BPI German Pharmaceutical Industry Association

Pharma-Data 2013

Pharma-Data 2013

BPI German Pharmaceutical Industry Association

Table of Contents

Preface

Now that the German parliamentary election of 2013 is history, the question has once again arisen as to how the German healthcare system should be reformed. Usually, the year following an election is characterized by multiple interim acts aimed at stabilizing the financial situation of the Statutory Health Insurance (SHI) system. The pharmaceutical industry is often the target of these governmental interventions and compulsory measures.

This year, things could be different because the SHI providers are entering the new legislative period with heretofore unknown surpluses. Neverthelss, the pharmaceutical industry continues to be vilified as a cost driver, as the past years have shown.

In this, both the political community and media appear to be happy to forget that there is no one homogenous „pharmaceutical industry“, just as there is no one stereotypical member of parliament. The industry is not a monolithic block. Instead, it is a heterogenous assortment of international concerns, purely national enterprises, generics manufacturers, research-driven pharmaceutical companies, biotech companies, manufactureres of anthroposophic and homeopathic medicines, herbal manufacturers and manufactureres of presciption and non-prescription drugs.

The industry faces many challenges. Whether is is the (now expiring) government-imposed compulsory measures such as mandatory rebates and a price moratorium, or the procedure for early benefit assessments, or the question regarding which non-prescription drugs will be included in the reimbursement catalog oft he SHI system, all these regulatory measures and interventions in the free market make life difficult fort he pharmaceutical industry in Germany.

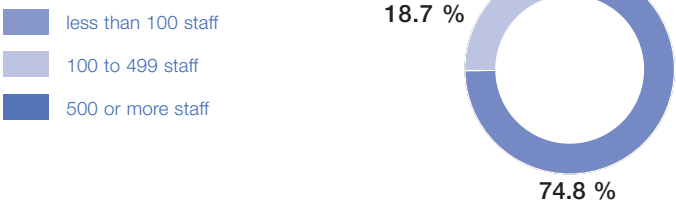
The pharmaceutical industry is more than just a cost driver in the SHI system. The pharmaceutical industry is an economic factor in Germany, an export driver, a significant motor for the German economy and an important employer. At the same time, the products oft he pharmaceutical industry are much more than just a cost driver fort he SHI system: the medicinal products provided by the pharmaceutical industry give hope to ailing people and are important economic goods. Through the use of these products, sick days can be reduced and in-patient treatments can be avoided. Last but not least, these products can provide relief and healing for many people and increase their quality of life.

In general, a fact-oriented and balanced debate regarding the system of supplying medicinal products in Germany is needed. Pharmaceutical drugs are just one cost factor of many. At the same time, they are often life-saving and essential fort he treatment ofmany illnesses. Pharmaceutical companies are of immense significance for the economic strength of Germany, as the more than 100,000 jobs in this sector clearly demonstrate. This 43rd edition of Pharma Data gives background information and facts in an attempt to lay the foundation for a fair and balanced discussion. A multitude of sources of data were tapped for this publication, which are listed in the chapter „Additional information“.

Sector structure

According to the trade register at the Federal Office for Statistics, for the year 2011, a total of 854 pharmaceutical companies* were registered in Germany. Over the course of the last 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 methodical differences on the other hand. 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. These data, however, are only partially captured by the Federal Office for Statistics.

Companies according to size in 2011 in %



Source: Calculation of the BPI, based on data of the VCI 2013 and of the Federal Office for Statistics 2013.

* In the “cost structure statistics”, the Federal Office for Statistics shows 248 companies (reporting category 20+). There are an additional 355 companies with less than 20 employees. The large number of registered companies can also be explained by the existence of many marketing authorization holders who are considered pharmaceutical companies.

The pharmaceutical companies include mid-tier 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 854 companies mentioned above. It is still true that nearly 95 % 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 its over 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.

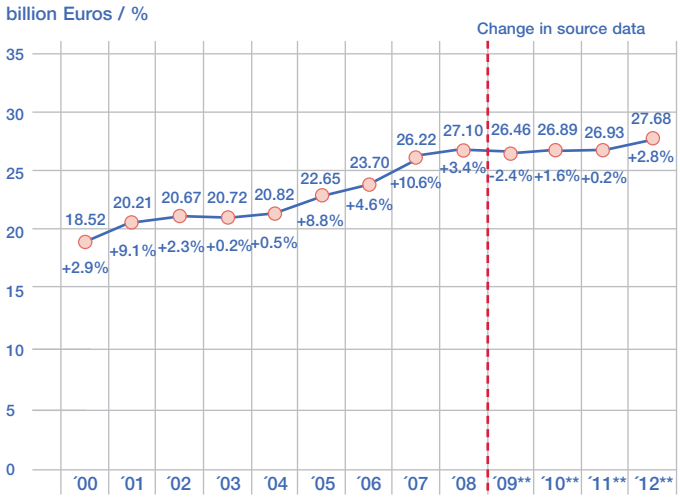
Production

In 2012, the pharmaceutical industry in Germany produced pharmaceuticals valued at 27.7 billion Euros.

This represents an increase of 2.8 % compared to the year 2011. Domestic production is highly dependent on pricing, pharmaceutical drug imports as well as export demand.

Pharmaceutical Production* from 2000 – 2012**

(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.

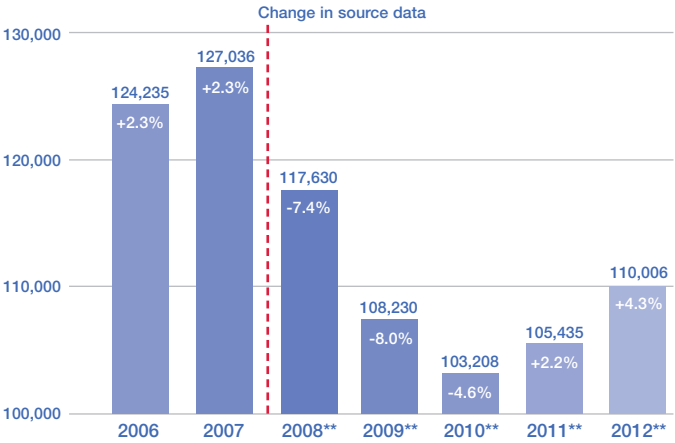
** Since 2009 the GP 21 (pharmaceutical and similar goods) has replaced the GP 244.This new statistical classification prevents a direct comparison with values from previous years.

Source: Illustration of the BPI, based on data of the Federal Office for Statistics 2013.

Employees

In 2012, 110,006 staff were employed by companies producing pharmaceutical goods. The good economic climate has led to a record high in employment in 2012 in Germany. An annual average of over 41.5 million people were employed. According to the Federal Office for Statistics, this was the highest employment rate since reunification. In comparison to 2011, ca. 416,000 people more were employed in 2011, which corresponds to an increase of ca. 1.0 %.

Development of staff numbers* in the pharmaceutical industry 2006 – 2012 (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 2013 and the Federal Office for Statistics 2013.

Foreign trade

In 2012, pharmaceuticals valued at 54.2 billion Euros were exported from the Federal Republic of Germany. This corresponds to an increase of 7.5 % compared to the year before. At the same time, pharmaceuticals valued at 38.2 billion Euros were imported into the Federal Republic of Germany. This constitutes an increase of 1.5 % compared to 2011. The main supplier of pharmaceuticals to Germany is USA, followed by Switzerland, the Netherlands, Great Britain, and Ireland.

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

* 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 2013 and the Federal Office for Statistics 2013.

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

	2008	2009	2010	2011	2012
USA	6,501.50	7,193.86	6,253.57	5,728.23	7,110.13
Switzerland	4,333.46	4,845.13	5,463.70	6,376.50	7,007.76
Netherlands	1,224.94	1,182.51	1,954.97	4,127.49	4,615.10
Great Britain	1,682.74	2,299.63	2,569.65	3,313.73	2,990.15
Ireland	8,985.03	7,934.95	6,751.54	4,653.31	2,880.42
France	1,842.35	1,741.96	2,331.83	1,754.11	2,013.64
Italy	1,415.20	1,546.32	1,702.05	1,792.42	1,975.65
Belgium	1,318.56	1,292.36	1,487.63	1,822.54	1,516.20
Spain	1,038.00	1,205.72	2,479.95	1,023.40	1,149.15
Sweden	1,029.17	1,106.91	1,217.70	1,035.44	1,143.18
Others	4,692.21	5,203.30	5,798.67	5,993.16	5,784.86
Total	**34,063.16**	**35,552.63**	**38,011.25**	**37,620.32**	**38,186.24**

* 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).

Source: Illustration of the BPI based on data of the VCI 2013 and the Federal Office for Statistics 2013.

Main importers of pharmaceutical drugs* from Germany (in million Euros)

	2008	2009	2010	2011	2012
USA	5,752.41	5,861.38	4,979.74	5,665.32	8,157.45
Netherlands	4,367.44	4,423.55	6,553.10	6,676.76	6,537.49
Belgium**	11,616.23	10,918.27	10,495.80	7,531.28	4,544.95
France	2,249.68	2,255.97	2,525.98	2,752.75	3,596.67
Switzerland	2,419.29	2,865.12	2,818.90	3,221.24	3,340.33
Great Britain	2,443.45	2,440.71	2,770.38	2,421.35	3,176.76
Italy	2,045.26	2,192.60	2,465.54	2,484.00	2,530.89
Russian Federation	1,099.05	984.30	1,390.49	1,626.93	1,842.74
Spain	1,207.85	1,254.42	1,375.34	1,449.00	1,629.52
Japan	924.48	1,151.52	1,162.35	1,326.45	1,619.03
Others	13,424.20	13,018.14	14,595.64	15,268.29	17,244.29
Total	**47,549.32**	**47,365.97**	**51,133.24**	**50,423.36**	**54,220.11**

* 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 rate is explained by the VCI as due to special circumstances.

Source: Illustration of the BPI based on data of the VCI 2013 and the Federal Office for Statistics 2013.

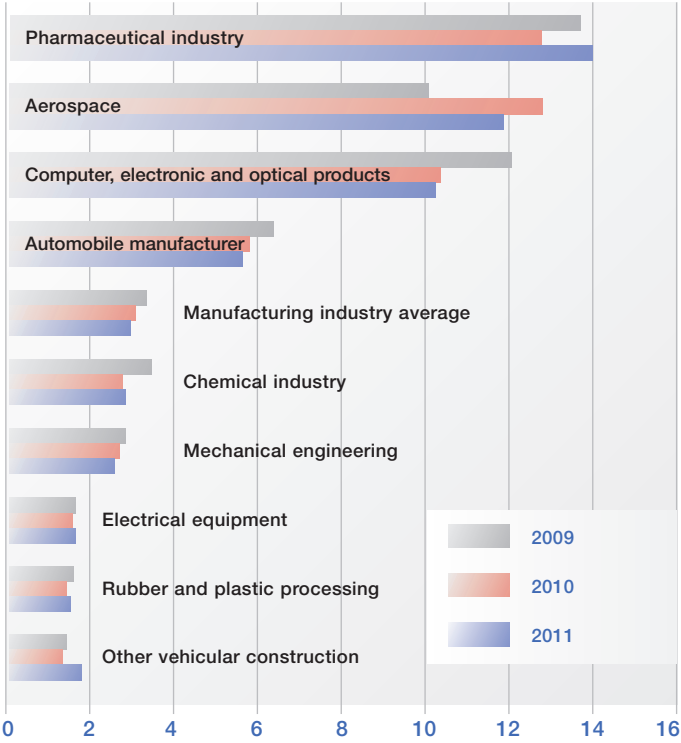
The long road to pharmaceutical innovation

In 2011, 2.9 % of the gross domestic product was invested in research and development R&D, putting Germany within easy reach of the Lisbon goal of 3 %. Of these investment, 1.9 % was contributed by the business sector. Research facilities and universities shared the rest. According to the most recent report of the Expert Commission for Research and Innovation (in German Expertenkommission für Forschung und Innovation (EFI)), the pharmaceutical industry invested 14 % of their own turnover in internal R&D projects. In this, the pharmaceutical sector is ranks highest in R&D investments, clearly ahead of the automotive and mechanical engineering industries as well as the chemical industry, making it the most research-intensive industry in Germany.

This trend is not restricted to Germany alone. Published at the end of 2012, the “EU Industrial Investment Scoreboard” ranked the pharmaceutical industry first, with a R&D-quota of more than 15 %, as the most innovation intensive industry. This was in the EU, Japan, and the US.

The high R&D expenditures of the pharmaceutical industry are partially due to the 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 could rise above one billion Euros.

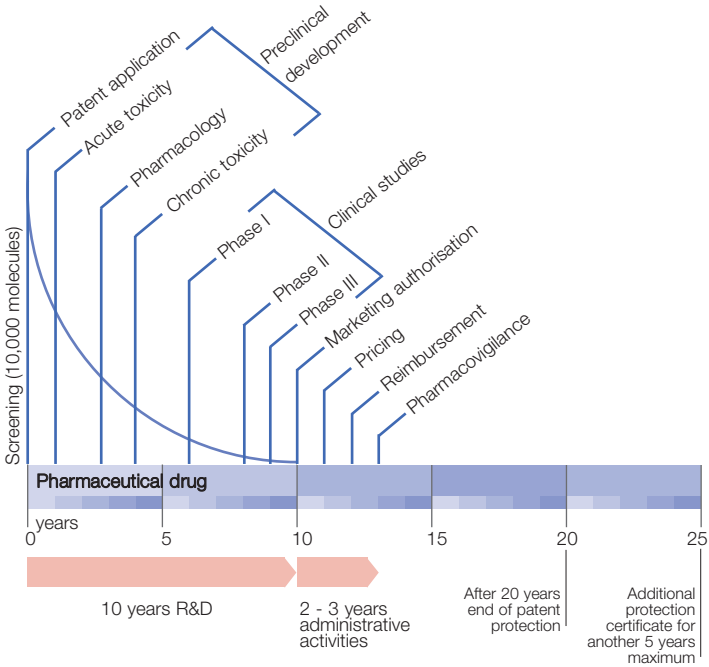
Share of internal R&D expenditures relative to sales turnover by sector in %



Source: Illustration of the BPI based on data of the Stifterverband Wirtschaftsstatistik 2013.

