A critical stocktaking from the perspective of the pharmaceutical industry

The new ‚guard rails' in the AMNOG process

The AMNOG process has been legally adapted several times in recent years. A significant change occurred most recently with the GKV-Financial Stabilisation Act (GKV-FinStG), which was passed at the end of 2022. The legal package of measures includes, among other things, new specifications for the reimbursement amount negotiations, which change the basic principle of the AMNOG. According to these new specifications (so-called ‚guard rails'), a new medicinal product may not cost more than the comparator therapy in certain cases despite the proven additional benefit. In the case of an unproven additional benefit, the costs must even be lower. The details of these new requirements are subjected to a critical analysis in the following.

>> The AMNOG requirements previously limited the negotiating scope of the contracting parties if the medicinal product could not prove an additional benefit. Section 130b of the German Social Code, Book V stipulated that for new medicinal products without proven additional benefit, a reimbursement amount should be agreed that does not lead to higher annual therapy costs than the appropriate comparative therapy (zVT) or the most economical alternative in the case of several zVT alternatives. In the case of an additional benefit, correspondingly higher prices could be agreed (principle of so-called ‚value-based pricing').

The newly implemented regulations, euphemistically referred to as ‚guard rails' in the legislative materials, start at this point and tighten the negotiation requirements in § 130b SGB V in a complex way. Their validity depends on two factors: Firstly, on the type of appropriate comparative therapy - the guard rails apply in those cases in which the G-BA has determined a medicinal product with an active ingredient as the zVT, for which patent or document protection exists. Secondly, of the extent of additional benefit - they apply when the additional benefit has been classified as unproven, low or non-quantifiable. Linking both factors, essentially three negotiation specifications are now made in §130b SGB V: a) If an additional benefit is not proven and if the zVT is a medicinal product with an active ingredient for which patent and document protection have ceased, a reimbursement amount should be agreed that does not lead to higher annual therapy costs than the zVT. b) If an additional benefit is not proven and if a medicinal product with an active substance for which patent or document protection exists is determined as the zVT, a reimbursement amount shall be agreed that leads to annual therapy costs that are at least 10 percent below those of the zVT. c) If an additional benefit cannot be quantified or is classified as low and if the zVT is a medicinal product with an active ingredient for which patent or document protection exists, a reimbursement amount must be agreed that does not lead to higher annual therapy costs than the zVT.

In addition, if several zVT alternatives have been determined, the zVT that represents the most economical alternative in terms of annual therapy costs is to be used when applying the upper guidelines. If a medicinal product with a patent-protected active ingredient that is not subject to the benefit assessment according to Section 35a was determined as the zVT, a fictitious discount of 15 percent is to be applied to the costs of this medicinal product.

Whereas the requirement mentioned under (a) corresponds in content to the status prior to the GKV-FinStG, the requirements under (b) and (c) represent a significant tightening. In the case of an unproven additional benefit, instead of a limit with a target specification, a minimum discount of 10 percent now applies, which acts as a hard price cap. In the case of an unquantifiable or low additional benefit, instead of the possibility of negotiating a higher reimbursement amount, a hard cap now applies at the level of the zVT (see Table 1).

Initial estimates assume that with these pricing requirements, no restrictions now apply to only every fifth subpopulation assessed and a reimbursement amount agreement above the zVT is possible. Around 3/4 of the new active substances would be affected by a restriction through the guard rails in an initial assessment (9). In addition, with the GKV-FinStG the retroactive effect of reimbursement amounts already applies from the 7th month instead of the 13th month after the start of the procedure.

Explanatory memorandum of the legislature

In the explanatory memorandum to the cabinet draft of the GKV-FinStG, the new guard rails for non-quantifiable or minor additional benefits are described as necessary and appropriate to ensure the financial stability of the SHI, since ‚the price level of patent-protected medicines is already in a range that isadequate for research-based pharmaceutical manufacturers ‚which doesnot justify additional surcharges for only non-quantifiable additional benefits or minor additional benefits , . Inaddition, the incentive is set , to place a greater focus on patient- and care-relevant questions for the benefit assessment in orderto be able toachieve a considerable or substantial additional benefit inthe benefit assessment.

