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Life Sciences and Biotechnology Industry Clusters in Europe - Building Bridges between Science and Industry -

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<Summary>

Life sciences and biotechnology is a strategically important area for Europe, identified as one of the key enabling technology to strengthen Europe's global competitiveness, economic growth and quality of life. Europe's unified effort to build and integrate a critical mass of research, expertise and resources have provided impetus for growth and development of Europe's biotechnology industry and clusters.

Europe's biotechnology industry ranks second after the world's dominant leader the United States and the largest biotechnology sector is healthcare and medical biotechnology.

Biotechnology firms are typically concentrated in "biotechnology clusters" mostly located in western and northern European regions or countries with a long tradition of life sciences and biotechnology research and activities in industries such as pharmaceutical, chemical, agro-production and medical technology.

Biotechnology clusters and cluster organizations play a crucial role in contributing to the industry growth and development by ways of providing a platform for academia, industry, policy makers and investors to interact and collaborate.

Key outcomes and benefits are improved potential for 1) innovation, 2) commercialization, 3) creation of spin-offs and start-ups, 4) funding and investment attraction and 5) business development opportunities.

Biotechnology cluster strength and focus areas vary representing Europe's diverse capabilities.

Efforts are helping shape supportive business environment and attract into the region, national and international partners and investors looking for business growth and new investment opportunities.

The recent developments and trends in the fields of 1) biopharmaceutical medicine, 2) advanced therapies, 3) personalized preventive or therapeutic medical care, 4) rare diseases and orphan medicinal products, 5) advanced medical technologies and 6) biotechnology-based industrial and environmental products are indicating potential for business opportunities in under-exploited or niche areas.

The recent rise in the interests from biotechnology clusters and their biotechnology companies to explore certain business partners for concrete collaboration in the markets worldwide by taking part in such as mission delegation trips and dialogue initiation represents potential opportunities.

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Introduction

Europe is home to leading life sciences and biotechnology industry clusters¹ active in medicine/healthcare, agricultural/food and industrial/environmental areas.

In Europe, life sciences and biotechnology industry clusters (which we will refer to as “biotechnology clusters” from here onwards) are geographically concentrated in regions and countries with a long tradition of life sciences research and activities in related industries such as pharmaceutical, chemical, agro-production and medical technology.

Biotechnology clusters are contributing to the growth and development of the biotechnology industry by ways of stimulating and fostering the academia and industry collaborations for improved knowledge base and commercialization of research findings.

This report provides insights into the European biotechnology industry’s current status, future directions and potential business opportunities by examining European biotechnology clusters’ key strengths and characteristics.

The report focuses on healthcare and medical biotechnology, one of the major biotechnology sectors in Europe.

1 Porter, 1998.
Clusters can be defined as “a geographical proximate group of interconnected companies and associate institutions in a particular field”.

Chapter 1. Life Sciences and Biotechnology Industry in Europe

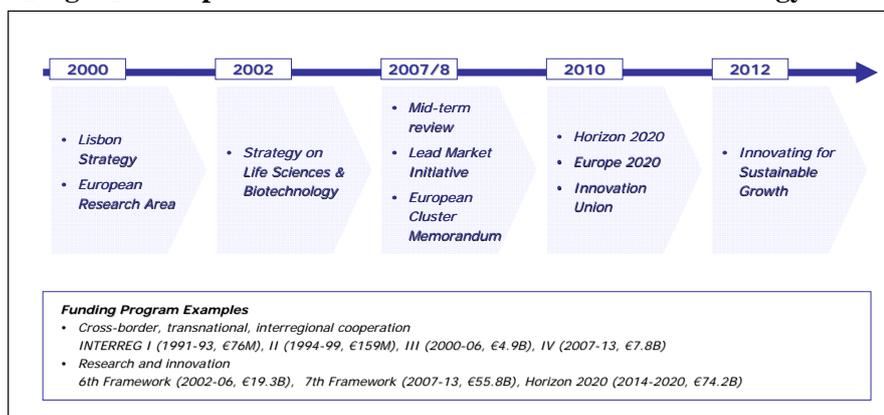
Life sciences and biotechnology is Europe's strategically important area

Life sciences and biotechnology is a strategically important area for Europe, identified as one of the key enabling technology to strengthen Europe's global competitiveness, economic growth (increased employment and productivity) and quality of life.^{2,3}

European Commission (EC) has launched and implemented various supportive measures and initiatives to promote research, development and commercialization of life sciences and biotechnology (fig. 1).

Action plans and strategies are mainly focused on trans-regional and trans-national collaborations, improved and more efficient access to information/collaboration networks, technology transfer⁴, funding programs and finance.

【Fig. 1】 Europe initiatives for life sciences and biotechnology



(Source) Mizuho Corporate Bank analysis on European Union (EU) and other public information

2 EC, 2002.

3 EC Directorate-General Enterprise and Industry, 2007.

4 Transfer of research results from universities or research institutions for commercial applications.

1.1. Life Sciences Industry

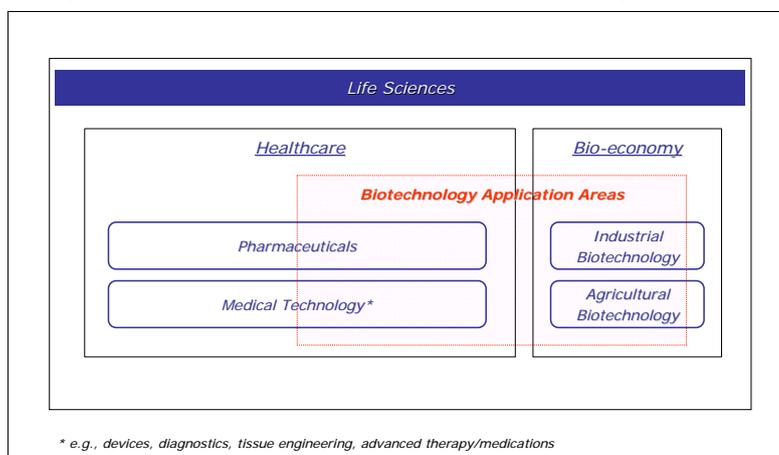
Life sciences refer to a study of living organisms involving commercial applications in several sectors

Life sciences in broad terms can be defined as “any of the branches of natural science dealing with the structure and behaviour of living organism which have commercial applications in wide-ranging number of sectors, including healthcare, food and agriculture, environmental goods and services and chemicals”.⁵

Life sciences industry in general covers healthcare (pharmaceuticals, medical technologies) and bio-economy areas.

Biotechnology plays an important role in both fields (fig. 2).⁶

【Fig. 2】 Life sciences industry and biotechnology



(Source) Mizuho Corporate Bank analysis on Department for Business Innovation and Skills (UK), European Union (EU) and other public information

5 Department for Business Innovation and Skills (UK), 2010.

6 Her Majesty's Government (UK), 2011 (a).

1.2. Biotechnology Industry

Biotechnology is a scientific application of living organisms to develop processes and materials

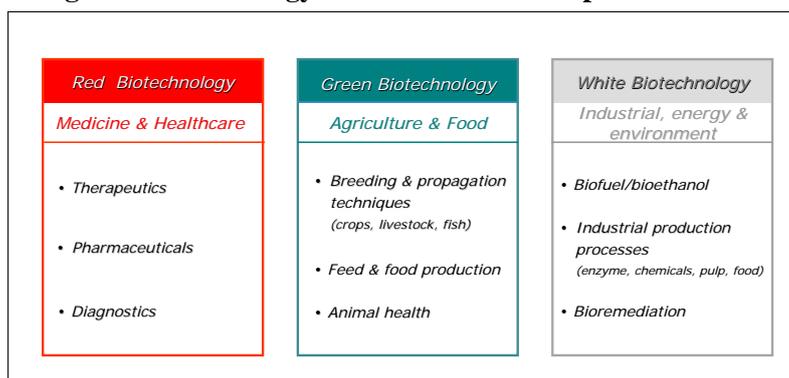
The Organization of Economic Co-operation and Development (OECD) defines biotechnology as “the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services”.⁷

Biotechnology is applied to the development and production of processes and materials in wide range of industries such as 1) pharmaceuticals, 2) medical technologies, 3) food, drinks and feed, 4) chemicals, 5) pulp and paper, 6) textile, 7) detergents, 8) starch, 9) energy and 10) agriculture.⁸

Biotechnology contributes to a wide range of industries and is often categorized in three subsectors

In Europe, biotechnology industry is often categorized in three different subsectors (fig. 3); 1) medicine and healthcare (i.e., called red biotechnology), 2) industrial productions, energy and environment (white biotechnology) and 3) agriculture, food, livestock and veterinary products (green technology).^{9,10}

【Fig. 3】 Biotechnology subsectors and examples



(Source) Mizuho Corporate Bank analysis on EU, OECD and other public information

7 OECD, 2009, 2005.

8 The European Association of Bioindustries (EuropaBio), European Federation of Biotechnology section on Applied Biocatalysis.

9 EuropaBio, <http://www.europabio.org/what-biotechnology> (January, 2013).

10 EC, <http://ec.europa.eu/enterprise/sectors/biotechnology/what-is-biotechnology/contribution> (January, 2013).

1.3. European Biotechnology Industry Overview

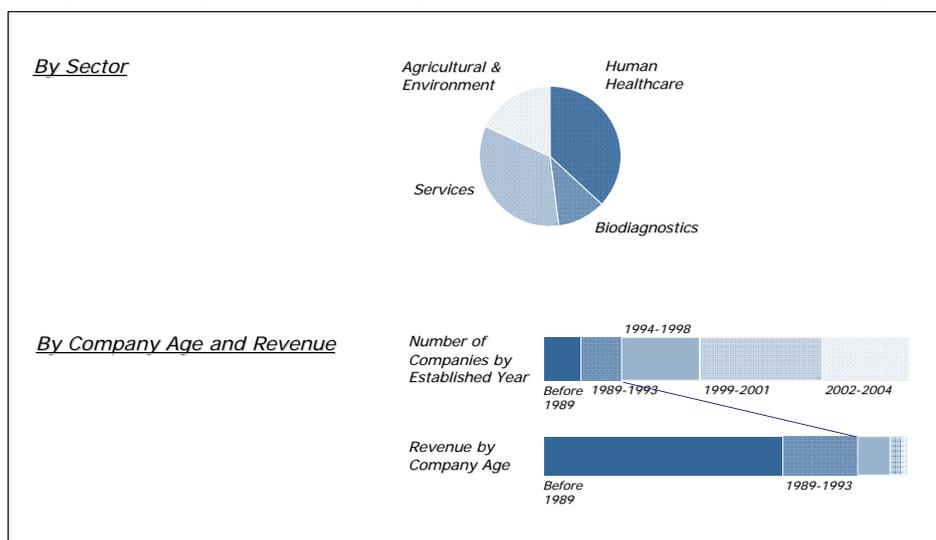
European Biotechnology industry is largely composed of SMEs focusing on healthcare and medical biotechnology

European biotechnology industry is largely composed of small and medium-sized enterprises (SMEs)¹¹ operating in the field of healthcare and medical biotechnology.

According to the European Association of Bioindustries (Europabio)'s study based on a total of 2,163 dedicated biotechnology companies in Europe, human healthcare sector accounts for around 40% of the whole industry in terms of company numbers (fig. 4).

Biotechnology companies in Europe are typically at the age of 6-10 years with 25-30 employees and more mature companies contribute to total revenue (fig. 4).¹²

【Fig. 4】 European biotechnology industry by sector and company age



(Source) Mizuho Corporate Bank analysis on EuropaBio, Critical I and other public information

11 Definition of SMEs.

micro enterprise; staff < 10, turnover ≤ €2M, balance sheet ≤ €2M

small; staff < 50, turnover ≤ €10M, balance sheet ≤ €10M

medium-sized; staff < 250, turnover ≤ €50M, balance sheet ≤ €43M

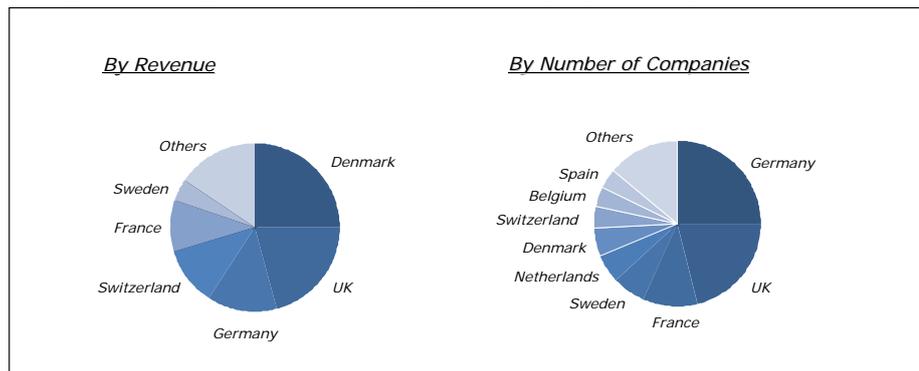
http://ec.europa.eu/enterprise/policies/sme/facts-figures-analysis/sme-definition/index_en.htm (January, 2013).

12 EuropaBio, Critical I, 2006.

Leading countries are in western and northern Europe

Leading countries in terms of both revenue and number of companies are Denmark, France, Germany, Switzerland, UK, Sweden and Switzerland (fig. 5)¹³.

