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White Paper: Orphan Drugs in Germany – lessons learned from AMNOG, best and worst practices and strategic implications

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Orphan Drugs in Germany – lessons learned from AMNOG, best and worst practices and strategic implications.

Abstract

The AMNOG, the legislative framework governing the market access of innovative prescription drugs in Germany, has implicated a paradigm shift in the examination of the value of a pharmaceutical and in the setting of an appropriate reimbursement level for the product. Based on the evidence of available study data, the additional benefit over the existing standard of care is assessed by the most powerful German health authority, the G-BA. Depending on the classification of the benefit category, the pharmaceutical manufacturer negotiates the final refunded price with the umbrella organization of the German statutory health insurances. For orphan drugs, there are specific challenges that the manufacturer has to meet. Due to the randomness of the disease, subpopulations are small and study data are scarce. This leads to a considerable uncertainty about the perceived value of the drug and, thus, to intense and sometimes tough negotiations with high rebates in the end. Pharmaceutical companies planning to introduce new orphan drugs into the German market should prepare well in advance a sound and stringent strategy to optimize the performance throughout the entire market access processes. This white paper elaborates on all relevant issues and describes important recommendations for manufacturers facing these challenges.

Traditionally, prices in Germany have always been highest in Europe but due to increasing drug expenditures, various cost-cutting measures have also been put into effect as in other European countries.

Germany was one of the few EU countries where, before 2011, pharmaceutical companies have been largely free to set the prices for their new drugs. This free price setting mechanisms in Germany led to high prices of patented pharmaceuticals and increasing expenditures in the pharmaceutical sector in the past. Like in most other countries of the European Union, the public spending on health care exceeded the GDP growth in Germany. The pharmaceutical spending of the Statutory Health Insurance (SHI), which covers more than 87.6% of the German population, for instance, increased from € 21.8 billion in 2000 to € 39.1 billion in 2015.

To curb these growing expenditures, a price moratorium has initially been introduced so that prices of prescription drugs keep the 2009 price level until the end of 2017. The German government's Act to Strengthen the Provision of Medicines in Statutory Health Insurance recently extended the price moratorium until the end of 2022. However, this measure does not affect the pricing of medicines for new active compounds introduced on the German market. Moreover, the mandatory manufacturer's discount, oscillating since 2003 between 6% and 16% (currently 7%), has become a major cost containment lever, allowing health politics to adjust the overall pharmaceutical spending. As the mandatory discount is a general rebate for each and every product, it does not reflect the individual value of the drug.

Meanwhile, many European countries counteract increased pharmaceutical spending by introducing regulatory frameworks and instruments for pricing or reimbursement. Although structural and organizational details differ widely in country-specific pharmaceutical systems, the applied different

pharmaceutical cost containment measures for new drugs are similar, the most prominent of which are more or less external price referencing and negotiations of reimbursement contracts, and to some extent value-based pricing [1]. Particularly critical issues in assessing patented pharmaceuticals include (1) how therapeutic innovations are evaluated and (2) how their prices are set.

Especially the assessment and reimbursement of orphan drugs is tricky because the prices of orphan drugs are often high compared to non-orphan drugs, due to the small patient population which subsequently leads to a lack of sufficient clinical and cost data. Many orphan drugs receive market authorization under exceptional circumstances, as their value claim is based only on phase II data. Making recommendations on the reimbursement of orphan drugs may therefore be difficult for European Health Technology Assessment (HTA) agencies due to these deficiencies [2].

The AMNOG regulation, introduced in 2011 in Germany, changed the game for new drugs completely.

In order to control patented pharmaceutical prices and to curb increasing pharmaceutical spending, the German parliament passed the Act to Reorganize the Pharmaceuticals' Market in the Statutory Health Insurance System (AMNOG) on November 11, 2010, which brought a paradigm shift in the use of drug innovations in Germany [3].

Within the first 12 months after pharmaceuticals' market authorization, manufacturers are still free to set their prices. Nonetheless, they are required to give statutory health insurances (SHIs) the mandatory discount of 7% on these pharmaceuticals. In contrast to the former situation in which pharmaceutical manufacturers were able to set prices at their determined price level, AMNOG aims to define an amount of reimbursement that reflects the additional benefit of a pharmaceutical based on an early benefit assessment after the first 12 months. Because Germany is one of the most influential reference countries in Europe, the reform has an impact also in Europe, particularly in those states using Germany as a reference country for price setting. This might trigger potential price spirals in countries that use Germany as a reference for pharmaceutical price setting (see also Figure 1) [3, 4].

Figure 1: Germany's impact as reference price country

Now, at the point of market authorization (or within 1 month after a label extension), the industry is required to submit a comprehensive dossier to the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA, the supreme decision-making body of the joint self-governing board of stakeholders in healthcare – physicians, dentists, psychotherapists, hospitals, and sickness funds in Germany) to demonstrate the additional therapeutic benefit of the newly approved pharmaceutical compared to an appropriate comparator therapy (ACT). The ACT is determined by the G-BA and can be finally discussed by the pharmaceutical company in an advisory meeting with the G-BA in advance.

