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Appropriate comparator therapy: Challenges & trends

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Goals of the plattform

Since the introduction of AMNOG in 2011, Germany has a well-established and widely accepted „adaptive system" for the assessment of the patient-relevant additional benefit (Health Technology Assessment, HTA). The assessment of the additional benefit by the Federal Joint Committee (G-BA) is the result of expert work based on a law (AMNOG) and procedural and methodical regulations.

The active players on the side of the G-BA and the health insurance funds are classified as scientists, hospital physicians and office-based statutory health insurance physicians, the Medical Service of the Health Funds and employees of the insurance fund administration, but also as patient representatives, however, they act on the basis of their own interests. Value dossiers for new pharmaceuticals, likewise qualified and interest-based, are submitted to the G-BA by the pharmaceutical companies, which serve as the basis for the assessment of the additional benefit.

Because the supply of pharmaceuticals to the population is significantly influenced by the assessment of the additional benefit, it makes sense to provide critical and careful support for the assessment process with a focus on identifying possible faults and counteracting imbalances. The Interdisciplinary Platform on Benefit Assessment set itself the task of supporting the benefit assessment within a small group of experts with the following objectives:

Discussing the procedures for the assessment of the additional benefit, including in relation to approval of pharmaceuticals,

Working towards international standards of evidence-based medicine and of health economy being adhered to as well as applied and further developed,

Determining whether and to what extent patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life, are identified and which methodological problems occur during the process,

dentifying possible undesirable developments, in particular with regard to supplying patients with new active substances,

Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure, e. g. on the further development of the legal framework conditions of AMNOG.

Moreover, the European perspective in HTA of innovative pharmaceuticals was reinforced by the European Commission's proposal for a Regulation on HTA in 2018. Monitoring the conflict between the well-established national assessment and the intended European HTA harmonisation is also a central concern of the platform. The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. According to the Advisory Council, an interdisciplinary dialogue about the results of the assessment and the applied benefit assessment methods is essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new pharmaceuticals for patients earlier than it was previously the case.

The Interdisciplinary Platform is a result of the discussion process between clinicians and experts. The mutual desire to pool specialist knowledge in the form of interdisciplinary seminars is supported by an open consortium of sponsors. These include AbbVie Deutschland GmbH & Co. KG, DAK Gesundheit, MSD Sharp & Dohme GmbH, Novo Nordisk Pharma GmbH, Roche Pharma AG, Association of Research-Based Pharmaceutical Companies (vfa e.V.) and Cencora Global Consulting Services.

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Comparator therapy in the context of national and European challenges

Professor Jörg Ruof

Dear Readers,

The tectonic financial pressures affecting the healthcare system as a whole, the often rather erratic debate surrounding Most Favoured Nation (MFN), the change in leadership at the Federal Joint Committee (G-BA), and the first experience gained with European benefit assessment will undoubtedly shape the agenda of the Interdisciplinary Platform on Benefit Assessment in 2026 and beyond.

Professor Hecken has led the G-BA since 2012 and played a major role in shaping the implementation of the AMNOG legislation. His exceptional expertise and commitment, always accompanied by a refreshing sense of humour despite the seriousness of the decisions involved, have undoubtedly contributed substantially to making Germany's benefit assessment process an international benchmark.

Over the past 14 years, AMNOG has succeeded to a considerable extent in reconciling three demanding objectives: rigorous scientific excellence, consistent cost awareness, and the establishment and further development of a leading position in Europe and internationally, while ensuring that innovative therapies offering genuine patient benefit are made available to patients without delay.

Professor Hecken's opening article to this volume provides an excellent overview and retrospective. On behalf of the Interdisciplinary Platform on Benefit Assessment, its Advisory Board, and its sponsors, I would like to express our sincere gratitude for his many years of outstanding and highly successful commitment.

Yet the system's pain points remain unmistakable. Indeed, with diminishing financial headroom, they are becoming ever more pronounced, one might even say increasingly acute. Maintaining a healthy balance between the indispensable goal of financial sustainability and the equally important openness to innovations that deliver meaningful patient benefit is becoming ever more challenging. The remaining discussions on the first day of the Platform's Spring Meeting, together with the articles by Ms Helmold, Mr Ermisch, and Ms Ruhwinkel in this volume, examine this tension from different perspectives.

Alongside these considerable national challenges, significant developments are also taking place at the European level. A number of major legislative initiatives aimed at strengthening the European Health Union seek to reshape the pharmaceutical landscape. These include the EU HTA Regulation, the EU Pharmaceutical Legislation, the European Biotech Act, and the Critical Medicines Act. In a remarkable joint declaration issued by the French and German Ministries of Health in early May 2026, six clear signals were set out with the aim of strengthening the importance and attractiveness of Europe as a location for pharmaceutical innovation. With regard to European benefit assessment, the declaration states: „Easing the market launch of new medicinal products by harmonising the benefit assessment."

It goes on to envisage a „binding European assessment." Whatever the intention behind the somewhat apocryphal term „binding", its direct relevance to the theme of this volume lies in the issue of the comparator, namely comparator therapy. Within the PICO methodology, which is central to European HTA, the choice of comparator therapy is of fundamental importance. The current European approach is guided more by the principle of equity than by that of excellence.

This means that the European assessment seeks to reflect all comparator therapies considered relevant across the different Member States within the PICO framework. However, if the objective is the harmonisation of benefit assessments envisaged by the two Ministers – effectively

creating a „one-stop shop" that enables Europe to remain competitive internationally – this approach should, from the perspective of excellence, evolve towards selecting the best available current standard of care as the comparator and focusing comparative assessments accordingly.

The articles by Ms Busies, Mr Rasch, Professor Lordick and Mr Rieke in this volume provide practical, experience-based perspectives on the many facets of the debate surrounding appropriate comparator therapy. They discuss the role of evidence from health services research, as well as the challenges that rapidly evolving treatment standards and advances in genetically targeted therapies create when determining an appropriate comparator therapy. Mr Huster concludes the articles with an analysis of the landmark Regadenoson judgment, focusing on the special case of determining the appropriate comparator therapy for therapies without a direct comparator.

As in previous years, Florian Staeck provides an excellent summary of the lively discussions that took place during the meeting. I would therefore like to extend my sincere thanks to all speakers and panellists, as well as to our sponsors for their continued support of the Interdisciplinary Platform on Benefit Assessment as a forum for discussion and exchange. My thanks also go to our colleagues at Springer, whose dedicated work once again made the publication of this volume possible. Finally, I would like to express my particular appreciation to the team at BMK.tv, who have provided outstanding technical support for the Platform meetings over many years, always professionally, reliably, and almost unnoticed in the background.

To you, our readers, I wish a few quiet moments and an enjoyable and thought-provoking read.

Yours sincerely,

Jörg Ruof
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AMNOG: A status report from the perspective of the Federal Joint Committee

Professor Josef Hecken | Until 30. June Independent Chair of the Federal Joint Committee (G-BA)

Since the introduction of the Pharmaceutical Market Restructuring Act (AMNOG) in 2011, more than 1,000 benefit assessment procedures have been completed. No additional benefit was demonstrated in 50.6% of procedures, while 1.8% showed a major additional benefit, 16.0% a considerable additional benefit, 13.7% a minor additional benefit and 16.0% an additional benefit that could not be quantified. Germany continues to occupy a leading position in Europe with regard to access to pharmaceuticals. More than 90% of newly authorised pharmaceuticals are available in Germany, with market availability achieved after an average of just 52 days. However, this broad and rapid access to innovative pharmaceuticals is also a major driver of expenditure. In 2024, pharmaceutical spending reached €55.3 billion, accounting for approximately 18% of total expenditure by the Statutory Health Insurance (SHI) system. Oncology products and orphan drugs account for less than 9% of prescriptions but almost one third of total pharmaceutical expenditure. As AMNOG continues to evolve, closer attention should be paid to the freely determined manufacturer launch price, the insufficient price dynamics following the initial benefit assessment, and the limitations of establishing an appropriate comparator therapy (ACT) on a binding basis before the start of a procedure. In addition, the gradual implementation of the European HTA framework will influence national assessment processes. AMNOG has proven to be an effective policy instrument. In its current form, however, it remains largely focused on a snapshot at the time of market entry. The growing importance of therapies characterised by limited evidence and high costs, particularly orphan drugs, gene therapies and products granted conditional marketing authorisation, highlights the need to develop the system into a learning framework. Such a framework should link prices dynamically to the evolving evidence base.

Background: current situation

Since the introduction of AMNOG in 2011, more than 1,300 benefit assessment procedures have been initiated. An analysis of the 1,007 completed decisions that remain in force shows that no evidence of additional benefit was found in 50.6% of cases. The categories of major, considerable, minor, and non-quantifiable additional benefit accounted for 1.8%, 16.0%, 13.7% and 16.0% of procedures, respectively (figure 1). Savings generated in the pharmaceutical sector through AMNOG, reference pricing and rebate agreements now correspond to approximately one contribution rate percentage point within the SHI system, equivalent to around €18.9 billion.

A comparison of the periods 2011–2017 and 2018–2024 reveals several structural trends:

- The proportion of antineoplastic agents (ATC group L01), endocrine therapies used in oncology (L02) and immunosuppressants (L04) increased by 10%, from 37.1% to 40.9%.
- Marketing authorisations granted under exceptional circumstances and conditional marketing authorisations (CMAs) increased by 75%, from 12.8% to 22.4%.
- The proportion of orphan drugs rose by 62%, from 22.4% to 36.3%.
- At the same time, the proportion of orphan drugs with a quantifiable additional benefit declined by 30%, from 41.0% to 28.6%.

These figures illustrate a structural tension within the system. Benefit assessment exerts its strongest downward pressure on prices when additional benefit can either be ruled out or quantified. Increasingly, however, this prerequisite is no longer met for a growing share of new active substances. The proportion of conditional approvals and orphan drugs continues to rise, while the share of orphan

drugs with a quantifiable additional benefit is declining. As a result, the steering effect of AMNOG is weakening precisely in those areas where price dynamics are most pronounced.

Germany continues to hold a leading position in Europe in terms of access to pharmaceuticals. More than 90% of newly authorised medicines are available to patients in Germany, and the average time between marketing authorisation and market availability is just 52 days (figure 2). It should be noted that „availability in Germany" refers to full access within both the statutory and private health insurance systems. In other European countries, many medicines are either available only to self paying patients or subject to restrictions on public reimbursement, including indication specific limitations. This advantage in patient access represents a major health policy achievement. At the same time, it also contributes to the overall cost challenge. Any reform of pharmaceutical pricing must preserve this strength rather than undermine it. The objective is therefore not to reduce access to innovation, but to align the pricing of innovative therapies more closely with the development of clinical evidence.

The broad and rapid availability of innovative pharmaceuticals is associated with substantial expenditure. In 2024, total pharmaceutical spending excluding NUB prescriptions amounted to €55.3 billion, representing approximately 18% of total SHI expenditure. Therapeutic areas accounting for less than 9% of prescriptions were responsible for a disproportionate share of these costs. Oncology products accounted for 1.2% of prescriptions but generated expenditure of €11.4 billion, corresponding to 20% of total pharmaceutical spending. Orphan drugs accounted for just 0.08% of prescriptions yet generated expenditure of €8.1 billion, representing 13% of total pharmaceutical spending.

The concentration of expenditure within a small number of therapeutic areas has important implications for the current reform debate. Oncology products and orphan drugs are often characterised by limited evidence at market entry, methodological challenges in conducting randomised controlled comparative studies, and, in the case of one time therapies, a particularly visible need for outcome based reimbursement models. Evidence gaps, expenditure concentration, and the need for effective system steering therefore converge within the same therapeutic areas. It is against this background that the following reform proposals should be viewed.

The findings outlined above point to three key areas for action. At the beginning of the product lifecycle, attention should focus on correcting the anchoring effect created by the freely determined manufacturer launch price. Subse-

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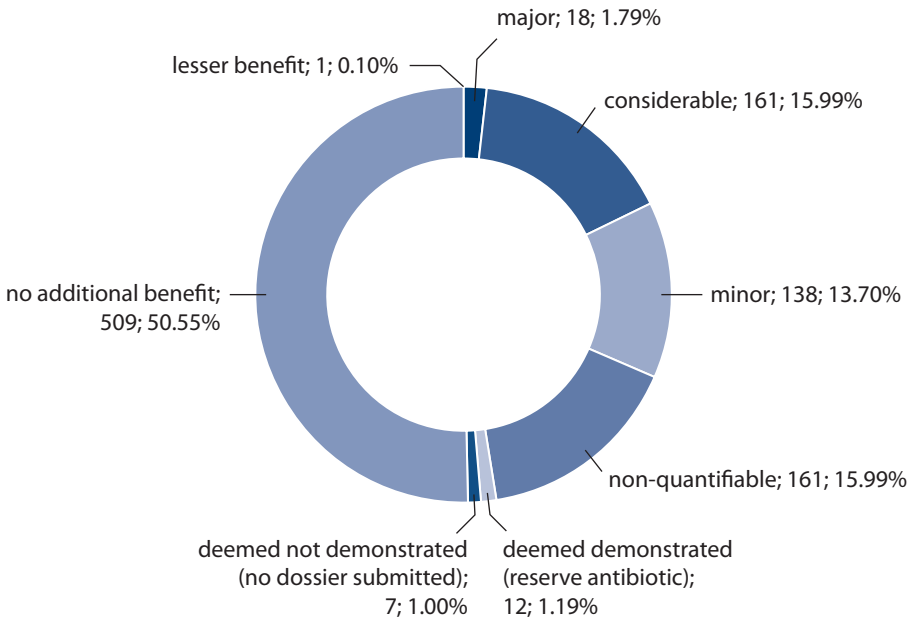
Prof. Josef Hecken *was Independent Chair of the Federal Joint Committee (G-BA) from July 2012 until 30 June 2026. Prior to 2012, he held several senior public sector positions, including State Secretary at the Federal Ministry for Family Affairs, Senior Citizens, Women and Youth; President of the Federal Insurance Office; Chair of the Bundesrat Health Committee and Deputy Chair of the Bundesrat Legal Affairs Committee; and Minister of Justice, Health, Social Affairs and Labour of the Saarland.*

Results of early benefit assessment: highest additional benefit category per procedure



Legend: n = 1,007, status as of 3 February 2026

Source: G-BA

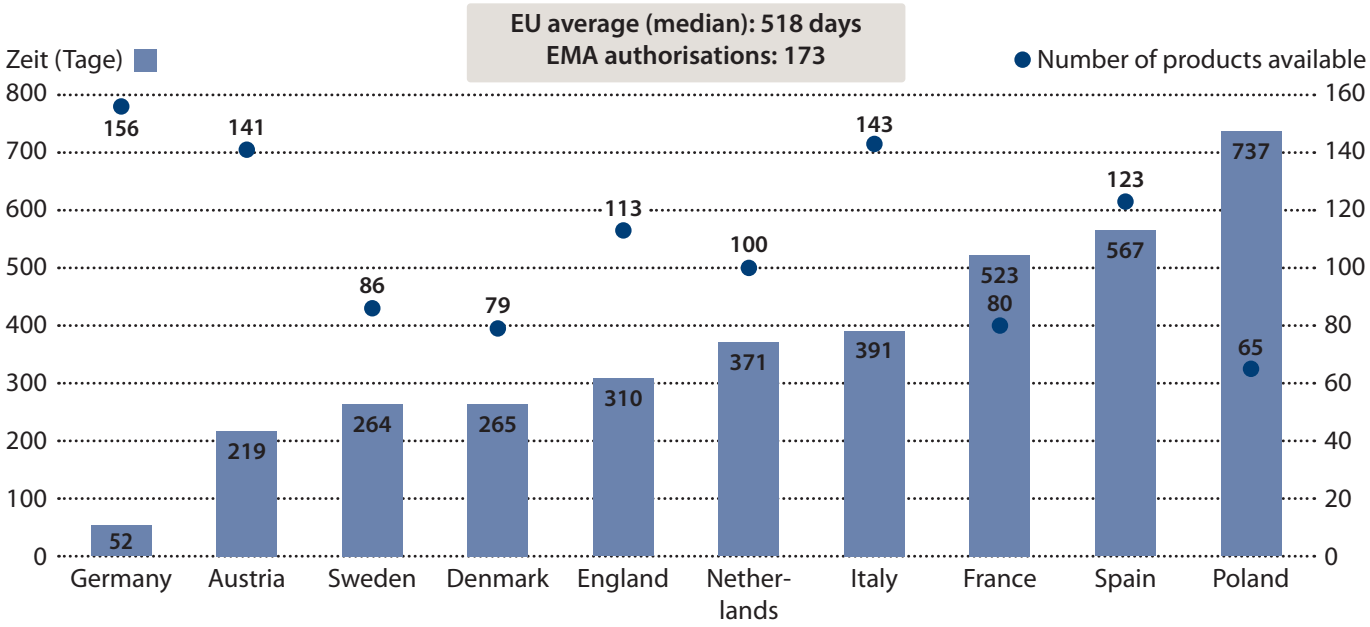
Figure 1: Procedures with a major additional benefit account for 1.79% of all assessments, while 15.99% fall into the considerable additional benefit category. A minor additional benefit was found in 13.7% of procedures, while in 15.99% the additional benefit could not be quantified.

quently, a systematic re evaluation based on real world data is required as the core element of a learning system. From a procedural perspective, the role of binding ACT determinations and their interaction with the European HTA framework also requires clarification. Together, these three elements form the basis for a pricing system that reflects evidence throughout the entire product lifecycle rather than relying solely on a snapshot at the time of market entry.

Further development of AMNOG

Several issues are at the forefront of current discussions on the further development of AMNOG. Particular attention should be paid to the freely determined manufacturer selling price at market entry, the insufficient price dynamics following the initial benefit assessment under the AMNOG process, and the limitations of establishing an appropriate comparator therapy (ACT) on a binding basis before the start of a procedure. In addition, the gradual implementation of the European HTA framework will influence national

Median time to availability of newly authorised products in Europe and number of products available



Legend: (Generation 2020–2023, status as of 5 January 2025). Temporary authorisations, early access programmes, and similar schemes not included.

