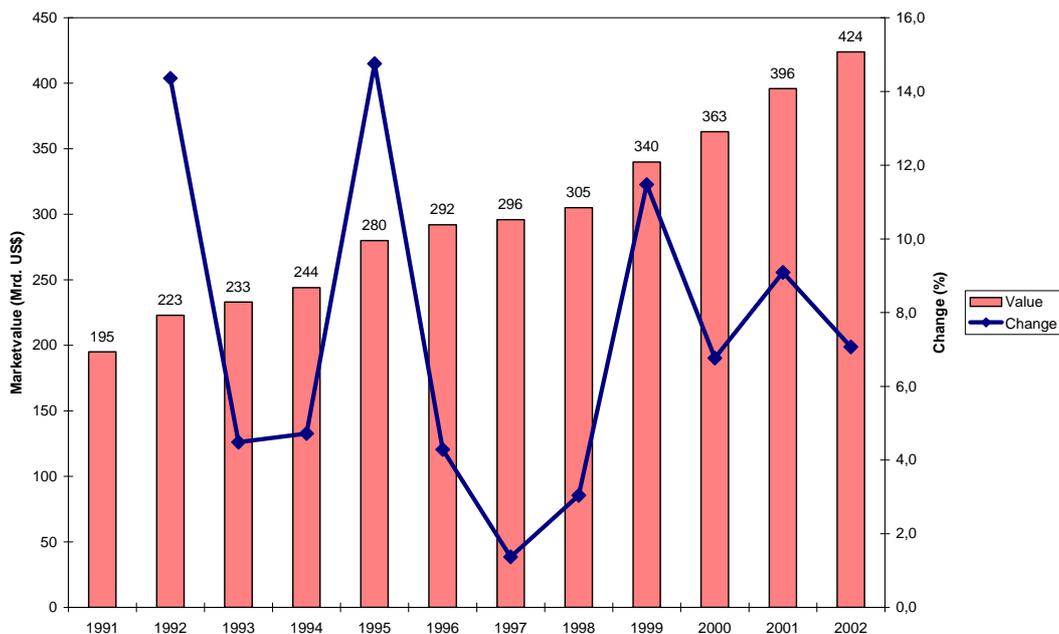
In summary, there was a clear improvement of entrepreneurship in Germany during the last ten years, so that lacking entrepreneurship cannot be considered as an important innovation barrier in the biopharmaceutical sector anymore. However, the required modifications in science education at universities, in a sense that the skills required for entrepreneurship should be integrated into science study courses, has not yet been implemented widely. The lack of such skills could be one reason for the fact that the commercially interesting output of some important relevant research activities in Germany is lower than expected by the biopharmaceutical industry.

## 5 Markets

### 5.1 General market trends

Between 1991 and 2002 the world market for pharmaceuticals more than doubled from 195 billion US\$ to 424 billion US\$ (figure 5.1) with annual growth rates between 2 % and 15 %.

Figure 5.1: World pharmaceutical market at ex-factory prices between 1991 and 2002 (source: IMS Health Data cited in BPI 2003 and VFA 2003)

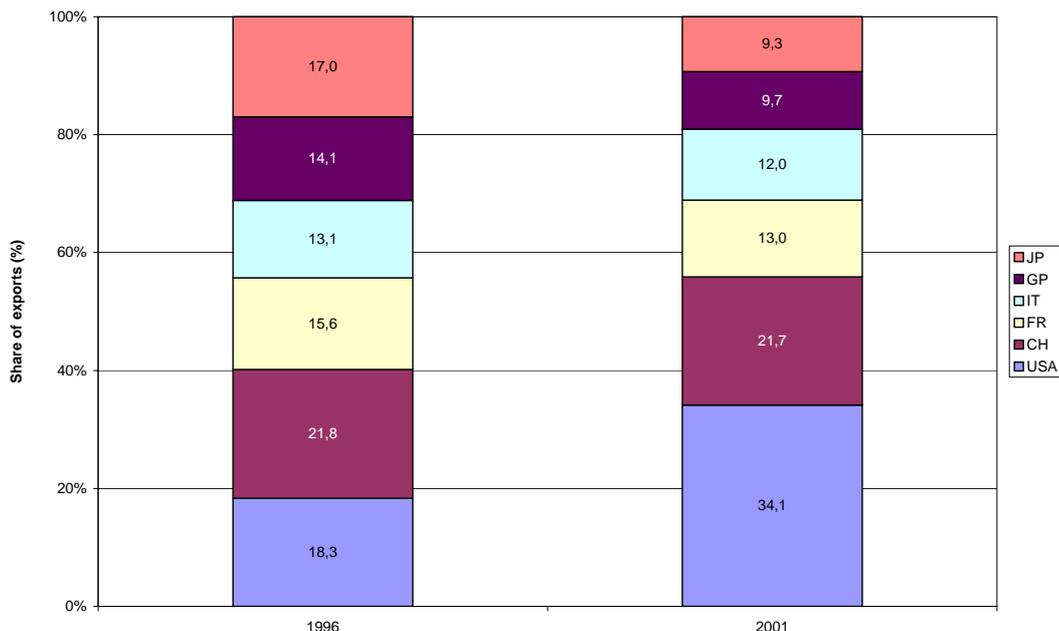


During this period important structural changes of the world market took place. While in the early 1990s the United States and Europe both contributed about one third to the world market, the US market grew by 11.6 % per annum well ahead of Europe with an average weighted growth rate of 7.4 % between 1991 and 2001, resulting in a market share of the US of 45 % in 2001 and close to 50 % in 2002. The European market share dropped at the same time to about one fourth of the world market (VFA 2003, EFPIA 2003). The market share of Germany dropped from about 8 % in the early 1990s to 4 % in 2002 (VFA 2003). These data indicate that the North American market could increase its attractiveness considerably

during the last ten years. This seems to be the case in particular for new medicines. According to IMS Health Data (cited in EFPIA 2003), 62 % of the sales of new medicines marketed since 1997 were generated on the US market compared with 21 % on the European market.

