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AMNOG 2.0: On the path to an efficient system

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Content

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 and Association of Research-Based Pharmaceutical Companies (vfa e.V.).

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

AMNOG 2.0: Increasing efficiency means more than saving money

Professor Jörg Ruof

Dear readers

In his observations on the crisis of meaning and being in hospitals, published in 2011 under the title „The efficient organization", the theologian and anthropologist Arne Manzeschke reflects on institutional developments in hospitals from an ethical perspective against the background of increasing economisation.

He considers the central paradox to be that economic constraints and requirements are both the starting point for change and the means by which change is to be managed. Saving as both an end and a means – this is a bad starting point for a good reform.

It is not only in the context of the current debate on hospital reform that these considerations appear to be as relevant as ever; in the area of pharmaceutical supply, too, the question must be asked as to which „guidelines" can serve as orientation aids for the further development of the AMNOG system beyond the pure pressure to save. This issue of the publication deals with this question from the perspective of patients, physicians, scientists, health insurances, industry, and politics.

At the previous conference – as well as in this publication – several presentations were each supplemented by a corresponding block of questions and comments. The short articles in the publication by Dr Danner, Dr Flume and Dr Herholz refer to the respective subsequent section of articles. The European perspective, which is increasingly relevant for the benefit assessment, is supplemented by the methodological explanations of the EUnetHTA guidance on direct and indirect comparisons by Professor Bucher and in the articles from France (Dr d'Andon) and the Netherlands (Professor Rutten).

- **Critical commentary on the regulations in the Financial Stabilisation of the Statutory Health Insurance (GKV-FinStG):** The fundamentally positive review of the history of the AMNOG is undisputed in all articles. Nevertheless, upon reviewing the articles, it becomes evident that, notwithstanding the financial constraints faced by health insurances, the potential for efficiency gains through additional incremental adjustments to the AMNOG framework is notably constrained.

For example, the regulations introduced in the GKV-FinStG were largely criticised. From the patient's point of view, Dr Danner mentions the relevance of smaller innovation steps for care, which is effectively devalued in the law, while Ms Jablonka points to the insufficiently realised savings potential of the individual measures anchored in the law. Both the health insurances (Mr. Fritz) and the doctor´s associations (Dr Herholz) and industry (Mr. Weppner) are extremely critical of the feasibility of the combination discount. Against this background, Dr Kippels attests to the need for further adjustments, which the Parliamentary Health Committee in Berlin must address.

- **Numerous options for further development of the AMNOG:** Numerous potential configurations of the AMNOG are explored in the articles. Examples include pay for performance approaches, the consideration of cost-benefit analyses, consideration of special therapeutic directions and therapeutic soloists or the flexibilisation of contract models. The basic principle of the AMNOG – the orientation of pricing towards additional benefits for patients – is supported by all speakers.

The health insurers have also brought cost-based pricing into the conversation. This is not supported in the article of Professor Greiner et al., although they do touch upon the confidentiality of reimbursement prices. The article authored by the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband, Dr Haas et al.) provides a detailed examination of both the therapeutic potential

and the challenges of evidence generation and pricing of gene therapies and presents the proposed solution of the „collective cohort model".

Dear readers, due to the focus on „efficiency", this publication has a much more economic perspective than previous issues of the Platform on Benefit Assessment. Nonetheless, in line with the platform's orientation and focus, it remains crucial to ensure both an optimal supply of pharmaceuticals and the long-term sustenance of research, innovation, and economic inventive capacity, despite the prevailing economic conditions.

Dr Kippels explicitly refers to the synergy potential of efficiency and innovation. In his opening speech at the conference and in the transcript in this publication, Professor Greiner commented on the need to keep an eye on the long-term effects of current regulations on innovative strength.

The reply to Arne Manzeschke's paradox quoted at the start of the conference would be this: Economic constraints can also be the starting point for further legal developments in the pharmaceutical sector, but the „guidelines" for orchestrating change should not be the devaluation of a small or unquantifiable additional benefit. Rather, they should prioritise:

i) the efficient provision of necessary and appropriate pharmaceuticals to the population; and

ii) the long-term focus on maintaining the research and innovation capabilities. Enjoy reading the exciting articles of this publication.

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AMNOG 2.0 – on the path to an efficient system? Main topics of discussion with the speakers

Dr Martin Danner | Federal Managing Director of BAG SELBSTHILFE

The basic idea of the AMNOG was to require study-based proof of additional benefit compared to the previous therapeutic standard when pricing new pharmaceuticals. This has undoubtedly brought a new rationality to the utilisation of the resources of the statutory health insurance system and has also enhanced the transparency of healthcare provision.

With the newly implemented „price-range regulation" for the AMNOG, more stringent criteria have been established, ensuring that only substantial innovations are rewarded with price adjustments. Conversely, modern pharmaceutical research is yielding highly targeted therapeutic options, the efficacy of which may only be substantiated by a limited body of evidence. The result is a struggle among experts for new study formats and for data generation after approval.

If both points are taken together, then from the patient's point of view the anxious question arises as to whether the focus on patient benefit, which once characterised the AMNOG, is slowly being lost sight of: Even a slight improvement can yield significant benefits for patients, particularly when it comes to pharmaceuticals relied upon by a large number of individuals. These incremental enhancements can often result in substantial positive outcomes. On the other hand, the question arises as to how patient benefit can be rationally defined, especially when pharmaceuticals are approved based on single-arm studies claiming a one-time cure at exorbitant costs. What overarching framework for assessing benefits can effectively integrate these diverse factors?

Dr Martin Danner *is a lawyer and the national managing director of the Federal Association of Self-Help for People with Disabilities and Chronic Illnesses and their Relatives (BAG SELBSTHILFE). After his studies in Heidelberg, he worked as a lawyer for several years specialising in health law before taking over as head of the health policy and self-help promotion department of BAG SELBSTHILFE. He is the spokesman for patient representation at the G-BA and, among other things, participates in the Scientific Advisory Board of the Medical Centre for Quality in Medicine (AZQ) and in the IQWiG Board of Trustees.*

This in turn gives rise to the following questions for the experts:

a) What potential for further development is there with regard to the determination of additional benefit?

- *The AMNOG once started with the idea of an „early" benefit assessment, i.e. an evaluation shortly after market entry, which is generally based on the data from the respective approval study. Won't we need continuous monitoring of the potential, but of course also of the risks of pharmaceuticals in future?*

- *The instrument of post-marketing data collection has already been introduced for this purpose, but pay-for-performance could also become an increasingly viable option in the course of the digitisation of healthcare provision.*

b) Could smaller incremental advancements, rather than adhering strictly to the „all-or-nothing" approach of the AMNOG additional benefit schemes, also warrant appropriate recognition and reward?

- *Patient organisations have consistently complained that enhancements in dosage forms and device improvements are disregarded within the AMNOG framework. Now, even minor additional benefits may no longer suffice to initiate price negotiations. However, the pertinent question remains: Can these factors truly be deemed irrelevant for the provision of care?*

c) Up to this point, the AMNOG has primarily followed a path focused on preparing price negotiations based on evidence of benefit. However, it's apparent that the new „price-range regulation" of the AMNOG aim to alleviate cost pressures on the system. Wouldn't it be more pragmatic to implement pricing based on cost-benefit assessments?

- *Nonetheless, this approach would necessitate clarification on the decisive rationale when determining whether to consider solely the costs of the statutory health insurance system, the costs of all social security systems, or even adopt an economic perspective. On the contrary, if a general metric like the gain in quality-adjusted life years were to be employed, it would signify a resurgence of the QUALY discussions that marked the inception of the AMNOG.*

Efficiency and efficiency potential of future AMNOG regulation

Professor Wolfgang Greiner, University of Bielefeld | Dr Daniel Gensorowsky and Dr Julian Witte, Vandage GmbH, Bielefeld

The introduction of the AMNOG over ten years ago was associated with considerable efficiency gains with regard to price negotiations based on the proven additional benefit of new pharmaceuticals. These effects relate in particular to allocative efficiency. Long-term effects of regulation, e.g. on innovative strength and willingness to invest, are less well known and more difficult to assess. In future, further development of pay-for-performance approaches and inclusion of cost-benefit analyses as well as the confidentiality of negotiated prices could increase the efficiency of the AMNOG procedure. Based on current knowledge, however, no improvements in efficiency are to be expected from cost-based approaches to pricing.

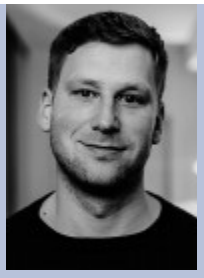
1 Background

Since 2011, a fundamentally changed evaluation and pricing of pharmaceuticals has been in force in Germany, which has become known as the AMNOG procedure (German Pharmaceutical Market Reorganisation Act (AMNOG). One of the main purposes of the AMNOG at the time was to reduce the price level of new pharmaceuticals coming onto the market, which was perceived as excessive.[1] At the time, manufacturers were able to set prices relatively freely. This is not an efficient solution in the specific case of pharmaceuticals, as these can be considered monopoly goods in individual cases and with existing patent protection and are also generally paid for in full by health insurances, except for minor co-payments by the insured. In this constellation, excessive prices are to be expected as compared to a theoretical equilibrium price (i.e. assuming equal market power on the supply and demand side).

The AMNOG procedure counters this inefficient market situation with a negotiated price based on evidence of efficacy. Here, too, a number of inefficiencies can occur, e.g. if the new pharmaceutical is a highly effective solitary product, i.e. a product that can hardly be withheld from the patient group concerned for ethical reasons due to the lack of effective treatment alternatives. This strengthens the manufacturer's negotiating position, as they always have the option of withdrawing the product from the German market if the manufacturer's price expectations are not met. Although this would lead to a loss of sales for the pharmaceutical company, leaving the market can still be rational from the manufacturer's point of view, as German prices serve as a basis for pricing in other countries as part of international price referencing. A relatively low price in Germany would thus also have an impact on the manufacturer's sales in other international markets.

Over the years, the AMNOG procedure has been repeatedly adapted in the sense of a „learning system", most recently in 2022 with the Financial Stabilisation of Statutory Health Insurance (GKV-Finanzstabilisierungsgesetz, GKV-FinStG), which included a series of measures to limit the prices of new pharmaceuticals. This is nothing unusual in principle: As markets and production processes change (e.g. towards personalised therapies), regulation must also adapt from time to time. However, a far-reaching change to the legal basis should always be accompanied by an evaluation of this reform, which compares the effect with the short and long-term objectives pursued with the reforms at an appropriate time interval and as independently as possible. An evaluation is also provided for in the GKV-FinStG, although an assessment of efficiency-enhancing or potentially negative consequences is not yet possible in a meaningful way just one year after the law was passed.

In the following, some fundamental considerations will be made on the question of efficiency and efficiency potential of the AMNOG regulations and reform options. To this end, the concept of efficiency will first be examined,



Professor Wolfgang Greiner *holds the Chair of Health Economics and Health Management at University of Bielefeld. From 2010 to 2023, he was a member of the Expert Council for the Assessment of Developments in the Healthcare System at the Federal Ministry of Health. He is also a member of the scientific advisory boards of various health insurance companies and the Federal Social Security Office for the further development of risk structure equalisation.*

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Dr Julian Witte *is the founder and managing director of Vandage GmbH, a boutique consultancy specialising in the generation of real-world evidence, health economic evaluation, pharmacoeconomics and statistics. He was previously a research assistant at the Chair of Health Economics and Health Management at Bielefeld University and wrote his doctoral thesis on the pricing of new pharmaceuticals. Dr Witte is co-author of the regularly published AMNOG Report of DAK-Gesundheit.*

approaches to its measurement explained and starting points for improving efficiency discussed.

2. The concept of efficiency

In economics, a fundamental distinction is made between technical and allocative efficiency.[2] Dynamic efficiency is also used in economic analyses. Technical efficiency is an expression of the economic principle, which addresses how, ideally, a given output level can be achieved at minimal costs. This can, for example, refer to the AMNOG procedure itself, i.e. the question of whether the (externally specified) number of new products to be assessed can be finalised in the specified time with a given quality of assessment and evaluation with minimal effort (e.g. in terms of human resources for expert opinions, time spent on meetings, etc.).

The question could also be raised as to whether the AMNOG procedure itself contributes to the technical efficiency of production, such as the discount agreements for generics, which have largely led to less efficient suppliers with comparatively expensive production having to leave the market. This example is also a good illustration of the principle of dynamic efficiency. Market restructuring, as in the case of generics manufacturers with extensive relocation of production to non-European countries, is not necessarily efficient in the long term if this results in supply difficulties or even political dependencies. It is therefore necessary to weigh up and harmonise different objectives.

Allocative efficiency is aimed at the question of whether supply corresponds to the preferences of demand or, in technical terms, whether the marginal costs of production correspond to the marginal benefits of demand. An important objective of the AMNOG reform at the time was to ensure that so-called me-toos, i.e. new pharmaceuticals coming onto the market without any demonstrable additional benefit (compared to the products already on the respective submarket), do not receive a higher price than the existing (possibly even generic) pharmaceutical alternatives.

The AMNOG procedure has fully met these expectations of separating the „wheat from the chaff" and in this respect has increased allocative efficiency, i.e. the harmonisation of the marginal costs of the pharmaceutical and its marginal benefit for patients. As a positive side effect, the discussions on data and decision transparency as well as the applied methods of evidence-based medicine have made far-reaching progress in Germany.

3. Measurement of efficiency depending on the objectives

It has already become clear from the above that there are various measures of efficiency that depend on the objectives of the decision-makers. In the pharmaceutical market, this could include promoting and rewarding innovations in the healthcare system with proven additional benefits to provide further incentives for innovation and research (dynamic efficiency). The new regulation introduced in 2022 with so-called „guidelines", according to which a minor additional benefit compared to an appropriate comparative therapy that is still under patent does not justify a price premium, can therefore be viewed critically insofar as incremental innovations are also recognised as having a value in healthcare.[3]

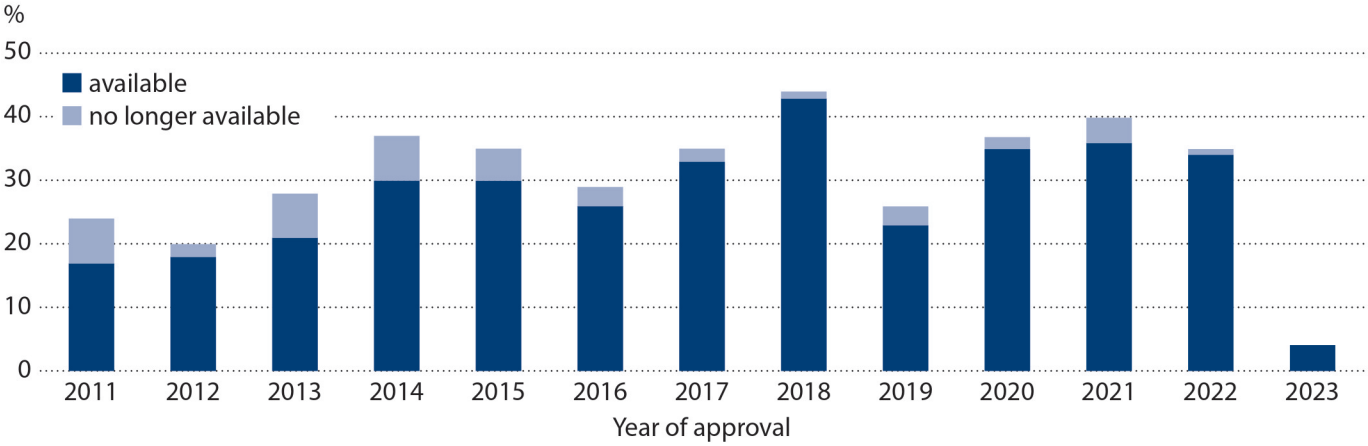
Another major aim of the AMNOG procedure from the outset was to make decisions more evidence-based, i.e. a form of scientification of the procedure. However, the recognisable trends in recent years towards earlier approval, less reliable evidence and increasingly available single-use therapies, whose long-term efficacy is naturally highly uncertain, require a readjustment of the previous evaluation

and pricing practice. This is because the current AMNOG procedure is not well prepared for these cases of high uncertainty regarding the efficacy of the products.