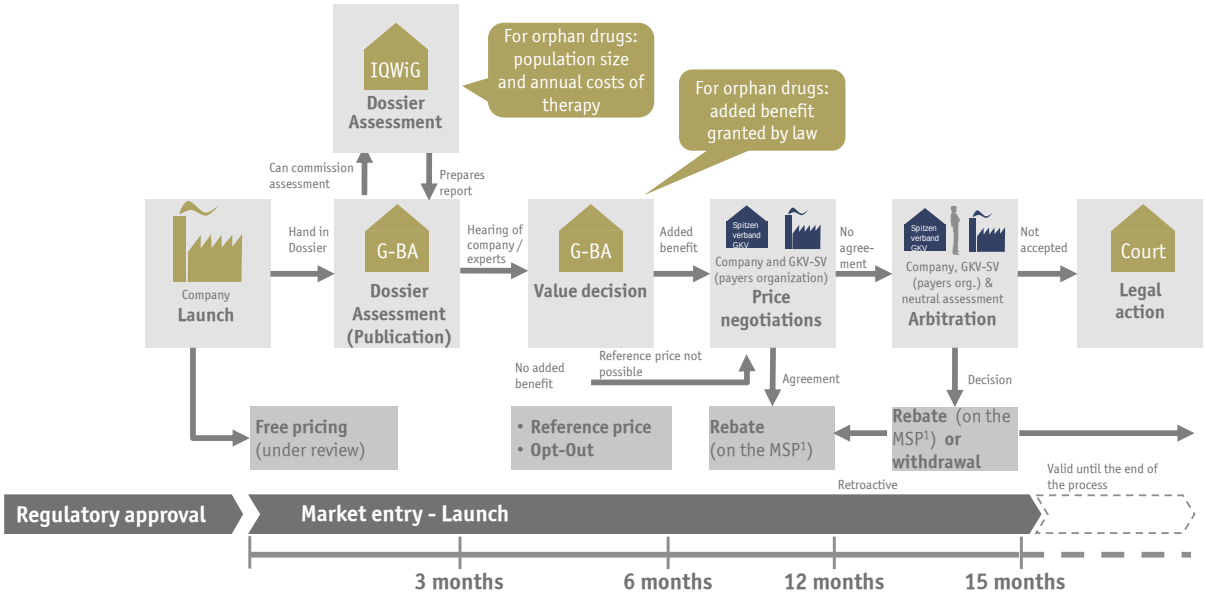

Figure 2: Overview of the Early Benefit Assessment process

After granting the extent of the additional benefit by the G-BA, the manufacturer is entitled to negotiate the reimbursement price with the GKV-SV (National Association of Statutory Health Insurance Funds). The reimbursement price is defined as a discount on the drug price at launch, or, as the insurances see it, as a premium on the comparator's price. As the price or discount negotiations between the manufacturers and the GKV-SV takes place behind closed doors, the factors influencing the results of the negotiation are not transparent (lessons learned from our experience as principal negotiators for the pharmaceutical industry: see below).

The process of the early benefit assessment according to AMNOG is very structured but still very complex and the dossier is just the first step (see Figure 2).

First step: Dossier assessment

With the exception of orphan drugs the G-BA by convention commissions the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) to initially evaluate the additional benefit. Three months after the dossier submission, the IQWiG's proposal on the extent and the probability of the additional benefit in comparison to the appropriate comparator will be published on the webpage of the G-BA. In the case of orphan drugs, the initial assessment is carried out by the G-BA itself, with the exception of the epidemiology and the annual therapy cost calculations.

After the publication of the initial dossier assessment the pharmaceutical company has the opportunity to react with a written statement within 3 weeks of time. After another two to three weeks the pharmaceutical company has to face up to the representatives of the health care system in an oral hearing before the final resolution on the basis of the initial assessment and the hearing procedure will be published by the G-BA on its webpage. Besides the synopsis, summarizing the decision, the main underlying reasons ("Tragende Gründe") are published in a detailed decision and documentation document. The final decision made by the G-BA may differ between patient subgroups. The agreement

between G-BA's and IQWiG's benefit ratings is substantial, with the IQWiG's ratings tending to be often lower [5-7].

There are six classifications concerning the extent of the additional benefit: (1) major additional benefit, (2) considerable additional benefit, (3) minor additional benefit, (4) non-quantifiable additional benefit, (5) no additional benefit and (6) less benefit. Based on this classification, one of two courses of action concerning the price setting of a pharmaceutical will follow. The number and characteristics of studies provided, the certainty of results, and the observed effects determine the level or quality of evidence ('proof ', 'indication' or 'hint').

The methodological basis of the underlying assessment and the uncertainties regarding outcomes and study results generally are in accordance with the principles of evidence-based medicine and are based on four patient-relevant outcomes: mortality, morbidity, side effects, and health-related quality of life (HRQoL), as defined in the Social Code Book V (''Sozialgesetzbuch V''; SGB V). The IQWiG publishes its own assessment methodology in a specific ''General Methods'' paper (Allgemeine Methoden) including precise key elements on how assessments are to be carried out. Otherwise the process follows the G-BA's rules of procedure.

However, these documents can only provide general guidance on benefit assessment. Using patient-reported outcomes (such as QoL) in comparative effectiveness studies can be challenging, for example when it comes to selecting the appropriate instrument or interpreting results. Although the G-BA sees itself as a normative body, each procedure has its specific characteristics and may bear not directly foreseeable risks. Therefore, a comprehensive knowledge and understanding of the completed procedures is very helpful. For example, a definition of QoL is neither to be found in the legal texts nor in the IQWiG's ''General Methods'', but in some assessment reports, the IQWiG explicitly defines QoL as ''a complex construct comprising psychological, physical, and social domains'' (aclidinium bromide; vandetanib par. 5b; axitinib) [2, 7].