Source: [1]

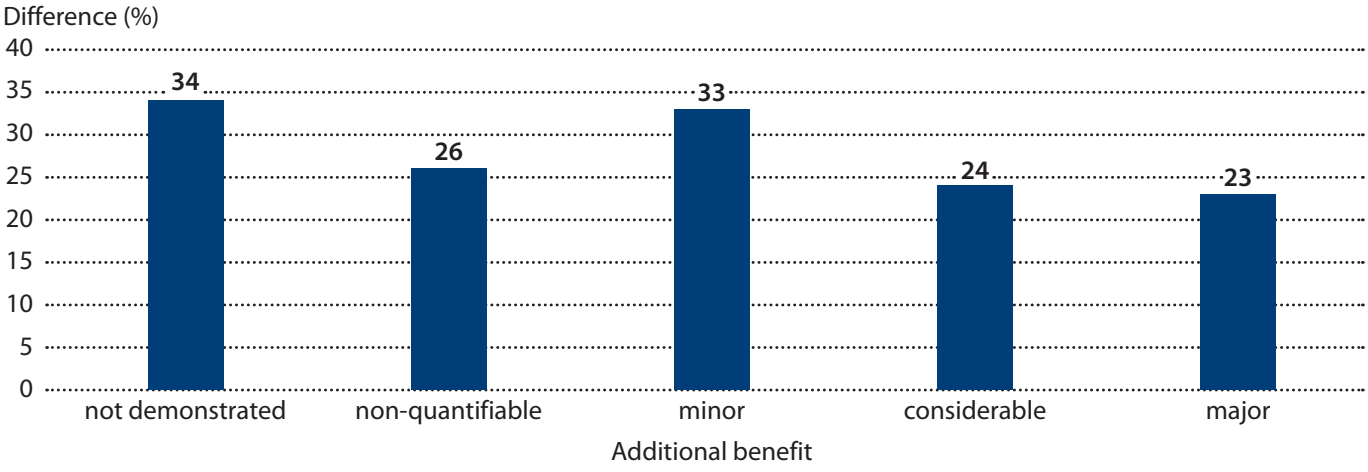
Figure 2: In Germany, the average time between marketing authorisation and market availability of a new pharmaceutical is only 52 days.

assessment processes. The first European assessments will be published this year.

1) Free determination of the manufacturer selling price at market entry (manufacturer launch price)

The Advisory Council on the Assessment of Developments in the Health Care System has examined the pricing of innovative pharmaceuticals in a „learning healthcare system" in detail in its 2025 report.[2] The Council notes that allowing manufacturers to determine the list price freely during the first six months after market entry creates both a psychological and an economic anchoring effect. The initial price reported in the Lauer-Taxe serves as a reference point for subsequent price negotiations, arbitration proceedings, and international price comparisons. At the same time, it regularly leads to excessive expenditure by the Statutory Health Insurance (SHI) system during the market entry

Average difference between manufacturer launch price and reimbursement amount



Source: [2]

Figure 3: The average difference between the manufacturer launch price and the negotiated reimbursement amount varies between 23% and 34%, depending on the level of additional benefit assigned.

phase, without any possibility of retrospectively correcting excessively high launch prices.

The Advisory Council therefore advocates the introduction of an externally determined interim price. On the one hand, this would be based on the cost of the most economical ACT alternative and, on the other, would be reconciled with the final reimbursement amount once price negotiations have been completed. Figure 3 illustrates the average difference between the manufacturer launch price and the negotiated reimbursement amount. Figure 4 additionally shows the declining number of prescriptions for patent protected pharmaceuticals over time alongside a marked increase in revenue per prescription.

From the perspective of the G-BA, the Advisory Council's proposal represents an economically sound approach to preventing undesirable incentives during the early phase following market entry. An interim price could neutralise the anchoring effect and provide short term financial relief for the SHI system. However, such a model would be viable only if different treatment settings were taken into account appropriately. For example, gene therapies and other novel therapeutic approaches often lack a comparable ACT in terms of either treatment modality or extent of use. In such cases, specific exemptions would be required. Similar considerations apply where ACT costs are exceptionally low. Here, a hardship mechanism would be necessary to prevent underfunding. In any event, both the framework itself and the underlying calculation and reimbursement methodology would need to be established in legislation.

2) Price dynamics following the initial assessment: the concept of „learning pricing"

An analysis of benefit assessment procedures conducted between 2011 and 2023 shows that 49% of all procedures

(n = 472) were initial assessments. A further 36% (n = 342) related to extensions of marketing authorisation, 7% (n = 71) were repeat benefit assessments following expiry of a time limit, 4% (n = 41) resulted from exceeding the revenue threshold or the loss of orphan drug status, 2% (n = 20) were initiated at the manufacturer's request, and 1% (n = 9) represented reassessments initiated by the G-BA on the basis of new scientific evidence. A further 1% (n = 8) were attributable to other reasons.

These figures demonstrate that re-evaluation of the initial benefit assessment occurs only to a very limited extent. There is currently no clear legal framework for such reassessments, and responsibilities and incentive structures remain poorly defined. As a consequence, reimbursement amounts often remain unchanged for years, even when new evidence becomes available. The Advisory Council therefore calls for:

- mandatory re-evaluation whenever new evidence emerges;
- a monitoring strategy for the systematic identification of new studies; and
- incentive mechanisms to encourage manufacturers to generate additional evidence.

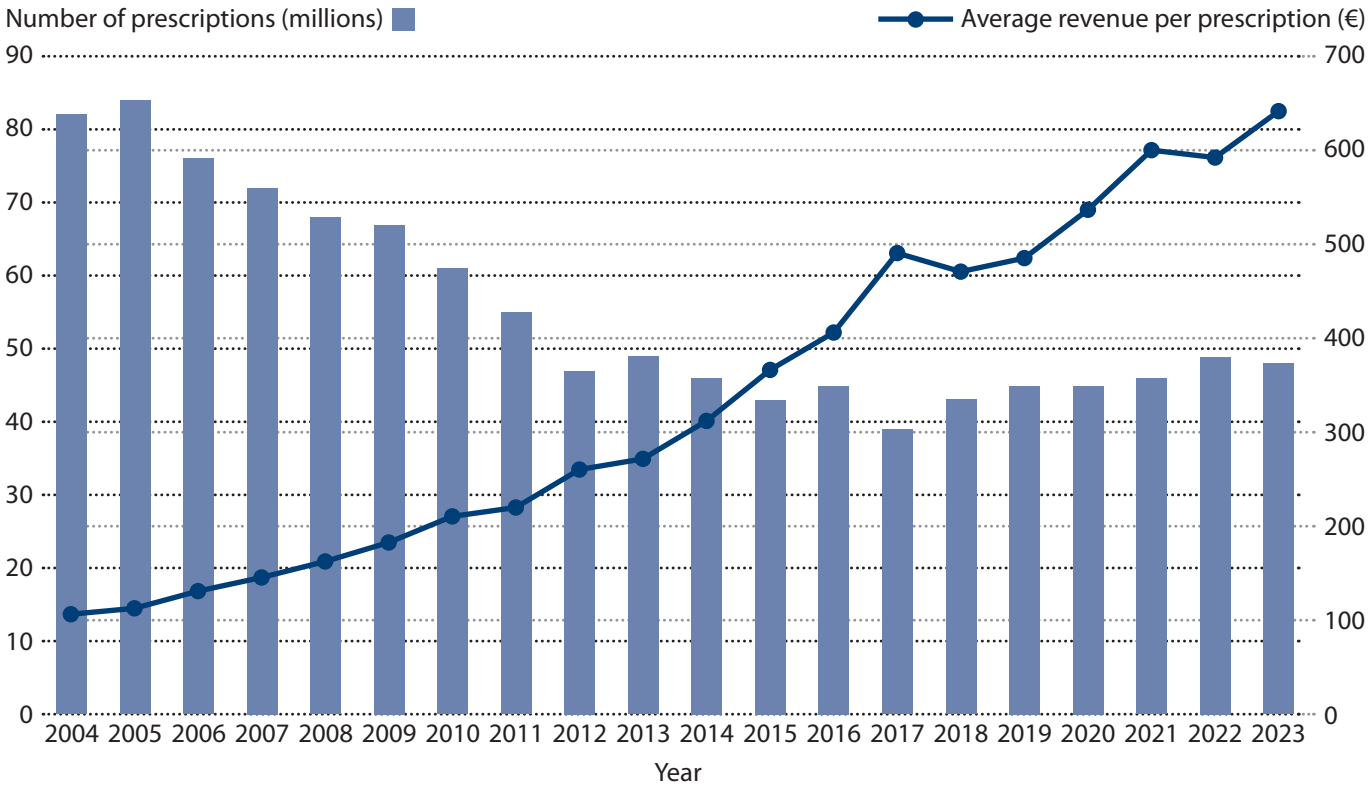
The aim is to establish a learning system in which both benefit assessment and pricing are continuously adapted in response to new evidence.[2]

The lack of price dynamics following the initial assessment should be regarded as a structural weakness. The legal framework remains unclear, including with regard to Section 3(1) No. 4 of the AM-NutzenV. These uncertainties make independent reassessment by the G-BA more difficult. One potential opportunity may arise from the draft Medical Registries Act adopted by the Federal Cabinet on 11 March 2026.[4] The intended improvement in the use of registry data should be pursued further, particularly within the AMNOG framework. To this end, the independent members of the G-BA submitted a specific legislative proposal on 20 November 2025.[5] Under this proposal, the G-BA would be empowered to establish disease specific and therapy specific registries by directive.

This would be accompanied by mandatory reporting obligations for healthcare providers, an opt out model for data collection and sustainable financing through a dedicated funding mechanism supported by federal funds and a manufacturer rebate pursuant to Section 130a of Book Five of the German Social Code (SGB V). Importantly, requests for additional registry based evidence within the benefit assessment process should no longer depend on regulatory status, such as orphan drug designation, conditional marketing authorisation, or authorisation under exceptional circumstances. Instead, they should be linked to the actual evidence deficit, namely situations in which no additional benefit has been demonstrated or in which an additional benefit exists but cannot be quantified.

As is well known, the current framework for post-authorisation evidence generation requires reform. The original purpose of this framework was to address evidence gaps after marketing authorisation. In practice, however, a number of shortcomings have become apparent, including structural challenges associated with the timely use of registry data, excessively long data collection periods and, in some cases, the complete failure to implement data collection, for example because of insufficient patient numbers or strategic considerations on the part of the pharmaceutical company. A further structural weakness is that the requirement for post-authorisation evidence generation is tied to regulatory status, such as orphan drug designation, conditional marketing authorisation, or authorisation under exceptional circumstances. This results in unequal treatment of comparable pharmaceuticals within the same

Prescriptions and revenue of patent protected pharmaceuticals in the SHI finished pharmaceutical market over time



Source: [3]

Figure 4: Over time, the number of prescriptions for patent protected pharmaceuticals has declined, while average revenue per prescription has increased markedly.

indication and creates undesirable secondary effects.

Among comparable available treatments, those associated with greater documentation requirements tend to be prescribed less frequently, thereby making it more difficult to recruit adequate patient numbers. A more appropriate approach would be to link evidence generation requirements directly to the actual evidence deficit. The forthcoming reform should therefore move towards a model of „learning pricing". In line with the Advisory Council's recommendations, standardised datasets should be developed, existing registries should be systematically improved and utilised, and benefit reassessment should be linked automatically to pricing decisions.

From the perspective of the G-BA, these recommendati-

Figure 5: In the collective cohort model developed by the National Association of Statutory Health Insurance Funds, data from the registration trial presented in the G-BA decision are additionally taken into account when determining the interim price.

ons are welcome. Practical experience with this framework has highlighted a number of structural limitations, including the lack of standardisation, substantial administrative burdens resulting from redundant documentation and duplicate data collection, and the isolated nature of individual projects. Future efforts should therefore focus on systematic registry based reassessment. Time limited benefit assessment decisions and registry based evidence obligations should be established in legislation. Disease specific registries should serve as the primary source of high quality, comparable and sustainably usable real world evidence. On the basis of this continuously evolving evidence base, the concept of learning pricing could then be implemented. In principle, this would involve:

- establishing an interim price for the pharmaceutical;
- measuring treatment outcomes, both success and failure, over several years in disease specific or indication specific cohorts; and
- dynamically adjusting the reimbursement amount on the basis of actual treatment outcomes.

A similar approach is reflected in the collective cohort model developed by the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband)[6] (figure 5). Under this model, data from the registration trial presented in the G-BA decision are also taken into account when determining the interim price. The model therefore addresses the same anchoring effect and could provide the structural basis for a learning pricing framework. Its advantages include legal certainty and transparency through predefined rules, cost efficiency through data driven ad-

justments and lower administrative complexity compared with selective pay for performance models. Challenges remain, however, particularly with regard to ensuring high quality data, linking outpatient and inpatient data sources, and establishing long term monitoring of treatment outcomes.

3) The limits of binding ACT determination before the start of a procedure

Changes to the appropriate comparator therapy (ACT) during an ongoing benefit assessment procedure are rare. Since 2024, the proportion of procedures in which ACT is amended in the final decision has been around 5 to 10%. There are many possible reasons for adjusting ACT during the course of a procedure, including:

- further development of the generally accepted state of medical knowledge;
- the introduction of newly authorised therapies or changes to clinical guidelines in the relevant indication; and
- clarifications based on statements by medical societies regarding the clinical care context.

Such changes to ACT during the procedure may have both positive and negative effects on how the evidence submitted by the manufacturer is taken into account. For example, studies conducted against a previous standard of care may subsequently be usable only to a limited extent. In principle, it is the manufacturer's responsibility to verify that the ACT is up to date, at the latest when preparing the dossier.

The G-BA has already increased transparency. Since 1 March 2026, ACT has been published on the website at the start of the benefit assessment procedure, whereas previously it became publicly available only together with publication of the dossier assessment. This change reflects the adaptation of G-BA processes to the requirements of the European HTA framework (EU HTA), with earlier transparency regarding the assessment basis used in procedures. The practical implications for manufacturers are positive. Where necessary, manufacturers now have until the end of the three month comment period to adapt their analyses to an updated ACT, covering the period of benefit assessment and the written commenting procedure. Before this change, manufacturers often had only the three week period for preparing the written comments to submit supplementary analyses against an updated ACT.

A specific challenge is that the final indication of an innovative pharmaceutical is usually defined only at the end of the marketing authorisation procedure. Binding determination of ACT several years before marketing authorisation, market entry and benefit assessment would conflict with the requirement that G-BA decisions reflect the current state of evidence.

Nor is it sufficient to rely exclusively on the comparator therapy defined in the EU HTA procedure, since more than one year often elapses between definition of the PICO framework and the start of the national assessment. Ultimately, ACT in the benefit assessment procedure must always reflect the current state of medical knowledge and routine care. Complete planning certainty for trial designs over many years is therefore structurally possible only to a limited extent.

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Benefit assessment in Alzheimer's disease

Professor Peter Berlit | Secretary General of the German Society of Neurology, Berlin

Monoclonal beta-amyloid (Aβ) antibodies represent the first causal treatment approach for Alzheimer's disease. However, they are effective only in the very early stages of the disease and only when Aβ pathology has been biologically confirmed. No approved therapy is currently available for the stage of mild cognitive impairment, making a meaningful benefit assessment against a comparator therapy virtually impossible.

Causal treatment in Alzheimer's disease

Extracellular beta-amyloid (Aβ) plaques and intracellular neurofibrillary tangles composed of tau protein play a central role in the pathogenesis of Alzheimer's dementia (AD). The accumulation of amyloid plaques results from an imbalance between the production, aggregation, and clearance of Aβ.

Passive immunotherapy with lecanemab and donanemab leads to amyloid clearance in the brain. These monoclonal antibodies target the N-terminal end of Aβ. Reduction of cerebral amyloid plaques following treatment can be demonstrated by positron emission tomography (PET) imaging.

Therapeutic effect can be demonstrated

A clinical treatment effect is primarily observed in patients with only low or moderate tau burden. In cases of high tau burden, the disease has presumably already progressed too far. Consequently, these agents are effective only in the very early stages of AD, particularly in so-called mild cognitive impairment (MCI). Clinically, a slowing of disease progression by approximately 30–35 per cent has been demonstrated.

Over a treatment period of 18 months, lecanemab reduced progression of cognitive impairment in early Alzheimer's disease by 27 per cent compared with placebo.1 Donanemab slowed disease progression in 35 per cent of patients compared with 22 per cent in the placebo group. In patients with low or intermediate tau burden on PET imaging, treatment with donanemab delayed disease progression by 7.5 months compared with placebo.2

Benefit-risk assessment

Despite the remarkable effect of immunotherapies on

amyloid deposition in the brain as visualised by PET imaging, monoclonal antibodies are not capable of curing the disease; they merely slow disease progression. This benefit must be weighed against the risk of treatment-related cerebral damage resulting from the mechanism of action. Treatment with monoclonal antibodies can lead to amyloid-related changes in the brain in the form of oedema or microhaemorrhages. These amyloid-related imaging abnormalities (ARIA) are detectable by magnetic resonance imaging (MRI).

In individuals with cerebral amyloid angiopathy and in carriers of the genetic trait ApoE-ε4 homozygosity, the risk of larger cerebral haemorrhages is significantly increased. In the registration trials, ARIA occurred in 12.6 per cent of patients receiving lecanemab and in 24 per cent of those receiving donanemab.1,2 In the registration trial for donanemab, three deaths occurred in the active treatment group and one in the placebo group.2 All deceased patients showed evidence of cerebral amyloid angiopathy on MRI.

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Early diagnosis of Alzheimer's dementia (AD)

In patients presenting with mild cognitive impairment or a diagnosis of early-stage dementia, it is essential to establish that the symptoms are in fact caused by underlying amyloid pathology. Vascular changes, other neurodegenerative disorders, and metabolic disturbances may also give rise to similar symptoms. However, causal treatment with specific antibodies can only be effective if the corresponding amyloid pathology is actually present.

Biomarkers measuring beta-amyloid (Aβ) and phosphorylated tau enable early diagnosis of AD. At present, biomarker detection is possible in cerebrospinal fluid and by means of positron emission tomography (PET) imaging. Detection of tau pathology already allows biomarker-based early diagnosis in serum within research settings. However, corresponding blood tests have not yet been approved.

Appropriate comparator therapy

No approved therapy is currently available for the stage of mild cognitive impairment (MCI). In patients with mild dementia symptoms, cholinesterase inhibitors are used for symptomatic treatment.

