BPI German Pharmaceutical Industry Association

Pharma-Data 2014

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Table of Contents

Preface

A critical review of the first twelve months of governance by the "Grand Coalition" can only lead to two conclusions: on the one hand, reverting back to behavioural patterns like short-term cost reduction measures clearly engenders a feeling of political security; on the other hand, there is a clear lack of the creative courage needed to take a critical look at the multiple legislative interventions in the pharmaceutical market that have been implemented in previous years and, when necessary, to revoke or adapt them.

This is all the more disappointing, as the political and economic climate at the beginning of the current legislative period seemed to favour more progressive, forward-looking pharmaceutical policies, so that the motto for all stakeholder should have been "If not now, then when?!". The comfortable parliamentary majority of the governing coalition would undoubtedly have provided a solid basis for implementing difficult reforms. At the same time, the financial situation of the Statutory Health Insurance was characterised by large reserve funding and secure premium income. However, hopes for objective and constructive changes were quickly dashed. Almost reflexively, cost saving measures and preliminary acts became the prelude to the subsequent political measures of the new legislative period. In December 2013, as its first measure, the governing coalition passed the 13th law amending German Social Code Book V, leaving the price moratorium in place, despite having previously communicated the contrary. Now that the 14th law amending German Social Code Book V is in effect, the price moratorium as well as the obligatory rebates, which increased from 6 % to 7 %, will remain in place until the end of 2017.

Pharmaceutical companies in Germany have been significantly strained by obligatory discounts, the continuing price moratorium, reimbursements at the end of early benefit assessment,

reference pricing, fixed pricing and rebate contracts. Despite lacking adequate avenues of compensation, the pharmaceutical industry has made a significant contribution to the good financial situation currently enjoyed by the Statutory Health Insurance.

At the same time, pharmaceutical companies are faced with ever increasing costs, including personnel costs, in order to implement European and national regulations. Each year, expenditure has increased – sometimes significantly – in multiple business units, including clinical research, regulatory affairs, and pharmacovigilance. The combined effects of different interferences and additional financial burdens increasingly restrict entrepreneurial freedoms. The resulting decrease in the variety of available pharmaceuticals, i.e. the required spectrum of high-quality, safe pharmaceuticals, has a negative impact on physicians' ability to choose appropriate treatments for their patients, which in turn decreases the quality of patient care.

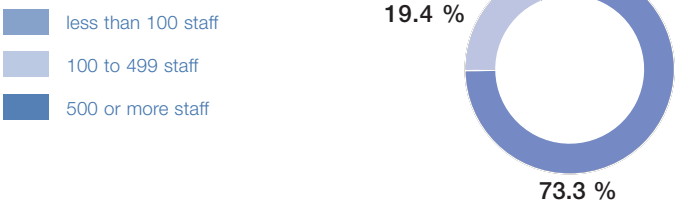
The development of new substances and the optimisation of treatment approaches demands a research-friendly regulatory framework, as well as stable funding. In other words: an environment which allows long-term planning. Pharmaceuticals and the industry that produces them are all too often seen only as a cost factor in the health care system. The pharmaceutical industry stands for highly qualified employees, significant investments in research and development, as well as the production of essential goods. Pharmaceuticals make a huge contribution toward curing illnesses or modifying their natural course, mitigating suffering and increasing quality of life.

The issue of drug supply requires a fact-oriented and balanced debate. In an attempt to lay the foundation for such a fair and balanced discussion, this 44th edition of the Pharma-Data brings together a multitude of facts and background information about the national and international pharmaceutical market.

Sector structure

According to the trade register at the Federal Office for Statistics, for the year 2012, a total of 817 pharmaceutical companies* were registered in Germany. In recent years, it has become increasingly difficult to determine the number of companies due to changing reporting groups at the Federal Office for Statistics on the one hand, and methodological differences on the other. Additionally, there may be conglomerates consisting of several different companies, which in turn can be composed of individual firms and specialist business units. Accordingly, determining the number of specialist business units – as a core element of pharmaceutical production – as well as determining the number of contract manufacturers would seem appropriate. This distinction, however, is only partially captured by the Federal Office for Statistics.

Companies according to size in 2012 in %



Source: Calculation of the BPI, based on data of the VCI 2014 and of the Federal Office for Statistics 2014.

* In the “cost structure statistics”, the Federal Office for Statistics shows 250 companies (reporting category 20+). There are an additional 311 companies with less than 20 employees. The large number of registered companies can also be explained by the existence of many marketing authorisation holders who are considered pharmaceutical companies.

The pharmaceutical companies include medium-sized companies, as well as companies under owner-management and German branches of multinational corporations. Furthermore, biotechnology companies are to be considered. These companies primarily develop and/or produce pharmaceutical drugs and diagnostic products, and are partially included in the 817 companies mentioned above. It is still true that nearly 93 % of companies manufacturing pharmaceutical drugs in Germany employ less than 500 employees.

The German Pharmaceutical Industry Association [Bundesverband der Pharmazeutischen Industrie e. V. (BPI)] is the only association in Germany that represents the entire spectrum of the pharmaceutical industry on a national and international level. Nationally oriented companies as well as internationally active corporations are represented in the BPI. This includes pharmaceutical companies with R&D programmes, generic companies, companies from the fields of biotechnology, phytopharmaceuticals, homeopathic / anthroposophic medicine, as well as pharmaceutical service providers. With more than 60 years of experience in the field of pharmaceutical drug research, development, drug approval, manufacturing and marketing, the BPI offers integrative solutions for the entire pharmaceutical market.

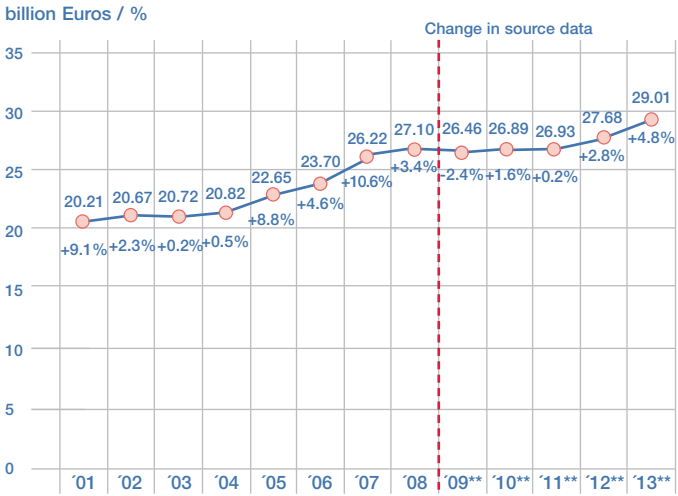
Production

In 2013, the pharmaceutical industry in Germany produced pharmaceuticals valued at 29.01 billion Euros.

This represents an increase of 4.8 % compared to the year 2012. Domestic production is highly dependent on pricing, pharmaceutical drug imports as well as export demand.

Pharmaceutical Production* from 2001 – 2013**

(Production value in billion Euros, changes relative to the previous year in %)



* Index of goods for statistics of production (GP 21), Production of pharmaceutical and similar goods.

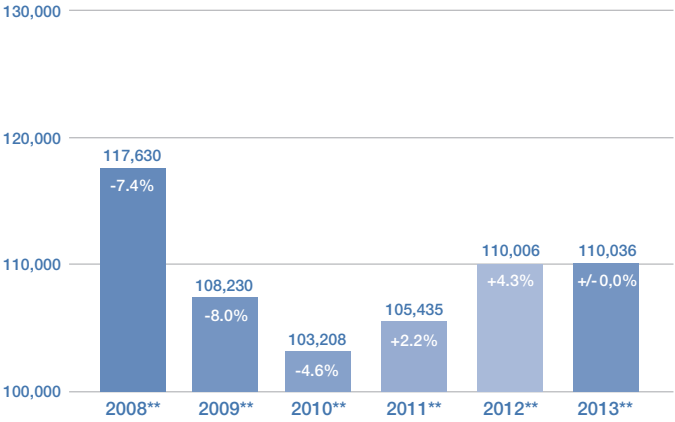
** Since 2009 the GP 21 (pharmaceutical and similar goods) has replaced the GP 244.This new statistical classification prevents a direct comparison with values from previous years.

Source: Illustration of the BPI, based on data of the Federal Office for Statistics 2014.

Employees

In 2013, 110,036 staff were employed by companies producing pharmaceutical goods. The number of employees from the previous year, 2012, was maintained. This is a reflection of the overall employment situation in recent years in Germany. The ongoing good economic climate has led to the further increase in employment in Germany. In the summer of 2014, over 42.5 million people were employed in the Federal Republic of Germany.

Development of staff numbers* in the pharmaceutical industry 2008 – 2013 (changes relative to the previous year in %)



* The data refer to companies (reporting category 20+). Compared to the information provided in the Pharma Data up to 2007, there has been a transfer of the specialist operating sectors to the level of "companies", because the reporting category 20+ for specialist operating sectors was removed in the course of the bureaucracy reduction law of the Federal Office for Statistics.

** For data from the year 2008 onwards attention should be paid to the change of the economy sector from WZ 24.4 to WZ 21. This new statistical classification prevents a direct comparison with data from previous years.

Source: Illustration of the BPI based on data obtained of the VCI 2014 and the Federal Office for Statistics 2014.

Foreign trade

In 2013, pharmaceuticals valued at 57.1 billion Euros were exported from the Federal Republic of Germany. This corresponds to an increase of 5.4 % compared to the year before. At the same time, pharmaceuticals valued at 36.5 billion Euros were imported into the Federal Republic of Germany. This constitutes a decrease of 4.5 % compared to 2012. The main supplier of pharmaceuticals to Germany is Switzerland, followed by the USA, the Netherlands, France, and Italy.

Import and export of pharmaceutical drugs*

(in million Euros, changes relative to the previous year in %)

Year	Import		Export**	
	million Euros	+/- %	million Euros	+/- %
2002	19,284.83	+60.0	18,835.18	-8.0
2003	19,327.83	+0.2	22,230.11	+18.0
2004	22,221.42	+15.0	28,681.63	+29.0
2005	25,585.17	+15.1	31,758.85	+10.7
2006	28,366.72	+10.9	36,474.52	+14.8
2007	32,706.83	+15.3	41,908.34	+14.9
2008	34,063.16	+4.1	47,549.32	+13.5
2009	35,552.65	+4.4	47,365.99	-0.4
2010	38,011.26	+6.9	51,133.24	+8.0
2011	37,618.32	-1.0	50,421.52	-1.4
2012	38,186.24	+1.5	54,220.11	+7.5
2013	36,470.92	-4.5	57,123,36	+5.4

* Business branch 21, Production of pharmaceutical goods. A new statistical classification was introduced in 2008. The production of pharmaceutical goods is now to be found in WZ 21 (previously WZ 24.4).

** Because of statistical peculiarities and different surveys, the production statistics and external trade statistics cannot be compared with each other.

Source: Illustration of the BPI based on data of the VCI 2014 and the Federal Office for Statistics 2014.

Main suppliers of pharmaceuticals* to Germany (in million Euros)

	2009	2010	2011	2012	2013
Switzerland	4,845.13	5,463.70	6,376.50	7,007.76	7,449.89
USA	7,193.86	6,253.57	5,728.23	7,110.13	5,729.16
The Netherlands	1,182.51	1,954.97	4,127.49	4,615.10	5,060.24
France	1,741.96	2,331.83	1,754.11	2,013.64	2,197.79
Italy	1,546.32	1,702.05	1,792.42	1,975.65	2,122.91
Belgium	1,292.36	1,487.63	1,822.54	1,516.20	1,983.70
Ireland**	7,934.95	6,751.54	4,653.31	2,880.42	1,934.73
Great Britain	2,299.63	2,569.65	3,313.73	2,990.15	1,775.78
Sweden	1,106.91	1,217.70	1,035.44	1,143.18	1,319.79
Spain	1,205.72	2,479.95	1,023.40	1,149.15	971.83
Others	5,203.30	5,798.67	5,993.16	5,784.86	5,925.11
Total	**35,552.63**	**38,011.25**	**37,620.32**	**38,186.24**	**36,470.92**

* Business branch 21, Production of pharmaceutical goods. A new statistical classification was introduced in 2008. The production of pharmaceutical goods is now to be found in WZ 21 (previously WZ 24.4).

** The remarkably high export rates up to the year 2011 are explained by the VCI as being due to special circumstances.

Source: Illustration of the BPI based on data of the VCI 2014 and the Federal Office for Statistics 2014.

Main importers of pharmaceuticals* from Germany (in million Euros)

	2009	2010	2011	2012	2013
USA	5,861.38	4,979.74	5,665.32	8,157.45	8,455.29
The Netherlands	4,423.55	6,553.10	6,676.76	6,537.49	6,452.43
Great Britain	2,440.71	2,770.38	2,421.35	3,176.76	5,142.60
Switzerland	2,865.12	2,818.90	3,221.24	3,340.33	3,679.37
Belgium**	10,918.27	10,495.80	7,531.28	4,544.95	3,571.14
France	2,255.97	2,525.98	2,752.75	3,596.67	3,386.32
Italy	2,192.60	2,465.54	2,484.00	2,530.89	2,211.14
Russian Federation	984.30	1,390.50	1,626.93	1,842.74	2,101.56
Japan	1,151.52	1,162.35	1,326.45	1,619.03	1,828.15
Austria	1,252.11	1,458.74	1,551.06	1,538.89	1,625.41
Others	13,020.45	14,512.24	15,166.23	17,334.92	18,669.95
Total	**47,365.97**	**51,133.24**	**50,423.36**	**54,220.11**	**57,123.36**

* Business branch 21, Production of pharmaceutical goods. A new statistical classification was introduced in 2008. The production of pharmaceutical goods is now to be found in WZ 21 (previously WZ 24.4).

** The remarkably high export rates up to the year 2011 are explained by the VCI as being due to special circumstances.

Source: Illustration of the BPI based on data of the VCI 2014 and the Federal Office for Statistics 2014.

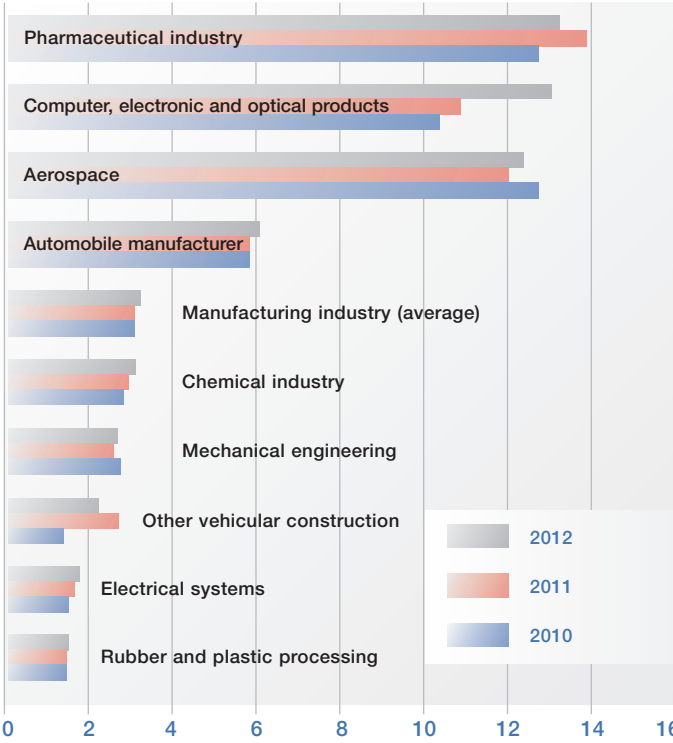
The long road to new pharmaceuticals

With 2.98 % of the gross domestic product invested in research and development (R&D), Germany finally reached the Lisbon objective of 3 % in 2012. According to the most recent report of the Expert Commission for Research and Innovation (German: Expertenkommission für Forschung und Innovation (EFI)), the pharmaceutical industry invested 13 % of their own turnover in internal R&D projects. In this, as in previous years, the pharmaceutical sector ranks highest in R&D investments, clearly ahead of the automotive, mechanical engineering and chemical industries, making it the most research-intensive industry in Germany.

This trend is not restricted to Germany alone. Also, the "EU Industrial Investment Scoreboard" published at the end of 2013 ranked the pharmaceutical industry first, with a R&D-quota of more than 14 %, as the most innovation-intensive industry-namely in the EU, in Japan, and the USA.

The high R&D expenditures of the pharmaceutical industry are due to the partially complex, time-intensive, highly sensitive and highly regulated development of pharmaceuticals. According to various scientists such as Donald W. Light, Rebecca Warburton, Matthew Herper or Joseph DiMasi, depending on the drug, the drug development costs can exceed one billion Euros.

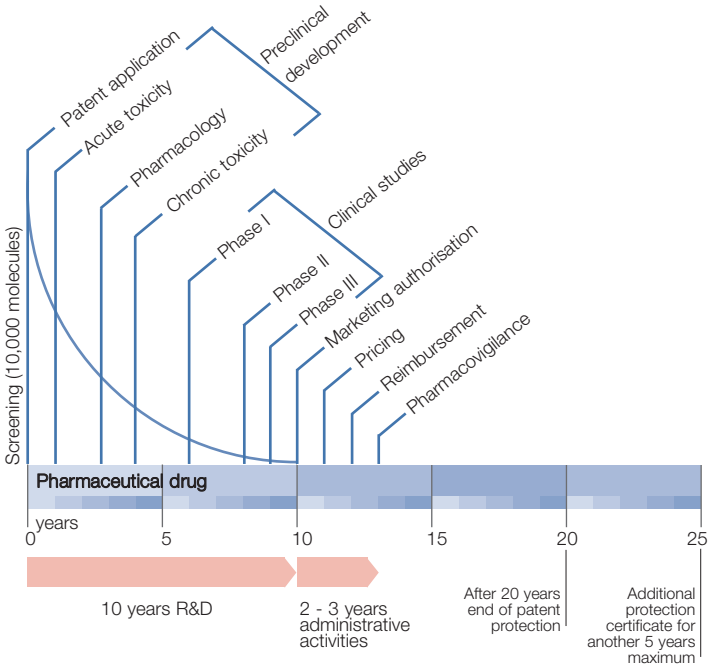
Share of internal R&D expenditures by sector and relative to sales turnover with own goods in %



Source: Illustration of the BPI based on data of the Stifterverband Wirtschaftsstatistik 2014.

Among 10,000 molecules screened as possible candidates at the beginning of the pharmaceutical development process, because they modulate disease-related parameters in the organism in general, only one successfully makes it through the authorisation process after about eight to twelve years.

Phases of pharmaceutical drug research and development in the EU



Source: Illustration of the BPI based on data of the European Federation of Pharmaceutical Industries and Associations (EFPIA) 2014.

Along the way, pharmaceutical companies will patent their invention in multiple countries at the same time and carry out laboratory investigations over a period of years to fundamentally clarify the questions of toxicity and efficacy and pharmacology. This research step is called the pre-clinical phase. Before the start of clinical phases I-III (efficacy, human toxicity, dosage, pharmaceutical forms – in healthy subjects and patients), in which thousands of people in different countries must be recruited depending on the indication and phase, the study protocol is designed and, in Germany, approved by an Ethics Committee and the regulatory authorities.

Should a drug candidate achieve the end of phase III study endpoints (for example higher efficacy or less adverse effects compared to the accepted treatment), the authorisation process begins. Given that the majority of pharmaceutical companies are internationally active and want to provide their products to patients in different countries, the necessary application and supporting paperwork is often submitted to multiple authorities, for example the Federal Drug Administration (FDA) in the USA and European Medicine Agency (EMA). Often, there are specific national requirements, for the marketing authorisation and the marketing of drugs, to be followed in the individual countries (Germany often acts as reference member state for other national markets) and in other countries that constitute important drug markets.

