

**Statement
for the German Federal Ministry of Health**

**On the experience of the research-based
pharmaceutical companies with the Act on
the Restructuring of the Pharmaceutical
Market (AMNOG)**

(Written inquiry of the German Federal
Ministry of Health to the associations
on February 14, 2013)

March 6, 2013

Contents

Seite 2/21

- 1. Introduction**
- 2. Results of the previous benefit assessments**
- 3. Cost of the procedure**
- 4. Appropriate comparative therapy**
- 5. Methodological questions**
- 6. Governance**
- 7. International reference pricing**
- 8. Prescription practice and economic efficiency**
- 9. Significance of orphan drugs**
- 10. Existing market**
- 11. Conclusion**

1. Introduction

Seite 3/21

With the AMNOG, the legislature has instituted a restructuring of the reimbursement conditions for innovative pharmaceuticals. The AMNOG provides a two-stage assessment and reimbursement process: Initially, pharmaceuticals with new active ingredients are subjected to an early benefit assessment based on which the pharmaceutical entrepreneurs will subsequently negotiate a reimbursement amount for the product with the SHI Head Association. Pharmaceuticals without an ascertained additional benefit are to be integrated into a reference price group.

The research-based pharmaceutical companies have accepted the challenge of the AMNOG. They do not shy away from a fair assessment of their products' benefits. However, the procedures must be designed in such a manner that innovative products continue to be provided with an opportunity to prove themselves in real-life health care situations and that the high expenses for the research and development of pharmaceuticals can be refinanced.

In the meantime, the AMNOG procedure has been completely implemented: Since January of 2011, about 50 early benefit assessment procedures have been started, among them the first procedures for new therapeutic indications of products that were already assessed and for products from the existing market. To date, 30 assessment procedures have been concluded. For about 20 products, reimbursement amounts have also been determined. Since February 1, 2013, the AMNOG discounts – as provided by the legislature – have been granted for each pharmaceutical sale at the pharmacy and passed on to health insurance funds and insured patients through the commercial chain. The procedure is under way and the pharmaceutical industry has contributed its part. Discount claims that became due before the cutoff date are bilaterally settled by the health insurance funds and the manufacturers.

However, the research-based pharmaceutical companies continue to see a need for optimization in the further design of the AMNOG process. Neither the procedure of the early benefit assessment nor that of setting reimbursement amounts runs really smoothly at present. The Federal Joint Committee (G-BA) often formulates unrealistic expectations regarding the manufacturers' proof of evidence and has decided for many procedures to restrict positive additional benefit assessments to small patient groups. The SHI Head Association is already a key participant during the advice process and the pharmaceutical assessment within the G-BA and subsequently dominates the reimbursement amount negotiations in a monopolistic position. As a result, from an institutional standpoint, fair pricing for innovative pharmaceuticals is not guaranteed. If the structures remained unchanged, this would have noticeable impacts on pharmaceutical care for patients in Germany. Prevented or delayed market

launches or market withdrawals (“opt out”) – still constituting a smaller problem during the starting phase of the AMNOG – could become an increasing challenge for the German health care system.

Seite 4/21

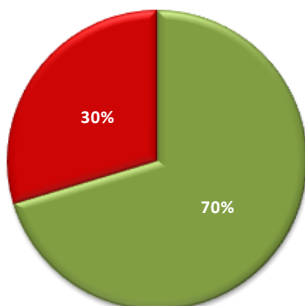
With this compressed experience report, vfa would like to create problem awareness for the pitfalls of the AMNOG procedure and encourage corrections that will make the procedure viable also for the pharmaceutical industry and safeguard patients’ access to innovative products. vfa supports a close monitoring of the AMNOG implementation by the Bundestag and Bundesrat while simultaneously advocating cooperative interaction between the pharmaceutical industry, the self-governing bodies and other stakeholders during the application and optimization of the new regulatory framework.

2. Results of the previous benefit assessments

An evaluation of the available benefit assessment decisions (n=30, as of: March 1, 2013) provides a differentiated picture: The G-BA attested an additional benefit to the large majority of the assessed active ingredients, but only for about half of the assessed patient subgroups and for an even smaller part of the patients affected by the disease. An evaluation according to prevalences shows that positive additional benefit decisions were made for only about 22 percent of the relevant patients (comp. Graphic 1 to 3). In addition, it must be noted that the G-BA typically rated the additional benefit as small – rather “slight” than “important” and rather an “indication” or even “hint” than “proof.” The highest additional benefit category of “major” has not been attributed even once so far (comp. Graphic 4).