In these specific areas, pay-for-performance approaches could be a way of meeting the associated special challenges, although this in turn raises questions of feasibility in terms of technical efficiency.[4] Corresponding service contracts would have to be concluded at a collective level, where they could also be processed administratively. So far, a lack of data availability or overly ambitious definitions of results have often stood in the way of this. Particularly in case of long-term contracts, adjustments would also need to be made to the risk structure equalisation between health insurances so that payments can be considered for more than just one year. The Federal Social Security Office (BAS) has already made proposals to this effect and should be implemented legislatively to improve the conditions for greater use of pay-for-performance contracts.[5]

Another important goal for an efficient system of early benefit assessment and pricing is the early availability of effective, innovative pharmaceuticals. The market exit of newly approved pharmaceuticals could be used as a measure of availability, as shown in figure 1. Accordingly, 44 (11.2%) of the 394 EMA-approved AMNOG pharmaceuticals were no longer available in October 2023. However, this figure is largely useless for assessing efficiency, as there are very different reasons for the market withdrawals (e.g. also market displacement by new, further improved innovations) and it does not reflect the relevance of supply, so it is not clear to what extent a market withdrawal of individual products cannot be at least partially substituted by others. Solitary products without an equally effective alternative are therefore associated with a greater loss of benefit for patients than more interchangeable products.

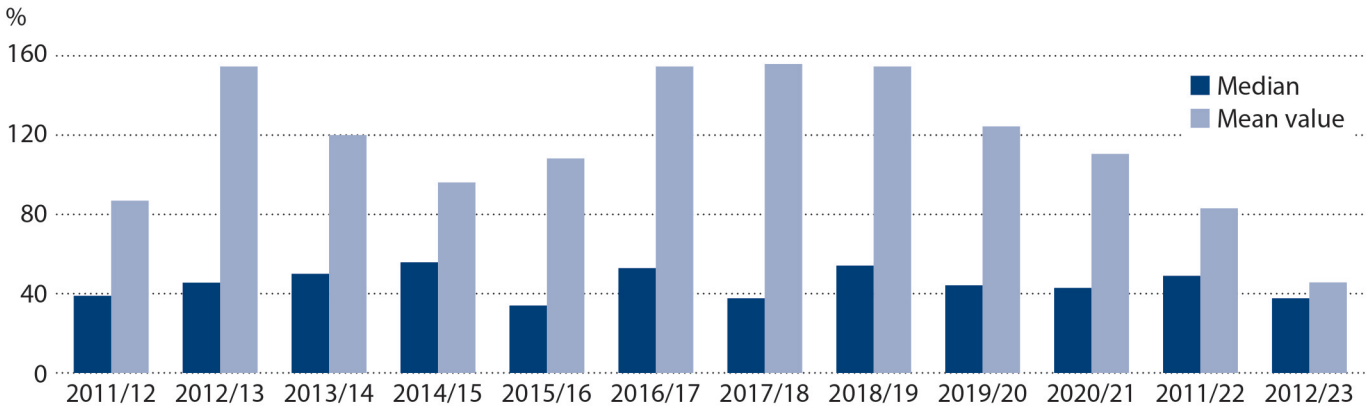
Availability of EMA-approved AMNOG pharmaceuticals in October 2023



Source: Own calculations

Figure 1: Of the 394 AMNOG pharmaceuticals approved by the EMA in October 2023, 44 – corresponding to 11.2% – were no longer available.

Time-to-market of potential AMNOG relevant EMA approvals (excl. hybrid pharmaceuticals and duplicates) from January 2011 until end of June 2023



*Median/mean time-to-market of all approvals from July of one year to June of the following year. Period: 1 June 2011 to 30 June 2023

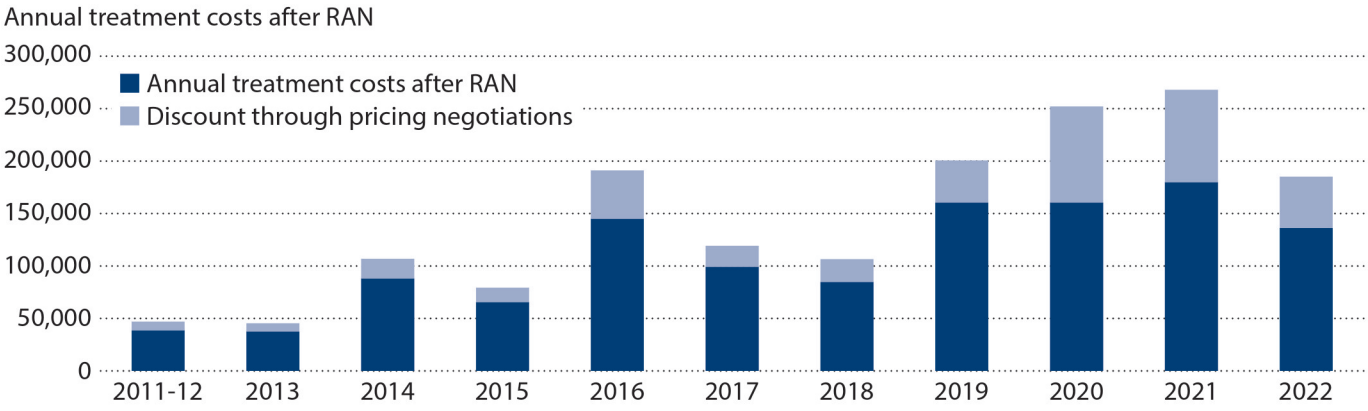
Source: Own calculations

Figure 2: The time span from the authorisation of a pharmaceutical to its market launch has remained constant at 40 to 50 days for years.

The time-to-market indicator, i.e. the period from the approval of a pharmaceutical to its market launch, presents a different picture. According to figure 2, the median remains fairly constant over the years, at around 40 to 50 days. This is a comparatively short period of time that only a few countries in the world achieve. Although this figure varies considerably, as can be seen from the median time-to-market of 119 days for EMA-approved AMNOG pharmaceuticals, overall it can be said that the median time-to-market is noticeably short. Free pricing by the manufacturer in the first six months certainly contributed to this. In contrast, the reduction in this period from twelve to six months in the course of the GKV-FinStG may also have contributed to allocative efficiency (in this case to avoid excessive prices). This situation clearly shows that even universally accepted objectives (in this case, early availability on the one hand and the rapid application of lower negotiation circles on the other) are often in competition with each other.

Finally, an overarching objective of the introduction of the AMNOG in 2011 was that the new government should also contribute to financial stability in the health insurance system. Figure 3 which shows the annual therapy costs of newly approved pharmaceuticals before and after reimbursement negotiations, shows that this objective has been achieved, at least in principle. This shows substantial savings effects, which, however, do not yet allow any conclusions to be drawn about external targets such as economic productivity and the effects of regulation on investments and the location of studies in Germany.

Average annual treatment costs of newly approved pharmaceuticals before and after reimbursement amount negotiations by years (2011-2022)



Source: Own calculations

Figure 3: The comparison of the annual treatment costs of newly approved pharmaceuticals before and after reimbursement amount negotiations clearly shows the savings effects as a result of the AMNOG procedure.

A comprehensive evaluation would also have to assess the external effects of the AMNOG procedure on these parameters to be able to comprehensively assess the efficiency of the procedure. However, this would require far-reaching assumptions to be made, which could make the evaluation results open to challenge. Nevertheless, such estimates would be very valuable for an overall assessment of reform measures and could, e.g. be carried out in scenarios with full disclosure of the assumptions used and the uncertainty associated with them.

4. Efficiency potential

In the previous section, it was already mentioned that changes in the market environment may necessitate readjustments to existing regulations to maintain the efficiency of the procedure. This applies, e.g. to a greater emphasis on pay-for-performance contracts in the pricing of some new pharmaceuticals to take account of the greater uncertainty in evidence generation. Data on efficacy could then be collected and used for pricing rather than only on a historical basis, as is currently the case.

Cost-based approaches to determining an appropriate price for innovative pharmaceuticals, on the other hand, are generally not very efficient because the necessary allocation of overheads to individual products poses problems that are difficult to solve for pharmaceutical companies.[6] For example, how should the costs of a company's failed research projects be correctly allocated to its successful products?

Simple lump sums to account for research expenses and profit are methodologically unsuitable because they can hardly adequately reflect the individual operational and project-related situation. Furthermore, cost-based pricing approaches also contradict the goal of technical efficiency,

as they offer no incentive for resource-conserving research if all costs incurred, regardless of patient benefit, could subsequently be allocated to the price.

An efficiency-enhancing alternative to the further development of the AMNOG would be to include optional cost-benefit analyses in the evaluation process.[7] Cost-benefit analyses are already common practice in the evaluation of new vaccines by the Robert Koch Institute (RKI) and its Standing Committee on Vaccination (STIKO). And in neighbouring countries such as France, the Netherlands and Denmark, none of the consequences feared in Germany, such as discrimination in the care of vulnerable groups, have yet materialised.

This was not to be expected, as the systematic comparison of costs and benefits as part of the evaluation procedure creates a better basis for rational decisions and can very transparently depict socially indispensable ancillary conditions such as the special promotion of therapies for rare diseases. The data and models required for this are already available, if only because all major European countries have been using cost-benefit analyses for years to supplement pricing. The basic structure of these would usually be relatively easy to adapt to Germany.

The high level of transparency in the negotiating circles for new pharmaceuticals is also a specific feature of the German healthcare system that no other comparable country has. Although total price transparency is an important prerequisite for optimal and therefore efficient allocation in perfect markets, the pharmaceutical patent market is not a perfect market by its very nature but is deliberately characterised by a monopoly that is limited in time for the duration of the patent. This applies at least if no other competing products with similar or even greater efficacy enter the market. In addition, confidential prices could be quite efficient from a microeconomic point of view, e.g. from the perspective of statutory health insurance (but also from that of pharmaceutical companies). Particularly in view of international price referencing, lower price offers on the part of manufacturers can be expected if they no longer have to fear that their offers will subsequently be used in another country as a starting point for negotiations at even lower prices.

This is precisely why the confidentiality of negotiated pharmaceutical prices is the rule internationally, whereas German transparency is the exception. The arguments put forward against confidentiality are of a more technical nature, e.g. more difficult settlement via the trade levels, which, however, occur in a similar way in the case of discount agreements for generics and obviously do not represent an unsolvable problem.[8]

5. Conclusions

The introduction of the AMNOG over ten years ago was a leap in efficiency from a world of monopoly-like prices to a rule- and evidence-based system that seeks a balance between the manufacturer's profit interests and the healthcare system's interests in medical progress and the affordability of the system. Overall, it has met the requirements in terms of efficiency and fairness, whereby the long-term effects of regulation (e.g. on innovative strength and willingness to invest) should also be considered in addition to static efficiency (e.g. from current savings successes). Regulation may need to be refined over time if evasive reactions by market participants become apparent or the market environment changes. However, such regulatory changes can also potentially lead to considerable transaction costs in the implementation process levelling out the intended efficiency advantage.3 This should be thoroughly evaluated following reforms. In future, the further development of pay-for-performance approaches and the inclusion of

cost-benefit analyses as well as the confidentiality of negotiated prices could increase the efficiency of the AMNOG procedure. Based on current knowledge, however, no improvements in efficiency are to be expected from cost-based approaches to pricing of pharmaceuticals.

References

[1] Ludwig WD (2020): Zehn Jahre AMNOG – Rückblick und Ausblick aus Sicht der Arzneimittelkommission der deutschen Ärzteschaft. (Ten years of AMNOG – review and outlook from the perspective of the Drug Commission of the German medical profession) Schwabe U, Ludwig WD (ed.) Pharmaceutical Prescription Report 2020: 185-200.

[2] Störmann W (2019): Gesundheits- und Umweltökonomik klipp & klar. Springer Gabler.

[3] Greiner W, Witte J, Gensorowsky D, Diekmannshemke J (2023): AMNOG-Kurzreport 2023 – Evaluation von Maßnahmen aus dem GKV-Finanzstabilisierungsgesetz – Status quo. (AMNOG Short Report 2023 - Evaluation of measures from the Financial Stabilisation of the Statutory Health Insurance (GKV-FinStG) – Status quo.). Contributions to health economics and healthcare research (Volume 45), medhochzwei-Verlag

[4] Dabbous M, Chachoua L, Caban A, Toumi M (2020): Managed Entry Agreements: Policy Analysis from the European Perspective. Value in Health 23(4): 425-433.

[5] Federal Social Security Office (2022), Sondergutachten zu den Wirkungen von Pay-for-Performance-Verträgen vor dem Hintergrund des Risikopools. (Special report on the effects of pay-for-performance contracts against the background of the risk pool.). Available at https://go.sn.pub/Mve5cM

[6] Hollis A (2016): Sustainable Financing of Innovative Therapies – A Review of Approaches. PharmacoEconomics 34:971-980.

[7] Ochalek J, Revill P, Drummond M (2020): Allocating Scarce Resources - Tools for Priority Setting. Revill P, Suhrcke M, Moreno-Serra R, Sculpher M (ed.): Global Health Economics Shaping Health Policy in Low-and Middle-Income Countries: 53-74.

[8] Bauckmann J, Laitenberger U, Schröder M, Telschow C (2017): Rabattverträge. (Discount agreements) Schwabe U, Paffrath D, Ludwig WD, Klauber J (ed.) Pharmaceutical Prescription Report 2017: 181-194.

AMNOG 2.0 – on the path to an efficient system? Perspective of DAK-Gesundheit

Marcel Fritz, LL.M., MBA | Division Manager Pharmaceuticals | DAK-Gesundheit

The statutory health insurance system is facing enormous challenges. On the one hand, the negative contribution margin between contribution income and benefit expenditure has increased from 11.7 to 16.9% between 2015 and 2022. The majority of this funding gap will be covered by contributors and the pharmaceutical companies through additional contributions, even before the regular federal subsidy.[1] Secondly, the increasing age ratio in the population will lead to higher benefit expenditures per insured person, particularly in the short term due to the advancing age of the so-called baby boomer generation.[2] This will result in rising non-wage labour costs. It is the duty of the health insurances as payers to point out efficiencies in the system that need to be realised to continue providing high-quality care through the solidarity-based statutory health insurance system.

