Kim Ribbink

GERMANY
A Market for Clinical Research

Scientific excellence from its universities and research centers, combined with a strong presence of international pharma companies and a vibrant biotech industry makes Germany a life-sciences leader, but political and commercial challenges remain.

Germany is a pre-eminent pharmaceutical market. In 2008, for example, the German pharmaceutical industry comprised 243 companies, employed 126,000 people, and generated EUR 41.5 billion ($53.8 billion) in revenue, according to Germany Trade & Invest, a German investment agency. Germany is the third-largest pharmaceutical market in the world (after the United States and Japan) and the largest in Europe.

"Germany continues to be the unchallenged leader in Europe in the production of genetically engineered biopharmaceuticals and is in second place worldwide after the United States," says Rolf Hoemke, Ph.D., senior manager scientific press, German Association of Research-Based Pharmaceutical Companies (vfa).

The German government makes a number of programs, financed through public resources, available to the life-sciences industry, Germany Trade & Invest notes in a report, The Pharmaceutical Industry in Germany, Issue 2011. Each year, the government invests about EUR4 billion ($5.2 billion) in its high-tech strategy and was expected to provide EUR1.2 billion ($1.6 billion) for R&D projects within the healthcare and biotech industries in 2011.

The Federal Ministry of Education and Research has launched the "Pharmaceuticals Initiative for Germany" to give new impetus to Germany's biotechnology and pharmaceuticals sectors, the report notes.

However, Dr. Hoemke describes government support for the industry as ambivalent, with efforts to foster research countered by restrictions on business development, such as regulations that limit the extent of reimbursement and the physicians' prescribing volume.

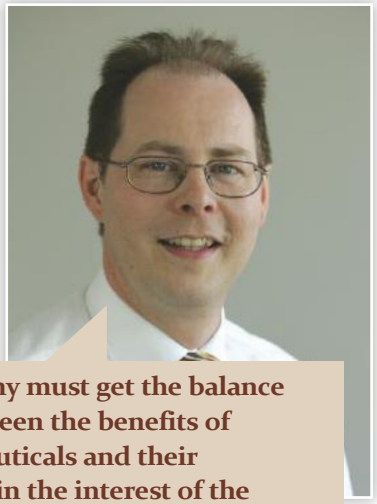
Pharmaceutical Opportunities

Germany has a long tradition in the pharma and chemistry industries and has a reputation for innovation and cutting-edge research, internationally renowned scientists, academic excellence, and the largest population in Europe.

"Merz was founded in 1908 by Friedrich Merz, a chemist and pharmacist; Boehringer Ingelheim was founded in 1885; and Farbwerke Höchst, part of Sanofi-Aventis today, was founded in 1883, to mention just a few examples," says Dr. Alexander Gebauer, chief scientific officer at Merz Pharmaceuticals.

He notes also that some major U.S. pharma companies have German roots or were founded by Germans. For example, Merck Inc. was a subsidiary of the German Merck company in Darmstadt, and Pfizer was founded by a German pharmacist.

The country benefits from several internationally established German research associations, all of which are active in the life sciences, according to the report. Among these are: the Max Planck Society, which maintains 80 research institutes dedicated to a wide range of fundamental research; the Fraunhofer Association, Europe's largest applied research associa-



> “Germany must get the balance right between the benefits of pharmaceuticals and their financing in the interest of the many patients who are eagerly awaiting innovative therapies.”
>
> **DR. ROLF HOEMKE**/ German Association of Research-Based Pharmaceutical Companies

> “While regulations limit promotion of pharmaceuticals to physicians and pharmacists, within these boundaries there are virtually no restrictions as long as all content is scientifically solid and adequately referenced.”
>
> **DR. IRENE HAAS** / Haas & Health Partner

A Market for Clinical Research

Germany is first in clinical trials conducted in Europe and second worldwide. While data quality is on a par with the United States, costs are up to 50% lower in Germany. The country’s key competitive advantage lies in the combination of lower costs for enhanced levels of expertise and quality. Such services are located, for example, in one of the 45 university hospitals and 118 clinical institutes involved in clinical trials.

