

## 2. Market Access in Germany

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### 2.1 General Outlook of Healthcare System and Health Policies

#### The Environment

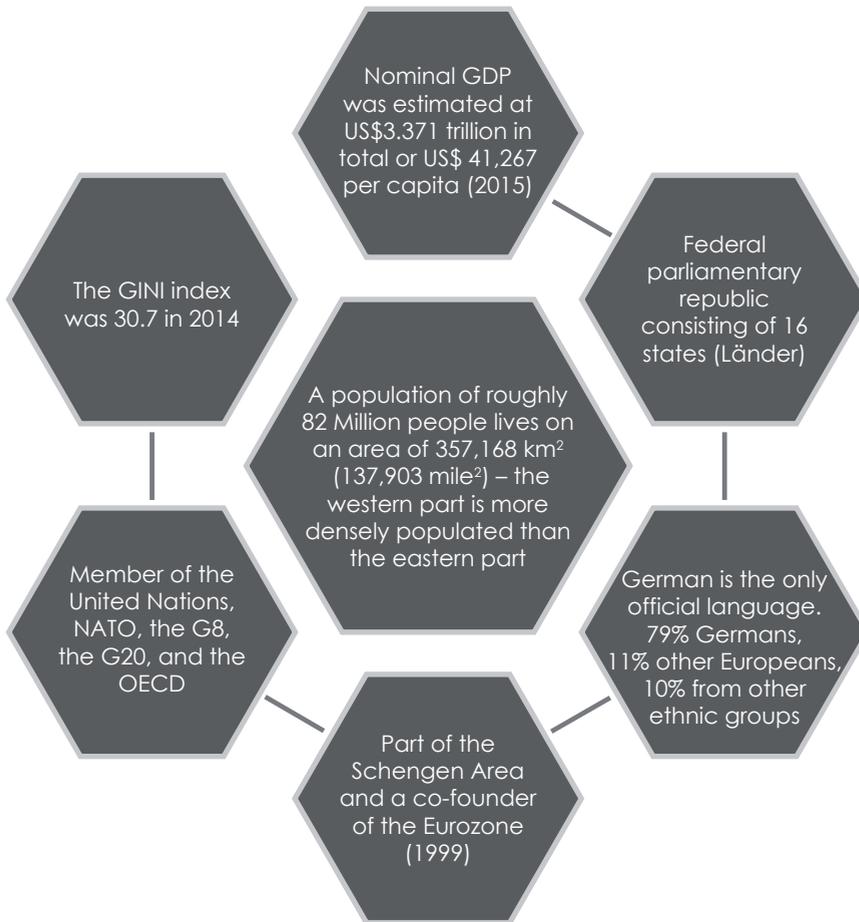
Being initiated under Chancellor Bismarck in 1883, Germany's social statutory insurance is one of the earliest systems offering formal healthcare coverage for employed people as a part of a social security system.

Since then, ever-changing environmental factors put continuous pressure on the functioning of the system:

1. the population grew to today approximately 82 million inhabitants,
2. scientific and medical progress has allowed the growth of an active healthcare industry, which today is an important pillar of the German economy,
3. better access to healthcare has increased longevity to a life expectancy at birth of 83.1 for women and 78.2 for men [1],
4. many otherwise deadly diseases can now be cured or controlled as chronic diseases, and
5. at the same time, the birth rate went down to currently about 1.5 children per woman (2015) [1] and therefore, a decreasing number of younger working people have to bear the increasing bill of total social security cost.

Due to all these developments, healthcare expenditure has been continuously increasing to today about 11.3% of the German Gross Domestic Product (GDP) [2] and throughout the ongoing dynamics, the German healthcare system has experienced many revisions and changes over the years.

Particular events were the split of Germany into two politically and economically strictly separated parts in 1949 and the reunification into the current Nation with the capital of Berlin in 1990. During these 50 years, the eastern part (about 1/3 of the territory; today 5 states plus Berlin) as "German Democratic Republic" was under the rule of the socialist Union of Soviet Socialist Republics (USSR) and the Western part (Federal Republic of Germany with 10 states) under temporary control of the 3 other victorious powers (USA, UK, France) favoring a democratic political system of social market economy. The reunification of the two healthcare systems after 1990 was driven by the social statutory insurance system established in the West. Figure 1 summarized facts and numbers about Germany.



**Figure 1.** Facts and numbers about Germany

## The Healthcare System

German citizens finance and access their healthcare through two insurance options, the public health insurance scheme (89% of the population) or private health insurance (11%) (Figure 2), through their tax contributions and through out-of-pocket expenditure. Total healthcare expenditure in 2016 was the 5<sup>th</sup> highest among the OECD countries after the USA, Switzerland, Luxembourg and Norway with USD 5,551/capita of which USD 23/capita were out-of-pocket costs [3].