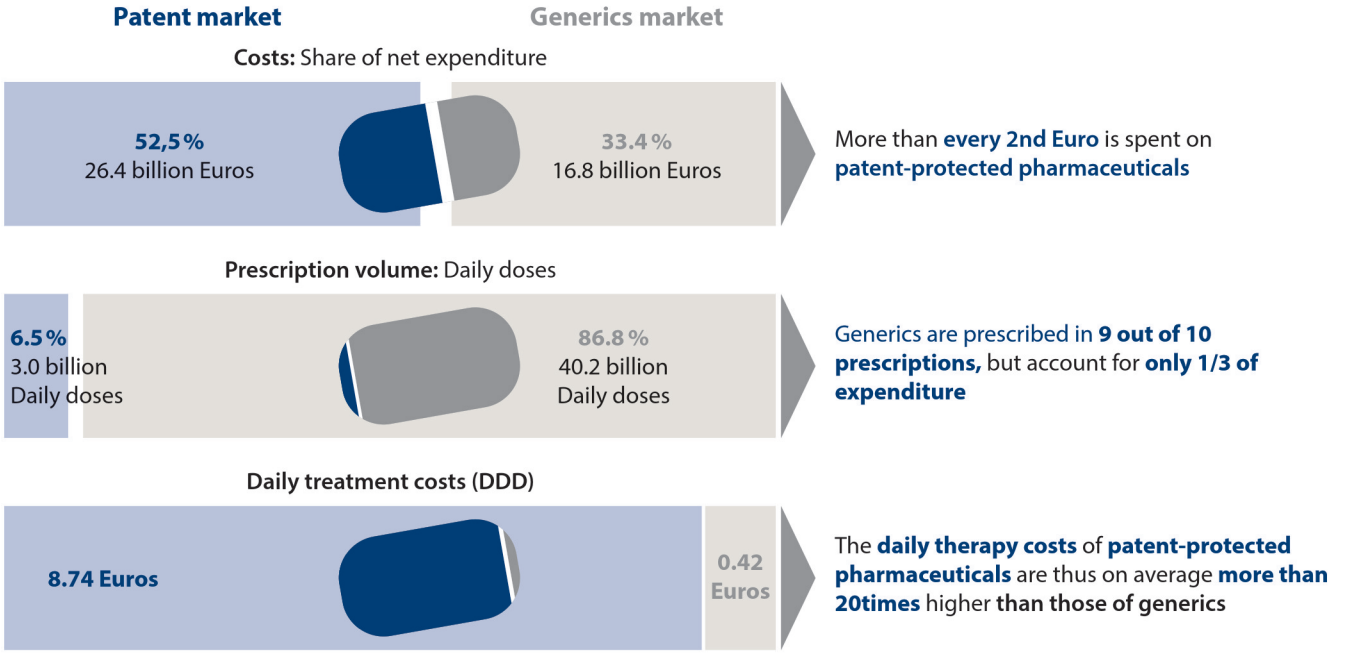
The cost development of pharmaceutical care

Despite all the gloomy predictions, the statutory health insurance system spends a lot of money on high-quality pharmaceutical care. More than one in six euros had to be paid by the health insurance funds for this in 2022. While total expenditure on benefits rose from 226.22 billion euros in 2018 to 274.23 billion euros in 2022 (+17.5%), expenditure on pharmaceuticals even increased by 26.3% in the same period.[3] Since 2019, health insurances have had to provide more funds for the provision of pharmaceuticals to their policyholders than for outpatient medical care as a whole. Pharmaceuticals have thus become the second largest area of expenditure in the statutory health insurance system after the costs of inpatient care.[4] In 2022, at 52.9 billion euros, expenditure exceeded the 50 billion euro mark for the first time and since then has been the undisputed leader in the statistics for percentage increases in expenditure within the largest statutory health insurance expenditure blocks.[5,6] These figures do not take into account the additional 1.2 billion euros that were invoiced separately to the statutory health insurance system by hospitals for AMNOG pharmaceuticals.[7]

I. Not all pharmaceuticals are expenditure drivers

Although almost 9 out of 10 prescriptions are for generics, 52.8% of net pharmaceutical expenditure is for patent-protected pharmaceuticals.[8] The daily treatment costs of patent-protected pharmaceuticals are therefore 20 times higher than those of generics.[9] In a different but equally accurate way, it can be said that the statutory health insurance system has to pay more than 50% of the pharmaceutical costs for approx. 6.5% of the pharmaceutical supply![10] The dynamics of the exorbitant increases in expenditure on the

Cost distribution in the patent and generics market



Source: Arzneimittel-Kompass 2022 (Medicines Compass 2022); presentation: DAK-Gesundheit

Figure 1: Almost 53% of net expenditure for pharmaceuticals is for patent-protected pharmaceuticals. The daily therapy costs in this segment are 20 times higher than in the generics market.

Marcel Fritz *is Head of the Pharmaceuticals Division at DAK-Gesundheit. As a lawyer with a master's degree in pharmaceutical law as well as in healthcare management, he coordinates the specialist areas of pharmaceutical management, discount agreements and pharmaceutical supply at Germany's third-largest health insurer. Mr Fritz is also involved in the reimbursement negotiations between GKV-Spitzenverband and pharmaceutical companies.*

patent-protected pharmaceutical market also clearly show that the expenditure value will not currently develop in favour of generics (see below).

II. From the willingness to pay to the ability of the statutory health insurance system to pay

The fact that patent-protected pharmaceuticals are more expensive than generic active ingredients is neither unusual nor a new finding. However, the question that must be asked is whether the insured will also receive better care for the sharp annual price increases described above, or whether they will continue to be prepared to pay rising contribution rates because, unlike in other EU countries, the enormous efficiencies in this area are not being realised in Germany. In times of increasingly scarce resources, a system cannot afford to pay higher prices for services without a clearly defined added value. But this is currently the case. Since 2011, no additional benefit has been proven for almost every second pharmaceutical that has been launched on the German market.[11]

If pharmaceuticals that only have a non-quantifiable additional benefit are added to this figure, the percentage value of new pharmaceuticals that have been launched on the market with a proven additional benefit is even lower.[12] What is even more worrying for the insured persons as patients is that a large proportion of extremely high-priced pharmaceuticals (orphan drugs) can enter the market so quickly due to political will that neither sufficient clinical studies regarding their efficacy nor their safety (!) have to be available; there is no need for an additional benefit.[13] Nevertheless, in Germany pharmaceuticals for rare diseases automatically receive the coveted additional benefit label to incentivise manufacturers to develop such urgent pharmaceuticals. The political decision-makers have thus conducted a blanket risk-benefit assessment of these often poorly researched pharmaceuticals by legal act, even for the patients concerned.

In any case, it should be noted that the market entry prices for new pharmaceuticals to be paid by manufacturers and the statutory health insurance system have also risen by 430% since 2011.[14]

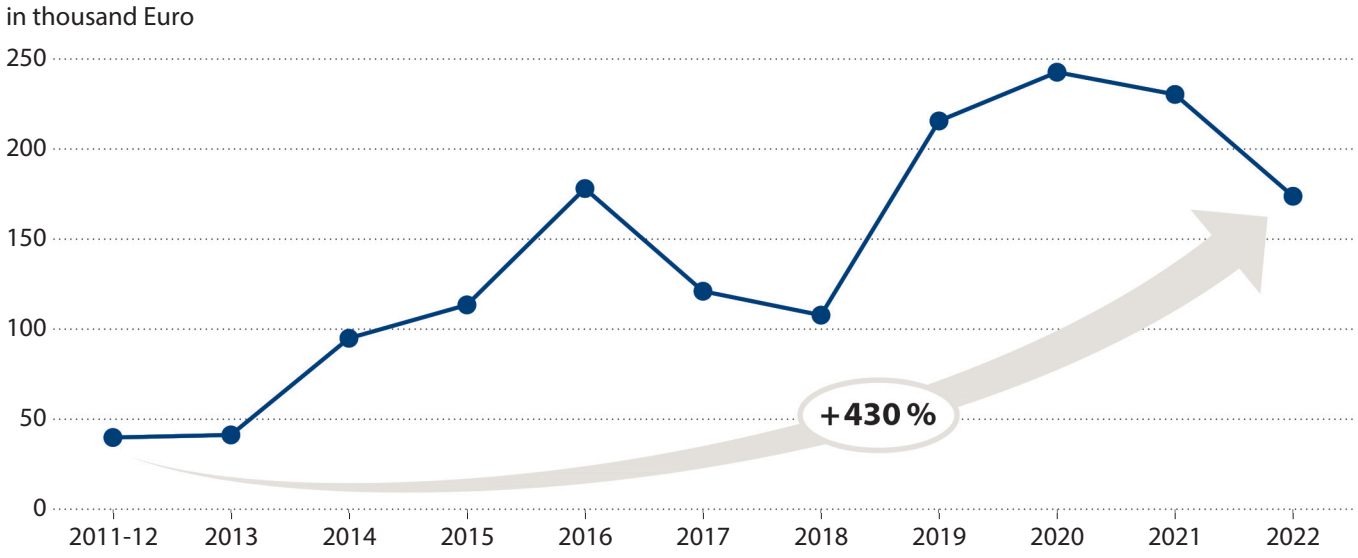
One consequence of all this is that „new" pharmaceuticals in Germany should not automatically be equated with „innovative" pharmaceuticals. Secondly, a balance between innovation and affordability has still not been achieved, even more than ten years after the introduction of the AMNOG.[15]

III. Measures to increase efficiency based on benefit and evidence

The information described under II. can be substantiated by the fact that in 2009, the reference year used to justify the AMNOG, pharmaceutical expenditure rose by 5.3%. At that time, the legislator rightly recognised an acute need for action and set benefit-oriented limits to the free pricing of private manufacturers with the aim of limiting pharmaceutical expenditure for pharmaceuticals without proven additional benefits.[16] Unfortunately, it must be noted that this goal was largely missed.

Between 2019 and 2022 alone, expenditure averaged 5.7% and thus exceeded the expenditure limit that prompted the legislator to pass the Pharmaceutical Market Reorganisation Act (AMNOG).[17] In addition, the AMNOG's efficiency increases to date should also be viewed with a certain degree of caution, as these figures are the result of strategic and ultimately arbitrary market entry prices set by the pharmaceutical industry and are therefore largely due to an initial situation that cannot be influenced.

Development of market entry prices for new pharmaceuticals since 2011



Source: G-BA; presentation: DAK-Gesundheit

Figure 2: The market entry prices to be paid by statutory health insurance system for new pharmaceuticals have risen by 430% since 2011.

IV. Efficiency gains through the GKV-FinStG

The fact that the AMNOG raises fewer efficiency reserves than assumed and hoped for was already criticised by the current Federal Minister of Health in the AMNOG Report 2020.[18] In the AMNOG Report 2022, authors from various areas of the healthcare system also highlighted proposed changes, in particular for the generation of evidence for new therapies or combination therapies for which the AMNOG system is inefficient.[19]

With the introduction of the GKV-FinStG at the end of 2022, some of these proposals were also found in an attenuated form. The legislator must be given credit for recognising the need to adapt the system and taking initial measures. Three specific disadvantages can be highlighted.

Firstly, the measures are not effective enough, e.g. to generate so-called price „blockbusters" from orphan drugs and to prevent exorbitant prices being charged for these pharmaceuticals, despite the aforementioned uncertainties regarding safety and efficacy. Since quite a few of these products are so-called single-use therapies, neither a sales threshold until the benefit assessment nor evidence generation in the future is of any use; free pricing is also counter-productive, regardless of its duration, and a main reason for false incentives in the direction of manufacturers.[20]

The general retroactive effect of the reimbursement amount for all new pharmaceuticals from the seventh month onwards may lead to increased reimbursements to

Expected savings potential of the tools in the GKV-Finanzstabilisierungsgesetz

	Implementation open?	Collateral effects	Annual savings		
			FinStG	AMNOGR 03/23	AMNOGR 09/23
Retroactive effect reimbursement amount	No	Unlikely	150 million Euros	Approx. 80 million Euros	Probably lower
Orphan sales threshold	No	Possible	100 million Euros	Up to 50 million Euros	Threshold not yet exceeded
Flat-rate combination discount	So far unresolved	Possible	185 million Euros	Not reliably calculable	Not yet implemented
Guidelines for reimbursement amounts	Rather yes	Possible	250–300 million Euros	Probably higher	Not yet reliably calculable
5 per cent increase in the general manufacturer discount	No	Possible	Approx. 1 billion Euros	Not quantified	Approx. 1.2 billion Euros

Source: AMNOG Short Report 2023

Figure 3: Savings as a result of the GKV-FinStG have so far fallen short of the legislator's expectations. Savings have been achieved in particular through the increased manufacturer discount.

the health insurances (but also to the manufacturers). Equally important, however, would be the retroactive effect to the market entry date as well as an interim price in order to avoid a period in which a pharmaceutical without proven additional benefit has to be subsidised by the statutory health insurance system, the market entry price has less of an anchoring effect in price negotiations and the price spiral can be weakened by orientation towards the appropriate comparative therapy (see Sabine Jablonka's article). On the other hand, the implementation of the combination discount in practice threatens to push the health insurances to the limits of their bureaucratic capacity. At the end of 2023, it is still not clear how billing shall be performed. Even if this framework is adopted by the Federal Ministry of Health, after the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) was predictably unable to reach an agreement with the stakeholders in the pharmaceutical industry beforehand, there is a threat of enormous obstacles to implementation on the part of the health insurances.[21]

Finally, the level of efficiencies does not appear to be developing in line with the legislator's calculations (figure 3). In 2023, the health insurances mainly benefited from the increase in the general manufacturer discount, a measure that was only introduced to make the transition easier for the health insurances until the levers from the GKV-FinStG take full effect. At the beginning of 2024, the increase in the general manufacturer discount will no longer apply, but most of the levers and measures from the GKV-FinStG, as described, will unfortunately still not have the desired effect,

if at all. To be able to meet the statutory health insurance system's enormous financial requirements in future, including the costs of new pharmaceuticals without proven or merely formally assumed additional benefits, it is not only its members with corresponding employers who should be held accountable. In addition, tougher frameworks are needed in which the benefit is one, but not the sole criterion for pricing. The current Federal Minister of Health also recognised this back in 2019 and made corresponding comments in the AMNOG Report 2020.

References

[1] Wasem J, 137th Workshop on pharmacotherapy counselling from 16 March 2023: Sind steigende Zusatzbeiträge der GKV-Versicherten unvermeidbar? (Are rising additional contributions by statutory health insured unavoidable?)

[2] Wasem J, op. cit.

[3] Federal Ministry of Health (BMG): Official statistics KJ1 for 2022.