Graphic 1:
Additional benefit for 27* assessed active ingredients
(G-BA decisions, as of March 1, 2013)

27 ingredients



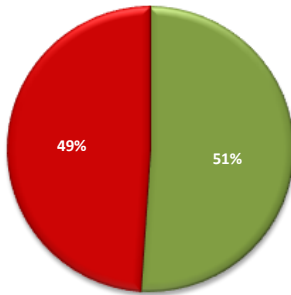
Additional benefit	Number	%
YES	19	70.4
NO	8	29.6
Active ingredients in total	27	100

* excl. bromfenac, azilsartan, pitavastatin (no dossiers submitted)

Graphic 2:
Additional benefit for 45* assessed subgroups
(G-BA decisions, as of March 1, 2013)

Seite 5/21

45 Subgroups

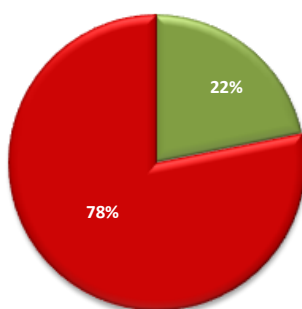


Additional benefit	Number	%
YES	23	51.1
NO	22	48.9
Subgroups in total	45	100

* excl. bromfenac, azilsartan, pitavastatin (no dossiers submitted)

Graphic 3:
Additional benefit according to prevalence
(G-BA decisions*, as of March 1, 2013)

2.680.922 Patients

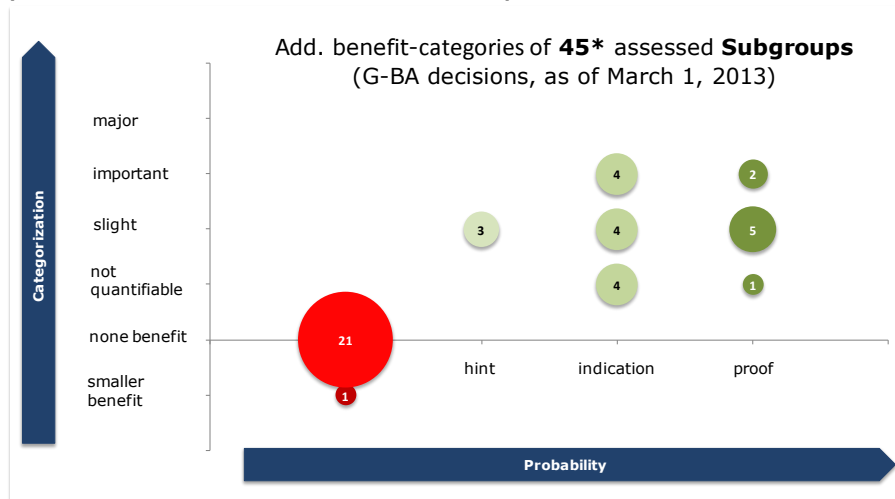


Additional benefit	Number	%
YES	585,022	21.8
NO	2,095,900	78.2
Patients in total	2,680,922	100

* excl. bromfenac, azilsartan, pitavastatin (no dossiers submitted)

Graphic 4:
Additional benefit categories according to extent and result certainty
(G-BA decisions, as of March 1, 2013)

Seite 6/21



* excl. bromfenac, azilsartan, pitavastatin (no dossiers submitted)

As a result, the early benefit assessment of the AMNOG presents itself as not very innovation-friendly. The assessment standards and evidence requirements of the G-BA – in connection with the Institute for Quality and Efficiency in Health Care (IQWiG) – are unrealistically high and can only be achieved partially in practice by the affected active ingredients. In addition, the rating of the additional benefit in the categories of “slight,” “important” or “major” has a purely normative character and eludes a scientific evaluation.

The G-BA views its own ratings in an international comparison as rather positive for innovative pharmaceuticals. vfa cannot share this point of view. In France, where a similar benefit assessment is conducted in part, fewer subgroups tend to be formed than in Germany. In a valid comparison, it must also be taken into account with which comparator the pharmaceuticals were assessed. For example, in France the gliptines were compared among each other, while in Germany a comparison was made with sulfonylureas, the low-cost generic substances. Overall, the AMNOG benefit assessment does not appear more innovation-friendly than the French system at all.

3. Cost of the procedure

Regarding the procedures, it must first be noted that the early benefit assessment procedure is currently associated with very large costs for all parties involved. The cost of dossier generation for new pharmaceuticals is estimated at EUR 450,000 to 600,000 by the affected companies. This experience value dramatically contradicts the original assumption of the legislature that dossier generation would cause additional costs of about EUR 1,250 for each procedure (BT-Drs. 17/2413 of July 6, 2010, p. 3; or EUR 3,750 according to

the justification for the Pharmaceutical Benefit Assessment Ordinance).

Seite 7/21

The manufacturers are obligated to submit all study results for their pharmaceutical. For example, for the benefit assessment in Germany, this also includes partially or completely translating a study that was submitted for marketing authorization in Japan and only published in Japanese. According to information from the companies, Module 5 of the manufacturer's dossier, which includes the trial protocols, technical documents, etc. and is not published by the G-BA, often includes several 10,000 pages. The dossier template by the G-BA alone now extends to more than 100 pages, with a degree of detail of the chapter divisions all the way to hierarchical level 6. Preparation within the companies – typically done with the involvement of external service providers and company headquarters – takes about 12 months. Due to the specific requirements of the IQWiG and the G-BA, generating synergies between benefit dossiers in different countries is only possible in limited fashion.