Problems with the IQWiG assessment

Three key issues led to the negative recommendation. These relate to the disease concept, the comparator therapy and the statistical methodology employed.

Disease concept: The assessment considered patients with MCI and early dementia separately. However, once Alzheimer's pathology has been biologically confirmed,

there is a continuum of disease with a gradual transition from MCI to dementia.

Comparator therapy: Additional benefit was assessed against acetylcholinesterase inhibitors (AChE), a purely symptomatic treatment that is not approved for MCI.

Statistics: The statistical analysis included patients with MCI without AChE treatment (27 per cent of the study population) and patients with mild dementia receiving AChE treatment (15 per cent of the study population). This reduction in sample size resulted in the loss of statistical significance.

Consequences of the negative G-BA assessment

The negative assessment issued by the Federal Joint Committee (G-BA) will result in these therapies being excluded from the catalogue of services covered by statutory health insurance, meaning that treatment costs will no longer be reimbursed (annual treatment costs for AChE comparator therapy approximately EUR 250 instead of EUR 25,000).

From the perspective of the German Society of Neurology, however, continued evaluation of indication-specific treatment pathways and long-term outcomes for the monoclonal antibodies lecanemab and donanemab is essential. From risk stratification and biomarker-supported diagnostics to monitoring of disease progression and adverse effects (including MRI monitoring for ARIA), and also with regard to potential combination therapy with AChE inhibitors, long-term real-world data must be collected systematically in order to enable an objective assessment of clinical benefit.

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Contribution rate stability and innovation – A contradiction?

Meike Helmold und Dr Felix Schönfeldt | DAK-Gesundheit

The financial stability of the Statutory Health Insurance (SHI) system is facing growing challenges. Despite political commitments to stable contribution rates, the financial situation continues to deteriorate. Owing to the unchecked growth in expenditure, particularly on patent protected pharmaceuticals, the current framework for benefit assessment and pricing is no longer sufficient. Structural reforms are urgently needed to reconcile the promotion of innovation with contribution rate stability. The objective is to align expenditure more closely with SHI revenues while preserving rapid access to medical innovation.

The Statutory Health Insurance (SHI) system has reached a turning point. Although policymakers emphasised contribution rate stability for 2026, the reality has once again been marked by contribution rate increases affecting more than half of all insured persons. This reflects the widening gap between the revenues and expenditure of the statutory health insurance funds. The market for patent protected pharmaceuticals in particular has developed a momentum that is pushing the current system of benefit assessment and pricing to its limits. Continuing along the current path would jeopardise the long-term financial sustainability of Germany's solidarity-based healthcare system.

The illusion of promised contribution rate stability

The financial position of the SHI system has deteriorated dramatically since the end of 2023. Despite historically high increases in supplementary contribution rates from an average of 1.36% in 2022 to around 2.94% at the beginning of 2025.[1] The system remains in a precarious financial position. The deficit of almost €10 billion recorded in 2024 could only be mitigated through short term measures and federal loans.

Projections by the IGES Institute on the future development of contribution rates across Germany's social security systems[2] paint a bleak picture for the SHI system. As early as 2027, a funding gap of around €12–15 billion is projected, rising to as much as €40 billion by 2030. This would correspond to a supplementary contribution rate of approximately 4.7% and an overall health insurance contribution rate exceeding 19%. Against this backdrop, the political promise of contribution rate stability increasingly appears to be an illusion.

Returning to a revenue-based expenditure policy

The persistent deficit, which has repeatedly had to be offset through increases in contribution rates, is primarily driven by the steadily widening gap between revenues and expenditure. Expenditure growth has become increasingly disconnected from revenue growth. While contribution-based revenues are expected to increase by only around 3% per year over the medium term, expenditure in many areas is rising at a significantly faster rate.

To address this imbalance and ensure the long-term financial sustainability of the SHI system, the Health and Long Term Care Financing Commission, chaired by Professor Greiner, clearly recommended a return to a revenue-based expenditure policy. This economically self-evident principle – that expenditure should not exceed available revenues – has also been adopted by Federal Minister of Health Nina Warken in her draft Statutory Health Insurance Contribution Rate Stabilisation Act (GKV-BStabG). In practical terms, this means that expenditure across all areas of healthcare should not increase more rapidly than SHI revenues.

Promoting innovation while maintaining financial sustainability

Since 2022, pharmaceutical expenditure has represented the second largest cost category within the SHI system and, owing to its unchecked growth, has become one of the principal drivers of expenditure.

Particular attention has focused on patent protected pharmaceuticals. Although these account for less than 10% of the prescribed volume (measured in defined daily doses, DDDs), they are responsible for more than half of total pharmaceutical expenditure. This demonstrates that, despite numerous regulatory provisions, Germany's framework for bringing new pharmaceuticals into routine clinical practice remains highly favourable to industry:

- No „fourth hurdle" for market access.
- Free pricing at market entry and during the first six months after launch.
- Immediate and full reimbursement by health insurers despite unrestricted manufacturer pricing.

As a result of these framework conditions, Germany ranks


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first in Europe both in terms of the availability of newly authorised pharmaceuticals and in terms of time to market, measured from EMA marketing authorisation to market launch.

Structural reforms to curb expenditure growth

Analyses presented in the AMNOG Report[3] show that innovative therapies often do not replace existing treatments but instead generate additional expenditure on top of current spending. This effect is particularly evident in oncology, where revenue growth has become almost entirely decoupled from prescribing volumes (DDDs). The increasing use of high cost therapies, often in combination, has created a cumulative expenditure burden that poses considerable challenges for the solidarity-based healthcare system. These developments underline the need for structural reforms capable of slowing expenditure growth while delivering meaningful financial relief. Possible measures include turnover based manufacturer rebates, systematic re-evaluation over the product lifecycle and the consistent implementation of price volume agreements.

Dynamic manufacturer rebates: For 2023, the manufacturer rebate for all patent protected pharmaceuticals was temporarily increased by a fixed amount. The pharmaceutical industry criticised this measure on the grounds that it was not sufficiently targeted. An approach discussed in the AMNOG Report, namely a turnover based manufacturer rebate, draws on a principle well established in German tax law whereby those with greater financial capacity should bear a greater share of the burden.

The AMNOG Report outlines a model in which the level of the manufacturer rebate is linked to the turnover generated by the active substance. The rationale is that products generating higher turnover place a greater financial burden on the SHI system, while a turnover based rebate would continue to provide manufacturers with sufficient scope for the reinvestment needed to support future innovation.

The report of the Health and Long Term Care Financing Commission (FKG), as well as the current drafts of the Contribution Rate Stabilisation Act,[5] also address this concept of a dynamic rebate. From 2027 onwards, a dynamic component is intended to complement the general manufacturer rebate by linking expenditure growth more closely to the revenue development of the SHI system.

Re-evaluation over the product lifecycle: The current pricing framework focuses primarily on two points in a product's lifecycle: market entry, through the benefit assessment, and patent expiry. The intervening period, during which both turnover and expenditure are at their highest, remains largely outside effective regulatory control. A future proof AMNOG framework must therefore address the entire product lifecycle.

The purpose of the AMNOG process is to establish an evidence-based price for newly introduced active substances. What remains unclear, however, is how long this „innovation price" should remain valid. Under the current framework, a demonstrated additional benefit results in a more costly therapy, while the price of the previous innovation remains unchanged. The resulting stepwise accumulation of higher prices is one of the factors driving the observed expenditure dynamics for patent protected pharmaceuticals. In competitive markets outside the pharmaceutical sector, competition between products generally leads to price reductions when improved innovations enter the market.

The AMNOG Report demonstrates that this mechanism does not operate in the pharmaceutical market. It therefore proposed, as early as its 2025 edition, extending the current framework by introducing the principle that the inno-

vation price should transfer to the new innovation, while the price of the previous innovation is reduced accordingly. Another possible approach would be the regular re-evaluation of benefit assessments in order to adapt prices to changing market conditions.

Strict implementation of price volume agreements: The legislator has already provided for financial relief through price volume agreements. These are intended to ensure that agreed price reductions take effect once specified turnover thresholds have been reached. Accordingly, volume related components are already mandatory elements of reimbursement agreements. In practice, however, these provisions have had very little effect. Price adjustments have generally been only marginal and the resulting savings correspondingly limited. Owing to the lack of clarity in the current legislation, arbitration board decisions relating to price volume agreements have been considerably weakened. The legislator should therefore revisit this area and provide a clearer legal basis to ensure that price volume agreements are implemented as originally intended.

Conclusion and outlook

Achieving a sustainable stabilisation of SHI finances requires a fair distribution of responsibility among healthcare providers, contributors and the state. The principle of a revenue-based expenditure policy, emphasised both by the Health and Long Term Care Financing Commission (FKG) and in the current drafts of the Contribution Rate Stabilisation Act (BStabG), provides the right way forward. The statutory objective of maintaining stable contribution rates must once again become a guiding principle of health policy, without compromising the quality of care.

The AMNOG framework has proved its value over many years, but it now requires evolutionary further development. A shift towards lifecycle based pricing and greater recognition of the realities of healthcare delivery is essential. Only in this way can the balance between rapid access to genuine innovation and the long-term financial integrity of the Statutory Health Insurance system be maintained.

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AMNOG & beyond: The perspective of the National Association of Statutory Health Insurance Funds on available methods and instruments

Dr Michael Ermisch, Matthias Müller, Marc Schmid, Dr Antje Haas | GKV-Spitzenverband

The early benefit assessment introduced under AMNOG, comparing new pharmaceuticals with the appropriate comparator therapy on the basis of patient relevant endpoints, has proved successful in its core principles. Nevertheless, it faces a number of challenges. This article outlines proposals to address two of them: the inherent tension between the requirements for consistency and currency in determining the appropriate comparator therapy, and the need for an appropriate approach to pharmaceuticals for rare diseases (orphan drugs).

Introduction

The early benefit assessment under Section 35a of the German Social Code Book V (SGB V) has proved successful. Conceived from the outset as a learning system,[1] it has been subject to numerous, in some cases far-reaching, legislative amendments to the AMNOG framework governing the assessment and pricing of pharmaceuticals containing new active substances.[2,3] The core principles of the benefit assessment itself, however, have remained largely unchanged. The benefit of pharmaceuticals containing new active substances is assessed against the standard of care designated as the appropriate comparator therapy and on the basis of patient relevant endpoints in the categories of mortality, morbidity, quality of life and adverse events. The objective is to provide transparency regarding the available evidence, thereby enabling evidence-based treatment decisions while also providing the basis for price negotiations founded on these findings.

However, the principle governing price negotiations, i.e. „no additional costs without additional benefit", has gradually been weakened through legislation and arbitration decisions and urgently requires correction through a return to this fundamental principle.[4] The proposals of the National Association of Statutory Health Insurance Funds in this regard are beyond the scope of this publication but are set out, for example, in its submission to the Health Finance Commission.[5]

This article focuses on two specific challenges within the early benefit assessment and outlines proposals for addressing them.

Challenge of currency

When determining the appropriate comparator therapy, the G-BA must strike a complex balance between the criteria set out in the Pharmaceutical Benefit Assessment Regu-

lation (AM-NutzenV). In addition to the evidence criterion under Section 6(2), the consistency criterion under Section 6(3) AM-NutzenV must also be taken into account. Not least in response to submissions from clinical stakeholders during the consultation procedure, the G-BA has in recent years given greater weight to the evidence criterion and sought to base the appropriate comparator therapy on the most up-to-date evidence-based treatment recommendations available at the time the decision is made.

This approach has consequences. Treatment recommendations may change after a pharmaceutical company has planned its study, with the result that the study comparator no longer corresponds to the appropriate comparator therapy, even if it was selected on the basis of earlier scientific advice. In other cases, however, such changes have made it possible for study comparators to be recognised as part of the standard therapies used in accordance with the current state of medical knowledge. Public debate often focuses in particular on the timing of changes to the appropriate comparator therapy.[6,7]

However, the dynamics and reasons underlying so-called changes to the appropriate comparator therapy must be taken into account. The G-BA makes determinations regarding the appropriate comparator therapy:

- when a pharmaceutical company requests scientific advice (a);


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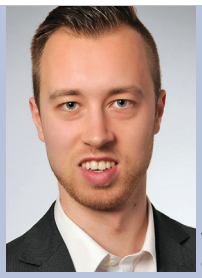
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- when a PICO is defined for EU HTA (b); and
- when the EMA has issued a positive opinion, enabling IQWiG to be commissioned appropriately at the start of the benefit assessment (c).

The impression that the decision is made at short notice therefore arises primarily from the procedure itself. Between scientific advice (a) and the CHMP recommendation for marketing authorisation (c), there is often no reason for the G-BA to review the appropriate comparator therapy and identify changes at an earlier stage. Moreover, Section 35a SGB V provides that the appropriate comparator therapy is not formally determined until the decision on the benefit assessment is adopted.

The G-BA bases its determination of the appropriate comparator therapy on the generally recognised state of medical knowledge at the time the scientific advice is provided, drawing on studies, systematic reviews and evidence-based guidelines. Where possible, the medical and scientific community is also consulted, although confidentiality requirements may mean that this is limited to medical societies and the Drug Commission of the German Medical Association. Such consultation is possible when a request for scientific advice has been submitted (a), when an EU HTA PICO is available (b) and, for the first time with the full involvement of the medical and scientific community, during the consultation procedure forming part of the benefit assessment decision-making process.

It would, however, be wrong to require studies to serve as the basis for a benefit assessment solely because their comparator could previously have been regarded as one of the appropriate therapies in the therapeutic area. This would clearly conflict with the requirement for decisions to be based on a comparison with the current standard of care. Comparisons with outdated therapies no longer allow a therapy's role in clinical practice to be determined and therefore fail to fulfil the purpose of a benefit assessment.

Nevertheless, the balancing of the criteria used to determine the appropriate comparator therapy should aim to ensure greater consistency in the designation of the appropriate comparator therapy without conflicting with the requirement for currency. In future, the introduction of a new treatment option should not automatically mean that therapies previously regarded as the standard of care are no longer considered appropriate. Clinical practice often moves away from established standards of care only gradually and over an extended period, depending on how new treatment options perform in practice. This is also a criterion under Section 6(2) AM-NutzenV. In addition, the G-BA should take fuller account of the consistency criterion under Section 6(3) AM-NutzenV and interpret it as also encompassing competing therapies developed in parallel and introduced within a similar timeframe, even where they do not belong to the same class of active substances, as is currently the case, for example, with bispecific antibodies and antibody-drug conjugates in haematological oncology.

This would allow previously undisputed standards of care to continue to serve as the appropriate comparator therapy even after new options have been introduced, provided that the clear majority of the medical community, as reflected in evidence-based guidelines, continues to regard the previous standard as adequate. Pharmaceuticals developed in parallel within innovation clusters and evaluated in clinical trials could then be assessed against the same comparator therapies for longer than at present.

As a result, the appropriate comparator therapy for such treatments could remain unchanged for longer while still satisfying the requirement for currency. The G-BA would consider newer therapies appropriate comparator thera-

pies only once they had become genuinely established in clinical practice and had largely replaced previous standards of care. This would not relieve pharmaceutical companies of their obligation to compare their products with current standards of care in clinical studies rather than continuing to use a comparator that merely meets the minimum ethical requirements. When planning studies, they should also pay greater attention to ensuring comparability with competitors' studies, for example to enable adjusted indirect comparisons.

Keeping the appropriate comparator therapy more consistent over time would also help to reduce the self-referencing of reimbursement amounts described above,[3] as it would at least partly prevent pharmaceuticals from achieving high reimbursement amounts solely because a new and usually expensive comparator therapy had been designated, without the company demonstrating that its pharmaceutical provided a comparable benefit.

The deemed additional benefit for orphan pharmaceuticals

When introducing the early benefit assessment, the legislature departed from AMNOG's evidence-based approach by deeming orphan pharmaceuticals to have an additional benefit.

By granting orphan designation, the European Commission confirms that the pharmaceutical concerned is intended to treat a rare disease. The statutory provisions establishing special authorisation conditions for these pharmaceuticals were based on the assumption that, without specific incentives, there would be insufficient economic incentives for the development and marketing of pharmaceuticals for rare diseases.[9] In view of the current prices and sales generated by this group of pharmaceuticals, as well as the general trend towards stratification and consequently smaller patient populations, both the continued validity and the scope of this assumption should be reviewed. Orphan designation is also associated with a finding that, at the relevant time, either no satisfactory method of treatment existed or the new therapy provided a significant benefit, as set out in Article 3(1)(b) of Regulation (EC) No 141/2000.

The rationale underlying AMNOG was that marketing authorisation had already established the additional benefit of all orphan pharmaceuticals. However, the criteria for marketing authorisation and the criteria for determining an additional benefit are not the same.

Finding that „no satisfactory method exists" does not mean that no therapies have previously been available, nor does it mean that the orphan pharmaceutical itself constitutes a satisfactory therapy. Such pharmaceuticals are therefore not necessarily stand-alone therapies for which a comparative assessment is impossible. Moreover, particularly where the previous standard of care must be regarded as unsatisfactory, it should also be possible to demonstrate an additional benefit in relatively small comparative studies. Such studies can also be conducted for orphan pharmaceuticals, which calls into question the need for a deemed additional benefit.

Likewise, the criteria used by the EMA's Committee for Orphan Medicinal Products (COMP) to determine a significant benefit, namely a clinically relevant advantage or a major contribution to patient care, do not correspond to the criteria for determining an additional benefit, either methodologically or in terms of the endpoints considered. Easier self-administration or improved adherence, for example as a result of a change in dosage form, may already be sufficient for this purpose.[11]

When the deemed additional benefit for orphan pharmaceuticals was first discussed during the 2010/2011 legis-

lative process, statements from the German Medical Association, the Drug Commission of the German Medical Association and IQWiG had already identified it as misguided and rejected it,[12] because it unnecessarily obscures the benefit of the therapies concerned and thereby makes evidence-based treatment decisions more difficult. In view of actual developments in the orphan pharmaceutical market, the time has now come to revise this provision. This is also consistent with the recommendations of the German Council of Health and Care Experts[13] and the Health Finance Commission.[14]

The fundamental problem is not that society cannot reach a consensus on providing particular support for therapies for rare diseases. Such support is already provided through special conditions governing marketing authorisation, and it is, of course, also necessary to consider when further support may be required. However, assessing orphan pharmaceuticals against an appropriate comparator therapy does not conflict with such support and, in the course of EU HTA, will gradually become standard alongside current assessment practice.