【Fig. 5】 European biotechnology industry by country



(Source) Mizuho Corporate Bank analysis on EuropaBio, Critical I and other public information

13 EuropaBio, Critical I, 2006.

1.4. Biotechnology Research and Development

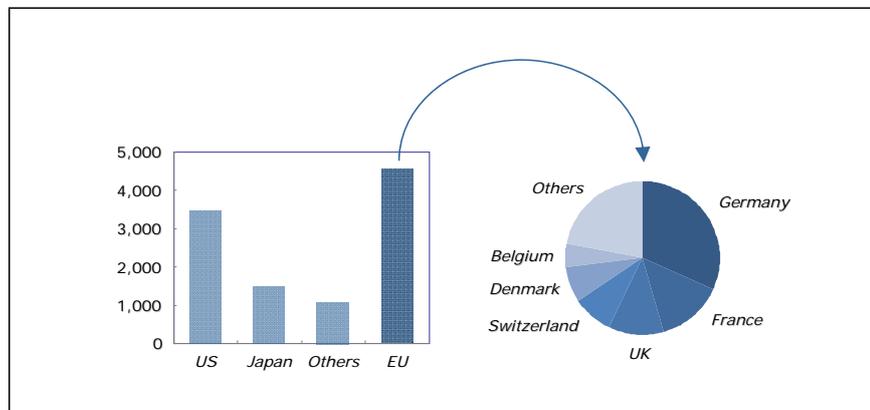
Biotechnology R&D base in Europe is concentrated in the western and northern European countries

European countries active in biotechnology research and development (R&D) include Denmark, France, Germany, Switzerland and the UK, representing a similar picture to the geographical distribution of biotechnology companies.

The number of biotechnology patents granted by the European Patent Office (EPO) provides some evidence on the comparative position of Europe in biotechnology R&D activities.

Between 2007 and 2011 Europe accounted for over 40% of total, of which leading three were Germany, France and the UK (fig. 6).

【Fig. 6】 Biotechnology patents in Europe by region

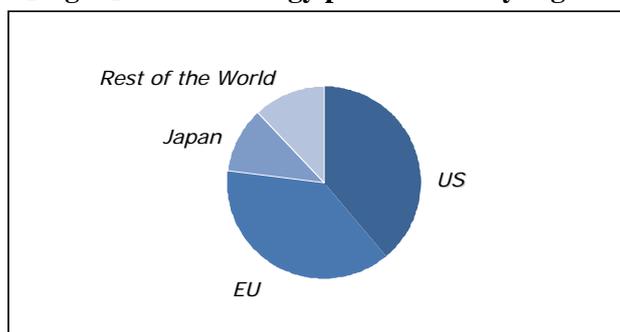


(Source) Mizuho Corporate Bank analysis on European Patent Office and other public information

The number of biotechnology research publications also suggests the position of Europe.

Europe is reported to have published 38% of the biotechnology research papers between 2002 and 2004 (fig. 7).

【Fig. 7】 Biotechnology publications by region

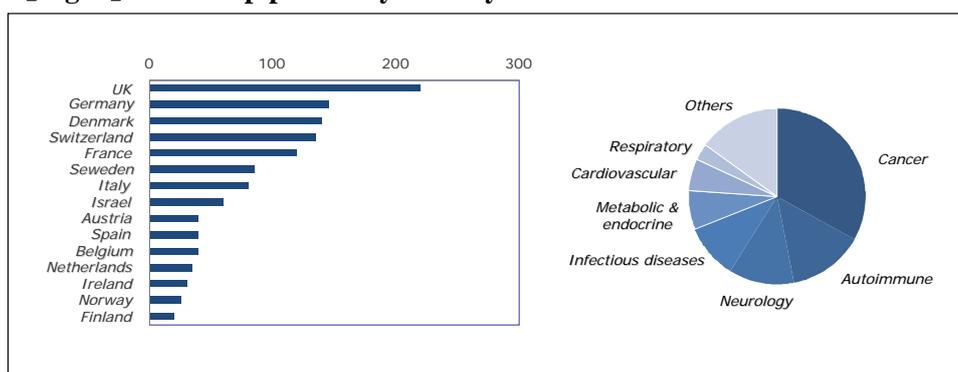


(Source) Mizuho Corporate Bank analysis on EC Directorate-General Joint Research Centre and other public information

Pipelines are lead by the UK, Germany, Denmark, Switzerland, France and major therapeutic areas are cancer, autoimmune diseases and neurology

Healthcare and medical biotechnology in terms of the number of clinical pipelines¹⁴ is reported to be lead by the UK, Germany, Denmark, Switzerland and France¹⁵ and major therapeutic focus areas are cancer, autoimmune diseases, neurology and infectious diseases (fig. 8).

【Fig. 8】 Clinical pipelines by country and indication



(Source) Mizuho Corporate Bank analysis on Ernst & Young and other public information

14 Clinical pipeline refers to drug candidates in clinical trial Phase I, II or III (P-I, II or III). Breakdown shows approximately 30-35% in P-I, 50-55% in P-II and 10-15% in P-III (Ernst & Young).
15 Ernst & Young, 2012.

1.5. Biotechnology Development and Financing

Biotechnology industry is not only research oriented, but also capital intensive

Biotechnology industry is research and capital intensive.

The industry is largely dependant on specialised knowledge and funding throughout research and product development stages.

The European pharmaceutical and biotechnology industry represent the highest research intensity of approximately 15% measured by R&D investment to net sales, significantly more than the 3% average of all sectors.^{16,17}

The European biotechnology industry is supported by approximately 96,000 people and 40-50% of them are estimated to be involved in R&D functions.

Biotechnology development consists of often complex, timely and costly processes.

Transforming research results into economic and financial return or to a marketable product/service requires processes such as obtaining patents and/or regulatory approvals, securing sufficient funding and investments for research projects.

As in the case of creating new drugs, it is reported to take generally 10 to 15 years from discovery to approval for human use (fig.9).

Probability of reaching the market is low with only one drug candidate in 10,000 molecules¹⁸ and cost of putting a new medicine onto the market from research and discovery of the candidate molecules to market launch is estimated to reach €1 billion on average for each new drug.¹⁹

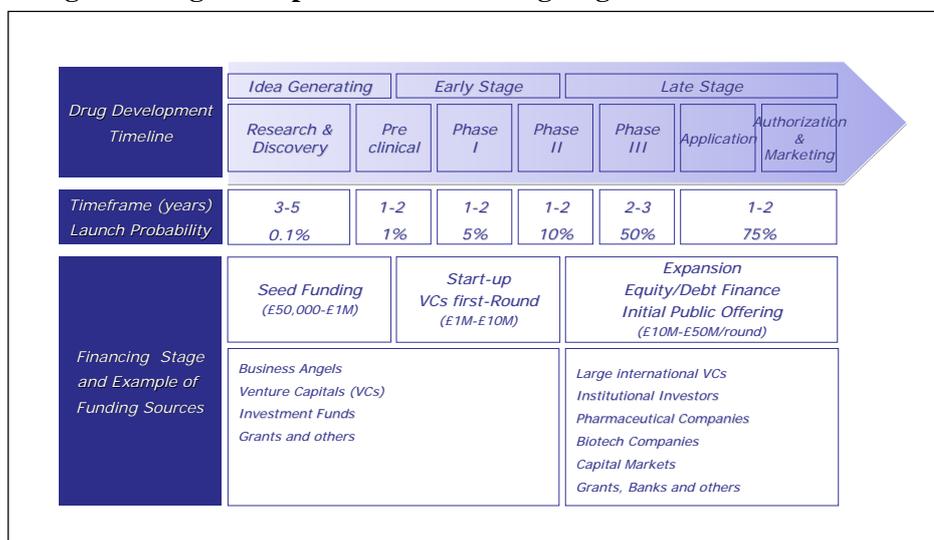
16 European Federation of Pharmaceutical Industries and Associations, 2012.
Sectors compared include software and computer services, technology hardware and equipment, leisure goods, healthcare equipment and services, electronic and electrical equipment and others.

17 EC, 2011 (a).

18 Innovative Medicines Initiative, 2011.

19 European Federation of Pharmaceutical Industries and Associations, 2012.

【Fig. 9】 Drug development and financing stages



(Source) Mizuho Corporate Bank analysis on Department for Business Innovation and Skills (UK), Department of Trade and Industry (UK), European Private Equity and Venture Capital Association and other public information

Funding is crucial and venture capital is an important source

For the reasons discussed earlier, biotechnology development is largely dependant on continued financing and funding.

Venture capital (VC) is an important source of funding especially for early-stage biotechnology start-ups.

One of the types of venture capital investment firms active in Europe is European national firms with dedicated focus on life sciences, biotechnology and information technology sectors.

Examples of leading venture capital investment firms include Life Sciences Partners (Netherlands), Techno Venture Management (TVM) Capital (Germany) and others.

Corporate venture capital firms established by pharmaceutical companies, such as Novartis Venture Funds (Switzerland) and Novo A/S (Denmark) are also active.

Other funding sources include domestic and foreign investors (business angels, family offices), private and public grants and funding (regional, national, EU, international), alliances (joint research and development, licensing), mergers and acquisitions (M&As), capital market initial public offerings (IPOs) and equity/debt financing (fig. 9).

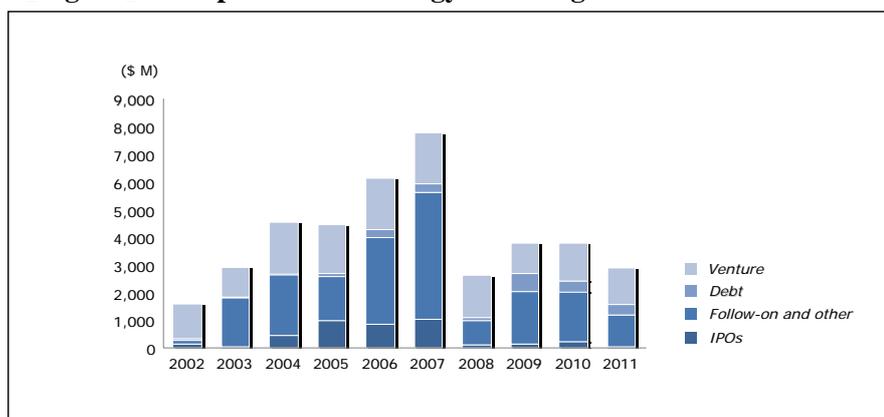
1.6. Biotechnology Funding and Investment Environment

Current though economic environment and uncertainty remain a challenge for biotechnology companies

Recent trends observed in Europe indicate a challenging environment for biotechnology companies.

The initial public offering window has been closed and other sources have slowed down since the economic downturn starting in 2008 (fig. 10).

【Fig. 10】 European biotechnology financing trend



(Source) Mizuho Corporate Bank analysis on Ernst & Young and other public information

Biotechnology’s high levels of development costs, risks and uncertainty also have had an impact on investors traditionally focused on life sciences. Recent changes in investors’ strategies observed are:^{20,21}

- Reduce the number of biopharmaceutical companies in their portfolio.
- Explore new paths to increase performance such as through funds-of-funds strategies.
- Support the development of existing portfolio companies or increase focus on companies with products in later stage clinical trials than early-stage companies.

²⁰ EC Directorate-General Enterprise and Industry, 2009.

²¹ Oxford Bioscience Network (OBN), 2011.

- Increase focus on less risky and higher growth/return sectors in comparison to pharmaceuticals and biotechnology, such as medical, environmental/clean, information/communication technologies.

Chapter 2. Position/Status of the European Biotechnology Industry

2.1. Biotechnology Companies

European biotechnology companies represent the second dominant presence next to the US

Europe, ranks second to the world’s dominant leader the United States (US) in most comparative analysis, representing half the size in terms of the number of public companies and employees (table 1).

【Table 1】 European and the US public biotechnology companies

	Europe	US
Market Capitalization (\$ B)	71.5	278.0
Revenue (\$ B)	18.9	58.8
Number of Public Companies	167	318
Number of Employees	48,440	98,560

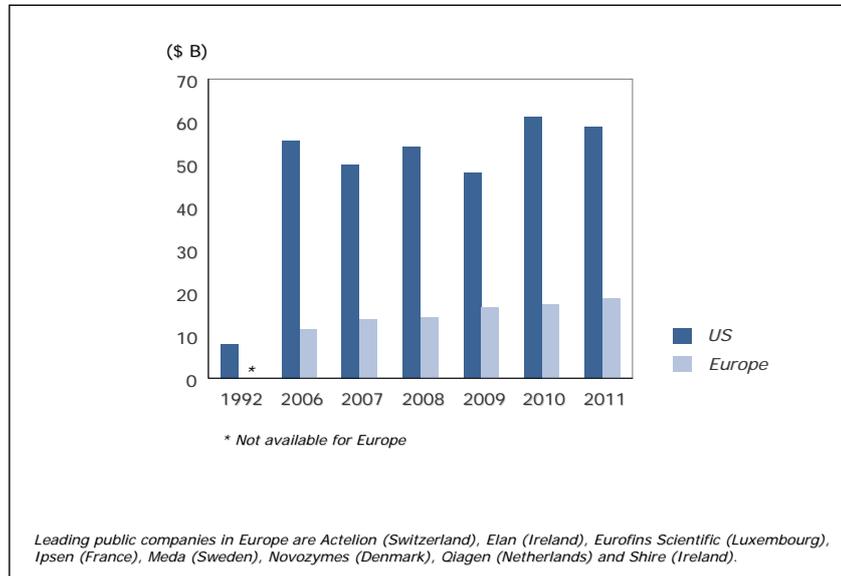
(Source) Mizuho Corporate Bank analysis on Ernst & Young

Revenue of the European public companies shows a stable growth, reaching at the level of one third of the US.

On the contrary, the US public companies’ revenue has fluctuated slightly and currently remains at the similar level of 2006 (fig. 11).

The upward growth trend observed with the European companies are mainly supported by 1) organic growth (e.g., sales revenue from newly launched products, licensing royalties) delivered by several companies, 2) relatively stable business environment in Europe, 3) market diversity of Europe, 4) continuous measures for operational efficiency improvements in companies and 5) mergers and acquisitions.

【Fig. 11】 Revenue of the US/Europe public biotechnology companies



(Source) Mizuho Corporate Bank analysis on Ernst & Young and other public information

Possible contributing factors for the comparative lead of the US, in maturity and profitability to Europe, are observed further in the comparison between Europe and the US on 1) historical development background, 2) funding and investment environment and 3) pharmaceutical industry/market dynamics.

2.2. Social and Economic Background and Regulatory Environment

The US biotechnology industry growth was aided by government support for the regulatory and research environment

While Europe was going through a social and economic integration process after the fall of the Berlin Wall in 1989, the US biotechnology industry started to form its shape in the early 1980s.