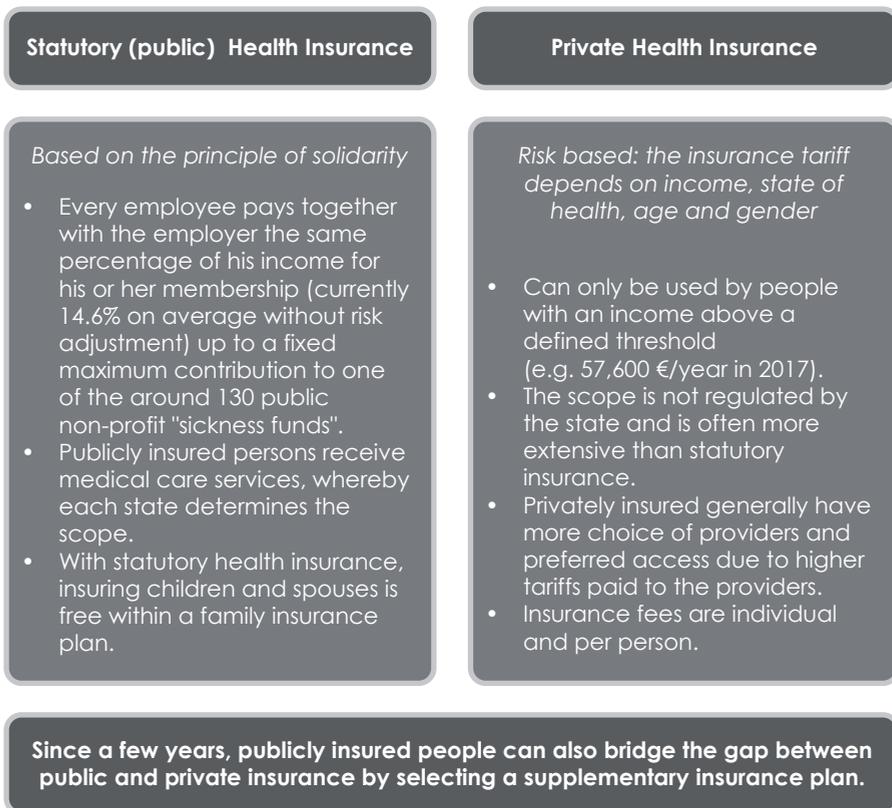
The entitlements, rights and responsibilities of insured individuals are defined in the German social legal code (*Sozialgesetzbuch – SGB*), most importantly in part V (*SGB-V*),

which establishes the regulatory framework for the Statutory Health Insurance (SHI) system. The aims of the German Statutory Health Insurance are summarized in Figure 3.

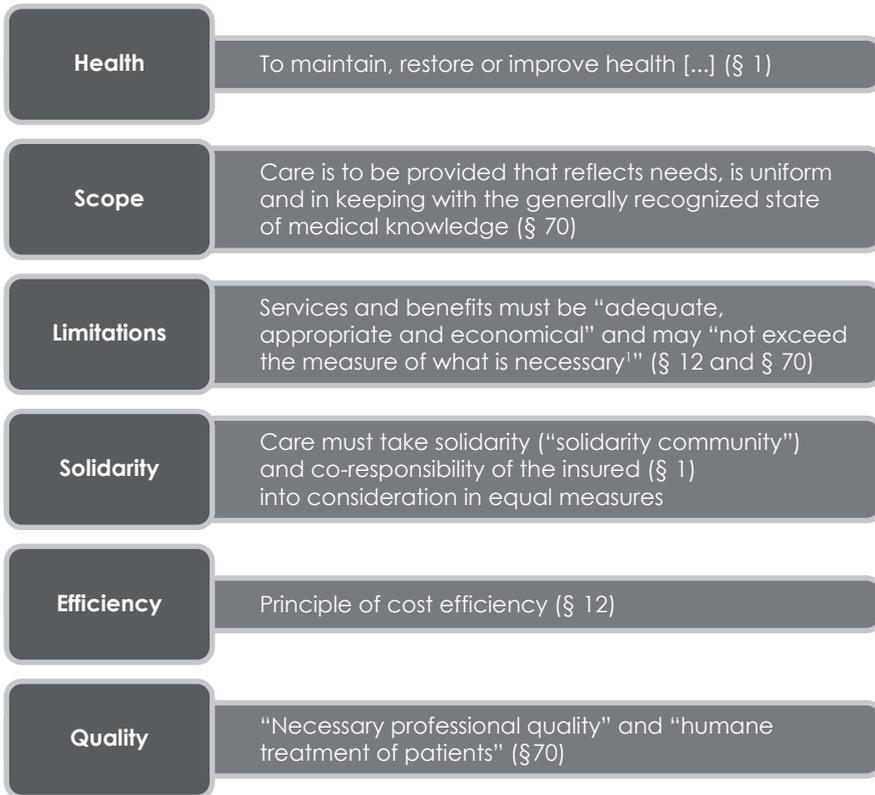
With an expenditure on pharmaceuticals of USD 678 per capita (USD PPP), Germany is one of the highest pharmaceutical spenders among OECD countries (OECD average USD 515 PPP) [4].

The latest major reform was introduced in 2011 with the Act on the Reform of the Market for Medicinal Products (*Arzneimittelmarktneuordnungsgesetz – AMNOG*), which regulates the processes for pricing and reimbursement of newly authorized pharmaceuticals.

More adaptations can be expected in future since the challenges continue to grow due to continuing dynamics and external pressures such as EU pressures around cross border healthcare or the influx of a considerable refugee population from economically and politically unstable regions in Asia, the Middle East and Africa.



**Figure 2.** Public and private health insurance in Germany



**Figure 3.** Aims and frame of the German Statutory Health Insurance System as defined in the social legal code (SGB-V)

<sup>1</sup> The 'necessity' needs to be proven by evidence; there is no right for access to a therapy if the evidence is missing [6]

In addition, there is still room for improvement. A recent study comparing 195 health-care systems worldwide through a Healthcare Access and Quality Index based on the Global Burden of Disease Study 2015 ranked Germany on place 20 after many other European countries and Australia [5].