The G-BA's code of procedures includes three turnover-dependent thresholds for exceptional rules for orphan drugs and insignificance.

That the AMNOG is a "learning system" which is continuously enhanced is shown by the first orphan drug which underwent the early benefit assessment, Pirfenidone. The G-BA commissioned the IQWiG to assess the additional benefit over the appropriate comparator, in this case best supportive care (BSC). The IQWiG's assessment, published on December 15, 2011, failed to demonstrate any additional benefit which was not seen in line with the legal requirements. The written statements and especially the oral hearing on January 24, 2012, finally led to adjustment of the procedure. On the basis of its market authorization and supporting studies, Pirfenidone's extent of additional benefit was classified as non-quantifiable by the G-BA in its resolution published March 15, 2012 [6].

After these lessons learned, the G-BA adapted its procedure and the legal framework led to important modifications for orphan drugs. From then on, the G-BA itself performed the benefit assessment of further orphan drugs and did not commission the IQWiG anymore. Thereby, before the G-BA resolution, no clear classification of the additional benefit into categories is made in the initial G-BA's dossier assessment. As a consequence of the legal wording, the additional benefit for orphan drugs is already granted by law through the market authorization. The G-BA only decides on the extent of the additional

benefit, which it can rate as 'major', 'considerable', 'minor', or 'non-quantifiable'. The categories 'no additional benefit' or 'less benefit' are not applicable as well as a categorization of the probability of the additional benefit in the form of 'proof', indication' or 'hint', which only applies to non-orphan drugs. The IQWiG is only commissioned for the assessment of the number of eligible patients (plausibility check of the epidemiological model) and the costs of the treatment.

The reduced basis for the assessment of orphan drugs is the dossier, the market authorization studies and associated documents, especially the European Public Assessment Report and not a comparison over an appropriate comparator therapy. At the same time, however, this supposed advantage also presents several challenges for the pharmaceutical manufacturer, e.g. the absence of a clear initial statement on the data as a first guidance, no obvious basis for a price comparison in the price negotiations and an imminent re-assessment with a full dossier depending on the sales.

Figure 3: Sales-dependent thresholds

If the actual sales of an orphan drug exceed €50 million at GKV expenses over the previous 12 months, a re-assessment with an appropriate comparator will be conducted under the involvement of IQWiG. In this case, the additional benefit is not legally assured. [5]. This exception, however, applies exclusively to orphan drugs. All other new patented pharmaceuticals are assessed under the conditions of full dossiers unless it can be reasonably substantiated that the sales of the new brand will not exceed the €1 million threshold (insignificance threshold; see Figure 3). In specific cases, the pharmaceutical company might choose to introduce the new product via this route in terms of a 'silent launch'. This market access strategy could be advisable when, due to the rareness of the disease, it is unclear how many patients actually do exist and the clinical pathway is not established yet. However, it must be noted that the insignificance track needs a close interaction with the G-BA and the authorities' previous approval.

Results from early benefit assessments of orphan drugs

Since the introduction of AMNOG and as of Sep 21st, 2018, 75 orphan drug procedures have been completed by the G-BA (see Figure 4).

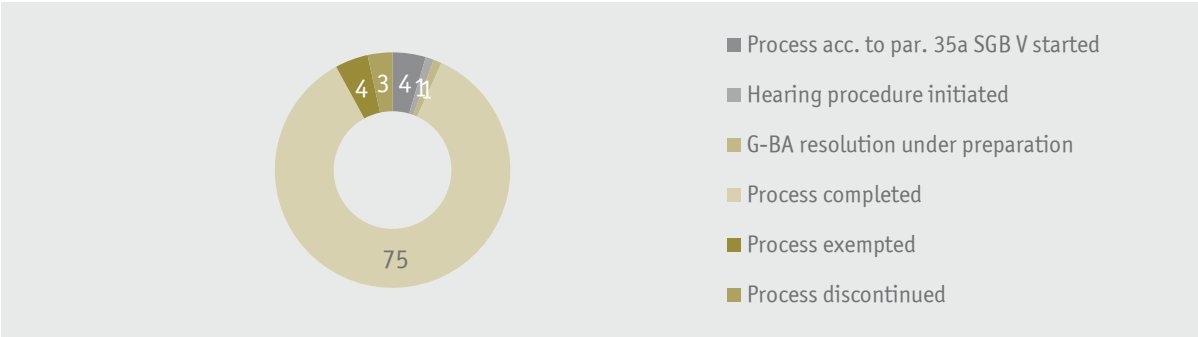

Figure 4: Status of the early benefit assessment processes with orphan drugs

As Figure 5 demonstrates, the main therapeutic area was oncology covering more than half of the active ingredients, followed by inherited metabolic disorders. All further disease areas were not particularly strongly represented.