Growth and development were supported by government-lead measures implemented with aims to 1) improve the regulatory and patenting and licensing systems and 2) launch government-lead research initiatives.²²

The Bayh-Dole Act of 1980 (amended in 1984), a legal framework for the transfer of university generated and government funded inventions to the commercial marketplace, played an important role in industry growth in the US.²³

The Act provided incentives for universities and industry to collaborate throughout the patenting and licensing process of innovations and fostered the commercialization of new technological advances.

In 1982, the first biotechnology drug Humulin[®] obtained the Food and Drug Administration (FDA)'s approval.

Humulin[®] is a recombinant human insulin for the treatment of diabetes, developed by the US biotechnology company Genentech²⁴ and produced and marketed by the US pharmaceutical company Eli Lilly's.

Examples of other US-based multinational biotechnology companies established and significantly developed since then are Amgen and Genzyme²⁵.

22 The North Carolina Biotechnology Center was established as the US first state-sponsored initiative to develop biotechnology, followed by thirty five other states.

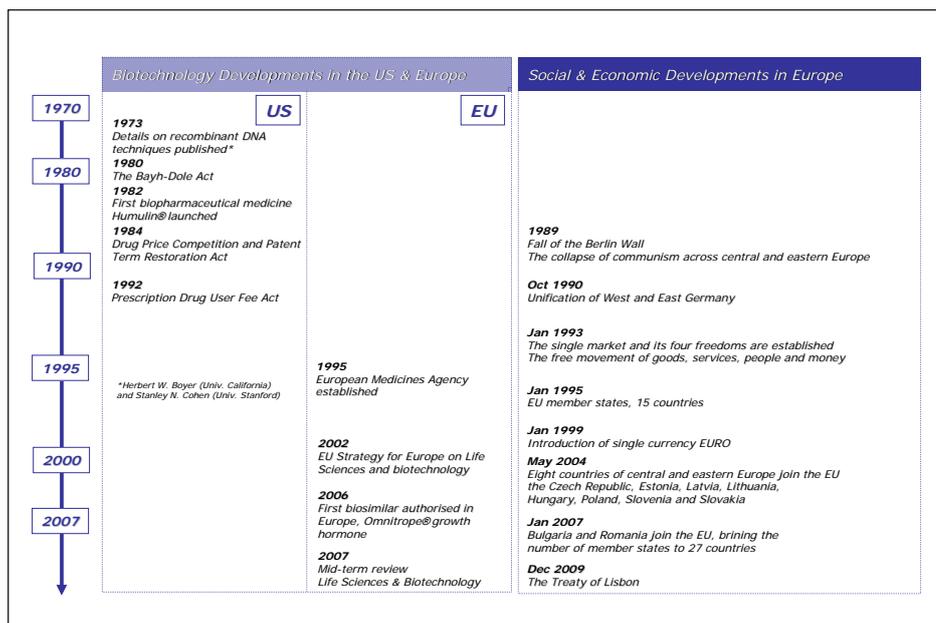
23 Council on Government Relations (US), 1999.

24 Genentech was founded in 1976 by a venture capitalist and Dr. Herbert Boyer. In 1973, Dr. Boyer of the University of California, and Dr. Stanley Cohen of Stanford University published details on new recombinant Deoxyribonucleic Acid (DNA) techniques (method of manufacturing proteins). In 2009, Genentech was acquired by Roche (headquartered in Basel, Switzerland).

25 A subsidiary of French pharmaceutical Sanofi since 2011.

It was only around in the mid-1990s, almost a decade later to the US, European biotechnology industry started to develop partly in response to EU-lead supportive measures (figs. 1 and 12).

[Fig. 12] Biotechnology industry historical timeline in the US and EU



(Source) Mizuho Corporate Bank analysis on EU and other public information

One example is the European funding programs for cross-border, trans-national and Interregional Cooperation Program (INTERREG) II (1994-1999) which provided an impetus to the establishment of trans-national biotechnology clusters such as BioValley (Switzerland, Germany and France) and Medicon Valley (Denmark and Sweden).

2.3. Funding and Investment Environment

Biotechnology R&D is largely dependant on public and private R&D funding

Biotechnology industry is largely dependant on public and private R&D funding to finance business requirements.

The below example data, indicating the US lead in both public and private R&D funding, suggest a more supportive R&D environment (table 2).

【Table 2】 Biotechnology R&D expenditure and public funding

	Europe	US
Private R&D expenditure (\$ B)	7.6	21.0
Public R&D funding (\$ B)	4.1	23.2

Private R&D expenditure represents 2004 figures, R&D expenditure by biotechnology companies. Public R&D funding represents 2005 figures.

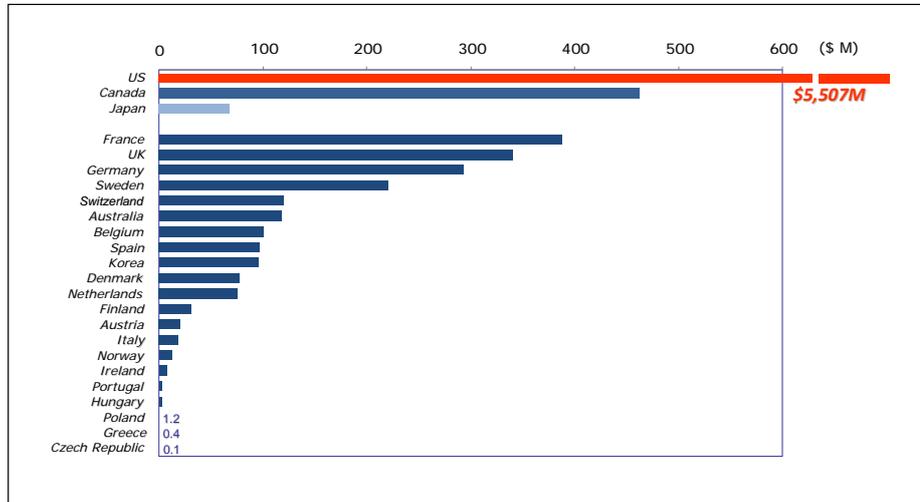
(Source) Mizuho Corporate Bank analysis on EU, EuropaBio, Critical I, OECD and other public information

Another important source of funding is financing provided by venture capitals.

France, the UK, Germany and Sweden as well as some other countries in Europe have achieved a certain level of investment inflows (fig. 13).

The contrast between the above four European countries with the higher level in Canada and the lower level in Japan, suggests differences in roles, effectiveness and activity levels of venture capitals within the industry.

【Fig. 13】 Venture capital investments in life sciences



(Source) Mizuho Corporate Bank analysis on OECD and other public information

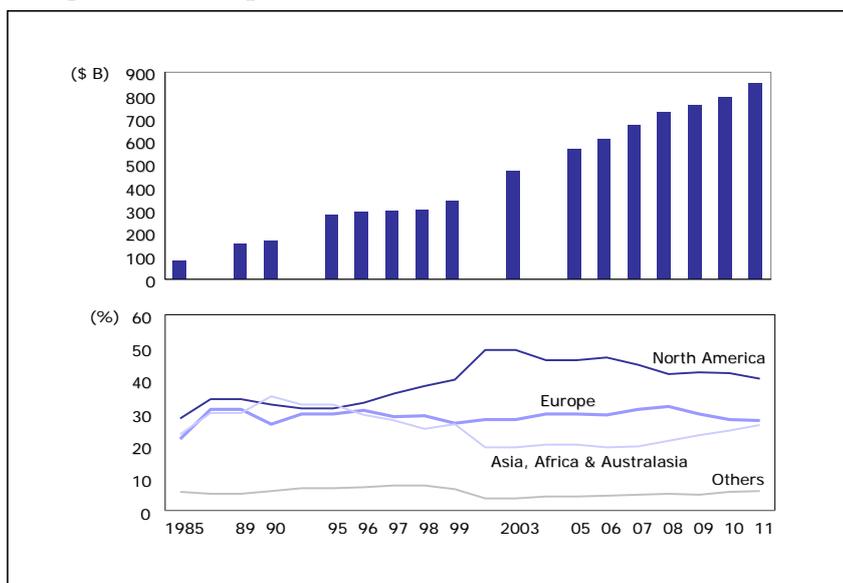
2.4. Pharmaceutical Industry

European pharmaceutical market is the second largest globally next to the US

Competitiveness observed in the European biotechnology industry shows a similar picture in the pharmaceutical markets.

Europe represents 25-30% of the global pharmaceutical market. Until the mid 1990s, Europe and the US each had shares of about 30% in the markets worldwide. The US since then has grown to approximately 50% in the early 2000s and has moderately decreased down to around 40% (fig. 14).

【Fig. 14】 Global pharmaceutical market



(Source) Mizuho Corporate Bank analysis on IMS World Review
(Copyright 2013 IMS Health. All rights reserved.)

Factors underlying the US lead in pharmaceutical industry are observed in the economic scale, high level of healthcare and pharmaceutical

expenditures, pharmaceutical pricing and reimbursement systems (table 3).

【Table 3】 Basic health economics data of Europe and the US

	Europe (EU-27)	US
Population (million, 2010)	501 (EU-5*, 315)	310
GDP (current, billion, 2010)	€12,268 (EU-5*, €8,741)	\$14,582
GDP per capita (current, \$PPP, 2010)	\$31,784	\$46,588
Total healthcare expenditure per capita (as % of GDP)	€2,192 (8.3%, 2008)	\$ 7,900 (17.6%, 2009)
Total pharmaceutical expenditure per capital (as % of GDP)	€376 (1.7%, 2008)	\$947 (2.1%, 2010)
Healthcare system	Social insurance	Private
Pharmaceutical pricing & reimbursement system**	Statutory	Free-pricing
Cost of medicine***	ca 80-120	ca 200-220
Market/Consumer access	Fragmented	Direct access to single market
Pharmaceutical R&D (million, 2010)	€27,796	\$40,688
Regulatory system	EMA	FDA

* EU-5: Germany, UK, France, Italy, Spain.

** Pharmaceutical pricing and reimbursement system varies significantly by member states.

*** Cost of medicine: price comparison with 2008 price index with UK=100 (basket of 150 pharmaceutical products)

(Source) Mizuho Corporate Bank analysis on Department of Health (UK), Department of Trade and Industry (UK), European Federation of Pharmaceutical Industries and Associations (EFPIA), Eurostat, OECD and other public information

Constant awareness and efforts of Europe to maintain business strengths and market attractiveness to compete globally may also have contributed to the development of the unified pharmaceutical regulatory system across Europe.

For example, EU established the European Medicines Agency (EMA) responsible for evaluation and supervision of EU centralized procedure for marketing authorizations.²⁶

Another examples is the recent proposed reform Regulation for the EU Clinical Trials Directive (2001/20/EC), driven by the need to improve attractiveness in clinical research in Europe.²⁷

26 Established as European Agency for the Evaluation of Medicinal Products (EMEA) in 1995 and renamed to EMA in 2004.

27 EC, Fostering EU's attractiveness in clinical research (press release, 17 July, 2012). The reform is planned to come into effect in 2016 taking a regulation form to ensure identical rules across EU and expected to contribute to savings of €800 million per year in regulatory costs. http://ec.europa.eu/health/files/clinicaltrials/2012_07/press-releases/ip-12-795_en.pdf (January, 2013).

Chapter 3. Biotechnology Clusters in Europe

3.1. Biotechnology Cluster Importance

Success factors for biotechnology industry growth are collaboration, commercialization and supportive business and financing environment

Success factors for biotechnology industry growth suggested by several studies together with comparisons between the Europe and the US biotechnology industries in this report are; 1) academic and industry collaborations, 2) commercialization paths (patenting, licensing, start-up and spin-off companies) and 3) supportive business and financing environment.

Biotechnology cluster is one of the key driving forces behind biotechnology industry/company growth.

Cluster organizations work to realize the above success factors by ways of providing tools and platforms for academia, industry and public sector to interact and collaborate.

The interaction and collaboration are of particular importance to the biotechnology companies, especially for the SMEs, for securing financial resource, business platforms and infrastructure required for biotechnology research or business development.

Furthermore, interaction and collaboration encourage interests in joint research programs, knowledge and best practice studies and shared infrastructure, as well as establishment of academic spin-offs, biotechnology companies, science parks, research centres, incubators and technology transfer offices.

Key outcomes and benefits are in general demonstrated in improved potentials for 1) innovation, 2) commercialization, 3) creation of spin-offs and start-ups, 4) funding and investment attraction and 5) business development opportunities.

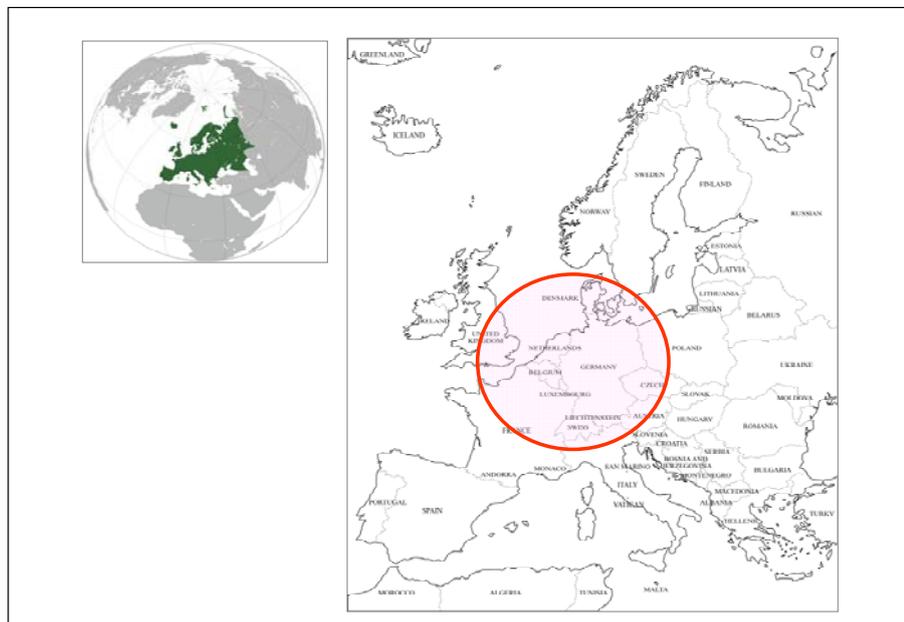
3.2. Geographical Distribution and Structure

Regions or biotechnology clusters with established research base are concentrated in the western and northern Europe

In Europe, many of biotechnology clusters and regions started to form around in the mid 1990s, typically in regions and countries with prominent university centres, with a long tradition of life sciences and biotechnology research base and activities in contributing industries such as pharmaceuticals and chemicals.