[4] BMG, op. cit.

[5] WIdO, press release from 7 November 2023: Mehr Geld für weniger Versorgung. (More money for less care.)

[6] BMG: Official statistics KV 45, quarters I-IV 2022.

[7] AMNOG Report 2023, chapter 3, p. 59 ff.

[8] WIdO, op. cit.

[9] Arzneimittel-Kompass 2022 (Medicines Compass 2022), chapter 18, p. 219 ff.

[10] Arzneimittel-Kompass 2022 (Medicines Compass 2022), op. cit.

[11] G-BA: Evaluation procedures between 2011 and 2022.

[12] G- BA, op. cit.

[13] Ludwig WD in: AMNOG Report 2022, chapter 4, p. 85 ff.

[14] G- BA, op. cit.

[15] AMNOG Report 2022, chapter 3. section 3.4, p. 73 ff.

[16] BMG, explanatory memorandum of 21 December 201: AMNOG; Lauterbach K in: AMNOG-Report 2020, chapter 3, section 3.2.2, p. 68.

[17] BMG: Official statistics KJ 1 2019 to 2022.

[18] Lauterbach K in: AMNOG-Report 2020, chapter 3, section 3.2.3, p. 71.

[19] AMNOG Report 2022, chapter 3.

[20] Lauterbach K in: AMNOG-Report 2020, chapter 3, section 3.2.2, p. 71.

[21] Also see: AMNOG Report 2023, chapter 2, section 2.4 and AMNOG Short Report 2023, chapter 5, p. 16.

AMNOG 2.0 – on the path to an efficient system? The view of the AOK-BV

Sabine Jablonka | Head of the Pharmaceuticals Department in the Supply Division of the Federal Association of Local Health Insurance Funds (AOK-Bundesverband)

The AMNOG system has proven itself in terms of quality, but the problems of excessively high prices for new pharmaceuticals have not yet been solved. The Financial Stabilisation of Statutory Health Insurance (GKV-FinStG) has imposed regulations which, if fully implemented, could have the potential to improve cost containment. However, market entry has so far been wrongly omitted: In order to create internationally comparable framework conditions, an interim price should be introduced that applies to a new pharmaceutical from day one and is later replaced by the reimbursement amount. In addition, greater cost-effectiveness could be achieved in the patent market by establishing cross-active ingredient contract competition, but also through a more cost-based approach to reimbursement negotiations. The confidentiality of the reimbursement amount, on the other hand, is an aberration at the expense of the solidarity community.

1 GKV-FinStG: Necessary strengthening of the balance of interests

Since the AMNOG reform in 2010, the regulations on early benefit assessment in the Federal Joint Committee (GB-A) and the subsequent reimbursement negotiations have been modified almost every year. Designed as a „learning system", not only have gaps been closed, but regulations have also been reorganised several times. There is no doubt that the introduction of the AMNOG system has created more transparency through the qualitative assessment of new pharmaceuticals and has helped to ensure that new preparations can be used in a more targeted manner for patients. So far, however, it has not been possible to slow down the spending dynamics in this market segment in the long term, as Marcel Fritz's article shows.

Most recently, the GKV-FinStG, a major reform programme with numerous regulations, attempted to have a dampening effect on pharmaceutical prices, particularly in the patent market. However, one year after the law came into force, it can be seen that the regulations have so far fallen short of expectations in economic terms. Nevertheless, the savings have already been budgeted for, as this should also cover the additional expenditure that will be channelled into the generic pharmaceutical market with the German Act to Combat and Improve the Supply of Medicines (ALBVVG).

In addition to an overestimation of the economic effects, the inadequate impact of the GKV-FinStG is also due to the lack of consistency of the statutory regulations. These placed a great deal of trust in partnership-based agreements between the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and pharmaceutical manufacturers or their associations – a hope that proved to be too optimistic. As a result, not only has the settle-

ment of the planned combination discount been hindered, but differences of interpretation between the contracting parties have also led to arbitration decisions, e.g. in the price-quantity regulation or the so-called guidelines, which are now subject of complaints. And that's not all – several companies have now lodged constitutional complaints against the provisions of the law: Above all, the combination discount and the amended pricing regulations on the reimbursement amount are seen as interfering with the established rules of pharmaceutical reimbursement in a way that is contrary to the system.[1]

Are the statutory regulations also bad from the payers' point of view? No. Even if the expectations regarding the speed of implementation and the economic yield were higher, the GKV-FinStG continues the path of the AMNOG: Other gaps will be closed, e.g. through the introduction of the combination discount, discards, a more timely application of the reimbursement amount and the early inclusion of pharmaceuticals for rare diseases

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Above all, however, the new guidelines for reimbursement negotiations define a narrower negotiating corridor. This was urgently needed in a situation in which only one of the two contracting parties can refuse an agreement, but the other is under obligation to contract. This is because, unlike in most European countries, the German statutory health insurance system cannot prevent excessive reimbursement amounts on its own. Even the arbitration board that may be called upon operates within the statutory negotiation framework, which means that decisions can be very different, especially if there is a wide scope for negotiation. In this respect, there is currently justified hope among payers that the desired limitation of price increases will take effect following further clarification and that the expected savings can therefore at least be realised to some extent.

Despite these important and generally correct steps, there is still a need for further action: It is not clear, e.g. that the quantities of pharmaceuticals to be regularly discarded are only taken into account above a de minimis limit when determining the reimbursement amount and, moreover, that this offsetting does not take place according to an algorithm, but rather depending on the negotiating skills of the respective contractual parties. Such a regulation is neither compatible with our social demands for environmental protection and resource conservation, nor is it sustainable.

Elaborately produced goods that are subsequently disposed of must indeed be the special exception. In future, there is a need for significantly stronger incentives for the development of customised pack sizes and research into the longest possible shelf life of stock solutions and products. This can be achieved by imposing the corresponding costs entirely on pharmaceutical companies without negotiation. This measure should not only apply to the patented pharmaceutical market.

The same should also apply to the combination discount, so that the proportion of combination uses of a new pharmaceutical would have to be taken into account mathematically in the determination of the reimbursement amount. Such an implementation would be realised with less bureaucracy and considerably fewer transactions than the intended bilateral settlement between pharmaceutical manufacturers and each individual health insurance.

The regulation according to which pharmaceuticals for rare diseases continue to enjoy a special status that ascribes them an additional benefit by law – up to a now lowered turnover limit – regardless of the available evidence, should also be reconsidered. It would be a step towards greater transparency and a reduction in bureaucracy to remove this special status altogether. However, such protection zones are not absolutely necessary, as previous analyses have shown: studies of appropriate quality are not generally excluded for these pharmaceuticals either.[2,3] On the contrary, the special status creates the false incentive that sound evidence is not necessarily required for these pharmaceuticals.

According to the 2021 IQWiG analysis, the determination of a fictitious additional benefit was misleading in more than half of the cases and was not confirmed in the regular benefit assessment. According to the conclusion, the resulting distorted picture of a new orphan drug not only leads to misleading communication, but also penalises existing treatment options that are placed in a worse position by the fictitious additional benefit of the new pharmaceutical. After all, all patients, including those with a rare condition, are entitled to the highest possible quality of evidence and transparency. Last but not least, the regulation creates unnecessary administrative work by controlling sales in the outpatient and inpatient sector and risks proceedings in quick succession if the sales threshold is reached shortly after market access.

The GKV-FinStG at least partially fulfils the GKV's long-standing demand for retroactive effect of the reimbursement amount, in that the negotiated reimbursement amount does not only apply after one year, but already from the seventh month after market entry or expansion of the approval. This means that the price demanded by the pharmaceutical company must still be taken into account in the first six months. Although the sums realised here are not usually significant, the pharmaceutical enters the reimbursement negotiations with the freely chosen price, which effectively acts as a price anchor.

Together with other parameters such as the prices of comparable pharmaceuticals and those for the new pharmaceutical in other European countries, this leads to an excessive increase in indication-specific price levels. This is because even if pharmaceuticals can be purchased more cheaply abroad by the payers there, these prices are usually confidential and therefore not available for negotiations on the reimbursement amount in Germany. Politically intended otherwise, the majority of price-driving factors have so far been included in reimbursement negotiations for pharmaceuticals with certified additional benefits.

II. Maximum prices for pharmaceuticals: whether you deserve what you earn...

The question of what prices are appropriate for a new pharmaceutical largely depends on the perspective of the person concerned. From the payers' point of view, the ever-increasing prices of new pharmaceuticals are incomprehensible. For a long time, expensive research and development costs and failed pharmaceutical research projects were cited as justification for the high prices of new pharmaceuticals. However, this is now being critically scru-

tinised.[4] Pharmaceutical companies often benefit from the results of publicly funded research when developing pharmaceuticals, but this is not reflected in the price.[5] This means that insured persons who have already supported corresponding research projects through taxes or donations pay again for the success of the research when a newly developed pharmaceutical is used. Particularly in case of high-priced gene therapies, which are receiving authorisation in the shortest possible time with ever shorter development cycles and in some cases studies with low case numbers, there is a clear disparity between the actual research investment and the expected return. At the same time, it cannot be legitimate for the insured community to have to refinance excessive prices due to the purchase of corresponding developments by large pharmaceutical companies.

In the meantime, the pricing of a new pharmaceutical is justified by the particular benefit of the product, especially for those affected.[6] In the context of society's „anticipated" willingness to pay, especially for certain groups of people and disease patterns, such as new cancer therapies or paediatric pharmaceuticals, high prices are easier to enforce. What remains unresolved is the fact that rapid and unhindered broad market access in Germany should actually lead to price discounts on the basis of limited evidence: After all, further evidence generation is no longer undertaken by studies at the expense of the pharmaceutical company, but by the insured community. Instead of lower entry prices, however, the German market is confronted with particularly high prices for new pharmaceuticals.[6] Reference is also made to the practice of price referencing in other countries, according to which a high pharmaceutical price in Germany is mandatory to achieve appropriate margins in other countries and prevent market withdrawal in Germany.[7]

III. Confidential reimbursement amount is a mistake

Pharmaceutical manufacturers have been campaigning for years in favour of a confidential reimbursement amount, as previously envisaged in the draft law on Strengthening Pharmaceutical Supply in Statutory Health Insurance:[8] Under confidentiality, a larger discount on the manufacturer's desired price could be granted – as in other countries – as confidentiality would remain without any knock-on effects due to cross-state price referencing. The plan was already rightly rejected at the time, as the desired effect on expenditure is hardly to be expected: For many reasons, price intransparency is likely to have the effect of increasing expenditure, not least because it is no longer subject to public discourse. If pharmaceutical companies were not to put their pharmaceuticals on the market on a commission basis and were to reimburse directly with the authorised payer, the payers would have to bear excessive trade margins. This threatens a significant shift in liquidity at the expense of the statutory health insurance system, which would also be burdened with considerable transaction costs due to the necessary subsequent reimbursements. However, according to the currently known drafts for a „new pharmaceutical strategy" of the German government, there is apparently a renewed willingness to take this path in favour of pharmaceutical manufacturers – despite the threat of additional costs that this measure is likely to entail for insured persons who are already heavily burdened by serious price increases in all areas of the market.

The fact that other countries are able to negotiate large discounts on pharmaceutical prices is unlikely to be due solely to the confidentiality of prices, but rather to the 4th hurdle that is common elsewhere : There, the payers – unlike the German statutory health insurance system – can decide not to include preparations in the catalogue of benefits at all, in whole or in part, if they consider this to be

more sensible and there is no agreement on the price. Only by granting this right of choice can a balanced basis for negotiation be created for both contracting parties in order to achieve fair prices. A confidential reimbursement amount will therefore not support parity in the negotiation situation in Germany – on the contrary; as a result, the intended cost neutrality is unlikely to be realistic. This applies all the more when confidential reimbursement amounts are available and the economic prescription in the therapeutic area is no longer transparent for physicians.

In any case, the existing system of reimbursement amount negotiations with its derivation of the reimbursement amount based on price comparisons is likely to be obsolete if confidentiality is realised: Without corresponding information on the actual price structure, neither the G-BA can determine an economically appropriate comparative treatment nor can negotiations be based on one. This would make a redefinition of the parameters for the reimbursement amount mandatory. The same also applies if an appropriate price level in the patent pharmaceutical market ultimately proves to be unrealistic, even with the new guidelines.

One such alternative could be a more cost-based approach, with which an appropriate reimbursement amount can be derived independently of the prices of other pharmaceuticals. In its „fair-price model“[9], AIM has proposed mark-ups for a base profit and incentivisation of the innovation of the new pharmaceutical as parameters for negotiation, in addition to taking into account the costs of research, development, production, sales, and information. In principle, these factors would also be suitable for the further development of reimbursement negotiations, whereby the appropriate negotiation corridors for the German market would have to be determined politically.

IV. Options against maximum prices

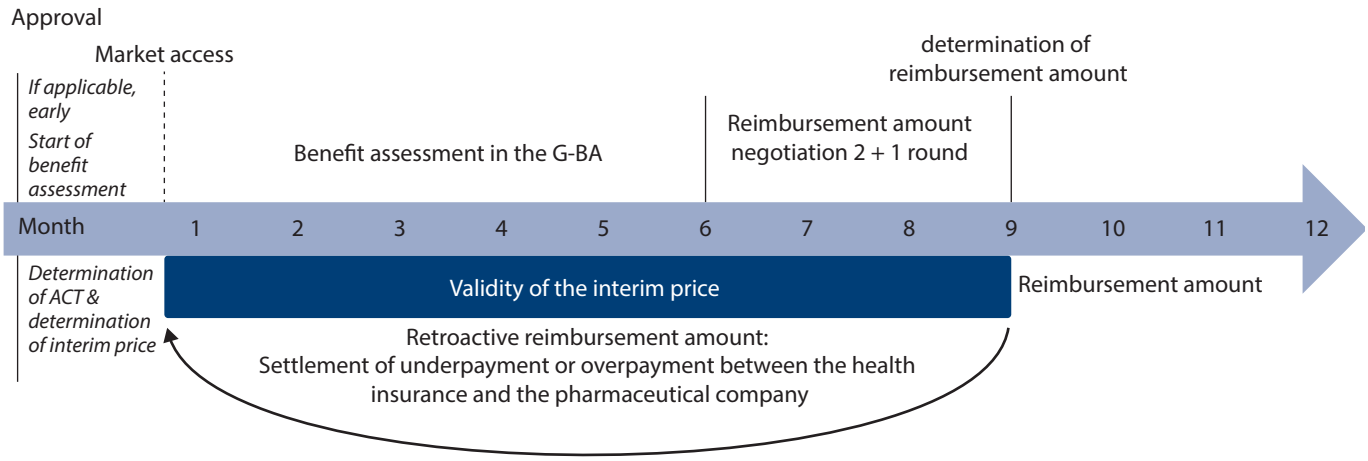
Even in the existing system, the correction of excessive prices in the patent market desired by the legislator would be easier to implement with just a few adjustments if market entry was already included: With an interim price as a provisional measure allocated to each new pharmaceutical prior to market entry, reimbursement amount negotiations would no longer be predisposed to the pharmaceutical company's desired price. The interim price would be derived by the GKV-Spitzenverband in a transparent procedure from the appropriate comparative therapy previously determined by the G-BA and would apply from the first day on the market. By streamlining the reimbursement amount negotiations to three months, the resulting reimbursement amount could retroactively replace the interim price after nine months (figure 1).