After the authorisation of a product, pharmaceutical companies perform further clinical trials and investigations. These studies are conducted in the context of so-called pharmacovigilance (drug safety). They serve to systematically monitor the safety of an authorised pharmaceutical product with the intention to discover, assess and understand adverse reactions that were not observed during phase I-III of the clinical development phases. Beyond this, these investigations serve to collect information on long-term effects and the efficacy profile of new pharmaceutical drugs, as well as interactions with other medications. These insights are gained in so-called phase IV clinical trials. Other ways to gather pharmacovigilance data include voluntary manufacturer-driven or compulsory clinical trials and non-interventional studies (NIS).

When regulatory authorities request further data on the safety of a particular medicinal product, these data are usually generated through Post-Authorisation Safety Studies (PASS) or Post-Authorisation Efficacy Studies (PAES).

A survey conducted by the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2012 revealed the following distribution of R&D expenditure for new actives across the different phases of drug development and authorisation:

Percentile distribution of R&D expenditures across the different phases of pharmaceutical drug development

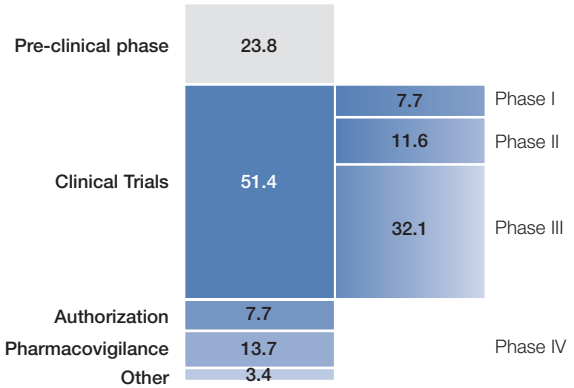


Illustration of the BPI based data from PhRMA, Annual Membership Survey 2014.

In the currently ongoing discussion regarding healthcare expenditure, the cost of drug development is repeatedly discussed. These costs have been estimated at around 900 million US-dollars by a working group headed by Joseph DiMasi in 2003, while other estimates even refer to expenditures up to 1.3 billion US-dollars. These assessments are based on the total costs for developing new chemical and biological compounds in relation to newly authorised drugs. The estimate also reflects the costs for the large number of unsuccessful development projects, as well as the opportunity costs associated with these projects (i.e. the income that might have been generated if the funds had not been invested in the unsuccessful project, but had instead been invested elsewhere).

The numbers remain controversial. However, even if only the "out of pocket expenses" are considered, R&D expenditure still amounts to ca. 540 million US-dollars. Even critical observers such as Donald W. Light and Rebecca Warburton estimate several 100 million Euros in development costs for new active substances. Therefore, the core message is the same, regardless of the debate about the methods for calculating the costs: the development of innovative drugs is a very involved, risky and protracted process.

Despite the ever-increasing complexity of the development process roughly outlined above, pharmaceutical companies deliver new drugs every year. In just the past year, 94 authorisations with new active substances (as per § 25 AMG) were registered*.

* New actives as defined in § 48(2)1 AMG, 2013 statistics of the Federal Institute for Drugs and Medical Devices (BfArM). According to statistics of the Pharmazeutische Zeitung, 23 new actives were authorised in 2013. The difference between the number of "new actives" and new substances, as per § 25 German Medicines Act (AMG), results from the fact that each strength and pharmaceutical form of the same active substance is assigned a separate authorisation number by the BfArM, so that each of these is individually counted in their statistics. In addition, 73 of the new substances counted for 2013 were parallel imports.

The high costs of R&D are sometimes given as a reason for the argument, that smaller companies do not stand a chance to compete in the innovation process, since companies without billions in turnover could not finance the process of developing a new active to the point of marketing. This, however, does not do justice to the many smaller companies such as biotech companies who often kick off innovative developments and then sell these parts of their pipelines to larger companies.

Biotechnology and Biopharmaceuticals in Germany

Germany is one of the most important biotech locations worldwide: at the beginning of the second quarter of 2014, the Federal Ministry of Education and Research (BMBF) published the results of a study on the status quo of the German biotech industry.

According to the BMBF report, the German biotechnology industry stagnated in 2013. The turnover of dedicated biotechnology firms* decreased slightly from 2.9 billion Euros in 2012, to 2.84 billion Euros in the last year. The number of employees also regressed by three percent to now only 16,950. Yet the number of "mostly biotech**" companies grew again from 565 to 570, including 13 start-ups.

* The OECD defines a dedicated biotechnology firm as a biotechnologically active firm whose predominant economic activity involves the application of biotechnology techniques to produce goods or provide services and/or the performance of biotechnology R&D.

** The OECD sees biotechnology as a collection of different processes and applications in a variety of industries. It 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".

R&D expenditure has however decreased again. At 899 million Euros, it still lies clearly below the billon mark (2012: 934 million Euros). This corresponds to a R&D ratio of more than 30 %, which is clearly ahead of the investment volume of the other traditional innovative industries.

The German Biotechnology industry 2014

Benchmark data of the corporate landscape	2008	2009	2010	2011	2012	2013
Dedicated biotech companies	501	531	538	552	565	570
Number of other biotech companies	92	114	125	126	128	130
Employees (dedicated biotech companies)	14,450	14,950	15,480	16,300	17,430	16,950
Employees (other biotech companies)	15,520	16,650	17,000	15,570	17,760	18,450
Turnover* (dedicated biotech companies)	2.19	2.18	2.37	2.62	2.90	2.86
R&D-expenditure* (dedicated biotech companies)	1.06	1.05	1.02	0.98	0.93	0.90

* in billion Euros.

Source: Illustration of the BPI based on BMBF 2014, www.biotechnologie.de and Biocom AG 2014.

Most of the companies active in the biotech sector are active in the healthcare field (48 %), according to a survey of the Federal Ministry of Research and Education. This includes around 50 companies who are committed to developing pharmaceutical drugs and have gained a total of ten new drug authorisations in previous years. These companies have faced a lot of challenges in connection with drug development. In comparison to 2012, the number of candidate actives in clinical testing slightly decreased from 93 to 91. Eighty-two of these have undergone testing in early phase (Phase I and II) trails, while nine products have reached the Phase III stage most relevant for authorisation. Four of these are biopharmaceuticals.

These pharmaceuticals, also referred to as “biologicals”, are produced with modern biotechnological processes requiring a high level of technology and are subject to complex development and production processes. They are developed in such a way as to directly modulate the body’s own cellular metabolism. For the most part, these substances are proteins (including monoclonal antibodies), but some are also nucleic acids (DNA, RNA such as antisense-RNA, as well as antisense-oligonuceotides).

The development of biopharmaceuticals involves not only biotech companies, which are usually small and medium-sized enterprises (SME) (ca. 87 % employ less than 50 employees), but also larger and multinational companies. The complex and expensive development process often leads to cooperation projects: the biotech company provides its ideas and technology, while the pharmaceutical company delivers specialised know-how regarding the realisation of clinical trials and the authorisation process. The latter also have an established distribution network. In 2013, Ernst & Young registered 94 alliances: cooperation’s, licensing agreements, service agreements or asset deals.

The biotechnology sector and pharmaceutical companies, both singly or in cooperation, generate promising innovations: the number of ongoing development projects for new biopharmaceuticals in 2013 increased to 587. These clinical development projects focus mainly on cancer treatment, autoimmune products and vaccines. R&D expenditures are well invested. The turnovers generated with biopharmaceuticals increased by 8.5 % to more than 6 billion Euros in the past year. For the second year in a row, genetically engineered medications have achieved a market share of more than 20 %. The number of employees in the medical biotechnology sector increased by around 1 % to ca. 36,400.

The innovative activities of the pharmaceutical industry are not restricted to biopharmaceuticals, however. In 2013 alone, the Federal Institute for Drugs and Medical Devices (BfArM) authorised more than 2,000 line extensions for established active substances, for example for new indications or improved pharmaceutical forms.

Innovation based on established active substances

Innovations in the pharmaceutical industry are achieved in a multitude of areas:

-> New active substances
Chemically defined active substances,
defined natural substances,
phytopharmaceuticals,
biopharmaceuticals,
“me-too” substances (molecular variants of known active substances with a similar chemical structure)

-> New pharmaceutical forms and new specifically active combinations of active substances

-> Extension of the indications of known active substances

-> Specific improvements of active substances, new application forms

-> Other new treatment options

-> Improved or new manufacturing technologies of active substances

Even a minimal change of the molecular structure of a substance can result in the reduction of side effects, enhanced efficacy with a reduced dose, increased bioavailability in the body or new beneficial effects. Improvements of the pharmaceutical form can increase benefit, make application easier or improve the dosing regimen. Therefore, incremental improvements based on established active substances are an essential part of progress in the pharmaceutical industry, as in other economic sectors (such as the automobile and computer industries).

This can be shown rather impressively with the example of acetylsalicylic acid. Teas of willow bark powder were used in multiple ways already in ancient Greece to treat fever and pain of all kinds. Hippocrates of Cos, Dioscorides as well as the Roman scholar Pliny the Elder viewed willow bark as a medicine.

The isolation of the therapeutic active substance from willow bark was not successful until 1828. This substance was named salicin after the scientific name of the plant from which it was derived, Salix.

Salicylic acid itself has only been manufactured on a large scale in Radebeul and used as a medicine since 1874. The bitter taste of the substance, the caustic effect of the acid in the mouth and the side-effects like gastric disorders greatly limited its range of applications. Only the acetylation of the acid and the production of acetylsalicylic acid in its pure form (1897) started the triumphal march to what is now widely known as Aspirin®.

Since then, the original pharmaceutical forms have multiplied. Today, tablets (sublingual, chewable, effervescent, sustained-release, film-coated, soluble or orodispersible), granules, capsules, solutions for injection, suppositories and

dragées are sold. This broad palette of pharmaceutical forms is also due to an expansion in indications. While the medication was originally given for fever or as an analgesic, today it is given as an anti-inflammatory, in prevention of thrombosis and myocardial infarction, and even in the prevention of some cancers as evidenced by publications in medical journals such as the Lancet.

Benefits for Society

Regardless whether a completely new drug (so called “first in class” or “new chemical entity” – NCE or “new biological entity” – NBE) is developed, or whether there is continuing development of an established active substance, innovation is the driving force for improvements in the treatment of patients and the successful economic development of pharmaceutical companies. New active substances, pharmaceutical forms and production methods secure not only better treatment options but also employment and tax revenues in Germany as a location for industry.

As early as 2011, a survey commissioned by the Federal ministry of economics confirmed the central role of pharmaceutical advances for the productivity of German society: in Germany, from 1998 to 2008, premature death decreased by 22 % and at the same time, the number of employees on sick leave decreased from 4.1 % to 3.4 % (in 1973 it was almost 6 %). This is attributed to the use of innovative pharmaceutical drugs.

New active substances like monoclonal antibodies (mAb) have been effectively used for years alongside immunotherapy as a treatment for cancer. A good example is their application in breast cancer therapy. The survival rate of

breast cancer patients in Germany has continued to improve over the last 20 years. In the early 80's, the relative five-year breast cancer survival rate was around only 70 %. Around the turn of the millennium, according to the Robert-Koch-Institute (RKI), it was already 81 %. This positive trend is certainly due to improved preventive measures, but also to the use of innovative cancer drugs – like the antibody trastuzumab, which is effective in about 20 % of all breast cancer patients.

The use of mAb in therapy and diagnostics has proven effective. In oncology, depending on the type of cancer, they are often the only hope of improving the course of the disease and accordingly increasing life expectancy.

On the whole, the RKI statistics show that the relative five-year survival rate in men with cancer improved from 38 % in the beginning of the 80's to 53 % in the 2000 - 2004 time period. In women this value improved from 50 % to 60 % for the same observation period. It should be noted that in the same period, even though a significant increase in the survival rate was recorded, due to an ageing population the number of new illnesses also increased.

The discussion about the cost of innovative pharmaceuticals must take into account the benefit for the patient as well as society. In the context of a steadily ageing society with active and productive seniors, the significance of these medications will increase.

Regulatory policies and consequences for innovation

In order to accurately calculate the development costs for pharmaceutical drugs, the regulatory framework – especially the reimbursement policies – within which the pharmaceutical industry operates, must be reliable. While regulatory requirements are mainly regulated centrally, reimbursement policies are regulated by each country on a national level. The ability to plan costs is an essential basis for investment decisions in the R&D sector. Unfortunately, the situation in Germany has not improved over the past few years, as demonstrated by the passage and implementation of more than 20 legislative reform acts in the health care sector since 1989. If this trend continues, it will be very difficult to predict what the reimbursement and market environment will look like in eight to twelve years when a product is ready for launch, following a development program initiated now. As such, the economic basis required for innovations – the ability to plan costs – is absent for companies who mainly generate their turnover in Germany.

The Act on the Reform of the Market for Medicinal Products (AMNOG) of 2011 and the Statutory Health Insurance Restructuring Act, which came into effect in 2010, are cases in point. The Statutory Health Insurance Restructuring Act is a cost-cutting measure to increase mandatory discounts, especially for innovative medicinal products, as well as a long-standing price moratorium. The price moratorium was originally meant to last until end of 2013, but was extended until 2017 as the first measure of the new government. The AMNOG is associated with particularly drastic changes for pharmaceutical companies. Neither of these measures were corrected by the federal government, in spite of the economic challenges faced by the industry.

In addition to the AMNOG, the early benefit assessment procedure was implemented for innovative pharmaceutical drugs. This approach leads to a constantly changing framework. As a result, the ability to plan innovative R&D programs in the industry continues to be difficult. In addition, the system for reimbursement of new pharmaceutical drugs has undergone profound changes. Through the international reference pricing system, which allows more than 80 countries to reference German prices for pharmaceutical drugs, this development has worldwide impact. In November 2013, three quarters of the German prices were below the European average; more than a third were the lowest in Europe.

The immediate results of these regulatory changes have led research-driven pharmaceutical companies to put drug development programs on hold. In the summer of 2012, the BPI conducted a survey of its members regarding the priority given to innovation. Almost 90 % of the respondents stated that the expected benefit assessment according to the AMNOG would partly prevent companies from recouping their R&D investments. This is a grave situation for innovation in Germany, as 78 % of the respondents also stated that promising development programs for prescription medications had been currently put on hold.

Proposals to subject well-established active substances to the early benefit assessment process for new indications, per § 35a SGB V, constitutes yet another impediment to progress, which would hinder improvements in patient care.

R&D-Programs

The mid-tier pharmaceutical sector is often unable to profit from national or European R&D-subsidies. This is a result of the special structure of the pharmaceutical industry. Although considered small or medium-sized enterprises based on the number of employees (more than 90 % of pharmaceutical companies employ less than 500 staff), the companies, due to their (successful) history, have annual turnovers in the tens and hundreds of millions. The typical BPI member company, for example, employs ca. 330 staff.

At the same time, the capital markets are not an option for innovative mid-tier companies in the pharmaceutical industry. Therefore, overcoming the financial hurdles associated with the move from early drug development to market entry (the "valley of death") is a major challenge for these companies.

In this context, it is necessary to specifically address the R&D-support provided for innovative mid-tier companies. Supporting start-up companies is not the only way to give incentives. It is also possible to incentivise innovation in established companies who often need to manage their smaller suppliers and therefore shoulder most of the risk associated with a new technology. Making the wrong investment decisions regarding R&D programs can spell ruin for these companies, including their supply chain.

The EU Commission's recommendation on the description of SMEs (2003/361/EC) published in 2003 (up to 250 employees and up to 50 million Euros annual turnover) is not useful in supporting the innovative output of the mid-tier pharmaceutical sector. Over the past 10 years, neither the number of employees, nor the annual turnovers were adapted to the inflation or sector-specific factors. In the case of

the pharmaceutical industry, this means that the citizens of the European Union are being indirectly deprived of the fruits of innovations in patient care.

A broad mid-tier sector is essential for a healthy economy. Experience has shown that mid-tier companies are able to compete with larger companies because of their flexibility. However, they are usually at a disadvantage when it comes to economies of scale in procurement, production and distribution.

To prevent distortions in competition in the overall pharmaceutical market resulting from inappropriate definitions, the German Federal Cartel Office recommends that the term “small and medium-sized enterprise” (SME) should be defined in the context of the applicable market structure. Therefore, whether or not a particular company is considered an SME should not be defined based only absolute numbers (such as annual turnover or number of employees), but should instead be judged based on the overall size of the companies found in the particular market sector. The term SME should be defined in terms of the size of the large companies found in the particular market sector, since these large competitors are the competitive benchmark for the support to be extended to the small companies. For example, in a market sector where the largest companies generate billions in turnover, a company with 100 million Euros annual turnover would be considered mid-size.

In this case, it would be helpful to use the increasingly accepted definitions for “intermediate-sized enterprises” (ISE) or “Mid-Caps” of the French National Institutes of Statistics and Economic Studies National Institutes of Statistics and Economic Studies.

These definitions include corporations that have between 250 and 5000 employees and a maximum annual turnover of 1.5 billion Euros. Companies with less than 250 employees, but more than 50 million Euros in turnover are also included.

Future Trends

For biopharmaceuticals there is enormous development potential. With the decoding of the human genome, increasing understanding of the function of proteins and peptides, and their extremely complex interactions due to systems biology, the knowledge base keeps growing. With the aid of bioinformatics, new techniques are developed in order to extract essential and required information from the enormous data volumes available. Integrating the different fields of knowledge will result in the development of new active substances, completely new mechanisms of action and therapeutic approaches.

Nowadays the individualisation of therapies is already noticeable, in addition to testing of individual drug effects or side effects of pharmaceutical drugs due to the use of pharmacogenomics or metabolomic examinations in the context of “stratified medicine”. This allows the analysis of differences between patient groups and makes these the basis of different therapeutic approaches.

Thirty-seven active substances are already on the market today, which are used in specific patient groups as personalised medicine. For 28 of these pharmaceuticals, diagnostic pretesting is required to determine the expected efficacy and individual risk for adverse reactions. For another nine products, such testing is recommended.

Beyond this, the fields of regenerative medicine and gene / cell therapy open up new prospects for treating or even eliminating complex diseases. At the end of 2012, the EU Commission granted a marketing authorisation to the first gene therapy pharmaceutical of the western world. The drug in question is indicated for a rare metabolic disorder called Lipoprotein Lipase Deficiency (LPLD), which affects 2 in 1 million people. The patients suffer from abdominal pain and have an increased risk of pancreatitis. The drug is intended to replace the defective gene in the body and thereby restore the natural function of the body.

Besides this, new perspectives in the field of “biosimilars” are opening up. This term is used to describe biologically active substances marketed as a generic preparation after the patent protection of the original pharmaceutical drug has expired. They are called biosimilars because biological molecules show minor differences and therefore are not completely identical.* For this reason, the effort for testing and authorisation of biosimilars is significantly higher than for other generics and the expected price drop is not as significant as it is for other pharmaceutical drugs.

In Germany, there are currently three different active substance classes with an SHI turnover of 67 million Euros in 2013 or 6.34 million so-called “defined daily doses” (DDD). The drugs in question are Epoetin, the granulocyte colony stimulating factor (G-CSF), Filgrastim, as well as Somatropin, a growth hormone used to treat growth hormone deficiency.