## 2.2 Pathways of Market Access (Regulation, Pricing, and Reimbursement)

### Market Authorization

The licensing of pharmaceutical products mostly follows EU laws and regulations, which were adopted to the German National Law. The admission of pharmaceuticals for

humans on to the market is the responsibility of the Paul Ehrlich Institute (blood, blood products, sera and vaccines) and the Federal Institute for Pharmaceuticals and Medical Devices (all other products) [6]. National regulation applies for those substances which have not yet undergone regulatory assessment by the European Medicines Agency (EMA).

## Coverage and Reimbursement of Pharmaceutical Products

Germany does not have a “positive list” of pharmaceuticals reimbursed (covered) by the German statutory health insurance (*Gesetzliche Krankenversicherung* – GKV). However, drugs which are not effective for the desired purpose or where the effect cannot be evaluated with certainty, can be excluded from reimbursement under SGB-V rules. Since 2004, the decision on reimbursement of drugs is under the responsibility of the Federal Joint Committee. Their decisions are legally binding and may also limit the prescription of drugs to certain indications, or determine the therapeutic steps in specific diseases.

On 11 November 2010, the German parliament passed the law called AMNOG which regulates pricing processes for newly authorized pharmaceuticals and their reimbursement by statutory health insurance providers. The core of this law is the benefit assessment in accordance with the German Social Code, Book Five (SGB-V), section 35a. The Federal Joint Committee (*Gemeinsamer Bundesausschuss* – G-BA) was charged with the implementation and with the activities of benefit assessment with the support of the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* – IQWiG). Pharmaceutical companies are obliged to submit a dossier on product benefit for all products newly launched on the German market or authorized for new indications.

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

The AMNOG defined a new way to assess the value of patented medicines and the reimbursement category at the time of launch. This was intended to counteract increasing prices of newly launched pharmaceuticals and to reduce the time until a fair price was determined.

### Steps to benefit assessment

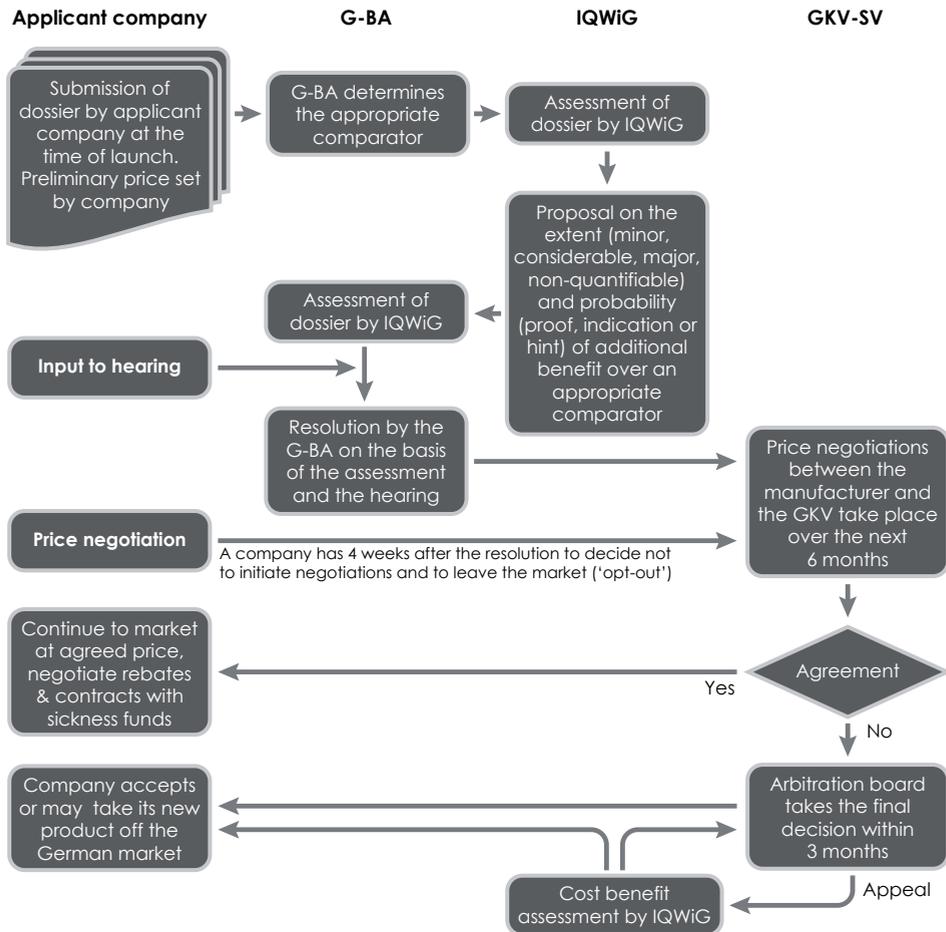
Figure 4 summarizes the 6-month process of deciding on the reimbursement price following the AMNOG.

1. At the time of launch of a new active substance or a new indication, the company submits an evidence dossier to the G-BA who, in most cases, will charge IQWiG with an evidence review for assessing the additional benefit relative to a comparator (standard of care as defined by G-BA). During the time of the assessment and decision process the product can be marketed at a price set by the company.
2. The strongest driver for the extent and probability of additional benefit are the results of the relevant randomized clinical trials. The G-BA will publish the results on the website based on the IQWiG report and potential additional considerations. The