With regard to the minimum discount in the case of an unproven additional benefit, the explanatory memorandum states that this change had become necessary because ‚practice has shown that the opening of the

Background

Since 2011, medicinal products with new active substances have been subject to price regulation, which was introduced with the AMNOG (Medicinal Products Market Reorganisation Act). The medicinal products are first assessed by the G-BA with regard to their additional benefit compared to the current therapeutic standard (so-called appropriate comparative therapy). On the basis of this additional benefit assessment, the negotiation of a reimbursement amount then takes place between the pharmaceutical company concerned and the GKV-Spitzenverband. The core principle of this regulation has so far been that prices follow the additional benefit. The negotiation of a reimbursement amount above the costs of the appropriate comparative therapy should be possible if the new drug could show an additional benefit. In the case of an unproven additional benefit, however, the costs of the comparative therapy should not be exceeded.

Since 2011, around 400 medicinal products have been subjected to such a process in over 850 procedures. In about 9 out of 10 cases, the GKV-Spitzenverband and pharmaceutical manufacturers were able to agree on a reimbursement amount. If certain issues remained in dispute, the AMNOG Arbitration Board was involved in order to set a reimbursement amount in a balance of interests. The framework for benefit-based pricing was thus basically given for all sides. Due to the positive incentives, Germany has so far been leading in Europe in the speed of market introduction and availability of innovative medicines.

cost ceiling for medicinal products without additional benefit introduced with the Act to Strengthen the Provision of Medicinal Products in Statutory Health Insurance (AMVSG) has led to the agreed reimbursement amounts regularly being above the most economical alternative of the appropriate comparative therapy in justified individual cases. In this way, the expenditure of the SHI for medicinal products without additional benefit could rise to a level that was not adequate for the benefit, from which subsequent active substances in particular could profit through a correspondingly higher price level.'

The new pricing requirements as well as the legal justifications listed above have become the subject of critical discussions. The points of criticism are explained in detail below.

Importance of an unproven, low or unquantifiable additional benefit

First of all, it must be questioned whether the systematic devaluation of a non-quantifiable or minor additional benefit of a new medicinal product is appropriate. First of all, it must be pointed out what is hidden behind a low or non-quantifiable additional benefit according to the legal requirements. According to the German Drug Benefit Assessment Ordinance (AM-NutzenV), a small additional benefit exists ‚if a moderate and not only minor improvement of the therapy-relevant benefit [...] isachieved compared to the appropriate comparator therapy, in particular a reduction of non-serious symptoms of the disease or a relevant avoidance of side effects' (see Tab. 2).

It is thus clear that the low extent already includes a minimum threshold for patient-relevant therapy effects, so that negligible or minor effects cannot be assumed. In the assessment practice of the G-BA, this also includes assessments with a prolongation of overall survival and avoidance of recurrences in oncological diseases or more frequent complete remissions of severe plaque psoriasis in children and adolescents (3, 4, 5).

According to the AM-NutzenV, an additional benefit exists in the case of a non-quantifiable additional benefit, ‚but is not quantifiable because the scientific data basis does not permit this' (see Tab. 2).

In the assessment practice of the G-BA, this has always been associated with an additional benefit, which can basically include all positive extent categories (1). A non-quantifiable additional benefit is thus at least small and at the same time includes the possibility of a considerable or substantial additional benefit with clear improvements in the course of therapy up to and including cure. Non-quantifiable added benefit also includes drug evaluations in which there is a clear prolongation of overall survival or cure of chronic hepatitis C in paediatric patients (6,7).

Overall, the general statement that there is ‚only' a small or unquantifiable additional benefit that does not require a reward must therefore be clearly questioned. Rather, the examples mentioned illustrate that such medicinal products can be of great importance in health care, but that this can no longer be adequately rewarded as a rule with the new regulations through the GKV-FinStG.

Regarding the unproven additional benefit, it should be noted that in most cases this determination was not made on the basis of a weighing of positive and negative effects, but because the available evidence from approval studies did not meet the requirements of the G-BA within the framework of its specific research question and was therefore not included in the benefit assessment (8). Moreover, every ‚equally good' drug expands the availabletherapy options in everyday care. A compulsory rejection of this fact is therefore not comprehensible.