Today, biotechnology clusters are concentrated in Belgium, Denmark, France, Germany, Italy, Spain, Sweden, Switzerland and the UK (fig. 15).

【Fig. 15】 Major biotechnology clusters/concentration in Europe



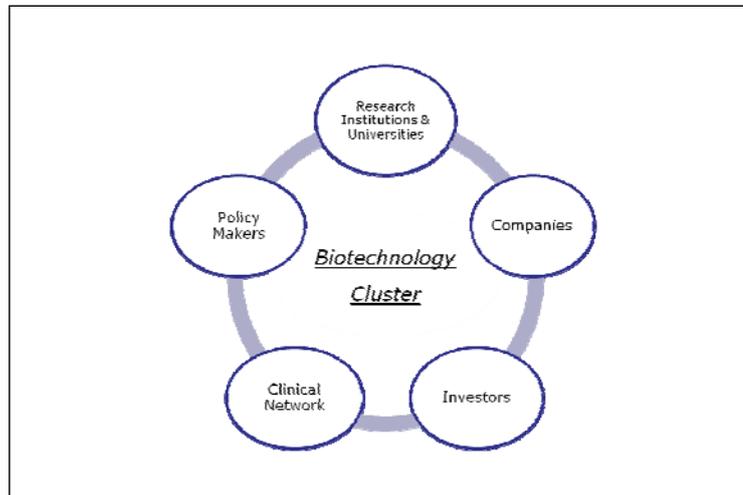
(Source) Mizuho Corporate Bank analysis on Wiki Commons and other public information

Biotechnology clusters are composed of diverse mix of participants

Biotechnology clusters are composed of diverse mix of participants (fig. 16).

The healthcare biotechnology clusters are typically structured with cluster organisations, policy makers (e.g., national and local authorities), research institutions and universities, companies (e.g., pharmaceutical, biotechnology, medical technology companies and specialist services providers), clinical networks (e.g., hospitals, contract/clinical research organisations) and investors.

【Fig. 16】 Biotechnology cluster structure



(Source) Mizuho Corporate Bank analysis on public information

3.3. Key Contributing Factors for Cluster Success

Cluster growth and development are enabled by several factors including strong science base and supportive business environment

In general, critical factors for developing and building successful biotechnology clusters are understood to be:²⁸

- Strong science base
- Entrepreneurial culture
- Growing company base
- Ability to attract key staff
- Access to/capability of funding and financing
- Premises and infrastructure
- Business support services and large companies in related industries
- Skilled workforce
- Effective networks
- Supportive policy environment
- Effective business plan

In Europe, biotechnology clusters and initiatives are managed by specialized institutions, known as cluster organizations, which take various forms, ranging from non-profit associations, public agencies to companies.²⁹

Often lead by highly experienced and entrepreneurial-minded leaders, cluster organizations offer one-stop support system designed to foster entrepreneurial business environment for both science and industry participants.

Initiatives and activities vary, but what leading biotechnology clusters have in common is the ability to adapt and evolve with the strategic vision in tune with the changing business environment and market demands.

²⁸ Department of Trade and Industry (UK), 1999 (a).

²⁹ EC, 2008.

Examples include providing specialist support for spin-off companies and SMEs, access to premises and infrastructure (incubator, accelerator and shared services), access to partnership events (match making, show-case, promotion and networking), thematic projects (e.g., personalized medicine), technology transfer programs and information-sharing platforms (e.g., online database of drug pipelines, company profiles, research papers and others).

Additionally and importantly, biotechnology clusters and cluster organizations function as the first introduction and contact point enabling national and international partners and investors to explore cluster potentials and new business opportunities with innovative life science companies.

3.4. Regional, trans-Regional and trans-National Biotechnology Clusters

Unique characteristic of biotechnology clusters in Europe is the unified and united approach for growth

One of the key and unique characteristics of biotechnology clusters in Europe is the importance of unified and united approach to cluster development as demonstrated in the establishment of trans-regional, trans-national clusters and pan-European networks (table 4).

For example, a pan-European network Council of European BioRegions (CEBR) was established in 2006 as a network linking clusters, with an aim to promote collaborations, provide policy support and share best practices between clusters.

Another key differential characteristic is the varied initial forces behind cluster establishments.

Establishment of biotechnology clusters in the UK were largely encouraged by market participants, as in the case of One Nucleus which was established in 2010 as a merger between London Biotechnology Network (LBN)³⁰ and Eastern Region Biotechnology Initiative (ERBI)³¹ in response to member requests.

On the contrary, government program and policy-driven forces provided the impetus to the growth and development of biotechnology clusters in Belgium, France and Germany.

30 London-based.

31 Cambridge-based.

【Table 4】 Biotechnology cluster and cluster organization examples

Cluster	Region	Country	Key Strengths
Regional & Trans-Regional Clusters			
One Nucleus	Cambridge London	UK	<ul style="list-style-type: none"> Established research base and pharmaceutical industry
OBN	Oxford	UK	<ul style="list-style-type: none"> Established research base Investor-focused approach (OBN Investment Network)
Bio^M	Munich	Germany	<ul style="list-style-type: none"> Portfolio of successful biotechnology firms Business-centric organizational structure (Bio^M AG and Bio^M Biotech Cluster Development GmbH)
BioTOP	Berlin Brandenburg	Germany	<ul style="list-style-type: none"> Focus on regenerative medicine R&D Partnerships with research institutions and clinical networks
Genopole	Evry (Paris)	France	<ul style="list-style-type: none"> Partnership with Essonne Development Agency Business-centric support provided by Genopole Entreprises
FlandersBio	Ghent	Belgium	<ul style="list-style-type: none"> Portfolio of successful biotechnology firms Partnership with VIB (Flanders Institute for Biotechnology)
Trans-National Clusters			
BioValley	Basel South-Baden Alsace	Switzerland Germany France	<ul style="list-style-type: none"> Established chemical and pharmaceutical industries with tri-national market access
Medicon Valley	Copenhagen Skåne	Denmark Sweden	<ul style="list-style-type: none"> Established pharmaceutical industry Active branding development in international markets Mobility of knowledge and capital
Pan-European Networks			
The European Association of Bioindustries (EuropaBio) Council of European BioRegions (CEBR) European Biotechnology Network <i>(all based in Brussels, Belgium)</i>			

(Source) Mizuho Corporate Bank analysis on public information

Today, there are two forces which further highlight the importance of biotechnology clusters and cluster organizations in Europe.

First is the current tough business and economic environment which continue to remain a challenge for many as it has become increasingly more difficult to secure sufficient investments and funding.

This is especially the case for SME biotechnology companies who rely on funding to help them achieve next generation technologies, platforms and/or pipelines.

Cluster organizations are proactively working to attract more partners and investors into the cluster and region for licensing agreements, joint ventures, merger and acquisitions, inward investments and other business

development opportunities.

Second is the increasing cluster focus and activities in specific areas such as personalized medical care and/or regenerative medicine.

Personalized medical care has been gaining attention as it is generating new business development opportunities in combining traditionally separate business areas such as diagnostics with targeted therapeutics.

For example, Switzerland-based multinational pharmaceutical company Roche is focusing on the development of companion diagnostics with 60% of pharmaceutical pipeline projects paired with accompanied diagnostics.³²

European biotechnology clusters are also actively pursuing potential opportunities.

Biotechnology clusters Bio^M and FlandersBio are members of the EuroBioForum, European level platform established to promote trans-regional partnerships in the areas of personalized medical care.

32 Roche, Roche committed to innovation and growth (media release, 5 September, 2012).
http://www.roche.com/media/media_releases/med-cor-2012-09-05.htm (January, 2013).

Current Status/Activities of Biotechnology Industry and Clusters in Europe

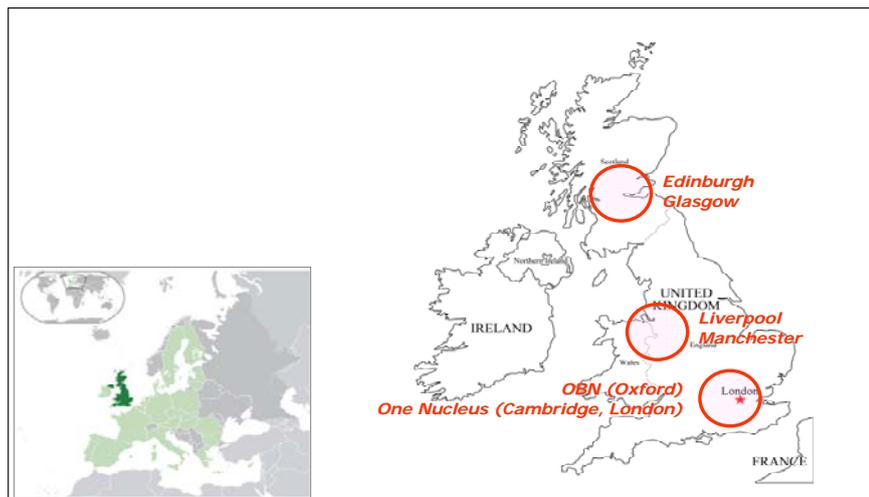
Chapter 4. United Kingdom

Overview

The UK life sciences industry is composed of over 300 pharmaceutical companies and 4,500 medical technology/biotechnology companies with an annual turnover of around £50 billion.³³

Leading regions/clusters in terms of number of companies and annual turnover are east/southeast of England (London, Cambridge and Oxford often referred to as the “Golden Triangle”), northwest of England (Manchester and Liverpool) and central Scotland (fig. 17).

【Fig. 17】 Biotechnology clusters in the UK



(Source) Mizuho Corporate Bank analysis on Wiki Commons and other public information

33 Her Majesty's Government (UK), 2012, 2011 (a).

The east/southeast of England and Scotland account for over a half of all medical biotechnology companies in the UK.

The southeast contains the largest number of vaccines/therapeutic proteins companies and the highest concentration of small molecule companies is observed in the east of England.

Research base in life sciences and biotechnology, history of government strategic measures for the area, access to finance, lower language barriers may have contributed to the relative maturity and the UK industry size.

UK scientists have been awarded more than 70 Nobel Prizes in biomedical science related disciplines and have contributed to some distinctive/groundbreaking research such as the DNA double helical structure, animal cloning (sheep) and induced Pluripotent Stem cells (iPS cells).

The Medical Research Council Laboratory of Molecular Biology alone has supported 14 Nobel Prize winning scientists.

Four of the world top ten universities are located in the UK; University of Cambridge, University of Oxford, University College London and Imperial College London.³⁴

In the early 1980s, the UK government established the Biotechnology Directorate with The Science and Engineering Research Council (SERC)³⁵ with an aim to fund academic biotechnology research.

The Biotechnology Unit within the Department of Trade and Industries (DTI)³⁶ was also established to further support the industry.

34 Office for Life Sciences (UK) and UK Trade & Investment, 2010.

35 Incorporated in Biological Sciences Research Council (BBSRC) in 1994.

36 DTI was renamed as the Department for Business, Enterprise and Regulatory Reform (BERR) in 2007.

The UK Government has been engaged in a long-term strategy following the 1993 white paper “Realising Our Potential: A Strategy for Science, Engineering and Technology”.

More recently in 2011, the UK government launched the ten-year strategy for the UK life sciences with aims to re-establish global leadership in life sciences sector and promote the UK as the destination for business.

Main measures include £1 billion a year investment to improve translational research infrastructure, manage talented human resources (attract, develop and reward) and facilitate healthcare innovation (through funding, regulator reviews)³⁷.

Better access to finance may be helped by the fact that 50-60% of UK venture capitals are reported to be concentrated in the London area³⁸ as well as by having access to the London Stock Exchange and financial services industry.

Oxfordshire Bioscience Network (OBN)’s recent study also confirms the concentration of investment activities with more than 80% of the UK investments in bioscience concentrated in the “Golden Triangle (London, Cambridge, Oxford)” region.³⁹

BERR and the Department for Innovation, Universities and Skills (DIUS) formed the e Department for Business, Innovation and Skills (BIS) in 2009.

37 Her Majesty's Government (UK), 2012.

38 Small Business Service, 2005.

39 OBN, 2011.

One Nucleus**Region**

- Cambridge, east of England and Greater London metropolitan area.

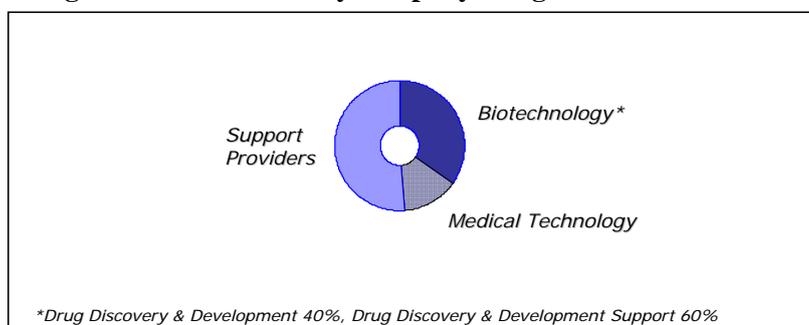
History

- Cambridge was one of the first clusters formed in Europe, triggered by the University of Cambridge spin-off companies and/or business development support provided by the St. John's Innovation Centre.⁴⁰
- One Nucleus was established in 2010 with the merger of two regional life science networks Cambridge-based Eastern Region Biotechnology Initiative (ERBI) and London Biotechnology Network (LBN).
- ERBI was established in 1997 by industry led initiative which started after discussions between a number of individuals from the local biotechnology community and local/national government officials.
- LBN was formed in 2000, as a regional support organization, supported by London's science and business community through "London First" a non-profit business membership organization, in response to the need for a coordinated approach to bioscience development in London.