In future, orphan pharmaceuticals should therefore be subject exclusively to a full benefit assessment against an appropriate comparator therapy from the time they are placed on the market. At the same time, ultra-orphan pharmaceuticals, which are used only in very small patient populations and can therefore genuinely be expected to generate only low sales, should receive even greater preferential treatment than at present. According to the commonly used definition, ultra-rare diseases have a prevalence of fewer than two cases per 100,000 inhabitants.

To avoid disputes arising from uncertainty regarding the validity of prevalence calculations, this could be implemented simply and with minimal bureaucracy by using sales as the relevant criterion. Orphan pharmaceuticals generating sales up to a specified threshold, for example EUR 10 million per year, could be exempted from reimbursement amount negotiations under Section 130b SGB V. Up to this threshold, the pharmaceutical company would be free to set its selling price. This would safeguard access to the German market for new pharmaceuticals used to treat rare diseases.

Once sales exceeded the threshold, the company and the National Association of Statutory Health Insurance Funds would negotiate the reimbursement amount under the standard rules and on the basis of the benefit assessment results. Where no pharmaceutical therapy is available as an appropriate comparator for an orphan pharmaceutical, its price could be determined using either a reference model based on pharmaceuticals with comparable characteristics or a cost based approach.

A key element of such a model would be an appropriate provision preventing orphan pharmaceuticals exempted from reimbursement amount negotiations from driving up prices through internal reference pricing. Where a pharmaceutical benefiting from preferential pricing as a result of the exemption itself had to be taken into account as the appropriate comparator therapy or as a comparable pharmaceutical in reimbursement amount negotiations, this existing preferential treatment would need to be reflected appropriately through notional discounts.

Where a company had subsequently obtained new scientific evidence with the potential to change the results of the original benefit assessment, it could apply for a new benefit assessment, as is already possible under the current system. Experience from previous benefit assessments shows, however, that relevant new evidence for benefit assessments is generated after authorisation far less frequently than had been hoped.[10]

This proposal would strengthen evidence-based treat-

ment decisions for patients and physicians, create incentives for evidence generation, support the development of orphan pharmaceuticals in a more targeted manner and reduce bureaucracy compared with the existing system.

Conclusion

The early benefit assessment is a well established and widely accepted instrument for underpinning treatment decisions and pharmaceutical prices with evidence, and its core principles must be preserved. Individual shortcomings should be addressed, with any changes being made at the lowest possible level of implementation. Together with the necessary corrections to undesirable developments in pricing and other necessary reforms to the statutory health insurance system, the current legislative term provides the right opportunity to implement these changes.

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The industry perspective: Further developing AMNOG while safeguarding patient access

Leonie Ruhwinkel | Head of Market Access, MSD Sharp & Dohme GmbH

The AMNOG framework has established itself as a globally recognised learning system, combining rapid market access, clinically evidence-based benefit assessment and negotiated pricing. It has enabled patients in Germany to gain rapid access to the latest therapeutic innovations. At the same time, international spill-over effects, increasing regulatory complexity and methodological inconsistencies are becoming more pronounced, while medical innovation continues to accelerate, driven for example by advances in biotechnology and personalised medicine. From the industry's perspective, targeted reforms are needed to ensure that AMNOG continues to secure patient access to innovation. Three priorities are particularly important: (1) restoring a consistently benefit based approach to pricing without additional automatic mechanisms, (2) modernising procedures in step with new biotechnologies and European HTA, and (3) strengthening the negotiating autonomy of the contracting parties while maintaining a consistent focus on patient benefit and healthcare delivery.

Introduction

The current debate on benefit assessment and reimbursement prices is shaped by high expectations. Financial sustainability of the Statutory Health Insurance (SHI) system, rapid access to innovation and the strengthening of Germany as a centre for pharmaceutical research and manufacturing are all expected to be achieved simultaneously. Against this backdrop, it is essential to preserve the proven core principles of the AMNOG framework while making targeted improvements where practical experience has revealed shortcomings and a need for modernisation.

2. AMNOG: proven, yet increasingly in need of adaptation

The AMNOG framework has been a success story. Its core principles enable rapid access to innovation through a benefit assessment based on clinical evidence, followed by price negotiations between the contracting parties. This system is complemented by competitive effects throughout the product lifecycle, particularly after patent expiry. Together, these features have enabled Germany to maintain a leading position in providing early access to innovative pharmaceuticals while generating substantial savings for the healthcare system.

At the same time, there is growing evidence that maintaining the balance between patient access, evidence requirements and economic sustainability is becoming increasingly difficult. Germany and Europe risk losing their leading position in access to innovation. One third of all pharmaceuticals newly authorised in the United States between 2016 and 2025 are currently unavailable in Germany. The US driven Most Favoured Nation (MFN) debate and the increasing use of international reference pricing have placed greater attention on German prices. At the sa-

me time, repeated interventions in the AMNOG framework in recent years have weakened the negotiating logic through evidence detached automatic mechanisms, rigid constraints and short notice methodological changes.

There is an urgent need for action to avoid negative consequences for patient care in Germany (figure 1).

3. Three priorities from the industry perspective

1. Returning to consistently benefit based pricing – negotiation rather than automatic mechanisms

AMNOG was designed as an evidence-based system – a principle rightly emphasised by all stakeholders in the healthcare sector. Additional regulatory interventions that disregard clinical evidence, such as blanket price volume mechanisms or automatic rebates, undermine the system's central logic of benefit assessment followed by price negotiation. In doing so, they weaken precisely the planning certainty that is indispensable for comprehensive development programmes and long-term investment decisions.

This raises a fundamental question: what is the purpose of the considerable effort invested in benefit assessment – both by pharmaceutical companies and by the authorities – if the resulting evidence is ultimately undermined by interventions that fall outside the logic of the system? Thousands of pages of clinical data, lengthy scientific consultations and extensive methodological discussions risk losing much of their value if their findings are no longer adequately reflected in pricing decisions.

The consequences of this development are already becoming apparent. Each year, the number of pharmaceuticals withdrawn from the German market continues to increase. Companies increasingly cite challenging economic conditions and restrictive price regulation as the principal reasons why marketing products in Germany has become less attractive. As the vfa has pointed out, the number of authorised pharmaceuticals that are not marketed in Germany continues to rise.

The international dimension adds a further important consideration. Pricing decisions in Germany serve as reference points for many markets around the world. A negative pricing signal from Germany may therefore have a disproportionate impact on the global recoupment of pharmaceutical research and development investments and, ultimately, reduce companies' willingness to launch innovative therapies early on the German market. Germany therefore risks losing its position as Europe's preferred launch market for innovative pharmaceuticals (figure 2).

2. Modernising AMNOG and HTA: recognising evidence, providing procedural stability and aligning effectively with European HTA

AMNOG was conceived as an evidence-based system. In

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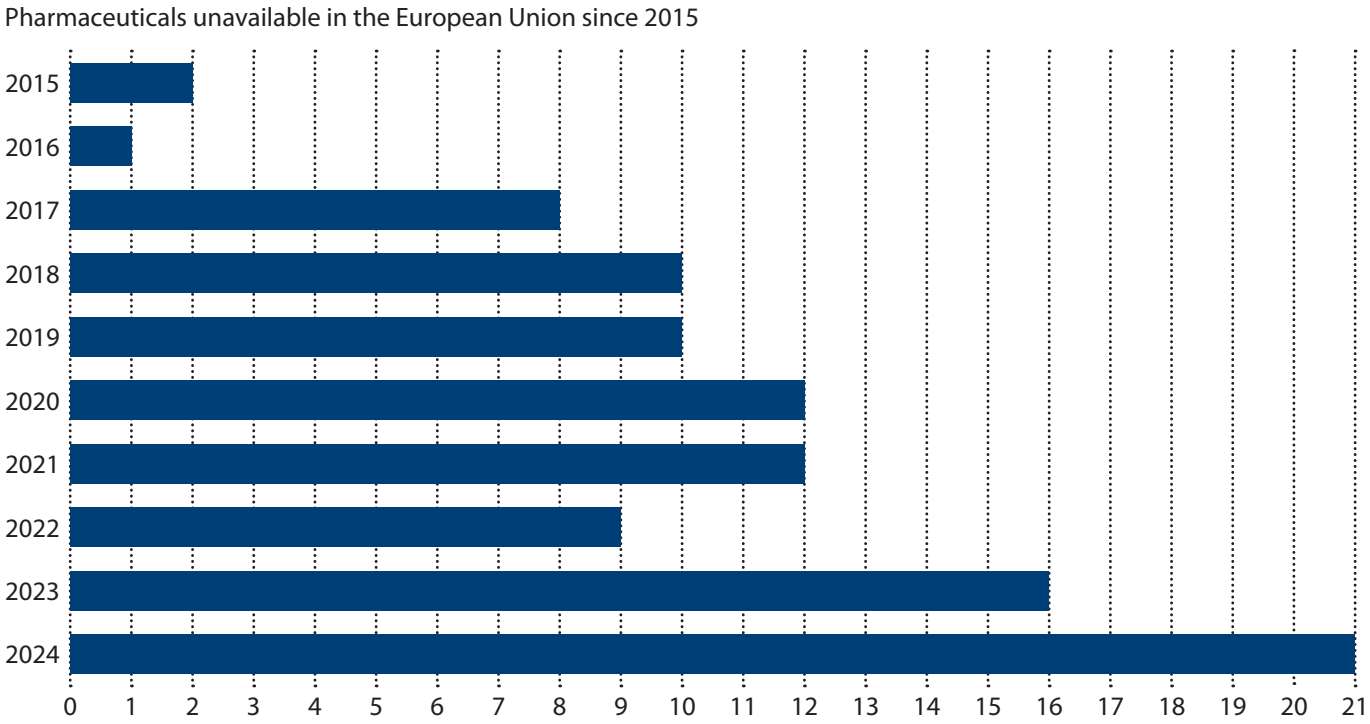
Number of pharmaceuticals authorised in the United States but not in the European Union, by year



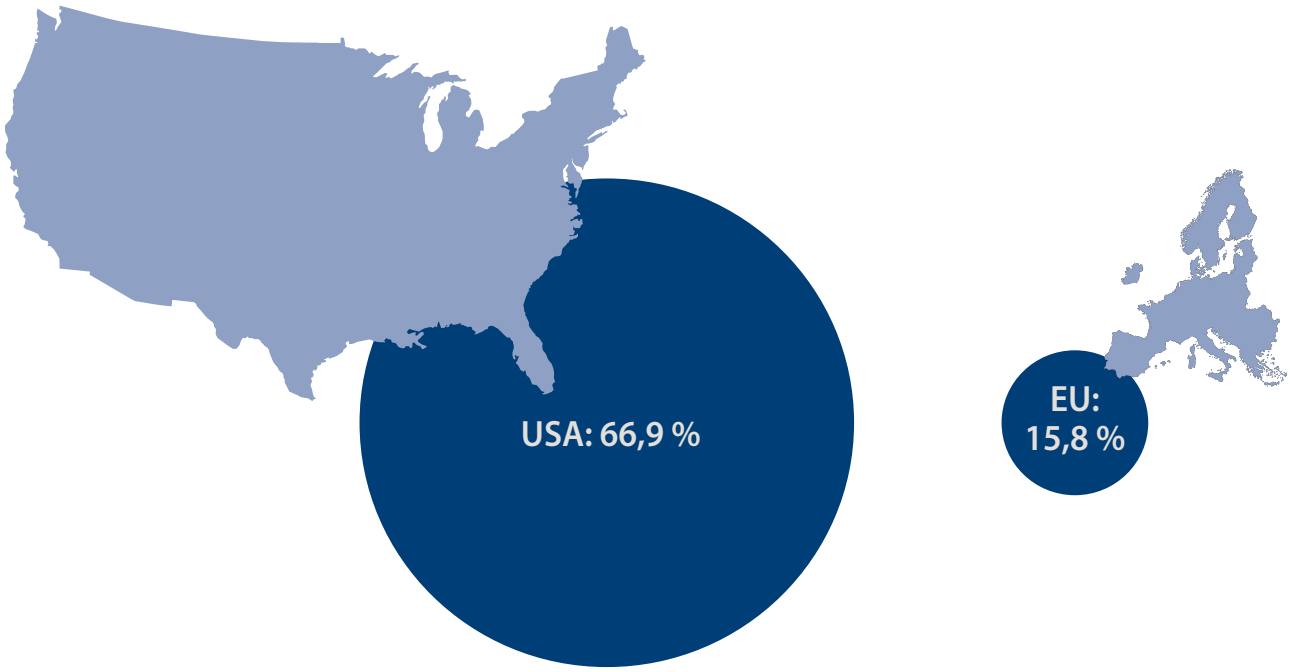
Source: vfa, based on EMA and FDA (as of January 2025)

Figure 1: One third of all pharmaceuticals newly authorised in the United States between 2016 and 2025 are currently unavailable in Germany.

practice, however, certain procedures repeatedly reveal tensions between methodological requirements and medical progress. Advances in biotechnology, personalised medicine and therapies for small patient populations increasingly give rise to evidence situations that cannot readily be accommodated within traditional head-to-head comparative study designs. Where high quality clinical evidence is not given appropriate consideration for purely formal reasons, the wrong signal is sent. Investments in demanding development programmes are devalued, even though they may make an important contribution to patient care. AMNOG therefore requires a clearly defined and objectively transparent framework for dealing with special therapeutic situations, ensuring that the best available evidence is consistently taken into account.

A further and increasingly important challenge concerns the predictability of the appropriate comparator therapy (ACT). If the ACT is changed at short notice after scientific

Global pharmaceutical market shares: United States compared with Europe



Source: EFPIA (2015) The Pharmaceutical Industry in Figures – Key Data 2025, p. 4 (accessed 10 June 2026).

Figure 2: Pricing decisions in Germany serve as reference points for many markets around the world. A negative pricing signal from Germany may therefore have a disproportionate impact on the global recoupment of pharmaceutical research and development investments.

advice has been completed and the study design has been finalised, evidence that has been generated systematically over many years may be rendered ineffective under an „all or nothing" approach, because no suitable evidence is available for the assessment of additional benefit and, for formal reasons, an additional benefit is therefore considered not to have been demonstrated. From the perspective of the research based pharmaceutical industry, evidence generated in accordance with the original scientific advice should continue to be given appropriate consideration, even where the appropriate comparator therapy is subsequently revised.

These issues become even more important in the context of European HTA. European PICO consolidation and the Joint Clinical Assessment (JCA) can only be integrated efficiently into national procedures if national deviations and short notice changes to assessment parameters are kept to a minimum. Germany therefore has a particular responsibility to ensure that its procedures are compatible with the new European framework (figure 3).

Examples of life saving therapies and vaccines, together with an overview of the additional benefit categories in AMNOG assessments

Around 40% of the increase in life expectancy can be attributed to the introduction of new pharmaceuticals.[3,4]

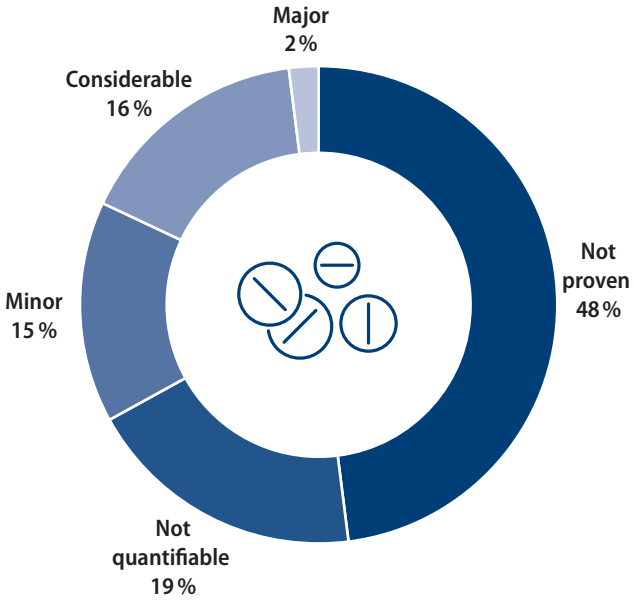
Antibiotics: In 2023, only 0.02% of deaths in Germany were attributable to infectious diseases. In 1950, the corresponding figure exceeded 7%.[5,6]

Cancer therapies: Today, more than 60% of patients with cancer survive for longer than ten years.[7]

Cardiovascular therapies: Far fewer people in Germany now die from cardiovascular disease than in 1950. At the same age, the risk of death has fallen by 75%.[8]

Vaccines: An estimated 1.4 million people in Europe did not die from COVID-19 because they were vaccinated.[9]

… and many more



Source: Vintura/LAWG e.V; 1. Federal Statistical Office, table Average life expectancy (accessed December 2024); 2. Statista (accessed December 2024); 3. Buxbaum et al, Health Affairs (2020); 4. Lichtenberg, NBER (2003); 5. Federal Statistical Office (accessed December 2024); 6. Statista (accessed December 2024); 7. NIH SEER (accessed December 2024); 8. Mensah et al Circulation Research (2017); 9. Mesléet al, Lancet Respiratory Medicine (2024)

Source: vfa, based on the AMNOG database maintained by Pharm Analytics GmbH; completed procedures from 2011 to 2025; highest category per procedure.

Figure 3: Where high quality clinical data are not adequately taken into account in special evidence situations for formal reasons, the wrong signal is sent for investment in demanding development programmes.

3. Strengthening the contracting parties and putting patient benefit at the centre: greater flexibility, less bureaucracy

A future proof benefit assessment requires clear responsibilities and a consistent separation of roles. Clinical assessment must remain methodologically robust and scientifically rigorous. Pricing, by contrast, should once again become primarily the responsibility of the contracting parties. In this context, reducing bureaucracy also means further developing the negotiation framework so that it can adequately reflect the realities of healthcare delivery, existing uncertainties in the evidence base and the tangible

benefit for patients.

This also requires giving greater consideration to the actual place of a therapy within clinical practice and to the underlying medical need. Where uncertainties in the evidence remain, for example regarding long term outcomes, outcome-based reimbursement models, such as risk sharing or pay for performance agreements, may represent valuable policy options, provided they are practical to implement and can be evaluated on the basis of robust data.