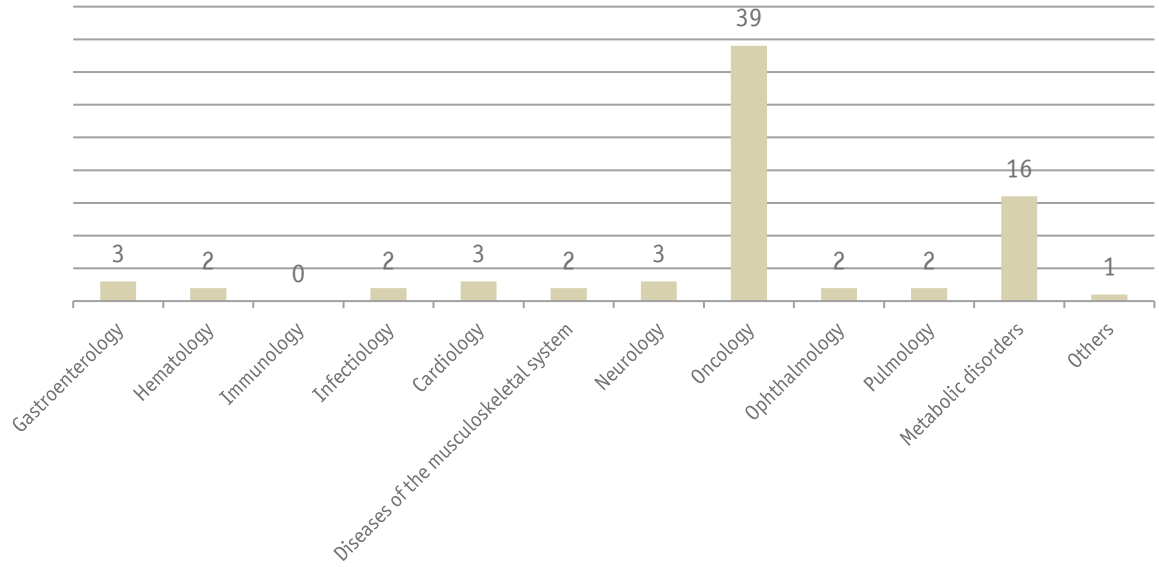

Figure 5: Disease areas of the benefit assessments for orphan drugs in the period from 2011 until today

This confirms the statements of Martinalbo et al. in "Early market access of cancer drugs in the EU" [8]. While often criticized for a slow approval process of new therapeutic options for cancer patients with a high unmet need, the European Medicines Agency (EMA) has recently shown greater flexibility in the approval of cancer drugs compared to other therapeutic areas [8].

The difference between the EMA's and the G-BA's standards becomes particularly obvious in the group of pharmaceuticals for the treatment of rare cancers. While the EMA accepts clinical data out of studies which do not score the highest evidence class (phase II, single-armed, no active comparator), and which use promising albeit not validated surrogate endpoints, the German HTA authority in principle demands the highest possible evidence level. Thus, it becomes clear that in the majority of cases, the G-BA decided to award the non-quantifiable contemporary for the product under consideration. In 20 (27%) so far assessed compounds, the additional benefit was minor, in 41 (54%) non-quantifiable, in 11 (15%) considerable and in only 1 (1%) major. In addition, the G-BA granted in 2 (3%) procedures no additional benefit after the sales of the corresponding drug exceeded the €50 million and thus had to be reassessed in comparison to an appropriate comparative therapy (see Figure 6).

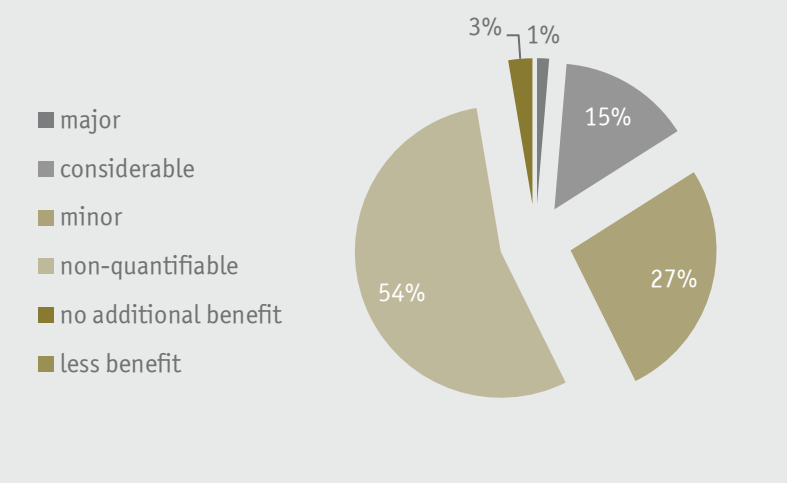

Figure 6: Additional benefit categories of orphan drug's assessments

The legal link of the orphan drug designation to the market authorization with the implications of a faster access (conditional marketing authorization) for patients certainly leads to the fact that 54% of the assessments result in a non-quantifiable benefit which usually also means that pending further scientific data, a classification in one of the other categories is not possible. In some cases, the G-BA puts a time limit on its resolution to be able to conduct a further assessment after a period of post-marketing experience.

Patient registry requirement

The "learning system" of the AMNOG has recently been demonstrated when in March 2016, the G-BA published its resolution for 3 orphan drugs: Strensiq® (Alexion), Kanuma® (Alexion), and Raxone® (Santhera Pharmaceuticals) – all of them were assessed with a „non-quantifiable" additional benefit and the period of validity of the resolution was set until December, 2018. In these cases, the G-BA requested the setup of a German registry in addition to the EMA-registry for the first time. A new benefit assessment based on these data will be conducted after the current resolutions have expired. The companies will then have to submit a new dossier.

> "The G-BA considers more evidence to be urgently needed to perform a new added-benefit assessment for these drugs. In general, orphan drugs should be evaluated the same as other drugs if they fail to produce the requested data in time for a second evaluation."
>
> Prof. Josef Hecken, G-BA's chairman

The challenge of uncertainty with regard to the price negotiations

Several early access instruments to expedite development and regulatory review have been in place for many years and, as demonstrated in Figure 7, the market authorizations of orphan drugs and market entries in Germany are continuously increasing. But these centralized European programs often lead to data which do not meet the evidence requirements for pricing and reimbursement (P&R) decisions at the national level. Above all, the decision on the coverage of high-priced cancer drugs by public health systems is a challenge for the decision-makers as well as the pharmaceutical manufacturers[8].