Structure

- Around 500 member companies.
- Biotechnology companies 30-40%.
Others, medical technology companies and support providers.

40 St. John's Innovation Centre was established in 1986 as Europe's first innovation centre and business incubator to support early-stage knowledge-based businesses.

【Fig. 18】 One Nucleus by company categories

(Source) Mizuho Corporate Bank analysis on One Nucleus and other public information

Key Therapeutic Areas/Target Technologies

- Anti-infectives, blood/blood-forming organs, nervous system, oncology and regenerative medicines.

Strategies, Strengths, Topics and Trends

- The cluster is home to established pharmaceutical and biotechnology companies such as Amgen, Millennium, Genzyme and Gilead Sciences.
- Cambridge has been recognized as one of the prominent science research base with 13 Nobel Prize winners in medicine and chemistry since Crick with Watson in 1962 (the discovery of DNA structure).
- Many of One Nucleus activities are driven by member needs. Life Science Leadership Series organized with thematic focus on oncology, healthcare technologies, central nervous system (CNS) and aging, provide a platform for members and non-members to showcase their technologies/products/services and explore commercial/business development opportunities.
- In response to member requests, recently signed Memoranda of Understanding (MOU) with the US clusters such as The Massachusetts Biotechnology Council (MassBio) and BayBio.

The strategic partnerships are aimed to provide members with access to potential partners and encourage collaborations between members.

Biotechnology Companies

【Table 5】 One Nucleus company examples

Company	Areas	Established	References
BioMoti	<ul style="list-style-type: none"> • Neoplasms • Oncology 	N/A	Platform technology Oncojan™ for the delivery of active agents to the intracellular space in cancer
Chroma Therapeutics	<ul style="list-style-type: none"> • Oncology • Inflammatory diseases 	2001	Based on chromatin biology and novel cell accumulation approaches
F-Star	<ul style="list-style-type: none"> • Antibodies 	2006	Based on Modular Antibody Technology
Neurotex	<ul style="list-style-type: none"> • Regenerative medicine 	2007	Silk-based textile approach to novel nerve repair materials and other applications

Companies active in cluster focus areas, with advanced pipelines, or with recent activity updates.

(Source) Mizuho Corporate Bank analysis on One Nucleus, company publications and other public information

OBN (Oxford Bioscience Network)**Region**

- Oxford and neighboring regions.

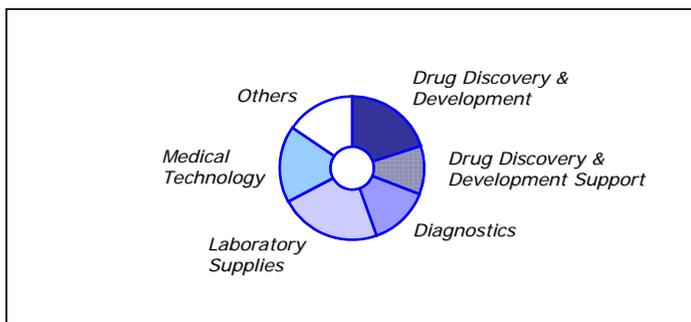
History

- The cluster was launched by the Minister of Science and Innovation in 1999 to develop and facilitate further biotechnology innovations/businesses.
- Since 1999, clustering has led to the establishment and growth of support/service providing companies such as contract research organizations (CROs) and reagents companies.

Structure

- Around 160 companies.
- Categories diversified across drug discovery/development and their support services, diagnostics, laboratory supplies, medical technologies and others.

【Fig. 19】 OBN by company categories

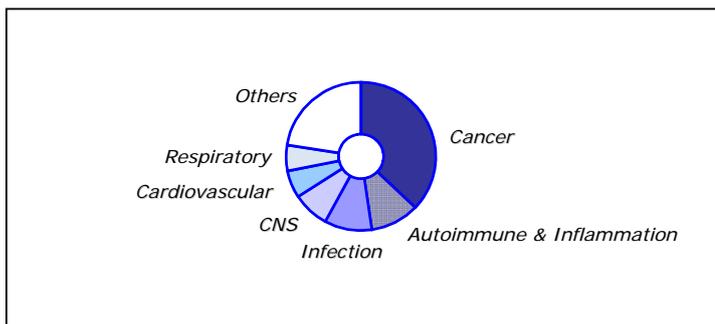


(Source) Mizuho Corporate Bank analysis on OBN and other public information

Key Therapeutic Areas/Target Technologies

- Approximately 300 pipelines, with more than half (around 170) in clinical stages and others in preclinical/discovery stages.
- Therapeutic areas; cancer, autoimmune/inflammation, infection, central nervous system, cardiovascular, respiratory and others.

【Fig. 20】 OBN by therapeutic areas



(Source) Mizuho Corporate Bank analysis on OBN and other public information

Strategies, Strengths, Topics and Trends

- University of Oxford is also a contributor.
- OBN Investment Network was established to direct members to investors and to support them throughout the process by providing advice on business plans, investor presentations, and business development opportunities thereafter.

Biotechnology Companies

【Table 6】 OBN company examples

Company	Areas	Established	References
CMP Therapeutics	<ul style="list-style-type: none"> • Infectious diseases • Inflammatory bowel diseases 	2004	University of Oxford spin-out Chitin microparticles (CMP)
e-Therapeutics plc	<ul style="list-style-type: none"> • Oncology 	2001	Brain cancer and solid tumour
Protaffin Biotechnologie AG	<ul style="list-style-type: none"> • Inflammatory diseases • Oncology 	2005	Austrian company. Protein-based products with CellJammer® technology (human chemokine proteins)
Summit plc	<ul style="list-style-type: none"> • Duchenne Muscular Dystrophy • Infectious diseases 	2003	Technology platforms in carbohydrate chemistry and zebrafish chemical genomics

(Source) Mizuho Corporate Bank analysis on OBN, company publications and other public information

Chapter 5. Germany

Overview

While the US was building the foundation of the biotechnology industry in the 1970s and 1980s, Germany faced divided social and political structures (i.e., East and West Germany) until the unification in October 1990.

The country is known to have experienced social unrest until the mid-1990s when Germany started to regain its political, economic and social stability.

In Germany, biotechnology cluster growth and development were triggered by the BioRegio contest⁴¹ launched by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung: BMBF) in 1995 to promote business development and commercialization of biotechnology.

Another driving force was the 1999's BioProfile competition designed to allow regions to define expertise within the overall biotechnology area in which they have a regional competitive advantage.

The initiatives facilitated industry growth with increase in the number of dedicated biotechnology companies from 250 in 1997 to over 500 in 2012.⁴²

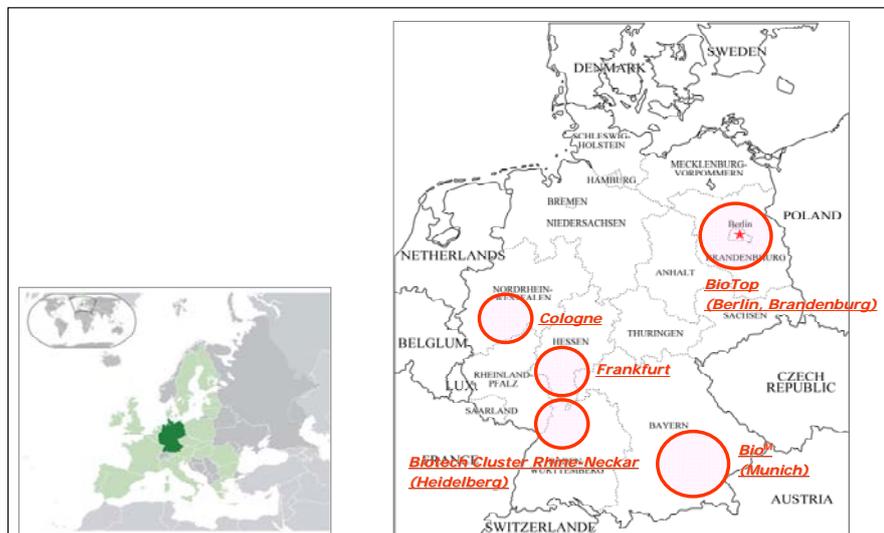
Today, there are about twenty industry relevant clusters in Germany.

Largest clusters are located in Berlin, Munich (München), the Rhine-Neckar Metropolitan Region (Metropolregion Rhein-Neckar), Cologne (Köln) and Frankfurt (fig. 21).

41 Biotechnology regions competed for public funding. Winners were Munich, Heidelberg, and Cologne.

42 Biotechnologie.de, 2012.

【Fig. 21】 Largest biotechnology clusters in Germany



(Source) Mizuho Corporate Bank analysis on Wiki Commons and other public information

One of the characteristics and strengths of biotechnology clusters in Germany is the varying state-level approaches as in the case observed with Bio^M and BioTOP.

Bio^M, centred in Munich, employs a unique organization structure divided in two firms/constitutions with different functions.

Bio^M AG is a for-profit organization specializing in more financial aspects of business (seed financing, venture capital fund management, consulting).

On the other hand Bio^M Biotech Cluster Development GmbH is a non-profit organization focused on cluster management.

BioTOP, located in Berlin, capitalizes on the extensive network composed of public research institutions and university hospitals especially in the field of regenerative medicine.

Bio^M**Region**

- Munich metropolitan region (München and Bayern in southern Germany).

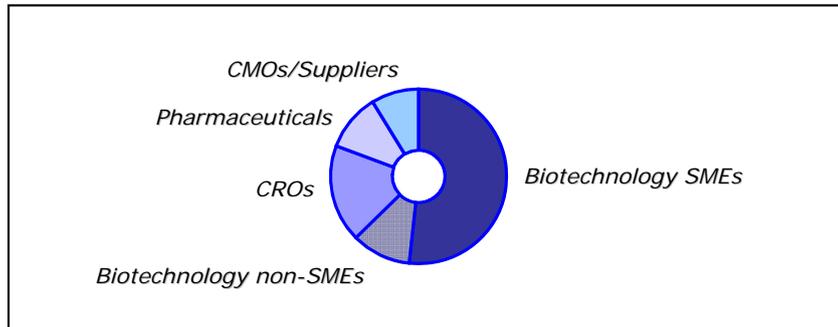
History

- Origination from the establishment of the Munich Gene Centre in 1984.
- As one of the three winners of BioRegio contest, Bio^M was established in 1997.
- Region's first biotechnology company Mikrogen was established in 1989.
- Reorganization of Bio^M AG and formation of Bio^M Biotech Cluster Development GmbH in 2006.
- The m⁴ program won the Leading-Edge Technology Cluster Contest in 2010.

Structure

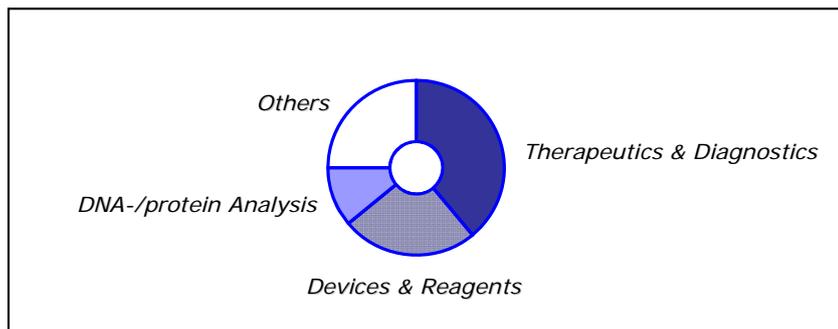
- More than 160 biotechnology SMEs and 35 non-SMEs (national or international subsidiaries).
- Others; 50-60 CROs, 30-40 pharmaceuticals and 20-30 contract manufacturing organizations (CMOs)/suppliers (fig. 22).
- Biotechnology SMEs subcategorized as therapeutics & diagnostics, devices & reagents, DNA & protein analysis and others (fig. 23).

【Fig. 22】 Bio^M by company categories



(Source) Mizuho Corporate Bank analysis on Bio^M and other public information

【Fig. 23】 Bio^M SMEs business areas



(Source) Mizuho Corporate Bank analysis on Bio^M and other public information

Key Therapeutic Areas/Target Technologies

- Therapeutic focus areas of pipelines are oncology, infection and cardiovascular.
- Technology focus areas are DNA/protein analytics, genomics/proteomics, nanotechnology, industrial biotechnology, personalized medicines and biomarkers.

Strategies, Strengths, Topics and Trends

- Established science base with over 80 pipelines in clinical trials and 5 products on the market.
- Over 60 of the biotechnology SMEs specialize in therapeutics or diagnostics.
- Currently promoting the m⁴ program for personalized medicines and targeted therapies, with €100 million funding granted from the Bundesministerium für Bildung und Forschung (BMBF; Federal Ministry of Education and Research)’s 2010 competition.
- Extensive ties with multinational pharmaceutical companies worldwide.

Biotechnology Companies

- Biotechnology SMEs (public and private) 2011 revenue accounts for €515 million.
- Pieris AG, focusing on anticalin based therapeutics, signed a multi-year and multi-target collaboration agreement with Sanofi and Sanofi Pasteur in 2010, and with Takeda in 2011.