We must ask the question if this survey cost is really goal-oriented and necessary. Therefore it appears meaningful if the Federal Statistical Office now also wants to investigate this issue as part of its "cost of bureaucracy measurement."

The benefit assessment itself is also designed in an extraordinarily complex manner. The G-BA differentiates its pharmaceutical assessment based on additional benefit category, result certainty, subpopulation and therapeutic indication. In an international comparison of health technology assessment (HTA) practices, this approach seems "over-engineered" and mainly owing to the logic of negotiation based on the benefit assessment. In addition, due to overformalization, the purely formal error susceptibility of the assessment also increases.

Considerable costs of bureaucracy are also incurred in the further process. For the handling of reimbursement amounts, the legislature has provided a separate, new billing procedure (Section 130b para. 1 of the German Social Code Book V), in addition to the two established paths of discount handling (statutory manufacturer's discounts, discount agreements). This handling method was selected in the past in order to allow the insured patients in private health insurance to also benefit from the AMNOG discounts and to keep the procedure as lean and unbureaucratic as possible. In fact, however, the technical establishment of this procedure was very time-consuming and costly for all parties involved. The procedure must additionally be supplemented by a retroactive handling procedure, in order to implement the AMNOG requirement regarding the applicability of reimbursement amounts after the 13th month following market launch. This coexistence of different discount handling procedures cannot be viewed as cost-efficient. vfa had pointed out the

costs to be expected early on and advocated a direct handling procedure for discounts with the cost payers (SHI and private health insurances/ZESAR).

Seite 8/21

4. Appropriate comparative therapy

A key “adjusting screw” in the entire AMNOG procedure is the selection of the appropriate comparative therapy (ACT). In the benefit assessment, the ACT is the comparator based on which the pharmaceutical entrepreneur needs to prove the additional benefit of his pharmaceutical. It is selected by the G-BA according to its own discretion pursuant to the Pharmaceutical Benefit Assessment Ordinance. In his dossier, the manufacturer can theoretically deviate from it. However, in practice, the IQWiG and the G-BA have never accepted the manufacturer’s justification for a deviation, and the consequence was that the manufacturer was given a negative additional benefit assessment for formal reasons.

The benefit assessment decision of the G-BA, in turn, represents the foundation for negotiating a reimbursement amount with the SHI Head Association. The annual cost of therapy of the determined ACT is a key variable in determining a discount. As a result, there is an incentive for choosing the cheapest possible comparator for the AMNOG procedure. In addition, there is the provision that the ACT immediately serves as guidance for reimbursement in a special constellation. If no additional benefit could be demonstrated as part of the early benefit assessment and the corresponding pharmaceutical could not be assigned to a reference price group, the reimbursement amount must not exceed the annual cost of therapy of the ACT (Section 130b para. 3 of the German Social Code Book V).

During the benefit assessment procedures initiated so far, the research-based pharmaceutical companies had problems with the determination of the ACT by the G-BA in many cases. From the individual cases, which cannot be discussed in this paper, the following general aspects should be emphasized:

- For the pharmaceuticals currently undergoing the benefit assessment procedure, the clinical trials were planned long before the AMNOG, they were reviewed by the ethics committees and conducted in various countries. In coordination with the corresponding regulatory agencies, a certain comparative therapy was agreed upon. If this therapy deviates from the comparator determined later in the early benefit assessment procedure, the manufacturer can attempt to conduct indirect comparisons. However, in practice, these comparisons are not accepted as proof of an additional benefit by the IQWiG due to rigid methodological requirements. As a result, the manufacturer may not be able to provide the desired evidence due to the pivotal study situation and the current methodological approach of the IQWiG.

- If the IQWiG and the G-BA later divide therapeutic indications into several partial areas for each of which an additional benefit must be proven against a special comparator, this requirement can typically not be met by the pivotal studies. In the common scenario where one or two pivotal studies with one or two comparators are available for a new pharmaceutical, this will deny an additional benefit for all the subgroups to which the G-BA has assigned a different comparator.
- Another problem arises, if only individual representatives of a drug class are designated as the ACT and not drug class per se. Trial data with a different active ingredient from the category are then excluded from the benefit assessment.

Seite 9/21

From the perspective of the research-based pharmaceutical companies, these practical problems could be solved based on two steps. First, it is important to detach the medical assessment of the pharmaceuticals from the determination of reimbursement amounts. The ACT must be the comparator for the medical assessment of the additional benefit according to the international standards of evidence-based medicine. Only in the second phase of the AMNOG procedure, during the reimbursement amount negotiations, cost aspects should play a role.

Second, it is goal-oriented if the G-BA, the manufacturers and the regulatory agencies deliberate early on which comparators are chosen in the pivotal studies and whether these comparisons could be meaningful for the assessment of the additional benefit. While such an early consultation is possible in principle, experience from the previous advice sessions has shown that the expert dialog of the G-BA with the affected companies must be further developed and that the expert knowledge of the regulatory agencies – despite the new legal requirement introduced with the Second Amendment Act to the German Medicinal Products Act – is still insufficiently used (only a written inquiry is made to the regulatory agencies). Such a pragmatic approach in selecting the ACT is also in agreement with the concept of evidence-based medicine. No trial evidence is ignored or rejected, but the best possible evidence available at the time of the assessment is considered.