This and the expected further growth in numbers of new orphan drugs will inevitably lead to an increasing importance of their assessment outcome. It can be assumed that the legal framework for the assessment of orphan drugs will be adjusted and harmonized in the future and that they thus will have to show their additional benefit like other non-orphan drugs.

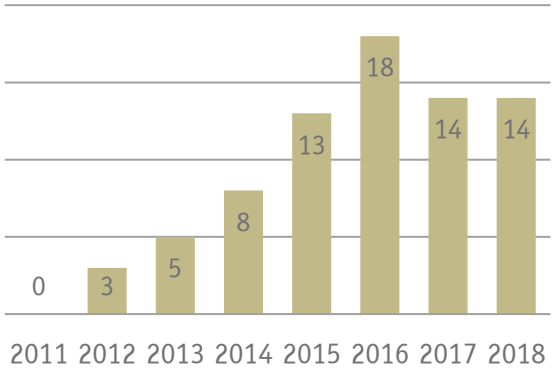

Figure 7: Completed AMNOG procedures of orphan drugs

Further plans by the EMA to expand its fast track approach to approving new drugs have recently provoked a tough response from IQWiG. IQWiG said that the report had failed to allay its concerns that no reliable method existed for using real world data to draw reliable conclusions. IQWiG criticised the lack of information about the drugs chosen

and the methods to be used [9].

As mentioned, the weak evidence basis is one of the challenges of the pharmaceutical manufacturer for the price negotiations. Another one is the missing comparator therapy on the basis of which the price of the new drug can be negotiated as a premium. No appropriate comparator means there is no obvious basis for a price comparison for use either by the manufacturer or by GKV-SV. However, the number of successful price negotiations (33) and the existence of only one market exit show that the G-BA produces solid value assessments on which to conclude negotiations. But the most recent results also show that negotiations are going tougher.

Second step: Price negotiations

The price negotiations between the pharmaceutical company and the Central Federal Association of Statutory Health Insurance Funds (GKV-Spitzenverband, GKV-SV) will begin within 4 weeks after publishing the resolution and take place over the next 6 months. Within 2 weeks of the first price negotiation round, a company can decide not to start the negotiations and to immediately leave the market ('opt-out'). According to the level of additional benefit, the price of the pharmaceutical will be negotiated as a discount to the manufacturer's launch price and will apply to both the statutory and the private health insurance as of month 13 after market authorization.

The G-BA's decision regarding the extent of the additional benefit and other criteria such as prices of pre-determined European countries, the expected sales and further comparable drugs beyond the appropriate comparator therapy are relevant for the negotiations between the GKV-SV and the pharmaceutical company.

Therefore, manufacturers are obliged by law to report the actual sales prices, which are the retail prices not including value-added tax minus the discounts that have been granted in the countries adjusted at purchase power parity. The European countries, which are looked at while comparing the prices, are included in a specific basket of countries. This basket was defined through a decision of the arbitration board in 2012 and includes the following countries: Belgium, Denmark, Finland, France, Greece, Great Britain, Ireland, Italy, the Netherlands, Austria, Portugal, Sweden, Slovakia, Spain, and the Czech Republic. The framework for the decision was based on three criteria:

1) countries from all states of the European economic area,
2) countries with an additive population of 80% of the European economic area (excluding Germany), and
3) countries with a similar economic performance compared with Germany.

In the case an additional benefit has not been proven, the actual selling prices for other European countries and the prices of comparable drugs will not be considered in the course of the negotiations and the reimbursement amount may not lead to annual therapy costs higher than the appropriate comparative therapy or the drug will be subject to reference pricing provided a reference price group exists (i.e., a group of active ingredients with a defined maximum price according to §35 SGBV). If multiple comparative drugs were determined by the G-BA, the reimbursement amount may not lead to more expensive therapies than the most economical alternative.

In the case an additional benefit has been proven, the G-BA's decision on additional benefit forms the basis for reimbursement price negotiations [5].

As part of the bargaining chips, the manufacturer and the National Association of SHI Funds can agree on redemption of the manufacturer discounts during the negotiation. The mandatory manufacturer discount for prescription drugs is presently 7% on the selling price (with regard to the net selling price: 5.88%). The redemption of the manufacturer discounts leads to marginal cost advantages for the SHI.

Outcome of the price negotiations

By September 2017, 48 of currently 72 in Germany newly introduced orphan drugs passed the AMNOG legislation comprising the assessment of additional benefit extent as well as associated price negotiations. Rebates range from 15.73% up to 73.65%.

Analyses of the additional benefit extent and the amount of the discount show no correlation between the two parameters. Although the AMNOG regulation implemented binding and strict rules for the benefit assessment itself, the outcome of the discount negotiations are still unpredictable. Obviously, negotiation tactics, the current political situation and soft factors seem to play a more influential role for the outcome of the negotiations than the obvious factors.

Third (optional) step: Arbitration

In case that no final agreement is achieved on the discount within the 6 months, arbitration will be initiated. During a 3-months timeframe, an official arbitration board will make the final price decision. As regulated in the German Social Code Book, the arbitration board is composed of one impartial chairman, two impartial members, as well as two representatives of each negotiation party. The representatives of the negotiation parties represent the interest of the respective party. Arbitration is a well-known legal regulation with a long tradition in the health care system ruling the German Social Code Book (e.g., within statutory outpatient and inpatient health care as well as statutory accident insurance and long-term care insurance) [1, 10].