【Table 7】 Bio^M company examples

Company	Areas	Established	References
4SC AG	<ul style="list-style-type: none"> • Oncology • Autoimmune diseases 	1997	Lead products include Vidofludimus (autoimmune) and Resminostat (pan-histone-deacetylase inhibitor)
Agennix AG	<ul style="list-style-type: none"> • Severe sepsis 	1998	Lead programs include a topical gel form of talactoferrin and a multi-targeted kinase inhibitor
Antisense Pharma	<ul style="list-style-type: none"> • Oncology 	1998	Antisense molecules targeting tumour-derived proteins Focus on glioblastoma, pancreatic cancer, malignant melanoma
Apceth	<ul style="list-style-type: none"> • Oncology 	2007	Cell and gene therapies
Pieris AG	<ul style="list-style-type: none"> • Oncology • Anemia 	2001	Anticalin therapeutics
Willex AG	<ul style="list-style-type: none"> • Oncology 	1997	Combined portfolio of therapeutics and diagnostics for antibody-based products

(Source) Mizuho Corporate Bank analysis on Bio^M, company publications and other public information

BioTOP

Region

- Berlin and Brandenburg.

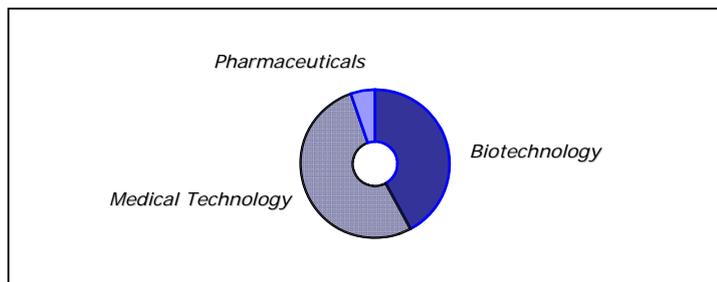
History

- Established in 1996 as a joint initiative of the federal states of Berlin and Brandenburg.

Structure

- Around 200 biotechnology companies, 250 medical technology companies and 25 pharmaceutical companies (fig. 24).
- More than 100 biotechnology companies created in the last 10 years.

【Fig. 24】 BioTOP by company categories



(Source) Mizuho Corporate Bank analysis on BioTOP and other public information

Key Therapeutic Areas/Target Technologies

- Regenerative medicines, in-vitro diagnostics, systems biology and bioinformatics, proteomics, ribonucleic acid (RNA) and glycol biotechnology and nutrigenomics.

Strategies, Strengths, Topics and Trends

- Umbrella organization under the TSB Innovationsagentur Berlin GmbH as well as a part of the regional health care industry promotion network The Network Health Economy Health Capital (HealthCapital Netzwerk Gesundheitswirtschaft).
- Contributed to attracting pharmaceutical companies in the region such as Sanofi (France), Pfizer (US), Shire (UK), Nycomed (a group company of Takeda, Japan).
- Additional contributing factor may be the less operational costs and more flexible operational conditions (e.g., office, real estate, staffing, others) in comparison to other cities in Europe.
- Active participant in European projects Common Tools in biotechnology (BioCT) and European networks such as Council of European BioRegions (CEBR).
- Additionally takes part in thematic networks and initiatives such as European Diagnostic Cluster Alliance (EDCA).

Biotechnology Companies

【Table 8】 BioTOP company examples

Company	Areas	Established	References
Alacris Theranostics	• Oncology	2008	Based on ModCell™, next-generation genome sequencing technologies
Epigenomics	• Oncology	1998	Oncology molecular diagnostics Focus on colorectal, lunge and prostate cancer
Mivenion	• Inflammatory • Autoimmune diseases	N/A	Focus on personalized medicine for inflammatory and autoimmune diseases
Scienion	• Oncology	2000	Biochips for cancer diagnostics based on piezo electric dispensing, surface modification and microarray manufacturing

(Source) Mizuho Corporate Bank analysis on BioTOP, company publications and other public information

Chapter 6. France

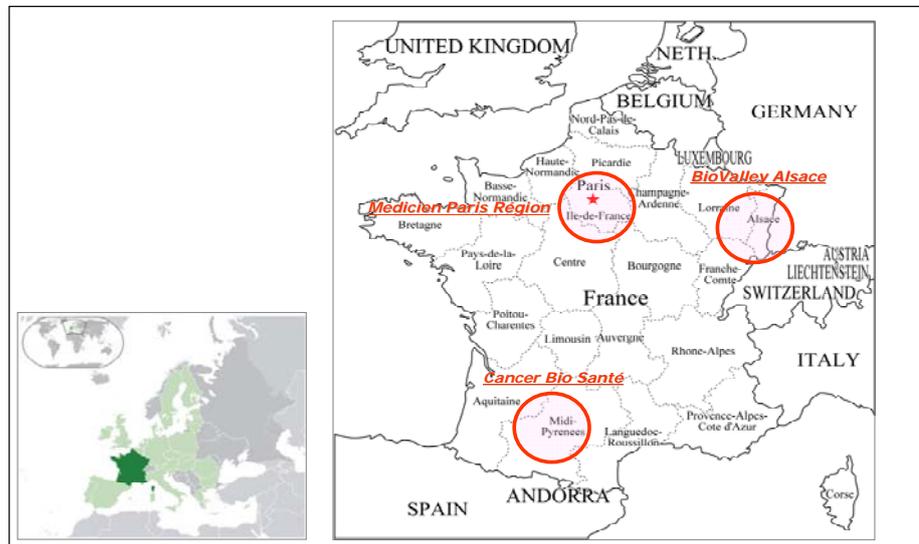
Overview

There are around ten biotechnology clusters focused on healthcare and medicines in France and most life sciences companies are concentrated in the “Medicen Paris Region” cluster.⁴³

Over 50% of pharmaceutical companies in France, around 50% of academic research and biotechnology companies, as well as 80% of CROs are located in the Medicen Paris Region.^{44,45}

Other biotechnology clusters in France include Cancer Bio Santé and tri-national cluster BioValley Alsace (fig. 25).

【Fig. 25】 Leading biotechnology clusters in France



(Source) Mizuho Corporate Bank analysis on Wiki Commons and other public information

43 Includes Paris, Hauts-de-Seine, Seine-Saint-Denis, Val-de-Marne, Essonne, Yvelines and Val-d’Oise. Medicen Paris Region is a cluster management organization established in 2005.

44 Medicen Paris Region.

45 Paris Region Economic Development Agency.

Medicen Paris Region is the result of the French government lead cluster development initiative launched in 2005 to promote “Competitiveness Clusters”⁴⁶ nationally and globally.

One of the bioparks in the Medicien Paris Region is Genopole. Genopole is a biotechnology dedicated science and business park established in 1998 by the French government, local authorities and the French Muscular Dystrophy Association (Association Française contre les Myopathies) to pursue genome /related researches.

Genopole since 1998, has initiated or supported the creation and the development of 125 companies working in close partnership with external organizations such as the Essonne Development Agency (l'Agence pour l'Economie en Essonne).

46 France General Directorate for Competitiveness, Industry and Services. Total of 71 competitive clusters across different areas such as transport, aeronautics and aerospace, agribusiness and bio-resources were identified. http://competitivite.gouv.fr/documents/commun/Documentation_poles/cartes-poles/carte.pdf (January, 2013).

Genopole®

Region

- Evry (Évry), in Essonne county 20-30km south of Paris.

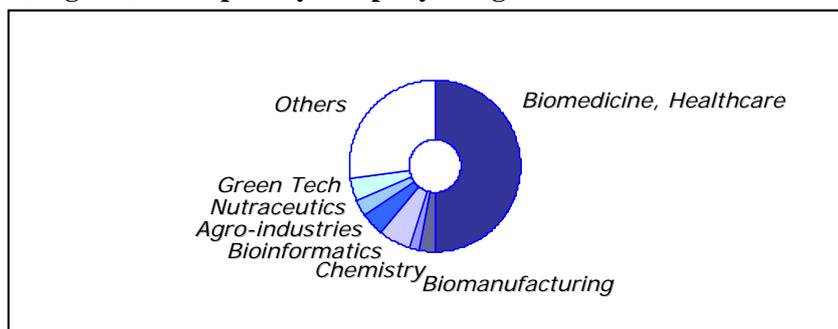
History

- Established in 1998 by the French government, Ile-de-France Regional Council (Conseil régional Île-de-France), Essonne County Council (L'Agence pour l'économie en Essonne) and the French Muscular Dystrophy Association (Association Française contre les Myopathies).

Structure

- Over 70 biotechnology companies, 20 academic research laboratories.
- Around 50% of total members represent biomedicine and healthcare (fig. 26).

【Fig. 26】 Genopole by company categories



(Source) Mizuho Corporate Bank analysis on Genopole and other public information

Key Therapeutic Areas/Target Technologies

- Stem cells, synthetic biology, gene therapy products and rare diseases.

Strategies, Strengths, Topics and Trends

- Pipelines with more than 25 molecules or biotherapies.
- One-stop service comprised of facilities, equipment, office spaces, good manufacturing practice (GMP) production centre, customized services, shared services, incubation services.
- Approximately 20 shared-access technology platforms and facilities including access to part-time administrative services, financial directors, IT maintenance and others.
- Dedicated teams for comprehensive on-site resources and support services for researchers and companies.
- High concentration of national research institutes, universities and biotechnology companies.

Biotechnology Companies

【Table 9】 Genopole company examples

Company	Areas	Established	References
Genethon	<ul style="list-style-type: none"> • Rare diseases • Neuromuscular diseases 	1990	Gene-based therapeutics
InGen	<ul style="list-style-type: none"> • Infectious diseases • Immunology 	2001	In-vitro diagnostics for immuno-infection, Alzheimer's disease, cancer
LTKfarma	<ul style="list-style-type: none"> • Autoimmune diseases 	2006	Cell therapy products for the treatment of leukemia, auto-immune diseases and solid tumours
Vaxon Biotech	<ul style="list-style-type: none"> • Oncology 	2004	Cancer therapeutics/vaccines for lung, prostate and breast cancers
Wittycell	<ul style="list-style-type: none"> • Infectious diseases • Oncology 	2005	Immunomodulator adjuvants based on natural killer T (NKT) agonists glycolipids

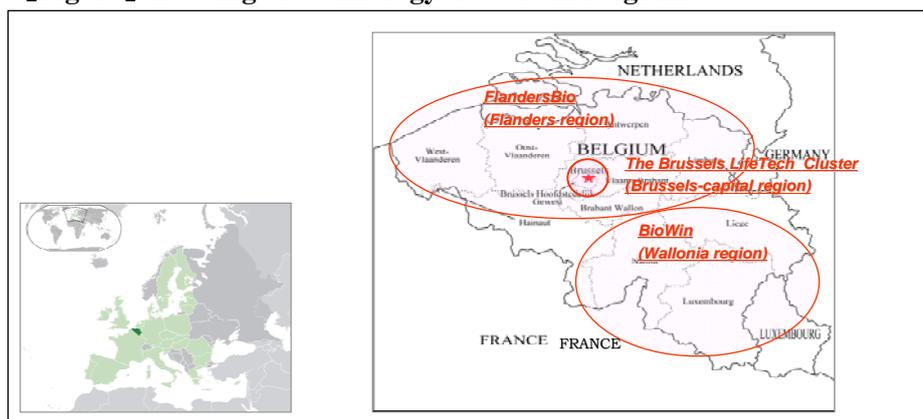
(Source) Mizuho Corporate Bank analysis on Genopole, company publications and other public information

Chapter 7. Belgium

Overview

The Kingdom of Belgium is a federal state structured by three regions: Flanders (north), Wallonia/Wallonia (south) and Brussels-Capital (centre). Each region has a devoted biotechnology organisation with a total of more than 300 biotechnology companies concentrated in Flanders 49%, Wallonia 34% and Brussels 17% (fig. 27).⁴⁷

【Fig. 27】 Leading biotechnology clusters in Belgium



(Source) Mizuho Corporate Bank analysis on Wiki Commons and other public information

Biotechnology industry in Flanders is largely supported by universities, academic institutions and research centres with a long-standing tradition of focus on healthcare and agricultural biotechnology.

Research breakthroughs achieved in the region include the first plant recombinant technology and discovery of several new medicines from Janssen pharmaceuticals and others.⁴⁸

⁴⁷ Belgian Foreign Trade Agency, 2011.

⁴⁸ FlandersBio, VIB, Flanders Investment & Trade, 2010.

Flanders' biotechnology cluster is supported by collaborative partnerships between three organisations; research institute Flanders Institute for Biotechnology (Vlaams Instituut voor Biotechnologie; VIB), cluster organisation FlandersBio and Flanders Investment & Trade (FIT).

VIB provides office and laboratory spaces and range of shared services through its subsidiaries/umbrella organizations Bio-incubator Leuven and Bio-Accelerator.

The cluster management by FlandersBio as well as collaborative partnership/promotion with VIB and FIT have contributed to the success of some biotechnology start-ups such as Ablynx.

FlandersBio**Region**

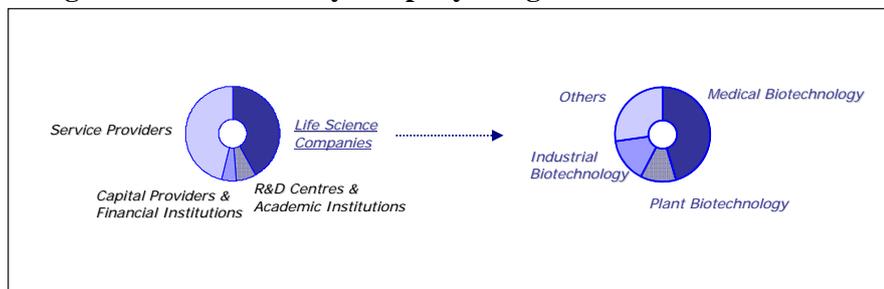
- Flemish region (north east of Belgium).

History

- VIB was established by the Flemish government in 1997 with an objective to bring academic research to market through patenting, licensing and the creation of new enterprises.
- The cluster organization FlandersBio was established in 2004 by VIB for cluster management and support.

Structure

- Total of around 250 companies of which more than 100 life science companies (fig. 29).
- Life science companies, categorized by medical biotechnology 45%, plant biotechnology (agricultural and food) 12% and industrial biotechnology 15% (fig. 29).
- Pharmaceutical companies; R&D centres (Johnson & Johnson, Bayer), production (Pfizer, MSD, Genzyme (Sanofi), Novartis) and clinical research (Amgen).