From among 10,000 molecules that are 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 authorization process after about eight to ten years.

Phases of pharmaceutical drug research and development in the EU



Source: Illustration of the BPI based on the European Federation of Pharmaceutical Industries and Associations (EFPIA) 2013.

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

Should a drug candidate achieve the end of phase III study endpoints (for example higher efficacy or lower adverse effect compared to the accepted treatment), the authorization 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 required for the marketing authorization 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 authorization of a product, pharmaceutical companies perform further clinical trials and investigations. These studies are conducted in the context of pharmcovigilance. They serve to systematically monitorthe safety of an authorized pharmaceutical with the intention to discover, assess and understand adverse events 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 in 2012 revealed the following distribution of R&D expenditures across the different phases of drug development and authorisation:

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

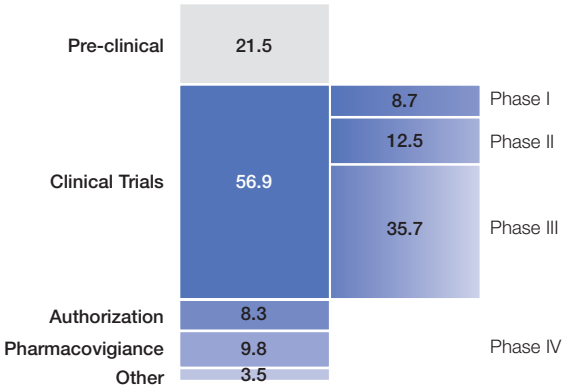


Illustration of the BPI based data from PhRMA, Annual Membership Survey 2012.

In the currently ongoing discussion regarding healthcare expenditures, the costs of drug development repeatedly comes up. These costs have been estimated to be around 900 million US-dollars by a working group headed by Joseph DiMasi, 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 for newly authorized drugs. The estimates also reflect the costs for the large number of unsuccessful development projects, as well as the opportunity costs associated with these project (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, the R&D expenditures still amount 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, 149 authorisation with new active substances (as per § 25 AMG) were registered (versus 101 in 2011)*.

* New actives as defined in § 48(2)1 AMG, 2012 statistics of the the Federal Institute for Drugs and Medical Devices (BfArM). According to the Drug Commission of the German Medical Association 22 new actives were authorized. The difference between the number of „new actives“ and new substances as per § 25 des Arzneimittelgesetzes (AMG) results from the fact that each strength and pharmaceutical form oft he 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, 96 of the new substances counted for 2012 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 tot he 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 dynamic biotech locations worldwide: at the beginning of the second quarter The Federal Ministry of Education and Research (BMBF) published the results of a study of the status quo of the German biotech industry.

The German biotechnology industry, according to the 2012 BMBF report, has continued to grow. Dedicated biotechnology firms* have generated a record turnover of 2.9 billion Euros (+ 11 %) with around 17,430 employees (+ 7 %), showing considerably job growth. In addition is the number of “mostly biotech**” companies grew from 552 to 565. Among those are 20 new founded – there have not been so many startups in the last ten years.

* The OECD defines a dedicated biotechnology firm as a biotechnology active firm whose predominant activity involves the application of biotechnology techniques to produce goods or 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”.

The R&D expenditures have however decreased. At 934 million Euros it is clearly below the billon mark (2011: 975 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 2013

Bench mark data of the corporate landscape	2007	2008	2009	2010	2011	2012
Biotech-Companies	496	501	531	538	552	565
Number of other biotech companies	91	92	114	125	126	128
Employees (dedicated biotech companies)	14,360	14,450	14,950	15,480	16,300	17,430
Employees (other biotech active)	15,210	15,520	16,650	17,000	15,570	17,760
Turnover* (dedicated biotech companies)	2.01	2.19	2.18	2.37	2.62	2.90
R&D-expenditures* (dedicated biotech companies)	1.05	1.06	1.05	1.02	0.98	0.93

* in billion Euros.

Source: Illustration of the BPI based on BMBF 2013, www.biotechnologie.de and Biocom AG 2013.

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 66 companies who are comitted to developing pharmaceutical drugs and have authorised a total of nine new drugs in the previous years. These companies faced a lot of challenges in connection with drug development. In comparison to 2011, the number of candidate actives in clinical testing has decreased from 109 to 93. 83 of these have undergone testing in early phase (Phase I and II) trials, while ten products have reached the Phase III stange most relevant for authorization. Six 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 specialized know-how regarding the realization of clinical trials and the authorization process. The latter also have an established distribuation network. In 2012, Ernst & Young registered 90 alliances: cooperations, 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 2012 increased to 578. These clinical development projects focus mainly on cancer treatment, autoimmune products and vaccines. The R&D expenditures of the involved companies are well invested:

The turnovers generated with biopharmaceuticals increased by 11 % to around 6 billion Euros in the past year. This means that genetically engineered medications have achieved a market share of more than 20 %. The number of employees in the medical biotechnology sector increased by 1 % to ca. 36,000.

The innovative activities of the pharmaceutical industry are not restricted to biopharmaceuticals, however. In 2012, the Federal Institute for Drugs and Medical Devices (BfArM) authorized more than 2,400 (2011: more than 2,500) 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 manifold 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 and also the roman scholar Pliny the Elder viewed willow bark as a medicine.

Only in 1828 was it managed to isolate a therapeutic active substance from willow bark. This substance was named salicin after the scientific name of the plant from which it was derived, Salix.

Salicylic acid itself has 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 the widely-known substance Aspirin®.

Since then, the original pharmaceutical forms have multiplied. Today, tablets (sublingual, chewable, effervescent, delayed-release, coated, or oral dispersible) granulate, 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 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 such as the medical journal 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 a 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.

A survey commissioned by the Federal ministry of economics already confirmed the central role of the pharmaceutical advances for the productivity of German society: in Germany, from 1998 to 2008, premature death decreased by 22 % and the number of employees on sick leave decreased from 4.1 % to 3.4 % in the same time (in 1976 it was almost 6 %). This attributed to the use of innovative pharmaceutical drugs.

Innovative pharmaceuticals like monoclonal antibodies (mAb) have been effectively used for years alongside immunotherapy as a treatment for breast 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 only around 70 %. Around the turn of the millennium, according to the Robert-Koch-Institute (RKI) it was already 81 %. This positive data is certainly due to improved preventive measures, but also the use of innovative cancer drugs – like the antibody trastuzumab, which is effective in 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 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 frame. In women this value improved from 50 % to 60 % for the same observation period. It should be noted that even though a significant increase in the survival rate was recorded, for the same period, due to an ageing population, the number of new illnesses 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 in the last 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 is hardly predictable what the situation concerning reimbursements and the market environment for a development program initiated now will look like in eight to twelve years when the product will be ready for launch. As such, the economic basis required for innovations – the ability to plan costs – is missing for companies which mainly generate their turnover in Germany.

The Act on the Reform of the Market for Medicinal Products (AMNOG) and the SHI System Modification Act passed in 2010 are a case in point: the SHI Modification Act is a cost-cutting measure which put in a place a particularly long price moratorium until end of 2013 as well as an increase of the mandatory discounts by 10 %, especially for innovative medicinal products. The AMNOG is associated with especially drastic changes for pharmaceutical companies. By the end of 2013, 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 constant change of the framework conditions. 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.

The Act to improve the health care service delivery by the SHI funds (2011) and the newest Amendments of the German Medicines Act (2012 and 2013) have also changed the regulatory framework.

The immediate results of these regulatory changes have led research-driven pharmaceutical companies to put drug development programs “on ice”. In the summer of 2012, the BPI conducted a survey of its members regarding the priority given to innovation. Almost 90 % of the respondants 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 % if the respondants also stated that promising development programs for prescription medications had been currently put on hold.

Another salient example for the dampening effects of the AMNOG on innovation is found in the field of paediatric medicines.

Children are not small adults. The dose and efficacy of administered pharmaceuticals do not behave proportional to body weight or volume. Medicines authorized for adults still are often prescribed for children. Pharmaceutical form, dosaging, and some excipient(s) such as ethanol make it unsuitable for pediatric use.

A study of the European Network on Drug Investigation of hospitals in different countries, showed for example 39 % of all pharmaceuticals prescribed to children were not designated for pediatric use ("Off-Label-Use"). For about 50 % of the drugs available for pediatric use In German hospitals, are used with no adequate tolerability and safety data exists. This is by no means trivial.

A salient example is dosing. If a child weighs half of what an adult does, then they receive half of the adult dose- this is a widespread rule of thumb. However, since the total body clearance* of children is higher (relative to body volume) than adults', this means that children may be underdosed.

This is only one aspect. In addition, there is a paucity of data on metabolization, possible effects of „Off-Label-Use" on developing organs and the influence on their rapidly changing metabolic processes.

In 2007, the EU Commission's new Regulation 1901/2006 sought to improve the pharmaceutical treatment of children. Besides giving incentive for the development of new active substances for paediatric use, the regulation also introduced a new Paediatric Use Marketing Authorization (PUMA) for established pharmaceuticals in paediatric care that protects pharmaceuticals authorized under this procedure as intellectual property (despite the active substance itself being off-patent).

* The rate at which a drug is removed from the body, considered as a single unit, the sum of renal clearance and metabolic (hepatic) clearance, expressed as volume per unit time.

In Germany, however, since 2011, medicinal products authorised under Article 38 Section 1 of the Paediatric Regulation are automatically considered „drugs with new active substances“ and therefore are subject to the early benefit assessment procedure.

This means that the incentives put in place by the EU five years ago to improve the supply of paediatric medicines are for nought. In its 5-year report (EMA/428172/2012) on the effects of the Paediatric Regulation the European Medicines Agency (EMA) reports that only one application for a PUMA has been submitted since 2007.

The methodology used in the early benefit assessment procedure for new active substances requires clinical trial data. PUMA, however, are granted for established active substances based on bridging studies and literature data. In particular, data on dosing in various paediatric populations is gathered, which is normally not available in the context of „Off-Label-Use“. In addition, pharmaceutical forms adapted to a particular age group may also be granted a PUMA. These products truly deliver an added benefit, but this benefit cannot be shown through the methodology applied in the early benefit assessment procedure.

R&D Programs

Policies on Research and Development (R&D) are intended to give incentives for companies to conducted R&D by reducing the risks associated with these programs and by mitigating the impact of marketing failures and the disadvantages faced by small and medium-sized enterprises. Innovation-driven companies are of particular interest. These companies face the highest hurdles for market entry. However, these companies are drivers of the structural transformation of the German

economy and secure the economic future of this country. Therefore, they deserve special support.

Due to their size and sometimes their company culture, the smaller innovation-driven pharmaceutical companies often encounter significant barriers in their ability to forge cooperations with research institutions.

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), some particularly successful companies 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 pahrmaceutical industry. Therefore, overcoming the financial hurdles associated with the phase from early drug development to market entry (the „valley of death“) is a major challenge for these companies.

In the context, it is necessary to address the R&D-support provided for innovative mid-tier companies in a special way. Supporting start-up companies is not the only way to give incentives. It is also possible to incentivize 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.

With support programs for R&D, the decision-making on R&D would most likely be more risk averse.

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 inlation 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 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) 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 tot he small companies. For example, in a market sector where the largest companies generated billions in turnover, a company with 100 million Euros annual turnover would be considered mid-size.

Because of the integration of R&D, production and distribution, mid-tier pharmaceutical companies usually do not conform tot he EU recommendations for SME classification. They often employ more than 250 employees or their turnover/ asset level is above the threshold, so they receive less support and often are categorically excluded from certain support measures. However, these companies are definitely “small” relative to the company size distribution within the pharmaceutical industry, which is dominated by companies with more than 10,000 employees.

On the one hand, these companies represent the opportunity to finance R&D without risk capital investments and using internal expertise and market knowledge, on the other hand these companies do not have access to the R&D budgets of large companies.

Therefore, an SME definition based on the size of a company relative to the averages of employee numbers, turnover and balance sheet totals of the largest companies within a sector would be more useful. In the interim, the BPI has pushed for doubling the current thresholds from 250 to 500 employees and from 50 million to 100 million Euros annual turnover.

Future Trends

For biopharmaceuticals there is an enomormus 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 individualization of therapies is already noticeable, as well as testing of individual drug effects or side effects of pharmaceutical drugs due to the use of pharmacogenomic or metabolomic examinations in the context of „stratifed medicine“, which allows the analysis of differences between patient groups and makes these the basis of different therapeutic approaches.

Thirty-one active substances which help in stratifying patient population are already on the market today. For 22 of these pharmaceuticals, diagnostic pretesting is required to determine the expected efficacy and invidivual 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. End of 2012, the EU Commission granted a marketing authorisation to the first gen 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.

According to the Generics Industry Association, biosimilars have been authorized in three substance classes in Germany: epoetins, used in anaemia treatment, the granulocyte colony-stimulating factor (G-CSF) Filgrastim, used for preventing febrile neutropenia during chemotherapy, and Somatropin, a growth hormone. These three substance classes were responsible for 62 million euros in turnover in the SHI system in 2012.

However, there is huge untapped potential in this sector. In 2014, biopharmceuticals with an overall turnover of ca. 370 million Euros will go off-patent in Germany. Das Potential ist jedoch groß. The Generics and Biosimilars Initiative (GaBi) forecasts that, worldwide, twelve biopharmaceuticals with an overall turnover of 67 billion US-dollars will lose their patent protection by 2020.

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

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 centers like 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, along with the relevant national and international regulatory requriements and other aspects – such as the cooperation between contract research organisations, compentency centers and authorities and factors such as study subject safety, patient information, insurance and legal issues.

In clinial 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. They are investigated in a clinical trial.

The results of this research must be submitted by the applicant 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 from these 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 authorized.

Clinical trial are divided into Phases I, II, III and IV. Until Phase III, the investigations are before authorization, Phase IV-investigations are afterwards.