Only the result of the G-BA's early benefit assessment and the price of the appropriate comparative treatment would have to be included in the reimbursement amount negotiations, as well as any deductions for combination therapies and discards. If the pharmaceutical company wants to start the benefit assessment procedure earlier and the G-BA agrees to this in individual cases, the period until the reimbursement amount is agreed could be shortened accordingly. Accompanying the market entry of new pharmaceuticals in this way could help to avoid excessive prices and promptly establish a fair balance of interests between payers and pharmaceutical companies.[10]

V. More competition in the patent market too

Last but not least, further profitability reserves should be generated by strengthening competition in the patent market. To date, competitive pressure in this market segment has been low and only takes place at the level of medical prescriptions. The payers can tap into the existing

Procedure for setting the interim price



Source: Own representation AOK-Bundesverband

Figure 1: With an interim price as a provisional measure, the reimbursement amount negotiations would no longer be predetermined by the pharmaceutical company's desired price.

profitability reserves before the patent or document protection expires by initiating cross-active ingredient contract competition. To this end, the G-BA could determine a group of pharmaceuticals with therapeutic comparability for an area of application, which could be used as the basis for selective contract tenders by the health insurances with pharmaceutical companies. Preferential prescribing by physicians requires a corresponding mapping of the contract information in the physician information system.

References

[1] Vfa press release 034/2023. https://go.sn.pub/2RwR8f. (Zugegriffen: 01 December 2023)

[2] Kulig M (2017) Nutzenbewertung von Orphan Drugs trotz unzureichender Evidenz und fehlenden RCT. (Benefit assessment of orphan drugs despite insufficient evidence and lack of RCTs.) In: Lücken in der Evidenz – was leisten Registerdaten? (Evidence gaps – What does registry data offer?) S-pringer-Medizin, Berlin. S 26-34. https://go.sn.pub/eDJfwl. (accessed: 01 December 2023)

[3] IQWiG-Reports No. 1269 (2021): Evidenz zu Orphan drugs. (Evidence on Orphan drugs.) https://go.sn.pub/jUzLAN. (accessed: 01 December 2023

[4] E.g. Angelis A et al.,(2023) High drug prices are not justified by industry's spending on research and development. BMJ 023;380:e071710. http://dx.doi.org/10.1136/bmj-2022-071710

[5] E.g. for Zolgensma®: Beckmann S, Schillinger G (2020) Geschäft mit der Hoffnung auf Heilung (Business with the hope of a cure) G+G 02/2020. https://go.sn.pub/zAiM50. (accessed: 01 December 2023)

[6] Vogler S (2021) Preisregulierung im internationalen Vergleich. (Price regulation in international comparison.) Medicines Compass 2022) chapter 9, pp. 125-138: https://link.springer.com/chapter/10.1007/978-3-662-63929-0_9 (accessed: 01 December 2023)

[7] Wasem J Volmer T (2023) AMNOG 2025: Thesen für eine Weiterentwicklung des AMNOG zu einem moderneren, europakompatiblen und patientenzentrierten System der frühen Nutzenbewertung neuer Arzneimitteltherapien. (Theses for a further development of the AMNOG towards a more modern, Europe-compatible, and patient-centred system of early benefit assessment of new drug therapies.) https://www.vfa.de/de/wirtschaft-politik/amnog. (accessed: 01 December 2023)

[8] Draft bill of the BMG (2016) Entwurf eines Gesetzes zur Stärkung der Arzneimittelversorgung in der GKV (GKV-Arzneimittelversorgungsstärkungsgesetz – AM-VSG). (Draft law on Strengthening Pharmaceutical Supply in Statutory Health Insurance (AMVSG)) https://go.sn.pub/hzVTMW. (accessed: 01 December 2023)

[9] Hendrickx A, Kanga-Tona T (2021) Ein transparentes Modell für einen fairen Preis für innovative Arzneimittel. (A transparent model for a fair price for innovative pharmaceuticals.) Medicines Compass 2022, chapter 11, pp. 155-173. https://go.sn.pub/d1jhqS. (accessed: 01 December 2023)

[10] Jablonka S, Bogum J, Opitz G. (2021). Ein neuer Weg zu fairen Preisen. (A new way to fair prices.) G+G 06/2021. https://go.sn.pub/ELkpOX. (accessed: 01 December 2023)

Challenges in different HTA systems: Main topics of discussion with the speakers

Dr Mathias Flume | Head of Member Services at the Westphalia-Lippe Association of Statutory Health Insurance Physicians

AMNOG 2.0 on the track to a more efficient system": Efficiency can only be achieved if experiences from our neighbouring countries can be incorporated. Dr Anne d'Andon spoke about the strengths and challenges of the French system and Professor Maureen Rutten on the strengths and challenges of the Dutch HTA system. Moreover, Dr Antje Behring from the Federal Joint Committee (G-BA) presented her view on the development perspectives of the AMNOG.

In the subsequent panel discussion, the speakers addressed the following specific aspects:

- **Challenges of regional governance and implications of the Joint Clinical Assessments (JCA) in the Netherlands:**
  From a Dutch perspective, the introduction of the Joint Clinical Assessments (JCA) is seen as positive, although - as in many other countries - many questions remain open. Professor Rutten therefore expects an intensive but open-ended discussion process in the coming period. Only then, in her view, will it finally become clear how strongly the Dutch benefit assessment will be influenced by the introduction of JCA.

- **Effects of the Financial Stabilisation Act on opt-outs by pharmaceutical manufacturers:**
  Some market exits of pharmaceutical companies in 2023 were justified by them with the effects of the Financial Stabilisation of the Statutory Health Insurance (GKV-FinStG). In the discussion with Dr Behring (G-BA), she analysed the opt-out situation in Germany. A long-term view shows that some pharmaceutical companies have always left the market due to the results of the early benefit assessment and the resulting price potential. The results of the benefit assessments are not necessarily surprising for the market exits that have taken place to date. To date, a direct impact of the GKV-FinStG can thus not be deduced from the opt-outs.

Dr Mathias Flume *studied pharmacy in Münster where he also obtained his doctorate. Since 2004, he has been Head of the Member Services at the Westphalia-Lippe Association of Statutory Health Insurance Physicians, specialising in the management of pharmaceutical supply. The benefit assessment of pharmaceuticals and its effects on regional patient care are another focus of his work.*

- **Impact of the JCA on the French assessment:**
  According to Dr Anne d'Andon, the final role of the Haute Autorité de Santé (HAS) has not yet been stipulated. In any case, the HAS is heavily involved in establishing the methodological aspects of the JCA. Influences on national legislation and thus the formal framework conditions are also not yet conclusively foreseeable. In principle, EU regulation takes precedence over national law, and it remains to be seen whether only substantive aspects will be incorporated into the national assessment and then developed further or whether there will be a need for legislative changes.

The impact on the French benefit assessment cannot yet be fully determined. As part of the analysis work is carried out at European level, it is important to define the interfaces with the JCA and to clarify what additional work needs to be carried out at national level. There will also be relevant work to accompany the PICO definition at European level. It remains the task of the national assessments to carry out a country-specific assessment. In any case, it will be several years before this process is finalised.

Strength and weakness of HTA in France

Dr Anne d'Andon

In France, the recognition of innovative pharmaceuticals is linked to the clinical added value granted by the Haute Autorité de Santé (HAS). This evaluation integrates the demonstration of efficacy versus the appropriate comparator with a high level of evidence, in the relevant population, and with a clinically meaningful magnitude of effect. This selective approach aims to address the challenges of innovation: paying accordingly to the magnitude of the innovation while maintaining the sustainability of the healthcare system. It relies on a robust, scientific, and independent agency, with clear definitions of innovation and how to demonstrate it to the Health Technology Assessment (HTA) committee in both early access programs and standard assessments.
This approach is then adapted to provide the population with the best healthcare possible while ensuring as much certainty as possible.

Among the new pharmaceuticals assessed by the Transparency Committee (TC) of the HAS, the French health technology body, only a few have been considered truly innovative. Zolgensma® (onasemnogene abeparvovec), Raxone® (idebenone), Glibera® (Alipogène tiparvovec), Kaftrio® (vacaftor/tezacaftor/elexacaftor), Sovaldi® (sofosbuvir), Veklury® (remdesivir), Carvykti® (ciltacabtagene autoleucel), Zalmoxis® (allogeneic T cells), Dupixent® (dupilumab), Spherox® (chondrocytes in spheroids).

Despite the inclusion of gene therapy products, cell therapies, biotherapies, or pharmaceuticals targeting novel modes of action, as well as addressing very severe diseases or diseases with high medical and therapeutic needs, the TC did not find this sufficient to recognise the progress provided compared to pre-existing therapeutic strategies and classify these pharmaceuticals as innovative.

The recognition of innovation is not solely based on the mode of action, even if it is new and sophisticated, or on the severity or rarity of the disease. Only Zolgensma®, Kaftrio®, Sovaldi®, and Dupixent® received recognition of a clinical additional value from the Transparency Committee (an ASMR of II, III, or IV at the initial assessment). This recognition was granted based on the appropriate demonstration of efficacy on clinically relevant endpoints compared to the appropriate comparator, supported by a high level of evidence, in the relevant population, and ultimately, with a clinically meaningful magnitude of effect. These are the requirements presented in the TC doctrine.[1]

The assessment of the clinical added value required for the innovation to be recognized follows a series of successive steps (figure 1). This doctrine isn't intended as a rigid perspective on HTA; rather, it serves as a guide for understanding how the TC evaluates pharmaceuticals, primarily based on evidence-based medicine. It is then allowing the

recognition of innovation.

There is a need to support the challenges of innovation and how they can be integrated into the healthcare system. In France, the principle is to pay for innovation and to adjust payment according to the magnitude of the innovation: the more innovative a health technology is, the higher its price. This necessitates administered pricing and the containment of prices for non-innovative pharmaceuticals.

To achieve this, it was decided in the early 2000s to establish an independent, robust, and scientific agency, the HAS, which integrated the pre-existing Transparency Committee. The agency and the committee possess the capability to provide opinions on healthcare technologies with a high standard of assessment and a high degree of independence, allowing them the freedom to publicly express pertinent information about the clinical interest of a pharmaceutical. This approach is tailored to offer the population the best healthcare possible, depending on the available data.

Aligned with the medical and scientific objective of providing medical treatment with as much certainty as possible, there is also an economic concern. Health technologies serve as drivers of economic growth and constitute an innovative sector of the economy, as emphasized by the 2021/2282 EU regulation on health technology assessment: „The development of health technologies is a key driver of economic growth and innovation in the Union and is key to achieving the high level of health protection that health policies need to ensure for the benefit of all. Health technologies constitute an innovative sector of the economy and form part of an overall market for healthcare expenditure that accounts for 10% of Union gross domestic product."[2]

The challenges the HTA agency and the HTA face in France include: How can we recognise innovation in the healthcare area? The answer provided by the French HTA body is:

- Provide an operational definition,
- Adapt the definition to the context; there cannot be only one definition,
- Provide a clear, common, and reproducible way of assessing a given pharmaceuticals based on the definition,
- Maintain equity of assessment between pharmaceuticals and with time,
- Provide a robust assessment of innovation to avoid inappropriate recommendations.

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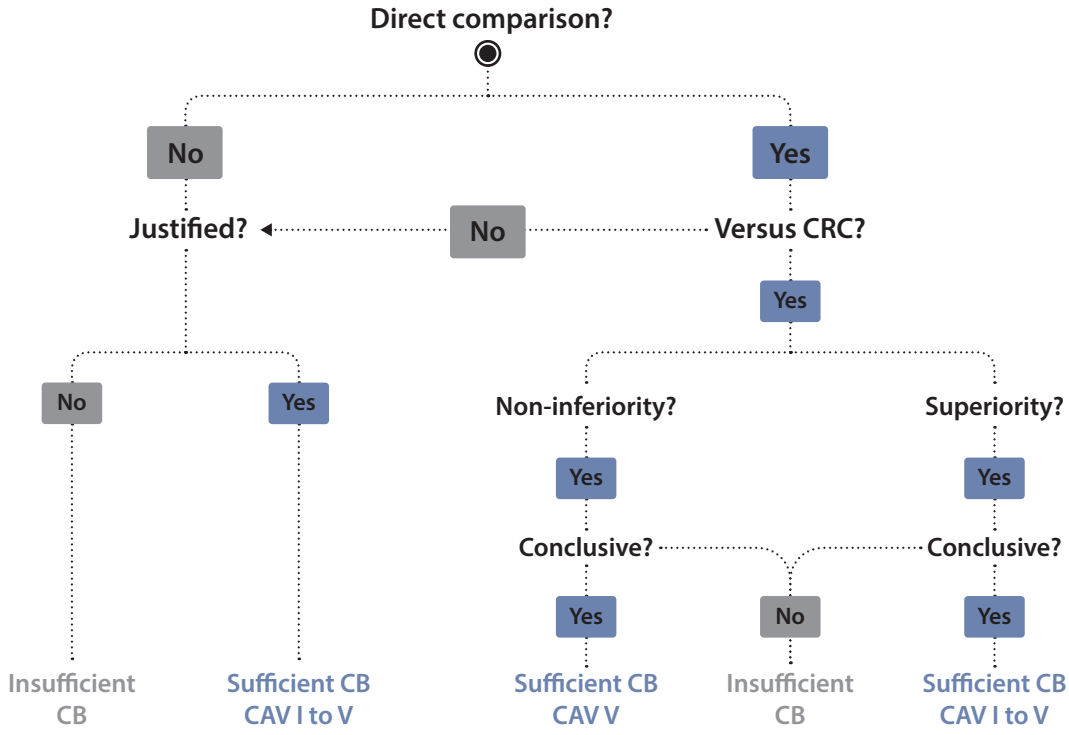
Comparison in the evaluations of the Transparency Committee



CRC: clinically relevant comparator; CBi: insufficient clinial benefit; CAV: clinical added value

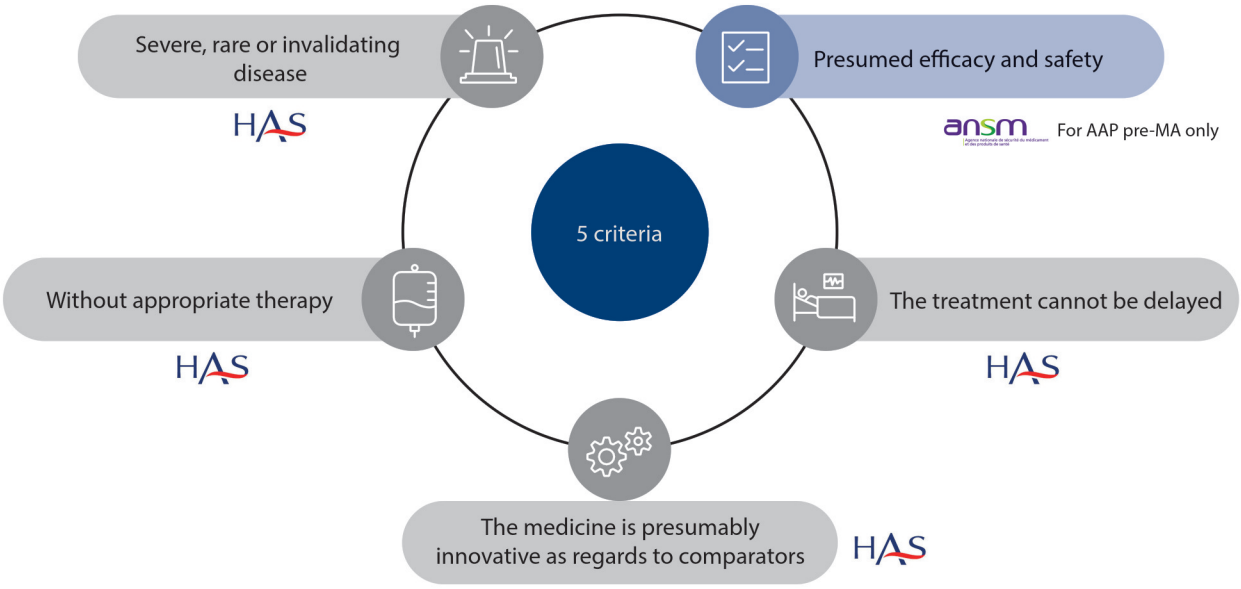
Source: Page 8 of the TC doctrine (https://www.has-sante.fr/upload/docs/application/pdf/2019-07/doctrine_de_la_commission_de_la_transparence_-_version_anglaise.pdf)

Figure 1: The assessment of the clinical added value required for the innovation to be recognized follows a series of successive steps.