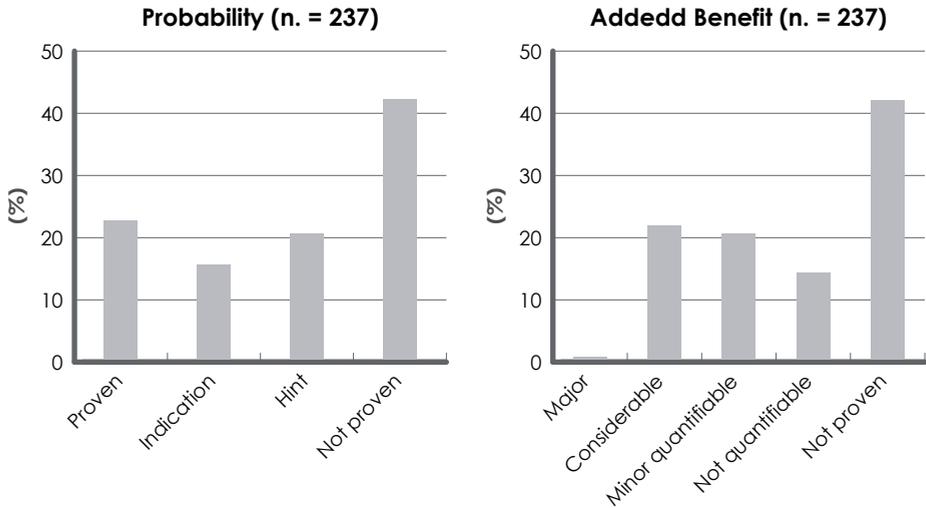
extent of benefit is categorized as major, considerable, minor, non-quantifiable, or worse while the probability can be described as no prove, hint, indication, or prove.

3. The company or other stakeholders can comment during a hearing
4. The G-BA will elaborate a resolution based on the assessment and the hearing

The same product can be rated with different results for different patient sub-populations. The results of G-BA decisions over the years 2011-2016 are summarized in Figure 5. Only few applications have been considered to have proof for considerable added benefit. Between 2011 and 2014, IQWiG had submitted 60 assessment reports on non-orphan therapies to the G-BA. Of these, 32 (53%) stated no additional benefit, and 28



**Figure 4.** Pricing and reimbursement process in Germany according to AMNOG  
 G-BA = Federal Joint Committee; GKV-SV = National Association of Statutory Health Insurance Funds; IQWiG = Institute for Quality and Efficiency in Health Care



**Figure 5.** G-BA extent of additional benefit for pharmaceuticals and stated probability in the period 2011–2016 (based on data from the G-BA website)

found additional benefit (47%) classified as major in 6 cases, considerable in 12 cases, minor in 8 cases, and not quantifiable in 2 cases [7].

## Orphan Drugs

A special legal framework allows the automatic recognition of additional benefit with an abbreviated submission dossier for drugs with European orphan drug designation [8] without additional benefit assessment in comparison to the current standard of care if the GKV expenses stay below € 50 million per 12 months [9]. Because of the legal link of orphan drug designation to the market authorization a large number of the assessments cannot conclude a quantifiable additional benefit due to lack of relevant evidence, and they are rated as ‘non-quantifiable additional benefit’. The G-BA may define a time limit for its resolutions to allow further assessment after a period of post-marketing experience. If the 12-month sales exceed the limit of € 50 million, IQWiG will be charged by the G-BA with conducting a full assessment versus an appropriate comparator. A few case studies have been summarized by Bouslouk and colleagues in 2016 (Box 1) [9].

Like with non-orphan drugs, the manufacturer of orphan drugs must negotiate the price with the GKV-SV. Although all negotiation up to now could be concluded successfully, this may be a challenge because of the lack of comparators or comparative data [9].

The AMNOG process had to be adapted for orphan drugs to compromise between the strict German requirements for high-quality evidence and the strive for faster market access for break-through therapies pushed by the EU and EMA. Similar adaptations may

### Box 1. Orphan Drugs. A Case Study

In 2013, the Vertex Pharmaceuticals cystic fibrosis drug Kalydeco (ivacaftor) has been given a high additional benefit rating in one group (12 years and older), and a low one in another (children between 6 and 11 years) for the treatment of cystic fibrosis (CF) in patients with the G551D mutation. Although Kalydeco had received European orphan status and Vertex had calculated that the annual cost of treatment in Germany with Kalydeco would be € 45 million (which was below the threshold of € 50 million for orphan drugs in Germany), it had to undergo the assessment of the benefit because the German Institute for Quality and Effectiveness in Healthcare (IQWiG) estimated that the actual figure will be about € 53 million [9].

happen in future but the political and institutional pressure for the AMNOG pathway in Germany will continue to be strong. Therefore, we will continue to see disputes such as a current example of Crizotinib in the treatment of lung cancer. G-BA decided that there is no prove for additional benefit, the medical professional societies however, see a major advancement for the 300-400 patients with lung cancer and the ROS1-gene mutation and recommend the product as first line treatment [10]. The discrepancy is caused by the limited evidence from randomized controlled trials, a consequence of a low number of patients and the ethical challenges.

### Pharmaceutical Care Strengthening Act (Arzneimittelversorgungsstärkungsgesetz – AMVSG)

Recently, a new law AMVSG (Figure 6) has been approved to complement AMNOG by strengthening and adapting the provision of healthcare, especially to special populations (rare diseases, pediatric diseases etc.) [11]. A key objective is again to further control the cost of pharmaceuticals and avoid overspending throughout the period of free pricing in the first year between launch and completion of the price negotiations with the GKV-SV.