What matters is the overall approach. New instruments should not be designed as additional barriers to patient access, for example in the form of mandatory rebates, priority lists or an expansion of rigid price volume controls. Rather, they should be developed as constructive options for safeguarding patient access to innovative therapies.

4. Conclusion and outlook

The pharmaceutical industry stands ready to contribute to constructive reforms, but not to further interventions that fall outside the logic of the system and undermine the negotiation process, and with it rapid access to innovation. From the industry's perspective, making AMNOG fit for purpose means giving full effect to benefit-based assessment and negotiated pricing, modernising procedures and methodology in line with European HTA and emerging therapeutic approaches, and maintaining a consistent focus on patient benefit. If policymakers, the self-governing institutions, academia and industry can agree on a shared roadmap with clear milestones, Germany will be well placed to preserve its role as a reliable location for pharmaceutical innovation and high-quality patient care over the long term.

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Registry data as an evidence base for the appropriate comparator therapy in AMNOG and the JCA

Dr Sabine Busies, Dr Martina Jänicke, Michael Pröschel | iOMEDICO

The appropriate comparator therapy (ACT) is at the heart of the early benefit assessment under AMNOG. In real-world clinical practice, however, the ACT rarely remains static, particularly in oncology. Standards of care evolve and new active substances enter the market, meaning that the gold standard at the start of a pivotal study may already be outdated by the time the benefit assessment takes place. Valid comparator data may also be lacking where early marketing authorisation is based on a single-arm study. This article examines how clinical registries can address three key evidence gaps relating to the ACT and the quality and planning requirements that need to be considered.

Evidence gaps relating to the ACT – How can registry data help?

1.1 What is the actual standard of care?

When determining the ACT, the Federal Joint Committee (G-BA) must follow Section 35a of Book V of the German Social Code (SGB V), Section 6 of the Ordinance on the Benefit Assessment of Pharmaceuticals and the relevant provisions of the G-BA's Rules of Procedure. In doing so, the G-BA generally relies on clinical guidelines to establish the „recognised medical standard". However, guidelines do not always fully reflect real-world clinical practice. Patient-specific factors or delays in updating guidelines may mean that the standard of care actually used in clinical practice differs from the ACT recommended in the relevant guideline.

Registry data can provide representative evidence of the therapies actually used in routine clinical practice and the patient subgroups in which they are used. This can provide an evidence base for discussions between the relevant stakeholders – pharmaceutical companies, the G-BA and IQWiG – about what constitutes a clinically relevant comparator.

1.2 The evolving ACT: When the control arm no longer reflects real-world clinical practice

Standards of care can change rapidly, particularly in oncology. As a result, the comparator selected at the start of a pivotal study may no longer represent the standard of care by the time the benefit assessment takes place. The comparison presented in the AMNOG dossier may therefore no longer reflect current clinical practice.

The prospective, longitudinal CARAT registry maintained by iOMEDICO provides a striking example. Between 2018 and 2024, second-line treatment of metastatic renal cell

carcinoma in Germany changed fundamentally, moving from mTOR inhibitors and tyrosine kinase inhibitors towards combinations based on immune checkpoint inhibitors (figure 1). If a pivotal study for marketing authorisation began before immune checkpoint inhibitors were approved, the standard of care reflected in that study may therefore already be outdated by the time of the benefit assessment.

Registry data can help in two ways. First, they provide real-time evidence of the treatments actually being used in clinical practice, thereby informing discussions about the relevant ACT. Second, they can provide comparative evidence that would otherwise be lacking by serving as an external control arm, with comparisons adjusted using methodologically robust approaches such as propensity score matching. Well-conducted confounder-adjusted comparisons that account for all relevant confounding factors, such as ECOG performance status, biomarkers, previous treatments and comorbidities, can provide robust evidence on additional benefit even in the absence of an RCT design (figures 2a and 2b).

The same issue arises in the international context of the JCA. Standards of care may differ between Member States depending on the availability of pharmaceuticals. Germany ranks among the leading European countries in terms of access to pharmaceuticals.[1] A new pharmaceutical may therefore have already established a different standard of care in Germany before it is authorised in other EU countries. Prospective, multicentre, longitudinal and quality-controlled registries can help capture PICO elements that


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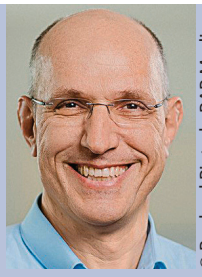
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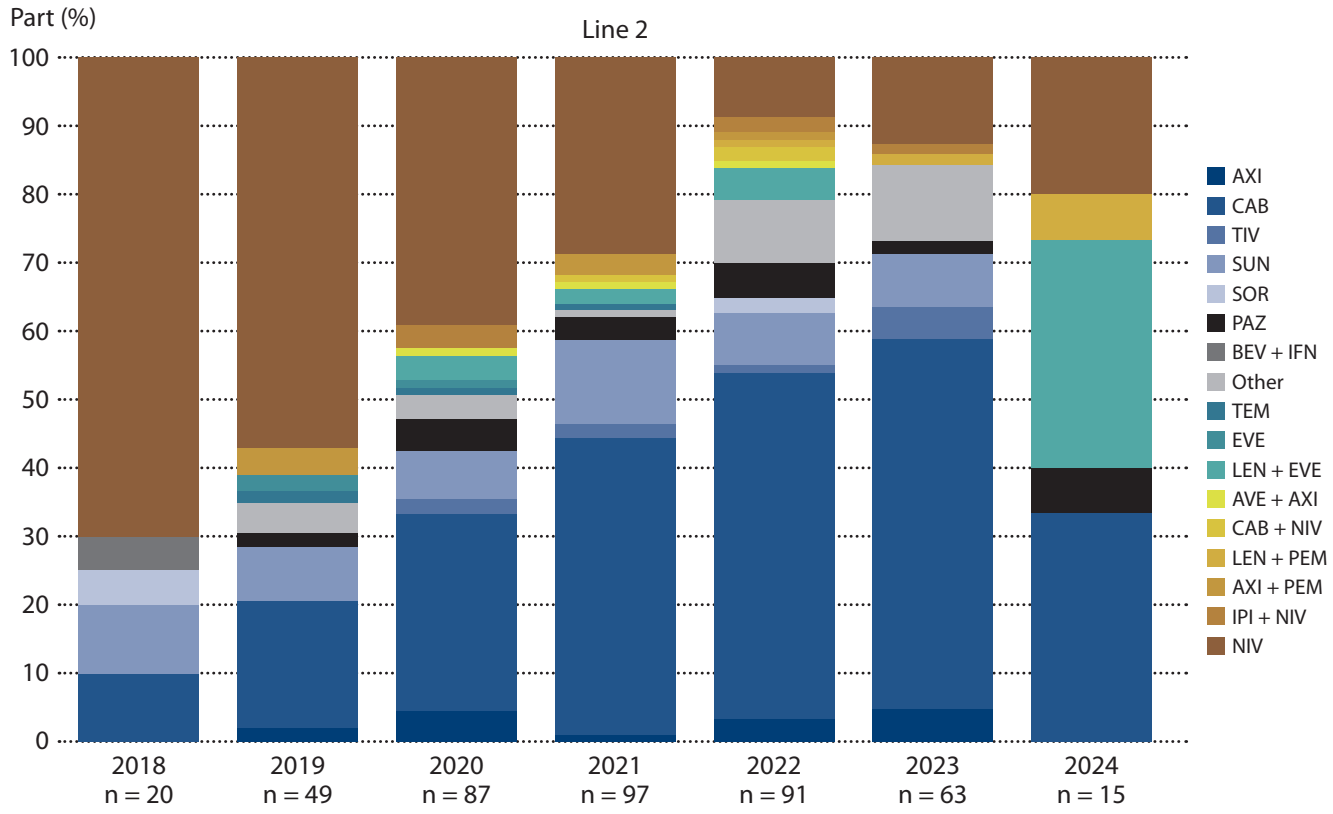
Dr Martina Jänicke *has been addressing evidence gaps using real-world data across the pharmaceutical product lifecycle for more than 15 years. She heads the Clinical Epidemiology and Health Economics department at iOMEDICO and specialises in the design, conduct and analysis of oncology registries and registry studies tailored to specific evidence needs and subject to appropriate quality assurance.*

The evolving ACT: Second-line treatment of renal cell carcinoma as an example



Source: CARAT-Registry, data as 31 December 2024

Figure 1: Between 2018 and 2024, the standard of care for second-line treatment of metastatic renal cell carcinoma in Germany changed fundamentally.

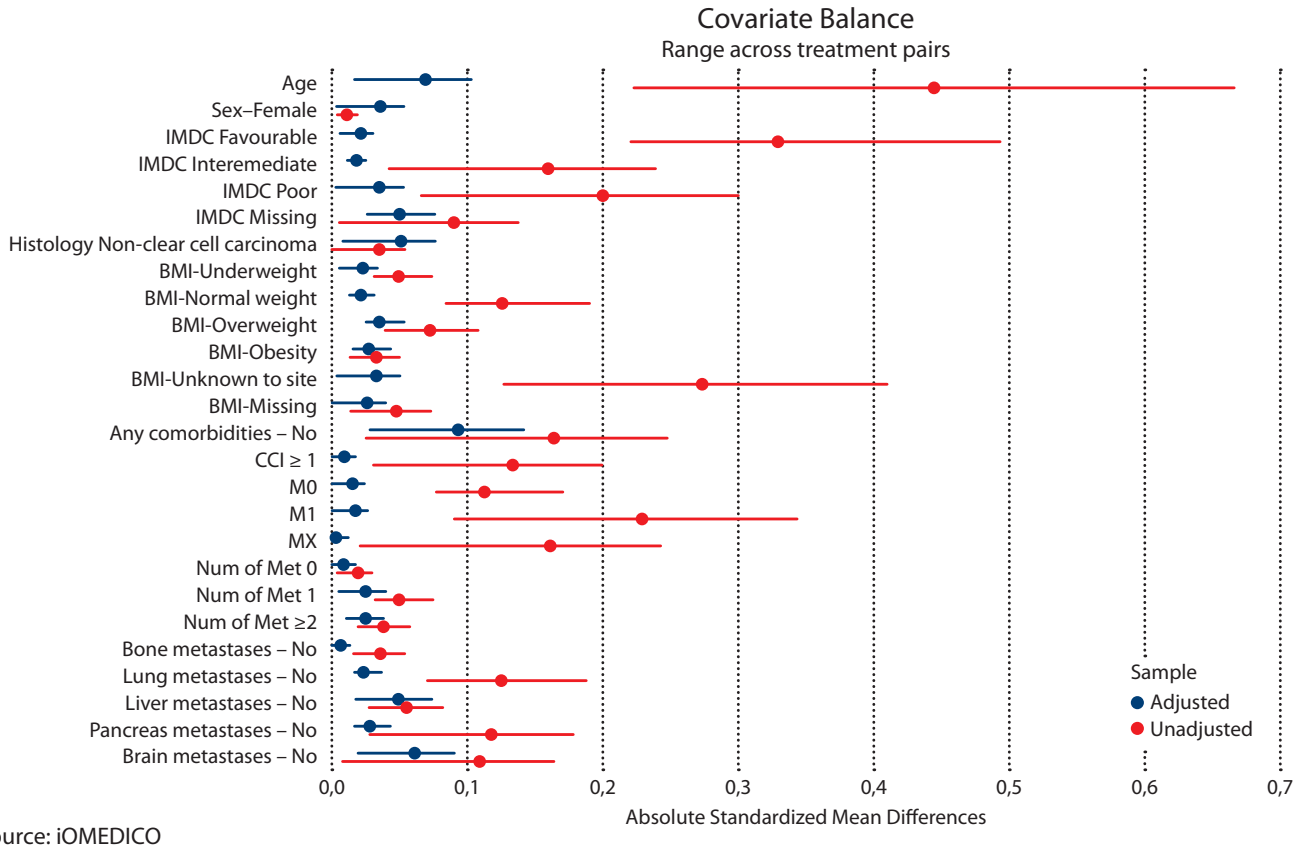
would otherwise be missing by providing evidence from current real-world clinical practice, thereby bridging the gap between the clinical study setting and HTA assessment.

1.3 Early marketing authorisation without a control arm: Single-arm studies and external comparisons

In oncology, particularly for rare diseases with a high unmet need or where accelerated authorisation pathways are used, a randomised controlled study is often not yet available at the time of the early benefit assessment. In such cases, there is no control arm and therefore no basis for a direct comparison with the ACT.

Registry data can fill this evidence gap by providing the missing control arm as an „external control arm", as described above, while accounting for potential confounders. IQ-

Effects of statistical adjustment



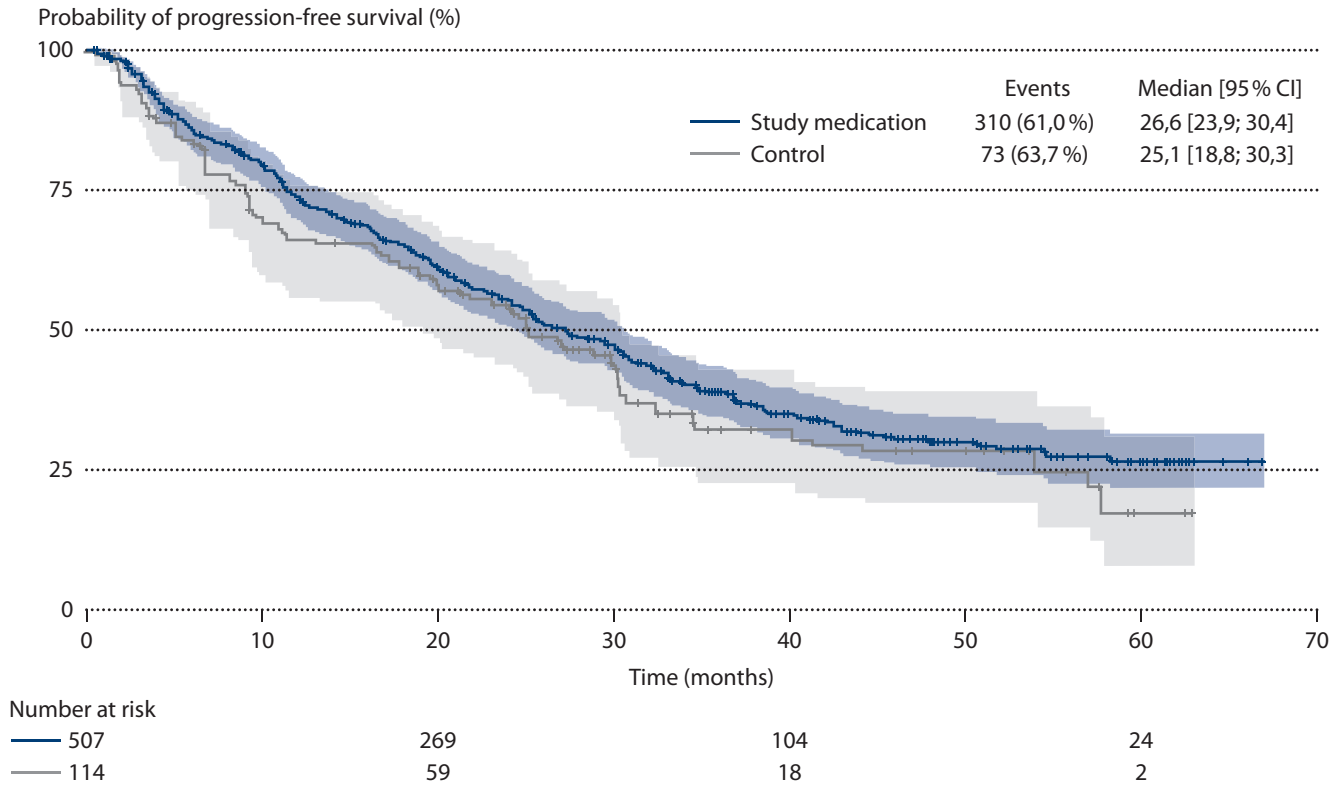
Source: iOMEDICO

Figure 2a: This example shows differences in the distribution of confounders before (red) and after (blue) statistical adjustment.

WiG recognises in principle that well-designed registries of sufficient quality can be used as evidence in extended benefit assessments.[2] In practice, however, analyses of HTA procedures to date present a different picture. One study covering the entire AMNOG period up to December 2024 found that pharmaceutical companies submitted data from single-arm studies (SATs)/external control arm studies (ECTs) for 202 of 1,491 (sub)populations. These data resulted in an additional benefit in 23 cases (11.4%) involving hepatitis C populations, compared with only four cases (2%) in indications other than hepatitis C.[3]

Another recent study examined 175 external control arms (ECAs) from 123 oncology assessments conducted between 2021 and 2023. Acceptance varied considerably between countries. England had the highest rate of ECAs that were not rejected, with 41% accepted with limitations,

Comparison of the study arm and external control arm



Source: iOMEDICO

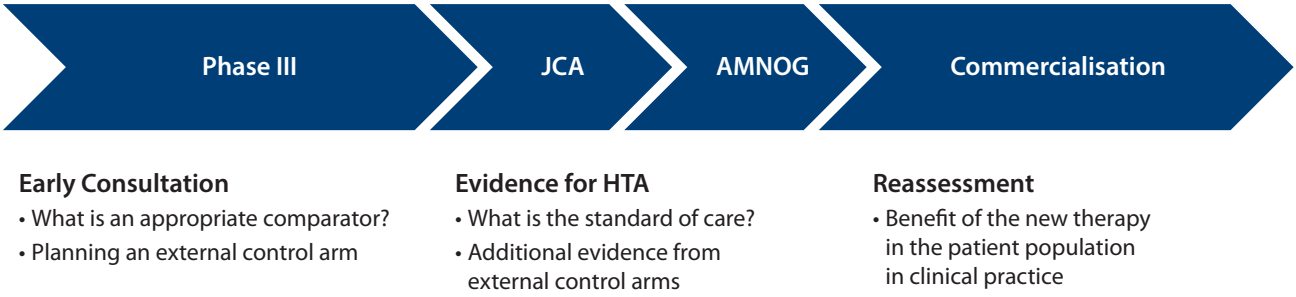
Figure 2b: This example shows the outcome of the comparison between the study arm (study medication) and the external control arm (control).

followed by France at 14%, whereas Germany and Norway rejected all ECAs. The main methodological issues identified were missing or unclear data (54%), heterogeneity between studies or risk of bias (51%), concerns about study design (29%) and limitations in statistical methodology (26%).[4]

2. Quality requirements for registries as a source of evidence

A number of quality criteria have been defined to ensure that registry data can provide valid evidence for determining the ACT, including in the IQWiG Rapid Report,[2] the registry report commissioned by the Federal Ministry of Health (BMG),[5] and the EMA Data Quality Framework for Real-World Data.[6]

Uses of registry data relating to the ACT in HTA processes



Source: iOMEDICO

Figure 3: Clinical registries can address key evidence gaps relating to the ACT by establishing the actual standard of care in real-world clinical practice or identifying when that comparator has changed since the start of a study.