* biosimilar medicinal product is a biological medicine which is similar to another biological medicine that has already been authorised for use. It serves as the “reference medicinal product” for the biosimilar. (EU-Consensus Information Paper (2013))

In addition, in the summer of 2013 the Committee for Medicinal Products for Human Use (CHMP) endorsed the authorisation of the first biosimilar monoclonal antibody (mAb), Infliximab, by the EMA. Both biosimilars are authorised for the same indications as the reference drug, including rheumatoid arthritis, Crohn's disease, ulcerative colitis and psoriasis.

In June 2014, the CHMP recommended market authorisation for an insulin analog, whose reference product currently has a yearly turnover of five billion Euros and which loses its patent protection beginning of 2015.*

The potential is huge. In the coming years, twelve biopharmaceuticals will lose their patent protection. In Germany alone, biopharmaceuticals with a turnover of around 370 million Euros will lose their patent protection in 2014; in 2015 the turnover will be closer to one billion Euros.

Upcoming patent expirations for top selling biopharmaceuticals

Active substance (Product name)	Patent expiration EU	Patent expiration USA
Insulin Aspart (Novomix®, Novorapid®)	expired	expired
Rituximab (Mabthera®)	expired	2018
Insulin Glargine (Lantus®)	2014	2015
Trastzumab (Herceptin®)	2014	2019
Etanercept (Enbrel®)	2015	2028 (extension)
Infliximab (Remicade®)	2015	2018
Interferon Beta-1A (Avonex®, Rebif®)	2015	2016
Pegfilgrastim (Neulasta®)	2015	2015
Ranibizumab (Lucentis®)	2016	2016
Glatiramer Acetate (Copaxone®)	2017	2014
Adalimumab (Humira®)	2018	2016
Bevacizumab (Avastin®)	2019	2019

Source: Illustration of the BPI based on IMS MIDAS 2013.

* Due to patent suits filed by the original manufacturer, the generic preparation cannot be marketed until 2016.

In the long run, a better understanding of pathomechanisms and treatment options developed on this basis will result in therapies for currently untreatable diseases. Aside from this primary goal, there is also the expectation that new revolutionary treatment approaches (e.g. by preventing the development of a disease or by treating the disease's root cause instead of its symptoms) will result in lower treatment costs.

Clinical Research for the development of pharmaceuticals

Clinical research in pharmaceutical companies and scientific centres, such as university clinics, is an important part of the development of a new drug. Clinical research includes the planning, conduct, analysis and publication of clinical trials, according to the relevant national and international regulatory requirements, as well as other aspects – such as the cooperation between contract research organisations, competency centres and authorities, with consideration of factors such as study subject safety, patient information, insurance and legal issues.

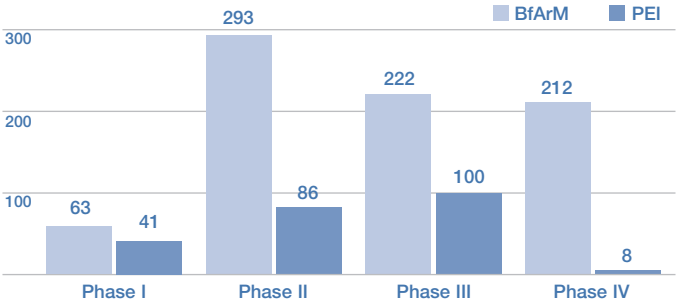
In clinical trials, active substances, substance combinations, new galenic forms or indications are tested for certain parameters, after they have been identified and successfully tested in the preclinical development phase (testing with cell, tissue and bacterial cultures and/or animal testing).

These parameters include safety, efficacy, quality, and the adverse reaction potential of the future drug and are investigated in a clinical trials.

The applicant must submit the results of this research when the company applies for a marketing authorisation from the Federal Institute for Drugs and Medical Devices (BfArM), the Paul-Ehrlich-Institute, or the European Medicines Agency (EMA). These authorities decide whether or not to grant the marketing authorisation based on the data produced by trials. The main criteria for this decision are the tolerability, efficacy and safety of the active substance. If these aspects were positively demonstrated in the clinical trials, the pharmaceutical can be authorised.

Clinical trials are divided into Phases I, II, III and IV. Phase I to III investigations are conducted before authorisation, Phase IV trials are conducted afterwards.

Number of clinical trial applications submitted to BfArM and PEI in 2013 divided by phase



Source: Illustration of the BPI based on BfArM 2014 and PEI 2014 data.

In May 2014, new European legislation on conducting clinical trials was passed. On 16 April 2014, the European Parliament and the EU Council adopted Regulation (EU) No 536/2014 concerning clinical trials of pharmaceuticals for human use and repealing Directive 2001/20/EC. This new regulation is intended to harmonise clinical trials in

the European Union and strengthen Europe as a location for clinical research. As an example, the new regulation harmonises the application procedures for clinical trials in the EU member states. The regulation will not be applied and enforced until 2016, at the earliest.

Phase I clinical trials are intended to investigate the tolerability, the metabolism or pharmacokinetics and interactions of an active substance. This active substance is referred to as the investigational medicinal product in all clinical trial phases. Another important aspect is dose finding. For this purpose, a “pre-phase I” trial phase has existed for several years, in which first-in-human application of microdoses is tested. These doses comprise of at most 100 micrograms of the active substance. The goal is to gain insight into the active substance’s behaviour in the human body at a very early stage. In phase I trials, this investigation is usually conducted in a small group of 20-30 healthy volunteers, usually men, in specialist research institutes.

In phase II trials, the substance is tested in patient volunteers suffering from the diseases for which the use of the substance is intended. Usually, several hundred patients take part in these trials and are monitored in hospitals, university clinics and doctors’ practices. The goal of this phase is to gather data on efficacy and other effects, dose finding and different routes of application.

Phase III clinical trials are intended to confirm the efficacy of the investigational medicinal product, but also to demonstrate its tolerability, so as to estimate the product’s benefit-risk-ratio. These studies comprise several thousand patients and usually last several years. The results, with a few exceptions, are the basis upon which regulatory authorities decide to grant a marketing authorisation.

Phase IV trials, which are conducted after the product is marketed, are performed to gather further data on patient safety, the overall safety profile, the efficacy and the effectiveness, interactions and treatment optimisation, especially in the context of long-term use.

In order for a pharmaceutical drug to be eligible for reimbursement, data on efficacy, safety, quality and benefit / added benefit must be submitted. This data is collected during the clinical trials. Usually, this also includes pharmacoeconomic data. Relevant aspects associated with patient benefit, such as surrogate parameters, quality of life are of increasing importance, along with the study design and the instruments used to capture the data.

The United States continue to have the highest number of clinical studies, thanks to a large patient pool and a research-friendly regulatory environment. As a result, the United States also continue to dominate the field of clinical research. This is demonstrated clearly by the fact that around 50 % of all the study centres found in the study registry “clinicaltrials.gov” are located in the United States and Canada, while 20 % are in Europe and 7 % the Asia-Pacific region. The consulting agency A. T. Kearney conducted a study that showed how individual regions and countries have positioned themselves in the field of clinical research, based on parameters such as staff, regulatory environment and patient availability. Germany is found in the middle field in the overall ranking. This is also confirmed by a variety of other findings from the international clinical trial environment. For example, around 50 % of all new pharmaceuticals are first launched in the United States, and the majority of the studies submitted to the Institute for Quality and Efficiency in Healthcare (IQWiG), in the context of the early benefit assessment procedure, in Germany were conducted in the United States.

A review published by the EMA analysed the information submitted with marketing authorisation applications using pivotal studies from 2005 to 2011. Selected results from this analysis are presented below.

From 2005 to 2011, a total of 897,891 patients participated in clinical trials worldwide.

Number of patients enrolled in clinical trials

	2005 – 2011	share in %	2011	share in %
EU / EEA / EFTA*	342,179	38.10	44,590	31.20
North America	305,762	34.10	44,987	31.50
ROW**	249,950	27.80	53,384	37.30
Total	897,891	100.00	142,961	100,00

Source: Illustration of the BPI based on EMA data 2013.

* European Union / European Economic Area / European Free Trade Association
** Rest of the world

From 2005 to 2011, a total of 70,291 study centres were recruited.

Number of study centres for conducting clinical trials

	2005 – 2011	share in %	2011	share in %
EU / EEA / EFTA*	25,420	36.20	4,548	35.20
North America	29,807	42.40	4,744	36.70
ROW**	15,064	21.40	3,636	28.10
Total	70,291	100.00	12,928	100.00

Source: Illustration of the BPI based on EMA data 2013.

* European Union / European Economic Area / European Free Trade Association
** Rest of the world

In 2005 to 2011, a total of 4,899 clinical trials were conducted worldwide. The number of participants per trial varied significantly.

Number of pivotal trials submitted to EMA from 2005 to 2011

USA	681
Canada	427
Germany	421
France	342
Great Britain	313
ROW*	2,715

Source: Illustration of the BPI based on EMA data 2013.

* Rest of the world

Average number of patients per clinical trial from 2005 until 2011

USA	391
Canada	93
Germany	145
France	78
Great Britain	60
EU / EEA / EFTA* total	1,810

Source: Illustration of the BPI based on EMA data 2013.

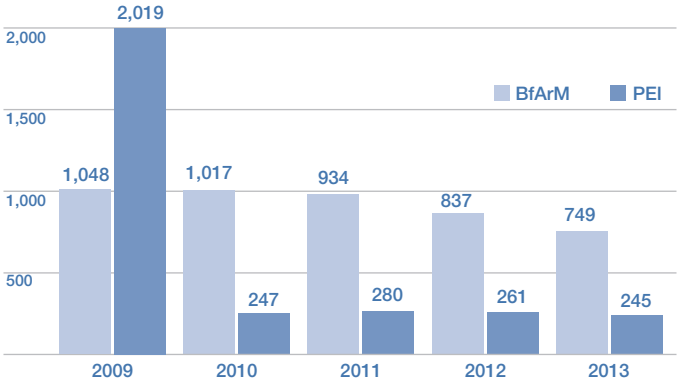
* European Union / European Economic Area / European Free Trade Association

On average, in the EU / EEA / EFTA* region, each study centre was running with 13 patients per clinical trial. In North America (USA & Canada), an average of 10 patients were participating in clinical trials, while in the rest of the world (including Africa, Asian, Easter Europe, Australian) an average of 17 patients were participating.

In reviewing the development of clinical research in Germany over the last 10 years it should be noted that the 10,000th application to conduct a clinical trial was submitted to the BfArM in 2014. This represents an average of 1,000 applications a year.

* European Union / European Economic Area / European Free Trade Association

Number of applications to conduct a clinical trial 2009 – 2013 submitted to BfArM and PEI



Source: Illustration of the BPI based on data from BfArM 2014 and PEI 2014.

Continuous monitoring of pharmaceutical drug safety / pharmacovigilance

The WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

The legal requirement for a pharmaceutical company to maintain an adequate pharmacovigilance system is defined in the German Medicines Act (AMG), which reflects the national implementation of the EU Directive 2001/83/EC (as amended with the Directive 2010/84/EU in the context of the “pharma package”). For example, this law requires all marketing authorisation holders in Germany to report all cases involving suspected serious

adverse reactions occurring in Germany to the relevant national authority immediately, but no later than 15 days (see § 63c AMG; Special requirements for documentation and reporting for blood and tissue preparations).

The national competent authorities in Germany are the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich-Institute (PEI). The Paul-Ehrlich-Institute (PEI) is the responsible national competent authority for vaccines, blood preparations and sera; for all other medicines, this is the Federal Institute for Drugs and Medical Devices (BfArM). The European Medicines Agency (EMA) is responsible for process implementation on the European level, and issues recommendations, which are then implemented in all member states through decisions of the European Commission in a legally binding manner.

In order to comply with these reporting requirements, pharmaceutical companies are required to appoint a responsible person for pharmacovigilance (or, according to German law, the so-called Stufenplanbeauftrager or Graduated Plan Officer). This person is responsible for collecting and evaluating safety information and for coordinating necessary measures to be taken. This person is personally liable for his or her activities. On a national (German) level, the so-called “Stufenplan” (graduated plan) as per § 63 German Medicines Act serves to monitor, collect and evaluate risks associated with pharmaceutical drugs.

When additional safety measures are deemed necessary to protect patients, these measures are implemented immediately. Usually, these measures are implemented by the pharmaceutical company, but they can also result from direct requirements imposed by the competent

national or European authorities The graduated plan described in the AMG regulates which measures should be implemented by the pharmaceutical company to improve patient safety. These measures range from changing the patient information leaflet to withdraw the drug from the market. Many pharmcovigilance procedures (so-called referrals) are primarily triggered on a European level and coordinated by the EMA (Regulation (EC) 726/2004 as amended by Regulation (EU) 1235/2010 in the context of the pharma package).

Identification of side effects in clinical trials

The data collected on side effects in clinical trials (i.e. under ideal controlled conditions) is not representative for the use of the drug in daily practice. On the one hand, the pre-defined inclusion and exclusion criteria for clinical trials narrow down the target population to such an extent, that an extrapolation from this population to the general public is not always valid. On the other hand, the frequencies of adverse drug effects in these relatively small patient collectives are often lower than the frequencies reported later in the general population.

As a result, certain side effects, for example those occurring with specific underlying conditions or with certain concomitant medications, are often not identified in the clinical trials.

The monitoring of drugs under the conditions of everyday practice, i.e. after market authorisation, is of the highest importance for furthering drug safety and therefore for quality management of treatments.

Reports of side effects

According to the BfArM, the authority received around 60,000 individual case reports of adverse reactions originating in Germany in 2013, including both initial reports and reports with follow-up information on the same case. The majority of these reports were submitted by the pharmaceutical industry (87 %).

According to the PEI, around 28,000 adverse reaction reports were received in 2013. Seventy-five percent of these were spontaneous reports, and 24 % originated from clinical trials; consumer reports constituted 0.8 %. As in previous years, the majority of reports have been received via the pharmaceutical industry (around 80 %).

EU-wide exchange of safety

In the field of drug safety (pharmacovigilance), the rapid exchange of information between the individual national competent authorities of the EU member states is of great significance. For that reason, the EU has created graduated information systems where, depending on urgency, the respective required procedures are applied. A so-called Rapid Alert System is used whenever one of the member states identifies a suspected change in the benefit-risk ratio of a given pharmaceutical drug, which might require changes to the approval status.

The German national competent authorities cooperate closely both with the local state authorities, and with those of other European nations. There are also close contacts with authorities of countries outside of Europe, the World Health

Organization (WHO), drug commissions of health care professional associations as well as with pharmacovigilance centres that collect reports of adverse drug effects.

“Rote Hand Brief” as a direct health professional communication

The “Rote Hand Brief”, (“Red Hand Letter”), is an instrument for direct health professional communication of newly identified, significant risks concerning the use and administration of pharmaceutical drugs, and measures for risk mitigation.

The statutes and codices of the pharmaceutical industry associations BPI and vfa require their members to communicate important information concerning pharmaceutical drug safety, in consultation with the national competent authorities, to health professional circles. This may include information on new serious side effects, recalls of defective lots, and other information that needs to reach the attending physicians and pharmacist directly to ensure patient safety. On letters and envelopes, the symbol of the red hand accompanied by the wording “Important information concerning a pharmaceutical drug” is to be used in order to sensitise the expert groups acordingly for these warnings. In particularly urgent instances, it can also be necessary to communicate this information verbally, by fax or via the public media (press, radio, television).

The global pharmaceutical market

In 2013, the global turnover of pharmaceutical drugs totalled 720 billion Euros (980 billion US-Dollars), an increase of 2.3 % compared to the previous year.

Development of the global pharmaceutical market

	2009	2010	2011	2012	2013
Total market (billion Euros)*	610.1	654.7	709.0	703.2	720.0
Total market (billion US-Dollars)	830.6	891.3	965.2	957.3	980.1
Change compared to previous year (in %)		7.3	8.3	- 0.8	2.4

* The Euro values are based on a recalculation of the market data of the base values in US-Dollars (Exchange rate: US-Dollars in Euros = 1.361 : 1).

Source: Illustration of the BPI based on data of IMS World Review Review 2014.

Over 70 % of the total turnover of the global pharmaceutical market is generated by North America, Europe and Japan. The turnover in North America decreased by 3.2 % to 265.3 billion Euros, which represents 37 % of the global pharmaceutical turnover in 2013. At the same time, the European pharmaceutical market actually increased by 5.6 % to 189.6 billion Euros. In Japan, however, pharmaceutical turnover decreased in 2013 by 16.1 % to 69 billion Euros.

Top 10 pharmaceutical markets worldwide and growth to LCD* (in %)

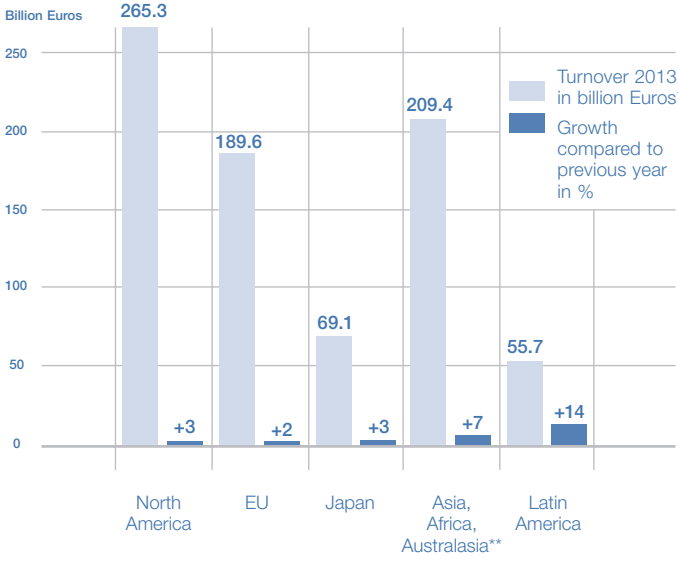
Country	Turnover 2013 (million US -Dollars)	Growth to LCD 2013 (%)*	Turnover 2013 (million Euros)**
USA	339,694	4	249,531
Japan	94,025	3	69,068
China	86,774	14	63,742
Germany	45,828	5	33,664
France	37,156	- 2	27,294
Brazil	30,670	16	22,529
Italy	27,930	3	20,517
Great Britain	24,513	17	18,007
Canada	21,353	0	15,685
Spain	20,741	1	15,236

* LCD: Local currency dollar – currency fluctuations in the country are not considered, so the growth rate is comparable across countries.

** The Euro values are based on a recalculation of the market data of the base values in US-Dollars (Exchange rate: US Dollars in Euros = 1.361 : 1).

Source: Illustration of the BPI based on data of IMS World Review Review 2014.

Global pharmaceutical market by region 2013



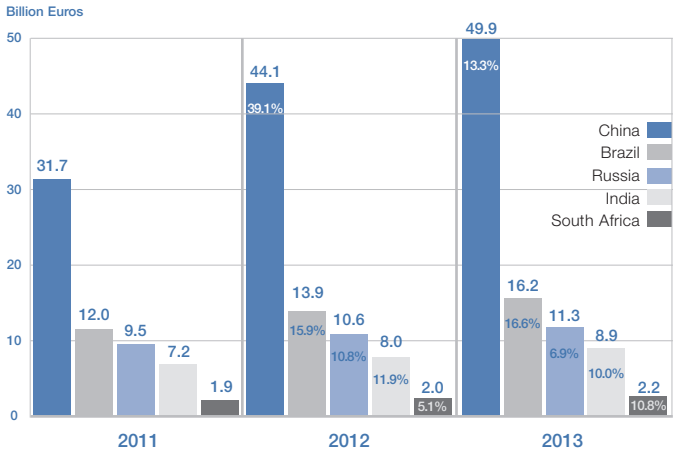
* The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro = 1,361 : 1).