The evaluation practice of the G-BA also shows that medicinal products with an unproven, low or non-quantifiable additional benefit are also of high relevance in health care. If AMNOG-evaluated medicinal products

Übersicht der wichtigsten Preisbildungsvorgaben

Ausmaß des Zusatznutzens	zVT*	Vorgaben
nicht belegt	G	soll nicht höher als zVT
	P/U	neu: muss mindestens 10% unter zVT
gering	G	Aufschlag auf zVT möglich
nicht quantifizierbar	P/U	neu: darf nicht höher als zVT
beträchtlich/erheblich	G oder P/U	Aufschlag auf zVT möglich

Tab. 1: Übersicht der wichtigsten Preisbildungsvorgaben. Legende: * G = generisch; P/U = Patent- oder Unterlagenschutz.

Kategorien des Zusatznutzenausmaßes

Zusatznutzen	Beschreibung nach AM-NutzenV
erheblich	wenn eine nachhaltige und gegenüber der zweckmäßigen Vergleichstherapie bisher nicht erreichte große Verbesserung des therapierelevanten Nutzens im Sinne von § 2 Absatz 3 erreicht wird, insbesondere eine Heilung der Erkrankung, eine erhebliche Verlängerung der Überlebensdauer, eine langfristige Freiheit von schwerwiegenden Symptomen oder die weitgehende Vermeidung schwerwiegender Nebenwirkungen
beträchtlich	wenn eine gegenüber der zweckmäßigen Vergleichstherapie bisher nicht erreichte deutliche Verbesserung des therapierelevanten Nutzens im Sinne von § 2 Absatz 3 erreicht wird, insbesondere eine Abschwächung schwerwiegender Symptome, eine moderate Verlängerung der Lebensdauer, eine für die Patientinnen und Patienten spürbare Linderung der Erkrankung, eine relevante Vermeidung schwerwiegender Nebenwirkungen oder eine bedeutsame Vermeidung anderer Nebenwirkungen
gering	wenn eine gegenüber der zweckmäßigen Vergleichstherapie bisher nicht erreichte moderate und nicht nur geringfügige Verbesserung des therapierelevanten Nutzens im Sinne von § 2 Absatz 3 erreicht wird, insbesondere eine Verringerung von nicht schwerwiegenden Symptomen der Erkrankung oder eine relevante Vermeidung von Nebenwirkungen
nicht quantifizierbar	Zusatznutzen liegt vor, ist aber nicht quantifizierbar, weil die wissenschaftliche Datengrundlage dies nicht zulässt
nicht belegt	kein Zusatznutzen belegt
geringer	Nutzen des zu bewertenden Arzneimittels ist geringer als der Nutzen der zweckmäßigen Vergleichstherapie

Tab. 2: Kategorien des Zusatznutzenausmaßes.

are themselves designated as new zVT in an area of application, around 2/3 of them have previously been able to show ‚only' an unproven, minor or non-quantifiable additional benefit. These zVT designations cover a whole range of indications such as cancer, skin, musculoskeletal or metabolic diseases. The relevance of such drugs is also reflected in the guidelines of the medical societies, where they have a fixed place. At the same time, even in the case of an unproven additional benefit, the G-BA repeatedly points out in the supporting reasons for the decisions that such medicinal products can be a relevant therapy option in individual cases. This is particularly the case if there is a great need for therapy in the care system or if the new medicinal product even represents the first approved therapy option in this indication. Also against this background, a blanket marginalisation of the importance of these medicinal products by the ‚guard rails' does not seem comprehensible.

Finally, the new guidelines must be viewed critically in the context of the innovation landscape of the last decades. They basically penalise companies for taking the risk of investing in the development of improved therapeutic approaches for a variety of diseases in the different therapeutic lines. So-called step innovations are the norm in drug research and development. Leap innovations are much less common. The new guard rails reduce incentives to search for patient-relevant improvements even after the initial approval of a drug and to show these in the benefit assessment compared to the therapy standard.