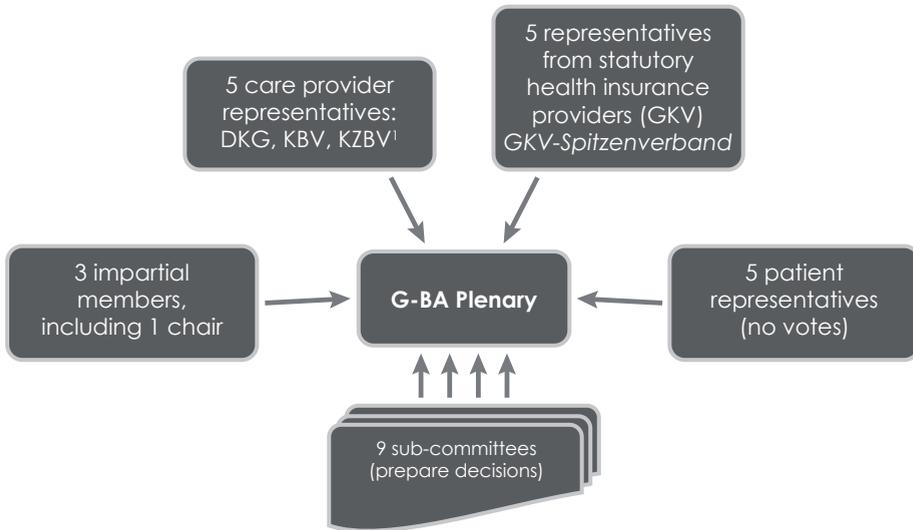
### The Role of the G-BA

The Joint Federal Committee (*Gemeinsamer Bundesausschuss* – G-BA) is the highest decision-making body of the joint self-governance of physicians, dentists, psychotherapists, hospitals, and health insurances in Germany. The G-BA “issues directives for the benefit catalogue of the statutory health insurance funds (GKV) for more than 70 million insured persons and thus specifies which services in medical care are reimbursed by the GKV” and “specifies measures for quality assurance in inpatient and outpatient areas of the health care system” [12].

The leading umbrella organizations of the self-governing German healthcare system form the G-BA: the providers (Physicians, Dentists, Hospitals) and the insurances (GKV-

<b>Pediatric Meds</b>	Consideration of specific properties of pediatric medicines in the benefit assessment
<b>Antibiotic resistance</b>	Consideration of the impact on antibiotic resistance in the benefit assessment
<b>Reduced year 1 budget impact</b>	Limitation of the free pricing period until a total cost of € 250 million
<b>Sub-Population Restrictions</b>	G-BA can exclude patient sub-groups from reimbursement if Added Benefit is not evident
<b>Provider Dissemination</b>	Integration of benefit assessment results into the electronic health record software in physician offices
<b>Re-Application Submission</b>	Shorter minimum time until a new application can be submitted with new evidence
<b>Individual cost exceptions</b>	Options for individual exceptions to the maximum budget to be spent for new medicines with unproven medical benefit
<b>Precision Medicine</b>	Improved regulation of reimbursement of diagnostics for targeted use of antibiotics
<b>Net price confidentiality</b>	The decision to refrain from transparency of net prices
<b>EU compatibility</b>	Other regulations to facilitate the provision of healthcare services and to make the German law compatible with new EU requirements

**Figure 6.** Constituents of the *Arzneimittelversorgungsstärkungsgesetz (AMVSG)* to be introduced in 2017 [11]



**Figure 7.** Composition of the G-BA [12]

<sup>1</sup> Care providers are entitled to vote only on issues affecting their area of expertise  
 GKV-Spitzenverband = National Association of Statutory Health Insurance Funds; DKG = German Hospital Federation; KBV = National Association of Statutory Health Insurance Physicians; KZBV = National Association of Statutory Health Insurance Dentists

SV). Patient representatives also participate in all sessions; they are entitled to put topics on the agenda, but not to vote.

The plenary decision body is composed of 13 voting members and 5 non-voting members (Figure 7).

### The Role of IQWiG

The Institute for Quality and Efficiency in Healthcare (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen – IQWiG*) was founded in 2004 with the mission to produce independent evidence based expert reports on the quality and efficiency of therapies in the German healthcare system, comprising pharmaceutical and non-pharmaceutical methods, clinical guidelines, and disease management programs. IQWiG will only analyze and assess existing data without having decision power or own research capacities.

IQWiG can be commissioned by the G-BA or the Ministry of Health (*Bundesministerium für Gesundheit*) or can conduct assessments on own initiative. Since 2016, additional assessments will be generated on selected therapies proposed by patients [13].

G-BA will consider the evidence review produced by IQWiG but will not always follow the recommendations. Between 2011 and 2015, G-BA deviated from IQWiG's recommendations in 32% of all judgements [14]. While IQWiG aims to follow a strict scientific analytical process, G-BA may see a broader picture of health policy and modulate its recommendations around the needs and input or various stakeholders in health-care [15].

## Methodological Requirements for Early Benefit Assessment in Germany

The main source for the assessment is the dossier provided by the applicant. The dossier to be submitted in German language has a defined structure and format including the technical standards and documentations. The template and guidance for completing the dossier can be downloaded from the G-BA website. The completeness of the dossier can be controlled using a standardized checklist (also available from the G-BA website). A normal dossier can have around 300 pages plus supporting documentation of about 1000 pages. A comprehensive and in depth description of the requirements can be found in a review by Ivandic et al [16].

## Impact of G-BA Decisions on Pricing and Reimbursement

During the 4 weeks after the resolution of the G-BA (see Figure 4), the company can decide to 'opt out' and discontinue to market the product in Germany. Otherwise, the published resolution of G-BA will inform the National Association of Statutory Health Insurances (*Spitzenverband der gesetzlichen Krankenversicherungen – GKV-SV*) for the price negotiations during the following 6 months. If a drug has been categorized differently for different patient sub-populations, the health insurers will aim to negotiate an average price which reflects the added benefit and number of qualifying patients in each of the sub-populations.