** The Region "Asia, Africa, Australasia" includes Japan.

Source: Illustration of the BPI based on data of IMS World Review 2014.

The economic influence of the five emerging markets, Brazil, Russia, India, China and South Africa (summarised under the expression "BRICS"), has increased significantly in recent years. This development also includes the pharmaceutical sector. The turnover of the pharmaceutical industry in 2013 in these countries totalled ca. 89 billion Euros, which constitutes an increase of almost 13 % versus the previous year (ca. 79 billion Euros). This has increased continuously in all five markets over the past three years. In contrast to the more pessimistic predictions for other pharmaceutical markets worldwide, continued market growth is foreseen in the BRICS countries. The significance of these markets for the pharmaceutical industry will continue to increase in the next years.

Turnover* in BRICS countries 2011 – 2013
(Changes relative to previous year in %)



LCD: Local currency dollar – currency fluctuations in each country are not considered, so the growth rate is comparable across countries.

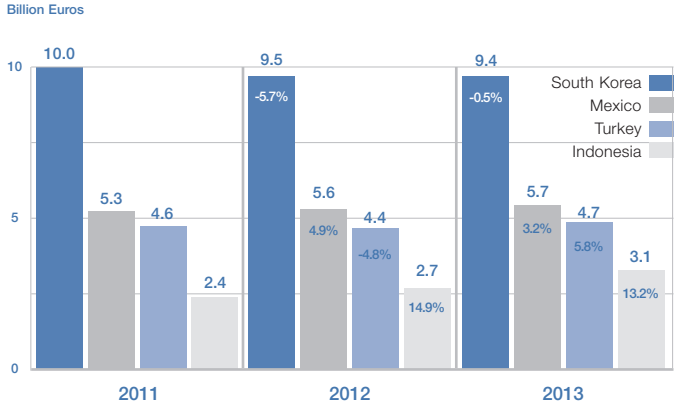
* The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro 1.361 : 1).

Source: Illustration of the BPI based on data of IMS Health MIDAS 2014.

Summarised under the expression “Next-Eleven” are eleven countries with a high number of inhabitants that could undergo a similar economic revival as the BRICS countries.

Four promising markets among these “Next-Eleven” countries are encapsulated with the acronym ´SMIT´ (South Korea, Mexico, Indonesia and Turkey). These are also classified as second tier emerging markets. The graph “Turnover* in SMIT countries 2011 – 2013” shows the dynamic development in these four pharmaceutical markets.

Turnover* in SMIT countries 2011 – 2013
(Changes relative to previous year in %)



LCD: Local currency dollar – currency fluctuations in each country are not considered, so the growth rate is comparable across countries.

* The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro = 1 : 1.361).

Source: Illustration of the BPI based on data of IMS Health MIDAS 2014.

Overall, the global health care market is a growing market with considerable employment potential. To date, many diseases are still untreatable, while increasing life expectancy and changing consumer interest, as well as the search for a higher quality of life, have increased the demand for health-related services and products. In addition, advances in the fields of medicine and pharmacy, particularly in molecular and cellular biology, generate novel innovation incentives. Furthermore, a trend toward personalised medicine in the form of individualised diagnostics and treatments is evident.

The European Pharmaceutical Market

Upon closer analysis, these pharmaceutical markets are heterogeneous with regards to market size and market development.

Pharmaceutical markets of the EU-15

EU member state	Turnover* for 2013 (Million USD)	Growth*** to LCD 2013 (%)	Turnover* for 2013 (Million Euros)****
Germany**	45,828	5	33,664
France**	37,156	-2	27,294
Italy**	27,930	3	20,517
Great Britain**	21,635	17	15,893
Spain**	20,741	1	15,236
Belgium**	6,122	0	4,497
Sweden**	4,464	0	3,279
Greece	4,460	-10	3,276
Austria**	4,261	2	3,130
The Netherlands	3,868	-3	3,086
Portugal	2,691	-1	2,841
Denmark**	2,691	2	1,977
Finland**	2,653	-3	1,949
Ireland**	2,397	0	1,761
Luxembourg	237	0,5	174
Total	188,644	2.98*****	138,573

* Turnovers from the markets observed, plus estimation of partial markets not observed, result in the total turnover of a member state at manufacturer price.

** Pharmacy market and hospital market data were available for these markets.

*** LCD: Local currency dollar – currency fluctuations in each country are not considered, so the growth rate is comparable across countries.

**** The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro = 1 : 1.361).

***** The total growth in LCD 2012 of 2.98 % is a weighted value (unweighted: 0.5 %).

Source: Illustration of the BPI based on data of IMS Health World Review 2014.

Pharmaceutical pricing and reimbursement are regulated in different ways in different countries. However, a common feature of these markets is an increasing competition in the generics sector.

The analysis of the annual turnover in the EU-15 in 2013 shows that, in absolute volume, Germany, France, Italy, followed by Great Britain represent the largest pharmaceutical markets. A comparison of the growth rates to the previous years shows a situation, that is still difficult in the different European pharmaceutical markets.

In the following section, selected eastern and central European countries with special economic relationships will be looked at in more detail.

The image “Total pharmaceutical market of Central and Eastern Europe 2013” shows the overall turnover and growth of the pharmaceutical market in these countries. By far the largest market is Poland, with 5.4 billion in turnover in 2013. Romania, Hungary, the Czech Republic, and Slovakia are also in the top five markets in this group of countries. The strongest growth in 2013 continued to be seen in the Bulgarian, Polish and Estonian pharmaceutical markets.

Total pharmaceutical market of Central and Eastern Europe* 2014

Turnover in million Euros**

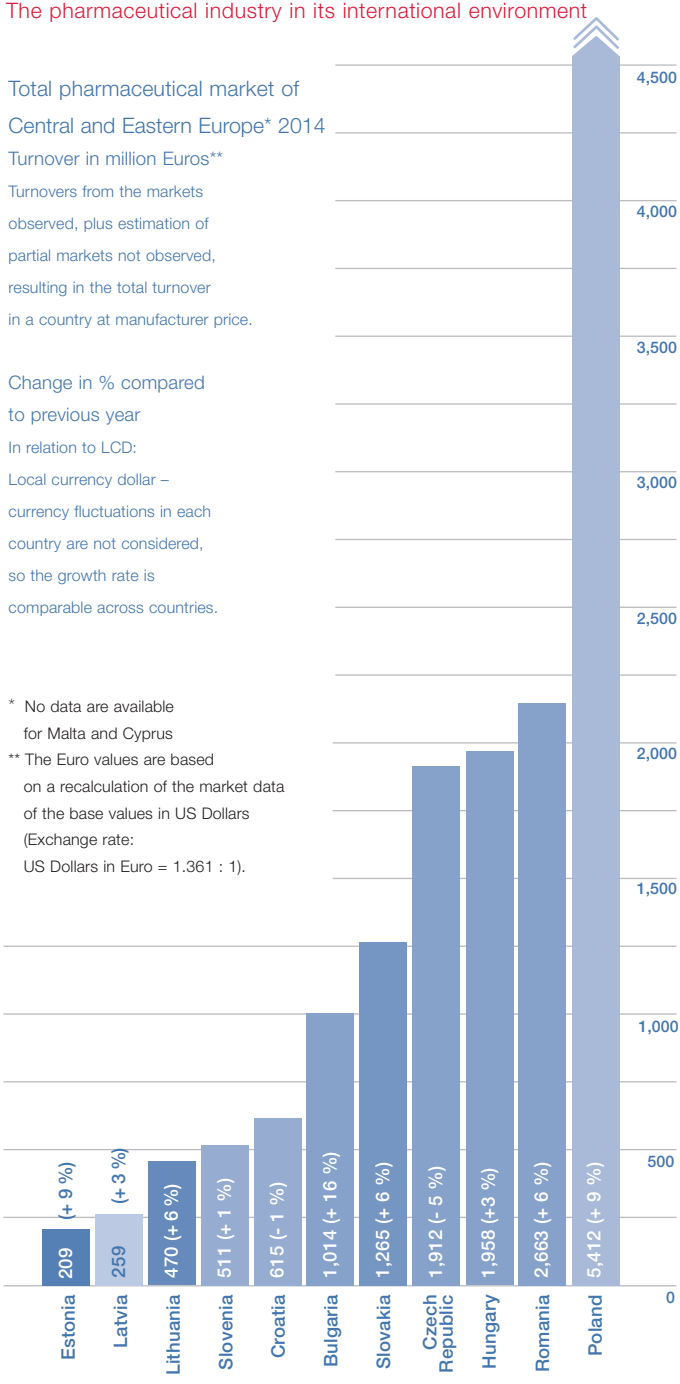
Turnovers from the markets observed, plus estimation of partial markets not observed, resulting in the total turnover in a country at manufacturer price.

Change in % compared to previous year

In relation to LCD: Local currency dollar – currency fluctuations in each country are not considered, so the growth rate is comparable across countries.

* No data are available for Malta and Cyprus

** The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro = 1.361 : 1).



Source: Illustration of the BPI based on data of IMS World Review 2014.

Over the next five years, IMS Health predicts 1.8 % average annual growth for EU member states. In contrast a growth of 2.9 % is predicted for non-EU countries while the global market is expected to grow by 5.1 %. The five most important markets are expected to grow by 1.9 %.

Market prognosis using constant exchange rates, growth in %, manufacturer price.

Europe	2012 – 2017
EU top five countries	1.9 %
EU member states	1.8 %
Non-EU countries	2.9 %
Global market	5.1 %

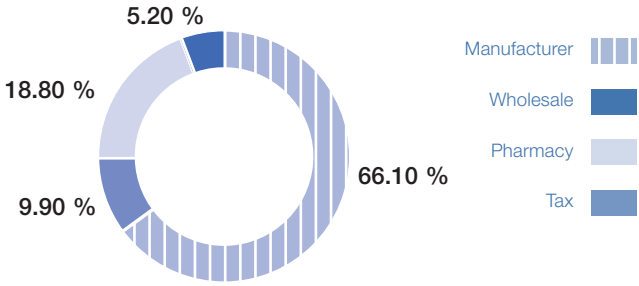
Source: Illustration of the BPI based on data of IMS Market Prognosis Global 2014.

International Comparison of Pharmaceutical Drug Prices

A pharmaceutical product varies in price from country to country for various reasons, including simple factors such as different VAT. In addition, direct governmental intervention often regulates the profit margins allowed to different trade levels (e.g. pharmacies, wholesalers). These factors account for the pricing variance across Europe. When conducting international comparisons of pharmaceutical drug prices, it is important to note that this is only possible based on individual trade levels. When selecting the dominant trade level in Germany, it is necessary to verify if this trade level is also dominant in other countries or at least has sufficient market relevance. Also, the data based on the manufacturer price is not available for all countries, so that the prices may need to be recalculated.

Political influences on pricing and reimbursement, as well as national prescribing and treatment habits also impact on drug pricing. When conducting overall market comparisons, volume adjustments are necessary.

Pharmaceutical price structure in Europe (2012)
– Based on pharmacy retail price



The values constitute an unweighted mean value for Europe.

Source: Illustration of the BPI based on EFPIA-Data 2014.

The graph of the pharmaceutical price structure shows the share of each individual trade level in the pharmaceutical drug prices in Europe. This clearly illustrates that the drug manufacturers are not the only group influencing drug prices, as the pharmacy retail price also contains components contributed by other factors such as distribution and VAT.

Value Added Tax (VAT) rates in Europe (as of 1 July 2014)

Country	Standard VAT rate (%)	VAT rates applicable to drugs Prescription-only (%)	OTC (%)
Austria	20.0	10.0	10.0
Belgium	21.0	6.0	6.0
Bulgaria	20.0	20.0	20.0
Croatia	25.0	5.0	25.0
Cyprus	19.0	5.0	5.0
Czech Republic	21.0	15.0	15.0
Denmark	25.0	25.0	25.0
Estonia	20.0	9.0	9.0
Finland	24.0	10.0	10.0
France[1]	20.0	2.1	7.0
Germany	19.0	19.0	19.0
Great Britain[2]	20.0	0.0	20.0
Greece	23.0	6.5	6.5
Hungary	27.0	5.0	5.0
Iceland	25.5	25.5	25.5
Ireland[3]	23.0	0.0 - 23.0	0.0 - 23.0
Italy	22.0	10.0	10.0
Latvia	21.0	12.0	12.0
Lithuania[4]	21.0	5.0	21.0
Luxembourg	15.0	3.0	3.0
Malta	18.0	0.0	0.0
Norway	25.0	25.0	25.0
Poland	23.0	8.0	8.0
Portugal	23.0	6.0	6.0
Romania	24.0	9.0	24.0
Slovakia	20.0	10.0	10.0
Slovenia	20.0	9.5	9.5
Spain	21.0	4.0	4.0
Sweden	25.0	0.0	25.0
Switzerland	8.0	2.5	2.5
The Netherlands	21.0	6.0	6.0

[1] Pharmaceutical drugs eligible for reimbursement: 2.1 %; Pharmaceutical drugs not eligible for reimbursement: 7.0 %

[2] Non-prescription drugs: 20.0 %, pharmaceutical drugs prescribed by NHS: 0 %

[3] Pharmaceutical drugs for oral administration: 0 %, others: 23.0 %

[4] Pharmaceuticals: 21 % starting December 31, 2013

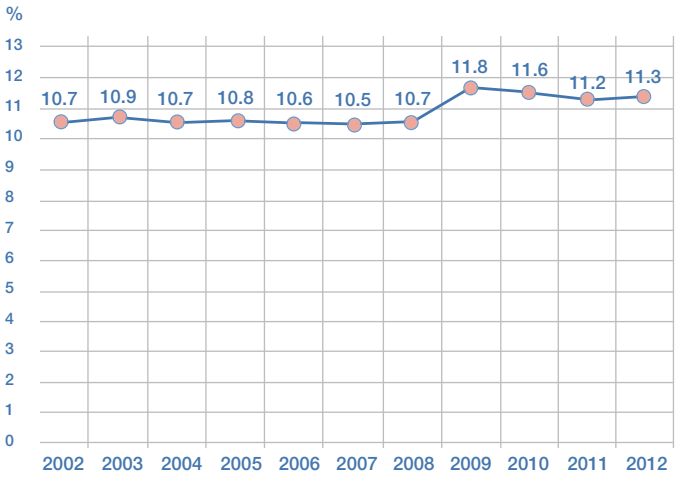
Source: Illustration of the BPI based on the European Commission 2014.

When comparing the VAT rates applied to pharmaceuticals, it may be noted that only Bulgaria, Denmark, Germany, Iceland and Norway apply the full standard VAT rate.

The Health Care Market in Germany

When analysing health care expenditure, it is important to note that a conclusive evaluation based solely on financial data, is not possible, especially when comparing health systems internationally. A more detailed and in-depth analysis is required of, for example, organisational structures or social circumstances and frameworks. However, the percentage of the GDP dedicated to a health care system, reflects the importance placed on health care by society. Therefore, a high percentage of GDP dedicated to health care does not necessarily constitute wasteful spending.

Development of health care expenditures – share of the GDP in %



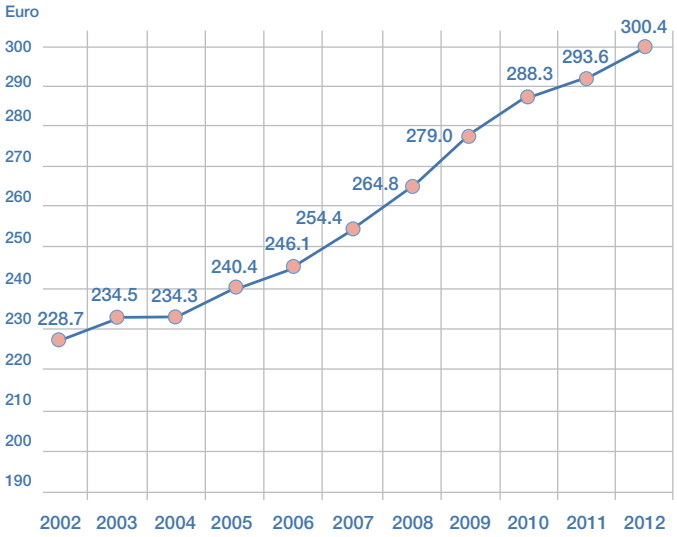
Source: Illustration of the BPI based on data of the Federal Statistical Office 2014.

The share of health care expenditures of the GDP has remained relatively stable in Germany; between 2002 and 2008 it was 10.5-10.9 % and between 2009 and 2012 it was 11.8 %-11.3 %. The relative increase seen in 2009 and 2010 is partially due to the statistical impact of the decreased GDP during these two crisis years.

For the first time in 2012, the nominal health care expenditures in Germany exceeded the 300 billion Euro mark. This constitutes an increase of 2.3 % compared to 2011.

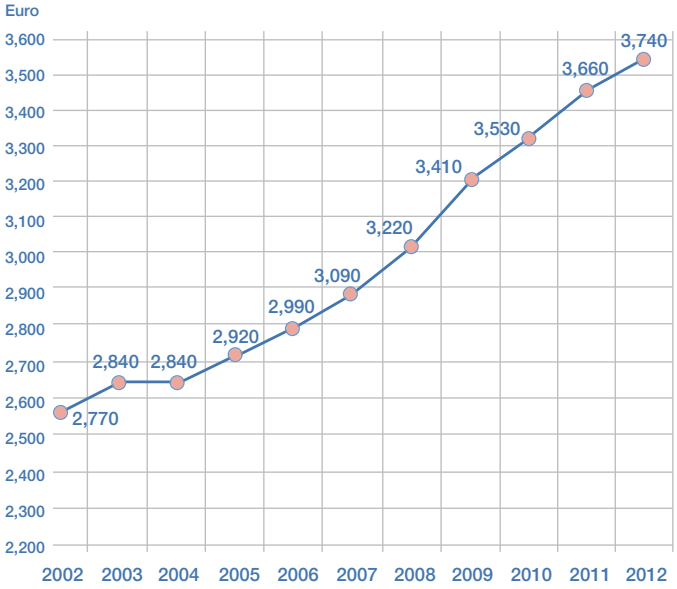
From 2011 to 2012, the per capita health expenditure have also increased by 2.2 % from 3,660 Euros to 3,740 Euros.

Development of nominal health care expenditure (in billion Euros)



Source: Illustration of the BPI based on data of the Federal Statistical Office 2014.

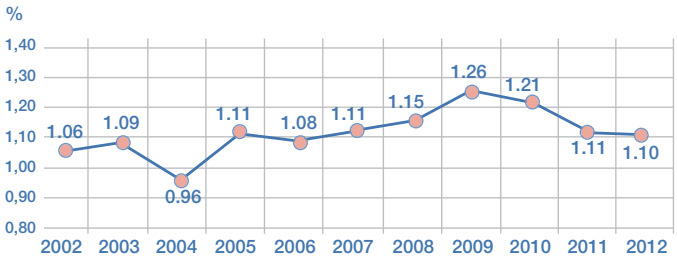
Development of per capita health care expenditure (in Euros)



Source: Illustration of the BPI based on data of the Federal Statistical Office 2014.

In 2012, the share of the SHI expenditure for pharmaceutical drugs, expressed as a percentage of GDP, decreased again by 0.01 % to 1.10 %.