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 at most 100 micrograms of the active. 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, the investigation is usually conducted in a small group of 20-30 healthy volunteers, usually men, in special research institutes.

In phase II trials, the substance is tested in patient volunteers suffering from symptoms / diseases for which the substance is intended as a treatment. 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 optimization, 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 pharmaco-economic data. Relevant aspects associated with patient benefit, such as surrogate parameters, quality of life are of increasing importantce, 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 the a result, the Unites States also continue to dominate the field of clinical research. This is demonstrated clearly by the fact that around 50 % of all the study centers 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 various other information available on the international clinical trial scene. 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 are from the United State.

A review published by the EMA analysed the information submitted with marketing authorisation applications with 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.

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

Number of study centers 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.

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

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

Number of clinical trials 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.

Average number of patients per clinical trail 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.

On average, in the EU / EEA / EFTA** region, each study center 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 Afrika, Asien, Osteuropa, Australien) an average of 17 patients were participating.

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

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 problem.

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 authorization holders in Germany to report all cases involving serious adverse reactions occurring in Germany to the relevant national authority within 15 days (see § 63c "Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften").

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" as per § 63 German Medicines Act serves to monitor, collect and evaluate risks associated with pharmaceutical drugs.

When safety measures are deemed necessary to protect patients, these measures are implemented immediately. Usually, these measures are implemented by the pharmaceutical company, but sometimes they 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 include changing the patient information leaflet or even taking the drug off the market. Many pharmcovigilance procedures (so-called referrals) are primarily triggered on a European level and coordinated by the EMA and run as Urgent Union Procedures (Regulation (EC) 726/2004 as amended by Regulation (EU) 1235/2010 in context of 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 extrapolating 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 is 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 authorization, is of the highest importance for furthering drug safety and so for quality management of treatments.

Reports of side effects

According to the BfArM, the authority received around 52,427 individual case reports of adverse reactions originating in Germany in 2012, 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 (86 %). The total number of case reports originating in Germany in 2012 was around 24,800. While the number remains largely stable relative to the previous year the number of case reports, the number of reports originating outside the EU has on account of legal requirements continued to increase considerably.

According to the PEI, 20,997 adverse reaction reports were received in 2012. Sixty four percent of these were spontaneous reports, and 34 % originated from clinical trials; consumer reports made up 0.9 %. Due to higher usage, the proportion of reports related to monoclonal antibodies has continued to increase. As in previous years the majority of reports have been received from pharmaceutical companies (around 70 %).

EU-wide exchange of safety

In the field of drug safety (pharmacovigilance), the rapid exchange of information between the individual 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 concerning pharmacovigilance is used whenever one of the member states identifies a suspected change of the benefit-risk ratio of a given pharmaceutical drug which might require changes to the approval status.

Both German national competent authorities cooperate closely 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), the pharmaceutical drug commissions of the health care professions, as well as with pharmacovigilance centers that collect reports of adverse drug effects.

“Rote Hand Brief” as a direct health professional communication

The “Rote Hand Brief” is an instrument for direct health professional communications concerning information on 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 oblige 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. The members of the pharma associations are required to use the symbol of a red hand with the wording “Important information concerning a pharmaceutical drug” on envelopes as well as on letters. In particularly urgent instances, it is necessary to also communicate this information verbally, via fax or through the public media (press, radio, television).

The global pharmaceutical market

In 2012, the global turnover of pharmaceutical drugs totaled 736 billion Euros (962 billion US-Dollars), an decrease of 0.3 % compared to the previous year.

Development of the global pharmaceutical market

	2008	2009	2010	2011	2012
Total market (billion Euros)*	611.8	636.1	682.5	738.4	736.2
Total market (billion US-Dollars)	799.0	830.8	891.3	964.8	961.5
Change compared to previous year (in %)		4.0	7.3	8.2	- 0.3

* 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 = 1.306: 1).

Source: Illustration of the BPI based on data of IMS World Review Review 2013.

More than 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 1.4 % to 267.1 billion Euros, which represents 33 % of the global pharmaceutical turnover in 2012. At the same time, even the European pharmaceutical market decreased by 6.5 % to 186.4 billion Euros, while on the contrary Latin America increased its pharmaceutical turnover significantly in 2012 by 3.0 % to 55.9 billion Euros.

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

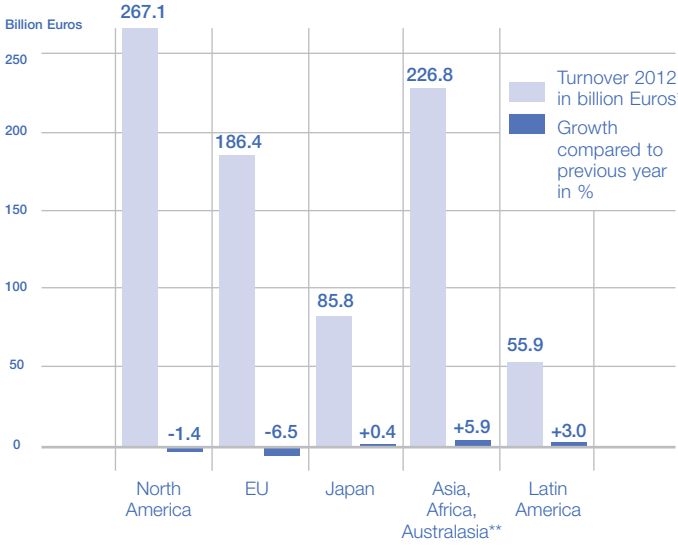
Land	Turnover 2012 (million US -Dollars)	Growth to LCD 2012 (%)*	Turnover 2012 (million Euros)**
USA	326,892	- 1	250,298
Japan	112,067	0	85,809
China	81,698	22	62,555
Germany	42,333	- 6	32,414
France	36,674	- 8	28,081
Brazil	29,112	- 6	22,291
Italy	26,231	- 8	20,085
Canada	21,877	- 2	16,751
Great Britain	21,635	0	16,566
Spain	19,935	- 12	15,264

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

** 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 = 1.306: 1).

Source: Illustration of the BPI based on data of IMS World Review Review 2013.

Global pharmaceutical market by region 2012



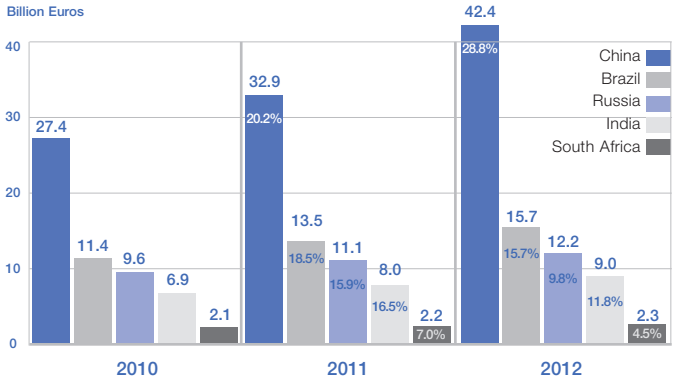
* The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro = 1,306: 1).

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

Source: Illustration of the BPI based on data of IMS World Review 2013.

The economic influence of the five emerging markets Brazil, Russia, India, China and South Africa (summarized under the expression "BRICS") has increased significantly in the last years. This development also includes the pharmaceutical sector. The turnover with pharmaceuticals in 2012 in these countries totaled ca. 81.6 billion Euros, which constitutes an increase of 20.4 % versus the previous year (ca. 67.8 billion Euros). The pharmaceutical turnover has increased continuously in all five markets over the past three years. In contrast to the more pessimistic prognoses for other pharmaceutical markets worldwide, the outlook for the BRICS countries' pharmaceutical markets foresees continued growth in turnover. The significance of these markets for the pharmaceutical industry will continue to increase in the next years.

Turnover* in BRIC countries 2010 – 2012
(Changes relative to previous year in %)



LCD: Local currency dollar - currency fluctuations in the individual countries are not reflected, allowing comparisons between the individual countries.

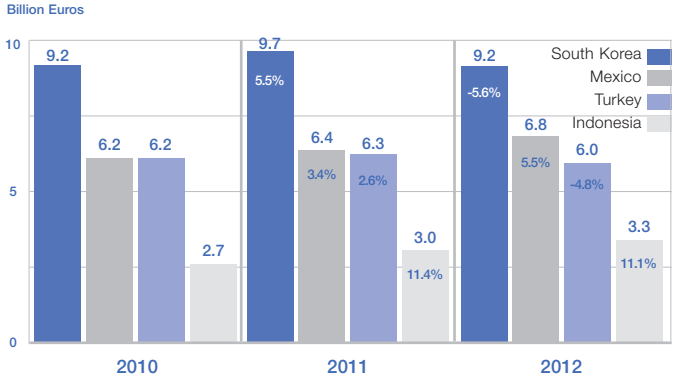
* The Euro values are based on a recalculation of the market data of the base values in US Dollars (Exchange rate: US Dollars in Euro 1.306: 1).

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

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

Four promising markets from the “Next-Eleven” countries are summarized under the expression SMIT countries (South Korea, Mexico, Indonesia and Turkey). These are also classified as second tier emerging markets. The graph “Turnover* in SMIT countries 2010 – 2012” shows the dynamic development in the four pharmaceutical markets.

Turnover* in SMIT countries 2010 – 2012
(Changes relative to previous year in %)



LCD: Local currency dollar - currency fluctuations in the individual countries are not reflected, allowing comparisons between the individual 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: 1.306).

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

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 personalized medicine in the form of individualized 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 2012 (Million USD)	Growth*** to LCD 2012 (%)	Turnover* for 2012 (Million Euros)****
Germany**	42,333	-6	32,414
France**	36,674	-8	28,081
Italy**	26,231	-8	20,085
Great Britain**	21,635	0	16,566
Spain**	19,935	-12	15,264
Belgium**	5,952	-8	4,557
Greece	4,820	-20	3,691
The Netherlands	4,440	-11	3,400
Sweden**	4,257	-6	3,260
Austria**	4,041	-6	3,094
Portugal	3,882	-13	2,972
Denmark**	2,563	-6	1,962
Finland**	2,524	-5	1,933
Ireland**	2,350	-4	1,799
Luxembourg	230	-6	176
Total	181,867	-7.3*****	139,254

* 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 the individual countries are not reflected, allowing comparisons between the individual 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: 1.306).

***** The total growth in LCD 2011 of - 7.3 % is a weighted value (unweighted: - 7.9 %).

Source: Illustration of the BPI based on data of IMS Health World Review 2013.

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 2012 shows that, in absolute volume, Germany, France, Italy, followed by Great Britain represent the largest pharmaceutical markets. In comparison to the previous year, nearly all the European pharmaceutical markets shrank considerably.

In the following, 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 2012” shows the overall turnover and growth of the pharmaceutical market in these countries. The by far largest market is Poland, with nearly 5 billion in turnover. Romania, the Czech Republic, Hungary, and Slovakia are also in the top five markets in this group of countries. The strongest growth was seen in the Bulgarian and Estonian pharmaceutical markets in 2012.

Total pharmaceutical market of Central and Eastern Europe* 2012

Turnover in million Euros**

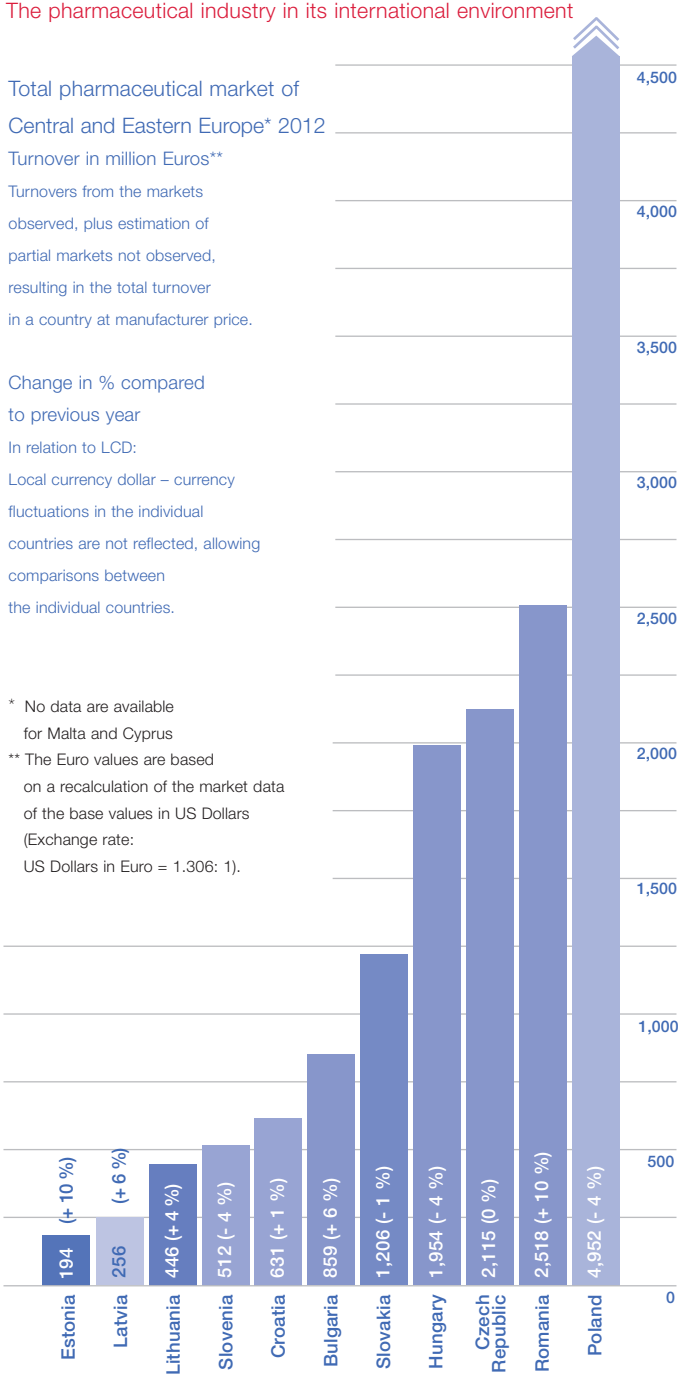
Turnovers from the markets observed, plus estimation of partial markets not observed, resulting in the total turnover in a country at manufacturer price.