This shift towards the US market is also indicated by the changes in the main trade partners of the German pharmaceutical industry (figure 5.2). In 1996 about 22 % of the exports of the German pharmaceutical industry were directed towards Switzerland which was the main trade partner in that year. The US held a second position with about 18 % of the exports. In 2001 the United States have almost doubled their share in the German exports. With about 34 % they are by far the most important trading partner. Switzerland could maintain its position while considerable reductions occurred in the case of Great Britain and Japan.

Figure 5.2: Main export regions of the German pharmaceutical industry (source: BPI 2003)



On the German market for pharmaceuticals we can also observe interesting structural changes during the last few years. In 1998 firms with a German origin held 45.5 % of the German pharmacy market<sup>38</sup>. (table 5.1) (BPI 2003). Until 2001 this share of the German industry dropped to 40 %. At the same time the pharmaceutical industry from the USA, Great Britain and France could improve its

<sup>38</sup> The German pharmacy market makes about 86 % of the total pharmaceutical market in Germany, measured in ex-factory prices (BPI 2003).

position on the German market by between 2.2 and 3.0 percent points. Switzerland as the second-best performing international country kept its market share of about 10.4 %. Obviously, the competitive position of German pharmaceutical firms on the German market became weaker<sup>39</sup>.

Table 5.1: International competition on the German pharmacy market (source: BPI 1999, 2003)

	Share of German pharmacy market (%)	
	1998	2001
DE	45.5	40.0
USA	21.1	23.9
CH	10.4	10.4
FR	5.6	8.6
UK	6.1	8.3
Other	12.0	7.0

Products of the biopharmaceutical sector are expected to contribute innovative solutions to medical problems. In order to assess the market perspective for such medications in Germany, it is important to analyse in which way innovative drugs contribute to the total market in Germany. During the last years almost all of the new molecular entities (NMEs) which were introduced worldwide also entered the German market. In 2001, NMEs introduced during the preceding 5 years gained a market share of 25 % in Germany (Kommission der Europäischen Gemeinschaften 2003). In Europe only Spain (30 %) and Switzerland (27 %) presented higher market shares for NMEs. However, in the USA NMEs could achieve a market share of even 32 %. In 2002, 27 NMEs were introduced in Germany, compared to 29 in the preceding year and 27 in the year 2000 (VFA 2003). However, only an average of 2 NMEs were introduced first in the German market.

By far the largest share of the German market (about 80 %) is made by prescription drugs which comprise among others all innovative medications for the treatment of important medical problems. This market segment is further characterised by strong growth during the last years. Between 1996 and 2002 it grew by 66 % (VFA 2003). This data indicate that the German market in principle is an interesting market for innovative drugs. This notion is further supported by the market development of biopharmaceuticals in Germany. Since 1996 this market segment could grow with annual growth rates of about 26 % reaching sales of 1.53 billion € (ex-factory

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<sup>39</sup> It should be noted that the creation of the French company Aventis in 1994 absorbing the German Hoechst most likely led to a shift of market shares from Germany from France. However, this effect does not account for the total shift of market shares from German firms to firms from abroad.

prices) in 2002 (VFA 2003). This corresponds to a market share of 8.3 %. The dynamics of the biopharmaceutical market segment is also underlined by the fact that 3 groups of biopharmaceuticals (erythropoietin, beta-interferon, insulin) are among the top 15 pharmaceuticals in Germany in terms of market growth (VFA 2003).

Taken together, the market data firstly indicate a strong trend towards the US market and an improving position of US American firms on the German market. Secondly, pharmaceutical firms with a German origin are getting increasingly under competitive pressure, not only internationally but also on their home market. Thirdly, even though the growth rate of the German pharmaceutical market is considerably lower compared to the US American market and also to some other international markets, Germany still seems to be an interesting market for innovative drugs in general and biopharmaceuticals in particular.

## **5.2 Organisation of the German health care system**

The German health care system is characterised as a so-called 'Bismarck system' which is financed by subscription fees. The principle is that health care insurance is part of social insurance and health care is warranted as a basic right. For financing subscriptions are taken from employees and employers each contributing 50 % of the total. Governmental intervention into the system is mostly direct and the role of professional organisations is strong.

The health care system comprises all organisations and persons which contribute to the maintenance, improvement or restoring of public health. A broad variety of different actors and institutions contribute to this general goal. They provide health service, are responsible for financing, for governance, consulting and controlling. Three main groups of actors can be differentiated:

- Patients, who's role will be discussed in more detail in section 5.4,
- Organisations offering medical service in the in-patient and the out-patient sector and
- Insurance companies which play an intermediate role between the other two groups, covering the costs and financing the various health services.

### **Health service providers**

Health service providers in the German system include physicians, dentists, physiotherapists, hospitals, pharmacies, the pharmaceutical industry, out-patient nursing services, rescue services and midwives. These groups are separated in the

German system into the out-patient sector and the in-patient sector. All in all, in the year 2000 more than 4 million people were employed in these different institutions (Federal Ministry of Health 2002).

Key actors of the out-patient sector are physicians, dentists, various nursing services and pharmacies. Physicians play a key role in the German system by providing the major share of health services. About 90 % are CHI physicians who take care of members of the compulsory health insurances (CHI).

The interests of CHI physicians are represented by more than 20 regional associations (Kassenärztliche Vereinigungen), which form key organisations of self-government in the health care sector. In addition to these organisations there is a federal association of CHI physicians. All these associations are governed by the Federal Ministry of Health and Social Security.

Key actors of the in-patient sector are hospitals, nursing homes and other related organisations. Similar to the associations of CHI physicians there exists also an interest group of hospitals which negotiates contracts with the associations of health insurance companies on the reimbursement of hospital services. In addition to the state level interest groups there is also a federal association of hospitals.

### **Insurance Companies**

A key element of the German health care system is the compulsory health insurance (CHI) which covers about 60 % of the total health expenditures in Germany. Some other social insurances also contribute payments to health care expenditures. In addition to these compulsory insurance systems there exists also a private health insurance, covering about 8 % of the health care expenditures. The private and the compulsory health insurances are financing about three quarters of the total costs for pharmaceuticals in Germany (Hüsing & Bührlen 2003). In 1999 88.5 % of the German population were members of the compulsory health insurance, 9 % had a private health insurance. In 2002 there were 355 compulsory health insurance companies and about 50 private insurance companies.