These principles are exemplified by programmes such as the Authorization of Anticipated Access (AAP), formerly known as Temporary Authorization for Use (ATU), which was deeply modified in 2021 and transferred to HAS. Among the five cumulative criteria for AAP one criterion is the presumed innovation by the pharmaceutical (figure 2).

In the context of AAPs, the definition of innovation encompasses a new treatment modality, which may include a new mechanism of action, providing substantial clinical benefit to the patient. The essence of AAP is to facilitate early availability of the pharmaceutical. Thus, preliminary data can be accepted if accompanied by a suitable development plan that complements these initial clinical results and addresses uncertainties. These plans should

Criteria for the Authorisation of Anticipated Access



Source: HAS

Figure 2: Among the five cumulative criteria for (AAP) one criterion is the presumed innovation by the pharmaceutical.

aim to fill gaps and uncertainties regarding the demonstration of effectiveness and safety compared to a reference therapeutic strategy in the near future. The third definition criterion is that the pharmaceutical meets an insufficiently covered medical need.

The transition of the Early Access Program (EAP) from ATU to AAP has significantly altered the terms for granting early access to pharmaceuticals. The idea of this reform was also to ensure continuity between the early evaluation and therefore early access and the common law access to the market.

AAP also reinforced the need for data collection, making it possible to describe the clinical situation of treated patients, effectiveness, and safety in a real-world context. The acknowledgment of presumed innovation is linked to a price defined by the company, which is fully reimbursed, subject to certain limits. Cumulative discounts may apply based on various events, such as failure to obtain marketing authorization, a low rating in the HTA appraisal, the absence of a price agreement with the Economic Committee for Health (CEPS), and/or the reimbursement of a new pharmaceutical identified by the HAS as better meeting the therapeutic need in the indication covered by AAP.

Another pathway for defining innovation stems from the assessment of the clinical added value (ASMR: amelioration du service medical rendu). This assessment is based on three pillars:

- Level of evidence – Quality of the demonstration, inclu-

ding the design for the comparison, choice of the comparators, overall methodological quality of the trial, adequacy of the population to the indication, and clinical relevance of key endpoints etc.

- Magnitude of the clinical effect in terms of efficacy, effectiveness, quality of life and modulated by the clinical impact of the safety profile,
- Clinical pertinence of the effect as compared to the clinically relevant comparator.

These two pillars are considered as regards to the medical need.

The more the assessment considers that these requirements are fulfilled, the more likely is the recognition of innovation.

The doctrine states that:[3] The TC may grant recognition to a pharmaceutical as representing major therapeutic progress [ASMR I] under certain conditions. This recognition occurs if the product exhibits a new mechanism of action and has demonstrated, with a high level of evidence, its superiority over a clinically relevant comparator. This assessment is typically made in the context of an inadequately met medical need for a serious disease.

Such situations are considered therapeutic breakthroughs, potentially saving, or significantly changing the lives of patients. When all determinants of clinical added value are deemed fully satisfied by the TC, the product may receive ASMR I designation.

This assessment corresponds to therapeutic breakthrough situations (that save or change the lives of patients with a serious disease) for which all the determinants of the clinical added value are judged by the TC to be fully satisfied.

The TC may also recognise a pharmaceutical as representing important or moderate therapeutic progress [ASMR II or III]. This recognition occurs if the product demonstrates superiority in terms of clinical efficacy, particularly in reducing mortality and morbidity, within the context of an inadequately met medical need. In such cases, the evaluation of efficacy may be positively adjusted by a substantial improvement in quality of life and/or safety. An important or moderate ASMR will qualify the clinical added value, depending on its intensity, the quality of the demonstration and the severity of the disease or symptom. Indeed, the value attributed to therapeutic progress increases in accordance with various factors, including the effect size, the quality of the demonstration, and the severity of the disease being addressed.

A minor clinical added value [ASMR IV] is allocated to progress that is considered small in comparison to existing therapies. This designation reflects a situation where the demonstration of efficacy, quality of life improvement, or safety profile may not be optimal given the medical context. For example, it may involve a pharmaceutical that demonstrates relevant efficacy but with a slight and acceptable decrease in quality of life or safety. Conversely, it could involve a product with minimal or sub-optimally demonstrated additional efficacy yet associated with an improvement in quality of life or safety. It may also be assigned to a product that brings about a major improvement in care conditions, either demonstrated or anticipated by the TC.

The elaboration of this doctrine and clarification of the way pharmaceuticals are assessed by the HTA committee, publicly available, has been possible because of the creation of an independent public agency without government supervision, complementary missions, including HTA for pharmaceuticals, medical device and procedures, clinical guidelines. The strength of the HTA is also based on a non-disputable technique of considering evidence and, as a mirror, uncertainty: evidence-based medicine. All phar-

maceuticals candidate for reimbursement are assessed, can be reassessed when needed. The TC can request real-world data collection. The clarification of the modalities of assessment by the publication of the doctrine since 2011, actualised regularly has provided a better readability about the approach and perhaps better predictability about the conclusions.

The opinions provided by the HAS are consistently adhered to by decision-makers, including the Ministry of Health and Social Security, as well as the National Health Insurance Fund. These opinions are widely regarded as robust, leading to minimal instances of legal challenge.

There are still some disagreements about the use of EBM, about the low number of ASMR of I, II, III which leads to difficult negotiation of price and lower price than expected by the pharmaceutical industry. This is the reverse side of the medal for the recognition of innovation linked to a higher price and the favouring of economic development by favouring the pharmaceutical industry in an economic situation where there is a need to constrain the healthcare expenses.

There is also a conflict between the standards set by the HAS regarding evidence and the demonstration of the significance of an effect for patients compared to the relevant comparator. It must be acknowledged that this demonstration necessitates a lengthy and expensive development process. The current trend towards short developments, non-comparative, thus not adapted to demonstrating the added value of the pharmaceutical but nevertheless aimed at supporting the justification of an innovation which should lead to a high price. This equation remains unresolved despite all the efforts made by HAS to define under what circumstances atypical designs of clinical studies can be accepted for the recognition of innovation.[4]

It's highly likely that these assessment modalities will be incorporated into the evaluation process for new pharmaceuticals with EU marketing authorisation, as part of the joint clinical assessments conducted by member states. Certainly, it's important to note that while the JCA are evaluations conducted collectively, the appraisals will continue to be a national privilege. The determinations regarding innovation will remain within the purview of national authorities.

There are many other points of view that could be developed: the participation of the patient in the HTA including for the early recognition of innovation, their participation at the European level assessment, but also the timelines of access to innovation etc. These topics could be developed as specific topics in further conferences.

In the interim, while acknowledging that my perspective may be biased as a former member of HAS, it's worth noting that the delicate balance between a robust HTA body, a well-defined approach to pharmaceutical assessment, and a high level of innovation recognition through pricing preferences are central aspects of the French HTA system, with both strengths and weaknesses.

References

[1] Transparency committee doctrine: Principes d'évaluation de la CT relatifs aux médicaments en vue de leur accès au remboursement. Actualisée le 15 février 2023. https://go.sn.pub/MW6x9C

[2] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

[3] https://go.sn.pub/Ylr7A4

[4] Vanier A, Fernandez J Kelley S et Al. 2023. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. BMJ Evidence-Based Medicine Published Online First: 14 February 2023. doi: 10.1136/bmjebm-2022-112091

The Dutch HTA system for high-priced in-hospital pharmaceuticals

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The Netherlands operates a mandatory social health insurance system with a relatively generous basic benefit package. To address the challenge posed by high-cost, in-hospital pharmaceuticals, the Dutch government has implemented the „lock procedure" for market access management. Under this procedure, pharmaceuticals that exceed certain cost per patient and/or budget impact thresholds require developers to submit a comprehensive pharmacoeconomic dossier alongside the clinical dossier. Subsequent evaluation is conducted by Zorginstituut Nederland (ZIN), and the „cost per Quality-Adjusted Life Year (QALY)" of an intervention is compared to a threshold value that increases as the severity of the disease increases. Final price negotiations are then conducted by a team from the Ministry of Health. Conceptually, ZIN is progressively transitioning to a risk-based and cyclical health technology assessment (HTA) system.

The Netherlands operates a mandatory social health insurance system with a relatively generous basic benefit package. In this open system, over 90% of services and technologies can be included in the benefit package without the need for a formal HTA or a national reimbursement decision.

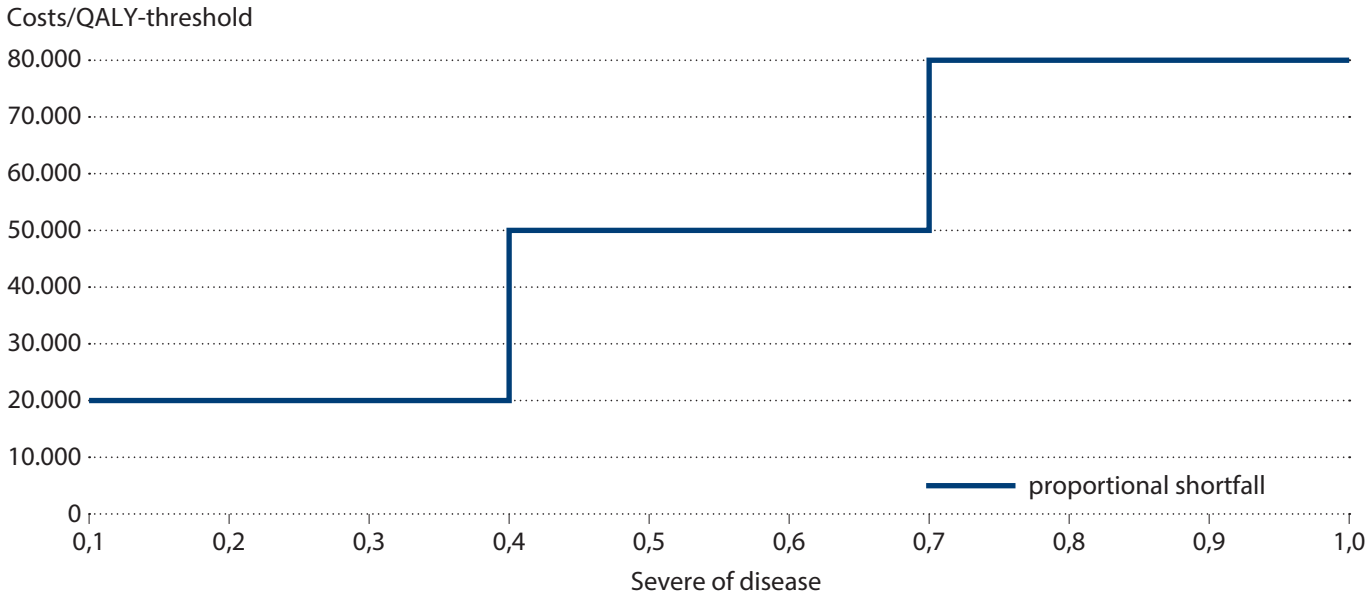
When medical professionals determine that the efficacy of a service or technology is sufficiently proven and the benefit-risk ratio is positive, they can offer it to patients. Negotiations with individual health insurance companies regarding reimbursement are then required. Only if a service or technology requires significant additional budget, a request for a new payment code must be issued. In such cases, the decision may be based on a formal HTA conducted by the Dutch HTA body, Zorginstituut Netherlands (ZIN).

The open inflow process encompasses three exceptions that necessitate mandatory HTAs: certain pharmaceuticals (figure 1), the national vaccination programme, and the national screening programme. The reimbursement of high-cost, in-hospital pharmaceuticals, notably oncology products, poses a substantial challenge, consuming an increasing portion of the hospital care budget. In response, the Dutch government has implemented the „lock procedure" for market access management. Pharmaceuticals are subject to the „lock" when they meet specific criteria:[1]

1. If the total costs for one new indication or multiple new indications combined are expected to exceed 20 million Euros per year, all new and future indications will be placed in the lock. (This threshold was previously set at over 40 million Euros before 1 July 2023).

2. If the total costs for one new indication are expected to be at least 50,000 Euros per patient per year AND the total costs are expected to exceed 10 million Euros per year, the indication will be placed in the lock.

Threshold values for costs per QALY gained in The Netherlands



Source: Own presentation

Figure 1: The cost of an intervention per quality-adjusted life year (QALY) gained is compared with a threshold value that increases with increasing disease severity.

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Within the lock procedure, pharmaceutical developers are required to submit a comprehensive pharmacoeconomic dossier alongside the clinical dossier. ZIN evaluates this dossier based on four key criteria:

1. Necessity, primarily determined by the severity of the disease, which necessitates treatment reimbursed from public resources.