Change in % compared to previous year

In relation to LCD:
Local currency dollar – currency fluctuations in the individual countries are not reflected, allowing comparisons between the individual 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 = 1.306: 1).



Source: Illustration of the BPI based on data of IMS World Review 2013.

Over the next five years, IMS Health is predicting 0.9 % 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 5.3 % The five most important markets are expected to grow by 0.9 %.

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

Europe	2012 – 2017
EU top five member states	0,9 %
EU member states	0,9 %
Non-EU countries	2,9 %
Global market	5,3 %

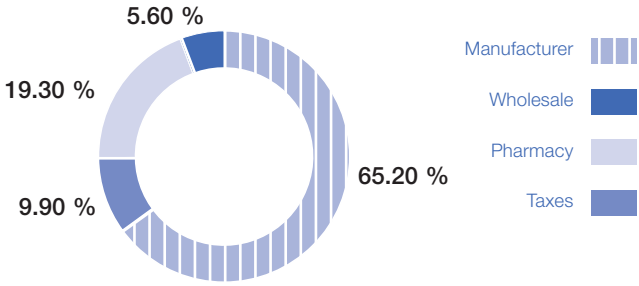
Source: Illustration of the BPI based on data of IMS Market Prognosis Global 2013.

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 (2011)
– Based on pharmacy retail price



The values constitute a unweighted mean value for Europe.

Source: Illustration of the BPI based on EFPIA-Data 2013.

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 August 2013)

Country	Standard VAT rate (%)	VAT rates applied to drugs Prescription (%)	OTC (%)
Belgium	21.0	6.0	6.0
Bulgaria	20.0	20.0	20.0
Denmark	25.0	25.0	25.0
Germany	19.0	19.0	19.0
Estonia	20.0	9.0	9.0
Finland	24.0	10.0	10.0
France[1]	19.6	2.1	7.0
Greece	23.0	6.5	6.5
Great Britain[2]	20.0	0.0	20.0
Ireland[3]	23.0	0.0 - 23.0	0.0 - 23.0
Iceland	25.5	25.5	25.5
Italy	21.0	10.0	10.0
Croatia	25.0	5.0	25.0
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
The Netherlands	21.0	6.0	6.0
Norway	25.0	25.0	25.0
Austria	20.0	10.0	10.0
Poland	23.0	8.0	8.0
Portugal	23.0	6.0	6.0
Romania	24.0	9.0	24.0
Sweden	25.0	0.0	25.0
Switzerland	8.0	2.5	2.5
Slovakia	20.0	10.0	10.0
Slovenia	20.0	9.5	9.5
Spain	21.0	4.0	4.0
Czech Republic	21.0	15.0	15.0
Hungary	27.0	5.0	5.0
Cyprus	18.0	5.0	5.0

[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 starting December 31, 2013: 21 %

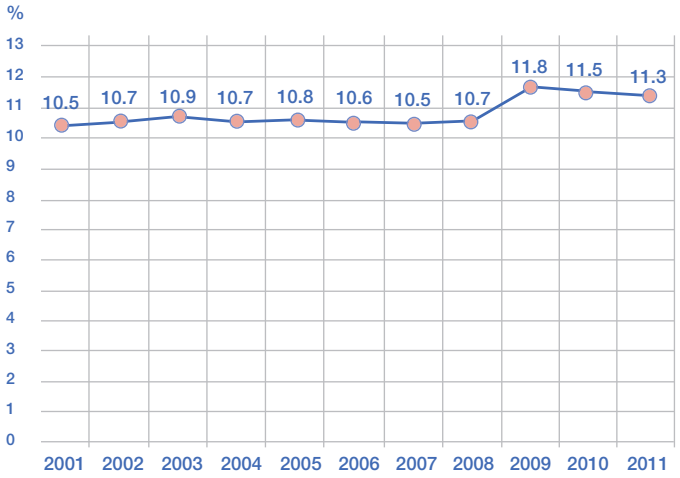
Source: Illustration of the BPI based on the European Commission 2013.

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 analyzing expenditures, it is important to note that a conclusive evaluation based solely on these figures is not possible, especially when comparing health systems internationally. This requires a more detailed and in-depth analysis of, for example, organizational structures or social circumstances and frameworks. However, the percentage of the GDP that a society dedicates to its health care system reflects the importance that society places on the health care system. 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 %



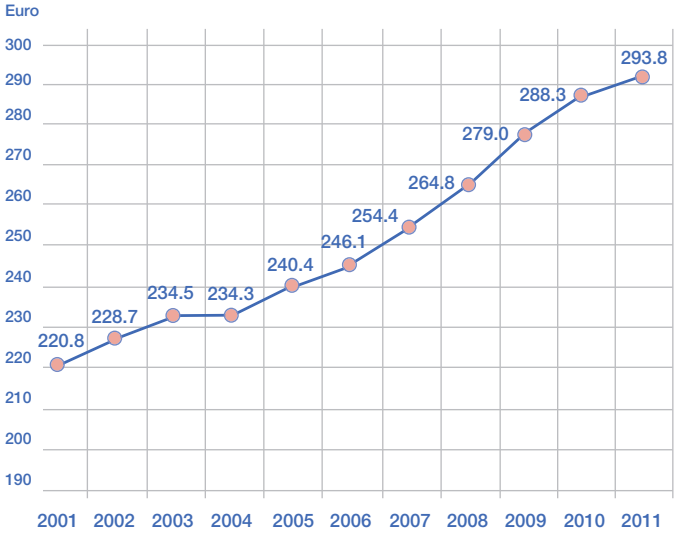
Source: Illustration of the BPI based on data of the Federal Statistical Office 2013.

The share of health care expenditures of the GDP has remained relatively stable in Germany over the course of the years: between 2001 and 2008, this percentage has been between 10.5 % and 10.7 %. The relative increase to be seen in 2009 and 2010 is partially due to a statistical effect resulting from a decrease in the GDP during these two crisis years.

The nominal health care expenditures in Germany have been on the rise continuously for years and, by 2011, were at 293.8 billion Euros. This constitutes an increase of 4.8 % compared to 2010.

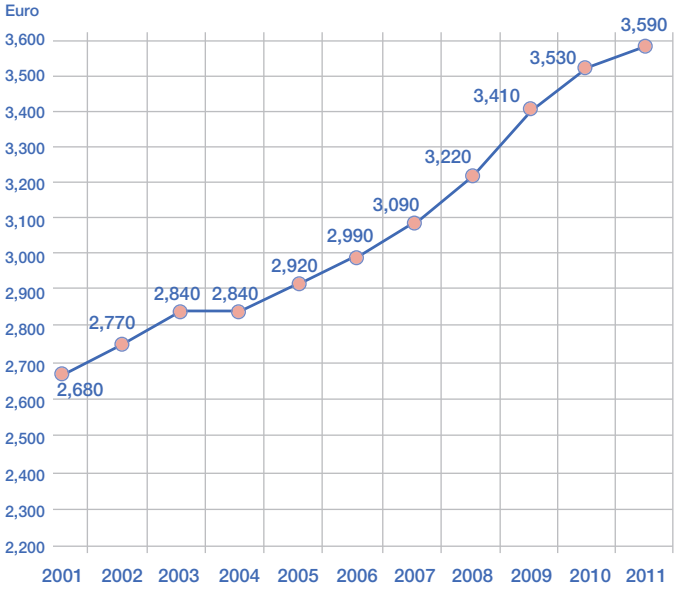
The health expenditures per inhabitant have, as the following graph will show, in the time frame 2010 to 2011 increased by 1.7 % from 3,530 Euros to 3,590 Euros.

Development of nominal health care expenditures (in billion Euros)



Source: Illustration of the BPI based on data of the Federal Statistical Office 2013.

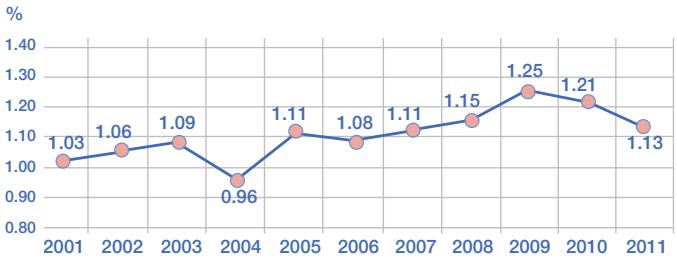
Development of health care expenditures per inhabitant (in Euros)



Source: Illustration of the BPI based on data of the Federal Statistical Office 2013.

In 2011, the share of the SHI expenditures for pharmaceutical drugs, expressed as a percentage of GDP, decreased again by 0.08 % to 1.13 %.

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



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

Source: Illustration of the BPI based on data of the Federal Statistical Office 2013.

According to current data for the crisis year 2011 from the Federal Statistical Office, more than 4.9 million people, i.e. ca. every ninth employee, were working in the German health care sector. The number of jobs in the health care sector rose by 1.9 % in 2011 compared to the previous year. The primary cause of this rise is an increase of health professions (e. g. physicians and other medical staff) and social professions (e.g. geriatric care). In 2011, the largest number of staff was employed in outpatient, inpatient and day-patient care health care facilities.

Because of the ageing society in Germany with a structural shift towards older, multi-morbid people and increasing disease chronification owing to lifestyle and nutritional habits, the 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 the last 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 seems to be a distant prospect.

The development of SHI expenditures is subject of health care political discussions on a regular basis. For many years, the SHI expenditures have been around 7.0 % of GDP (2011: 6.7 %). In 2011, the SHI expenditures for drugs were 1.13 % (2010: 1.21 %) of GDP and therefore again showed a slight decrease in 2010. The SHI expenditures for drugs did not increase faster compared to 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 earned income
-> Increase in the number of mini-jobs
-> Salary receipt with simultaneous increases in other sources of income
-> Decreasing pension payments with an increasing number of pensioners
-> Shift toward 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

The reforms during the past years have not led to a sustainable stabilization 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 Optimization of Pharmaceutical Care Act (Arzneimittelversorgungs-Wirtschaftlichkeitsgesetz, AVWG), introduced in 2006, mainly focused on cost reduction only 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 in the health care sector. The Statutory Health Insurance Restructuring Act (GKV-ÄndG 2011) 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 constitutes a measure purely for cost reduction. From the perspective of the pharmaceutical industry, the increase in the mandatory discounts of a maximum of 16 % and the heretofore longest price moratorium lasting three and a half years 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 Euro in 2011 and 2012 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.

In the course of further reforms, the increasing trend toward standardization of therapies needs to be stopped. At a time where the pharmaceutical industry is ever more capable of developing individualized treatment options and applying them in medical practice, the manifold 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.

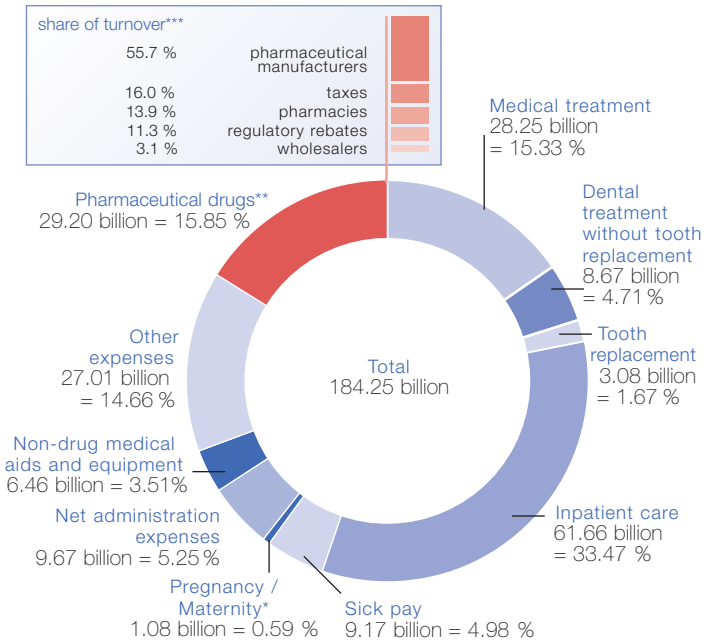
A first step toward a financially sustainable reform of the SHI system was performed with freezing the employer's contribution and uncapping the upper limit of the supplemental premiums. This way it was possible to partly decouple the health care costs and labor costs. Furthermore the supplemental premiums can be used as regulating measure of the SHI market. The insured persons are 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 increase the supplemental premiums.

In general, health care reforms should contribute significantly to deregulation and streamlining of administration in favor 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 still remains true. 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) 2012
(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 as well as savings due to voluntary rebate contracts of the pharmaceutical industry are accounted for.

*** The shares in turnover cannot be directly applied to the absolute numbers of the drug expenditures in published in KJ1 because the absolute number in the ring diagram already reflects the mandatory discounts.

Source: Illustration of the BPI based on KJ1 2013; Drug prescription report 2012.

Inpatient care, at 61.66 billion Euros in 2012, is the most cost-intensive sector of the SHI system. The combined expenditures for pharmaceutical drugs (29.20 billion Euros) and for medical treatment (28.25 billion Euros) amount to 57.45 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 15.9 % of the total SHI expenditures.

When analyzing the SHI pharmaceuticals expenditures, the amounts the different trade levels contribute to these costs are often neglected, i.e. the proportion of the wholesalers' and pharmacies' margins, and the Value Added Tax. If a given pharmaceutical drug at manufacturer price costs one Euro, on average, one needs to add the wholesaler margin, the pharmacy margin as well as 19 % Value Added Tax. The pharmacy retail price would total just about 12 Euros. This price is only valid as an operand, as obligatory discounts, pharmacy discounts, and patient co-payments are deducted, leaving the actual burden on the SHI significantly lower.

Irrespective of this, the rising pharmaceutical expenditures of the last years are partially 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, the shift in services has not been followed by a shift in the required funding.