### **Governance**

The central governing organisation of the German health care system is the Federal Ministry of Health and Social Security (BMGS). Several independent authorities are affiliated with the BMGS, among these the Paul Ehrlich Institute and the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) which are responsible for the registration and approval of medicines in Germany.

A key characteristic of the German system is the self-government of the system by representatives of the compulsory health insurance companies and representatives

of physicians. These two groups form the Federal Committee of Physicians and Sickness Funds (Bundesausschuss der Ärzte und Krankenkassen) which exerts important functions in the German health care system:

- It takes decisions on guidelines for physicians, patients and insurance companies which detail the specific health services.
- It takes decisions on the authorisation of new medical treatments for reimbursement by the compulsory health insurance companies.
- It defines groups of medicines for which fixed prices can be set.
- It develops criteria for assessing the quality of the services of CHI physicians.
- It decides on the therapeutic benefit and value of new medicines.

In summary, the German health care system is on the one hand a highly regulated system, and on the other hand is characterised by self-governance. Key actors in the system are the compulsory health insurance companies and their representations, CHI physicians and their interest groups and hospitals. The strong positions of intermediate organisations is an important feature of the German health care system.

The self-governance principle allows that the involved actors and interest groups can contribute to the functioning and future development of the health care system. However, the broad variety of different actors and different interests which influence the whole system makes coordinated activities difficult and also leads to a certain inertia of the system. For this reason reforms of the German health care system are a challenging task where advances can only be expected if compromises are made which are supported by the key actors of the system.

### **5.3 Regulation of market access**

Two different procedures need to be discussed concerning market access of products of the biopharmaceutical industry. On the one hand, there are the regulations for approval of medicines and their implementation. On the other hand, due to the great importance of the compulsory health insurance system in Germany (see previous section), the procedures for getting reimbursement for drugs form another important precondition for market access.

#### **Approval procedures for drugs**

Since 1978 all medicines need an approval in Germany in order to assure their safety. Homeopathic medicines are exempt from this ruling, however, they need to be registered. Since 1995 a European approval procedure has been established for

the Member States which complements national approval procedures. Accordingly, the following agencies are important for getting approval of new drugs in Germany:

The London-based European Agency for the Evaluation of Medicinal Products (EMA) coordinates the scientific resources of the Member States in order to evaluate and supervise medicinal products for both human and veterinary use throughout the European Union. Within the EMA, the Committee for Proprietary Medicinal Products (CPMP) is responsible for preparing the agency's opinions on questions relating to the evaluation of medicinal products for human use. It is made up of 30 members nominated by the Member States. The Committee for Orphan Medicinal Products (COMP) is in charge of the designation of new pharmaceuticals as orphan drugs, and the Committee for Veterinary Medicinal Products (CVMP) gives advice on medicines for veterinary use.

In Germany the registration of new pharmaceuticals is regulated by the German Drug Law (Arzneimittelgesetz; AMG) introduced in 1961. The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) is the federal authority which controls the reviews of efficacy, safety and adequate pharmaceutical quality of finished medicinal products on the basis of the German Drug Law and grants marketing authorisation. Licenses are limited to five years. Renewals are granted upon application and after new evaluation. The BfArM must be notified of variations to already licensed medicinal products. Major variations can only be implemented after authorisation by the BfArM. The Paul Ehrlich Institute is commissioned with the granting of marketing approvals and the batch control of (immuno-)biological and haematological drugs. The German authorities are given advice by expert approval commissions (Abraham & Lewis 2000, Bundesinstitut für Arzneimittel und Medizinprodukte 2003).

The general requirements for safety and efficacy testing of a new drug are agreed internationally, and therefore the implementation of regulations is similar in all countries with a major pharmaceutical industry. The process for the approval of a new drug or medical device takes several years on average. Of the many compounds that are tested by drug manufacturers for therapeutic benefits, only 5 in 5,000 that enter preclinical testing actually make it to human testing. Only 1 out of these 5 makes it through the approval process and onto the market (Alliance Pharmaceutical Corp. 2003).

The first step in a pharmaceutical product development is preclinical testing, where the pharmaceutical company conducts laboratory and animal studies to show the biological activity of the compound against the targeted disease and the compound is evaluated for safety. These tests take on average approximately three and a half years (Alliance Pharmaceutical Corp. 2003).

After completing preclinical testing, the company files an Investigational New Drug Application (IND) with its respective competent authority to begin to test the drug in people. The IND shows results of previous experiments, how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured.

Clinical trials, i. e. tests of the active compound in humans, are conducted in three different phases plus a fourth after approval.

Phase I tests take about a year and involve about 20 to 80 healthy volunteers. The tests study a drug's safety profile, including the safe dosage range. The studies also determine pharmacokinetics and pharmacodynamics (i. e. how a drug is absorbed, distributed, metabolised and excreted, the duration of its action), and possible and optimal methods of drug administration.

In Phase II, controlled studies of approximately 100 to 300 volunteer patients (people with the disease) assess the drug's effectiveness, which takes on average about two years. More safety data is gained as well as information concerning the effectiveness of the drug at treating the symptoms or conditions it is proposed for. It is focused at determining the therapeutic effectiveness in subjects, with further attention to safety. The results of phase II are used to establish the parameters of phase III.

This final phase of clinical trials involves several hundred to thousands of individual subjects who suffer from the specific condition or conditions that the drug is intended to treat. This phase aims at determining if the benefits of a treatment with the tested compound are significant enough to outweigh the risks. The tests used in this phase must be extremely thorough and meet rigorous standards, as they are the basis for the approval of the drug.

The cost for clinical trials can reach considerable amounts. Depending on the indication they range between 1000 € (e. g. high blood pressure) to 10.000 € (e. g. cancer or cardiology) per patient (Novartis 2003).

The conduct of clinical trials is regulated in detail by national or transnational legislation which reflects the standards of "Good Clinical Practise" (GCP) developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the World Medical Association's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (World Medical Association 2002).

Following the completion of all three phases of clinical trials, the company analyses the complete data and files a New Drug Application (NDA) with its competent

authority if the data successfully demonstrate safety and effectiveness. The NDA must contain all of the scientific information that the company has gathered. Once the NDA was approved, the new medicine becomes available for physicians to prescribe. The company must continue to submit periodic reports to the authority, including any cases of adverse reactions and appropriate quality-control records.