Equalisation of unequal circumstances

The new regulations of the GKV-FinStG also lead to regular unequal treatment in the AMNOG system. Substantially identical circumstances, i.e. medicinal products comparable in the benefit assessment, are treated unequally in pricing. If, for example, a second representative of an active substance class is comparable to the first representative, which has become the therapeutic standard in the meantime, the second representative is systematically treated worse with the minimum discount regulation. At the same time, substantially unequal situations, i.e. medicinal products with proven additional benefit compared to their inferior appropriate comparative therapy, are treated equally. In addition, the application of guard rails equates the conduct of comparative studies with the absence of such evidence. Such a blanket malus regulation therefore also appears to be extremely problematic systematically.

Shifting negotiating positions

In the draft law, the introduction of guard rails is justified, among other things, with the objective of strengthening the position of the GKV-Spitzenverband (GKV-SV). This justification is not comprehensible, since the GKV-SV is in a quasi-monopoly situation anyway. In addition, it plays a key role in the entire AMNOG process. As the decisive bench in the G-BA, it is directly involved in the benefit assessment process and also decides on the exact wording of the zVT and the extent of the additional benefit in the consultations with the pharmaceutical companies as well as in the subsequent decisions - and thus precisely on the levers for the possible application of the guard rails in the subsequent reimbursement amount negotiation. Intuitively, this points to a governance problem. Empirically, this is also reflected in the dissenting voting results in the G-BA plenum. In such cases, the GKV-SV has, without exception, always voted for a worse evaluation of the respective drug compared to the other G-BA benches since 2011. The GKV-SV is also the only party to have a complete overview of all price negotiations that have ever taken place and are ongoing, which means a clear negotiating advantage.

Reduction of flexibility in negotiations

The guard rails significantly limit the room for manoeuvre of the contracting parties in the reimbursement price negotiations. The justification that the creation of a

The justification that the creation of a target regulation has led to the agreed reimbursement amounts regularly being above the most economical alternative of the zVT must be questioned. On the one hand, there is no empirical evidence that such an excess occurred not only in individual cases, but on a regular basis. On the other hand, a situational application would indicate the existence of a justified individual case. The target regulation was specifically introduced in 2017 with the Act to Strengthen the Provision of Medicines (Arzneimittel-Versorgungsstärkungsgesetz - AMVSG) for such individual cases in order to agree on a reimbursement amount above the most economical comparative therapy in special circumstances, even for medicines without an established additional benefit. This was intended to make narrow, rigid specifications more flexible in order to ensure more negotiating leeway for an appropriate price. Such special circumstances may also exist in the case of a patent-protected comparator therapy. However, the guard rails now limit the possibilities for the negotiating parties or the arbitration board to take these circumstances into account.

Effects on certain therapy situations

Chronic diseases

The blanket guard rail rules also show their limitations with regard to certain therapies. In the case of chronic diseases, for example, it should be noted that the AMNOG has so far hardly been able to demonstrate a considerable or even substantial additional benefit (e.g. in the case of drugs for the treatment of diabetes mellitus type 2 or mental diseases). Thus, if according to the explanatory memorandum, a greater incentive is to be directed towards other issues than have been addressed so far, the guard rails could even prove to have a counterproductive effect here, since the threshold of at least considerable added benefit for such diseases could only rarely be reached in recent years, also due to the specifics of the therapies and the AMNOG requirements. Especially for the development and introduction of medicinal products in such indication areas, the incentives would therefore be even lower and market access would be additionally impeded (10).