The general public often does not realize that manufacturers as well as wholesaler pharmacists are required to grant an obligatory discount for the stabilization of the SHI expenditures. In addition in 2011, the wholesalers had to burden an obligatory discount of 0.85 % based on the manufacturer price and in the beginning of 2012 a wholesaler margin was re-assessed. Since this time, the wholesaler rebate has been discontinued, because the targeted savings of the SHI can be achieved with a new arrangement of the wholesaler margin. In addition to the obligatory discounts already described, patients also contribute to the stabilization of SHI spending through their 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 % - 16 % outside of the reference price (SGB V, § 130a Section 1a and § 130a Section 3)
- 10 % so-called generic discount, applied to reference price (SGB V, § 130a Section 3b)
- 6 % for OTx (SGB V, § 130a Section 1)
- Price moratorium (SGB V, §130a Section 3a)
- Vaccination discount (SGB V, § 130a Section 2)
- 16 % in hospital use / compound products (SGB V, § 130a Section 1)

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 wholesalre 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 2013.

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)
- 6 % rebate for OTx-Products, not applicable to drugs under reference pricing
- redemption of the obligatory discount up to 6% (§ 130a Section 1a)
- 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)

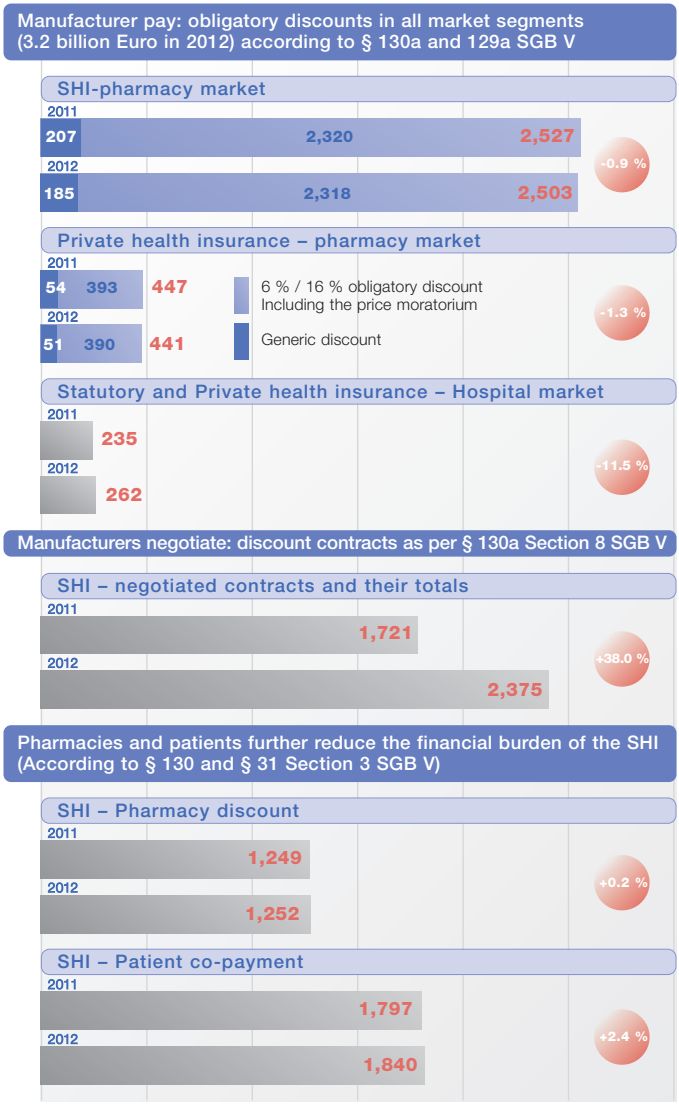
Patients

- 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 2013.

The 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. There is a trend that shows that the obligatory discounts are adjusted depending on 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 2013. The obligatory discounts are based on certain priciples and include several exemptions, which are summarized briefly below.

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



* There was a special wholesaler rebate in 2011, in 2012 the wholesale margin was reduced

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

In 2012, the cost burden for the pharmaceutical industry due to the obligatory discounts (SHI and private health insurance in pharmacy and hospital markets) amounted to approximately 3.2 billion Euros. The small- and medium-sized enterprises are particularly hard hit by these additional costs because they are unable to cross-subsidize the expenditures from other parts of their product palette. Such political interventions contradict the official commitment to supporting small- and medium-sized enterprises. State interventions accelerate the consolidation of the market in favor of larger pharmaceutical companies or companies with very diverse product portfolios.

Discount / Rebate Contracts in the SHI System

Since 2003, the SHI providers have had the legal option (§ 130a sect. 8 German Social Code V) to negotiate individual rebate / discount contracts with pharmaceutical companies. In the first few years, this regulation 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 the 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 cartel laws and after involvement of the EU Commission was the Act to enhance the organizational Structures of Statutory Health Insurance passed. This law provides that when entering into contracts as per German Social Code V § 130a sect. 8, procurement law is applicable.

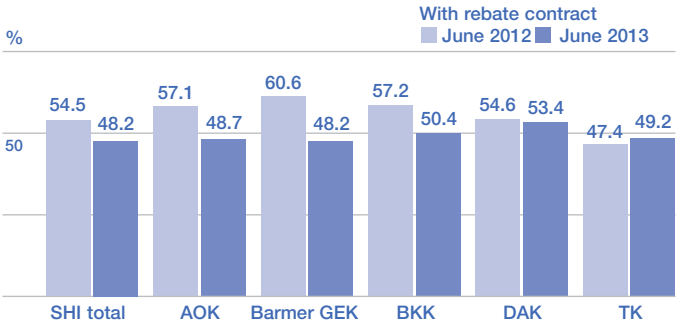
The Act for the Modernization of Procurement Law of 24 April 2009 is also of great importance. This regulation requires the calls for tender to be divided into partial and/ or specialist lots,

something that can be helpful to small- and medium-sized enterprises. But 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 coming into force of the Second Act amending the German Medicines Act and other regulations on 26 October 2012, the rule of 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 could again raise unpleasant legal questions, e.g. regarding the obligation for calls for tender for rebate contracts for drugs under patent protection.

Meanwhile, the number of drugs subject to rebate contracts is on a consistently high level for all SHI providers. In June 2012, the BEK (Barmer Ersatzkasse) had the highest market share of rebated drugs (61 %) in the generics segment. The share varies by to contract durations and individual tender.

Share of discounted drugs in different Statutory Health Insurance providers (market share in %)



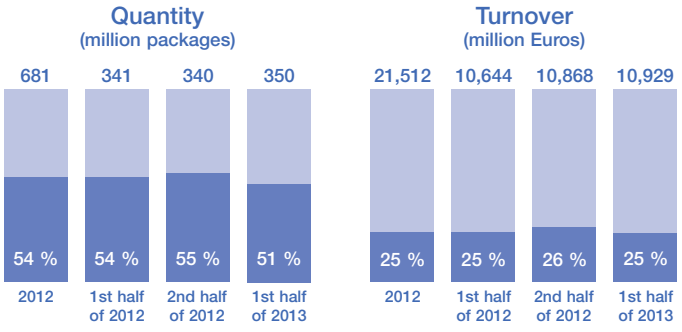
Source: Illustration of the BPI based on IMS Contract Monitor 2013.

According to IMS Health, nearly half of the dispensed medications in the SHI market were subject to rebate contracts as of June 2013. In December 2011, 152 health insurance providers had 11,256 rebate contracts in place with 63 pharmaceutical companies covering 31,581 pharmaceuticals. In December 2012, 147 health insurance providers had contracts with 176 manufacturers according to IMS Health. There were 14,003 contracts in place covering more than 31,942 pharmaceuticals.

Being excluded from a rebate contract has the same effects as a 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 outbidded supplier is not distributed any longer.

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 cartel 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 2013.

Regarding the applicability of cartel laws, changes in this direction were implemented pursuant to the coming into force of 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 until now no effect. In addition, the legislation changed the previously dual legal procedure for disputes arising with the SHI providers to a single procedure under solely civil jurisdiction.

In general, selective contracting between manufacturers and SHI providers is undertaken within a highly regulated system characterized by massive market interventions, considerable pressure to discount on the side of the, as well as the monopolistic position of the SHI providers. In order to guarantee working competitive and sustainable drug supply on 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 in order to allow the assessment of the early benefit in relation to an adequate comparative therapy and to allow the negotiation of reimbursement for costs of innovative pharmaceutical

drugs. For pharmaceutical drugs with new active substances under patent protection the pharmaceutical companies have to submit a dossier at the latest when the product is first placed on the market in Germany. This dossier is subject to an assessment of the Federal Joint Committee (G-BA). The result of the assessment serves as the basis for the negotiations of the future remuneration with the Federal Association of Statutory Health Insurance Funds in the form of a discount on the manufacturer price. Without an agreement 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 on a system for negotiation of reimbursements. The legislative body has considered many of the ideas, but made the decision for centralized negotiations at the end, which can only be complemented with decentralized negotiations in a second step.

Until the end of August 2013 the G-BA has completed 48 assessment procedures. In three cases the obligation to submit a dossier was waived. This is only possible when the product is expected to only cause negligible expenses for the SHI. The assessment of negligibility is based on the data provided to the SHI about the expected costs and the expected turnover of the drug with the SHI. As long as the expenses for outpatient care do not exceed 1 million Euros within 12 calendar months they are regarded as negligible. However, the applicant has to prove in practice that the turnover will remain below this limit in the long run.

To date, 48 decisions of the G-BA have effected 78 subpopulations. Until now, no product has achieved the highest possible category of additional benefit. A significant additional benefit was achieved 9 times after including assessed populations. A lower additional benefit was found for 18 subpopulations. On the contrary in 43 cases, the assessed did not show any additional benefit. One of the main problems continues to be the

comparator treatment stipulated by the G-BA, which the applicant is often not able adequately integrate into clinical studies.

Overall, it is clear that because the assessments do not reflect the principle information 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 in the approval of endpoints, in the stratification into a multitude of subpopulations and in the „net balance“ approach to benefit and risk.

The selection of the appropriate comparator treatment by teh G-BA as the SHI-baseline therapy is a challenge not only fort he 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 as the upper limit for price negotiations with the SHI representatives. As a result, four pharmaceuticals were withdrawn from the German market and are therefore 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 certified by the European Commission by granting the marketing authorization. This confirms that with this drug a satisfactory therapy option is available for the first time or where another therapy is available the new drug proved to have a substantial benefit. 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). In the further course of the process the G-BA revised this approach and decided to perform the assessment procedure for orphan drugs below the turnover threshold of 500 million Euro as well.

The results of these negotiations to date have shown that the early assessment procedure's primary goal is to demonstrate an added benefit, which makes a change in bureaucratic effort accompanying the process necessary, for there is no correlation between the attested added benefit and the level of the rebate agreed upon. This is hardly surprising, as the price fixed for the reimbursement of a medicinal product with added benefit must also reflect the 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 16 % obligatory rebate as per § 130a SGB V) for pharmaceuticals with attested added benefit.

A relatively recent chapter in the „AMNOG"-sage concerns the assessment of the legacy market, so the pharmaceuticals already on the market in Germany before 1 January 2011, but which are still under data exclusivity and are therefore „new substances".Although the savings targets to be generated by the AMNOG were formulated as a "should" and not a "must", the G-BA has used the fact that the 2 billion Euro target was not reached as a reasons to develop a concept for regular assessments of the legacy market pharmaceuticals, in order to achieve the desired savings. At the same time, there is no concrete savings target stipulated in the AMNOG itself; instead, the legislation states that cost increases associated with pharmaceuticals are to be limited.

Even in the draft bill of the AMNOG, the Federal Ministry of Health only estimated a savings potential of 2 billion Euros, but for the entire reference priced market (based on turnovers in 2009 and manufacturer price, assuming a fictitious rebate of 12 %) and for an unspecified timeframe. Nevertheless, the G-BA has operationalized the criteria of patient care relevance and competition through a weighted forecast of future turnovers and prescriptions volumes. It has also announced that, for the purposes oft he procedure according to it § 35a SGB V, it would work through the resulting list of pharmaceuticals successively. This is expected to clearly demonstrate the problems associated with the mandatory early assessment procedure.

The German Pharmacy Market

The developments in the German pharmacy market present a very heterogeneous picture. Compared to 2011, the total turnover in the pharmacy market assessed at manufacturer prices rose in 2012 by 2.2 % to a total of 26.8 billion Euros. For prescription drugs, there was an increase in turnover of 2.4 %. The turnover with OTC medications increased by 0.04 %.

*For this survey, the wholesale turnovers and the 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.

Turnover developments in the pharmacy market 2009 – 2012 (in million Euros)

	2009	2010	2011	2012	Change vs. previous year in %
Total	24,690.8	25,636.6	26,186.5	26,755.7	2.17
Prescription only	19,425.6	20,403.3	20,750.5	21,245.5	2.39
Pharmacy only	2,918.5	2,823.7	2,903.4	2,904.5	0.04
Non-drugs	1,368.4	1,415.8	1,508.5	1,517.8	0.61
Controlled drugs	789.5	814.8	835.9	880.0	5.29
GSL medicines	183.5	173.9	183.0	202.5	10.62
Drugs and Chemicals	5.2	5.2	5.2	5.4	3.92

Source: Illustration of the BPI based on data of Insight Health 2013.

Sales trends in the pharmacy market 2009 – 2012 (packages in millions)

	2009	2010	2011	2012	Change vs. previous year in %
Total	1,603.7	1,557.4	1,605.8	1,556.9	- 3.04
Prescription only	728.6	709.1	723.8	685.6	- 5.28
Pharmacy only	678.8	650.2	676.7	661.3	- 2.28
Non-drugs	137.9	142.1	147.7	150.1	1.61
Controlled drugs	48.2	45.4	46.5	48.4	3.90
GSL medicines	9.7	10.0	10.5	11.0	5.36
Drugs and Chemicals	0.6	0.6	0.5	0.5	0.22

Source: Illustration of the BPI based on data of Insight Health 2013.