5. Methodological questions

Seite 10/21

During the early benefit assessment, many methodological problems arose, three aspects of which can only be shown briefly here. One critical point during the assessment of the evidence submitted is the acceptance of endpoints. In this respect, the IQWiG and the G-BA set high obstacles that cannot be overcome in some therapeutic indications. This explains the numerous cases of downgrading in the previous benefit assessment decisions:

- In its Rapid Report on surrogate endpoints in oncology, the IQWiG stipulates, among others, their intervention-specific validation, which can by definition never be implemented in practice for novel active ingredients. Due to the severity of oncological diseases, pivotal studies in oncology are subject to methodological particularities that must be taken into account during the selection of endpoints and the interpretation of the results. For example, not every study design can be practically implemented for ethical reasons. When the tumor disease of a trial patient progresses, one typically switches from the control therapy, which is no longer effective, to the new pharmaceutical (cross-over). As a result, the survival benefits of a new active ingredient are no longer visible in the study. The European authorities, supreme federal government agencies and ethics committees in charge have stipulated specific requirements for the study design of oncological products. The IQWiG and the G-BA must not ignore these requirements during the assessment of patient-relevant benefit.
- The IQWiG does not even recognize endpoints such as progression-free survival (PFS) or disease-free survival (DFS) as meaningful, even if they are considered relevant by the European Medicines Agency (EMA) in their recently updated guideline for the clinical development of pharmaceuticals for cancer patients.
- A similar case is the reduction of the viral load for infectious diseases such as hepatitis C and HIV/AIDS, which the IQWiG does not recognize as patient-relevant endpoints either, despite the fact that they are globally accepted as healing parameters in a clinical setting and all marketing authorizations of pharmaceuticals in these therapeutic indications are based on them.
- So far, quality of life as an independent patient-relevant endpoint has not played a role in any benefit assessment procedure.

Another critical point must be seen in offsetting benefits and risks. Here, the IQWiG and the G-BA take a separate path and conduct yet another risk-benefit assessment, which was already done as part of marketing authorization. The IQWiG had initially submitted its own construct for quantifying the additional benefit and the risks, which

was not accepted by the G-BA. The G-BA currently offsets risks and benefits as part of the individual decision in question. This harbors the risk of proceeding inconsistently, as seems to be the case during the comparison of various pharmaceuticals in oncological indications.

Seite 11/21

Subsequent subgroup formation by the IQWiG and the G-BA constitutes another problem area. This primarily represented a problem during the first assessment procedures but did not manifest as frequently during the most recent decisions, since these mainly pertained to narrow therapeutic indications. vfa believes that the division of target populations into several subgroups *post hoc*, i.e. after the conclusion of the trials, will not achieve objectives. Typically, it will lead to downgrading or denying the additional benefit.

Overall, the research-based pharmaceutical companies demand that the early benefit assessment be conducted according to international methodological standards, as provided by the German Social Code Book V. Methodological questions in dispute should be discussed openly and solved pragmatically, if possible. This requires that the G-BA and the IQWiG also be prepared to deal with constructive methodological suggestions by the pharmaceutical industry and the scientific expert circles. Unfortunately, in the September 2012 expert discussion of the G-BA on methodological questions, an open dialog was not yet apparent.

6. Governance

The research-based pharmaceutical companies see one key problem in the governance, the steering structure and the lack of a "division of power" during the early benefit assessment, and the determination of reimbursement amounts. The AMNOG does not provide a clear separation of assessment, decision-making and negotiation as it exists in other countries. Instead, the SHI Head Association is empowered to take significant influence in all stages: In the G-BA, the SHI Head Association holds 50 percent of the votes (in the case of parity, the unbiased member will cast the deciding vote). It initially determines the specific requirements for the early benefit assessment in the G-BA (selection of the ACT, among others) the pharmaceutical entrepreneur and the IQWiG must follow. During the next phase, it decides on the benefit assessment result of the G-BA and subsequently conducts the reimbursement amount negotiations with the pharmaceutical entrepreneur. Therefore, figuratively speaking, the SHI Head Association participates in the AMNOG process as a regulator, arbitrator and player.

In addition, the SHI Head Association acts as a demand monopolist in the central reimbursement amount negotiations and typically also has an information lead compared to the pharmaceutical entrepreneur. It knows all the deliberation processes within the G-BA and

conducts all individual negotiations (also for products that are in direct competition with each other), whereas the pharmaceutical entrepreneur only knows his individual case, is not allowed to enter into an exchange with other manufacturers for antitrust and legal confidentiality reasons, and can therefore gather negotiation experience only over a longer period of time based on several of his own AMNOG procedures.