There are two procedures to receive approval for NASs (New active substances) in more than one EU Member State: the centralised procedure and the mutual recognition (“decentralised”) procedure. Under the decentralised procedure a company or a Member State can ask two or more Member States to recognise the marketing authorisation granted by the Member State of the first approval (the “Reference Member State”). Marketing authorisations by one Member State ought to be recognised by the other Member States. Disagreements must be resolved by EMEA’s scientific committee, the Committee for Proprietary Medical Products (CPMP), the outcome is binding for the Member States concerned. Refusal to accept an authorisation of another Member State requires the statement of reasons to suppose that the authorisation might present a risk to public health within a short time frame (Abraham & Lewis 2000).

The centralised procedure is mandatory for products derived from biotechnology (“List A products”) and optional for other NASs including products from human blood or blood products (“List B products”). The decision is made by the CPMP and is binding on all Member States.

In addition to the centralised or the decentralised European approval procedures, medicines can also be approved only for the German market by the BfArM.

For generic products a relieved approval procedures applies which can refer to the approval of the original product.

On the German market there is also a number of medicines which had been marketed before the mandatory approval requirements of 1978. These medicines needed to be registered in addition until the end of 1999. If the producer did not file such an admission, they have to be removed from the market in January 2005.

In order to get an impression of the performance of the various national authorities which are responsible for the approval procedures as perceived by the pharmaceutical industry, in the following data are presented on the intensity by which Member States are selected as reference Member States in the decentralised European approval procedure. In this procedure pharmaceutical companies applying for approval of new drugs can select a certain national authority for the scientific evaluation and documentation of the approval. The quality of this scientific assessment is crucial for the mutual recognition of the application. Therefore,

industry preferably selects reference countries where the respective authorities are known for their high scientific competencies.

Table 5.2 shows how different countries perform in the mutual recognition procedures between 2000 and 2002. The following information is presented: firstly, the total number of mutual recognition procedures between 2000 and 2002; secondly, the share of each country in all mutual recognition procedures during that period; thirdly, the number of mutual recognition procedures performed in each country for new active substances and the respective share of these procedures in all procedures per country.

Table 5.2: Performance of selected Member States as reference Member States in the decentralised European drug approval procedure. MR: mutual recognition, NAS: new active substances (source: Mutual recognition facilitation group: <http://heads.medagencies.org./mrfg/mrfg-statistics.htm>)

	<b>Mutual recognition procedures</b>		
	<b>2000</b>	<b>2001</b>	<b>2002</b>
DE total	48	71	45
DE share of all MR (%)	15.7	16.0	10.7
DE NAS	3	8	10
DE share NAS (%)	6.3	11.3	22.2
GB total	71	90	79
GB share of all MR (%)	23.2	20.3	18.8
GB NAS	12	10	6
GB share NAS (%)	16.9	11.1	7.6
NL total	59	48	57
NL share of all MR (%)	19.3	17.8	16.4
NL NAS	11	5	6
NL share NAS (%)	22.4	16.7	19.3
DK total	44	88	86
DK share of all MR (%)	14.4	19.9	20.5
DK NAS	1	0	4
DK share NAS (%)	2.3	0.0	8.7
total	306	443	420
total NAS	48	37	39
total share NAS (%)	15.7	8.4	9.3

Overall, the number of mutual recognition procedures increased in Europe from 306 in 2000 to 420 in 2002. In 2001 with 443 an even higher number of procedures was handled. During the same period the share of new active substances in the total

procedures decreased considerably between 2000 and 2001 and stayed at about the same level in 2002. German authorities (BfArM) were chosen in 10.7 % to 16.0 % of all procedures as reference. From 2001 to 2002 a sharp drop of the popularity of Germany as a reference Member State can be observed. If we consider the German pharmaceutical market which is the largest in Europe with a (European) share of about 23 % (EFPIA 2003) in 2001, there is a considerable discrepancy to the significance of Germany in the approval procedures. This becomes even more obvious if it is compared with other reference countries. The Netherlands with a market share of 3.2 % (EFPIA 2003) acted as reference country in 16.4 % of all procedures in 2002, Sweden with a market share of 2.7 % (EFPIA 2003) in 13.6 % of the cases and Denmark which covers only 1.3 % of the European pharmaceutical market (EFPIA 2003) was the preferred reference country in 2002 with a share of 20.5 % of all procedures. Of the most important reference countries only France is performing worse in relation to its market share. With about 21 % France constitutes the second-largest European pharmaceutical market, however, it was selected only in 5.5 % of all cases as a reference country in the mutual recognition procedures.

A different picture emerges if we consider only procedures for new active substances. While Germany was not very familiar as reference country in 2000 for such medication, a strongly increasing trend could be observed until 2002 where 22.2 % of all procedures with Germany as reference country were related to new active substances. Only Sweden was selected in more cases compared to Germany. In the United Kingdom an opposite trend can be observed: the share of new active substances among all procedures decreased continuously between 2000 and 2002.

The analysis of the role of the different countries as reference Member States in the mutual recognition procedure indicates two counteracting trends in Germany. On the one hand, looking at all applications Germany is not playing an important role as reference Member State, indicating that the international pharmaceutical industry seems not to acknowledge the competencies of the German authorities. On the other hand, in the case of new active substances Germany is gaining influence as a reference country. This could indicate that for such substances competencies are available at German authorities which are rated highly by the pharmaceutical industry. Interviews with representatives of the biopharmaceutical industry seem to confirm such diverging trends. On the one hand, a low customer orientation of the BfArM was criticised, while on the other hand no major complaint with registration and approval procedures in Germany were reported.

Another critical factor in Germany in the context of registration and approval are ethical assessments in the context of clinical trials. The requirement that at each location of clinical trials an ethical assessment needs to be made is considered as a certain obstacle for the whole process. Another problem with clinical trials in

Germany is recruiting of patients. It is becoming increasingly difficult to find a sufficiently high number of patients for large clinical studies.