The decisions of the arbitration board are discretionary decisions, but it is important that the decision path is transparent and the arguments for the discretion reasonable. The German Social Code Book regulates that the arbitration board has to make a decision only after consideration of all the circumstances of every individual case and after taking into account all peculiarities of the respective therapeutic area. The correction or adjustment of the decision of the G-BA is not within the responsibilities of the arbitration board. According to the German Social Code Book, the arbitration board should not follow any algorithm in the decision making but rather weight all criteria depending on the case [1].

The subsequent oral proceedings start with the opportunity for both negotiation parties to explain their positions. The impartial members of the arbitration board try to reach a common solution. Oral proceedings and consultations are non-public. If it is not possible to reach a common solution, it is the task of the arbitration board to make a decision. The progress of the consultancy and the minutes of the meeting are kept confidential. The arbitral award is drawn up in writing by the chairman and is accessible only in Berlin. Finally, the arbitration board acts in a very narrow legal framework and

especially in the situation of the absence of an additional benefit the room for maneuver is extremely limited [1].

The negotiated (or arbitrated) price becomes effective in retrospect starting with the 13th month after market launch, while companies are free to set the price for the first 12 months [10].

So far, the prices of about 42 drugs have been arbitrated, 6 of them of orphan drugs. These were Pomalidomide, Siltuximab, Ataluren, Idebenone, Blinatumomab and Tasimelteon.

In the case of Pomalidomide, the determined reimbursement amount refers to reference values less than 3 mg. For all reference values more than 3 mg, the reimbursement amount is a so-called flat price and is therefore unattached to the potency. There was a disagreement between both negotiation parties only for reference values less than 3 mg. The manufacturer demanded a flat price for all potencies, whereas the SHI preferred a linear pricing based on the different potencies. The arbitration board decided for a reimbursement amount with linear pricing and set the reference level to 3mg (€404.76/3 per mg active substance for potencies <3 mg), whereas the SHI claimed a reference level of 4 mg with the same reimbursement amount (€404.76/4 per mg active substance for potencies < 3 mg) [1].

Siltuximab, being an absolute soloist in an orphan disease, had no appropriate comparative therapy and comparable drugs in the authorized indication. The arbitration board ascertained a reimbursement amount very close to the average of the European prices, which served in the absence of the other two criteria (not quantifiable additional benefit and no comparable drugs) as a price anchor, reflecting a weighting factor of 100%.

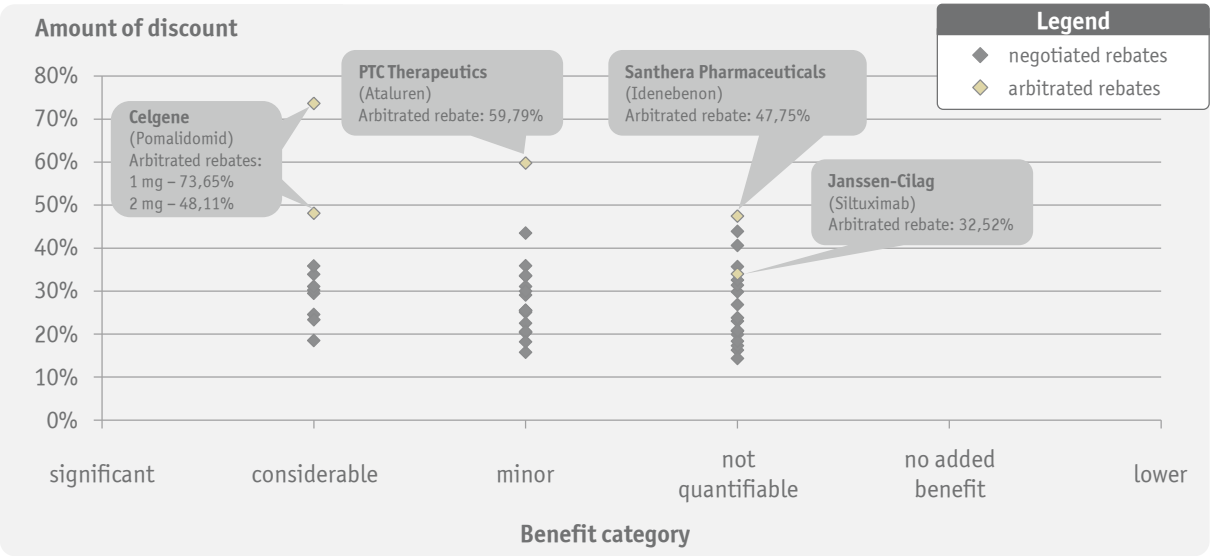

Figure 8: Amounts of negotiated or arbitrated discounts

An analysis of the orphan drug discounts as demonstrated in Figure 8 shows that the arbitration board has not made orphan friendly decisions so far and that arbitration, based on the hitherto existing experiences should be avoided as far as possible. In certain cases, a company may even decide to take its new product off the German market after the arbitration board's decision as Celgene has done with potencies < 3mg and PTC Therapeutics has done with Ataluren.