Seite 12/21

The objection that a demand monopolist would be necessary in the procedure in order to meet the pharmaceutical manufacturer with his patented product at eye level does not hold up. Pharmaceutical entrepreneurs are in keen competition during the research and development of innovative pharmaceuticals. Even in a specific patented market segment, they almost never reach a monopoly position. Moreover a demand monopolist has no interest in the adequate compensation of innovative products but will instead exert high pressure on prices, at the risk of stifling the innovative activities of the pharmaceutical industry.

vfa believes that a solution of these governance problems is urgently required. This would create the procedural prerequisites for a fair benefit assessment and fair pricing for innovative pharmaceuticals. The following adjustments in the regulatory framework seem goal-oriented and could be implemented as a first step:

- The early benefit assessment must be conceptualized as an expert medical evaluation of innovative pharmaceuticals, and the normative assessments should be reduced to a minimum. As explained above (see Section 4), this means: The selection of the ACT must be made solely based on medical criteria. Beforehand, during the advice discussions, a genuine expert dialog with the pharmaceutical companies on the selection of the comparator and additional questions of trial planning and evidence submission must be held with the active participation of the regulatory agency.
- In its implications, the benefit assessment decision of the G-BA is of considerable significance for all parties involved, especially the affected manufacturers. Nevertheless, a review of the decision in terms of an early fact check for correctness is not provided in the procedure. The hearing only refers to the IQWiG evaluation of the manufacturer's dossier; the G-BA decision is merely announced and not subject to any review for the foreseeable future. According to the principle of good governance, more measures ensuring greater trust and acceptance of decisions need to be created without questioning the decision-making authority of the G-BA per se. This concern could be addressed by establishing an appeals body at the G-BA (staffed with independent experts appointed by the German Federal Ministry of Health), as it is also known to other HTA agencies. This body re-

views the decision-making document of the G-BA for the early benefit assessment before it makes its final judgment. The validity of the reimbursement amounts from the 13th month onward would not have to be affected.

Seite 13/21

- In view of the structural dominance of the SHI Head Association in the individual negotiations, the framework for determining reimbursement amounts should be stipulated more strongly. The legislature should ensure that a price comparison should only be allowed between economically comparable countries in order to maintain fairness and to prevent undesirable distortions (see Section 7).
- Furthermore, more leeway should be given for decentralized reimbursement amount agreements between health insurance funds and companies, so that the SHI Head Association cannot act as a demand monopolist with only a cost containment objective. This however would require upgrading the decentralized negotiations, which are currently only provided further down the line as add-on-regulation (pursuant to Section 130c of the German Social Code Book V), to genuine alternative negotiations. Practice shows that, in contrast to the SHI Head Association, individual health insurance funds are actually interested in optimizing health care for their insured patients.

Finally, a brief comment on the reports of the G-BA and the SHI Head Association, according to which affected pharmaceutical companies – in contrast to their association – do not complain about the procedure: With this statement, it is obviously intended to undermine the legitimization of the association as the voice of the pharmaceutical industry. However, due the companies' great dependence on the G-BA and the SHI Head Association, it does not come as a surprise that the affected companies withhold public criticism and address their plain statements through their association.

7. International reference pricing

vfa and its members have pointed out time and again that the AMNOG has an effect not just on Germany but also abroad, which in turn has repercussions for the determination of reimbursement amounts domestically. The problematic mechanism in question is international reference pricing. The research-based pharmaceutical companies must live with this regulatory instrument, and the decision makers of the national health care system must handle it responsibly.

When setting their own pharmaceutical prices, a large number of countries orient themselves on the pharmaceutical price that applies in Germany. As mentioned earlier, reimbursement amounts have now been set for about 20 pharmaceuticals. These reimbursement

amounts are generally known. Therefore, it must be assumed that they will be taken into account for reference pricing in the future. In addition, the AMNOG procedure also considers international prices, resulting in circular referencing. If the pharmaceutical entrepreneur enters into another round of negotiations with the SHI Head Association, the regulated price in other price-referencing countries can then again serve as the basis for the German reimbursement amount. This makes differentiated pricing, which is especially desirable for countries with lesser economic power, impossible.

The following two alternative solutions would be conceivable for eliminating the problems of mutual reference pricing: First, all countries on a Europe-wide scale could agree on foregoing the regulatory instrument of international reference pricing. Such an agreement cannot be realistically achieved and could hardly be enforced either. The second option would be to forego a public listing of the reimbursement amount. This could help avoid the problematic reciprocal effect of international reference pricing, which would also be beneficial for the insured patients in Germany. This would not negatively impact the effect of the AMNOG in Germany but merely limit its effects on other countries and their repercussions.

vfa continues to expressly advocate this second option. Arguments in favor of a mandatorily necessary publication of the AMNOG discount go in the wrong direction. As described above, after a decision of the arbitration board, a subsequent billing procedure of the discount in a direct connection between health insurance fund and manufacturer is always required anyway (see Section 3). vfa advocates standardizing the procedure for handling reimbursement amounts and to systematically convert to direct handling with cost payers (insurers) alone. This way, a public listing of AMNOG discounts could be foregone from a technical perspective.