The manufacturer can continue to market the product in Germany after the agreement. Without agreement, an arbitration board will make the final decision within 3 months. An in-depth cost-benefit assessment by IQWiG may be requested. In the end, the manufacturer must accept the final decision on the reimbursement price or leave the market.

If no added benefit was proven by the submitted evidence, the health insurers will aim to fix the price in relation to the price of the comparator treatment, which may be a low-cost treatment. In most cases (about 80%) between 2011 and 2016, the negotiations between the GKV-SV ended with an agreed reimbursement which up to now, was rarely fixed to a reference group (about 2%). In about 13% of cases, an arbitration board had to make the final decision on the reimbursement. Some manufacturers (< 10%) decided after a negative outcome of the G-BA decision to opt-out and to not market their product in Germany; another 10% decided to withdraw the product from the market (mostly products for chronic diseases with low-cost comparators).

The rating will be the base for the reimbursement discussions, but the resulting price is influenced by additional factors such as added benefit in different subgroups, the choice of comparator on subgroup level, or even by political or contextual healthcare considerations [15]. Price premiums are driven by health gain, the share of patients benefiting from a pharmaceutical, European price levels, and whether comparators are generic [17].

## 2.3 Mapping and Structure of Decision Makers (Reimbursement/HTA)

### Healthcare Policy

Healthcare related decision making is shared by the states (*Bundesländer*), the federal government and institutionalized civil organizations.

Key players with impact on healthcare on the **federal level** are the Federal Assembly (*Bundestag*), The Federal Council (*Bundesrat*), and the Federal Ministry of Health (*Bundesministerium für Gesundheit*). The Ministry supervises a few agencies including the Federal Institute for Pharmaceuticals and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*), which authorizes pharmaceuticals or medical devices and supervises their safety, the Paul Ehrlich Institute (Federal Institute for Vaccines and Biomedicines) organizing licensing of vaccines and biomedicines, the German Institute for Medical Documentation and Information (*Deutsches Institut für Medizinische Dokumentation und Information – DIMDI*) charged with information services around medicines, medical devices, life sciences, and healthcare and with publishing the German versions of classification systems such as the International Classification of Diseases (ICD-10-GM), the International Classification of Functioning, Disability and Health (ICF) and the German Procedure Classification (*Operationen- und Prozedurenschlüssel*).

### Payers

As mentioned above, about 72 million people in Germany are insured in one of the 113 sickness funds (status of 1. January 2017) [18]. Since 2008, all sickness funds are represented on a federal level by the Federal Association of Sickness Funds (*GKV-Spitzenverband*) in all non-competing matters and negotiations. Leading sickness funds are the Techniker Krankenkasse (7.4 million members, 9.9 million insured in 2017), the Barm-er GEK (7.5 million members, 9.4 insured), and the Deutsche Angestellten Krankenkasse (4.7 million members, 5.8 insured) [19]. The Federal Association of Sickness Funds delegates 5 members to the Joint Federal Committee (G-BA) and thus, strongly influences the key decisions in healthcare.

Private health insurance companies have formed an own association (*Verband der privaten Krankenversicherungen*) through which they lobby for their interests.

## 2.4 Organizations/Physician or Patient Organizations

A few quasi-public **institutionalized civil organizations** represent key stakeholders in the healthcare system. Physicians and dentists must be registered members in regional and federal physician associations (*Kassenärztliche Vereinigungen*), with representation at federal level by the Federal Association of GKV Physicians (*Kassenärztliche Bundesvereinigung*). All healthcare providers must also be members of their respective professional chambers (physicians, pharmacists, psychologists, etc.) and adhere to their educational and ethical standards. In addition, there are many medical or scientific professional organizations which are either engaged in lobbying activities or have scientific-medical objectives.

Over the last years, patients have gained more visibility and influence on healthcare decisions. There are an uncounted number of local self-help organizations and patient counselling groups, some of them are semi-organized on the federal level by taking part in the forum for the Chronically Ill and Disabled (*Forum chronisch kranker und behinderter Menschen*) or by participating in the Association of Independent Voluntary Welfare Organizations, or the Federal Alliance for the Support of the Disabled (*Bundesarbeitsgemeinschaft Selbsthilfe von Menschen mit Behinderung und chronischer Erkrankung und ihren Angehörigen*) or the German Disability Council (*Deutscher Behindertenrat*) for lobbying activities.

Hospitals are also members of self-governing organizations such as the German Hospital Federation which is also represented in the G-BA.

The pharmacists are members in the regional chambers and, for the majority, in the German Organization of Pharmacists (*Deutscher Apothekerverband*) with a high lobbying profile.

Germany is home to many pharmaceutical companies. Their network organizations differ from each other by the type of member companies (e.g., the Association of Research-based Pharmaceutical Companies – *Verband forschender Arzneimittel-Hersteller*, VFA) represents the companies with strong research arms, the Federal Association of the Pharmaceutical Industry (*Bundesverband der Pharmazeutischen Industrie*) represents small and medium-sized companies, the Federal Association of Pharmaceutical Manufacturers (*Bundesfachverband der Arzneimittel-Hersteller*) lobbies for manufacturers of over-the-counter (OTC) pharmaceuticals, and the German Generics Association (*Deutscher Generikaverband*) and Pro-Generics for generics manufacturers. In addition, there are associations for medical device manufacturers or for other healthcare technologies.

## 2.5 Challenges and Catalyzers for Market Access

While the G-BA considers the implementation of AMNOG and the supporting processes mostly a success story, there are also critical voices from other stakeholders such as medical societies or the pharmaceutical industry. Some of the challenges or potential catalyzers are discussed in more detail below.