【Fig. 29】 FlandersBio by company categories

(Source) Mizuho Corporate Bank analysis on FlandersBio, VIB and other public information

Key Therapeutic Areas/Target Technologies

- Molecular biology, industrial biotechnology and green biotechnology.
- Therapeutic areas include immunology, neurosciences, oncology, infectious diseases and others.

Strategies, Strengths, Topics and Trends

- In 2010, VIB signed 83 R&D licensing agreements bringing the total number since 1996 to 643.
The 2010 agreements generated €13.5 million.
- More than 50 pipelines in clinical trials, 6 products approved and 12 on the market.
- Total of 33 companies in the cluster hold 941 patents, averaging 29 per company.
- Since 2005, six Flemish biotechnology companies achieved initial public offerings and have raised a total of €310 million.
- Since 2005, the cluster has been hosting/organizing an annual life sciences convention “Knowledge for growth”⁴⁹, the largest regional biotechnology event in Europe.

49 <http://knowledgeforgrowth.be/> (January, 2013).

Biotechnology Companies

【Table 10】 FlandersBio company examples

Company	Areas	Established	References
Ablynx	<ul style="list-style-type: none"> • Haematology disorder • Immunology • Oncology 	2001	Focused on the discovery and development of Nanobodies®, a novel class of antibody-derived therapeutic proteins based on single-domain antibody fragments
Galapagos	<ul style="list-style-type: none"> • Immunology • Oncology 	1999	Specialised in the discovery and early development of small molecule and antibody therapies
MDxHealth	<ul style="list-style-type: none"> • Oncology 	2003	Formerly OncoMethylome Sciences Develops molecular diagnostic products for cancer
Multiplicom	<ul style="list-style-type: none"> • Diagnostics 	2011	Genetic test kits based on molecular diagnostic technologies
ThromboGenics	<ul style="list-style-type: none"> • Ophthalmology • Oncology 	1991	Lead product, ocriplasmin for the treatment of symptomatic Vitreomacular Adhesion (VMA)
TiGenix	<ul style="list-style-type: none"> • Autoimmune and inflammatory disease 	2000	Lead product, ChondroCelect®, for cartilage repair in the knee, is the only approved cell-based product in Europe

(Source) Mizuho Corporate Bank analysis on FlandersBio, VIB, company publications and other public information

Chapter 8. Switzerland

Overview

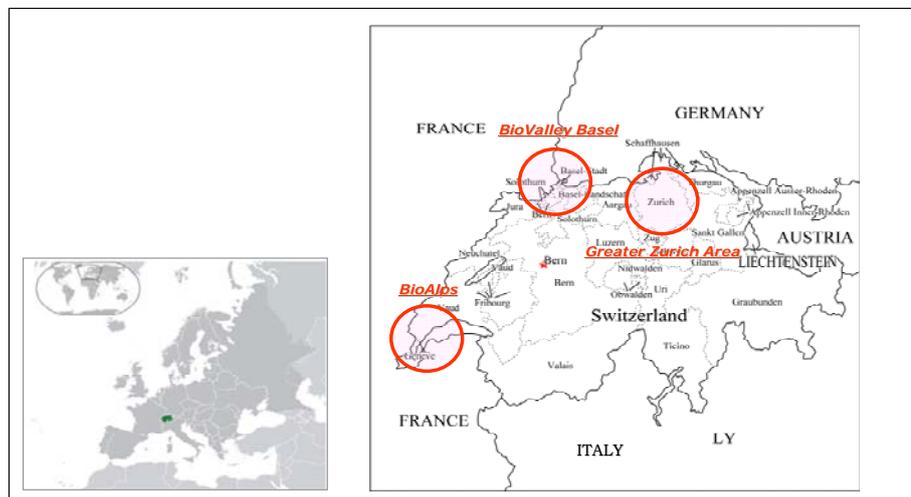
Switzerland is a federation of 26 cantons (member states of the Swiss Confederation) with four official national languages.

Languages spoken are German, French, Italian and Romansh and the country is surrounded by Germany, Austria, Italy, and France.⁵⁰

There are five regional biotechnology clusters in Switzerland in Basel, Greater Zurich, Lake Geneva⁵¹, Berne Capital and Ticino⁵².

Approximately 80% of all Swiss biotechnology companies are located in Basel, Zurich and Geneva (fig. 30).

【Fig. 30】 Major biotechnology clusters in Switzerland



(Source) Mizuho Corporate Bank analysis on Wiki Commons and other public information

50 Swiss Federal Chancellery, <http://www.ch.ch/behoerden/00215/index.html?lang=en> (January, 2013).

51 BioAlps.

52 Biopolo.

Of total of 249 Swiss biotechnology companies, approximately 75% are dedicated to biotechnology with R&D programs and 25% are services providers, suppliers and others.⁵³

One of the strengths of the Swiss biotechnology industry may be the presence of leading multinational corporations in pharmaceutical and related industries such as Novartis, Roche, Lonza and Actelion, of which majority are concentrated in the Basel Area.

In addition, favorable tax environment and incentives may be a supporting factor.⁵⁴

Other contributing factors to Swiss biotechnology strengths are proximity and mobility to neighboring European countries as well as cultural/linguistic/national diversity which biotechnology clusters benefit from.

The mobility and transferability of people are demonstrated with approximately 60,000 people commuting daily from France and Germany to northwest Switzerland.

Diverse business environment supported by multi languages and cultures as well as multinational organization/clusters may facilitate improved knowledge sharing, collaborations and innovation.

BioValley, a tri-national cluster between Switzerland, Germany and France was established in 1997, in response to the EU initiative with an aim to capitalize on the already established pharmaceutical and chemical industries.

53 Swiss Biotech Association, 2012.

54 EuropaBio, Ernst & Young, 2012.

For up to a maximum of 10 years, cantons are free to grant full or partial relief from corporate income tax and capital taxes to newly established companies, those relocating a new business to Switzerland, and those contemplating a significant expansion of an existing business.

BioValley Basel**Region**

- Region Upper Rhine; Basel (northwest Switzerland), South Baden (Germany) and Alsace (France).

History

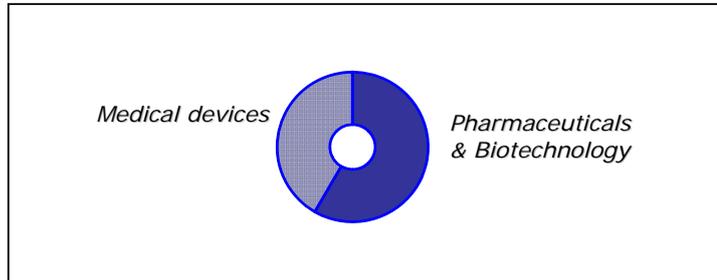
- The cluster was initially established in 1996, as one of the first biotechnology clusters in Europe, by two Swiss businessmen with a vision to reproduce the US “Silicon Valley”.
- In 1997, “Life Sciences Network BioValley” was established within the framework of EU initiative INTERREG II 1996-1999⁵⁵.
- Other forces include the merger of Ciba-Geigy and Sandoz to become Novartis in 1996, and the establishment of Novartis Venture Fund in 1997 as well as HBM BioVentures AG in 1998.

Structure

- The cluster comprises three organizations, BioValley Basel (Switzerland), BioValley Baden-Württemberg (Germany) and BioValley Alsace (France).
- Composed of 350 pharmaceutical and biotechnology companies, 250 medical devices companies (fig. 31).
- In addition, 10 universities, academic institutions dedicated to life sciences and 11 life science parks.

55 Cross-border, transnational, interregional cooperation initiative.

【Fig. 31】 BioValley by company categories



(Source) Mizuho Corporate Bank analysis on BioValley and other public information

Key Therapeutic Areas/Target Technologies

- Leading therapeutic areas are oncology, neurosciences, infectious diseases and immunology.
- Additional areas include nanotechnology, agricultural sciences and nutrition.

Strategies, Strengths, Topics and Trends

- Dedicated matchmaking team “Tri-national BioValley Matchmaking Team” in each region.
- Presence of major healthcare companies in the tri-national regions.⁵⁶
- Five scientists from BioValley won the Nobel Prize in the disciplines of bio/medicine and chemistry.
- Effective information sharing system since 1998 with the tri-national database of companies and research results (publications, doctoral theses, patent/licensing from BioValley universities).

56 Switzerland; Actelion, Basilea Pharmaceuticals, Genzyme, Novartis, Roche.
 Germany; Agilent Technologies, DSM, GE Healthcare, Pfizer, Phadia.
 France; Capsugel, Pfizer, Lilly, Millipore, Sanofi, Transgene.

Biotechnology Companies

【Table 11】 BioValley Basel company examples

Company	Areas	Established	References
4-Antibody	<ul style="list-style-type: none"> • Infectious Disease • Oncology • Immunology 	2002	Antibody drug-discovery technology platform
NBE Therapeutics	<ul style="list-style-type: none"> • Oncology 	2012	Focus on antibody-based New Biological Entities (NBEs)
Polyphor	<ul style="list-style-type: none"> • Drug delivery technologies 	1996	MacroFinder® and PEMfinder® platforms for discovering potent and selective modulators of Protein-Protein Interactions (PPI) and other targets
Proreo Pharma	<ul style="list-style-type: none"> • Pulmonary hypertension • Cognitive, muscular and endocrine disorders 	2002	Lead pipelines for aura migraine and pulmonary hypertension

(Source) Mizuho Corporate Bank analysis on BioValley, company publications and other public information

Chapter 9. Denmark and Sweden

Overview

Denmark and Sweden are world renowned for their established research base.

Denmark and Sweden were both ranked as “innovation leaders” with performance well above the EU27 average as well as countries recognized with high knowledge/technology-intensity.⁵⁷

In Denmark, biotechnology industry is concentrated in the Copenhagen region with about 160 dedicated biotechnology companies.

Areas of research focus in Denmark include metabolic diseases, inflammatory and infectious diseases and neuroscience.

Sweden has four major biotechnology clusters, Stockholm-Uppsala Life Science, GöteborgBIO (Gothenburg), BioTech Umeå (Umea) and Medicon Valley (Swedish side encompasses Skåne (Scania) region).

Stockholm-Uppsala region is home to more than 50% of biotechnology companies.

Scania region has strength in diabetes, cancer, inflammation and CNS and the region is characterized by a high concentration of pharmaceutical industry with 60% of total number of companies in the country.

Greater Copenhagen and the neighbouring Swedish region Scania together forms the Medicon Valley cluster.

Branding of “Medicon Valley” is promoted by a Copenhagen-based cluster organisation Medicon Valley Alliance (MVA) in partnership with foreign investment agencies Invest in Skåne and Copenhagen Capacity.

57 EC Directorate-General Enterprise and Industry, 2012.

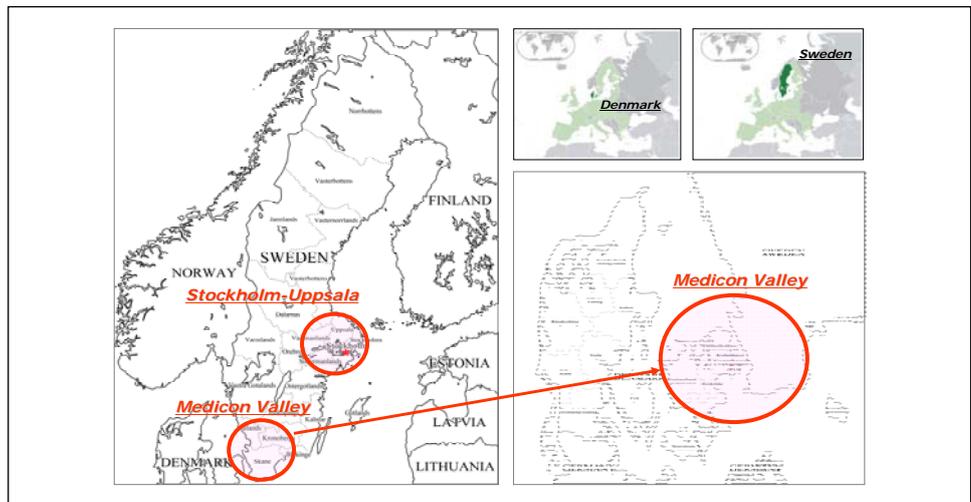
Countries are assessed against 25 different indicators ranging from research systems, intellectual assets, firm investments, human resources and others.

In the study, Germany and Finland, as well as Denmark and Sweden, are recognized as “innovation leaders”.

Denmark and Sweden’s trans-national initiative Medicon Valley has been helped by the Øresund Bridge inaugurated on 1 July 2000.

The bridge interconnecting the two regions is encouraging more knowledge, capital and people mobility and transfer.

【Fig. 32】 Dominant biotechnology clusters in Denmark and Sweden



(Source) Mizuho Corporate Bank analysis on Wiki Commons and other public information

Medicon Valley**Region**

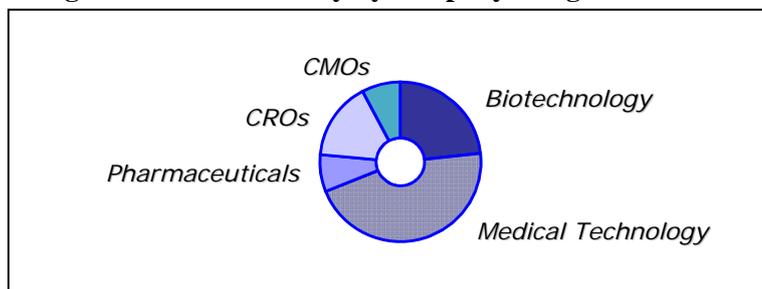
- East Denmark (Copenhagen region) and south-west Sweden (Scania (Skåne) region).

History

- Inspired by the US's "Silicon Valley" success, two scientists from universities in Lund and Copenhagen started informal discussions in 1992.
- Later in 1997, Medicon Valley Alliance (MVA; formerly known as Medicon Valley Academy) was established within the framework of EU initiative INTERREG II 1994-1999.