- Prospective planning and data collection: Information relevant to future research questions should be collected systematically in the registry from the time of diagnosis, before treatment decisions can introduce bias into the data. Registry studies based on these data should be planned prospectively in advance.
- Systematic capture of confounders: Prognostically relevant factors such as ECOG performance status, biomarkers, previous treatments and comorbidities must be documented in a structured manner from the outset.
- Patient Reported Outcomes (PRO): The patient perspective, including quality of life, symptom burden and functional status, should form an integral part of any high quality registry.
- Representativeness: Complete coverage of the target population is not essential, but the relevant patient group must be represented in a transparent and robust manner.
- Established quality processes: Standardised data collection instruments, plausibility checks, data validation and consistent documentation of deviations are essential.
- Independence: Registries should have governance structures in place to ensure that they operate free from commercial conflicts of interest.
- Fitness for use: The EMA assesses data quality across five dimensions – reliability, extensiveness, coherence, timeliness and relevance – in relation to the specific research question. These dimensions should be evaluated for the relevant question before a registry study begins.
- Controlling data drift: Data distributions and the clinical significance of variables may change over time. Prospective registries have an advantage over routinely collected data used retrospectively because they can systematically capture and control for data drift.[6]

3. Early planning of registries and registry studies

Identifying suitable registries at an early stage is essential to address anticipated evidence gaps in the marketing authorisation and HTA processes. Equally important is the ear-

ly planning of the corresponding registry studies, including the analysis plan. Suitable registries can be identified, for example, through the EMA Catalogue of Real-World Data Sources,[7] the registry search category of the US National Institutes of Health's global clinical study database,[8] or the database of medical registries in Germany.[9]

The EMA recommends that registries and registry studies should be initiated prospectively, for a defined purpose and ideally alongside the marketing authorisation of a pharmaceutical, rather than only after years of use in clinical practice. A statistical analysis plan (SAP) defined before the registry data are examined is a fundamental methodological requirement. The EMA guidelines also provide recommendations on what the SAP should include.

As Volker Vervölgyi (IQWiG) put it succinctly: „Investing substantial effort in planning a non-randomised study from the outset not only reduces the effort required to conduct the study, but also produces more meaningful data."[10]

Careful planning at an early stage can generate high quality evidence based on registry data to support the marketing authorisation and HTA processes and facilitate timely patient access to innovative therapies within European healthcare systems. At the same time, it lays the foundation for generating further evidence following successful marketing authorisation.

4. Real-world data in Reassessment

Reassessments based on real-world data are already established practice under AMNOG, particularly for early marketing authorisations based on single-arm studies. The G-BA may require routine practice data collection (anwendungsbegleitende Datenerhebung, AbD) in order to systematically generate evidence from clinical practice following market launch and reassess the additional benefit.

There is also ongoing discussion about developing this approach further by introducing a structured cohort model in which the reimbursement amount for a pharmaceutical would be adjusted at regular intervals based on outcomes observed in routine clinical practice.[11] Such an iterative approach to benefit assessment requires registry data to be collected prospectively and for a defined purpose. These data can capture clinical practice over time and allow study results to be validated in the broader patient population. They can therefore provide robust evidence for reassessments and show whether the benefit observed in the pivotal study also applies to the population actually treated in clinical practice. To date, registry data in the AMNOG process have mainly been used to address epidemiological questions, leaving their potential as an evidence base for iterative benefit assessments largely untapped.

5. Conclusions

Clinical registries can address key evidence gaps relating to the ACT. They can establish the actual standard of care in real-world clinical practice, identify when that comparator has changed since the start of a study, and provide comparative evidence that would otherwise be lacking through external control arm analyses (figure 3). In this way, they can close evidence gaps and improve the quality of the HTA process.

This requires high quality registries and early planning. The IQWiG Rapid Report on routine practice data collection (2025), the EMA Data Quality Framework (2026) and the German Registry Act planned for 2026 indicate a shift towards viewing clinical registries not merely as tools for documentation, but as key research platforms for generating evidence from real-world clinical practice. This could enable HTA processes such as AMNOG and the JCA to provide even higher quality evidence to support the introduction of new therapies.

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Appropriate comparator therapy: Trends from the industry perspective

Dr Andrej Rasch | Verband forschender Arzneimittelhersteller e.V. (vfa)

Appropriate comparator therapy (ACT) provides the central reference framework for benefit assessment under the AMNOG process and is therefore critical to the evaluation of the additional benefit of new pharmaceuticals. From the perspective of the pharmaceutical industry, however, increasing challenges are emerging with regard to both its definition and application. Using selected examples, this article analyses current developments and identifies three key areas of concern: the interpretation of the standard of care, the increasing dynamism resulting from short notice changes to ACT, and the segmentation of patient populations. In addition, shortcomings in communication between the Federal Joint Committee (G-BA) and pharmaceutical companies are highlighted, particularly the lack of proactive notification regarding changes to comparator therapy. These factors create substantial uncertainty in clinical trial planning and may limit the usability of clinical evidence within the benefit assessment process. Against this backdrop, the article proposes measures aimed at improving planning certainty, strengthening communication, and making better use of available evidence.

Introduction

Appropriate comparator therapy (ACT) lies at the heart of the AMNOG process. It is a key determinant in the assessment of the additional benefit of a new pharmaceutical. The issue extends beyond the results of the pivotal trial itself and encompasses the suitability of that trial in light of how the current standard of care is interpreted and applied by the G-BA. Among the many challenges currently facing the AMNOG process, the increasing dynamism and segmentation of ACT have become particularly important.

Interpreting the standard of care

When determining an appropriate comparator therapy (ACT), the G-BA generally places considerable weight on clinical guidelines. This is understandable, as up-to-date evidence-based guidelines are intended to reflect the current state of medical knowledge. However, examples from dermatology illustrate that translating guideline recommendations into ACT decisions is not always straightforward. In some assessments, such as hidradenitis suppurativa, formal recognition of an additional benefit under AMNOG has not been a prerequisite for designation as ACT. Instead, greater emphasis has been placed on the treatment's position within clinical guidelines. As the G-BA has argued, a therapy may qualify because it has already been incorporated into relevant guideline recommendations and because its role in routine care has been reaffirmed by scientific and medical societies during the consultation process.[2]

Guideline recommendations, however, are not always the decisive factor. In plaque psoriasis, for example, the G-BA refers to the relevant guideline but includes only those pharmaceuticals in its ACT basket that have previously demonstrated an additional benefit under AMNOG. Accor-

ding to the G-BA, treatments that failed to show additional benefit over the designated comparator therapies cannot be regarded as equally appropriate therapeutic alternatives.[1]

At the same time, even where pharmaceuticals have the same level of recommendation in clinical guidelines, a recognised additional benefit under AMNOG does not appear to be sufficient to guarantee their subsequent acceptance as ACT. In atopic dermatitis, for example, the G-BA decided not to designate JAK inhibitors as ACT despite favourable guideline recommendations and recognised additional benefit. The decision was justified by factors such as the relatively short period of market availability and limitations in the safety profile.[3] Taken together, these examples suggest that ACT determination does not follow a consistent algorithm based solely on either guideline recommendations or recognised additional benefit. While guidelines undoubtedly play a central role in the AMNOG process, the examples also point to a decision-making framework that is heterogeneous and not always fully transparent.

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Interpreting implementation

How ACT is implemented depends just as much on the G-BA's interpretation as on its formal wording. Where only a single comparator is specified, or where several alternatives are linked by an „or" relationship, implementation requirements are generally relatively easy to anticipate. Greater uncertainty arises with ACT concepts such as „optimised standard therapy" or „individualised therapy", both of which leave substantial room for interpretation. An optimised standard therapy is inherently dynamic, as its assessment depends on the G-BA's view of whether the therapies offered in the comparator arm of a completed or ongoing study adequately reflect the contemporary standard of care at the time of benefit assessment.

By contrast, an individualised therapy typically consists of a predefined and often extensive range of treatment options that usually need to be offered within the framework of a multiple-comparator study. This raises a number of practical questions. How many of the specified alternatives must actually be available to satisfy the ACT requirement, every option or only a selection of them? And will implementation ultimately be considered adequate for the overall research question, or will the final decision divide the population into multiple subgroups, some judged to have implemented ACT appropriately and others not?

Dynamics of appropriate comparator therapy

The growing dynamism of ACT determination has a direct impact on both the interpretation of the standard of care

and its implementation. Because comparator therapy must reflect the current state of medical knowledge, the required comparator may be revised at any point during the product lifecycle. The rationale for such changes does not follow a predefined methodology or formal algorithm. Rather, the G-BA decides on a case-by-case basis whether a revision is warranted and, if so, on what grounds.[6]

An ACT may therefore change only a few months after scientific advice has been provided, while a study using the previously advised comparator is already under way, immediately before dossier submission, or even after the dossier has been submitted. In some cases, several revisions may be made by the G-BA during this period. A change may also occur immediately before or after dossier submission. Similarly, the G-BA may decide to amend the ACT during an ongoing procedure only at the point of its final decision. In addition, changes to the ACT for a given therapeutic indication may also result from a decision and subsequently become relevant for later procedures.

Changes to appropriate comparator therapy

When and how often do such changes occur? Until now, transparency after the event has existed only where changes were made during an ongoing procedure, usually after the consultation process. In recent years, this has been the case in one in five assessments. However, this is likely to represent only the visible tip of the iceberg. Changes made before the start of a procedure have not been reported by the G-BA in the reasons supporting its decisions and therefore cannot be quantified.

Some of these adjustments may lead to the recognition of clinical studies. Particularly problematic, however, are changes that devalue completed studies, making it impossible to demonstrate additional benefit.7 In recent months, there has been an increasing number of cases in which changes to ACT were communicated to IQWiG „shortly before dossier submission", „shortly after dossier submission" or „on the day of submission", as could be seen from the IQWiG reports. A routine review by the G-BA of whether ACT is up to date immediately before the start of a procedure therefore appears to have become the new practice.7

It must be acknowledged that ACT should reflect the generally accepted state of medical knowledge and routine care. It is equally understandable that these conditions may change over time. In some therapeutic areas, such as oncology, this shift can occur very rapidly as a result of innovative treatment options.

Such changes must also be reflected in the ACT specified in a G-BA decision. At the same time, other factors need to be taken into account if the overall framework of pharmaceutical research followed by HTA regulation is to function effectively. Planning certainty is essential for pharmaceutical companies. This becomes a particularly relevant problem when a change in ACT means that a study conducted in accordance with G-BA requirements is subsequently classified as no longer usable. Investments made in reliance on G-BA advice to generate suitable clinical evidence are then not adequately recognised either in the assessment or in the subsequent reimbursement situation. This creates considerable uncertainty for manufacturers.4

Potential improvements in communication

In recent years, pharmaceutical companies have had various ways of obtaining information about changes to ACT. First, after completion of G-BA advice, companies were subsequently informed by the G-BA itself if changes to ACT had been made. Second, manufacturers could request information on changes by submitting a new request for advice to the G-BA. Third, information on current comparator therapies could be derived from the G-BA's decision-ma-

Changes to appropriate comparator therapy (ACT)

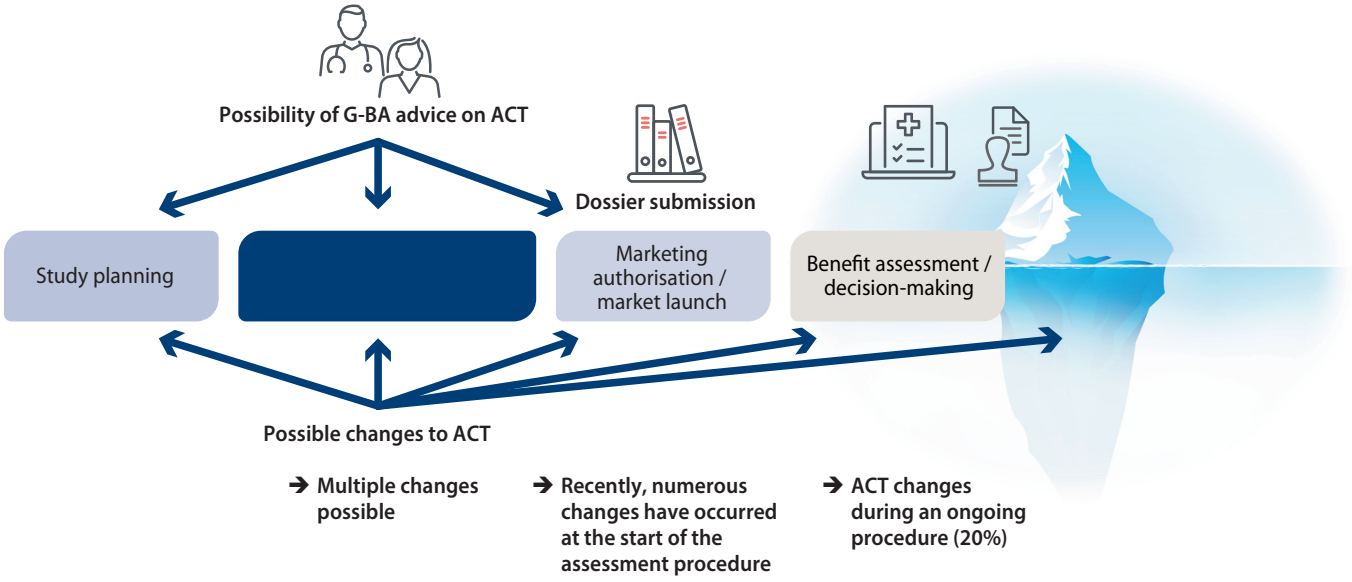

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Figure 1: Planning certainty is essential for pharmaceutical companies. Changes to ACT become particularly problematic when a study conducted in accordance with G-BA requirements is subsequently considered no longer usable as a result of such changes.

king practice, provided that the wording of the relevant therapeutic indications allowed conclusions to be drawn for other procedures.

In 2022, however, the G-BA discontinued its practice of proactively communicating changes. Since then, pharmaceutical companies have no longer received information after completion of an advice procedure. It is now therefore solely the responsibility of the pharmaceutical company concerned to verify whether the ACT is still up to date, at the latest when preparing a dossier for benefit assessment. In this context, the G-BA refers to the possibility of requesting further advice.

Combined with the non-binding nature of the advice, this means that the advice provided offers no reliability and may, within a very short time, no longer correspond to a newly defined G-BA position on ACT. This not only calls into question the informative value of advice as such. Advice has particular importance, not least because of the far-reaching exclusion of legal remedies. For this reason, and in line with the principle of fair procedure, the G-BA should inform pharmaceutical companies as early and comprehensively as possible of any changes to its advice and thus of changes to the basis for its decisions.6

At least since 1 March 2026, the G-BA has changed its

practice regarding publication of ACT, which is now published at the start of the procedure where it has already been defined, rather than only when the benefit assessment is published. The document „Information on appropriate comparator therapy" contains understandable and therefore welcome information on the search strategy and the results of that search.

However, the underlying considerations remain insufficiently transparent. The supporting reasons for determining ACT are still published only together with the final decision. This delay in publishing the relevant information is understandable on the one hand, since the final ACT is only established with the benefit assessment decision; on the other hand, important information needed to ensure transparency in the G-BA's determination of ACT remains unavailable.

Industry proposals regarding the dynamics of appropriate comparator therapy

The challenges outlined above could be addressed through two targeted changes:

- If an ACT has been used in a clinical study in accordance with G-BA advice, it should also be possible to demonstrate additional benefit against that therapy.
- Following advice on ACT, the G-BA should proactively inform pharmaceutical companies at the earliest possible stage about any changes made and about the wording of the ACT.

Where a change in ACT is necessary, supplementary consideration in the form of a bridging provision would improve planning certainty in the AMNOG process. At the same time, this would allow the best available evidence to be taken into account more appropriately while still giving due consideration to the current state of medical knowledge. Early communication of changes to requirements is essential not only for a fair procedure; it would also contribute to the generation of knowledge.

Is there a better way to deal with segmentation?

Another challenge within the AMNOG process is the segmentation of ACT and the resulting practice of slicing clinical studies into separate subpopulations. This raises two key questions. First, is it always necessary to define separate subgroups, or could a common comparison against a single ACT, for example, an individualised therapy, also be considered appropriate? Second, where separate subgroups are assessed independently and evidence has been generated for each of them, to what extent can findings from the overall study population be considered transferable?

In both cases, the retrospective reduction of study populations may lead to a substantial loss of statistical power. These limitations have largely remained unaddressed within the AMNOG process for many years. As a result, the procedure proposed by IQWiG to allow the transfer of evidence to subpopulations has likewise remained without practical application in benefit assessment.5

A further question is whether some of the subgroups created during ACT determination are meaningful from a methodological perspective. Advanced or metastatic breast cancer provides an illustrative example. In AMNOG procedures for this indication, a separate subgroup is often defined for the very small population of male patients. While this distinction is biologically understandable, it almost inevitably results in a patient population that is too small to recruit in sufficient numbers within a registration trial and in which statistically significant differences in treatment effects are unlikely to be demonstrated.

This example also highlights a broader issue: applying identical evidentiary standards to every subgroup may not

be appropriate. Nevertheless, AMNOG assessments invariably assume the availability of two adequately powered randomised controlled trials for all subgroups and treatment settings. This expectation is reflected in IQWiG methodology for determining the extent of additional benefit. Although the G-BA has formally stated since 2011 that it does not rely on this methodology directly, it nevertheless continues to influence AMNOG decisions. Similar expectations apply when assessing the certainty of evidence. Both IQWiG and the G-BA generally require two or more studies in order to award the highest level of certainty, namely „proof" of additional benefit.