Currently, the example of Greece shows how real the described problems of international reference prices are in reality: There, the government agency in charge of pharmaceutical pricing has asked that the crisis-related, low pharmaceutical prices not be used as a basis for international reference pricing in other countries. At the same time, it has imposed an export ban for important drugs in order to prevent parallel importers from making a profit from the crisis and from aggravating the domestic supply situation.

Especially in times where European income levels are drifting apart, it must be ensured that only such countries are included in reference pricing that can be considered comparable in terms of their economy and their supply situation. Otherwise, an orientation on the lowest European price would trigger a downward spiral with significant consequences for patient health care (also in Germany). Therefore, it must be questioned whether the countries of Greece, Portugal, Slovakia and the Czech Republic, which are to be used by the arbi-

tration board in the AMNOG procedure, can be viewed as economically comparable. Furthermore, vfa advocates only using such countries for reference pricing that are economically comparable to Germany. In terms of economic comparability, the above-mentioned countries are out of the question.

Seite 15/21

While the legislature has attempted to achieve economic comparability of the foreign prices used in the AMNOG procedure with the recent changes as part of the Second Amendment Act to the German Medicinal Products Act, the adjustment made based on the economic key indicators of sales and purchasing power parity can only be viewed as a stopgap, since the problem arises as early as with the selection of the comparison countries. Basically, any adjustment of prices is insufficient, because it will never be able to adequately take into account all key indicators that have an influence on the price differences that are noticeable in the countries in question. Price differences arise for very different reasons (preferences, transportation costs, national specifics of how reimbursement is regulated, supply situation, etc.) – purchasing power parity and sales are just two influencing factors out of many. The example of Greece shows that the purchasing power parity adjustment is insufficient. The national price regulation systems that specifically act on pharmaceutical prices are not adequately taken into account through purchasing power parities.

8. Prescription practice and economic efficiency

It was the intention of the legislature to introduce mandatory discounts for innovative pharmaceuticals with the AMNOG. Furthermore, physicians were supposed to be relieved from restrictions and controls on the demand side for innovative pharmaceuticals with an additional benefit ("consideration as a practice specialty"). In principle, vfa welcomes such a renunciation of demand regulation and a turn toward supply management. However, dual regulation must be avoided at all cost.

However, currently there are technical and administrative obstacles in the regions that make the practical implementation of these relief measures difficult for physicians. It has become known that several requests were made by various Regional Associations of SHI-accredited Physicians to their members to exercise special caution in prescribing innovative pharmaceuticals until their early benefit assessment by the Federal Joint Committee was concluded. Such requests are clearly objectionable, since it was the declared goal of the AMNOG to preserve the patients' immediate access to innovative pharmaceuticals directly upon their market launch. The unfounded guarded prescription of innovative pharmaceuticals is neither justifiable in terms of the patients nor legally tenable.

Similar difficulties or misunderstandings seem to arise in the handling of practice specialties regarding pharmaceuticals with a positive benefit assessment decision: So far, practice specialties were agreed upon for only three of these pharmaceuticals and only for a few subgroups, even though this is a "should-legislation" according to the AMNOG. From vfa's perspective, additional steps will be required on the part of the health insurance funds and the Regional Associations of SHI-accredited Physicians at the state and federal level in order to make the system viable and to facilitate patients' access to those products whose additional benefit has been proven.

vfa would also welcome more general clarity to be created regarding the question of the economic efficiency of a pharmaceutical that was positively assessed pursuant to the AMNOG. Here, different approaches of an either more differentiated or more general review of economic efficiency would be conceivable. Overall, it must be noted that the legislature has so far not succeeded in keeping its promise of eliminating existing overregulation in the pharmaceutical sector. This means that a price- and volume-regulated product currently is – in many cases – regulated once more based on individual prescription limits and prescription quota. Such dual regulation is not goal-oriented.

The handling of parallel-imported AMNOG pharmaceuticals must also be put to the test. At least for pharmaceuticals that received a positive assessment according to the AMNOG and whose economic efficiency has been established in negotiations, separate promotion of parallel-imported pharmaceuticals is no longer tenable. Therefore, the Parallel Import Promotion Clause must be eliminated.

9. Significance of orphan drugs

For orphan drugs, the AMNOG provides a lean form of the benefit assessment (Section 35a para. 1 clause 10 of the German Social Code Book V), since these pharmaceuticals already had to prove a significant additional therapeutic benefit compared to other possibly already approved pharmaceuticals as part of the European marketing authorization procedure. This special regulation, which is applicable up to a sales volume of EUR 50 million, has so far applied to seven out of 49 benefit assessment procedures. The share of these seven products in both overall sales and the number of prescriptions is very small. Patient numbers for these products amount to about 9,000; this is less than 0.5 percent of the total of patients affected by AMNOG procedures. vfa cannot understand why the G-BA and the SHI Head Association assess the situation differently in terms of this issue and problematize the special regulation for orphan drugs.