Structure

- More than 80 biotechnology companies, 160 medical technology companies, as well as 27 pharmaceutical companies, 57 CROs and 28 CMOs.
- High presence of major (multinational, pan-European) pharmaceutical and biotechnology companies including Novo Nordisk, Lundbeck, AstraZeneca, Biogen Idec, Genzyme, Iperion, Bactiguard, Genentech, Wyeth Pharmaceuticals, Roche, Daiichi-Sankyo and Lilly.

【Fig. 33】 Medicon Valley by company categories

(Source) Mizuho Corporate Bank analysis on MVA and other public information

Key Therapeutic Areas/Target Technologies

- Around 150 compounds in development in areas of oncology, nervous systems, immunology and others.

Strategies, Strengths, Topics and Trends

- Recent initiatives are based on Medicon Valley Alliance's awareness of global competitive environment and pharmaceutical companies' business focus changes.
- Priority measures for turning Medicon Valley into an internationally competitive and attractive region for performing R&D include "Medicon Valley Beacon Initiative"⁵⁸, "Drug Delivery Initiative"⁵⁹ and "Life Science Ambassador Program"⁶⁰.
- Other measures include match-making events to identify in-licensing opportunities for multinational pharmaceutical companies.

⁵⁸ Focusing on areas including drug delivery, healthy ageing, imaging and oncology.

⁵⁹ Create an open platform for drug delivery research and translational development centre.

⁶⁰ MVA ambassadors are positioned in Kobe Kansai (Japan), Seoul (South Korea) and Boston (US). Potential areas include Beijing, San Diego and San Francisco.

- Mid- and long-term national-level strategies for attracting life sciences and biotechnology communities from the world.

Projects include establishment of the 1) scientific research centre ESS (European Spallation Source), 2) national laboratory and synchrotron facility MAX⁶¹ Laboratory IV and 3) Science City Medicon Village⁶².

Biotechnology Companies

【Table 12】 Medicon Valley company examples

Company	Areas	Established	References
Evolva Holding	• Metabolic diseases • Infectious diseases	2004	Lead pipeline for the treatment of diabetic complications
Essentys	• Osteoporosis	2004	Lead pipeline for the treatment of osteoporosis
NeuroSearch	• CNS	1989	Lead pipelines for orodipidine and seridopidine
NsGene	• CNS	1999	Spin-off from NeuroSearch. Focus on Alzheimer's disease, neuropathic pain and Parkinson's disease
Santaris Pharma	• Infectious diseases • Metabolic diseases	2003	RNA-targeted medicines

(Source) Mizuho Corporate Bank analysis on MVA, company publications and other public information

61 National research infrastructure in Lund (Sweden) inaugurated in July 2010.

MAX stands for Macrotron Accelerator for X-rays.

62 Former AstraZeneca R&D Center.

Currently includes Center for Cancer Research, Life Science Innovation Center, Life Science Company Park, Investment Partners and Medicon Skills Center.

Conclusion and Outlook

Strategic and unified approach of Europe to biotechnology industry cluster development is built upon the necessity to combine competencies/resources to reach a sufficient critical mass for improved global competitiveness and business/market attractiveness.

This approach has helped encourage various types of participants in biotechnology (e.g., cluster organizations, governments, policy makers, regulatory bodies, universities, research institutions and others) to work together.

The collaborative efforts are facilitating the growth of biotechnology clusters and industry through increased 1) commercialization of research results and 2) access to information, skill and knowledge, human and financial capital necessary to secure continued growth and success.

Key trends observed in cluster development strategies in Europe are increased emphasis on SME support and internalization.

Recent collaboration efforts in Europe are focused on supportive measures specifically designed for SMEs in line with the EU's increased recognition of SMEs' role in innovation as well as SME's growth contribution to the economy⁶³

Biotechnology clusters are increasingly involved in extending their global reach, in response to the above directions.

For Example, BioX4Clusters (BIO crossing borders of 4 European Clusters

63 EC Directorate-General Enterprise and Industry, Advanced Biotech Cluster platforms for Europe (ABCEurope). A pan-European partnership of 13 cluster organizations across Europe. <http://www.europe-innova.eu/web/guest/cluster-cooperation/cluster-innovation-platform/abceurope/about> (January, 2013).

for a joint international strategy) launched in 2012 aims to support SMEs' global reach namely to China, Brazil and the US.

Strength and focus areas vary by cluster and country, reflecting the diversity of Europe.

Efforts are helping shape supportive business environment and attract into the clusters, national and international partners as well as investors looking for business growth and new investment opportunities.

In particular, recent developments and trends in the following fields are indicating potentials of business opportunities in under-exploited or niche areas:

1) **Biopharmaceuticals or biotechnology-derived NMEs**

- About a half of all medicines in the global pipelines and one fifth of the NMEs (New Molecular Entities) launched on the world market each year are estimated to be derived from biotechnology.^{64,65}
- Biotechnology-derived medicines account for 10-15% of the current pharmaceutical market and this number is expected to continue to grow.⁶⁶
- Patent expiries of small and large molecule blockbuster drugs between 2010 and 2015 are expected to bring business opportunities, e.g., biosimilar market growth.
- The first biosimilar product to receive European Medical Agency (EMA) authorisation was Omnitrope[®] (growth hormone, somatropin/somatrophin) in April 2006 and 11 more products have been authorized since then.

2) **Advanced therapies**

- Advanced therapies encompass gene therapy, cell therapy and tissue engineered products, used for healing or replacement of organs or tissues damaged by aging, injury or degenerative

⁶⁴ EuropaBio, Ernst & Young, 2012.

⁶⁵ European Federation of Pharmaceutical Industries and Associations, 2010.

⁶⁶ European Biopharmaceutical Enterprises.

http://www.ebe-biopharma.org/index.php?option=com_content&task=view&id=26&Itemid=102 (January, 2013).

diseases such as Parkinson's disease.

- Examples include skin tissue, bone tissue, artificial blood, tissue engineered full organ, knee cartridge and others.⁶⁷

3) Personalized preventative or therapeutic medical care

- An example of personalized medical care⁶⁸ is the use of diagnostics in combination with therapeutics to improve prevention, diagnosis and treatment of diseases.
- Swiss company Roche markets Zelboraf (vemurafenib) and companion diagnostic the Cobas[®] 4800 BRAF V600 Mutation test, for the treatment of skin cancer BRAF mutation-positive metastatic melanoma.
- Patients diagnosed with the same disease may have different symptoms and react differently to the same treatment.
- Biotechnology-driven supporting diagnostic tools such as biomarkers⁶⁹, pharmacogenomics⁷⁰ and bioinformatics⁷¹ are expected to contribute towards identifying indicators on a molecular level that provide information on a personal level.
- Better use of a therapy, increased safety and efficacy of drugs are expected.
- Potential application areas are oncology, infectious diseases, haemostasis, inflammatory conditions including rheumatoid arthritis and asthma.

4) Rare diseases and orphan medicinal products

- Orphan medicinal products are for treating rare diseases possibly life threatening or with serious debilitating conditions such as multiple sclerosis, Crohn's disease and others.
- Rare diseases are identified as incidence of 5 or fewer in every 10,000 people and it is estimated 5,000 to 8,000 rare diseases exist

⁶⁷ Europe Innova, 2011.

⁶⁸ Also referred to as "stratified medicine" or "personalized medicine".

⁶⁹ Biomarkers are tests used to follow body processes and diseases in humans/animals and used to predict how a patient will respond to a medicine or whether they have, or are likely to develop, a certain disease.
http://www.emea.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000349.jsp&mid=WC0b01ac05800baedb (January, 2013).

⁷⁰ Pharmacogenomics is the study of how the variability of the expression of genes between people leads to differences in susceptibility to disease and responses to medicines.
http://www.emea.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000347.jsp&mid=WC0b01ac05800baeda (January, 2013).

⁷¹ Construction of databases on genomes, protein sequences; modelling complex biological processes, including systems biology.
http://ec.europa.eu/enterprise/sectors/biotechnology/what-is-biotechnology/definition/index_en.htm (January, 2013).

today with 80% due to genetic causes.⁷²

- Recent Thomson Reuter's study on economics of orphan drug finds orphan drugs represent commercial and revenue generating potential regardless of small patient population.⁷³

5) Advanced medical and information/communication technologies

- Advancement of healthcare/medical technology and information/communication technology are contributing to healthcare and drug discovery and development processes.
- Examples include 1) biomedical instruments and equipment such as biosensors, analytical device which converts a biological response into an electrical signal and bio-devices, devices constructed from biological components, as well as 2) imaging technology for detecting and treating diseases.
- EU is aiming to provide digital health records to patients in several diseases by 2015.⁷⁴

6) Biotechnology-based products (industrial/environmental)

- Biotechnology-based products include bio-based plastics, bio-lubricants, bio-fibers for textiles, composite materials for construction and automotive, chemical and pharmaceutical building blocks, organic acids, amino acids and enzymes.
- OECD suggests that industrial and plant biotechnology will overtake health biotechnology by 2030 and account for 75% of the total gross value added by the biotechnology sector.
- EU has identified biotechnology-based products as one of the six areas of lead markets to be supported in the EC Lead Market Initiative.⁷⁵

7) Change strategies of pharmaceutical companies

- Patent cliff and healthcare cost reductions (pressure on pricing and others) have had an impact on pharmaceutical company revenues and their strategies across the drug discovery and development value chain.

72 European Biopharmaceutical Enterprises.
http://www.ebe-biopharma.org/index.php?option=com_content&task=view&id=36&Itemid=135 (January, 2013).

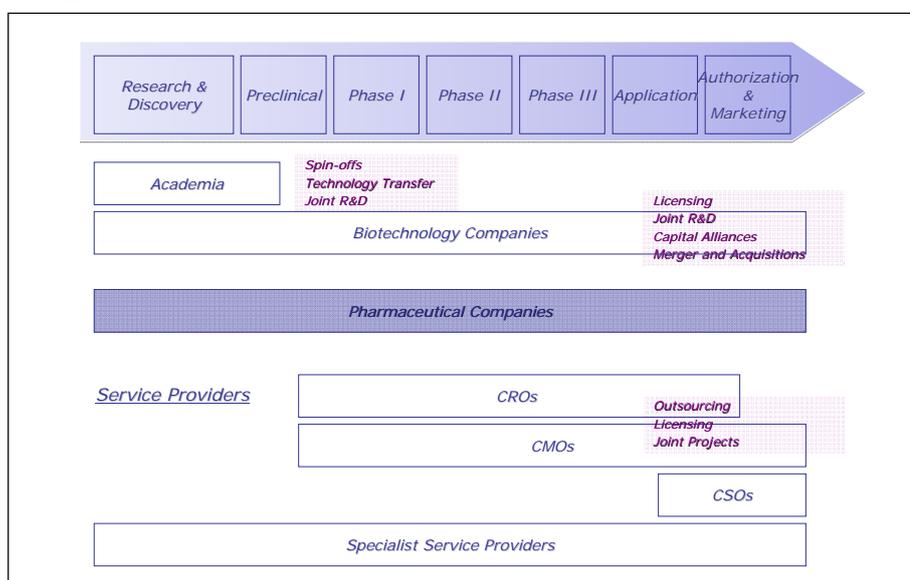
73 Thomson Reuters, 2012.

74 EU's initiative on Electronic Health Records.

75 Lead Market Initiative.
http://ec.europa.eu/enterprise/policies/innovation/policy/lead-market-initiative/biobased-products/index_en.htm
(January, 2013).

- Many pharmaceutical companies are exploring new revenue streams, e.g., different therapeutic areas (chronic and/or life-threatening diseases), biopharmaceuticals, medical devices, personalized medical care, orphan drugs, generics, over-the-counter drugs/consumer products and emerging markets.
- Pharmaceutical companies have been active in merger and acquisitions and forming alliances (licensing, joint R&Ds and ventures) with innovative biotechnology firms with potentials in drug discovery and development and drug delivery systems.
- To improve cost effectiveness and strengthen business results, pharmaceutical companies are exploring outsourcing and off-shoring across value chain factors/functions in business, e.g., research, clinical development, manufacturing, sales and marketing.
- Pharmaceutical company strategy changes discussed above have provided commercial opportunities for CROs, CMOs and Contract Sales Organisations (CSOs) and other service providers (fig 34).

【Fig. 34】 Pharmaceutical business value chains



(Source) Mizuho Corporate Bank analysis on public information

8) Bio-economy

- Recent global move towards the “Bio-economy”, an expansion of strategic focus from healthcare/medical to industrial and environmental biotechnology sectors.^{76,77}
- EU bio-economy has an annual turnover of about €2 trillion with more than 22 million employed, accounting for 9% of total employment in the EU.⁷⁸

Biotechnology clusters and cluster organisations will continue to play a vital role in providing crucial ingredients for growth and success, by ways of improving potential partners and investors’ access to cluster’s knowledge, technology, people, products, services, information as well as to their member companies.

The recent rise in the interests from biotechnology clusters and their biotechnology companies to explore certain business partners for concrete collaboration in the markets worldwide by taking part in such as mission delegation trips and dialogue initiation represents potential opportunities.

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76 EC, 2012 (a).

77 OECD, 2007 (a).

78 EC, 2012 (a).

<List of Abbreviations>

CMO	Contract Manufacturing Organization
CNS	Central Nervous System
CRO	Contract/Clinical Research Organization
CSO	Contract Sales Organization
DDS	Drug Delivery System
DNA	Deoxyribonucleic Acid
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EuropaBio	The European Association of Bioindustries
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
INTERREG	Interregional Cooperation Program
IPO	Initial Public Offering
iPS cells	induced Pluripotent Stem cells
M&As	Mergers and Acquisitions
NCEs	New Chemical Entities
NMEs	New Molecular Entities
OBN	Oxford Bioscience Network
OECD	The Organization of Economic Co-operation and Development
OTC	Over-the-Counter
R&D	Research and Development
RNA	Ribonucleic Acid
RNAi	RNA interference
SMEs	Small and Medium-sized Enterprises
VC	Venture Capital

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