## Comparison to Other Countries

An international comparison of decisions for comparable patient groups resulting from health benefit assessment of pharmaceuticals during the 4 years of 2011 to 2014 in Germany versus the UK National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC) and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) revealed astonishing disagreements [20]. Only 40% of the final G-BA decisions were in line with those of NICE, 47.6% with SMC, and 48.7% with those of Australia's PBAC. The differences start already with the definition of the comparator. The agency's conclusions on comparative effectiveness only overlapped slightly more: G-BA agreed with NICE in 52.7%, with SMC in 64.5%, and with PBAC in 69.7% of patient subgroups.

## Categorization into 'No Prove for Additional Benefit'

Often, the reason for the classification of 'added benefit not proven' is not the lack of evidence but rather that the submitted evidence was disqualified during the process [21].

## Patient Subgroup Analysis and Subgroup Exclusion

G-BA has always insisted in the analyses of subgroups with the clinical trial data ("slicing of data"), which has strongly influenced the categorization of the result [21]. With the new Pharmaceutical Care Strengthening law (AMVSG) introduced in 2017 G-BA can decide to exclude patient sub-groups from reimbursement if the Added Benefit is not evident and thereby, G-BA will limit the treatment choice of physicians. Sub-group analysis may require higher patient numbers and IQWiG may rate studies low if a patient subgroup fails due to low patient numbers and the exclusion of patient sub-groups from reimbursement limits the treatment choices available to the physicians and patients. For companies submitting dossiers for new pharmaceuticals in Germany, it will be important to anticipate the extensive sub-group analysis and to be prepared for contingencies with limited reimbursement [22].

## Additional Turnover Threshold for the First-Year Sales

Estimates are that the newly introduced first-year budget impact threshold of € 250 million will hit about 50% of all new agents. Manufacturers must anticipate the Net Present Value impact of crossing the € 250 million threshold and develop appropriate contingency plans [22].

## Selection of Comparator

The selection of the comparator by the G-BA is strongly driven by the organizations represented in this decision board and is often not aligned with the clinical guidelines or

clinical expertise of medical societies. The cost-effective comparative therapies are often generic drugs or “best supportive care” and this comparator will also be used by the GKV-SV to negotiate the price. A 2013 revision of AMNOG permits G-BA to name several comparators. This allows companies to submit studies which are using any of these comparators and hence, increase the flexibility for evidence submission. However, there is still a perception, that the selection of the comparator often does not follow medical-clinical criteria but more the need for a subsequent low-cost negotiation base [21].

Initiating specific studies for Germany to improve the rating is often not justifiable due to the extra-cost of development. Hence, some manufacturers decided to not market a product in Germany, when the discussion about the choice of comparator could not be resolved.

## Patient Relevant Endpoints

The AMNOG requires the comparison of impact on patient relevant clinical endpoints, namely measures like morbidity, mortality, and quality of life, as opposed to surrogate endpoints. This limitation causes heated discussion between the decision-making body, the pharmaceutical companies, and the clinical community (Box 2). For example, Progression Free Survival (PFS), which is used as a key endpoint by the clinical community, is often not accepted as endpoint for comparison because it combines mortality and morbidity.

## Early Advice by G-BA

The G-BA offers non-binding early advice for pharmaceutical companies planning to access the German market with a new therapeutic. The best time for such interaction is when the company has formed a clear position on the expected value proposition and evidence generation strategy and study protocols have been designed but can still be modified.

The formal request for the process to G-BA must use a standard template and include a summary of the study design, the questions, and the own standpoint what the answers to these questions will be (in German language). G-BA has 8 weeks to prepare the response. A face to face meeting lasting between 20 and 120 minutes will take place with G-BA ex-

### **Box 2. Patient Relevant Endpoint. An Example**

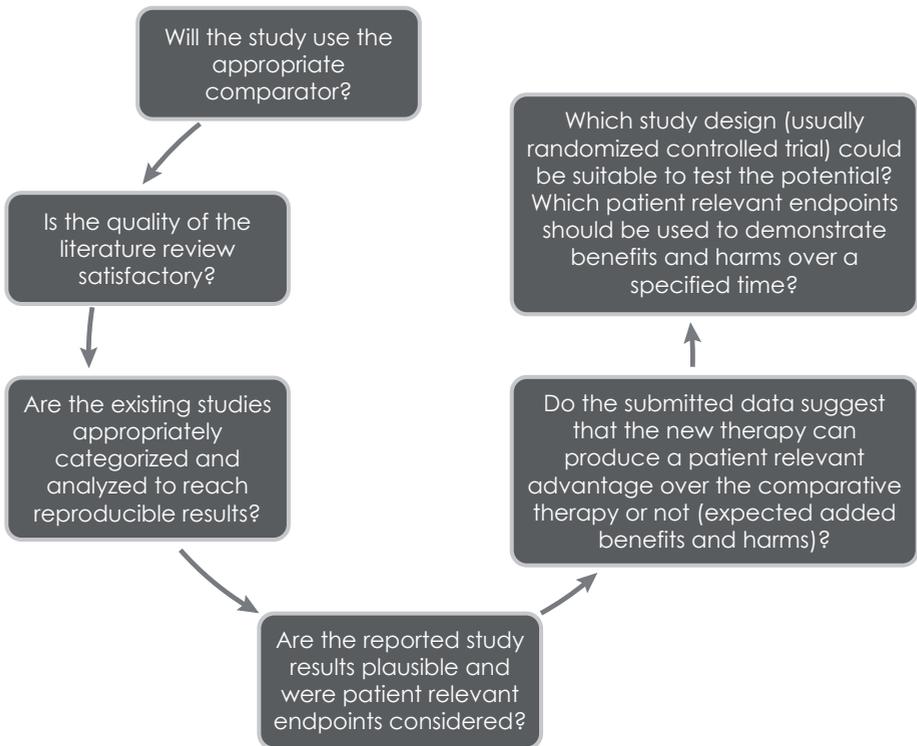
In the case of the hepatitis drugs Victrelis (boceprevir) and Incivek (telaprevir), IQWiG refused to recognize sustained viral response (SVR) as patient relevant endpoints and consequently the clinical evidence measuring SVR was rated as not relevant and therefore, no proof for added benefit was recognized. However, after heated discussions with the other stakeholders, G-BA deviated from IQWiG's recommendation and rated the products as “benefit not quantifiable”, which allowed to negotiate a reimbursement price with the insurers.