2. Relative effectiveness, measured by the additional therapeutic value compared to the existing standard of care;

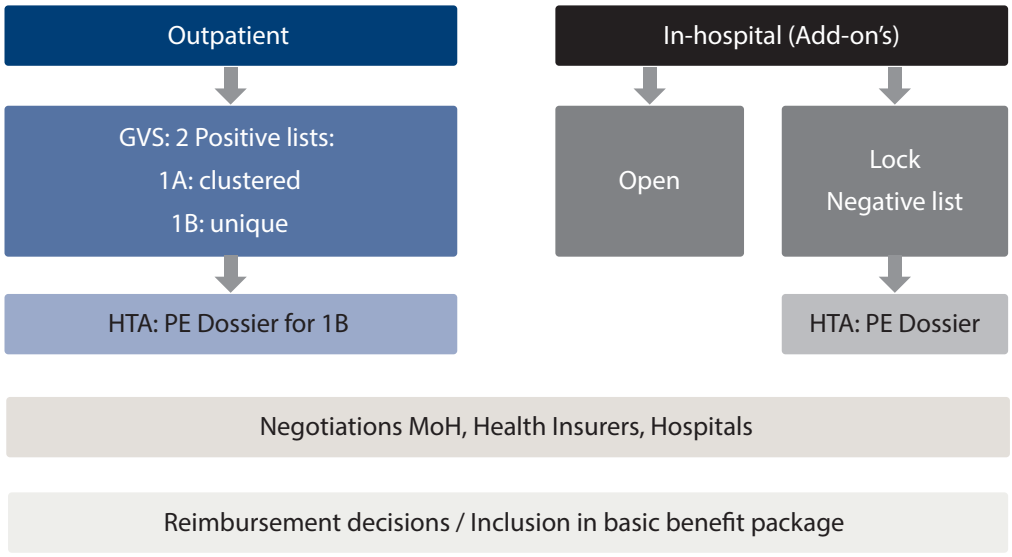
3. Cost-effectiveness, assessed in terms of costs per quality-adjusted life year (QALY) gained;

4. Feasibility, predominantly defined from a financial standpoint, ensuring a budget impact that is affordable.

The „costs per QALY" of an intervention are compared to a threshold value that increases as the severity of disease increases (figure 2).[2] If the costs per QALY fall below the threshold, the pharmaceutical is considered cost-effective.

Depending on the assessment, ZIN may recommend negotiating a discount on the pharmaceutical's price to enhance cost-effectiveness and mitigate budget impact. Price negotiations are then conducted by a team from the Ministry of Health. In 2021, the negotiating team achieved an average discount of 46%, resulting in a reduction of 745

Medicines for which a pharmaco-economic dossier is required in The Netherlands



GVS: Medicine reimbursement system [Geneesmiddelenvergoedingssyteem]; MoH: Ministry of Health, Welfare and Sport; PE Dossier: Pharmako-ökonomisches Dossier

Source: Own presentation

Figure 2: The „lock procedure" has been introduced in the Netherlands to manage market access for the reimbursement of high-priced medicines in hospitals.

million Euros in expenditures. While this outcome appears successful from a public standpoint, the extent to which developers anticipated this level of discount remains uncertain. However, negotiations do not always yield positive results, as demonstrated by the Minister of Health's decision in 2023 not to reimburse Troveldy and Libmeldy.

The „lock procedure" emerged as a replacement for a relatively unsuccessful experiment involving conditional reimbursement agreements, which required reassessment after four years of additional data collection.[3] In many cases, the data collected failed to significantly reduce uncertainties surrounding effectiveness and cost-effectiveness estimates. Although conditional reimbursement remains an option in the Netherlands, its utilisation is minimal. Furthermore, outcomes-based managed entry agreements are not widely adopted due to concerns about societal risk tolerance, feasibility challenges, administrative burdens, costs associated with outcome measurement, discussions on compensation in case of treatment ineffectiveness, and the lack of supportive facilities for physicians to monitor outcomes. As a result, managed entry agreements in the Netherlands primarily revolve around financial arrangements.

What's intriguing is that ZIN has introduced a novel assessment framework specifically tailored for tumour-agnostic medicines and those endorsed by the European Medicines Agency (EMA) based on single-arm studies.[4] Depending on the context, ZIN may consider:

- Evidence from single-arm basket trials, even if they don't allow for assessing effectiveness per tumour location;
- Acknowledgement of potential data gaps in natural history or standard care for patients with the same mutations targeted by tumour-agnostic pharmaceuticals, as these patients were not tested in the past;
- Acceptance of intermediate outcome measures such as Objective Response Rate (ORR), Duration of Response (DoR), Disease-Free Survival (DFS), and Progression-Free Survival (PFS), provided that the choice of outcome measure and the minimal important difference (MID) are defined in the PICO (Population, Intervention, Comparator, Outcome) during the scoping phase, and these outcomes are predictive of Overall Survival (OS). ZIN evaluates the latter on a case-by-case basis;
- Recognition of the necessity to construct a synthetic control arm in health economic models.

These considerations largely depend on the plausibility of the assumption that without treatment, there will be no tumour response at all.

ZIN is gradually transitioning to a risk-based and cyclical HTA system.[5] This transition begins with a robust horizon scanning mechanism designed to early detect potentially transformative health technologies and quantify associated risks. Following this, there is a swift assessment of risks, which encompasses uncertainties regarding therapeutic value, financial considerations, and the potential for inappropriate use. These risks are effectively addressed through prudent risk management strategies. These strategies include HTA, conditional reimbursement, controlled enrolment programmes, price negotiations, and agreements ensuring appropriate usage in practice.

References

[1] https://go.sn.pub/OMADRo

[2] https://go.sn.pub/0zFr9n

[3] https://www.valueinhealthjournal.com/article/S1098-3015(16)30111-5/pdf

[4] file:///C:/Users/19680mvm/ Downloads/Module+Beoordeling+SWP+tumoragnostische+geneesmiddelen.pdf

[5] https://go.sn.pub/uq4HXl

Direct and indirect comparisons: Commentary on the EUnetHTA Guidance

Von Prof Heiner C. Bucher | MPH, Emeritus, Professor of Clinical Epidemiology, University of Basel, Department of Clinical Epidemiology, University Hospital Basel

With the introduction of the new EU Regulation on Health Technology Assessments (HTA), HTAs will, for the first time, be conducted across national borders within the European Network for HTAs (EUnetHTA) starting in 2025. EUnet HTA has developed methodological standards aimed at harmonising HTA activities. Specifically, guidelines on indirect comparisons of non-randomised controlled studies for market approval hold significant relevance for investigators and applicants of innovative life science products, especially in cases involving limited patient numbers or rare diseases. In the guidelines for HTAs of indirect comparisons, EUnetHTA places the emphasis of methodological criteria on the evidence synthesis of indirect comparisons, but neglects more binding specifications on validity criteria for network meta-analyses and on the methodology of indirect adjusted comparisons using external controls from observational studies. However, this increases the risk of different assessments of HTA applications by HTA experts in the individual HTA organisations of the member states. This article presents options for standardising the validity criteria of indirect comparisons for HTAs, which should enable a transparent and more uniform assessment of the added benefit of interventions that use externally obtained evidence to prove their effectiveness.

Introduction

As part of the new EU Regulation on Health Technology Assessments (HTA), which came into force in January 2022, HTAs will be carried out jointly for the first time by a consortium of 13 HTA organisations from 12 member states in so-called Joint Scientific Assessments (JSA) from 2025. The aim is to coordinate HTA activities within the EU, which were developed in the three previous Joint Actions programmes of the European Network for HTA (EUnetHTA), under one roof and, where possible, standardise and simplify them.

Building on the previous Joint Actions Programmes of EUnetHTA, an agreement was signed by the European Health and Digital Executive Agency (HaDEA) to establish a European HTA system, which includes the promotion and standardisation of HTA assessment processes and methodology. As part of these activities, several methodological HTA guidelines were developed, the Methodological Guideline 4.3.2 on direct and indirect comparisons[1] and the Practical Guideline D 4.3.1. on direct and indirect comparisons.[2]

In this article, the practical aspects of Methodological Guideline D 4.3.1. on direct and indirect comparisons of network meta-analyses will be critically analysed. This guideline is of great interest because the Joint Scientific Assessments are to be introduced in a first step only for HTAs in the field of oncology and the methodological challenges of HTAs based on indirect comparisons are of great importance here.

The Practical Guideline D 4.3.1 for direct and indirect comparisons is an update and supplement to earlier guidelines[3] resulting from the Joint Action Program and describes the methods available for direct and indirect comparisons. It has been developed by a Hands on Group (hereinafter referred to as the working group) of expert

organisations consisting of the German Federal Joint Committee (G-BA), the French Haute Autorité de Santé (HAS), the German Institute for Quality and Efficiency in Health Care (IQWIG), the Irish National Centre for Pharmacoeconomics, St. James Hospital (NCPE), and the Norwegian Medicines Agency (NOMA) and has been revised and approved by a committee and the consortium of all member states active in the EUnetHTA programme. The guideline is explicitly intended for HTA assessors and co-assessors.

This article provides a critical assessment of the EUnetHTA Practical Guideline D 4.3.1. For practical reasons, we limit ourselves to indirect comparison methods of network meta-analyses. A comprehensive assessment of all methods described in the guideline, in particular on propensity scores or target trial simulation options, is beyond the scope of this article. Their importance has already been explained in earlier articles by the author in this journal.[4,5]

Prof Dr Heiner C. Bucher, *Emeritus, served as Professor of Clinical Epidemiology at the University of Basel and Consultant at the Department of Infectious Diseases and Hospital Hygiene, University Hospital Basel, from 2001 to 2021. From 2017 to 2021, he held the position of Associate Professor at ETH Zurich in the Department of Health Sciences and Technology. He conducted research stays at the University of California, Berkeley, USA, McMaster University in Hamilton, Canada, and Stanford University in Palo Alto, USA. The method for indirect comparisons developed by Prof. Bucher has been widely used in the HTA field and was the starting point for the development of the network meta-analysis technique.*

Scope and aim of the Practical Guideline D 4.3.1. on direct and indirect comparisons of EUnetHTA

The aim of the guideline is to provide practical guidance on evidence synthesis (sic!) in JCA reports, as well as guidance for reviewers on how to deal with HTA reports on direct and indirect comparisons. In particular, the guidelines should enable reviewers to identify potential problems, biases, and uncertainties of direct and indirect comparisons. In this context, the working group mentions that a certain degree of subjectivity cannot be denied in the assessment of validity criteria and assumptions of indirect comparisons, which can lead to different assessments of the evidence presented between experts in the member states. The guideline, and consequently the ensuing argumentation, does not aim to provide explicit recommendations for individual member states regarding the acceptance or rejection of HTA reports based on direct or indirect comparisons. Rather, its objective is to establish the necessary conditions for member states to conduct individual assessments through methodological specifications.

It is also made clear that „in exceptional situations, evidence synthesis methods may be used despite uncertainty or doubt about their validity“ (...) and that their use should be „minimised and only applied in situations where there are no other options for generating relative evidence“ (...).

Conceptual problems of the Practical Guideline D 4.3.1. on direct and indirect comparisons

The introductory choice of words and the further structure of the guidelines already reveal several fundamental

problems with the document.

Firstly, the document is primarily a guide to the assessment of direct and indirect comparisons using meta-analytical synthesis techniques (17 of 31 pages are dedicated to this), with an ex-post chapter of only 3 pages on indirect non-randomised comparison methods using propensity scores. The Practical Guideline thus suggests that indirect meta-analytical synthesis methods are more important than the generation of new evidence from high-quality cohort studies with standardised, prospective data collection and analytical methods that are based e.g. on a target trial simulation.[6,7]

The lack of stringency in the structure of the document underlines this way of thinking. In the introductory chapter 3 e.g. the general considerations are limited in their explanations of the assessment of the exchangeability of the study groups based on the assessment of similarity, homogeneity, and the consistency of treatment effects of direct and indirect comparisons in (network) meta-analyses. There is not a single general statement on indirect, non-randomised comparisons in the general comments.

Secondly, the introduction and subsequent argumentation fail to elucidate the conditions under which „exceptional circumstances of evidence generation“[2] occur and when evidence from non-randomised studies might be considered admissible. The European Medicines Agency EMA, on the contrary, defines exceptional circumstances „as a type of market authorisation where the applicant is unable to provide comprehensive data on the efficacy and safety of an active substance under normal conditions because the condition to be treated is rare, or obtaining the complete necessary information is not possible or unethical“.[8] The working group's argument completely ignores the need for indirect non-randomised comparative studies for innovative pharmaceuticals in haematology/oncology, rare diseases or paediatrics, where evidence from randomised controlled studies is less and less available at the time of approval, let alone the possibility of evidence synthesis based on randomised studies.

Thirdly, the lack of specification of exceptional situations for the generation of evidence in HTA applications that are not based on randomised studies, as well as validity problems of indirect comparisons in (network) meta-analyses, increases the importance of subjective assessments of HTA reports based on indirect comparisons, especially by different member states. The guideline focuses on reporting standards, which is emphasised by means of key points listed in boxes, and not on a detailed and well-founded description of validity criteria for indirect comparisons, which would enable a uniform assessment of the evidence presented across member states. Thus, the guideline – in its current form – undermines the original intent of the Joint Scientific Assessments. These assessments were designed to create robust cross-national standards with clear methodological criteria and validity measures, offering reviewers and applicants a more enforceable framework for evaluating and presenting HTA reports.

Fourthly, the guideline sends the wrong signal by suggestively equating high quality evidence with indirect evidence syntheses based on randomised controlled studies and emphasising certain study designs and analytical methods that should be preferred. It thus undermines the principle of decision-making in clinical and public health, which is based on the best available evidence, considering known standards and validity criteria. The listing of methodological procedures and guidance on reporting is undoubtedly necessary, but not sufficient in the assessment of evidence for decision-making. Justification of the safety and reliability of evidence for a particular decision is mandatory, but its derivation is inadequate or absent in

the present EUnetHTA guidelines.

Fifthly, far too little attention is paid to the selection and determination of the target population, comparator(s) and outcomes in the development of the PICO question. Considering the intricate landscape of HTA across various member states, it appears somewhat theoretical to address the PICO question solely from the perspective of the „research question", without acknowledging the significant impact of economic or system-specific constraints on selecting the most appropriate comparative therapy.