First, the lean form of the benefit assessment of orphan drugs is appropriate. The additional benefit of pharmaceuticals that have successfully passed the marketing authorization process as an or-

phan drug is not "fiction" but a medically justified, official determination by the regulatory agency EMA. The orphan status has a time limitation (10 years from marketing authorization) and is mandatorily linked to strict requirements (a disease with no more than one affected individual out of 2,000 EU citizens for which no treatment or no satisfactory therapy was available in the past). Without a "soloist" status or a major additional benefit compared to the previous therapy, the EMA is not allowed to recommend approval as an orphan drug. Immediately prior to marketing authorization, the EMA reviews once more whether the criteria for orphan status still apply. If this is not the case, the orphan status of the drug is withdrawn by the European Commission. Of course, the ascertainment of an additional benefit, which is mandatorily associated with the orphan status, is also binding for subsequent administrative acts, which includes a decision by the G-BA.

Second, the orphan regulation does not provide a loophole for circumventing the early benefit assessment, since the EMA categorically excludes "slicing," i.e. division of a therapeutic indication into smaller "orphan-eligible" subindications. The corresponding regulation (EMA/COMP/15893/2009) literally states: "This is imperative to prevent the slicing of common conditions into invalid subsets. It is important that sponsors [...] are aware that this is an important issue that will be reviewed by the Committee." The same applies to therapies of personalized or stratified medicine to which the EMA does not grant orphan status. Some rejections of orphan status applications for the therapy of patient subgroups show that it is also very strictly handled in practice. Only very few orphan drugs are currently approved for more than one indication – and an increasing trend cannot be observed.

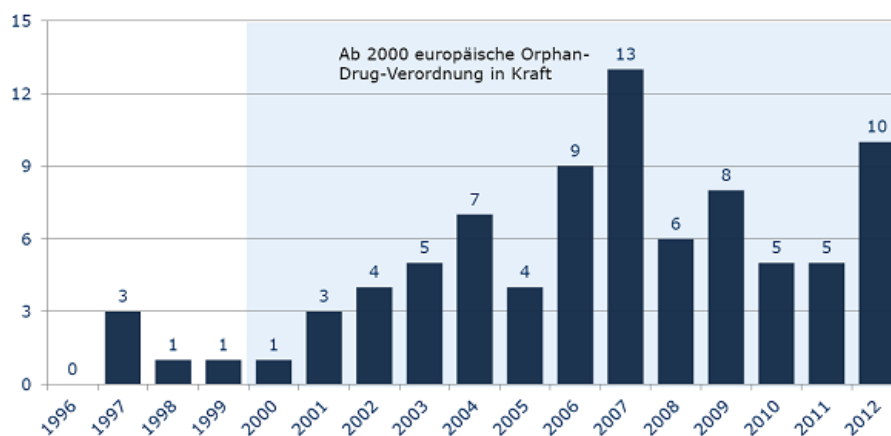
Third, it must be considered that the development of orphan drugs is a political objective: It is for this reason that the EC Directive on Orphan Drugs became effective at the start of 2000. After the 2009 decision of the EU health ministers, the National Action Alliance for People with Rare Diseases (Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE)) was initiated in Germany under the leadership of the German Minister of Health. This alliance, in which the G-BA is also represented, must generate an action plan for the improvement of health care for people suffering from rare diseases by 2013. This plan will also include the forceful advancement of the research and development of orphan drugs.

In the meantime, the EC Directive shows its effect: A series of orphan drugs have been approved, so that patients suffering from rare diseases can be helped for the first time or helped better. However, a strong increase of orphan drug authorizations cannot be recorded – certainly not since the AMNOG has become effective (see Graphic 5). A glance at the submitted marketing authorization applications shows that no strong increase should be expected for 2013

either (about 10 to 12 marketing authorizations). From a commercial standpoint, most orphan drugs are absolute niche products (with sales of less than EUR 10 million per year). Therefore, it is not justifiable – neither from a medical nor regulatory perspective – to question the documented additional benefit of orphan drugs during the benefit assessment and to thwart the politically intended and supported development of these therapies by eliminating the special regulation for orphan drugs in the AMNOG.

Seite 18/21

Graphic 5:
Marketing authorizations for orphan drugs in the EU



10. Existing market

The AMNOG provides the G-BA with the opportunity to also initiate a benefit assessment for pharmaceuticals that are already being marketed, i.e. products from the existing market. In the meantime, the G-BA has summoned one active ingredient group of oral antidiabetics, the so-called gliptines (DPP-4 inhibitors). After the decision of the State Social Court of Berlin-Brandenburg not to grant legal protection to one affected company, the G-BA can continue its summons procedure unhindered. In addition, the G-BA has announced that it will submit a concept with legally certain criteria for summoning products from the existing market. There is currently no need for action on the part of the legislature for the existing market issue.