Lessons learned from AMNOG and its strategic implications

The health care reform is a first step to decision making based on "value for money". The impact factors of the AMNOG are manifold and can cause significant collateral effects beyond Germany. The structural changes in Germany are of importance for pricing decisions in many European countries both from a political point of view and for the strategic planning of pharmaceutical manufacturers, which may have an effect on insured patients' access to pharmaceuticals altogether. Therefore, the process is composed of several "corresponding tubes" and needs to be managed comprehensively and should be strategically thought through in advance in order to be able to respond to the challenges at an early stage. Besides the procedure-specific challenges by the formal requirements, the budget impact, comparable drugs, the level of European prices and the heterogeneity of evidence in possible subpopulations, the pharmaceutical company has to consider the technical issues like the package size, the notification requirements at the IFA and provision and service levels. Figure 9 gives a first impression of the possible implications to be taken into account by the early benefit evaluation.

As in orphan drugs there is no clear categorization of the additional benefit in the first G-BA assessment, it is necessary to highlight the importance of the written statement and the oral hearing and the involvement of stakeholders – including patient representatives within the G-BA – in determining the additional benefit. This makes the early integration of KOLs, patient representatives and other advocacy groups all the more important.

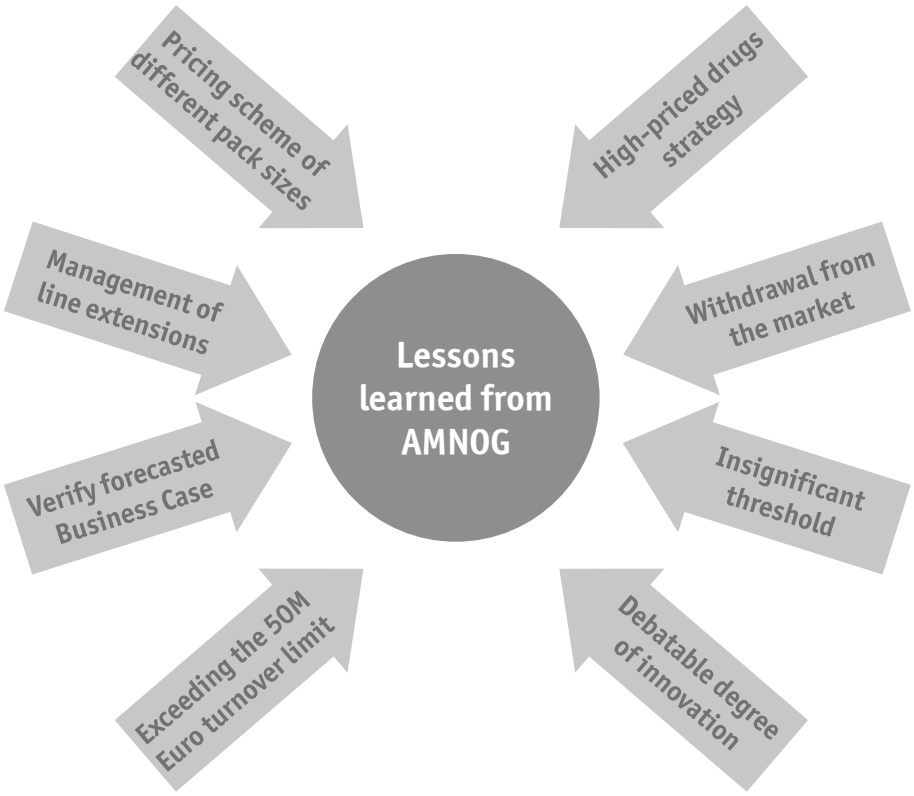

Figure 9: Lessons learned from AMNOG

The sales threshold as described in Figure 3 should also be taken into account by pharmaceutical companies early in the process. Especially pharmaceutical companies with ultra, ultra-orphan diseases with an anticipated budget impact of less than 1 M Euro should realize that they are not affected by the early benefit assessment with an expected budget impact below € 1 million. On the other end of the scale, the re-assessment after sales reach the €50 million threshold is a considerable challenge, as it could be observed with Ruxolitinib, Pomalidomid, Ibrutinib and Macitentan so far. Consequently, a full dossier is required, including data analyses over the appropriate comparator, as the same procedure for non-orphan drugs is applied. IQWiG is commissioned for a dossier assessment and the benefit assessment of the drug against the appropriate comparator. Ruxolitinib has successfully overcome this challenge with the resolution from November 6th, 2014 and an improvement of the additional benefit level from minor to considerable. This was not totally the case for Pomalidomid and Ibrutinib. The G-BA has finally categorized some subgroups of both drugs with 'no additional benefit' because the available evidence could not show an advantage over the appropriate comparator therapy. In the cases of Macitentan and the recent Ibrutinib assessment, no additional benefit was granted by the G-BA for the entire target population.

Another important challenge is the line extension management especially for orphan drugs in oncology as it was the case with Ramucirumab. After introducing Ramucirumab as an orphan drug with the indication gastric cancer in 2015, the manufacturer extended the field of application to the non-orphan indications colon and lung cancer which had the consequence that the indication gastric cancer now had to be reassessed due to the loss of the orphan status, too. The additional benefit of the lung and colon cancer indications could not be proven and also the gastric cancer indication lost its additional benefit in one of the two subgroups. It can be anticipated that the price negotiations become pretty tough because of the huge impact of the patient population sizes of colon and lung cancer compared to the very small gastric cancer population.