Development of pharmaceutical drug* expenditure of the SHI providers – Percentage of GDP



* Pharmaceutical drug defined according to health care expenditure calculation of Federal Statistical Office.

Source: Illustration of the BPI based on data of the Federal Statistical Office 2014.

According to the most recent data from 2012 from the Federal Statistical Office, more than 5.2 million people, i.e. ca. every eighth employee, were employed in the German health care sector. The number of jobs in the health care sector increased by 950,000 in 2012, compared to the year 2000, the first year for which data is available. This constitutes a growth of 22.6 %. Compared to the previous year, the number of employees in the health care sector grew by 95,000. The primary cause of this rise is an increase in health professions (e. g. physicians and other medical staff) and social/caregiver professions (e.g. geriatric care). In 2012, the largest number of staff was employed in outpatient, inpatient and day-patient care health care facilities.

Due to an ageing population, Germany is undergoing a structural shift towards an older society, with multimorbidity and an increasing number of chronic diseases owing to lifestyle and nutritional habits. Health care policy must find sustainable solutions. To do this, the potential of a strong, innovative, job-intensive health care sector must be strengthened, not weakened.

Health care policy interventions over recent years display a tendency toward encouraging competition between stakeholders, and toward integrative health care solutions. However, a financially sustainable health care system in Germany still appears to be a distant prospect.

The development of SHI expenditure is subject to regular health care political discussions. For many years, SHI expenditure has been around 7.0 % of GDP (2012: 7.3 %). SHI expenditure for drugs as a percentage of GDP did not increase faster than the general economic growth rate when taking the effects of the financial crisis into account. In view of this development, there is no evidence of a “cost explosion” in the health care sector.

The financial situation of the SHI is particularly influenced by structural problems on both the revenue and expenditure side.

The following factors may have a negative impact on the revenue side:

-> Loss of income subject to social insurance deductions
-> Stagnating income
-> More “mini-jobs“
-> Salary increases relative to increases in other sources of income
-> Decreasing pension payments with an increasing number of pensioners
-> Shift towards private health insurance

Need for action on the expenditures side develops due to:

-> Medical and technological progress in combination with a shift in the ageing structure
-> Increase of chronic diseases
-> Remuneration increase for physicians working in outpatient care
-> Hospital tariff contracts
-> Expansion of the SHI services, e.g. palliative care and discontinuation of the mandatory practice fee
-> burden due to Value Added Tax (VAT) of 19 %
-> Implementation of the European legislation on working hours

Reforms over the past few years have not led to sustainable stabilisation and restructuring of the financial situation of the SHI. Because of the stable economic situation and increased employment in the German economy, the public health fund and the individual SHI providers are running surpluses, these may vary between providers.

While the German Economic Optimisation of Pharmaceutical Care Act (Arzneimittelversorgungs-Wirtschaftlichkeitsgesetz, AVWG), introduced in 2006, mainly focused on cost reduction of the expenditures for pharmaceutical drugs, the German Act to Reinforce Competition between the German Statutory Health Insurance providers (GKV- Wettbewerbsstärkungsgesetz) in 2007 aimed to foster competition within the health care sector. The Statutory Health Insurance Restructuring Act (GKV-ÄndG) as well as the Act for restructuring the drug market (AMNOG) resulted in further regulatory measures in certain areas, in particular the supply of pharmaceutical drugs. The Statutory Health Insurance Restructuring Act is a measure purely for cost reduction. From the perspective of the pharmaceutical industry, the many years of increasing mandatory discounts to a maximum of 16 % and the longest ongoing price moratorium to date, are of particular importance. The burden placed on pharmaceutical companies by mandatory discounts (SHI and private health insurance in the pharmaceutical- and the hospital market on the whole) amounted to 3.2 billion Euros in 2011, 2012, and 2013 alone. However, the AMNOG represents a significant paradigm shift in view of price formation for pharmaceuticals in Germany. In the future, the price determined by the manufacturer for an innovative pharmaceutical drug will only be reimbursed for the first year after market launch. The level of reimbursement after this first year will be largely determined by the results of the newly implemented early benefit assessment procedure.

This increasing trend toward standardisation of therapies needs to be stopped. At a time where the pharmaceutical industry is ever more capable of developing individualised treatment options and applying them in medical practice, the variety of therapy options must not be restricted solely for the purpose of cost reduction, e.g. through treatment guidelines or exclusions published by the self-government of SHI providers. Innovation must become part of patients' health care experience.

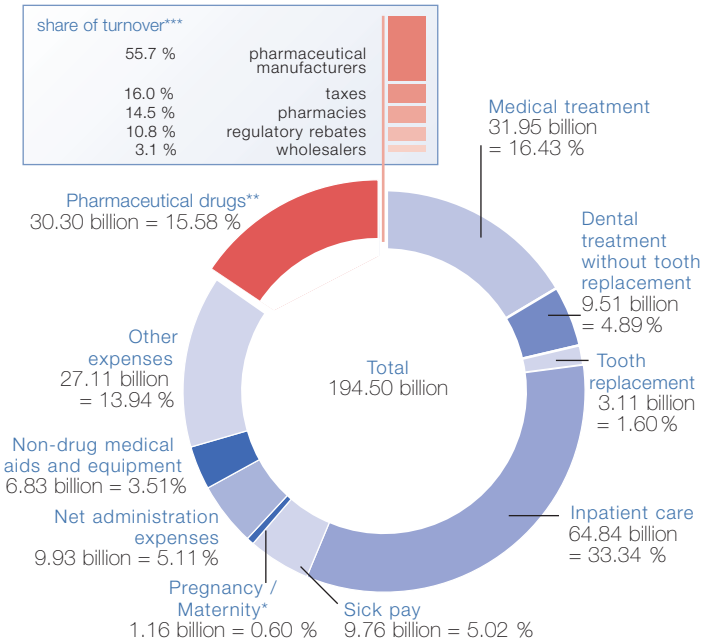
The first step towards a financially sustainable reform of the SHI system was performed by freezing the employer's contribution and uncapping the upper limit of the supplemental premiums. It was therefore, possible to partly decouple the health care costs and labour costs. Furthermore, supplemental premiums can be used as a regulating measure of the SHI market. The insured person is better able to make decisions in choosing his or her SHI provider. Due to the present positive financial situation, no health insurance company needs to levy supplemental premiums.

In general, health care reform should contribute significantly to deregulation and streamlining of administration in favour of increased personal responsibility and entrepreneurial freedom for the stakeholders concerned. The goal should be to allow the service providers in the health care sector to concentrate the greatest share of their energy on providing the best possible care to patients.

Cost Structure of the Statutory Health Insurance (SHI) System

The statement made by the national expert panel ten years ago on the issue of cost limitations remains true today. According to that statement, the goal of cost limitation is always a “precarious balance between withdrawal effects that cause increasing premiums, primarily outside the health sector, for consumers and investors, and the positive effects that are generated by health costs and the services financed by them” (expert opinion in 2003).

Cost structure of the Statutory Health Insurance (SHI) 2013
(in billion Euros and as % of all SHI-expenditures)



* not including in-patient delivery (obstetric).

** including VAT, regulatory obligatory discounts for pharmaceutical manufacturers and for pharmacies, and savings due to voluntary rebate contracts of the pharmaceutical industry are accounted for.

*** including VAT, regulatory obligatory discounts for pharmaceutical manufacturers and for pharmacies, and savings due to voluntary rebate contracts of the pharmaceutical industry are not accounted for.

Source: Illustration of the BPI based on KJ1 2014; Drug prescription report 2014.

Inpatient care, at 64.84 billion Euros in 2013, is the most cost-intensive sector of the SHI system. The combined expenditures for pharmaceutical drugs (30.30 billion Euros) and for medical treatment (31.95 billion Euros) amount to 62.25 billion Euros, which accounts for nearly the total expenditures of the inpatient care sector. The share of pharmaceuticals expenditures alone, including levels of trade and VAT, was 15.6 % of the total SHI expenditures.

When analysing pharmaceutical expenditure within the SHI, the amount contributed by each trade level is often neglected, i.e. wholesalers' and pharmacies' margins and VAT. If a given pharmaceutical drug at manufacturer price costs one Euro, one needs to add the wholesaler and pharmacy margins, as well as 19 % Value Added Tax. The pharmacy retail price would total approximately 12 Euros. This price is only valid as an operand, as obligatory discounts, pharmacy discounts, and patient co-payments are deducted, significantly reducing the actual burden on the SHI.

Irrespective of this, rising pharmaceutical expenditure over recent years was partly caused by the increase in outpatient treatment options, as well as a general shift from inpatient to outpatient care. The Diagnosis Related Groups (DRGs) and the resulting shorter inpatient stays are going to reinforce this tendency even more in the years to come. As in the past, this shift in services has not been followed by a shift in the required funding.

The general public often does not realise that manufacturers as well as wholesaler and pharmacists are required to grant an obligatory discount in order to stabilise SHI expenditure. In addition, in 2011 wholesalers took the burden of an obligatory discount of 0.85 %, based on the manufacturer price, and in the beginning of 2012 the wholesaler margin was re-assessed. Since this time, the wholesaler rebate has

been discontinued, because the targeted savings can be achieved by rearranging the wholesaler margin. In addition to the obligatory discounts already described, patients also contribute to the stabilisation of SHI spending through their co-payments.

Fundamentals of obligatory discount in the German pharmaceutical market

Manufacturers payments to SHI for prescription-only drugs (based on manufacture price, ex-post)

- 6 % - 7 % outside of the reference price (SGB V, § 130a, Section 1 in conjunction with Section 3)
- 10 % so-called generic discount, applied to reference price (SGB V, § 130a Section 3b)
- 7 % for OTx (SGB V, § 130a Section 1)
- Price (increase) moratorium (SGB V, §130a Section 3a)
- Vaccination discount (SGB V, § 130a Section 2)
- 6% or 7% in hospital use / compound products (SGB V, § 130a Section1)

Manufactures pay private health insurance for prescription medicines (based on manufacture price, ex-post)

- Rebates according to the drug rebate law and SGB V § 130a Section 1, 1a, 2, 3, 3a, 3b

The wholesaler contribution regulated by new remuneration regulation since 2012, in 2011 a wholesaler rebate was levied

Pharmacist pay

- Arbitral award: 1.75 Euro per package in the first half of 2013; 1.85 Euro In the second half of 2013; 1.80 Euro for 2014 and 1.77 Euro for 2015 for prescription-only drugs (SGB V, § 130 Section. 1)
- 5 % of the pharmacy price prescribed non-prescription (SGB V, § 130 Section 1)

Patients pay a co-payment

- 10 %, at least 5 Euro, at most 10, - Euro (SGB V, § 61), but not more than the cost of the drug.

Source: Illustration of the BPI 2014.

Exemptions to obligatory discounts in the German pharmaceutical market

Manufacturer

- § 130a Section1, 1a and 2 not applicable for drugs under reference pricing (§ 130a Section 3)
- 7 % rebate for OTx-Products, not applicable to drugs under reference pricing
- exemption from generic rebate possible when price reduced to 30 % below reference price (§ 130a Section 3b)
- In contracts as per § 130a Section 8(3) redemption of the obligatory discount can be agreed upon (valid for obligatory discounts as per § 130a Section 1, 1a, 2 not valid for obligatory discounts according § 130a Section 3a, 3b)

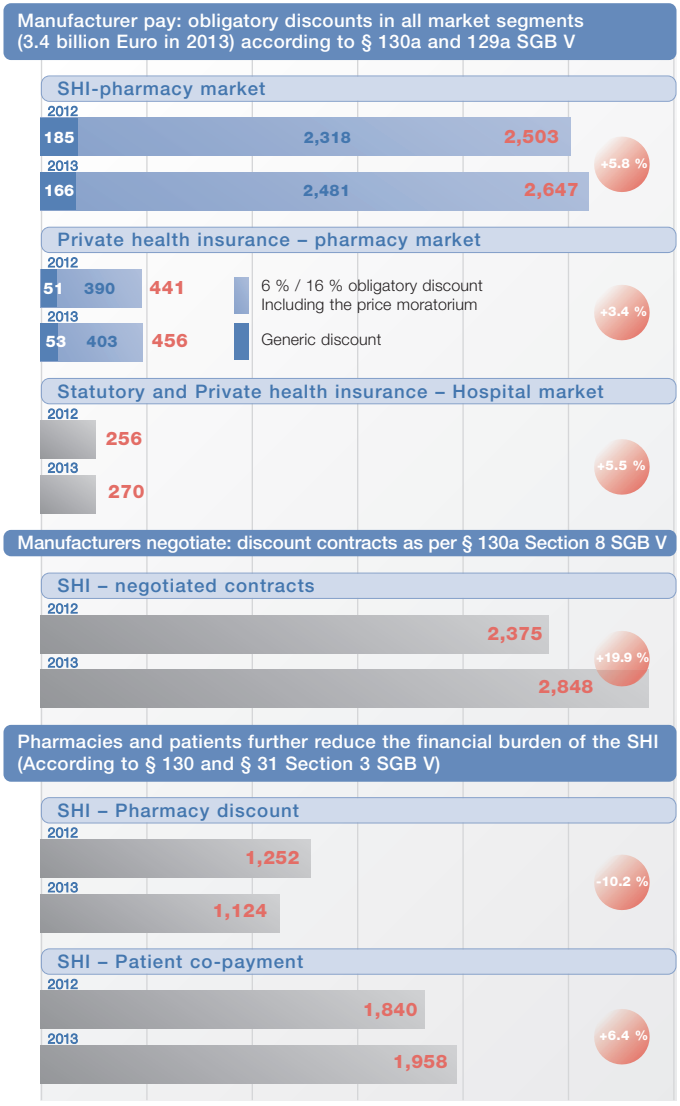
Patients

- Patient co-payments are adapted to the individual ability to pay (according to SGB V, § 62). This means 2% for gross annual income. For the chronically ill it is 1%.

Source: Illustration of the BPI 2014.

Obligatory discounts have been mandatory since the solidarity tax was instituted in 2002 (200 million Euros). Aside from the voluntary discounts, these obligatory discounts are of increasing importance. The trend is that obligatory discounts are adjusted according to the level of public deficits and political agendas. In addition, there is a price moratorium in place (prices fixed at level of 1 August 2009) for the timeframe from 1 August 2010 to 31 December 2017. The obligatory discounts are based on specific principles and include several exemptions, which are summarised briefly below.

Obligatory discounts, Negotiated Rebates and Manufacturer Co-payments, Trade Levels and Patients (in million Euros)



Source: Illustration of the BPI based on IMS HEALTH 2014.

In 2013, the cost burden for the pharmaceutical industry due to obligatory discounts (SHI and private health insurance in pharmacy and hospital markets) amounted to approximately 3.37 billion Euros. The small and medium sized enterprises are particularly hard hit by these additional costs, because they are unable to absorb the losses by spreading it across their product portfolio. Such political interventions contradict the official commitment to supporting small and medium sized enterprises. State interventions accelerate the consolidation of the market in favour of larger pharmaceutical companies or companies with very diverse product portfolios.

Discount / Rebate Contracts in the SHI System

Since 2003, SHI providers have had the legal option (§ 130a sect. 8 German Social Code Book V) to negotiate individual rebate / discount contracts with pharmaceutical companies. In the first few years, this regulation has had nearly no practical significance. However, with the Act to Reinforce Competition between the German Statutory Health Insurance (GKV-WSG) effective as of 2007, this instrument has rapidly gained momentum as a result of auxiliary measures, such as its relevance for performance audits for doctors, reduced co-payments for patients and the legal requirement of preferential dispensing of rebated drugs in the pharmacies. Only after lengthy legal disputes about the application of distribution, competition and antitrust laws, and after the involvement of the EU Commission, was the Act passed to enhance the organisational Structures of Statutory Health Insurance. This law provides that procurement law is applicable when entering into contracts, as per German Social Code Book V § 130a sect. 8.

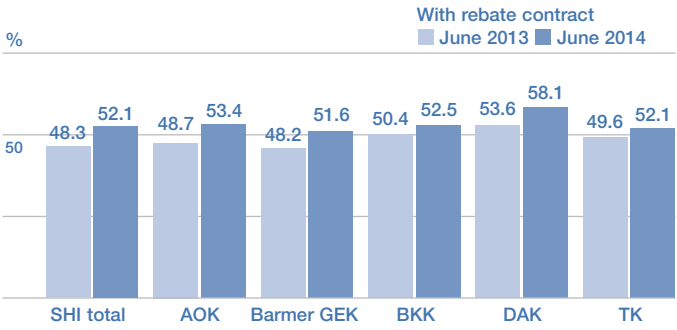
The Act for the Modernisation of Procurement Law of 24 April 2009 is also of great importance. This regulation requires calls for

tender to be divided into partial and/ or specialist lots, something that can be helpful to small and medium sized enterprises. The act also contains important regulations for legal protection of the stakeholders, in particular regarding the invalidity of illegal de facto procurement (§ 101b sect. 1 GWB). However, this invalidation only applies if a complaint is submitted to the procurement chamber within 30 days of obtaining knowledge of the contract or no longer than six months after the contract is signed (§ 101b sect. 2 GWB).

With the Second Act amending the German Medicines Act and other regulations on 26 October 2012, the rule that public procurement law for old discount contracts that are not compliant with regulatory requirements, was abolished so that such contracts become ineffective as of 30 April 2013. This has led to a general consolidation of the rebate contracts through tender renewal.

The number of drugs subject to rebate contracts is on a consistently high level for all SHI providers. In June 2014, the DAK (Deutsche Angestellten Krankenkasse) had the highest market share of rebated drugs (58 %) in the entire SHI market. This share varies by to contract durations and individual tender.

Share of discounted drugs in different Statutory Health Insurance providers by number of package units (market share in %)



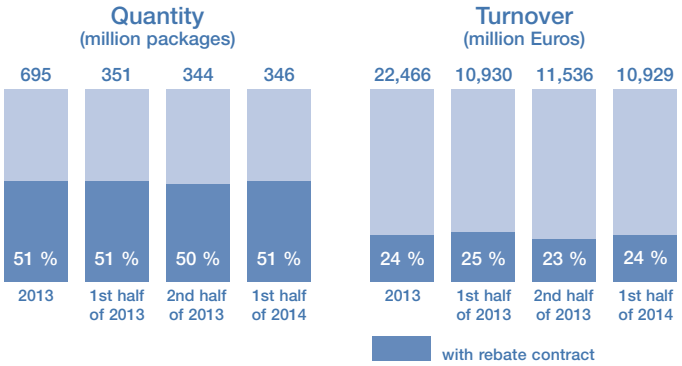
Source: Illustration of the BPI based on IMS Contract Monitor 2014.

According to IMS Health, nearly half of the dispensed medications in the SHI market were subject to rebate contracts as of June 2014. In June 2013, 147 health insurance providers had 11,043 rebate contracts in place with 147 pharmaceutical companies covering 16,097 pharmaceuticals. In June 2014, 136 health insurance providers had contracts with 144 manufacturers according to IMS Health. There were 10,929 contracts in place covering more than 15,952 pharmaceuticals.

Being excluded from a rebate contract has the same effect as partial exclusion from the market, since the contractually set time period (usually two years) stipulates the preferred distribution of the discounted pharmaceuticals, and the drug of the losing supplier is no longer dispensed.

It is necessary to level the competitive playing field for all stakeholders in the health care market: all contractual arrangements between SHI providers and care givers and pharmaceutical companies need to be subject to antitrust and competition regulations (GWB and UWG, respectively). As more and more SHI providers merge, the market leverage of the SHI providers is growing steadily.