perts but not with the actual current decision makers. Therefore, there is no room for including additional information, data, or arguments. The request should already include all material of interest.

Two weeks after this meeting, the G-BA will provide written minutes, to which the company can provide written comments.

### Coverage with Evidence Development

An option for new treatment alternatives with insufficient evidence was introduced in 2013 with the law for improvement of the health service structure (§137e SGB-V). If the potential of the new therapy is recognized after review of the evidence base or manufacturers propose such a solution, G-BA can now allow access to a new therapy under the condition that additional evidence will be developed in a clinical study which has been designed in agreement with the G-BA. For the applicant, this allows early access to promising new therapies and for G-BA it is now possible to design a subsequent study of high relevance for G-BA (Box 3).



**Figure 8.** IQWiG's 6 steps for assessing the potential for improving the evidence base for a new therapy [23]

### Box 3. Coverage with Evidence Development. An Example

In May 2017, Germany's Federal Joint Committee (G-BA) issued its assessment of Lartruvo (olaratumab; Eli Lilly, United States) in the treatment of adult patients with advanced soft-tissue sarcoma, in combination with doxorubicin, in the case of patients who cannot undergo surgery or radiotherapy and who have not previously been treated with doxorubicin. Because of the orphan drug status, the G-BA assessed its additional benefit based on a Phase 2 study in which Lartruvo in combination with doxorubicin was compared with doxorubicin in monotherapy on a conditional base (pending more data). According to the G-BA, Lartruvo demonstrated a considerable improvement in overall survival of on average 11.8 months. Because data for the assessment of health-related quality of life and disease-specific symptoms were missing, the G-BA restricted the duration of the validity of its decision on Lartruvo's added benefit for 3 years expecting the results from a Phase 3 clinical trial.

IQWiG will assess the potential of the product to be a new and necessary treatment alternative based on the mode of action and the existing evidence base as documented in the application. The review follows 6 key steps (Figure 8) and a recommendation must be given within 6 weeks of the application [23].

### Adaptive Pathways

In August 2016, IQWiG took a critical position against the report of the European Medicines Agency on the pilot study for adaptive pathways. The use of real world data to produce evidence on benefits and harms after the market authorization was not seen as a sufficiently resilient procedure.

### Uptake of Products after Positive G-BA Decision and Conclusion of Price Negotiations

The uptake of innovative products even after a positive G-BA decision and conclusion of price negotiations may remain limited due to demand regulations on the prescriber side, which prevent doctors to make full use of new medications and patients from having access [21].

## 2.6 Key Success Factors for Market Access in Germany

While the final reimbursement price cannot be predicted from the outset of the evidence analysis and price setting process, there are a few key items that should be considered when planning to market a product in Germany:

- Using the opportunity for early guidance by G-BA will improve the understanding of the data and endpoints needs and the appropriate comparator in the target population or some of the expected sub-groups.
- Follow the rules, use the dossier template and instructions, and fulfill the requirements for data, endpoints, and the choice of comparator in the clinical trial design.
- Anticipate the need for subgroup analysis and its potential impact on the perceived benefit of the therapeutic.
- Understand the stakeholder roles as decision makers or influencers including the clinical community, the patient advocates, the payers, or health policy.
- Understand G-BA and the health insurers to build your negotiation “tool box”.

Finally, the cost of meeting all the requirements of the German decision bodies may be high. It will be important to manage and monitor the risks connected with the German submission.

## 2.7 Look-out for Near Future

Comparing prices for pharmaceuticals between countries is generally difficult due to a lack of price transparency and variable components of retail prices. Yet, Germany is frequently counted among the countries with comparably high prices for new patented drugs such as for treatment of cancer or rare diseases [4]. Some of these new medicines may bring great benefits to patients, but others may provide only marginal or even no improvements. The proliferation of high-cost specialty medicines and increasing patient pressure for access to these medicines will continue to be a major challenge to the efficiency of pharmaceutical spending in Germany. Therefore, cost-containment measures are applied frequently, including the freeze on the prices of medicines not included in reference-pricing groups and mandatory discounts, which all have a negative effect on producers' profitability. It can be expected that the German health policy makers will continue to support initiatives aiming at prescription and consumption of lower-price generics or biosimilars, applying value-based pricing models centered around added benefit of new medicines, and increasing the transparency of reimbursement prices, e.g., through publication of net prices [24].

Further reforms may also be expected concerning the German dualistic health insurance system. For example, the model of a citizen insurance has been discussed in order to ensure future financing and improved equity in German healthcare [25]. However, the focus of the German health policy will for the next years remain more efficient use of resources, strengthening primary care, reducing pharmaceutical spending, and reducing risk factors such as harmful alcohol consumption.

## 2.8 Acknowledgements

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## 2.9 References

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