### **Reimbursement**

Basically, most of the approved medicines are eligible for getting reimbursement by the compulsory health insurances in Germany. However, there are some exceptions: Drugs for minor diseases such as common colds and so-called non-economical medicines are exempt from reimbursement. For this group of drugs a so-called negative list has been set up. In addition to this list, there are guidelines for medicines which lead to additional exemptions from reimbursement of certain drugs.

Due to the rising expenditures of the compulsory health insurance companies for medicines, various efforts aiming at cost containment have been made during the last years. In addition to the negative list, the following measures have been implemented:

- Since 2001 on a yearly basis a total volume which can be spent for drugs needs to be negotiated.
- For certain drugs fixed prices have been introduced. These form the highest price that may be reimbursed by the CHI. Patented drugs are exempt from this rule.
- For patented drugs (which are not covered by the fixed-price regime) producers have to give a discount of 6 % to the CHI (since March 2003).
- Incentives for parallel and reimports of cheaper drugs have been created.
- A so-called “aut-idem” rule has been issued which requires the physician only to prescribe the active substance, while the pharmacist has to chose medicines from the lower price segment containing these substances.

In addition to these legal measures, the research-intensive pharmaceutical industry made a voluntary payment of 200 million € to the CHIs in 2002, which had been negotiated with the BMGS. As a compensation the government had assured the industry to set aside further legal price regulations in 2002 and 2003.

The limitation of health care expenditures is also one of the goals of the health care reform<sup>40</sup> which was passed by the German parliament in October 2003. Concerning medicines the reform plans additional measures. Firstly, the fixed price regulation will be expanded, in a sense that the fact that a drug is protected by a patent not automatically implies that it will be exempt from the fixed price rule. Only patented drugs that deliver an appreciable therapeutic improvement to the patient will be

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40 [www.die-gesundheitsreform.de](http://www.die-gesundheitsreform.de)

excluded from the fixed price scheme. Until the implementation of this new rule the rebate that producers have to offer for patented drugs which are exempt from the fixed price ruling will be raised from 6 % to 16 % in the year 2004. No-prescription drugs will be ruled out from reimbursement by the CHIs. In order to improve competition, mail order business for medicines will be admitted.

There has been an intensive debate in Germany on the health care reform during 2003. Some of the new rules are criticised by the biopharmaceutical industry because it is expected that they will have negative effects on competitiveness. In particular the fixed price rule for patented drugs and the increase of rebates for non-fixed price drugs are perceived as main obstacles for the German biopharmaceutical innovation system. It is argued that such measures will have negative impact on the growth potential of the German pharmaceutical market. At the same time the US American and also the Japanese Markets are enjoying increasing growth rates. This situation might have implications on future decisions on innovation investments of the German biopharmaceutical industry. The argument is as follows: strong market growth will offer the opportunity of making higher earnings. This in turn would lead to a higher tax load which can be reduced by investing in innovation. In consequence, strongly growing markets attract innovation investment.

#### **5.4 Role of users**

The role of the following user groups will be considered in this section: patients and patient organisations, insurance companies, physicians and their organisations and hospitals.

There are more than 500 patient groups in Germany which are engaged in many different disease areas. Their attitude to biopharmaceutical innovations is at least as diverse as their interests in various diseases. Some groups including e. g. interest groups of disabled persons are opposing innovative solutions based on genetic engineering. Others such as Parkinson or Multiple Sclerosis interest groups are rather positive about innovative medical solutions based on biotechnology. To obtain a complete picture of the interests and perceptions of all these groups about biopharmaceutical innovations was not possible in the frame of this study. Therefore, a number of organisations which are active in disease areas where biopharmaceutical innovations look promising were selected for interviews.

The results of the interviews indicate that so far these groups have not much influence on the innovation process in biopharmaceuticals. Some exceptions concern rare diseases where patient groups succeeded to initiate the development of medical treatments by some interested smaller firms. From the perception of patient

organisations there seems to be, however, some improvement in a sense that on the side of the pharmaceutical industry patient interests seem to get more attention.

The lacking involvement of patients in the innovation process could create some barriers for innovations due to the following mechanisms: the practical experience of patient groups with specific diseases could help to better identify and define the medical needs which could form the starting point for the initiation of an innovation project by the pharmaceutical industry. Secondly, a stronger involvement of patient groups could also contribute to an improvement of clinical trials: the recruitment of participants in trials could be facilitated and also the comparability of clinical studies with the real world could be enhanced. At present there is a certain gap between clinical trials which are performed under optimum conditions and the applications of new drugs in the real world. Finally, information about new therapeutic approaches could be channelled via patient organisations to physicians and insurance companies, thereby influencing their decision on prescription or reimbursement and thus facilitating market access of innovations. Up to now the German biopharmaceutical industry seems not to take advantage of these potential functions of patient groups in the innovation process.

Insurance companies and CHI physicians and their associations play an important role in the innovation process due to their function in the decision on reimbursement of new drugs (see previous section). In particular the role of physicians is considered as rather strong by the interviewees from patient organisations and also from organisations of physicians. As one interviewee put it there is no other country where physicians exert such a strong influence as in Germany.

The influence of insurance companies and associations of CHI physicians on the innovation process seems to be more conservative in a sense that they do not belong to the main drivers of innovative solutions.

Hospitals are another important player from the demand side in the innovation process. Innovative pharmaceuticals are introduced first via hospitals in the context of clinical studies. For this reason hospitals are an important route for getting innovative drugs to the market. Accordingly, contacts with opinion leaders in hospitals are important from the perspective of the pharmaceutical industry. The cooperation with these opinion leaders is not only important for achieving good results with the clinical trials, which in turn will facilitate the approval procedures. It also helps to disseminate the knowledge about new drugs in the medical communities due to the fact that these opinion leaders will report about such innovations on meetings and conferences and also in their routine contacts with colleagues.