SHI-market and pharmaceutical drugs subject to rebate contracts



Source: Illustration of the BPI based on IMS Contract Monitor 2014.

Changes towards the applicability of antitrust laws were implemented following the Act on the Reform of the Market for Medicinal Products (Arzneimittelmarktneuordnungsgesetz – AMNOG), effective as of 1 January 2011. These changes particularly affect the regulations concerning formation of cartels (§§ 1-3 GWB) and the regulatory tools and sanctions allowed by the Federal Cartel Authority (Bundeskartellamt). These regulations, in the discount contract market, have had no effect until now. In addition, the legislation changed the previously dual legal procedure for disputes arising with the SHI providers to a single procedure solely under civil jurisdiction.

In general, selective contracting between manufacturers and SHI providers is undertaken within a highly regulated system characterised by massive market interventions, considerable pressure to discount on the side of the supplier, as well as the monopolistic position of the SHI providers. In order to guarantee working competitive and sustainable drug supply in the long term for the insured, the “regulatory jungle” – including reference pricing and co-payment waivers – needs to be reviewed. Therefore it is necessary to work against the current trends of the generic discount market.

The Act on the Reform of the Market for Medicinal Products (AMNOG)

With the AMNOG coming into force on 1 January 2011, the procedure of the early benefit assessment was implemented as a tool to assess the early benefit in relation to a standard comparative therapy, and to facilitate negotiation of reimbursements for innovative pharmaceutical drugs. For

pharmaceutical drugs with new active substances under patent protection, pharmaceutical companies have to submit a dossier when the product is first placed on the market in Germany at the latest. This dossier is subject to an assessment by the Federal Joint Committee (G-BA). The result of the assessment serves as the basis for negotiations on future remuneration with the Federal Association of Statutory Health Insurance Funds. When no agreement is reached, an arbitrative board has to make the decision on the reimbursement discount. The BPI with its position paper “Dezentral vor zentral” was the first pharmaceutical industry association to contribute to the discussion concerning the system for negotiation of reimbursements. The legislative body took many of the proposed ideas under consideration, but finally made the decision in favour of centralised negotiations, which can only be supplemented with decentralised negotiations in a second step.

By the beginning of September 2014, the G-BA had completed 90 assessment procedures. In six cases the obligation to submit a dossier was waived. This is only possible when the product is expected to cause negligible expenses for the SHI. The assessment of negligibility is based on data concerning expected costs and turnover of the drug with respect to the SHI. As long as the costs of a drug in the outpatient setting do not exceed 1 million Euros within 12 calendar months and on a long-term basis, they are regarded as negligible. However, the applicant has to prove that the turnover will remain below this limit in practice in the long run.

To date, 90 decisions of the G-BA have effected 168 subpopulations that represent 23 million patients in total. Until now, no product has achieved the highest possible

category of additional benefit. Significant additional benefit was achieved 19 times after including all assessed populations. A lower additional benefit was found for 37 subpopulations. In 11 subpopulations, the additional benefit was not quantifiable, while in 100 cases no additional benefit was seen. In one assessment, one subpopulation was even judged to have a lower additional benefit than the comparator. One of the main problems continues to be the comparator treatment stipulated by the G-BA, which the applicant is often not able to adequately integrate into clinical studies.

Overall, it is clear that because the assessments do not reflect the principal conditions of the marketing authorisation (although this is actually a requirement), proving an additional benefit in the early assessment procedure is difficult. This is particularly clear with the approval of endpoints, in the stratification into multiple subpopulations and in the “net balance” approach to benefit and risk.

The selection of the appropriate comparator treatment by the G-BA as the SHI-baseline therapy is a challenge not only for the early benefit assessment process. If the pharmaceutical company is unable to demonstrate an added benefit for the product, the baseline therapy also serves as a cost benchmark for the upper pricing limit in negotiations with the SHI. As a result, four pharmaceuticals were withdrawn from the German market and are therefore now unavailable to patients in Germany.

The AMNOG states that an additional medical benefit for Orphan Drugs is already evident through the marketing authorization. This is consistent because an additional benefit for these drugs was already confirmed by the European Commission by granting the marketing authorisation.

This confirms that with this drug a satisfactory therapy option is available for the first time or has a substantial benefit compared to other available therapies. At first, the G-BA decided to delegate the assessment of the dossiers to the Institute for Quality and Efficiency in Healthcare (IQWiG; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen). Subsequently, the G-BA revised this approach and decided to perform the assessment procedure for orphan drugs below the turnover threshold of 50 million Euro itself.

The results of these negotiations to date have shown that in order to achieve the primary goal of the early assessment procedure, in demonstrating an additional benefit, a change in the bureaucratic process is needed as there is no correlation between the attested additional benefit and the level of the rebate agreed upon. This is hardly surprising: the stated goal of AMNOG is to establish “fair” pricing for new pharmaceuticals. The price fixed for the reimbursement of a medicinal product with additional benefit must also reflect pricing in other countries in Europe, adjusted for turnover and buying power, as well as yearly treatment costs of similar drugs. Finally, the price at market launch is critical. In this, it is clear that the accusation that the pharmaceutical industry is fixing astronomical prices for its products is not valid, considering that there is an average cumulative rebate of 24 % (including an obligatory rebate as per § 130a SGB V) for pharmaceuticals with attested additional benefit.

The option originally contained in the AMNOG to assess the existing drug market (i.e. pharmaceuticals already on the market before 1 January 2011, but still under patent protection thus containing “new actives”), was removed from the SGB V effective 1 January 2011. Instead, further

cost savings in the pharmaceutical market are currently being realised under the continuing price moratorium until December 31, 2017 and a 7 % obligatory discount.

The German Pharmacy Market

Developments in the German pharmacy market present a very heterogeneous picture. Compared to 2012, the total turnover in the pharmacy market*, assessed at manufacturer prices, rose in 2013 by 5.5 % to a total of 28.2 billion Euros. For prescription drugs, there was an increase in turnover of 5.8 %. The turnover of OTC medications increased by almost 7 %.

Turnover developments in the pharmacy market 2010 – 2013

(in million Euros)

	2010	2011	2012	2013	Change vs. previous year in %
Total	25,636.6	26,186.5	26,755.7	28,241.3	5.55
Prescription only	20,403.3	20,750.5	21,245.5	22,487.3	5.85
Pharmacy only	2,823.7	2,903.4	2,904.5	3,064.9	5.52
Non-drugs	1,415.8	1,508.5	1,517.8	1,552.8	2.31
Controlled drugs / narcotics	814.8	835.9	880.0	914.3	3.90
General sales medicines	173.9	183.0	202.5	216.6	6.96
Drugs and Chemicals	5.2	5.2	5.4	5.4	0.00

Source: Illustration of the BPI based on data from Insight Health 2014.

Sales trends in the pharmacy market 2010 – 2013

(packages in millions)

	2010	2011	2012	2013	Change vs. previous year in %
Total	1,557.4	1,605.8	1,556.9	1,637.5	5.18
Prescription only	709.1	723.8	685.6	716.8	4.55
Pharmacy only	650.2	676.7	661.3	700.9	5.99
Non-drugs	142.1	147.7	150.1	156.4	4.20
Controlled drugs / narcotics	45.4	46.5	48.4	50.8	4.96
General sales medicines	10.0	10.5	11.0	12.0	9.09
Drugs and Chemicals	0.6	0.5	0.5	0.5	0.00

Source: Illustration of the BPI based on data from Insight Health 2014.

* For this survey, the wholesale turnovers and direct sales of manufacturers to pharmacies was recorded. Afterwards, these were re-assessed using the manufacturer price. Turnovers of manufacturers with hospitals are not included.

A look at the volume trends in the overall market reveals that there was a slight increase in 2013. The largest changes were seen in controlled drugs and narcotics with a growth of 9.1 %, and in the pharmacy only sector with an increase of 6.0 % compared to the previous year.

When comparing the development of each pharmaceutical drug sector in 2013 according to sub-categories, the largest growth in comparison to the previous year was once again seen in the biopharmaceutical category. All other sub-categories showed either a marginal growth or loss.

Turnover development of pharmaceutical drug sectors according to sub-categories 2010–2013 (in million Euros) in the pharmacy market

	2010	2011	2012	2013	Change vs. previous year in %
Total	25,636.6	26,186.5	26,755.7	28,241.3	5.55
Pharma. drugs for human use	19,144.1	19,345.2	19,443.3	20,437.4	5.11
Biopharmaceuticals	3,915.8	4,184.4	4,656.3	5,086.3	9.23
Others*	851.3	925.1	922.1	947.8	2.79
Phytopharmaceuticals	777.0	758.5	748.7	775.9	3.63
Diagnostics	646.3	667.1	675.3	664.0	- 1.67
Homeopathic medicines	252.8	253.3	256.3	271.4	5.89
Anthroposophic medicines	49.3	52.8	53.8	58.4	8.55

* Hygiene products, injection equipment, disinfectants, side-line products, drugs, medical devices, chemicals, veterinary medicines, nutritional supplements, dietary products

Source: Illustration of the BPI based on data of Insight Health 2014.

In terms of volume, Pharmaceutical drugs for human use increased the most in 2013 by 5.6 %. The sales volumes (packages) of Biopharmaceuticals declined by about 0.6 % in the same time frame.

Sales volumes of pharmaceutical drug segments according to sub-categories 2010–2013 (in million packages) in the pharmacy market

	2010	2011	2012	2013	Change vs. previous year in %
Total	1,557.4	1,605.8	1,556.9	1,637.5	5.18
Pharma. drugs for human use	1,205.4	1,248.4	1,196.9	1,263.8	5.59
Phytopharmaceuticals	122.3	127.3	127.8	133.4	4.38
Others*	126.4	125.8	126.0	131.1	4.05
Homeopathic medicines	49.4	48.7	48.5	49.5	2.06
Diagnostics	29.1	30.3	31.1	32.6	4.82
Biopharmaceuticals	16.8	16.7	17.7	17.6	- 0.56
Anthroposophic medicines	8.1	8.5	8.9	9.5	6.74

* Hygiene products, injection equipment, disinfectants, side-line products, drugs, medical devices, chemicals, veterinary medicines, nutritional supplements, dietary products

Source: Illustration of the BPI based on data from Insight Health 2014.

In Germany, over 100 pharmaceutical companies with highly qualified staff are engaged in producing anthroposophic and homeopathic medicines. Germany is the market leader in the fields of phytopharmaceuticals, anthroposophic and homeopathic medicines. The medicines are used all across the European Union.

In Germany alone, there are some 60,000 physicians who regularly prescribe homeopathic and anthroposophic medicines. Outside of Europe, homeopathic treatments enjoy global popularity, especially in the USA, Central and South America, Asia, India, and South Africa. Anthroposophic medicine is especially popular in North and South America, as well as in Australia and New Zealand.

An analysis of the Top 10 indications according to the Anatomical Therapeutic Chemical Classification (ATC-3) shows an overall slightly positive trend in sales volumes. In comparison to the previous year, the largest growth in sales volumes was seen in expectorants without anti-infectants, followed by topical nasal preparations with 15.1 % and 10.3 %, respectively.

Top 10 leading indication areas (ATC-3) in the pharmacy market 2013 by sales volumes

Indication areas (ATC - 3)	Packages in thousands	% to prev. year	share of total turnover in %	share of total sales in %
Total	1,637,473.9	5.12	100.00	100.00
N02B Other analgesics	150,511.4	7.62	9.19	1.86
R01A Nasal preparations, topical	89,742.2	10.30	5.48	0.72
R05C Expectorants without anti-infectants	74,742.2	15.08	4.56	1.08
V03X Other therapeutic preparations	43,871.0	1.00	2.68	0.71
A02B Ulcer treatments	42,526.3	2.59	2.60	1.54
C07A Beta-blockers, pure	41,309.7	9.15	2.52	0.61
M01A Anti-phlog. /anti-rheumat., non-steroid.	40,132.8	6.15	2.45	0.74
M02A Anti-rheumat. and analgesics, topical	36,482.6	7.35	2.23	0.70
R02A Throat preparations	31,599.1	5.72	1.93	0.42
B01C Anti-platelet treatments	30,090.7	7.84	1.84	1.08

Source: Illustration of the BPI based on data of Insight Health 2014.

The turnover developments in the Top 10 indications according to ATC-3 show the highest increases (as compared to the previous year) in antineoplastic protein kinase inhibitors and other immunosuppressants. The share of these two groups in the total turnover in the pharmacy market was 6.0 % in 2013.

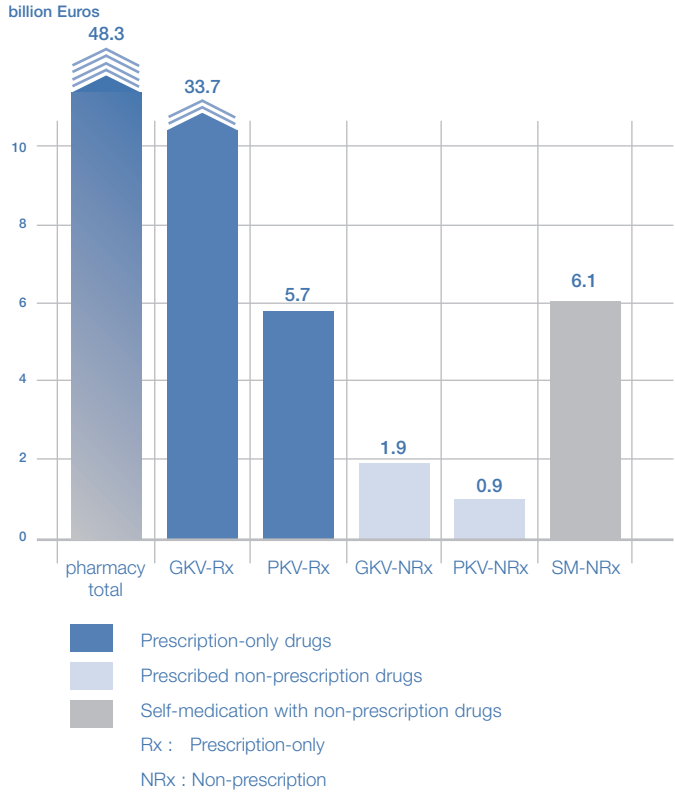
Top 10 leading indication areas (ATC-3) in the pharmacy market 2013 by turnover

Indication areas (ATC - 3)	in thousand Euro	% to prev. year	share of total turnover in %	share of total sales in %
Total	28,241,312.0	5.53	100.00	100.00
L04B Anti-TNF preparations	1,345,952.1	16.62	4.77	0.03
A10C Human insulin and analogs	973,113.4	3.80	3.45	0.79
L01H Antineoplast. protein kinase inhibit.	887,652.2	23.34	3.14	0.02
L04X Other immunosuppressants	809,297.2	20.49	2.87	0.13
N02A Analgesics, narcotics	808,255.2	1.14	2.86	0.52
L03B Interferons	746,559.3	5.83	2.64	0.02
J05C Antivirals for the treatment of HIV	672,928.2	13.16	2.38	0.05
N03A Antiepileptics	658,032.6	3.37	2.33	0.74
N05A Antipsychotics	612,116.5	- 11.03	2.17	0.83
T02D Diabetes tests	600,698.8	- 0.96	2.13	1.75

Source: Illustration of the BPI based on data of Insight Health 2014.

The following illustrations show different sectors of the drug market in pharmacies. The turnover for the pharmacy market, including pharmacy mail-order sales, totalled 48.3 billion Euros in 2013. For prescription drugs assessed with the pharmacy's retail price, IMS Health determined a total turnover of 39.4 billion Euros for 2013. The turnover with prescription-only pharmaceuticals reimbursed by the SHI was around 33.7 billion Euros in 2013. The turnover with prescribed OTC drugs reimbursed by SHI and private health insurance was 1.9 billion Euros and 0.9 billion Euros, respectively. Sales volumes in the area of self-medication with OTC drugs came to approximately 6.1 billion Euros.

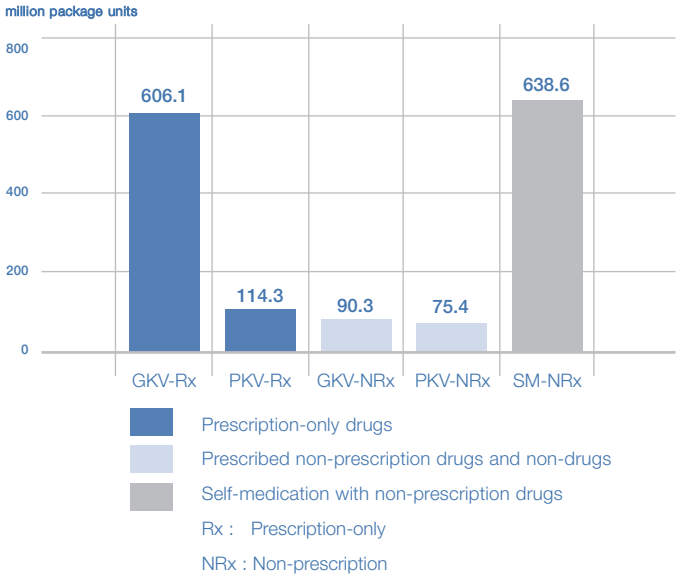
Turnover of pharmaceutical drugs in pharmacies and pharmacy mail-order in 2013 at pharmacy retail prices (in billion Euros)



Source: Illustration of the BPI based on data of IMS PharmaScope® National 2014.

Around 166 million package units of non-prescription drugs were reimbursed by the SHI and private health insurance in 2013, while 639 million package units were bought for self-medication in pharmacies and through pharmacy mail-order services. The volume in package units added up to around 1,524 million package units.

Sales volumes of the drug market in pharmacies and pharmacy mail-order 2013 (in million package units – PE)



Source: Illustration of the BPI based on data of IMS PharmaScope® National 2014.

The reason for the differences between turnover and sales volumes is primarily due to different pricing levels. The price difference between prescription-only drugs and drugs available without a prescription reflect the different competitive environments of these products. Non-prescription drugs are well-established, have been on the market for some time and often have generic competitors. This sector of highly active products also contains many phytopharmaceuticals.

The sector of prescription-only drugs contains many newly developed products, some of them still under patent protection, and whose higher price contributes to covering the high costs of research and development.

The SHI pharmaceutical market

The SHI pharmaceutical market gives an overview of prescriptions as well as turnover financed by the SHI system. Turnovers are calculated on the basis of pharmacy retail prices; therefore, they include the respective wholesaler and pharmacy margins, as well as VAT.

Number of prescriptions paid for by the SHI system 2011 – 2013

Subcategory	2011	2012	2013
Total	679,655,727	676,679,323	688,445,205
Pharmaceuticals*	641,375,152	640,465,652	652,033,583
Diagnostics	24,283,589	24,306,123	25,141,682
Others**	6,390,533	4,947,385	4,150,913
Phytopharmaceuticals	5,043,601	4,679,297	4,881,346
Homeopathic medicines	1,764,365	1,538,930	1,488,220
Anthroposophic medicines	798,487	741,936	749,461

* including biopharmaceuticals

** Hygiene products, injection equipment, disinfectants, side-line products, drugs, medical devices, chemicals, veterinary products, nutritional supplements, dietary products

Source: Illustration of the BPI based on data of Insight Health 2014.

In 2013, an overall volume of 688 million prescriptions were financed through the SHI system. Pharmaceuticals represent around 94.7 % of this total. Looking at changes in the volume of prescriptions since 2011, it becomes clear that prescribed diagnostics have continuously increased, currently making up 3.7 %. Phytopharmaceuticals are prescribed in 0.7 % of cases and homeopathic medicines in 0.2 %.