A look at the volume trends in the overall market reveals that there was a slight decrease in 2012. The largest changes were seen in prescription drugs with a drop of - 5,3 % and the highest increase of 5.4 % compared to the previous year is found in the “controlled drugs” sector

When comparing the development of the pharmaceutical drug segments in 2012 according to sub-categories, the largest growth in comparison to the previous year was only found in the category. All other sub-categories showed either a marginal growth or loss.

Turnover development of pharmaceutical drug segments according to sub-categories 2009 – 2012 (in million Euros)

	2009	2010	2011	2012	Change vs. previous year in %
Total	24,690.8	25,636.6	26,186.5	26,755.7	2.17
Pharma. drugs for human use	18,643.2	19,144.1	19,345.2	19,443.3	0.51
Biopharmaceuticals	3,484.6	3,915.8	4,184.4	4,656.3	11.28
Others*	817.7	851.3	925.1	922.1	- 0.32
Phytopharmaceuticals	807.7	777.0	758.5	748.7	- 1.30
Diagnostics	632.0	646.3	667.1	675.3	1.22
Homeopathic medicines	258.5	252.8	253.3	256.3	1.17
Anthroposophic medicines	47.1	49.3	52.8	53.8	1.91

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

Source: Illustration of the BPI based on data of Insight Health 2013.

In terms of volume, only biopharmaceuticals and anthroposophic medicines increased in 2012 (5.8 % and 4.17 %, respectively). The volume in the sub-category “Pharma. drugs for human use” has especially declined.

Sales volumes of pharmaceutical drug segments according to sub-categories 2009 – 2012 (in million packages)

	2009	2010	2011	2012	Change vs. previous year in %
Total	1,603.7	1,557.4	1,605.8	1,556.9	- 3.04
Pharma. drugs for human use	1,247.3	1,205.4	1,248.4	1,196.9	- 4.13
Phytopharmaceuticals	121.5	122.3	127.3	127.8	0.40
Others*	129.8	126.4	125.8	126.0	0.17
Homeopathic medicines	52.4	49.4	48.7	48.5	- 0.38
Diagnostics	28.3	29.1	30.3	31.1	2.45
Biopharmaceuticals	16.8	16.8	16.7	17.7	5.78
Anthroposophic medicines	7.6	8.1	8.5	8.9	4.17

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

Source: Illustration of the BPI based on data of Insight Health 2013.

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, the homeopathic field enjoys 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 decreasing trend in sales volumes. Compared to the previous year, the largest decline (- 11.4 %) was in the field of Anti-rheumatic treatments, followed by other analgesics (- 8.9 %).

Top 10 leading indication areas (ATC-3)
in the pharmacy market 2012 by sales volumes

Indication areas (ATC - 3)	Packages in thousands	% to prev. year	share of total turnover in %	share of total sales in %
Total	1,556,895.6	- 3.04	100.00	100.00
N02B Other analgesics	139,851.6	- 8.92	8.98	1.87
R01A Nasal preparations, topical	81,148.8	3.31	5.21	0.67
R05C Expectorants without anti-infectants	64,953.7	- 2.11	4.17	0.99
V03X Other therapeutic preparations	43,758.3	0.97	2.81	0.72
A02B Ulcer treatments	41,451.8	- 1.11	2.66	1.73
C07A Beta-blockers, pure	37,846.6	-5.10	2.43	0.63
M01A Anti-phlog. /anti-rheumat., non-steroid.	37,808.3	- 11.41	2.43	0.73
M02A Anti-rheumat. and analgesics, topical	33,913.6	2.73	2.18	0.65
R02A Throat preparations	28,670.8	1.25	1.84	0.40
B01C Anti-platelet treatments	27,901.8	- 1.85	1.79	1.18

Source: Illustration of the BPI based on data of Insight Health 2013.

The turnover developments in the Top 10 indications according to ATC-3 show the highest increases (as compared to the previous year) in “other immunosuppressant” and anti-TNF preparations. The share of these two groups in the total turnover in the pharmacy market was 6.9 % in 2012.

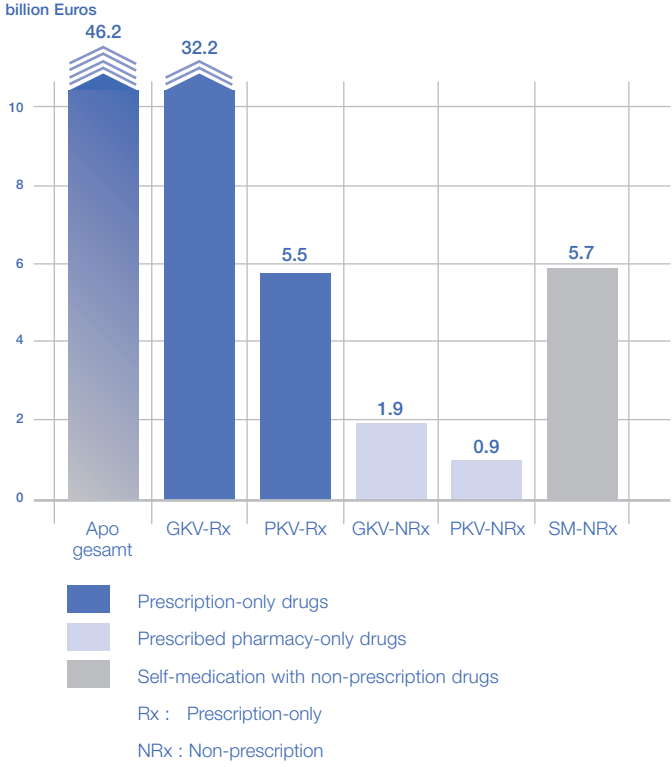
Top 10 leading indication areas (ATC-3) in the pharmacy market 2012 by turnover

Indication areas (ATC - 3)	in thousand Euro	% to prev. year	share of total turnover in %	share of total sales in %
Total	26,755,748.3	2.17	100.00	100.00
L04B Anti-TNF preparations	1,154,167.6	15.92	4.31	0.02
L01X Other antineoplastic agents	1,022,935.0	15.07	3.82	0.06
A10C Human insulin and analogs	937,453.6	5.32	3.50	0.82
N02A Analgesics, narcotics	799,157.9	4.86	2.99	0.60
L03B Interferons	705,422.2	4.09	2.64	0.02
L04X Other immunosuppressants	695,808.2	18.56	2.60	0.13
N05A Antipsychotics	687,992.0	- 18.93	2.57	0.86
N03A Antiepileptics	636,596.2	- 2.08	2.38	0.74
C09D Angiotensin II antagonists	611,199.6	- 10.02	2.28	0.68
T02D Diabetes tests	606,498,5	-0.49	2.27	1.75

Source: Illustration of the BPI based on data of Insight Health 2013.

The following illustrations show different segments of the drug market in pharmacies. The turnover for the pharmacy market including pharmacy mail-order was in total 46.2 billion Euros for 2012. For prescription drugs assessed with the pharmacy's retail price, IMS Health for 2012 determined a total turnover of 37.7 billion Euros. The turnover with prescription-only pharmaceuticals on SHI expenses was 32.2 billion Euros (85.4 %) in 2012. The turnover with prescribed OTC drugs on SHI expenses and private health insurance was 1.9 billion Euros and 0.9 billion Euros, respectively. Self-medication with OTC drugs came to approximately 5.7 billion Euros.

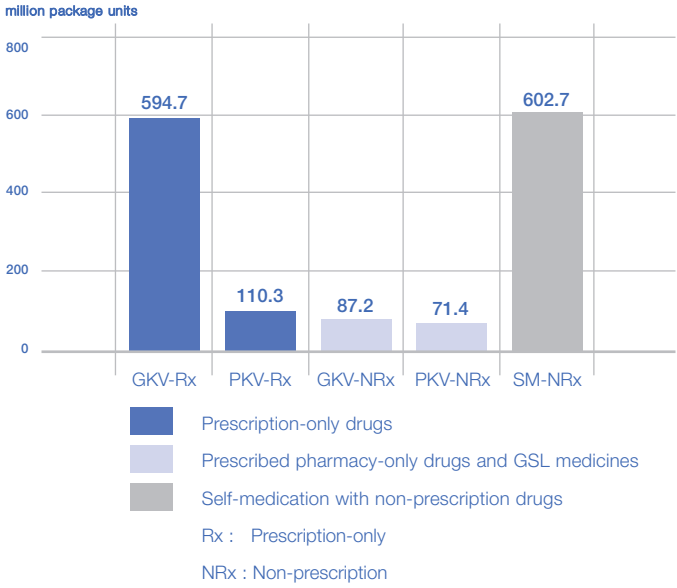
Turnover of pharmaceutical drugs in pharmacies and pharmacy mail-order in 2012 at pharmacy retail prices (in billion Euros)



Source: Illustration of the BPI based on data from IMS PharmaScope® National 2013.

Around 159 million package units of OTC drugs were reimbursed by the SHI and private health insurance in 2012, while 603 million package units were bought for self-medication in pharmacies and pharmacy mail-order. The volume in package units added up to around 1,466 million package units.

Sales volumes of the drug market in pharmacies and pharmacy mail-order 2012 (in million package units – PE)



Source: Illustration of the BPI based on data from IMS PharmaScope® National 2013.

The reason for the differences between turnover and sales volumes is primarily in the different pricing levels of the drugs under review. 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 segment of highly active products also contains many phytopharmaceuticals. The segment 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 the 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 2010 – 2012

Subcategory	2010	2011	2012
Total	676,556,256	679,632,524	676,650,899
Pharmaceuticals*	638,031,701	641,385,409	640,472,442
Diagnostics	23,930,931	24,283,583	24,306,071
Others**	6,580,111	6,383,268	4,937,939
Phytopharmaceuticals	5,256,140	5,034,296	4,671,945
Homeopathic medicines	1,949,923	1,764,273	1,538,912
Anthroposophic medicines	807,450	781,695	723,590

* including biopharmaceuticals

** Hygiene products, injection equipment, disinfectants, sideline products, drugs, medical devices, chemicals, veterinary products, nutritional supplements, dietary products

Source: Illustration of the BPI based on data of Insight Health 2013.

In 2012, an overall volume of 677 million prescriptions were financed through the SHI system. The share of pharmaceuticals in the total prescription volume is around 94.5 %. Looking at the development of the volume of prescriptions, it becomes clear that the volume of prescribed diagnostics has continuously increased, currently making up 3.6 % of the total volume of prescriptions. Phytopharmaceuticals are prescribed in 0.7 % of cases, homeopathic medicines in 0.2 % of cases.

Turnover financed by the SHI system 2010 – 2012, pharmacy retail price in Euros

	2010	2011	2012
Total	31,922,996,672	32,146,598,188	32,422,122,531
Pharmaceuticals*	30,670,446,471	30,898,256,604	31,257,820,504
Diagnostics	945,558,363	954,985,504	934,026,808
Others**	188,409,811	179,705,795	129,098,341
Phytopharmaceuticals	77,050,067	75,472,098	70,155,420
Anthroposophic medicines	18,909,321	17,506,407	15,570,576
Homeopathic medicines	22,622,640	20,671,780	15,450,883

* including biopharmaceuticals

** Hygiene products, injection equipment, disinfectants, sideline products, drugs, medical devices, chemicals, veterinary products, nutritional supplements, dietary products

Source: Illustration of the BPI based on data of Insight Health 2013.

Development of market shares as financed by the SHI system 2010 – 2012 in %

	Prescriptions			Turnover		
	2010	2011	2012	2010	2011	2012
Total	100.00	100.00	100.00	100.00	100.00	100.00
Pharmaceuticals*	94.31	94.37	94.65	96.08	96.12	96.41
Diagnostics	3.54	3.57	3.59	2.96	2.97	2.88
Others**	0.97	0.94	0.73	0.59	0.56	0.40
Phytopharmaceuticals	0.78	0.74	0.69	0.24	0.23	0.22
Anthroposophic medicines	0.29	0.26	0.23	0.06	0.05	0.05
Homeopathic medicines	0.12	0.12	0.11	0.07	0.06	0.05

* including biopharmaceuticals

** Hygiene products, injection equipment, disinfectants, sideline products, drugs, medical devices, chemicals, veterinary products, nutritional supplements, dietary products

Source: Illustration of the BPI based on data of Insight Health 2013.

In looking at turnover, it is clear than the turnover in pharmaceuticals 2012 was 31.3 billion Euros or 1.3 % 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 15.4 million Euros or a mere 0.05 % in SHI expenditures.

Top 10 leading indications (ATC-3) in the SHI market 2012 by sales volumes

Indications (ATC-3)	Prescriptions	% to previous year	% share of total volume	% share of total turnover
Total	676,650,899	- 0.44	100.00	100.00
C07A Beta-blockers, pure	36,157,044	2.49	5.34	1.74
M01A Anti-phlog. /anti-rheumat., non-steroid.	35,421,429	- 1.93	5.23	1.83
N02B Other analgesics	35,162,631	0.07	5.20	1.94
A02B Ulcer treatments	30,405,642	4.69	4.49	2.51
C09A ACE inhibitors, pure	25,427,989	1.42	3.76	1.05
T02D Diabetes tests	23,808,000	0.14	3.52	2.72
C03A Diuretics	22,357,111	4.11	3.30	1.09
H03A Thyroid preparations	21,546,736	- 0.01	3.18	1.25
N06A Antidepressants / mood stabilizers	20,574,672	1.95	3.04	2.35
C10A Lipid modifying agents	18,357,631	2.77	2.71	1.46

Source: Illustration of the BPI based on data of Insight Health 2013.