EU-HTA: An opportunity to reduce segmentation and improve planning certainty

The introduction of European health technology assessment under the EU HTA Regulation, particularly through the Joint Clinical Assessment (JCA), offers an opportunity to address some of the challenges currently encountered within the AMNOG process. In particular, it may provide solutions to the current segmentation of ACT and the limited degree of planning certainty available to pharmaceutical companies.

A key lever lies in the definition of PICO frameworks. In future, these should not be driven solely by national requirements but should be aligned more closely with the evidence generated by health technology developers (HTDs) at the European level. Such an approach would improve the alignment of clinical development programmes with subsequent benefit assessments and help reduce discrepancies between regulatory studies and HTA requirements. In addition, the process for agreeing PICO elements within the JCA framework creates an opportunity for early consolidation. This process of PICO consolidation should be used systematically to limit fragmentation into numerous individual subquestions. Greater alignment with a consensus-based European assessment framework could therefore reduce the degree of segmentation currently observed while at the same time strengthening the robustness of the underlying evidence.

Equally important is the mandatory use of JCA reports within the AMNOG process. Systematic and binding consideration of European assessments would not only avoid duplication of work but would also promote greater consistency in assessment standards. This, in turn, could improve the transparency of decision-making and significantly enhance planning certainty for pharmaceutical companies.

Overall, EU HTA offers an opportunity to recalibrate the balance between evidence-based assessment and practical implementation at the national level – with the potential to reduce segmentation, improve efficiency and increase predictability within the AMNOG process.

Conclusion

Appropriate comparator therapy remains the central reference point within the AMNOG process. At the same time, it is increasingly characterised by a high degree of dynamism and by a level of segmentation that warrants critical examination. In practice, these developments create considerable uncertainty in the planning and conduct of clinical studies and, in extreme cases, may call into question the usability of evidence within the benefit assessment process.

Short-notice changes to ACT present a particular challenge for pharmaceutical companies. At the same time, increasing segmentation, combined with uniform evidentiary requirements across all treatment settings, gives rise to important methodological concerns. Against this background, targeted refinements to the AMNOG framework

are needed. These include, above all, greater reliability, and transparency in the determination of comparator therapy, as well as a more appropriate approach to the segmentation of evidence. In addition, European HTA cooperation has the potential to make a significant contribution. Through harmonised PICO definitions and the use of common assessment frameworks, it can help reduce fragmentation and improve planning certainty.

Ultimately, a better balance is needed between scientific currency and a predictable regulatory environment. Only by achieving this balance can evidence-based benefit assessments and innovation-friendly conditions for pharmaceutical development be safeguarded in the long term. Such adjustments are particularly important in the current period of geopolitical uncertainty.

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Appropriate Comparator Therapy from a Clinical Perspective

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Appropriate comparator therapy (ACT) forms the methodological foundation of early benefit assessment within the AMNOG framework. From a clinical perspective, however, it is not a static construct but rather a dynamic concept situated at the intersection of evidence-based medicine, rapid therapeutic innovation, biomarker-driven treatment decisions, and individual patient preferences. Using recent developments in gastric and oesophagogastric cancer as examples, this article illustrates how ACT frequently evolves more rapidly than the underlying clinical evidence base. This creates significant challenges for trial design, benefit assessment, and routine clinical care. A future-oriented definition of ACT should therefore place greater emphasis not only on randomised evidence, but also on the rapid pace of innovation in oncology, increasing molecular stratification, patient perspectives, and real-world data.

Significance of appropriate comparator therapy

Appropriate comparator therapy represents the central reference point for early benefit assessment within the AMNOG system. From a methodological perspective, it serves as the defined comparator used to quantify the additional benefit of new medicinal products.

From a clinical perspective, however, ACT addresses a pragmatic question: which therapy used in routine care would actually be replaced by a new intervention? This makes it clear that ACT is not merely a methodological parameter, but also a clinically shaped concept.

Principles of evidence-based medicine

Clinical decision-making is based on the principles of evidence-based medicine. Sackett et al. defined these principles as the integration of:

- the best available scientific evidence (data)
- clinical expertise, including assessment tailored to the specific situation and individual patient
- patient values and preferences (Sackett DL et al., BMJ 1996).

This three-dimensional framework is central to the evaluation of ACT. A definition based exclusively on data from randomised trials falls short because it fails to take into account both clinical experience and the patient perspective.

Stakeholder perspectives

ACT emerges within a field of tension shaped by differing stakeholder interests:

- HTA bodies and the Federal Joint Committee, with a focus on methodological validity
- the pharmaceutical industry, with a focus on regulatory acceptance
- clinical practice, with a focus on patient-centred care.

These perspectives may diverge, particularly in situations characterised by rapid innovation and multiple treatment alternatives.

Dynamics of therapeutic innovation

Oncology is characterised by an exceptionally rapid pace of innovation. In advanced gastric cancer, several phase III trials have changed the treatment standard within a short period of time:

- CheckMate 649 (nivolumab + chemotherapy)
- KEYNOTE-859 (pembrolizumab + chemotherapy)
- RATIONALE-305 (tislelizumab + chemotherapy)
- Keynote-811 (pembrolizumab + trastuzumab + chemotherapy).

These studies established immune checkpoint inhibition in combination with chemotherapy and HER2-targeted therapy as the new first-line standard in stage IV disease.

At the same time, targeted therapies have continued to evolve:

- SPOTLIGHT trial: zolbetuximab + FOLFOX chemotherapy in CLDN18.2-positive tumours
- GLOW trial: zolbetuximab + CAPOX chemotherapy in CLDN18.2-positive tumours
- HERIZON-GEA-01: zanidatamab ± immunotherapy + chemotherapy in HER2-positive tumours.

This gives rise to a central challenge: by the time benefit assessments are conducted, the comparator therapy used in many clinical trials no longer reflects the current standard of care.

Heterogeneity of the patient population

Increasing molecular characterisation of oncological diseases is leading to growing fragmentation of the patient population.

In gastric cancer, relevant biomarkers overlap:

- HER2
- PD-L1
- CLDN18.2
- Microsatellite instability (MSI).

This overlap results in a wide range of potential treatment options and complicates the definition of a single appropriate comparator therapy.

Biomarker-based treatment decisions

The choice of optimal therapy is increasingly determined by molecular subgroups. Examples include:

- HER2-positive disease: anti-HER2-based combination therapies
- CLDN18.2-positive disease: zolbetuximab-based therapy
- PD-L1-positive disease: immunotherapy

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- MSI disease: immunotherapy.

ACT therefore becomes a stratified parameter that depends on the individual tumour profile.

Patient perspective and treatment goals

Consideration of the patient perspective is a central component of evidence-based medicine. In routine clinical practice, treatment decisions are strongly influenced by the following factors:

- quality of life
- adverse event profile
- treatment duration and intensity
- individual treatment goals.

Particularly in older patients and those with comorbidities, these factors frequently lead to deviations from guideline recommendations. Any ACT definition that fails to take patient preferences into account remains clinically incomplete.

Guidelines and clinical reality

Clinical guidelines define evidence-based standards but do not always reflect real-world clinical practice. One example is perioperative therapy:

- guideline recommendation: FLOT
- clinical reality: modified regimens are often required in older or comorbid patients (average age at diagnosis of gastric cancer: >70 years).

The MATTERHORN trial also illustrates the continued evolution of standards through the integration of immunotherapy (durvalumab). This raises the question of whether guidelines alone are suitable as ACT or whether a definition more closely aligned with real-world care is required.

Implications for benefit assessment and trial design

From a clinical perspective, the following requirements emerge:

- dynamic adaptation of comparator therapy: regular adjustment to current standards of care
- integration of the patient perspective: systematic consideration of patient preferences
- biomarker-stratified comparators: moving beyond the concept of a single uniform comparator
- incorporation of real-world data: strengthening external validity
- early multidisciplinary coordination: closer integration of regulatory authorities, HTA bodies and clinical practice.

Conclusion

Appropriate comparator therapy is not a static reference point, but a dynamic concept situated at the intersection of evidence, innovation, and patient-centred care.

In line with the principles of evidence-based medicine, it must:

- take scientific evidence into account
- integrate clinical expertise
- incorporate patient preferences.

The increasing complexity of oncological therapies requires a further evolution of current assessment approaches. A comparator therapy can only be considered truly appropriate if it is actually used in routine clinical practice.

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ACT: Experiences and Challenges in the Context of Precision Oncology

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Cancer is a genetic disease. Comprehensive molecular tumour analyses can therefore reveal mechanisms of oncogenesis. Through the development of molecularly targeted agents and an improved understanding of signalling pathways, molecular alterations are increasingly being used as predictive biomarkers for targeted cancer therapy. This concept of integrating molecular tumour analyses for personalised treatment guidance is referred to as precision oncology. This paradigm shift – from a histologically defined to a molecularly defined disease classification – gives rise to new challenges in the evaluation of therapeutic concepts. The following article provides an overview of the background, current standards, and possible future developments in this field.

Molecular tumour stratification – subgroups or distinct diseases

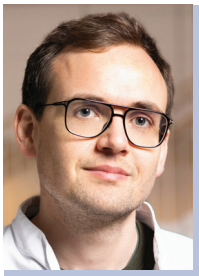
The detection of HER2 oncogene amplifications in a subgroup of breast carcinomas, followed by the development of HER2-targeted therapies in the 1990s, represents a landmark example of the emergence of molecularly stratified treatment approaches in oncology.[1,2] Today, the integration of molecular (immunohistochemical) testing underpins the established classification of breast cancer into hormone receptor-positive, HER2-positive and triple-negative tumours.[3] These subgroups are not merely biologically distinct entities; owing to their differing responses to molecularly stratified therapies, they also have predictive relevance. As a consequence, modern clinical trials are now predominantly designed with these biologically and therapeutically distinct subgroups in mind.

Rapid advances in sequencing technologies now enable fast, reliable, and cost-effective identification of tumour alterations, including at the genomic level. The discovery of activating EGFR mutations in a subgroup of lung cancers, together with the subsequent demonstration that these alterations predict response to EGFR-targeted therapies, marked the first genetic substratification of lung cancer based on defined molecular alterations.[4] Since then, the identification of numerous additional oncogenic alterations and the development of corresponding targeted therapies have resulted in a clinically relevant distinction between more than ten different driver-positive lung tumour subtypes.[5] These subgroups, too, are defined by the availability of targeted agents and thus by predictive biomarkers.

Many molecularly defined subgroups are rare, making conventional clinical trial designs difficult to implement. Consequently, studies in these patient populations are fre-

quently conducted as single-arm phase II trials. Despite these methodological limitations, a considerable number of such studies have nevertheless led to regulatory approvals of targeted therapies. Examples include approvals for therapies targeting BRAF p.V600E mutations and RET fusions.[6,7] In some cases, the clinical efficacy of these agents has also been demonstrated in large international trials against chemoimmunotherapy, which remains the standard treatment for driver-negative lung cancer.[8]

The exclusion of numerous driver-positive tumours from relevant pivotal trials for new agents in lung cancer, as well as the reduced efficacy particularly of immunotherapy options, nevertheless highlights the distinct nature of these molecularly defined subgroups. In this context, the use of conventional treatment regimens as comparator arms in registration trials – as currently seen, for example, in the development of new HER2-targeted therapies for HER2-mutant lung cancers – can also be critically questioned.



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Tumour-agnostic therapy

Many predictive biomarkers can be detected across a wide range of tumour entities, albeit at varying frequencies. It is therefore a logical step to investigate effective targeted therapies in a molecularly defined, tumour-agnostic setting. Owing to the rarity of many alterations and the absence of established standard therapies in such cross-entity settings, these studies are likewise frequently conducted as single-arm trials. Nevertheless, the high efficacy of certain agents has already resulted in the first approvals of molecularly stratified therapies for the treatment of cancers harbouring defined molecular alterations.[9,10] This tumour-agnostic approach places the molecular alteration itself – rather than histology or tissue of origin – at the centre of therapeutic decision-making and thus represents a paradigm shift in oncology.

For some of the rare tumour entities included in these studies, tumour-agnostic approvals represent the first approved treatment options available at all. At the same time, however, no universally accepted comparator therapy exists in such tumour-agnostic settings, where treatment is often interpreted in the sense of „best supportive care". Nevertheless, the clinically and biologically distinct behaviour of molecular tumour subgroups, the marked efficacy of some targeted therapies and the lack of standard treatment options for certain included entities all justify critical discussion of these approaches.

Evidence supporting the efficacy of molecularly stratified treatment concepts in cancer-of-unknown-primary and tumour-agnostic settings has been provided by two randomised phase II studies. In both trials, targeted therapies selected on the basis of individual molecular alterati-

ons proved more effective than standard therapies chosen according to conventional clinical decision-making parameters.[11,12]

From subgroup classification to individualised assessment – is every tumour a unique case?

The logical continuation of the substratification approaches outlined above is a highly individualised assessment of each patient's molecular tumour profile. Given the large number of genetic alterations found in cancer, identical molecular profiles are rarely observed, effectively rendering every patient a unique case. In such a context, controlled clinical trials become difficult to envisage. Nevertheless, several studies have demonstrated that complex molecular profiles can influence treatment response. Various genetic signatures were used as „meta-biomarkers" in these analyses.[13,14,15] Although the use of such biomarkers has not yet been prospectively validated, they may offer a potential strategy for addressing molecular complexity.

From a therapeutic perspective, personalised drug combinations may ultimately become necessary in order to achieve effective targeted treatment in diseases characterised by multiple genetic lesions. Here too, conventional prospective controlled study designs are practically infeasible because of the vast number of potential treatment combinations. One possible approach is the use of intraindividual comparative data within so-called N-of-1 study designs.[16,17]

Conclusion

Today, molecular tumour analyses and the resulting stratified, personalised treatment decisions are an established part of routine clinical care in the context of precision oncology. The classification of cancers on the basis of individual predictive biomarkers can still be evaluated relatively effectively using conventional assessment frameworks. However, the shift towards molecularly defined disease entities, the rarity of many alterations and the increasingly individualised understanding of disease require the consideration of novel study designs in order to evaluate promising therapeutic approaches and integrate them into routine care in line with the principles of personalised and evidence-based medicine.

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Appropriate comparator therapy for stand-alone therapies – A legal perspective

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The appropriate comparator therapy (ACT) is of vital importance in the AMNOG process because the price of a pharmaceutical is determined solely by the additional benefit it demonstrates over that comparator. Difficulties arise in particular where the appropriate comparator therapy is unclear or absent, for example in the case of so-called stand-alone therapies. Using the example of regadenoson, this article shows that therapies used off-label may also serve as comparators. A judgement of the Federal Social Court called this approach into question, but subsequent legislative amendments corrected this by clarifying that, as a general rule, all new pharmaceuticals should undergo benefit assessment. Despite these amendments, determining the appropriate comparator therapy remains a complex issue in both legal and practical terms, particularly where no standard therapy exists or off-label use is involved.

1 AMNOG establishes a system of price determination based entirely on outcomes. The reimbursement amount does not depend on the costs of developing or manufacturing a new pharmaceutical but solely on the additional benefit it provides. This makes the benchmark against which that additional benefit is assessed – and ultimately translated into a reimbursement amount – of vital importance. In other words, the key question is which treatment the new pharmaceutical should be compared with, both clinically and economically. The statutory framework provides a clear answer: the benchmark is the existing standard of care, referred to as the appropriate comparator therapy (ACT). The additional benefit must be demonstrated in comparison with this therapy. Likewise, the reimbursement amount is linked to the annual treatment costs of the ACT. Where no additional benefit has been demonstrated, those costs generally[1] act as a ceiling for the reimbursement amount (cf. Section 5(1) Framework Agreement). Where an additional benefit has been demonstrated, its monetary value is reflected as an increment above the costs of the ACT (Section 5(2) Framework Agreement).[2]

It is therefore unsurprising that, in proceedings before the AMNOG Arbitration Board, determining the appropriate comparator therapy and establishing its costs are regularly among the central issues. For the Arbitration Board, this is primarily a matter of interpretation, since both the choice of the ACT and its costs are specified in the benefit assessment decision of the Federal Joint Committee (G-BA). Difficulties arise whenever the G-BA's decision leaves room for interpretation. For example, it is not uncommon for several appropriate comparator therapies to be identified, requiring the Arbitration Board to decide whether, under Section 130b(3) SGB V, it can simply rely on the most economical alternative or whether it must instead

base its calculation on a mix of treatments because different patient groups receive different treatments in clinical practice. Determining the relevant costs may also prove difficult, for example where the G-BA specifies only a cost range rather than a single figure.

For the G-BA itself, the principal challenge is to determine the appropriate comparator therapy in a legally robust manner. A particular difficulty arises in cases where no established standard of care – and therefore no appropriate comparator therapy – appears to exist.

2. A somewhat unusual set of circumstances arose in the case of Rapiscan (active substance: regadenoson), which is authorised as a pharmacological stress agent for measuring the fractional flow reserve of a stenosis (FFR measurement). It was initially unclear whether the pharmaceutical was required to undergo a benefit assessment, since FFR measurement – and therefore the diagnostic agent used for this purpose – had already been subject to a methods assessment under Section 135 SGB V. After a somewhat unfortunate series of exchanges, the G-BA ultimately required the pharmaceutical company to submit a dossier. When the company failed to do so, the G-BA concluded on that basis alone that no additional benefit had been demonstrated. It designated „pharmacological stress induction at the physician's discretion" as the appropriate comparator therapy, identifying adenosine and nitroprusside – both regularly used in clinical practice for this purpose despite not being authorised for such use – as „suitable comparators".

After negotiations between the parties proved unsuccessful, the Arbitration Board under Section 130b SGB V – chaired by the author – determined a reimbursement amount. In doing so, it considered itself bound by the findings set out in the G-BA's benefit assessment decision and its supporting reasons: that an AMNOG procedure was required in this case, that no additional benefit had been demonstrated and that „pharmacological stress induction at the physician's discretion" was to be used as the appropriate comparator therapy. On this basis, the Arbitration Board determined the reimbursement amount by reference to the costs of the „suitable comparators" identified by the G-BA, including a very modest reduction because no dossier had been submitted at all. This reduction was provided for in the former Section 130b(3), sentence 5, SGB V and is now set out in Section 130b(3), sentence 4, SGB V.[3] Contrary to the approach proposed by the National Association of Statutory Health Insurance Funds, however, the Arbitration Board did not base its calculation solely on the less expensive of the two „comparators". Instead, it interpreted the reference to the „physician's discretion" as meaning

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that neither comparator constituted the appropriate comparator therapy in its own right. Rather, both were to be taken into account when determining the cost of the appropriate comparator therapy and, in the absence of more detailed information on how frequently each was used, were given equal weight.