## 5.5 Lead market features

In principle, Germany is an interesting market for biopharmaceutical innovations due to its size and also due to the reimbursement possibilities for innovative drugs (see section 5.1). Financing of medicines by the risk-independent subscription fee scheme of the CHIs basically exerts a supportive effect on market access for innovative drugs. At the same time such a scheme tends to weaken price consciousness of patients thus having a negative impact on the competitive position of generics. In general, price competition on the German pharmaceutical market is considered as rather weak (Burr and Musil 2003). The question is whether the German market for pharmaceuticals also could be considered as a lead market (Porter 1990) in a sense that it would be a preferred location for the introduction of innovative drugs compared to other regions. Such lead markets are characterised by one or more of the following conditions (Gerybadze et al. 1997):

- Demand driven by high income and low price elasticity or high per capita income in combination with a willingness to accept innovation
- Registration procedures that set standards for other regions
- Problem pressure supporting innovation
- Flexible and innovation-friendly framework conditions for users and producers

According to the present analysis of the German biopharmaceutical innovation system, only the first condition seems to be fulfilled, at least to some extent, if we consider the growing expenditures for pharmaceuticals in Germany compared to the international context and the low price elasticity of the market. There are many innovative drugs on the German market and so far they get reimbursed by the CHIs. The willingness to accept innovation in the medical sector seems to be given, too. At least there is no general acceptance gap for biopharmaceutical innovations in the population as is indicated, for example, by the high speed in which recombinant insulin replaced conventional insulin during the last 20 years (Hinze et al. 2001). The situation seems to be different among the self-governing bodies of CHIs and physicians. According to some of the interviewed experts from industry and from the demand side, the openness for innovation could be improved there.

Standard setting registration procedures and a problem pressure supporting innovation are not given in Germany at the moment. Registration standards are set by the American FDA and in a European comparison German regulatory authorities seem not to be appreciated highly by the pharmaceutical industry. A key problem of the German health care system (and also of systems in other countries) are exploding costs. In this context, innovation is frequently considered as a cost driver, for example, by providing highly priced innovative medications. A potential cost-saving dimension of innovation so far seems to be no important issue in the debate. If, for example, compared to established procedures a new innovative medication

would have less side-effects and lead to lower follow-up medical services such as reduced hospital stays or rehabilitation periods, innovation could contribute to cost savings. A prerequisite for evaluating such potential effects would be a comparative overall cost-efficiency analysis of available medical options, which is not yet established in Germany. In conclusion it could be argued that there is an economic problem pressure in the German health care system which could support innovations if framework conditions (health technology assessment) would be adjusted accordingly.

Finally, the framework conditions for users and producers in the biopharmaceutical sector give no clear push to innovation. The discussions about the health care reform have been perceived by producers and their interest organisations as counteracting to innovation. Concerning the regulatory framework, flexibility of the handling of biotechnology-specific rules is acknowledged. On the other hand, the high density of all types of regulations leads inevitably to a certain degree of inflexibility.

In an analysis of the lead market Germany Beise et al. (2002) argue that Germany presently does not form a lead market for pharmaceuticals because of the demand structure in Germany, i. e. the demand generated by the German health care system cannot be translated into an advantage on other markets. Accordingly, the pharmaceutical industry has oriented itself for quite some time towards the USA which seems to be the most important lead market for pharmaceuticals today.

Results of the interviews with the biopharmaceutical industry confirm this conclusion. From the perspective of the pharmaceutical industry the trend towards the US market as the lead market for biopharmaceutical innovations seem to increase. This is mainly due to the much stronger growth of the US market compared to the German market. In consequence it is more rewarding to strive to introduce new products in the USA first.

Another trend in the pharmaceutical industry seems to be that new products are increasingly introduced in a parallel strategy in the main markets of the world. This contrasts to previous strategies where new products were first introduced in Germany, then expanding to Europe and finally in the United States. This tendency also seems to counteract the lead market idea.

## 6 Synthesis and conclusions on research questions

In the preceding chapters various parts of the German biopharmaceutical innovation system were discussed: the public research and education system, the industrial system, the demand and market side, and institutions and framework conditions. Based on these analyses in this final section the main research question of the project will be addressed:

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

### 6.1 Systemic imperfections

Systemic imperfections can be defined as mismatches between elements in the innovation system. They hinder the functioning of an innovation system, the flow of knowledge and therefore reduce the system's overall efficiency. The causing factors for systemic imperfections can be classified into four broad categories: absent or inappropriate innovation functions, absent or inappropriate actors, absent or inappropriate institutions and too much or too little interaction. In the following section systemic imperfections will be discussed along these four dimensions.

#### **Innovation functions**

Concerning the research function with relevance for the biopharmaceutical sector we firstly observe that the scientific output in biopharmaceuticals increased considerably during the 1990s. Main drivers of this trend were the universities. However, there are some indications that the efficiency of the German biopharmaceutical research function is lower compared to other European countries. Probably more important for the overall performance of the biopharmaceutical system are the following two more qualitative developments. There seems to be a certain imbalance in the research functions, in a sense that there are comparably low public pharmaceutical research activities in Germany. The research agenda is

dominated by large pharmaceutical companies. This may bear a certain danger in a sense that research routes with a long-term perspective, that do not generate short term rewards for R&D investment, might be neglected. Further, the maintenance and expansion of the knowledge base for less research intensive medium-sized pharmaceutical firms may be endangered.

The second tendency concerns patient-oriented clinical research. This line of research is not well developed in Germany. Since such research is crucial for innovations in biopharmaceuticals, the biopharmaceutical industry looks abroad for getting access to such knowledge.

Innovation financing from private sources is becoming increasingly difficult in Germany. Still there is quite some venture capital available. However, venture capital companies are shifting their investments from early-stage financing to later stages and to less risky investments. In consequence, the conditions for biotechnology start-up firms are becoming unfavourable, resulting in impacts on technology transfer discussed below.

### **Actors**

Concerning human resources in general, presently there is no shortage in skilled personnel for the biopharmaceutical sector except in some specific areas such as patient-oriented medical research, natural scientists with management and economic know-how, and in general scientists with well-developed communication and team work skills. However, scenarios of the future development of the supply of academics indicate that a shortage in most of the natural sciences and engineering disciplines, which are important for the sector, could be expected.

Market entrance for biopharmaceuticals in the German health care system is among others dependent on the fact that physicians prescribe new medicines. A number of factors influence the physicians' decisions such as e. g. budget limitations. However, it also turns out that the qualification and education of physicians can present innovation barriers. Due to lacking knowledge some tend not to prescribe biologicals, so that such innovative solutions might get prevented from market access.