When looking at sales volume in 2012, the “ulcer treatments” 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 2012 according to turnover

Indication areas (ATC-3)	In million Euros	% to previous year	% share of total volume	% share of total turnover
Total	32,422.1	0.86	100.00	100.00
L04B Anti-TNF preparations	1,413.2	13.52	4.36	0.05
A10C Human insulin and analogs	1,246.5	2.51	3.84	1.78
N02A Analgesics, narcotics	1,015.1	2.73	3.13	1.22
N05A Antipsychotics	971.5	- 18.22	3.00	1.79
L01X Other antineoplastic agents	905.8	11.40	2.79	0.07
T02D Diabetes tests	881.7	- 2.35	2.72	3.52
L04X Other immunosuppressants	868.3	16.68	2.68	0.26
L03B Interferons	843,3	3.62	2.60	0.05
N03A Antiepileptics	840.5	- 3.28	2.59	1.44
A02B Ulcer treatments	814,2	0.99	2.51	4.49

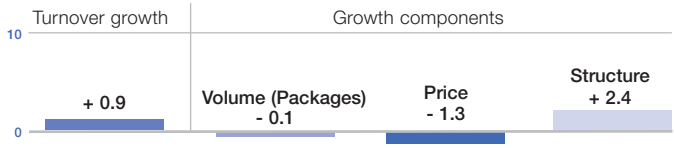
Source: Illustration of the BPI based on data of Insight Health 2013.

With respect to turnover in 2012, the other immune suppressants and the “anti-TNF preparations had the highest growth rate in comparison to the previous year. The decline in antipsychotics showed the highest change in comparison to the previous year (18.2 %).

The SHI structural component

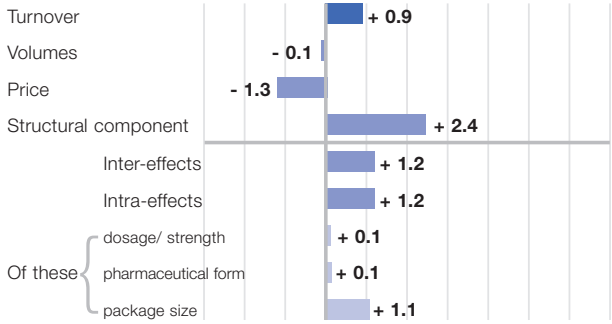
The structural component allows a detailed analysis of trends in factors affecting SHI pharmaceutical expenditures. It is possible to identify to what extent there has been a trend toward the prescription of innovative and patented pharmaceutical drugs. The structural effect comprises different effects attached to a specific product (package size, dosage / strength and pharmaceutical form) and effects within and / or among pharmaceutical segments as well as indication groups. The SHI structure 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 2012 (changes to previous year in %)



Source: Illustration of the BPI based on data of the IMS® SHI-Structural component study 2013.

Growth components in 2012 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 2013.

In 2012, the IMS structural component was 2.4 %. In the past, this component has been at a significantly higher level. The price level in the SHI pharmaceutical market decreased by 1.3 % and the volume by 0.1 %.

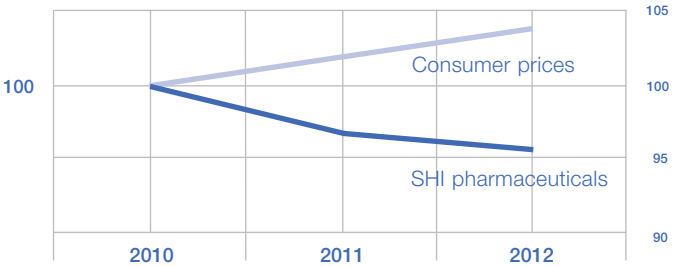
The "Pharmaceutical Atlas" published by the Institut für Gesundheits- und Sozialforschung (IGES) uses the ATC classification, similar to the IMS structure component analysis. The IMS structure component analysis examines all ATC groups (ATC 1 to ATC 4) and thus allows for indication-oriented analysis 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 different definition of the components. When it comes to 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 30 indications with the most prescriptions. The quantitative unit of measure used in the Atlas refers to the Defined Daily Dose (DDD). The IMS HEALTH structure component analysis is based on quantitative units such as packages units or tally units.

It has been shown that changes in pricing, volumes and quality all have an influence on expenditures. Innovative pharmaceuticals, which generate high costs in development, naturally have a higher price level, 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 drugs' 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, especially when compared with the development of consumer prices. Voluntary rebate contract entered into in 2012 alone resulted in saving of 2.38 billion. Currently the rebate volumes are still increasing.

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



Sources: Illustration of the BPI based on data of the WidO and the Federal Statistical Office 2013.

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

Price development according to market segments between January 2011 – July 2013 (January 2011 = 100)

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

The OTC-Market

In general for 2012 the turnover in the German OTC market has developed positively (in pharmacy and pharmacy mail-order). The turnover for in-pharmacy (+ 0.8 %) as well as for pharmacy mail-order (+ 8.5 %) sales grew in comparison to the previous year. When looking at the sales volume, for brick-and-mortar pharmacy it has been decreasing for years (2011 to 2012: - 1.2 %), even the positive development for pharmacy mail-order (2011 to 2012: + 8 %) could not balance this out. The values for turnover and sales volumes are also around the from 2004, the year in which the health care modernization act eliminated, with a few exceptions, reimbursement of non-prescription drugs.

The strongest product category in the OTC market is still pharmacy-only drugs with a turnover share of 76.1 % (share of sales volumes: 77 %). They clearly outstrip the turnovers achieved with of the non-pharmacy-only drugs (turnover share 4.9 %) and non- health products (GMS, Gesundheitsmittel)*, which totaled 19% share overall turnover of the OTC market.

* GMS: Defined as products competing with pharmaceutical drugs.

However, for the past years, the share of health products in the pharmacy market has been increasing (share in turnover 2008: 15.2 %, in 2012: 19 %). 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 2008: 15.6 %; in 2012: 17.3 %).

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

Turnover in thousand Euros at pharmacy retail price

	2008	2009	2010	2011	2012
In pharmacy drugs					
- Pharmacy-only	5,045,054.4	4,919,854.2	4,762,450.7	4,685,196.2	4,698,146.5
- OTC	334,207.3	316,642.3	301,170.2	290,249.7	304,317.3
GMS pharmacy	943,257.9	1,001,784.1	1,041,915.6	1,090,349.5	1,114,563.6
In pharmacy total	6,332,519.6	6,238,280.7	6,105,536.5	6,065,795.4	6,117,027.4
Pharmacy mail-order (MO)					
- Pharmacy-only	373,334.0	471,687.4	508,822.8	539,232.2	568,479.3
- OTC	24,054.3	28,641.3	30,807.9	32,395.0	36,597.5
GMS Pharmacy MO	96,985.3	133,067.9	145,556.6	170,820.9	200,420.4
MO total	494,373.6	633,396.6	685,187.3	742,448.2	805,497.2
In Pharm. & MO total	6,816,893.2	6,871,677.2	6,790,723.9	6,808,243.6	6,922,524.7

Market share in %	2008	2009	2010	2011	2012
In pharmacy drugs					
- Pharmacy-only	74.01	71.60	70.13	68.82	67.87
- OTC	4.90	4.61	4.44	4.26	4.40
GMS Pharmacy	13.84	14.58	15.34	16.02	16.10
In pharmacy total	92.75	90.78	89.91	89.09	88.36
Pharmacy mail-order (MO)					
- Pharmacy-only	5.48	6.86	7.49	7.92	8.21
- OTC	0.35	0.42	0.45	0.48	0.53
GMS Pharmacy MO	1.42	1.94	2.14	2.51	2.90
MO total	7.25	9.22	10.09	10.91	11.64
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 Offtake 2013.

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

Volume in thousands of package units

	2008	2009	2010	2011	2012
In pharmacy drugs					
- Pharmacy-only	615,932.3	605,068.5	582,758.9	569,669.0	559,374.8
- OTC	45,954.1	45,522.7	42,869.9	41,204.6	41,650.1
GMS pharmacy	124,192.7	127,969.1	127,606.9	126,109.8	127,113.6
In pharmacy total	786,079.1	778,560.4	753,235.7	736,983.4	728,138.5
Pharmacy mail-order (MO)					
- Pharmacy-only	36,847.4	49,760.1	58,842.5	63,137.5	66,993.8
- OTC	1,976.6	2,541.0	2,875.8	3,239.5	3,634.8
GMS Pharmacy MO	6,127.4	8,581.0	10,328.4	12,128.3	14,167.1
MO total	44,951.5	60,882.1	72,046.7	78,505.2	84,795.6
In Pharm. & MO total	831,030.5	839,442.4	825,282.5	815,488.6	812,934.2

Market share in %	2008	2009	2010	2011	2012
In pharmacy drugs					
- Pharmacy-only	74.12	72.08	70.61	69.86	68.81
- OTC	5.53	5.42	5.19	5.05	5.12
GMS Pharmacy	14.94	15.24	15.46	15.46	15.64
In pharmacy total	94.59	92.75	91.27	90.37	89.57
Pharmacy mail-order (MO)					
- Pharmacy-only	4.43	5.93	7.13	7.74	8.24
- OTC	0.24	0.30	0.35	0.40	0.45
GMS Pharmacy MO	0.74	1.02	1.25	1.49	1.74
MO total	5.41	7.25	8.73	9.63	10.43
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 Offtake 2013.

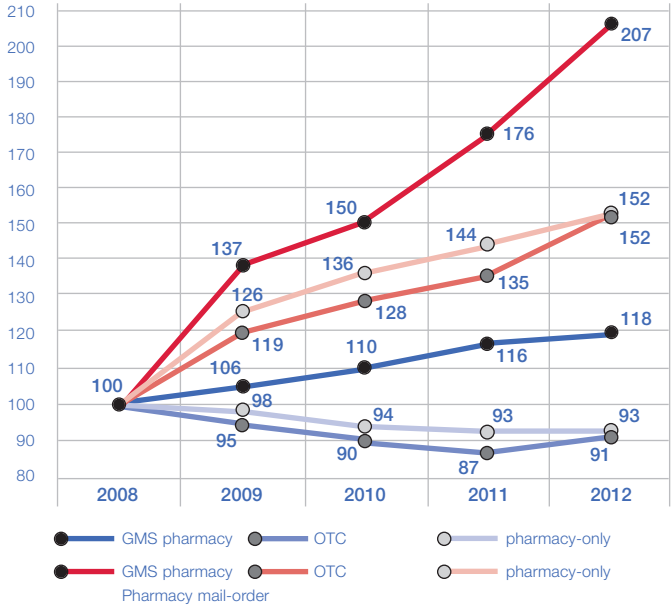
In comparison to the prescription market, the profit in the OTC segment has been of major importance for years. However, there has been a decrease in the previously observed double digit growth rate. In 2012, the pharmacy mail-order market share was 11.6 % of the total OTC market. The market shares shown in the table above are averages which may significantly vary for individual products. Especially the more expensive and strong OTC-brands may reach mail-order shares far above the market average, in some cases more than 30 % for bulk packs. As in in-pharmacy sales, the pharmacy-only pharmaceuticals as a product group (79 % of overall sales)

have the largest share in the turnovers (70.6 %) in the mail-order market. They are followed by the non-drug healthcare products with 24.9% turnover share and 16.7 % share in overall sales. The pharmacy mail order business has become very established over the past years, although this segment continues to be very dynamic due to acquisitions and divestments.

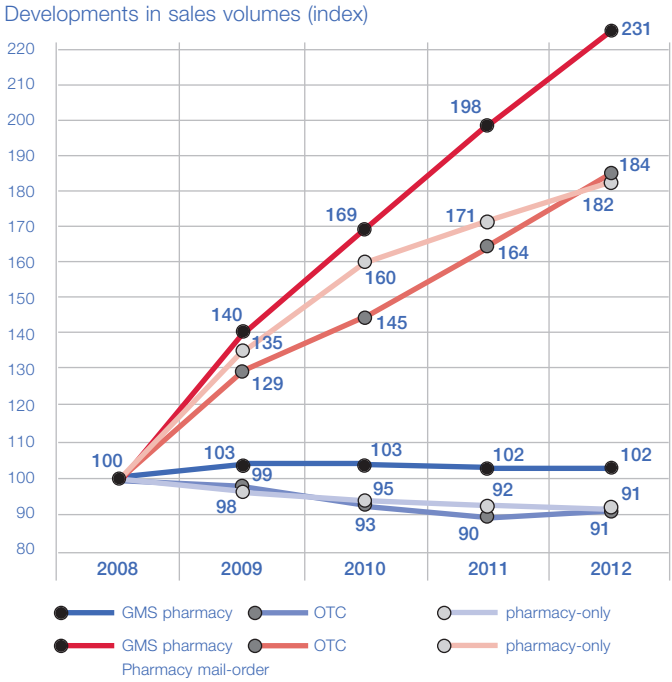
Almost every fourth non-prescription product sold in pharmacies is also a non-pharmacy-only product (share in sales volumes: 22.8 %; share in turnover: 23.9 %) and 80 % of these products are not even drugs. In the last years health products especially pharmacy mail order have greatly increased. The following images show the development for the different categories.

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) 2008 = 100; based on sales volumes: units 2008 = 100)

Developments in turnover (index)



Source: Illustration of the BPI based on data from IMS Health 2013



Source: Illustration of the BPI based on data from IMS Health 2013

In the category of non-drugs, higher quality products are increasingly on offer. As an example, the average price of a non-drug health product sold in pharmacies increased from 7.98 Euros in 2008 to 9.31 Euros in 2012.

In 2012, the average pharmacy retail price of a product on the German pharmacy market was 8.52 Euros. The average price in the category with the highest sales volumes (pharmacy-only drugs) was 8.41 Euros in 2012, and is therefore slightly higher than the average price in 2010 and is also 1.3 % higher than the average pharmacy retail price in 2006. Therewith, the price of high quality -, OTC – and pharmacy-only drugs remained stable over years and they secure the drug supply for self-medication.

Average pharmacy retail price for OTCs in the pharmacy market

Prices in Euros	2008	2009	2010	2011	2012
Pharmaceutical drugs					
- Pharmacy-only OTCs	8.30	8.23	8.22	8.26	8.41
- Non-pharmacy OTCs	7.47	7.18	7.26	7.26	7.53
GMS* pharmacy	7.98	8.31	8.61	9.12	9.31
Mean value**	8.20	8.19	8.23	8.35	8.52

* 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-GMS Report 2013.