Advanced therapy medicinal products

The explanatory memorandum to the cabinet draft of the SHI FinStG also states that the price level of patent-protected medicinal products is within an adequate range for the new medicinal products. These should therefore be able to realise a comparable price. This sweeping statement must also be questioned. Even patent-protected medicinal products can have substantially different price levels. Particularly in the case of advanced therapy medicinal products (ATMPs), constellations are conceivable where an additional benefit can only be classified as non-quantifiable, but the price level of the existing therapy standard is not adequate. The hard price cap does not allow any fle-

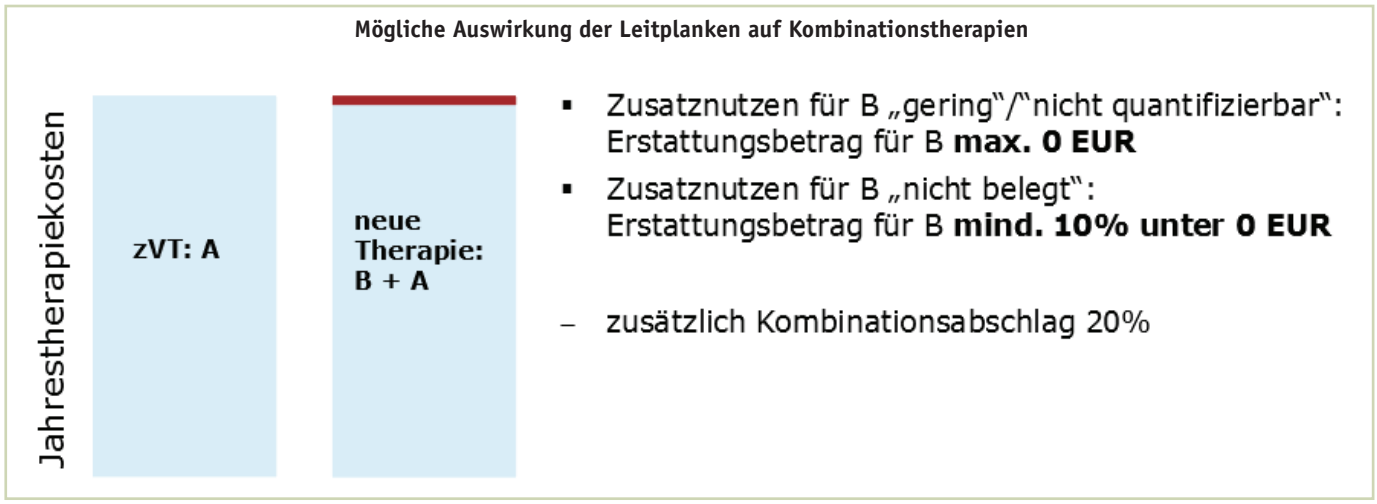


Abb. 1: Mögliche Auswirkung der Leitplanken auf Kombinationstherapien.

xibility for these cases to take into account the special circumstances of the individual case.

Add-on combinations

Other constellations also do not appear to be well thought out in the guard rail system. An example is drug B, which is used as an add-on to A in combination therapy. Despite survival benefits, the G-BA only classifies the additional benefit of B as low or unquantifiable. According to the guard rail specifications, the drug should not lead to higher costs overall than the annual therapy costs of the basic therapy A. This would mean that the new therapy may cost a maximum of 0 euros despite additional benefit. In the case of an unproven additional benefit, the reimbursement amount would even have to be at least 10% below 0 EUR. Taking into account further regulatory measures, such as the combination discount, this should therefore lead to the demand for even lower prices (see Fig. 1).

Initial effects in valuation practice and supply

Assessments of the effects are only possible to a limited extent in the short term, since a meaningful number of cases within the scope of the new guard rails must first be reached. Nevertheless, the first undesirable developments are already evident a few months after the law came into force. The new regulations are obviously also taking effect in areas where they were most likely not intended - for example, in innovations with significant prolongations of overall survival that are already establishing themselves as the new standard of care. This became clear early on with the example of the active substance trastuzumab-deruxtecan for the treatment of patients with advanced breast cancer. In second-line treatment, the drug shows very clear advantages in terms of overall survival and severe side effects - a clear case of considerable added benefit in the G-BA's previous practice. Unexpectedly, however, the G-BA classified the added benefit for this indication as non-quantifiable (6).