However, vfa questions whether the early benefit assessment procedure can be extended to the existing market in a meaningful fashion. The first early benefit assessment procedures already show how demanding and expensive they are (see Section 3 above). Benefit assessments for existing market products will be even more expensive than those for new pharmaceuticals:

- Products that have been marketed for years often have several therapeutic indications.
- There are significantly more studies available for these products; the numbers can be in the hundreds.
- The volume of the dossiers to be assessed will be exponentially higher.

Seite 19/21

As early as during the summons of the gliptines, a search in generally accessible databases (e.g. Pubmed) shows a large number of relevant clinical studies that must be taken into account. Compared to the number of studies for newly launched pharmaceuticals (two to three studies), the number for products in the existing market can be exponentially higher. Older products in the existing market can have 500 or more randomized clinical trials that would have to be considered. For assessments of the existing market, a dossier volume of several hundred thousand pages must be expected, at least for Module 5. This shows the enormous expense for dossier generation and the challenge for the self-governing bodies to ensure a correct review and content evaluation of the materials submitted over the planned time periods.

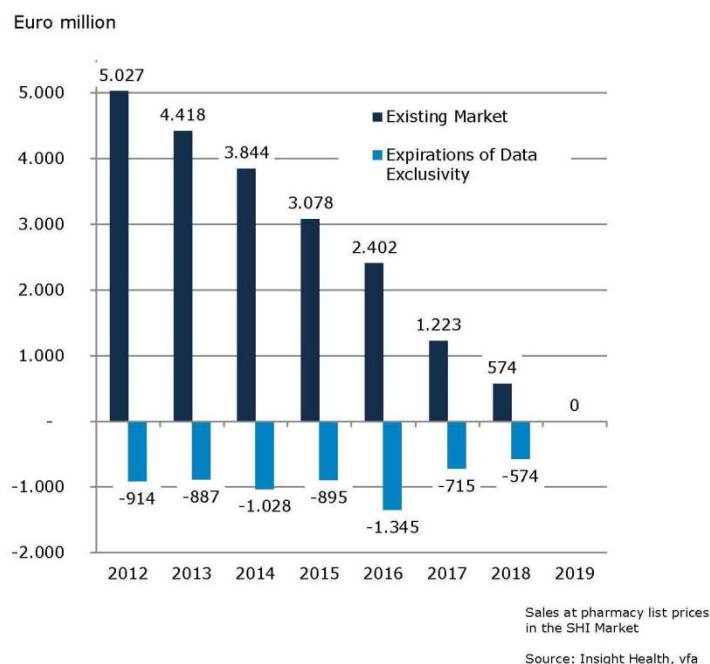
In addition, competitive aspects must be observed as well, since each summons of products from the existing market represents a selective market interference. This starts with the question of who is viewed by whom as a competitor and continues with the issue at what time the summons is made. Finally, this raises the subsequent question of possible additional summons to avoid additional distortions of the competition. One summons of just a few products may ultimately result in an avalanche of new summons for competitor products, which will no longer be manageable for the self-governing bodies in terms of capacity.

Problems will also arise under legal aspects. When deciding which pharmaceuticals from the existing market will be summoned, the G-BA must comply with the equality principle and the discrimination ban derived from it. This results in high legal requirements for the planned summons concept of the G-BA.

In light of the practical and legal problems and obstacles, the question must be asked if a summons of the existing market is meaningful and necessary at all. On the one hand, it must be considered that reimbursement amounts for new pharmaceuticals will also successively have an impact on similar products from the existing market; their sales and possibly their prices will decrease as well. In that case, a separate benefit assessment including the setting of a reimbursement amount will no longer be required.

On the other hand, the patents of important pharmaceuticals in the existing market will soon expire. This will free these products up for the generic competition. The sales volume of products with data exclusivity that are not yet subject to the AMNOG procedure (products with new active ingredients that were launched from 2002 to 2010 according to vfa information) was about EUR 5 billion in 2012. Based on patent expirations, the volume of the protected market will successively decrease until in 2019 there will be no more patented products in the market that have not been subjected to the AMNOG procedure (comp. Graphic 6). Within the foreseeable future, the problem of integrating the existing market will take care of itself.

Graphic 6:
Decline of the existing market from 2012 to 2019



11. Conclusion

The AMNOG processes must be further improved. Currently, the early benefit assessment rather tends to slow down innovation. New pharmaceuticals often receive a positive additional benefit rating only for some of the reviewed subgroups. In many cases, this is due to unrealistic expectations toward the evidence provided by the manufacturers and problematic initial stipulations by the G-BA such as the choice of the comparator, which leads to the non-consideration of available evidence.

The current governance structures in particular are emerging as the central flaw of the AMNOG. As explained above, the SHI Head Association is significantly involved in the advice process and pharma-

ceutical assessment of the G-BA and subsequently dominates the reimbursement amount negotiations in a monopolist position. Adjustments in this respect are important for facilitating fair benefit assessments and pricing for innovative pharmaceuticals. The outlined problems of international reference pricing must also be urgently addressed. vfa believes that close monitoring of the AMNOG implementation will be required and would be happy to contribute its expertise.