Turnover financed by the SHI system 2011 – 2013, pharmacy retail price in Euros

	2011	2012	2013
Total	32,151,721,751	32,423,305,650	33,654,408,892
Pharmaceuticals*	30,900,737,014	31,257,569,591	32,552,492,131
Diagnostics	956,474,498	934,081,067	895,009,246
Others**	180,358,178	129,960,399	103,587,713
Phytopharmaceuticals	75,548,976	70,228,324	72,491,494
Anthroposophic medicines	21,085,376	15,895,408	15,528,752
Homeopathic medicines	17,517,709	15,570,861	15,299,556

* including biopharmaceuticals

** Hygiene products, injection equipment, disinfectants, side-line products, drugs, medical devices, chemicals, veterinary products, nutritional supplements, dietary products

Source: Illustration of the BPI based on data of Insight Health 2014.

Development of market shares as financed by the SHI system 2011 – 2013 in %

	Prescriptions			Turnover		
	2011	2012	2013	2011	2012	2013
Total	100.00	100.00	100.00	100.00	100.00	100.00
Pharmaceuticals*	94.37	94.65	94.71	96.12	96.40	96.73
Diagnostics	3.57	3.59	3.65	2.97	2.88	2.66
Others**	0.94	0.73	0.60	0.56	0.40	0.31
Phytopharmaceuticals	0.74	0.69	0.71	0.23	0.22	0.20
Anthroposophic medicines	0.12	0.11	0.11	0.07	0.05	0.05
Homeopathic medicines	0.26	0.23	0.22	0.05	0.05	0.05

* including biopharmaceuticals

** Hygiene products, injection equipment, disinfectants, side-line products, drugs, medical devices, chemicals, veterinary products, nutritional supplements, dietary products

Source: Illustration of the BPI based on data of Insight Health 2014.

The turnover of pharmaceuticals in 2013 was 32.6 billion Euros or 4 % above the levels in the previous year. The market share of pharmaceuticals is 97 %. The relatively small share of phytopharmaceuticals (0.2 %) in SHI spending is primarily due to the lower average price for such products. The same applies to homeopathic medicines, which account for 15.3 million Euros or a mere 0.05 % in SHI expenditures.

Top 10 leading indications (ATC-3) in the SHI market 2013 by sales volumes

Indications (ATC-3)	Prescriptions	% to previous year	% share of total volume	% share of total turnover
Total	688,445,205	1.74	100.00	100.00
N02B Other analgesics and antipyretics	37,991,749	8.05	5.52	1.96
C07A Beta blocking agents	36,950,087	2.19	5.37	1.72
M01A Antiinflamm./anti-rheumat., non-steroid.	35,646,734	0.64	5.18	1.83
A02B Drugs for peptic ulcer and GORD	31,262,265	2.82	4.54	2.34
C09A ACE inhibitors, plain	25,552,594	0.49	3.71	1.04
T02D Diabetes tests	24,632,480	3.46	3.58	2.50
H03A Thyroid preparations	23,512,700	5.17	3.42	1.12
C03A Diuretics	21,550,344	0.02	3.13	1.26
N06A Antidepressants / mood stabilizers	20,816,542	1.17	3.02	2.40
C10A Lipid modifying agents	18,757,476	2.18	2.72	1.33

Source: Illustration of the BPI based on data of Insight Health 2014.

When looking at sales volume in 2012, the “Drugs for peptic ulcer and GORD” and “Thyroid preparations” showed the highest growth rates. Overall the growth in the top ten indication was low and sometimes absent.

Top 10 leading indications (ATC-3) in the SHI market 2013 by turnover

Indication areas (ATC-3)	In million Euros	% to previous year	% share of total volume	% share of total turnover
Total	33,654.4	3.80	100.00	100.00
L04B Anti-TNF preparations	1,604.8	13.56	4.77	0.06
A10C Human insulin and analogs	1,287.3	3.27	3.82	1.76
N02A Analgesics, narcotics	1,018.2	0.31	3.03	1.11
L04X Other immunosuppressants	977.8	15.31	2.91	0.26
L01H Antineoplastic protein kinase inhibitors	955.3	20.26	2.84	0.03
N05A Antipsychotics	876.3	- 9.80	2.60	1.78
L03B Interferons	875.8	3.86	2.60	0.05
N03A Antiepileptics	866.3	3.06	2.57	1.48
J05C Antivirals for the treatment of HIV	853.3	7.90	2.54	0.11
T02D Diabetes tests	842.8	- 4.42	2.50	3.58

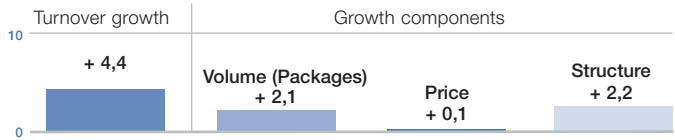
Source: Illustration of the BPI based on data of Insight Health 2014.

With respect to turnover in 2013, “Antineoplastic protein kinase inhibitors“ and “Other immunosuppressants“ had the highest growth rate in comparison to the previous year. The biggest decline was seen in antipsychotics with 9.8 %.

The SHI structural component

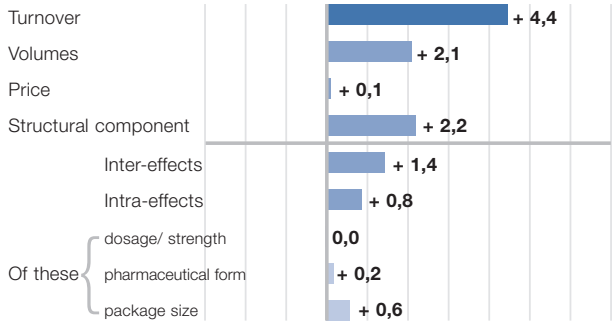
The structural component allows a detailed analysis of trends in factors affecting SHI pharmaceutical expenditures. It is possible to identify to what extent there has been a trend toward the prescription of innovative and patented pharmaceutical drugs. The structural effect is composed of effects within or among products (package size, dosage / strength and pharmaceutical form) and effects within and / or among pharmaceutical sectors as well as indication groups. The SHI structural component study of IMS Health, as a quantitative instrument of market research and health care policy, shows the individual components (price, volume and structure) of changes in turnover.

Growth components in the SHI pharmaceutical market 2013 (changes to previous year in %)



Source: Illustration of the BPI based on data of the IMS® SHI structural component study 2014.

Growth components in 2013 as a cause of the turnover developments in the SHI market, divided into sub-groups (in %), pharmacy retail price



Price basis: pharmacy retail price including VAT, without rebates

Source: Illustration of the BPI based on data of the IMS® SHI structural component study 2014.

In 2013, the IMS structural component was 2.2 %. In the past, this component has been at a significantly higher level. The price level in the SHI pharmaceutical market increased by just 0.1% and volumes by 2.1 %.

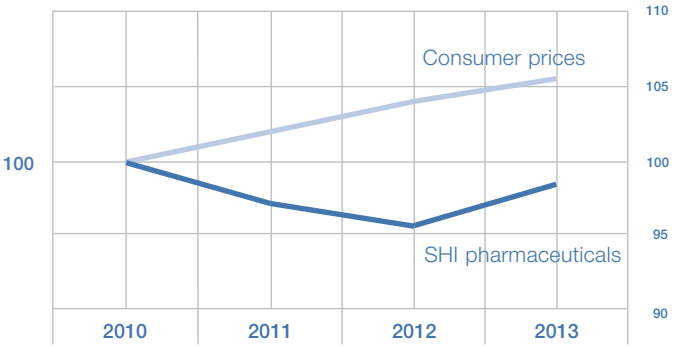
The “Pharmaceutical Atlas” published by the Institut für Gesundheits- und Sozialforschung (IGES) uses the ATC classification, similar to the IMS structural component analysis. The IMS structural component analysis examines all ATC groups (ATC 1 to ATC 4) and thus allows for indication-focussed analysis of the individual growth factors at all levels.

The “Pharmaceutical Atlas” of the IGES takes a different approach. The essential difference to IMS is in the definition of the components. When it comes to the structure of the turnover components, the IGES looks at consumption, treatment approach, generics, dosage/package size, manufacturer and pricing components. There are detailed analyses for the 31 indications with the most prescriptions. The quantitative unit of measure used in the Atlas refers to the Defined Daily Dose (DDD). The IMS Health structural component analysis is based on quantitative units such as package units or tally units.

It has been shown that changes in pricing, volumes and quality all have an influence on expenditure. Innovative pharmaceuticals, which generate high costs in development, naturally are higher-priced, but they also contribute significantly to the treatment of previously untreatable or insufficiently treatable diseases, offering a significant benefit to the affected patients. At the same time, many well-established (often generic) drugs are available for the treatment of less severe diseases. These price levels have been trending downward since 2006, though the actual price level is obscured by rebate contracts.

The SHI-Pharmaceuticals Index, which is based on a slightly different calculation method compared to the figures of the IMS structural analysis, also confirms this decline in drug prices in the SHI system for 2012. This is especially true when compared with the development of consumer prices. Voluntary rebate contracts entered into in 2012 alone resulted in savings of 2.38 billion Euros. Currently, the rebate volumes are still increasing.

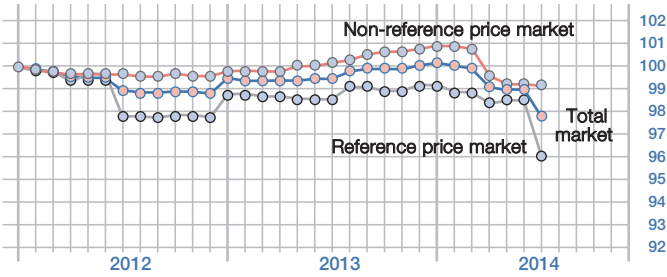
Price development for pharmaceuticals
Price indices in comparison
(2010 = 100)



Source: Illustration of the BPI based on data of the WidO and the Federal Statistical Office 2014.

The consequences of the major interventions in the German pharmaceutical market by to the Statutory Health Insurance Restructuring Act (GKV-ÄndG) and the Act on the Reform of the Market for Medicinal Products (AMNOG), are clearly evident in the illustration below. Prices in the reference as well as the non-reference price markets are continuously decreasing.

Price development according to market sectors between January 2012 – July 2014 (January 2012 = 100)



Source: Illustration of the BPI based on data of the WidO 2014.

The OTC-Market

After positive developments in turnovers of the German OTC market in 2012 (in pharmacy and pharmacy mail-order), turnover again increased considerably in 2013. The turnover for in-pharmacy (+ 6.1 %) as well as for pharmacy mail-order (+ 6.6 %) sales grew in comparison to the previous year. While there was consistent positive growth in the mail-order pharmacy market in previous years (2011 to 2012: + 8 % and 2012 to 2013: + 5.6 % based on sales volumes), the brick and mortar pharmacies sales volumes grew by 5.3 % from 2012 to 2013) for the first time in years.

Despite this positive development, the turnovers are just below those of 2003, the last year in which non-prescription drugs (with a few exceptions) were covered by the SHI. When looking at sales volumes, around 100,000 fewer packages of OTC products were sold in comparison to 2003.

The strongest product category in the OTC market is still pharmacy-only drugs with a turnover share of 75.9 % (share of sales volumes: 77.2 %). They clearly outstrip turnovers achieved by the non-pharmacy-only drugs (turnover share 5 %) and non-drug health products (GMS, Gesundheitsmittel)*, which had 19.2 %

share in overall turnovers in the OTC market. However, in the past few years, the share of non-drug health products in the pharmacy market has been increasing (share in turnover 2009: 16.5 %, in 2013: 19.2 %). When one looks at the corresponding sales volumes, however, it is clear that there were significant price increases, while the increases in sales volumes were relatively moderate (share in sales volumes 2009: 16.3 %; in 2013: 17.3 %).

Development of turnover in the German OTC pharmacy market (In pharmacy & pharmacy mail-order)

Turnover in thousand Euros at pharmacy retail price

	2009	2010	2011	2012	2013
In pharmacy drugs					
- Pharmacy-only	4,919,854.2	4,762,450.7	4,685,196.2	4,691,504.8	4,974,636.8
- OTC	316,642.3	301,170.2	290,249.7	308,122.8	328,118.9
GMS pharmacy	1,001,784.1	1,041,915.6	1,090,349.5	1,118,877.4	1,189,361.1
In pharmacy total	6,238,280.7	6,105,536.5	6,065,795.4	6,118,505.0	6,492,116.8
Pharmacy mail-order (MO)					
- Pharmacy-only	471,687.4	508,822.8	539,232.2	567,677.4	601,439.5
- OTC	28,641.3	30,807.9	32,395.0	37,278.2	39,286.9
GMS Pharmacy MO	133,067.9	145,556.6	170,820.9	200,666.2	218,086.3
MO total	633,396.6	685,187.3	742,448.2	805,621.8	858,812.7
In Pharm. & MO total	6,871,677.2	6,790,723.9	6,808,243.6	6,924,126.8	7,350,929.6

Market share in %	2009	2010	2011	2012	2013
In pharmacy drugs					
- Pharmacy-only	71.60	70.13	68.82	67.76	67.67
- OTC	4.61	4.44	4.26	4.45	4.46
GMS Pharmacy	14.58	15.34	16.02	16.16	16.18
In pharmacy total	90.78	89.91	89.09	88.37	88.32
Pharmacy mail-order (MO)					
- Pharmacy-only	6.86	7.49	7.92	8.20	8.18
- OTC	0.42	0.45	0.48	0.54	0.53
GMS Pharmacy MO	1.94	2.14	2.51	2.90	2.97
MO total	9.22	10.09	10.91	11.63	11.68
In Pharm. & MO total	100.00	100.00	100.00	100.00	100.00

Source: Illustration of the BPI based on data from IMS OTC® Report, IMS® Gesundheits-MittelStudie 2014.

* GMS: Defined as non-drug products competing with pharmaceutical drugs.

Development of sales volumes in the German OTC pharmacy market (In pharmacy & pharmacy mail-order)

Volumes in thousand of package units

	2009	2010	2011	2012	2013
In pharmacy drugs					
- Pharmacy-only	605,068.5	582,758.9	569,669.0	558,597.6	590,662.0
- OTC	45,522.7	42,869.9	41,204.6	41,935.0	43,577.1
GMS pharmacy	127,969.1	127,606.9	126,109.8	127,889.6	132,841.4
In pharmacy total	778,560.4	753,235.7	736,983.4	728,422.2	767,080.5
Pharmacy mail-order (MO)					
- Pharmacy-only	49,760.1	58,842.5	63,137.5	66,938.5	70,462.9
- OTC	2,541.0	2,875.8	3,239.5	3,665.8	3,812.3
GMS Pharmacy MO	8,581.0	10,328.4	12,128.3	14,192.0	15,236.6
MO total	60,882.1	72,046.7	78,505.2	84,796.3	89,511.8
In Pharm. & MO total	839,442.4	825,282.5	815,488.6	813,218.5	856,592.2

Market share in %	2009	2010	2011	2012	2013
In pharmacy drugs					
- Pharmacy-only	72.08	70.61	69.86	68.69	68.95
- OTC	5.42	5.19	5.05	5.16	5.09
GMS Pharmacy	15.24	15.46	15.46	15.73	15.51
In pharmacy total	92.75	91.27	90.37	89.57	89.55
Pharmacy mail-order (MO)					
- Pharmacy-only	5.93	7.13	7.74	8.23	8.23
- OTC	0.30	0.35	0.40	0.45	0.45
GMS Pharmacy MO	1.02	1.25	1.49	1.75	1.78
MO total	7.25	8.73	9.63	10.43	10.45
In Pharm. & MO total	100.00	100.00	100.00	100.00	100.00

Source: Illustration of the BPI based on data from IMS OTC® Report, IMS® Gesundheits-MittelStudie 2014.

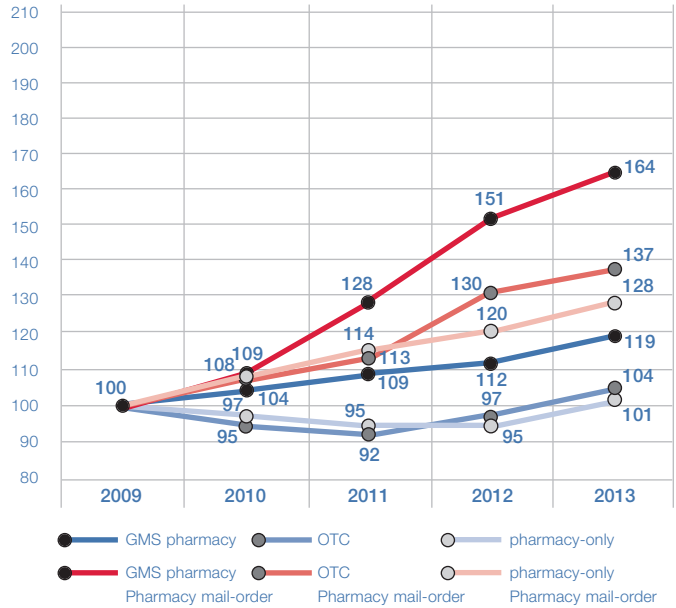
In contrast to the prescription market, the profit of mail-order pharmacies has been of major importance to the OTC market for years. However, there has been a decrease in the previously observed double digit growth rate. In 2013, the pharmacy mail-order market share was 11.7 % of the total OTC market. The market shares shown in the table above are averages, which may significantly vary for individual products. Especially the stronger and more expensive OTC-brands may achieve mail-order shares far above the market average, in some cases more than 30 % for bulk packages. As with in-pharmacy sales, pharmacy-only pharmaceuticals as a product

group (78.7 % of overall sales) have the largest share of turnover (70 %) in the mail-order market. They are followed by the non-drug health products with a 25.4% turnover share and 17 % share in overall sales. The pharmacy mail-order business has become a very established distribution channel over recent years.

Almost every fourth non-prescription product sold in pharmacies or through pharmacy mail-order, is also a non-pharmacy-only product (share in turnover: 24.1 %; share in sales volumes: 22.8 %) and indeed 79.3 % of these products are not drugs. In recent year's non-drug health products, especially pharmacy mail order, have greatly increased. The following graphics show the development of each category within the OTC sector.

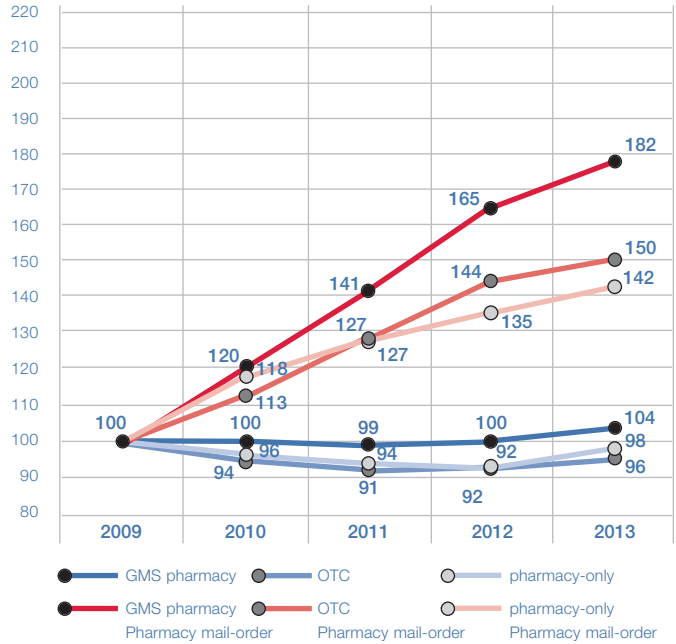
Indexed illustrations of turnover and sales development of over-the-counter drugs in the German pharmacy market (index comparison, based on turnover (pharmacy retail price) 2009 = 100; based on sales volumes: units 2009 = 100)

Developments in turnover (index)



Source: Illustration of the BPI based on data from IMS OTC® Report, IMS® Gesundheits-MittelStudie 2014.