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, a more differentiated approach is required in this matter, as the method for tallying the number of drugs differs internationally. As of 14 August 2013, there were about 93,000 marketing authorization for pharmaceutical drugs in all indications according to statistics of the BfArM, of those 46,000 prescription drugs (including “controlled drugs” and T- prescriptions, thalidomide/ lenalidomide containing).

In Germany, a separate marketing authorization is required for each pharmaceutical strength and each pharmaceutical form of a single active substance. This means there is a separate marketing authorization 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 authorization.

Furthermore, the statistics of the BfArM 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 authorization does not necessarily imply the necessity to market the drug. It is not unusual for marketing authorization holders to only place part of the authorized products in the company portfolio on the market. However, the marketing authorization of a drug that is not placed on the market will expire after three years (Sunset Clause). Partially medicines are also removed from the market, also a consequence of AMNOG (early benefit assessment), but the authorization and the packaging remain in the statistics of the BfArM.

A comprehensive spectrum of the pharmaceuticals currently on the market in Germany are presented in the products by Rote Liste Service GmbH (“Rote Liste®”, Fachinfo-Service, Patienteninfo-Service).

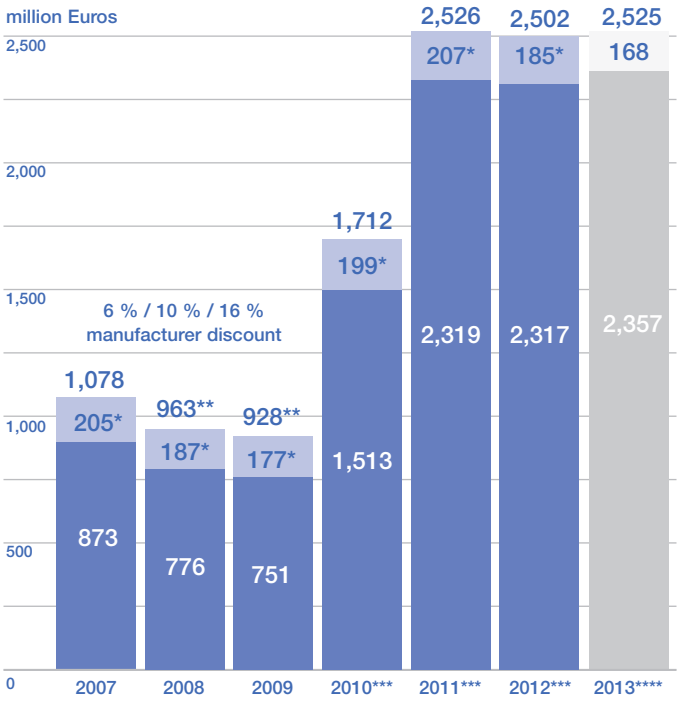
In the “Rote Liste®”, 94 % of the newly authorized pharmaceutical since January are registered. The “Rote Liste®” is open to all suppliers of pharmaceutical drugs. This registry is particularly popular with physicians, so that most pharmaceutical companies wishing to have their products prescribed by 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 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 for supply amplitude and supply depth of the market and says little about a possible over-saturation of the market, since the sole number of drugs does not give information on the actual use of the drugs.

Interventions in the pharmaceutical drug market – future prospects

The 2013 Pharma Data make one thing clear; the state of the pharmaceutical industry is problematic, even though this is one of the industry segments that has weathered the economic crisis and continues to provide positive prospects for employment and the German economy as a whole. Nevertheless, the governmental regulations and massive interventions to restrict the industry's economic freedom have made the situation more and more difficult from year to year. In the past five years alone, the pharmaceutical industry has paid aournd 7.7 billion Euros in obligatory rebates. For 2013, further obligatory rebates amounting to 2.5 billion Euros are forecasted. And these do not even reflect the payments that the individual companies have made to the SHI-proiders, or the immense costs that habe been incurred by the three-and-a-half-year price moratorium for the pharmaceutical industry.

Cost burden of the pharmaceutical industry due to obligatory discounts 2007 – 2013 (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 2013; based on data for half of the year 2013, the mandatory discounts for the private health insurance (applicable since 2011) sector are not included

Source:: Illustration of the BPI based on IMS Health PharmaScope® National 2013.

Important for companies will be, that the 18th legislature period will pass without renewed federal regulation instruments. Price moratoriums and increased obligatory discounts must expire end of 2013, if nothing else but the financial situation is characterized as profitable. Only then will all companies be able to participate in the economic process. For one thing is clear:

these measures, which the government presents as unproblematic because they are basing their evaluations on the numbers of a few large multinational companies, will severely affect the mid-tier pharmaceutical sector. These companies generate their revenue in the German market. When this sales volume burdened by increased obligatory discounts, immediately net operating profit. When this revenue is burdened by obligatory discounts, it immediately crushes the operating results of the company, and thus at the same time, the possibility to make investments or to retain or create jobs.

Another “work in progress”, as again demonstrated in the Pharma-Data 2013, is the early benefit assessment procedure. In this, the savings generated to date are not the issue, since the savings targets of 2 billion Euros circulating in the media were not the goal. The goal of the AMNOG was to care for people with the best and most effective pharmaceutical at cost-effective and economical prices. The lawmakers wanted with the law to create a reliable framework for innovation and the preventative care of patients and create jobs.

What is really problematic with the early benefit assessment still is the results. With regards to appropriate comparative therapies, it is evident that regulators need to to make improvements. This is because the G-BA and the GKV-Spitzenverband have lost sight of the benefit the early assessment is supposed to for to patients, and instead look only at costs. It is significant that the chairman of the G-BA himself has to admit that these considerations often do not reflect the realities the patients are facing. Now it is on them to set it right.

Overall, the message of the 2013 Pharma-Data is clear: over-regulation, governmental intervention, and a focus concentrated solely on cost minimization will make it difficult in the long term for the pharmaceutical industry to survive, to produce nationally, to innovate. Those who want this to ensure the pharmaceutical industry's survivial, especially in view of the publicized debate about delivery problems and the increasing dependency on other countries for drug supplies, have to find another more intelligent ways to control costs. This will be a major challenge for the newly elected government if they want to continue to have a high quality, comprehensive and secure pharmaceutical supply in Germany.

Additional Information

ABDA: Zahlen Daten Fakten 2012,
URL: http://www.abda.de/fakten_zahlen.html (Stand: 03.09.2013).

Biotechnologie.de: Die deutsche Biotechnologie-Branche 2013,
URL: http://www.biotechnologie.de/BIO/Navigation/DE/Hintergrund/studien-statistiken,did=163892.html?listBIId=74636& (Stand: 03.09.2013).

Boston Consulting Group: Medizinische Biotechnologie in Deutschland 2013,
URL: http://www.bcg.de/documents/file141456.pdf (Stand: 03.09.2013)

Bundesministerium für Wirtschaft und Technologie: Innovationsimpulse der Gesundheitswirtschaft – Auswirkungen auf Krankheitskosten, Wettbewerbsfähigkeit und Beschäftigung,
URL: http://www.bmwi.de/Dateien/BMWi/PDF/innovationsimpulse-der-gesundheitswirtschaft,property=pdf,bereich=bmwi2012,sprache=de,rwb=true.pdf
(Stand: 02.09.2013)

Deutsches Bundesamt für Statistik,
URL: https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Gesundheit/Gesundheit.html (Stand: 03.09.2013).

Die deutsche Biotechnologie-Branche 2013: Daten & Fakten,
URL: http://www.biotechnologie.de/BIO/Redaktion/PDF/de/umfrage/2013-umfrage,property=pdf,bereich=bio,sprache=de,rwb=true.pdf
(Stand: 04.09.2013).

DiMasi, Grabowski: “The Cost of Biopharmaceutical R&D: Is Biotech Different?”, Managerial and Decision Economics 28, 2007, S. 469-479.

DiMasi, Hansen, Grabowski: “The price of innovation: new estimates of drug development costs“, Health Economics 22(3), 2003, S. 151-185.

Donald W. Light/Rebecca Warburton: Demythologizing the high costs of pharmaceutical research. In: BioSocieties, 2011, S. 1-7.
URL: http://www.palgrave-journals.com/biosoc/journal/v6/n1/abs/ bio-soc201040a.html (Stand: 04.09.2013).

EFPIA: The Pharmaceutical Industry in Figures - Edition 2013,
URL: http://www.efpia.eu/uploads/Figures_Key_Data_2013.pdf
(Stand: 03.09.2013).

Ernst & Young: Deutscher Biotechnologie-Report 2013
URL: http://www.ey.com/Publication/vwLUAssetsPI/Deutscher_Biotechnologie-Report_2013/$FILE/EY-Biotech-Report_D_2013.pdf
(Stand: 03.09.2013).

European Medicines Agency: Clinical trials submitted in marketing-authorisation applications to the European Medicinnes Agency,
URL: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf (Stand: 03.09.2013).

Expertenkommission für Forschung und Innovation: Jahresgutachten zu Forschung, Innovation und technologischer Leistungsfähigkeit Deutschlands 2013.,
URL: http://www.e-fi.de/gutachten.html (Stand: 03.09.2013).

Genercis and Biosimilars Initiative (GaBi): Reports.
URL: http://www.gabionline.net/Reports (Stand: 28.08.2013).

IMS Health: Datenbanken: IMS Contract Monitor; IMS World Review; IMS Pharmascope,
URL: http://www.imshealth.com/portal/site/ims (Stand: 03.09.2013).

INSIGHT Health GmbH & Co. KG: Datenbanken: NVI, NPI,
URL: http://www.insight-health.de (Stand: 03.09.2013).

Kearney AT. Make Your Move: Taking Clinical Trials to the Best Location.
URL: http://www.atkearney.com/paper/-/asset_publisher/dVxv4Hz2h8bS/content/make-your-move/10192 (Stand: 04.09.2013).

Schwabe, Paffrath: Arzneiverordnungsreport 2013, Aktuelle Daten, Kosten Trends und Kommentare, S. 207-209.

Stapff, Manfred: Klinische Prüfungen unter IND-Bedingungen; in: die pharmazeutische Industrie, Band 75, Heft 5 2013, Seite 756-763.

Stifterverband für die Deutsche Wissenschaft: Statistik und Analysen: FuE-facts 2013,
URL: http://www.stifterverband.info/statistik_und_analysen/ wissenschaftsstatistik/publikationen/fue_facts/fue_facts_2013-01.pdf (Stand: 03.09.2013).

Stifterverband für die Deutsche Wissenschaft: Statistik und Analysen: FuE-Datenreport 2013,
URL: http://www.stifterverband.info/statistik_und_analysen/wissenschaftsstatistik/publikationen/fue_datenreport/fue_datenreport_2013.pdf (Stand: 03.09.2013).

Wissenschaftliches Institut der AOK (WidO): GKV-Index, Preisentwicklung auf dem Arzneimittelmarkt,
URL: http://www.wido.de/arz_preisinformation.html (Stand: 03.09.2013).

Index

Acronyms

AKG	Arzneimittel und Kooperation im Gesundheitswesen
AMG	Arzneimittelgesetz
AMNOG	Arzneimittelmarktneuordnungsgesetz
AOK	Allgemeine Ortskrankenkasse
ApU	Abgabepreis pharmazeutischer Unternehmen
ATC Code	Anatomisch-Therapeutisch-Chemische (ATC) Klassifikation
AVP	Apothekenverkaufspreis
AVWG	Arzneimittelversorgungs-Wirtschaftlichkeitsgesetz
Barmer GEK	Barmer Gmünder Ersatzkasse
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BIP	Bruttoinlandsprodukt
BKK	Betriebskrankenkassen
BMBF	Bundesministerium für Bildung und Forschung
BMG	Bundesministerium für Gesundheit
BMWi	Bundesministerium für Wirtschaft und Technologie
BPI	Bundesverband der Pharmazeutischen Industrie e. V.
DAK	Deutsche Angestellten Krankenkasse
DDD	Defined Daily Dosis (definierte Tagesdosis)
DRGs	Diagnosis Related Groups
EAFTA	East Asian Free Trade Area
EFPIA	European Federation of Pharmaceutical Industry and Associations
EMA	European Medicines Agency
EU	Europäische Union
F&E	Forschung & Entwicklung
FSA	Freiwillige Selbstkontrolle Arzneimittelindustrie
G-BA	Gemeinsamer Bundesausschuss

GKV	Gesetzliche Krankenversicherung
GKV-OrgWG	Gesetz zur Weiterentwicklung der Organisationsstrukturen in der Gesetzlichen Krankenversicherung
GKV-SV	Spitzenverband der Gesetzlichen Krankenkassen
GKV-WSG	GKV-Wettbewerbsstärkungsgesetz
GMG	GKV-Modernisierungsgesetz
GMS	Gesundheitsmittelstudie
GWB	Gesetz gegen Wettbewerbsbeschränkungen
IGES	Institut für Gesundheits- und Sozialforschung
IMS	IMS HEALTH GmbH & Co. OHG
Insight Health	INSIGHT Health Management GmbH
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LCD	Local Currency Dollar
Mio.	Millionen
Mrd.	Milliarden
MwSt.	Mehrwertsteuer
NCE / NBE	New Chemical or New Biological Entities
OTC	Over-the-counter / Selbstmedikation
OR	Outcomes Research
PE	Packungseinheit
PEI	Paul-Ehrlich-Institut
Phytos	Herbal Medicinal Products / Pflanzliche Arzneimittel
PKV	Private Krankenversicherung
ROW	Rest of the World
SGB V	Sozialgesetzbuch V
SGG	Sozialgerichtsgesetz
TK	Techniker Krankenkasse
UAW	Unerwünschte Arzneimittelwirkung
WHO	World Health Organisation
WidO	Wissenschaftliches Institut der Ortskrankenkassen

BPI German Pharmaceutical Industry Association

Publisher:

German Association for Pharmaceutical Industry e. V. (BPI)

Friedrichstraße 148
10117 Berlin
Tel.: +49 30 2 79 09 - 0
Fax: +49 30 2 79 09 - 3 61
E-Mail: info@bpi.de
Internet: www.bpi.de

Design:
Netrixx Communications GmbH, Hamburg

43rd revised edition, December 2013