- **The Charité in Berlin is Europe’s largest university hospital.** Most of the clinical trials conducted in Germany are located in the Berlin region, followed by Hamburg, Munich, and the Rhine-Main area.
- **University hospitals located in these areas enjoy excellent national and international reputations.**
- **German hospitals are known for their consistent and reliable collection of data in clinical test series.**
- **The conditions and infrastructure for conducting clinical trials in Germany are second to none.** This is not only due to the high quality of R&D conducted at German universities, but to research institutes and the reputation of German university hospitals. The country’s high population density facilitates swift recruitment of eligible participants, while the dense network of healthcare facilities, doctors in own practice, and universities offers optimal clinical trial conditions. Germany boasts 34 physicians and 83 hospital beds per 10,000 inhabitants (in comparison, the United States has 26 physicians and 32 hospital beds per 10,000 inhabitants).
- **In addition, there has been fairly strong government support for clinical research.** The Federal Ministry of Education and Research (BMBF) together with the German Research Association (DFG) launched a joint initiative for patient-oriented medical research in 2003. This ensures that clinical trials are funded irrespective of funding programs limited to specific topics. The program was introduced in 2005 and has an annual budget of 20 million Euro ($25.9 million). BMBF provides funding for noncommercial clinical trials on pharmacological therapies as well as for systematic reviews of clinical trials in line with international standards. Funding is closely coordinated with the DFG, which provides funding for non-commercial clinical trials on nonpharmacological therapies as well as diagnosis studies, forecast studies, and controlled studies for secondary prevention.
- **Cooperation between universities and pharmaceutical companies ranks high on the agenda.** Bayer-Schering Pharma, for example, closely cooperates with the University of Cologne in the fields of preclinical research and clinical trials. The pharmaceutical industry in Germany is highly engaged in clinical trials: more than 70% of clinical trials are industry funded.
- **Pharmaceutical companies in Germany are highly engaged in the research and testing of drugs and improving medication** in the fields of the most common causes of death (i.e. cardiovascular diseases and cancer) as well as in the field of geriatric disorders. The developing e-clinical trial trend is present in Germany, and the country is already a hub for a number of budding biotechnology companies that form the potential target client base for e-clinical technology vendors.

This makes Germany an optimum market for vendors bringing e-clinical trial products to market.

Source: Federal Ministry of Education and Research, Clinical Trials, www.bmbf.de and The Pharmaceutical Industry in Germany, Issue 2011, Germany Trade & Invest, gtai.de

tion; the Helmholtz Association, the biggest research association in Germany, with 16 scientific-technical and biological-medical research centers nationwide; and the Leibniz Association, an interdisciplinary scientific community of 86 German research institutes, of which 25 specialize in life sciences. All of these research institutes closely cooperate with universities and industry in order to advance basic and applied research and to discover and bring new products to market.

“In Germany, we have a critical mass of pharma companies with their own R&D departments,” Dr. Gebauer says. “Furthermore, the companies maintain a close link with universities and non-university research facilities, such as the German Max Planck Institute. The close interaction creates synergies and enables the greatest possible level of efficiency.”

A further advantage, he says, are very good clinics that enable research companies to perform clinical studies at the highest level.

Dr. Gebauer says because Germany is export-oriented, and this has enabled products to reach other markets and become blockbusters.

“Memantine, our active substance for the treatment of moderate to severe Alzheimer’s-induced dementia is prescribed not only in the home market, but also in many countries worldwide,” he says.

Merz itself has also been assisted by a long history of being outward looking. Dr. Gebauer says Friedrich Merz understood the entrepreneurial opportunities of internationalization even as far back as the early 1920s.

Cluster of Activity

Germany also has several pharma/biotech

> **“Germany’s healthcare system provides people with broad access to healthcare and pharma companies with a rather homogeneous market as compared with Medicare/Medicaid in the United States.”**
>
> **DR. CLAUDIA GUTJAHR-LÖSER** / MorphoSys

clusters, with the most prominent being around Munich, Berlin, and Heidelberg, says Claudia Gutjahr-Löser, Ph.D., head of corporate communications and investor relations for MorphoSys.

The regional structure harks back to the federal BioRegio competition, which really kicked-off commercial biotechnology application in Germany, she says.

“The biotech cluster in Munich has picked personalized medicine as one key growth driver for the foreseeable future,” Dr. Gutjahr-Löser says. “The cluster management company BioM has pooled the strengths of the hospitals and scientific institutes, the biotech and pharmaceutical companies under the brand m4. MorphoSys has currently two research programs ongoing under this initiative.”

MorphoSys’ programs include MOR202, a novel targeted therapy for the treatment of multiple myeloma and structure-based characterization of therapeutic antibodies.