In the proceedings before the Arbitration Board and, in particular, in the subsequent proceedings before the Berlin-Brandenburg Regional Social Court (LSG), following an action brought by the pharmaceutical company, the parties disputed, among other matters, whether the pharmaceutical was „new" and how the methods assessment already conducted under Section 135 SGB V related to the AMNOG procedure. An obvious question was whether, and to what extent, a pharmaceutical used solely as part of a diagnostic procedure could demonstrate an additional benefit in terms of patient relevant endpoints within that procedure. Another issue was whether the pharmaceuticals identified as „comparators" could be used to establish a price benchmark for the appropriate comparator therapy even though they were being used off-label for this purpose. The LSG ultimately upheld both the Arbitration Board's decision and, in its incidental review, the G-BA's benefit assessment decision, and dismissed the pharmaceutical company's action.[4]

3. The Federal Social Court (BSG), however, reached a different conclusion on appeal.[5] It held that the G-BA's benefit assessment decision was unlawful because the pharmaceutical was a „therapeutic stand-alone" and should therefore never have been subject to a benefit assessment in the first place. It followed as a matter of course that the Arbitration Board's decision, which was based on the G-BA's decision, was likewise declared unlawful and set aside. The BSG's judgement was surprising at least in the sense that it turned primarily on an issue that had played only a minor role in the proceedings up to that point: whether the AMNOG procedure applied at all to „stand-alone" pharmaceuticals.

In fact, the status of such stand-alone pharmaceuticals in the context of price regulation has been debated for some time. Under the statutory framework that preceded AMNOG, provision had been made for setting a maximum reimbursement amount, although this mechanism was never implemented in practice. The legislation expressly provided that „pharmaceuticals [...] for which a cost-benefit assessment can only be conducted by comparison with no treatment because no appropriate therapeutic alternative exists [...] are to be exempt from the setting of a maximum reimbursement amount" (Section 31(2a), sentence 7, SGB V, in the version applicable until 31 December 2010). The political intention to close this gap through AMNOG was evident, and the provision quoted above was repealed when AMNOG was enacted. Attempts to argue as a matter of law that AMNOG did not apply to stand-alone pharmaceuticals[6] attracted little support. It is therefore unsurprising that the legislature responded promptly to the BSG judgement by amending the law.[7]

Given this legislative correction, the question of whether the BSG judgement – which, after all, departed from the G-BA's long-standing practice – was legally convincing is now largely of historical interest. The answer depends to a considerable extent on how pharmaceuticals used off-label are viewed. Those who regard actual clinical practice as the relevant basis for determining the appropriate comparator therapy will have little difficulty with off-label use. By contrast, those who consider off-label use outside the conditions laid down in Section 35c SGB V problematic will be reluctant to take the „comparators" into account and will instead regard the newly authorised pharmaceutical as a „marketing-authorisation stand-alone".[8]

The BSG's reliance on the amendment to Section 92(1), sentence 1, SGB V introduced by AMNOG is hardly persuasive. The fact that the G-BA has since been prohibited from excluding a pharmaceutical from prescription solely because there is insufficient evidence of benefit scarcely supports the conclusion that therapeutic stand-alone pharmaceuticals may no longer be assessed for additional benefit for the purposes of price determination.[9]

It must also be borne in mind that an „off-label appropriate comparator therapy" is only one possible scenario. The problem of assessing stand-alone pharmaceuticals may equally arise where the only possible appropriate comparator therapy is watchful waiting or best supportive care. It may also arise where the only option is to designate „treatment at the physician's discretion" as the appropriate comparator therapy, since an individually tailored form of treatment may lack the degree of standardisation required for this purpose.

4. It is inherent in the logic of AMNOG that all new pharmaceuticals should undergo early benefit assessment unless they are expressly exempt, as is the case with orphan drugs and reserve antibiotics. The aim is to prevent pharmaceutical companies from being able to set prices freely on a permanent basis across the market. It is therefore understandable that, in response to the BSG's judgement, the legislature sought to „clarify" this point in the ALBVVG[10] – initially by expressly stipulating in Section 35a(1), sentence 1, SGB V that „all" new pharmaceuticals are to undergo benefit assessment. In cases such as this, a „clarification" can mean one of two things: either the position was already clear and is merely being restated, or it was unclear and has now finally been resolved. Supporters and critics of the BSG judgement will inevitably take different views on which of these applies.

The new provisions presented few difficulties in cases where no treatment at all – or at least no treatment with curative intent – is available, meaning that the pharmaceutical under assessment is a „therapeutic stand-alone" in this sense. Section 6(2) AM-NutzenV was intended from the outset to „clarify" that the relevant benchmark is „the treatment situation that would exist without the pharmaceutical under assessment" and that the appropriate comparator therapy may also consist of „a non-pharmaceutical treatment, best supportive care including symptomatic, palliative medical or palliative nursing care, or watchful waiting".[11] The argument that this gives rise to constitutional concerns[12] rightly did not prevail, since the issue here is not patients' entitlement to healthcare benefits but the comparative framework used for price determination.

Responding to the off-label scenario raised by the BSG – involving a pharmaceutical that is a „regulatory stand-alone" – proved more difficult. In addition to off-label use authorised by a G-BA decision under Section 35c SGB V, the BSG considered it possible for a pharmaceutical to be a regulatory, rather than a therapeutic, stand-alone „for other reasons".[13] At the same time, however, drawing on a decision of the Federal Constitutional Court,[14] it held, on grounds concerning the legal basis for the G-BA's decision-making powers, that the G-BA could not be afforded substantial discretion in this regard and that the law had to provide „sufficiently detailed guidance".[15] The impartial members of the G-BA therefore called during the legislative process for a more differentiated provision based on the concept of a „comparator therapy for assessment purposes".[16] This approach was subsequently incorporated, following the recommendation of the Health Committee,[17] into Section 6(2), sentence 3, AM-NutzenV:

„By way of exception, the Federal Joint Committee may designate the use of pharmaceuticals outside their authorised indication as the appropriate comparator therapy or

as part of the appropriate comparator therapy if, in its decision on the benefit assessment under Section 7(4), it determines that, according to the generally recognised state of medical knowledge, such use constitutes the standard of care or part of the standard of care in the therapeutic indication under assessment and in the treatment setting referred to in sentence 2, and if

1. the pharmaceutical under assessment is the first pharmaceutical authorised for the therapeutic indication concerned;

2. according to the generally recognised state of medical knowledge, the off-label use is routinely preferred to pharmaceuticals previously authorised for the therapeutic indication; or

3. according to the generally recognised state of medical knowledge, the off-label use is routinely preferred to pharmaceuticals previously authorised for the therapeutic indication for relevant patient groups or areas of indication."

This provision should make it possible in most cases to accommodate the practical need to recognise off-label use as the appropriate comparator therapy in benefit assessments.[18] However, highly specific statutory requirements of this kind also have their drawbacks. If the conditions laid down in Section 6(2), sentence 3, AM-NutzenV are not met – for example, because there are doubts as to whether the off-label use is „routinely" preferred – there is little room for alternative solutions. In view of the BSG's constitutional requirement for „sufficiently detailed" statutory guidance, the G-BA can hardly be expected to interpret these requirements with any great degree of flexibility.

5. It may be regrettable that the provision introduced by the ALBVVG no longer ensures complete alignment between the rules governing entitlement to healthcare benefits and those governing price determination.[19] This is, however, difficult to avoid as long as actual clinical practice is shaped in part by unregulated off-label use and price determination is intended to reflect that clinical reality, as is now expressly provided for in Section 6(2), sentence 2, AM-NutzenV. Nor is there any reason to assume that the AMNOG procedure is incapable of determining an appropriate price for „stand-alone" pharmaceuticals within the meaning of Section 6(2), sentence 2 et seq., AM-NutzenV. In such cases, it will typically be possible to demonstrate an additional benefit, leaving greater scope for price determination because the „guardrails" laid down in Section 130b(3) SGB V, as amended by the GKV-FinStG, do not apply.

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[1] Apart from a departure from the provision framed as a general rule, the Arbitration Board's application of which was upheld by the LSG in two decisions; see LSG Berlin-Brandenburg, judgement of 16 June 2025, L 9 KR 251/22 KL (selpercatinib), and judgement of 26 November 2025, L 1 KR 106/23 KL (dostarlimab).

[2] This wording may be considered unfortunate because it links the monetisation of the additional benefit too closely, and in a potentially misleading manner, to the costs of the appropriate comparator therapy; see Huster, NZS 2017, 681, 685 et seq.

[3] Arbitration award of 1 July 2020, 3 P 4-20.

[4] LSG Berlin-Brandenburg, judgement of 24 September 2021, L 28 KR 329/20 KL, PharmR 2022, 124 et seq. See also the case notes by Fiekas, A&R 2022, 52 et seq.; Nitz, PharmR 2022, 147 et seq.

[5] BSG, judgement of 22 February 2023, B 3 KR 14/21 R, MedR 2023, 662 et seq. See also Anders, PharmR 2023, 346 et seq.; Gaoener/Strömer, GuP 2023, 154 et seq.; Mertens, G+G 2023, No. 6, 35; Penner, SGb 2023, 635 et seq.; Volkwein, MedR 2023, 667 et seq.

[6] See in particular Stallberg, PharmR 2016, 109 et seq.

[7] See section 4 below.

[8] See BSG, cited above, para. 27 et seq.

[9] This appears, however, to be the position taken by the BSG, cited above, para. 22.

[10] Gesetz zur Bekämpfung von Lieferengpässen bei patentfreien Arzneimitteln und zur Verbesserung der Versorgung mit Kinderarzneimitteln (Act to Combat Supply Shortages of Off-patent Pharmaceuticals and Improve the Supply of Paediatric Pharmaceuticals; Arzneimittel-Lieferengpassbekämpfungs- und Versorgungsverbesserungsgesetz – ALBVVG), BGBl. 2023 I No. 197 of 26 July 2023.

[11] This was already provided for in Article 6 of the draft ALBVVG; see BT-Drs. 20/6871, p. 17.

[12] See the statement by the vfa, pp. 4 et seq. (Ausschuss-Drs. 20(14)113(1)).

[13] BSG, cited above, para. 32.

[14] See BVerfGE 140, 229 et seq.

[15] BSG, cited above, para. 37.

[16] See their statement of 8 June 2023, pp. 8 et seq.

[17] See BT-Drs. 20/7397, pp. 37 and 67.

[18] See also Rasch, Monitor Versorgungsforschung 4/23, 36.

[19] For criticism of the provision, see, for example, Penner, SGb 2023, 635, 638 et seq.

[20] See also the explanatory memorandum to the legislation, BT-Drs. 20/6871, p. 35.

Appropriate comparator therapy: New dimensions to a long-standing debate

Florian Staeck

The question of how the appropriate comparator therapy (ACT) should be determined, and whether it can be changed during an ongoing benefit assessment procedure, has accompanied AMNOG since its introduction in 2011. At its heart lies a fundamental tension within the early benefit assessment process. On the one hand, under Section 6 of the Ordinance on the Benefit Assessment of Pharmaceuticals, the ACT must reflect the generally accepted state of medical knowledge and actual clinical practice. On the other hand, research-based pharmaceutical companies need a predictable framework to ensure that evidence generated in clinical trials can also be taken into account in the benefit assessment.

Pharmaceutical companies can seek advice from the Federal Joint Committee (G-BA), including on the determination of the ACT. However, this advice is intended to provide guidance and is not legally binding. At the same time, companies can no longer adapt the design of completed studies if the ACT changes shortly before marketing authorisation. The debate surrounding the ACT therefore invariably reflects current trends and challenges in the implementation of AMNOG procedures.

Against this background, participants in the Interdisciplinary Platform on Benefit Assessment met in Berlin on 20 and 21 March 2026. The meeting was held under the title „Appropriate comparator therapy: Status, pitfalls and trends." It coincided with a change in practice: since 1 March 2026, the ACT has been published on the G-BA website at the start of the benefit assessment procedure. Previously, it was not made public until the dossier was published. The reasons for selecting the ACT, however, continue to be published only with the benefit assessment decision.

One indication of how controversial the determination of the ACT remains is the apparent lack of consensus even on the scale of the issue. Estimates presented at the meeting put the proportion of benefit assessment procedures involving a change to the ACT at anywhere between five to ten per cent and 20 per cent.

Participants involved in clinical practice emphasised that the ACT was not a static concept but a „moving target". Treatment goals, they noted, were always determined in the context of clinical judgement, patient preferences, and benefit-risk considerations. In practice, there was an inherent tension between clinical guidelines, real-world clinical practice and cost-effectiveness that was difficult to resolve. As a result, the comparator selected for the pivotal trial might no longer reflect the standard of care by the time of the benefit assessment.

The meeting also included extensive discussion of ways to generate evidence as early as possible. One proposal was to use horizon scanning, beginning three to four years before an active substance is authorised. This would involve pharmaceutical companies, medical societies and the G-BA working together. Such an approach to evidence generation was said to offer many advantages, for example compared with routine practice data collection (anwendungsbegleitende Datenerhebung, AbD). Other participants advocated including Phase I clinical study data in registries. One question left unresolved was how such models could be funded.

Participants also criticised the fact that Federal Social Court case law had created obstacles for the G-BA. They argued that this hampered a „learning approach to pricing" within the AMNOG process, as the G-BA was not permitted to initiate a new benefit assessment on its own initiative. Pharmaceutical companies, it was noted, would generally request a new assessment only when they had positive results to present.

Industry positions: Industry representatives emphasised that the ACT was a pivotal element of the AMNOG process, while the G-BA alone had the authority to determine the standard of care. They criticised the fact that the Committee did not inform pharmaceutical companies if the ACT changed following a consultation, arguing that this was incompatible with a fair procedure. Instead, they called on the G-BA to communicate any such changes proactively and at the earliest possible opportunity following an ACT consultation.

Given the increasingly rapid changes in comparator therapies in some therapeutic areas, industry representatives put forward specific proposals. Where an ACT had been used in a clinical trial in accordance with G-BA advice, they argued that it should remain possible to demonstrate additional benefit against that therapy. More generally, they questioned whether the large number of separate subquestions relating to the ACT in benefit assessment procedures was always necessary. They also expressed the hope that European benefit assessment (EU HTA) would involve less segmentation and provide greater planning certainty in future.

Others argued, however, that a proposal made during the German government's Pharma Dialogue – that the ACT should no longer be changed during an ongoing benefit assessment procedure once a consultation had taken place – was problematic. With the emergence of new classes of active substances, they noted, the ACT could then cease to be consistent with the latest clinical guidelines.

Health insurance fund positions: Other participants indicated that they would like the issue of the ACT to be considered as part of a broader structural reform of the AMNOG process. They pointed out that in half of all cases where the ACT is changed at the start of or during the benefit assessment procedure, the evidence is ultimately considered suitable. This determination, they explained, is made during the commenting procedure.

Others criticised the fact that the process has so far focused primarily on two stages in the lifecycle of active substances: market entry and patent expiry. What was lacking, they argued, were mechanisms through which older active substances could be displaced by newer ones. In practice, new pharmaceuticals were invariably added „on top" of existing treatments. In response, it was pointed out that two thirds of all AMNOG products undergo at least two price reductions during their lifecycle.

Health insurance fund representatives identified reassessments over time and the strict application of price-volume agreements as important options for action. However, the legislature had so far failed to provide a clear statutory basis for price-volume agreements, even though participants estimated that this instrument could generate annual savings of EUR 50 to 100 million. Under such an arrangement, previously agreed price reductions would take effect once an active substance reached a specified level of sales. Participants noted, however, that decisions by the Arbitration Board could not subsequently compensate for the absence of a sufficiently robust statutory basis.

Health insurance funds have long criticised the deemed additional benefit for orphan pharmaceuticals. They argued that deeming an additional benefit to exist was not an appropriate instrument for promoting active substances for rare diseases and that such support should instead be provided through other mechanisms.

Potential of registry data in determining the ACT: Registry data could help in two ways. First, they could provide real-time evidence of which therapies are currently being used. Second, adjusted comparisons using an exter-

nal control arm could provide comparative evidence that would otherwise be lacking. Participants noted that this could generate robust evidence on additional benefit even in the absence of a randomised controlled trial. Essential quality requirements for registries included prospective planning and data collection, the identification of confounders and the collection of patient-reported outcomes (PROs). As regards representativeness, participants stressed that registry data did not need to cover the entire population, but should provide a robust sample of the relevant patient population. Registry studies should ideally begin as early as Phase III. At the same time, participants acknowledged that data from external control arms had so far been accepted only in exceptional cases in AMNOG procedures and that routine practice data collection had fallen far short of expectations.

Dealing with „stand-alone therapies" when determining the ACT: Determining the ACT poses particular challenges where there appears to be no standard therapy that could serve as a reference. In such cases, the difficulties concern not only the identification of an appropriate comparator but also how the costs of the ACT should be determined. In a 2023 decision that was widely regarded as surprising, the Federal Social Court held that the AMNOG procedure could not be applied to „therapeutic stand-alone therapies". This was seen as conflicting with the legislature's original intention that all newly authorised pharmaceuticals should undergo early benefit assessment.

Although the legislature responded later that same year by clarifying that only orphan pharmaceuticals and reserve antibiotics were exempt from this requirement, cases in which the ACT involves off-label use remained problematic. The Ordinance on the Benefit Assessment of Pharmaceuticals now provides that, by way of exception, the Federal Joint Committee may designate the off-label use of pharmaceuticals as the ACT. Participants expressed regret that the widespread use of pharmaceuticals off label meant that the rules governing SHI coverage and those governing pricing diverged in this respect.

One conclusion was that case-by-case rules imposed by the Federal Ministry of Health did not really work. If AMNOG was to operate as a „learning system", participants argued, the legislature and the regulatory authorities needed to give the institutions of joint self-government sufficient scope to develop the system organically.

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