In the biopharmaceutical business sector after years of growing foundation rates we observe a decrease in new entrants to the system. This can be considered as a normal consolidation process of the biopharmaceutical industry. However, since the foundation of biotechnology firms out of universities and other public sector research units has been an important way of technology transfer in the German system, decreasing foundation rates may in the long run have negative impacts on the valorisation of public sector research for the biopharmaceutical industry. In this sense, an important innovation function could be endangered.

The trend towards internationalisation of the pharmaceutical industry has led to a situation where only few international pharmaceutical firms have kept their main activities in Germany. Due to their dominating role in financing and conducting biopharmaceutical research and in drug developments, such firms are key actors of the biopharmaceutical system. A continuation of this trend might have negative implications on other actors of the system (e. g. by depleting the number of potential cooperation partners for small and medium-sized biotechnology firms) and decrease competitiveness of the system as a whole.

### **Institutions**

There is a general conflict (probably not only) in Germany between two different policy goals associated with the biopharmaceutical sector: on the one hand the wish to keep health care affordable results in various cost containment programmes. On the other hand there is an interest in supporting innovation and commercial competitiveness. In this context innovation is mainly perceived as a cost-driving factor. The concept of improving cost efficiency through innovation is still not widely spread. This conflicting situation is further sustained by the fact that different Ministries are setting the two diverging targets.

Regulations for reimbursement of pharmaceuticals in Germany seem to be guided by no unifying goal. In particular, they are not oriented towards fostering innovation (Burr and Musil 2003). Some rules such as the negative list, the fixed-price rule or the aut-idem regulation tend to support the development of innovative solutions since (so far) they do not apply for patented (innovative) drugs. Others, such as the discount for patented drugs and in particular the perceived arbitrariness by which discount rates are set (change from 6 % to 16 % within one year), do not contribute to creating planning security for innovation projects in the pharmaceutical industry. In summary, so far the (fluctuating) financial situation of the CHIs seems to form the main driving force for the development of reimbursement regulations.

The dual health care system in Germany with out-patient and in-patient care leads to some frictions when innovative solutions are approaching the market. In the out-patient world cost containment measures guide the behaviour of key actors. Physicians can prescribe drugs only for limited budgets. Innovative drugs which might be more expensive could break the budget of the physicians. In consequence, the propensity to prescribe such drugs could decrease. On the other hand, industry provides new drugs to hospitals for reduced prices or even free. Patients who got used to such innovative treatment will expect the same treatment when leaving the hospital and using out-patient care of their home physician, who for economic reasons might not be able to prescribe the desired medicines.

A prerequisite for getting approved clinical trials in Germany are the votes of ethics committees at each location of the trial. This leads to considerable time lags if

multi-centre studies are planned. The argument for such a setting from the ethical point of view is that the different ethical assessments need to get balanced by comparison with several views. In consequence, less clinical trials will be carried out in Germany and the products which finally will enter the German market will have been tested in trials in regions where no such ethical balancing took place.

For biopharmaceuticals the European registration procedure is mandatory. However, this procedure is much more costly than the national procedure. For medium-sized companies these costs might be prohibitive. In consequence, those actors who are expected to contribute considerably to innovations in biopharmaceuticals are faced with a certain institutional obstacle.

### **Interactions**

As the cooperation analysis and interviews with the biopharmaceutical industry have shown, there are intensive interactions between the different actors of the research system and of the commercial system. However, the direction of these interactions seem to be mainly horizontal. Vertical integration in a sense that interactions are established reaching from basic biopharmaceutical research until clinical development seem to be less common which is considered as a disadvantage of the German system.

Another dimension of interaction which seems to be characterised by some frictions are interactions between regulatory authorities and biopharmaceutical companies, aiming at getting new drugs registered and approved. Communication channels between these two types of institutions sometimes are not very efficient leading to delays in the whole procedure of drug development.

Finally, also interactions between the research sector and commercial actors of the biopharmaceutical innovation system on the one hand, and patients or patient groups on the other hand are not well developed. This issue will be discussed in more detail in section 6.3.

## **6.2 System openness**

### **Geographic perspective**

In general, the German biopharmaceutical system is oriented internationally in particular concerning commercial activities as indicated, for example, by the strong international component of business-related cooperations, the significance of exports and the trends in main trade partners. The preferred country for all these activities are the USA. The cooperation between biotechnology firms and research

partners on the other hand has a strong domestic component. These observations support the notion that there exists a combination of international system openness and regional innovation clusters.

While it is argued in the literature that system openness is beneficial for the performance of the system, because it contributes to the introduction of diversity in the system and the selection of best-suited alternatives (Dosi 1997), there are some doubts whether this is also the case for the biopharmaceutical system in Germany. The international openness of the business system has drawn a number of activities of large biopharmaceutical firms to other countries which in the long run will weaken the German system. This indicates that system openness per se cannot be considered as a supporting element for the performance of the innovation system. Rather it depends on the way and direction of openness.

### **Actor dimension**

Concerning biotechnology firms the strong push of new entrants during the last years recently lost momentum so that the system seems to become more closed for new entrants. The difficult financing situation as discussed above is an important reason for this trend. On the side of “big pharma” also some barriers for new entrants could be identified. These are mainly related to soft factors such as lacking trust and self-confidence in own capabilities.

Concerning large pharmaceutical firms, their international orientation will increase the geographic openness of the system but also lead to increasing international competition for the German situation.

Small and medium-sized pharmaceutical firms are important actors in the German pharmaceutical sector as a whole. However they play no important role in biopharmaceuticals. It seems that the biopharmaceutical system presently is closed for these actors leading to the question of future perspectives for such types of firms. Will there emerge business opportunities for them in the biopharmaceutical area and if yes what type of competencies could they bring in? Or will only some niches be left?

## **6.3 Role of demand**

The final user, the patient, plays no important role in the German biopharmaceutical innovation system so far. It could be argued that this deficit might lead to a certain neglect of medical needs in industrial innovation activities because these are best known by patients and patient groups. Further, a stronger integration of patients or patient groups could also facilitate clinical trials by getting direct access to relevant

patient groups which could be recruited for such trials. These would be examples of a different concept for the role of patients. He/she would no more be just considered as an object and final target of a new medical treatment, but rather as an important additional source of knowledge fuelling into the innovations process.