This classification means that the second-line drug falls under the new rigid price regulations of the GKV-FinStG. The G-BA decision is justified in particular by the formal uncertainty with regard to quantification, since a subgroup analysis of the pivotal study shows survival benefits (of considerable magnitude according to IQWiG) for the larger group of people under 65 years of age, while for people 65 years of age or older the effect is not significant. According to the DGHO (German Society for Haematology and Medical Oncology), however, there is no biological rationale for the subgroup findings. Based on the study results, the drug even replaces the previous therapy standard in this indication in Germany (11). According to the current evaluation of the European Society For Medical Oncology (ESMO), the degree of innovation is also 4 out of 5 possible points on the ESMO-MCBS (Magnitude of Clinical Benefit Scale) (12). In the ESMO-MCBS system, this corresponds to a ‚substantial magnitude of clinical benefit', which overall calls into question the classification made by the G-BA as non-quantifiable as well as the scope of application of the guard rails here.

The application of the guard rails for such cases is questionable in terms of regulatory policy, as innovations relevant to the provision of health care are not rewarded for the additional benefit. A non-quantifiable extent of additional benefit has a much more restrictive effect on subsequent negotiations in the system of the new guard rails. Furthermore, the question arises at what level of methodological uncertainty a quantification of the extent (as at least considerable) is possible and the guard rails should not apply. This also reinforces the question of when residual methodological uncertainties are not reflected in the probability of additional benefit (e.g. downgrading from an indication to a clue), but instead or additionally in the classification of the extent of additional benefit by the G-BA.

In the case of Eptinezumab for use in migraine prophylaxis, it is exemplary that the guard rails lead to unequal treatment and inconsistency. The previously AMNOG-evaluated drugs of this drug class were each compared to Best Supportive Care (BSC) as zVT and were each able to prove a considerable additional benefit. In the case of eptinezumab, however, the specification of the zVT was previously changed in the consultation to drugs that had already been assessed. A proof of added benefit compared to BSC was therefore no longer possible here. As a result, a minimum discount of 10 per cent even applies. The guard rails thus exacerbate an inconsistent assessment in this situation. In addition, in this case, the question also arises as to the significance of the guideline according to Section 6 (3) of the AM-NutzenV at the G-BA, according to which the same appropriate comparative therapy must be used for medicinal products of the same active substance class in order to ensure a uniform assessment. To make matters worse, the G-BA's decision on the requirement for a change at a certain point in time does

not appear to be sufficiently transparent (14). The example also illustrates that the amendment of a CVT can also develop into a strategic lever for the application of the guard rails.

Another example is the failure to introduce the fixed combination of nivolumab and relatlimab for the first-line treatment of advanced melanoma in adults and adolescents aged 12 years and older as a result of the new regulation. Although the dual immunotherapy shows clear benefits in improving progression-free survival (PFS), in this country PFS is not recognised as a patient-relevant endpoint and as an additional benefit. For this combination therapy, the current assessment of the European professional society sees 3 out of 5 points on the ESMO-MCBS (13). Together with the new guard rails, the added value of this therapeutic approach can thus no longer be reflected, according to the company concerned, so that marketing of the medicinal product will not take place for the time being.

Further direct consequences for the supply cannot be assessed at the present time, since the guard rails will have their effect primarily in the medium and long term. In addition to recording the non-intended use cases, further effects on the availability and speed of market access in Germany must therefore continue to be monitored.

Conclusion

It should be noted that with the new ‚guard rails', the basic principle of the AMNOG (value-based pricing with higher prices for a higher additional benefit) was restricted in a number of cases. The resulting blanket handling of the significance of an unproven, low or unquantifiable additional benefit appears questionable. Equally debatable seems to be a further shift in negotiating positions in the case of already existing governance problems as well as the restriction of flexibility in negotiations. The consequences for certain therapeutic situations, such as chronic diseases, advanced therapy medicinal products or combination therapies, appear to be partly ill-conceived. In terms of regulatory policy, a counterproductive effect of the guard rails also appears possible, since research and development for certain therapies, according to current AMNOG practice, do not regularly result in at least considerable additional benefit. The lack of remuneration for the research risk in step innovation as the backbone of drug research also seems debatable. Even if meaningful assessments of the effects in practice are still hardly possible, the first examples of contentious applications of the guard rails and of effects on the availability of medicines are nevertheless emerging. The upcoming evaluation of this new set of regulations should thus take into account the existing problems and lead to a revision. <<

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