In the first program, the company has developed a highly specific, human recombinant monoclonal antibody (MOR202) against CD38, a membrane protein that is highly expressed on malignant plasma cells and is thus a promising target for multiple myeloma. MOR202 is a tumor targeting, monoclonal antibody intended to recruit and activate specialized killer cells that can destroy the tumor cells. The antibody has demonstrated efficacy in a number of preclinical myeloma models, supporting entry into early-phase clinical testing for safety and preliminary efficacy in a Phase I/IIa clinical trial in patients with relapsed/refractory myeloma.

The project will be performed in collaboration between MorphoSys and the Klinikum rechts der Isar. Other clinical study centers in Germany and Austria also will be included.

In the second program, MorphoSys is working with Proteros biostructures, a biotech company in the area of X-ray protein structure analysis, to establish a technology platform for efficient elucidation of antibody-antigen-complex structures. MorphoSys will provide relevant antigen and antibody molecules, Proteros will provide advanced x-ray technology and structure solution know-how. The high resolution access to antibody-antigen-complex structures is expected to allow a faster and more efficient engineering of therapeutic antibodies.

Meanwhile, the Berlin-Brandenburg region has one of the largest teaching hospitals worldwide, Charité University Medicine Berlin, as well as 480 life-sciences companies and more than 100 non-university research institutes, according to Berlin Partners. Pfizer, for example, moved its German headquarters to Berlin, where it employs around 500 people and has a strong center for clinical research, particularly in oncology.

Bayer Schering Pharma also has its headquarters in Berlin and conducts much of its research in the area.

“Our activities here cover the entire value chain from research in the fields of oncology, women’s healthcare, and diagnostic imaging, all the way to development and production,” says Andreas Fibig, CEO of Bayer Schering Pharma AG.

“It is not only German companies that have major sites for drug discovery in the country but also Abbott in Ludwigshafen, Amgen in Regensburg, Sanofi in Frankfurt am Main, and Roche in Penzberg near Munich,” Dr. Hoemke says.

Rules and Regulations

The regulatory framework for developing drugs in Germany is, to a large extent, determined by the regulations of the European Union (EU). This means that pharma companies do not have to adapt to national specifications but can apply SOPs developed for EU countries in general, Dr. Hoemke says.

“The German authorities that approve and oversee clinical studies have done a lot to speed up their decision-making processes in recent years,” he says. “This is good news for pharma companies, and one of the reasons why Germany is second only to the United States in terms of clinical studies.”

FAST FACT

IN 2008, THE PHARMACEUTICAL INDUSTRY IN GERMANY COMPRISED 243 COMPANIES, EMPLOYING A WORKFORCE OF 126,000, WHO HELPED GENERATE TURNOVER OF EUR 41.5 BILLION ($53.8 BILLION).

Biotechnology Competitions Open Doors to Buoyant Industry

With about 500 dedicated biotechnology companies, Germany is today Europe’s leader — a development triggered by the BioRegio competition of the Federal Ministry of Education and Research (BMBF) in 1995.

The BioRegio Initiative has opened the door wide for the successful use of biotechnology in Germany and has set off a dynamic innovation process. The intention of the competition, i.e. to link up biotechnological research with application in industry, has been implemented successfully.

Young biotechnology companies in which researchers are translating their knowledge into marketable products have been established in numerous places. In parallel, sustainable structures that support technology transfer in a targeted way have been developed. The BioProfile competition builds on the experience and results of the BioRegio Initiative. However, BioProfile is addressed in particular to those regions that boast special strengths particularly in future-oriented fields of application of modern biotechnology. These strengths must be identified and systematically built upon.

As a result of competitions such as BioRegio and BioProfil, there are 25 bio-regions in Germany today with about 500 young companies, of which as many as 220 work in the biomedical field. This has brought Germany to the top Europe-wide. In addition to public funding, a considerable amount of private capital for developing biotech companies has been mobilized. In some regions, in the model regions of Heidelberg and Munich for example, this mobilization effect amounts to more than 1,000%.

Source: Research in Germany, Federal Ministry of Education and Research (BMBF), http://www.research-in-germany.de

However, Germany's recent Law on the Reorganization of the Pharmaceutical Market (AMNOG), which came into force Jan. 1, 2011, has substantially changed the rules for the introduction of new medicines on the German market.

Dr. Gutjahr-Löser says the new legislation represents a major change for the local pharmaceutical market since the former system gave companies large freedom in prescription drug pricing.

Following the marketing authorization, the drug maker will now determine the price for new and innovative medicines for the first year after launch, she explains. An assessment is then conducted into whether the product offers an additional benefit, and the price is then negotiated between the Federal Association of the health insurance funds and the company. In the case that no additional benefit can be determined, the new medicine will be part of the lower fixed price system.