Outlook and recent developments

Six years after the AMNOG has been introduced, it can be stated that the law clearly achieved the objective of regulating, controlling and limiting the price of new drugs in Germany. Although the expectation of more than €2 billion savings annually was not fully met, the average reimbursed price for new pharmaceuticals in Germany is now significantly lower than the European average. In fact, it lies within the lowest third of the European pharmaceuticals price band. For orphan drugs, it can be expected, that the situation will get tougher in the future. All kinds of different stakeholders, not only the payers but also the physicians claim that a further 'orphanization' should be counteracted by even tougher regulations. This would include a full benefit assessment, requiring a full dossier and a high evidence leveled study with validated endpoints and data against an active comparator, a reduction of the period of free pricing (from 12 months down to 7, 6 or even 0 months) and an even stronger decision power on the G-BA's side allowing to exclude products or subpopulations from the reimbursement altogether. In the future, it becomes even more important than before, to design and execute a stringent and smart strategy and to involve the market access perspective as early in the process of research and development as possible. Internal processes should be aligned and the collaboration between R&D, Medical, HEOR, Regulatory, Legal and Pricing & Reimbursement departments should be especially fostered to answer the challenges of the new procedure.

In summary, six recommendations for a successful orphan drug market access in Germany: Think through the business case, anticipate obstacles at an early stage, and have fallback options.

1. Check early on whether your drug is affected at all by the early benefit assessment due to the 1M Euro turnover threshold.
2. Think through your Business Case regarding your line management. Check your strength of the available evidence and anticipate the possible price anchors.
3. Bear in mind, that you have to prove the additional benefit against a comparator therapy in case your drug turnovers exceed the 50M Euro threshold. Anticipate this point in time and prepare yourself.
4. A comprehensive value story and an explanation of the burden of disease is very important in case of a debatable degree of innovation or very high-priced drugs.
5. Keep in mind that even the most experienced pharmaceutical companies have a lag of experience compared to the cumulative experience specialized consultancies with their expert knowledge.
6. Prepare for surprises by setting up a flexible team: there is always something that has not yet been thought of!

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Our Services

We illuminate your way –
so you can reach your target safely.

SKC is an expert in answering strategic questions within the health care system. Together with its clients, SKC develops solutions that shape the future of the industry. We have a broad experience in all phases of the AMNOG process as well as in a wide variety of indications. SKC has the strongest track record in supporting pharmaceutical companies with meeting the specific German market access challenges for orphan drugs. No other professional services company has consulted more clients more successfully than SKC.

Example work packages

AMNOG process

Overall AMNOG strategy: process preparation	Dossier preparation	Aligning and facilitating Benefit Assessment	Leading through Price Negotiations
Building of a cross functional team	G-BA advice meeting	Analysis of the G-BA's / IQWiG's benefit assessment	Analysis of the G-BA resolution
Risk Assessment	Dossier compilation	Preparation of the written statement	Negotiation strategy
Development of a value story related to the German healthcare context	Submission of the dossier	Preparation for the oral hearing	Training and preparation of the negotiation team
Overall and AMNOG pricing strategy			Serving as the negotiation team leader if requested

Stakeholder Management: activation of relevant stakeholders

Initiating of the stakeholder management: Analyzing & identifying relevant stakeholders; planning communication	Implementation of the stakeholder management: mobilizing relevant stakeholders during the benefit assessment

Market preparation

Mobilizing the market: Pre-launch	Mobilizing the market: using the free-pricing period
Identification of relevant payer organizations, key clinical experts and advocacy groups	Preparation and negotiation of selective contracts with SHIs
Development of a engagement plan and assistance in communication activities, e.g. for payer organizations	Writing of NUB-applications according to § 6 Abs. 2 KHEntgG

Our Team

Professionals are the most valuable resource in any industry and we hire only the best of them.

Prof. Matthias P. Schönermark, M.D., Ph.D.

- Head and Neck Surgeon, Ph. D. in Molecular Oncology
- Post-doc in immunology
- University Professor of Medical Management (Hannover, Cologne, Harvard Business School)
- 20 years of international top management consulting experience (BCG, A.T. Kearney, SKC) focused on strategy in healthcare
- Key areas: Strategy, Leadership, Market Access, Negotation

Ms. Heike Kielhorn (business graduate)

- Industrial clerk
- Business Graduate
- 20 years of international top management consulting (KPMG, BCG, SKC)
- 20 years of international management consulting experience (KPMG, BCG, SKC)
- Key areas: Strategy, Business Modeling, Market Access, Corporate Finance

Why SKC

Customers from around the world trust our advice.

During the last seven years, SKC has supported numerous top companies in their market access processes beginning with the dossier compilation, the written statement and oral hearing up to the price negotiations, keeping its competitive advantage in this field of consulting and making SKC's track record among the strongest in the industry.

"Thank you for all your tremendous support and guidance throughout the AMNOG process. The result was outstanding, and made possible through your steadfast advice.
Though I realize that more challenges lie ahead, I wanted to let you all know how much I appreciate your experience, your candor, your abilities, your counsel, your humor, your friendship. It´s great to work with the A-Team! Looking forward to working together more in the future!"

Senior Vice President, Global Government Affairs

With its state-of-the-art analytics and a pragmatic focus on implementation SKC tackle complex structural changes in the health care system. The strong affiliation with science allows SKC to go ahead and detect future trends and long term consequences early on.

To enable optimal reactions to the challenges of the Pharmaceutical Market Restructuring Act and the opportunities of the Care Structures Act SKC develops strategic concepts with you. In our understanding, successful consulting means assisting you in decision-making, which you can implement and which promise a long-term success.

Thank You.

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collegen

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