Intermediate organisations play an important role in the German system. In particular the self-governing boards of CHIs and CHI physicians control access to a large share of the German market by their recommendations and decisions on reimbursement. It seems, however, that the openness of these bodies for innovative solution is limited which would lead to weak incentives for innovations from the demand side.

Concerning lead markets, Germany cannot compete with the USA, which presently form the preferred lead market for pharmaceuticals. We observe an increasing shift towards the USA not only in terms of general market shares but also in terms of introduction of innovative drugs and investment in innovation. This move is only partly driven by the need to get into close contact with excellent research establishments. The market dimension seems to play another important role. Strongly growing markets as in the USA tend to attract investment into innovation. These trends support the significance of lead market considerations when evaluating innovation processes.

## 6.4 Policy implications

As legitimation for government intervention in the innovation process usually systemic imperfections or market failures are put forward (e. g. Smits & Kuhlmann 2002). Therefore, in this section policy implications arising from the main systemic imperfections identified and also from results concerning the demand side of the innovation process are summarised. It should be noted that policy intervention in most cases is only *one* factor contributing to problem solution. In addition, various policy-independent settings, actions or events might be important which, however, will not be discussed in this section.

### 1a) Findings:

The efficiency of the science system in biopharmaceuticals in Germany ranks just below the European average. Important lines of biopharmaceutical research such as patient-oriented biomedical research are not well established in Germany. In addition, pharmaceutical research in general is to a large extent not well presented in the public domain, rather it is promoted mainly by the (large) pharmaceutical industry. In general, public funding for biopharmaceutical research (on a per capita basis) is lower compared to important competitors. These imperfections could impede the future orientation of the biopharmaceutical research system.

*1b) Policy implications:*

*The development of the performance of the biopharmaceutical research system should be monitored closely over time. Funding programmes aiming at improving patient-oriented clinical research, such as the programme supporting coordination centres for clinical research, should be monitored and their outcomes evaluated in comparison to the needs of patients and the biopharmaceutical industry. More general, the amount of public funding for biopharmaceutical research should be reassessed from an international perspective.*

## 2a) Findings:

The gap in early-stage financing of biopharmaceutical firms in Germany is widening leading to decreasing start-up activities. In consequence, knowledge transfer from academia to industry could suffer.

*2b) Policy implications:*

*Incentives for private financiers to redirect their engagement to early-stage investments should be developed.*

## 3a) Findings:

There is a shortage of specific academic qualifications for the biopharmaceutical sector. These include managerial, communication, and economic skills.

*3b) Policy implications:*

*Curricula of the respective study courses should be amended in order to include the required courses.*

## 4a) Findings:

Qualifications of health care professionals are frequently not suitable to assess the medical value of biopharmaceutical innovations adequately, thus leading to obstacles to the market access of such innovations.

*4b) Policy implications:*

*Additional, on-going training oriented towards innovation should become mandatory for CHI physicians.*

## 5a) Findings:

In a medium term a shortage of qualified natural scientist and engineers, who are also important for the biopharmaceutical sector, can be expected in Germany.

*5b) Policy implications:*

*This problem is not specific to the biopharmaceutical sector. Rather it underlines the importance of a sustainable supply of a highly qualified workforce for the competitiveness in high tech sectors. Short-term policy interventions seem not suitable to tackle his problem. Rather, this trend calls for a systemic policy*

*approach in a sense that education policy elements become an integral component of innovation policy.*

6a) Findings:

Innovation as a means to improve the efficiency of the German health care system is not very popular. Rather, innovation and cost containment are frequently considered as conflictive forces, which is also reflected by different Ministries being responsible for the two parts. Reimbursement regulations which are key factors for market access do not provide planning security for innovative activities. Thus, the biopharmaceutical system is faced with conflicting policy signals: contribute to cost containment and contribute to innovation and competitiveness.

6b) *Policy implications:*

*The development of a systemic policy approach which tries to combine different objectives such as improving international competitiveness and enabling the existence of a high quality and affordable health care system seems essential. Since the health care system comprises a multi-actor arena where many conflicting interests are exerting influence, such a policy approach necessarily will be a medium-term process which requires the involvement of the key stakeholders from the beginning.*

7a) Findings:

The conduct of multi-center clinical trials in Germany is hindered by complex ethical assessments requiring several ethical views to be balanced.

7b) *Policy implications:*

*Ethical assessment procedures for clinical trials should be evaluated and adjusted in order to achieve a better balance between different interests. A guideline for such an exercise could be the question of risks and benefits from the patient's perspective.*

8a) Findings:

European harmonisation of institutions guiding registration of new biopharmaceuticals can facilitate market access for industry actors. However, for small and medium-sized firms the European procedures are (too) costly thus counteracting the intention of a common market.

8b) *Policy implications:*

*Cost benefit evaluation of the European registration procedures could provide a sound basis for potential modifications.*

9a) Findings:

Patient- and product-oriented R&D-networks are not well established in the German biopharmaceutical system. There is a lack of interaction.

9b) *Policy implications:*

*Systemic policy instruments to support such networks should be developed.*

10a) Findings:

The demand side (patients) has only very limited influence on the biopharmaceutical innovation process in Germany. Knowledge and experience from the demand side related to medical needs is not utilised efficiently in the process, and the facilitating role of patient groups during clinical trials and market access is deployed only scarcely.

10b) *Policy implications:*

*Initiatives of health care policies to support patient organisations should be expanded by taking into account their role as actors in the innovation process. Coordination between health and innovation policy would facilitate such efforts.*

11a) Findings:

There is evidence for the USA being the lead market for biopharmaceuticals. The market attractiveness of the USA increasingly exerts a pull effect on innovative activities of international firms in the biopharmaceutical sector. In Germany only a few lead market features are given presently. These include the reimbursement possibilities for innovative medical solutions and the size of the German market.

11b) *Policy implications:*

*The lead market concept contributes to explaining recent international developments in the biopharmaceutical system. Lead market features are supportive to international competitiveness. Therefore it could be useful to integrate a lead market perspective in the current discussion on health care reforms and innovation crisis in the (bio)pharmaceutical industry.*

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