"AMNOG is likely to favor innovative drug makers and places more emphasis on evidence-based medicine," she says

The law has come under some attack, with concerns that it will hamper novel drugs from reaching the German market.

"Boehringer Ingelheim and Lilly's decision in September 2011 not to launch the diabetes drug Trajenta in Germany due to their dissatisfaction with the review process underscored that the AMNOG's influence on the German market is not yet fully understood," Dr. Gutjahr-Löser says.

Dr. Irene Haas, founder, Haas & Health Partner, adds that the new law comes with many new opportunities.

"One opportunity is the chance to manage the challenge of demonstrating improvement by a target-oriented study design from a very early stage," Dr. Haas says. "Another opportunity is to work with new stakeholder audiences, which helps reduce the cost for keeping an expensive sales force in favor of a small group of market access specialists, who understand the needs of the payers and liaise with them."

Marketing and Education

Germany is one of the most regulated European markets in marketing, communication, and medical education, Dr. Haas says. These activities are governed legally by the German Drug Promotion Act (Heilmittelwerbegesetz, HWG) and by self-imposed codes developed by voluntary organizations, Freiwillige Selbstkontrolle für die Arzneimittelindustrie (FSA), meaning Voluntary Self-Control for the Pharmaceutical Industry, and Arzneimittel und Kooperation im Gesundheitswesen (AKG) , meaning Pharmaceuticals and Cooperation in the Healthcare System. Both these associations were founded by pharmaceutical companies and set out the terms of cooperation with healthcare professional audiences and patients.

Promotion and advertising of prescription-only products is strictly limited to physicians and pharmacists, Dr. Haas says.

"Within these boundaries there are virtually no restrictions, not even in terms of competitive claims, as long as all content is scientifically solid and adequately referenced," she says.

She adds, however, there has been a shift away from advertising toward channels such as congress events, meetings, public relations activities and key opinion leader-led educational programs.

"The same applies to the sales forces, formerly key communicators toward physicians, as statutory health funds have recently been granted to negotiate individual contracts for single drugs and complete packages with the Associations of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen) or with an individual company, either covering a federal state or other defined region," she says.

Prescription products cannot be advertised to the public, while some OTC products can be advertised, though nothing related to heart disease or cancer, for example.

Medical education, meanwhile, is regulated by law and by the Gemeinsamer Bundesausschuss (G-BA; the Joint Federal Committee is the paramount decision-making body of the joint self-governing body of physicians, dentists, hospitals and health insurance companies in Germany). It is also regulated by the Chambers of Physicians (Ärztekammern) who authorize the CME credits of which physicians are required to achieve 250 every five years. Medical education is driven by the Chambers of Physicians, Medical Associations and also to a large extent by pharmaceutical companies, Dr. Haas says.

"In spite of all its regulations the German pharmaceutical market still allows companies to offer clearly branded medical education programs," she says. "These can be highly credited, depending on (nonpromotional) content, scope, and length of educational session, not on who initiated the program."

In terms of access to patients, Germany remains conservative and though the EU intended to facilitate company-patient interaction in terms of information and education, companies have only recently been allowed to post the SPCs of their prescription products on their websites for patients to access, Dr. Haas says. PV

> "In Germany, we have a critical mass of pharma companies with their own R&D departments, which otherwise are only to be found in the United States."
>
> **DR. ALEXANDER GEBAUER** / Merz Pharmaceuticals

EXPERTS

ROLF HOEMKE, PH.D. Senior Manager Scientific Press, German Association of Research-Based Pharmaceutical Companies (vfa), the trade organization of research-based pharmaceutical companies in Germany. For more information, visit vfa.de.

CLAUDIA GUTJAHR-LÖSER, PH.D. Head of Corporate Communications and Investor Relations, MorphoSys, a biotechnology company that has developed and established fully human antibody technologies. For more information, visit morphosys.com.

DR. IRENE HAAS. Founder, Haas & Health Partner, part of global health communications group Chandler Chicco Companies (CCC), a pure-play healthcare communications agency in Germany. For more information, visit haas-health.de.

DR. ALEXANDER GEBAUER. Chief Scientific Officer, Merz Pharmaceuticals, an independent German pharmaceutical company with its own research and development, focused on drugs for the treatment of illnesses in the fields of neurology, psychiatry, and dermatology. For more information, visit merz.com.