Developments in sales volumes (index)



Source: Illustration of the BPI based on data from IMS OTC® Report, IMS® Gesundheits-MittelStudie 2014.

In the category of non-drugs, higher priced products are increasingly on offer. For example, the average price of a non-drug health product sold in pharmacies increased from 8.31 Euros in 2009 to 9.50 Euros in 2013.

In 2013, the average pharmacy retail price of a product on the German non-prescription pharmacy market was 8.58 Euros. The average price in the category with the highest sales volumes (pharmacy-only drugs) was 8.43 Euros in 2013, and is therefore slightly higher than the average price in 2012 and is also 2.4 % higher than the average pharmacy retail price in 2009. This shows that prices for high-quality OTC drugs and pharmacy-only drugs remained stable over the past years, ensuring an adequate drug supply for self-medication.

Average pharmacy retail price for OTCs/GMS in the pharmacy market including mail-order business

Prices in Euros	2009	2010	2011	2012	2013
Pharmaceutical drugs					
- Pharmacy-only OTCs	8.23	8.22	8.26	8.41	8.43
- Non-pharmacy OTCs	7.18	7.26	7.26	7.57	7.75
GMS* pharmacy	8.31	8.61	9.12	9.29	9.50
Mean value**	8.19	8.23	8.35	8.51	8.58

* GMS: Defined as products competing with pharmaceutical drugs.

** Mean value (weighted by sales volumes in each category)

Source: Illustration of the BPI based on data of IMS OTC® Report, IMS® Gesundheits-MittelStudie 2014.

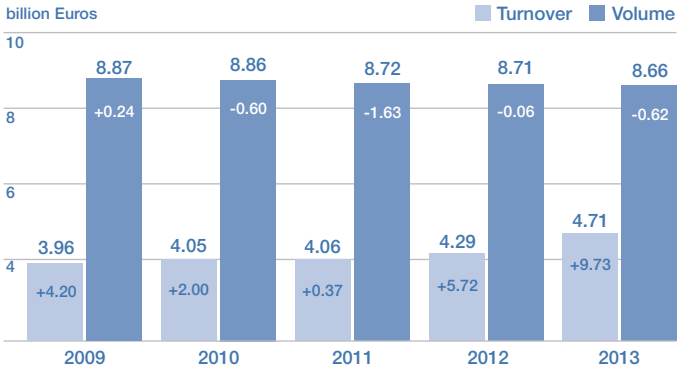
The hospital market for pharmaceuticals in Germany

The inpatient drug supply in German hospitals takes place using either the hospital pharmacy as per § 14 Section 1 Pharmacy Act (German: Apothekengesetz or ApoG) or a hospital-servicing pharmacy as per § 14 Section. 4, 5 ApoG contracted by the hospital. The hospital pharmaceutical market differs significantly from the drug market in outpatient care. Contrary to the outpatient care sector, inpatient institutions are largely autonomous in how they utilize pharmaceuticals. Limitations on prescriptions as they exist in the outpatient sector are not applicable in the inpatient setting. Methodological freedom and the so-called reservation prohibition (§ 137c SGB V) apply. This means that in the hospital setting, unless it is specifically prohibited by a decision of the G-BA following an assessment according to § 137c SGB, everything is allowed within the limits of medical practice and is covered by the SHI.

The purchase of pharmaceuticals by hospitals is usually managed using individual drug lists with around 1,500 to 3,000 pharmaceuticals, which are compiled collaboratively by hospital

physicians and the head of pharmacy within the hospital's drug committee. Pharmaceuticals that are delivered to a hospital, or the hospital pharmacy, are reimbursed outside of the scope of the pharmaceutical drug price ordinance (§ 1 section. 3 Nr. 1 and 2 AMPreisV). This means individual contracts are negotiated with the hospital operator. The prohibition of bonus in kind is also valid for pharmacy-only drugs (§ 7 section 1 number 2b HWG). According to § 116b SGB V, pharmaceuticals for outpatient treatment in a hospital may only be dispensed at the expense of the SHI when a contract as per § 129a SGB V exists between the hospital operator and the respective insurance provider or insurance association. In these contracts, the sales price for drugs dispensed to SHI-insured patients are defined. Billing takes place directly between the hospital and the insurance provider.

Development of turnover in the hospital market 2009 – 2013 (changes relative to the previous year in %)



Source: Illustration of the BPI based on IMS Dataview hospital 2014.

The use of pharmaceuticals is significantly influenced by the remuneration of hospitals. Hospitals are reimbursed at a flat rate for inpatient pharmaceutical therapy. The flat rate reimbursement is based on the German Diagnosis Related Groups System (G-DRG-System). The allocated flat rate reflects the national average cost for a particular treatment. The actual price paid (purchase price) by a selection of hospitals is used as a basis to calculate the average cost. Particularities of individual hospitals are not taken into consideration. Therefore, hospitals have a strong incentive to negotiate their own supplier contract with high rebates. There are no legal requirements for supplier contracts and there is contractual freedom. The G-DRG-System provides a few exceptions to flat rate remuneration when a pharmaceutical cannot be included for computational reasons. This can be the case when a pharmaceutical is very expensive and cannot be specifically allocated to a "typical" treatment (i.e. products for haemophiliacs). In these cases additional remunerations (outside of the flat rate) are made available.

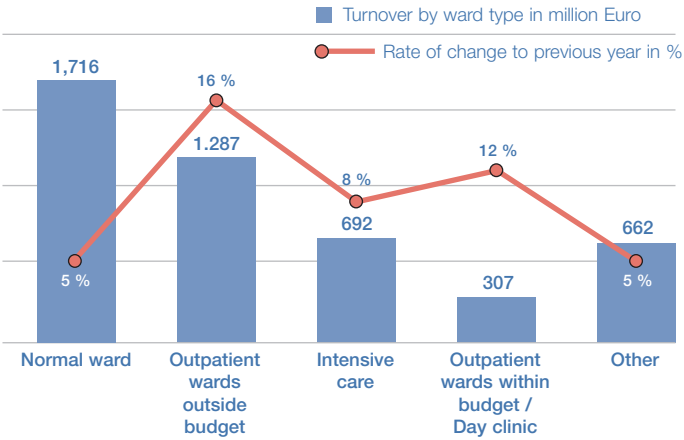
Top 10 leading indication areas (ATC-3) in the pharmacy market 2013 by turnover

Indication areas (ATC-3)	Turnover in million Euros 2012	2013	Changes compared to previous year in %
Total	4,292.0	4,664.1	8.7
L01X Other antineoplastic agents	789.9	918.7	16.3
B02D Antihaemorrhagics	276.9	331.3	19.6
J02A Antimycotics for systemic use	178.9	208.4	16.5
L04X Other immunosuppressants	127.5	155.3	21.8
J06C Polyval. Immunglobul., i.v	111.4	130.3	17.0
J01X Other antibacterials	110.0	122.5	11.4
L01B Antimetabolites	107.3	116.4	8.4
L04B Anti-TNF preparations	106.4	114.5	7.6
N01A General anaesthetics	109.5	111.9	2.1
S01P Oph. antineovascular. prod.	98.6	108.8	10.4
Total TOP 10	2,016.5	2,318.0	14.9

Source: Illustration of the BPI based on data of IMS Dataview hospital 2014.

Another exception is in the case of completely new treatments, where there are currently no comparable treatments on the market (Directives on the implementation of new examination and treatment methods (NUB)). In such cases, the hospital can try to negotiate additional remuneration for these pharmaceuticals via individual contracts with SHI providers. Both possibilities require that the pharmaceutical therapy is not already covered by flat rate remuneration. Whether or not this is the case is assessed and decided by the responsible Institute for Hospital Remuneration System (InEK). Experience shows these exceptions are handled in a very restrictive manner.

Distribution of pharmaceutical turnover in the hospital market 2013 by functional area



Source: Illustration of the BPI based on data of IMS Dataview hospital 2014.

The number of pharmaceutical drugs in Germany

One focus of criticism is the relatively high number of pharmaceutical drugs on the German market in an international comparison. However, in this matter a different approach is required, as the method for counting the number of drugs differs internationally. As of 12 September 2014, there were about 99,000 marketing authorisations/ registrations for pharmaceutical drugs in all indications according to statistics of the BfArM; of these, 47,000 were prescription drugs (including “controlled drugs/narcotics” and T- prescription only drugs).

In Germany, a separate marketing authorisation is required for each pharmaceutical strength and each pharmaceutical form of a single active substance. This means there is a separate marketing authorisation for each cream, ointment or salve of the same active substance. This is a German phenomenon. In other countries, as well as the European Medicines Agency, preparations with the same strength, but different pharmaceutical forms, are still counted as one single marketing authorisation.

Furthermore, BfArM statistics simply represent the maximum number of preparations that may be marketed in Germany. This does not necessarily mean that all of these products are indeed marketed at all times. The granting of marketing authorisation does not necessarily imply the necessity to market the drug. It is not unusual for marketing authorisation holders to place only part of the authorised products portfolio on the market. However, the marketing authorisation of a drug that is not placed on the

market will expire after three years (Sunset Clause). In some cases, pharmaceuticals are later removed from the market, often as a consequence of the AMNOG (early benefit assessment), but in such cases the authorisation and the packaging remain in the statistics of the BfArM.

An extensive spectrum of the pharmaceuticals currently on the market in Germany are presented in the products by Rote Liste Service GmbH ("Rote Liste®", Fachinfo-Service, and Patienteninfo-Service).

The "Rote Liste®", contains 94 % of the pharmaceutical authorised since January 2011. The "Rote Liste®" is open to all suppliers of pharmaceutical drugs. This registry is particularly popular with physicians, therefore most pharmaceutical companies wishing to have their products prescribed by physicians have a vested interest in having their products listed. Drugs intended primarily for self-medication are not listed as extensively as prescription drugs. However, a listing of these self-medication drugs is still relevant, as even non-prescription medications may be covered by the SHI in the context of drug reimbursement guidelines (the so-called OTC-reimbursement list). The "Rote Liste®" is also a reference for other health professionals such as pharmacists.

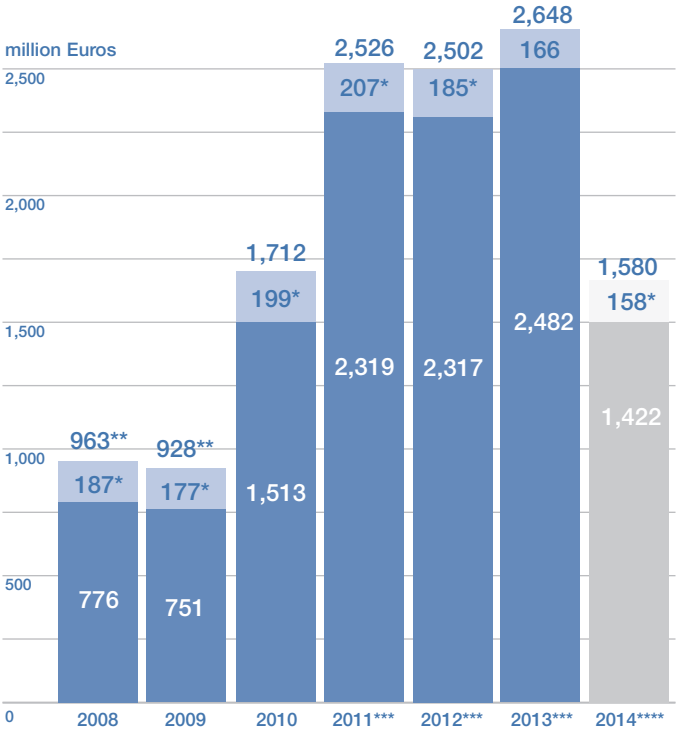
The number of pharmaceutical drugs available on the German market cannot be determined with absolute certainty. In general, the number of drugs available on a single market is a measure of the breadth and depth of the available drug supply and says little about possible oversaturation, since the number of drugs itself does not give information on the actual use.

Interventions in the pharmaceutical drug market – future prospects

The BPI Pharma Data 2014 reflects the ongoing tense situation and challenging prospects for the pharmaceutical industry in Germany. Revenue and costs are increasingly being looked at and evaluated independently of each other. Companies are faced with ever more requirements and restrictions, resulting in continuously increasing costs, and are therefore losing their entrepreneurial margin to offset the burden. This will reduce the diversity of pharmaceutical companies and available pharmaceuticals in the German market. As a result, alternate manufacturers for products with supply shortages and treatment alternatives for patients with unmet treatment needs will disappear.

The sweeping statement that the pharmaceutical expenditures in the SHI have gotten out of hand over the course of the last few years is factually incorrect. SHI pharmaceutical expenditure is comparable to 30 years ago. In 1985 the expenditures were 15.2 % and currently they are 16.2%. As neither the price moratorium was revoked, nor the mandatory discounts returned to their baseline level or abolished, the pharmaceutical industry will continue to shoulder significant burdens in 2014 and 2015. Since 2010, the pharmaceutical industry has paid 11 billion Euros in mandatory discounts alone.

Cost burden of the pharmaceutical industry due to obligatory discounts 2008 – 2014 (in million Euros), manufacturer price in SHI market



* so-called "generics discount"

** Discount decrease due to (among other factors) the price moratorium ending in April 2008

*** price moratorium discount is included

**** Estimates for 2014; based on data for half of the year 2014, the mandatory discounts for the private health insurance (applicable since 2011) sector are not included. Since April 2014 a 7% mandatory discount is applicable

Source:: Illustration of the BPI based on IMS PharmaScope® National 2014.

In addition to the direct discount, rebate payments and other price regulations, further burdens increase the pressure on companies. An example of this is the binding implementation of the Directive 2011/62/EU, the so-called “Falsified Medicines Directive”, which implemented new measures to increase the protection against drug falsification. These additional and cost-intensive regulatory projects require enormous effort. These costs cannot be offset by sales prices because of the constraints of the price regulation instruments and the price moratorium. The artificially absence of inflation as a result of the price moratorium since 2010, only serves to make the situation worse. As total expenditure of the SHI will only increase due to the increasing disease burden of the insured, there is little hope of improvement in the near future. Moreover, the federal government has cut tax subsidies to the public health fund, and slow economic growth in the second and third quarters of 2014 will increase the calls for cost saving measures.

An inter-ministerial project of the federal government brings hope of long-term change. Counterfeit pharmaceuticals, supply shortages, and withdrawal of innovative and established active substances from the market are only selected buzzwords to describe complex problems that have gained the attention of those responsible in politics and administration. The overall tense situation in the pharmaceutical industry can no longer be ignored. The so-called “Pharma dialogue” agreed upon by the governing coalition began in September 2014. Led by the German Federal Minister of Health, together with the Federal Minister of Research and the Parliamentary Secretary at the Federal Ministry of Economics and Technology, representatives from politics, administration, the scientific community and the IG BCE trade union met with representatives of the pharmaceutical industry. The stated goal was to make Germany a sustainable location for pharmaceutical research, development, and production. It remains to be seen, at the end of the dialogue, to what extent tangible results can be achieved based on the mutually defined goals.

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Index

Acronyms

AKG	Arzneimittel und Kooperation im Gesundheitswesen / Pharmaceuticals and Cooperation in the Health Care Sector
AMG	Arzneimittelgesetz / German Medicines Act
AMNOG	Arzneimittelmarktneuordnungsgesetz / Act on the Reform of the Market for Medicinal Products
AOK	Allgemeine Ortskrankenkasse
ApU	Abgabepreis pharmazeutischer Unternehmen / Manufacturer price
ATC Code	Anatomisch-Therapeutisch-Chemische (ATC) Klassifikation / Anatomical Therapeutic Chemical Classification
AVP	Apothekenverkaufspreis / Pharmacy retail price
AVWG	Arzneimittelversorgungs-Wirtschaftlichkeitsgesetz / Economic Optimization of Pharmaceutical Care Act
Barmer GEK	Barmer Gmünder Ersatzkasse
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte / Federal Institute for Drugs and Medical Devices
BIP	Bruttoinlandsprodukt / GDP Gross Domestic Product
BKK	Betriebskrankenkassen
BMBF	Bundesministerium für Bildung und Forschung / Federal Ministry of Education and Research
BMG	Bundesministerium für Gesundheit / The Federal Ministry of Health
BMWi	Bundesministerium für Wirtschaft und Technologie / Federal Ministry of Economics and Technology
BPI	Bundesverband der Pharmazeutischen Industrie e. V. / German Pharmaceutical Industry Association
DAK	Deutsche Angestellten Krankenkasse
DDD	Defined Daily Doses
DRGs	Diagnosis Related Groups
EAFTA	East Asian Free Trade Area
EFPIA	European Federation of Pharmaceutical Industry and Associations
EMA	European Medicines Agency
EU	European Union
F&E	Forschung & Entwicklung / R&D Research and Development
FSA	Freiwillige Selbstkontrolle Arzneimittelindustrie / voluntary auto-monitoring of the pharmaceutical industry
G-BA	Gemeinsamer Bundesausschuss / Federal Joint Committee

GKV	Gesetzliche Krankenversicherung / SHI Statutory Health Insurance
GKV-OrgWG	Gesetz zur Weiterentwicklung der Organisationsstrukturen in der Gesetzlichen Krankenversicherung / The Act on the Further Development of Organisational Structures in Statutory Health Insurance
GKV-SV	Spitzenverband der Gesetzlichen Krankenkassen / National Association of Statutory Health Insurance Funds
GKV-WSG	GKV-Wettbewerbsstärkungsgesetz / The Act to Strengthen Competition in Statutory Health Insurance
GMG	GKV-Modernisierungsgesetz / The SHI Modernisation Act
GMS	Gesundheitsmittelstudie
GWB	Gesetz gegen Wettbewerbsbeschränkungen / The Act against Restraints of Competition
IGES	Institut für Gesundheits- und Sozialforschung / Institute for Health and Social Research
IMS	IMS HEALTH GmbH & Co. OHG
Insight Health	INSIGHT Health Management GmbH
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen / Institute for Quality and Efficiency in Health Care
LCD	Local Currency Dollar
Mio.	Million
Mrd.	Billion
MwSt.	Mehrwertsteuer / VAT Value Added Tax
NCE / NBE	New Chemical or New Biological Entities
OECD	Organisation for European Economic Co-operation
OTC	Over-the-counter
OR	Outcomes Research
PE	Packungseinheit / Package Units
PEI	Paul-Ehrlich-Institut / Paul Ehrlich Institute
Phytos	Pflanzliche Arzneimittel / Herbal Medicinal Products
PKV	Private Krankenversicherung / Private health insurance
ROW	Rest of the World
SGB V	Sozialgesetzbuch V / Social Code Book
SGG	Sozialgerichtsgesetz / Social Courts Act
TK	Techniker Krankenkasse
UAW	Unerwünschte Arzneimittelwirkung / ADR Adverse Drug Reaction
WHO	World Health Organisation
WidO	Wissenschaftliches Institut der Ortskrankenkassen

BPI German Pharmaceutical Industry Association

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