Methodological aspects of network meta-analyses in the EUnetHTA practical guideline D 4.3.1

Guideline D 4.3.1 lacks information on the assessment of the validity of the methodology of indirect comparisons. As the methodology of indirect comparisons is complex, the importance of validity criteria for assessing the quality and evidence of network meta-analyses is very important. Based on the principles of methodology groups of the Cochrane Collaboration, the Confidence in Network Meta-Analysis (CINeMA) assessment system for validity criteria of network meta-analyses was developed.[9-13] The integration of CINeMA into the guidelines would increase transparency and reproducibility in the assessment of the validity of network meta-analyses and will therefore be presented in a summary of the key publication.[9]

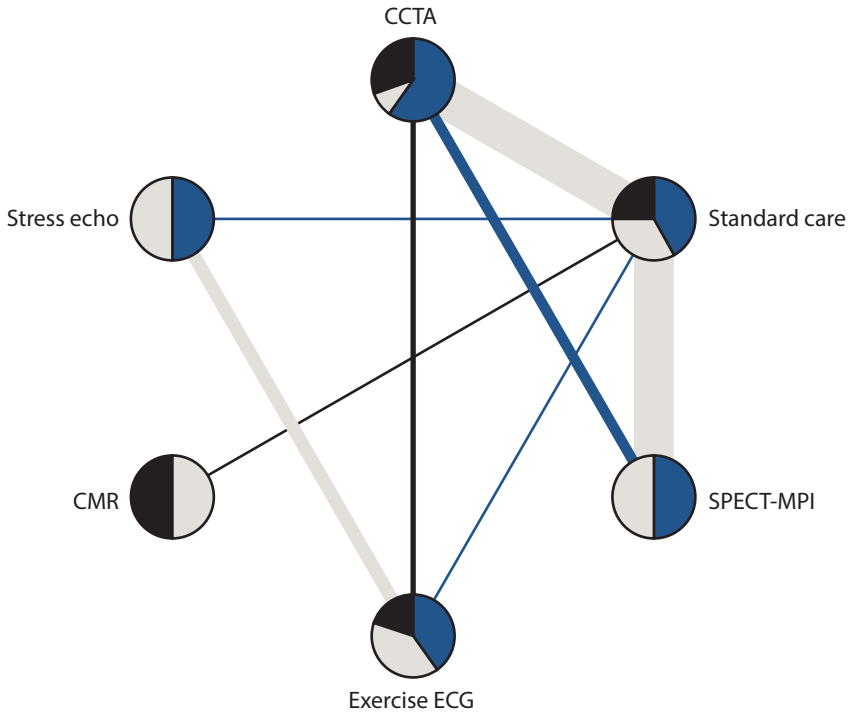
The CINeMA assessment system for the validity of network meta-analyses includes six areas: Within-study bias, reporting bias, indirectness, precision of effect estimates, heterogeneity, and incoherence.[9] The areas of within-study and reporting bias are of less interest here and will not be discussed further, as they also occur in meta-analyses of direct comparisons and their importance is well known. Within-study bias refers to the validity criteria, adequate randomisation, blinding of study participants and clinical staff, blinded endpoint determination, and completeness of follow-up. Reporting bias is based on one-sided, incomplete or unsystematic inclusion of studies, which may be caused by publication bias.

In complex network meta-analyses, evidence can be obtained for indirect comparisons across multiple loops of treatments that have never been directly compared. Another advantage of including indirect evidence is that more precise effect estimates can be obtained for direct comparisons than in direct pairwise comparisons. However, it should be noted that direct comparisons and those of large studies can contribute more and more robust evidence to a network than stepwise comparisons across multiple loops. This means that a comparison's contribution to the network depends not only on its accuracy, but also on its position in the network. Figure 1 shows an example of a network meta-analysis of diagnostic tests for acute coronary heart disease.

In this network, the indirect evidence of a comparison of stress ECGs and SPECT-MPI comes from two closer loops (via CCTA or via standard care) and two more distant loops (via CCTA-standard care, stress echo standard care, standard care-CCTA). The indirect comparison of exercise ECG and SPECT-MPI via the closer loop is more important than the two-stage loop comparison with twice the number of patients, despite the low number of patients. The percentage share of each study in the network for a specific comparison can be listed in a matrix table.

A major advantage of the CINeMA tool is that it combines the bias assessment with the weight of a study in the network and thus provides a more transparent matrix approach to assessing the validity of a network meta-analysis. In contrast to the GRADE approach, the assessment of the validity of a network meta-analysis is not based on a metric approach of assessing heterogeneity

Example of a network meta-analysis with risk of bias information for direct and indirect comparisons of diagnostic tests for the detection of coronary heart disease



Colors of connections and nodes refer to the risk of bias: low (blue), moderate (gray), and high (black) Key: CCTA coronary computed tomography angiography, CMR cardiovascular magnetic resonance, ECG electrocardiogram, echo echocardiography, SPET-MPI single photon emission computed tomography myocardial perfusion imaging.

Source: [9]

Figure 1: Example of a network meta-analysis of diagnostic tests for acute coronary heart disease.

and consistency, but on assessing the impact of these parameters on clinical decision making regarding tested intervention comparisons. That is, CINeMA provides transparent estimates of when we should trust or distrust effect estimators on indirect and direct comparisons regarding their susceptibility to bias in a network.

Indirectness refers to the most important model assumption in network meta-analyses, namely that the condition of transitivity is met: In a connected network, the assumption of consistency yields a coherent set of effect estimates for any intervention in the network (e.g. in the simplest case of a network AB versus BC versus AC) relative to another intervention comparison. In a fixed effect model, e.g. this means that the true effect diXY of intervention Y relative to intervention X is the same in every study in the network – regardless of the intervention currently being

evaluated.[14] However, this requires that all effect modifiers, such as patient characteristics or prognostic factors, are collected and equally distributed in the comparison arms. In a broader sense, transitivity means that each individual whose data are included in a network meta-analysis should be randomisable to any intervention tested in the network. The hypothetical example in figure 2 shows the network for the comparison of four chemotherapeutic agents against a specific tumour.[10]

Therapy D is only used in tumour stage II, therapy A in tumour stages I and II, and therapies B and C only in tumour I. The comparisons of A and D for tumour stage II and A, B and C in tumour stage I obviously violate the transitivity assumption, since not all individuals included in the network are eligible for all therapies. Violation of transitivity leads to inconsistency of treatment effects based on direct and indirect comparisons.

Network meta-analyses without interconnected loops (a loop consists of at least three nodes (treatment comparisons), a small number of included studies, and the low power of statistical methods to test for inconsistency, make it difficult or even impossible to analyse treatment effects. Results of empirical meta-research of over 200 network meta-analyses show that inconsistency between direct and indirect comparisons was present in one in 5 or 7 network meta-analyses, depending on the statistical method chosen.[15] Since the statistical power of global tests for inconsistency is low, an even greater problem must be assumed. For this reason, instructions for estimating inconsistency in network meta-analyses are helpful, which, as in the present guidelines,[2] go beyond a brief description of common statistical methods for their assessment (Bucher method for individual loops, Bayesian inconsistency and node-splitting methods).

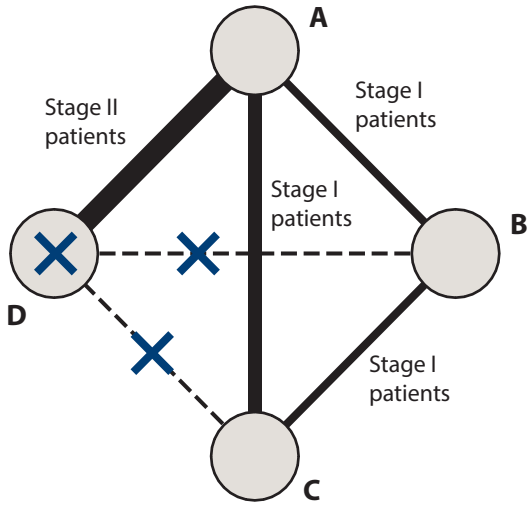
The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group therefore recommends pairwise testing of consistency at the loop level even for statistically insignificant global tests for inconsistency in a network.[16] However, this method is not expedient, particularly when analysing consistency in complex networks, where indirect evidence is sometimes generated via several loops. In addition, an examination of the overlap or differences in confidence or credible intervals of direct and indirect comparisons is advisable, in addition to the examination of the network geometry and the existence of multi-arm studies, which per se (with adequate methodology and randomisation) are free of inconsistency. Furthermore, medical clinical expertise in the interpretation of consistency of network meta-analysis data may be necessary.

Figure 3 shows a bar chart of the network with direct and indirect comparisons on the quality of tests for the diagnosis of coronary heart disease, which illustrates the extent of bias for each comparison depending on the study weight in the network.[11] Each bar represents a relative comparison, as shown in figure 1 on the network configuration. The white break lines represent the percentage contribution to the effect size of individual studies with a low, moderate, or high risk of bias.

For example, while the percentage of studies with a high risk of bias is very low for the comparison of exercise ECG versus stress echocardiography, there is a moderate to high risk of bias of over 60% for the comparison of exercise ECG with coronary computed tomography angiography (CCTA).

Indirectness determines the transitivity in a network, i.e. the extent to which additional indirect evidence of treatment effects can be included in a network to determine effect estimates from direct comparisons.[9] Each study in the network is categorised as low, moderate, or high indirectness in relation to its relevance to the research

Hypothetical example of a network meta-analysis of four chemotherapeutic agents against a specific tumour, with violation of the transitivity assumption



Source: [10]

Figure 2: The comparisons of A and D for tumour stage II and A, B and C in tumour stage I obviously violate the transitivity assumption.

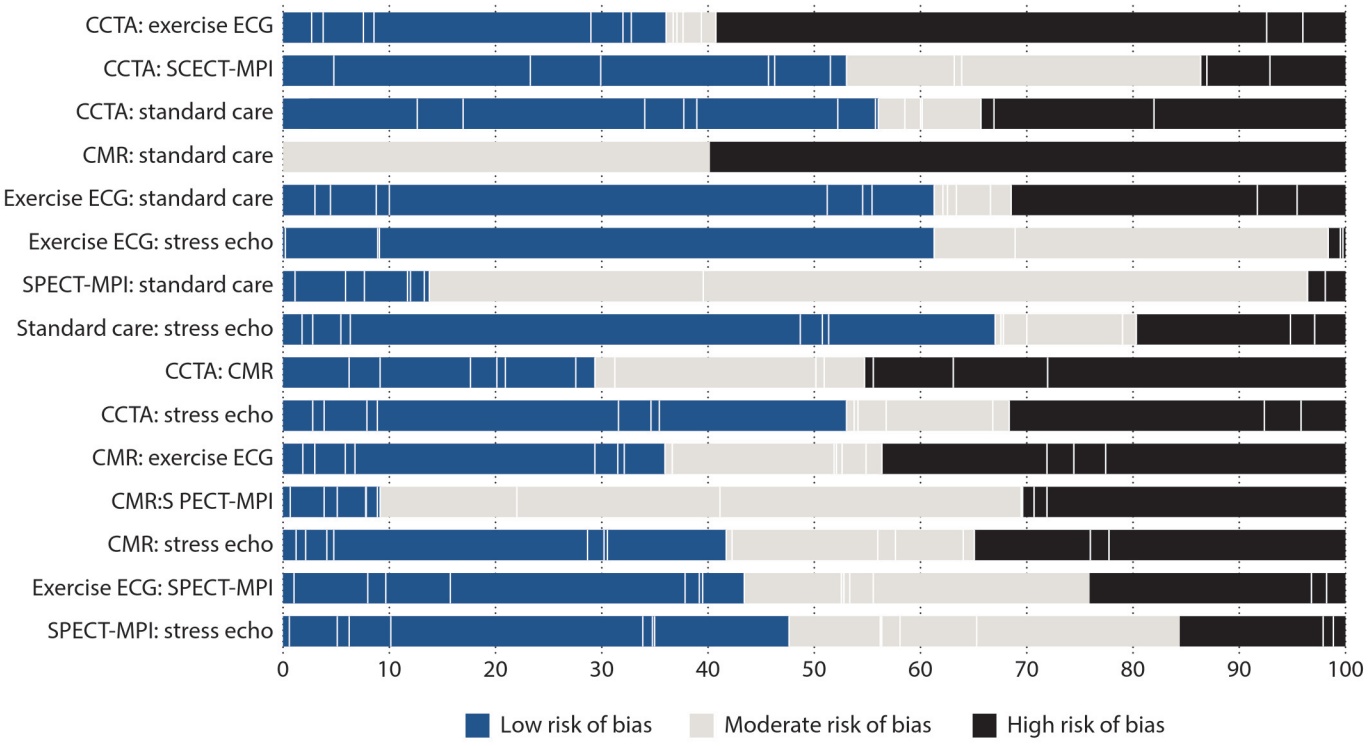
question. For this purpose, only patient characteristics, intervention, and characteristics of the outcomes that may be associated with the relative treatment effect under investigation (so-called effect modifiers) are considered. Different distribution of effect modifiers in a network means intransitivity and is associated with a higher probability of bias. Intransitivity often occurs when there are too few studies in a network, effect modifiers are not measured or reported, and when studies in a network are incompletely linked. The extent of indirectness of individual studies in the various comparisons can in turn be visualised in a bar chart using the matrix structure.

Incorporating external evidence via indirect comparisons has the potential to enhance the precision of effect estimates in a network meta-analysis. The CINeMA approach divides the precision of effect estimates into three categories: A better, no difference between A and B, and B better, where the middle range is defined as the equivalence range corresponding to a clinically irrelevant difference. This should correspond to an absolute effect that is relevant (in our case not relevant) for patients. If the 95% confidence interval extends beyond the equivalence range beyond the zero-effect line of the point effect estimator, a rating of „large imprecision" is applied

The precision of an effect estimator is classified as imprecise if the confidence interval extends into the equivalence range but does not extend beyond the equivalence range beyond the zero line (scenario 2 in figure 4). There is no imprecision if the confidence interval lies completely on one side of the zero line or completely in the equivalence range (scenarios 3 and 4 in figure 4).

Heterogeneity refers to genuine variability of effect estimates from individual studies that goes beyond random scattering. In network meta-analyses, there is variation in treatment effects between studies, i.e. heterogeneity and variation between treatment effects of direct and indirect comparisons, which in CINeMA (in contrast to GRADE) is referred to as incoherence. The variance of the distribution of an underlying treatment effect (τ 2) is a measure of heterogeneity and is determined in a random effect model and with a prediction interval, which shows in which range the true effect of a new study, similar to the existing studies, is to be expected. In the CINeMA approach, heterogeneity is again assessed in terms of the overlap of the confidence and prediction intervals with the equivalence ranges of effect estimates. If, as in scenarios 1, 2, 5, and 7 in figure 4, both scenarios are congruent, low heterogeneity is assu-

Bar chart showing the proportional contribution of studies in a network of direct and indirect comparisons on diagnostic procedures for coronary heart disease and the respective risk of a bias of a certain relative effect estimator



Source: [9]

Figure 3: The bar chart illustrates the extent of bias for each comparison as a function of study weight in the network.

med. In cases where confidence and prediction intervals, the zero line or the equivalence range are exceeded, a certain (scenarios 3 and 6) or large heterogeneity (scenarios 4 and 8 in figure 4) is assumed.

Incoherence refers to the extent of transitivity calculated using statistics, i.e. the assumption that relative effect estimates of direct comparisons and indirect comparisons via a bridge comparator are congruent. If direct and indirect comparisons are not congruent, the assumption of transitivity is violated and there is incoherence. The extent of coherence can be calculated using various methods. The „node splitting" method (so-called local or loop method) determines the consistency for each direct and indirect comparison in the network by determining the ratio (ratio with 95% confidence interval of the odds ratios for the direct and indirect comparison) or the difference for the

two comparisons.

A broader or global approach is the simultaneous modelling of all comparisons and consistency ratios in the network, with the determination of the extent of coherence by means of a design-by-treatment interaction test of direct and indirect comparisons. There is low statistical power for both approaches. Scenario 3 in figure 4 shows different possibilities of incoherence, the extent of which can be assessed for clinical decision making with the CINeMA approach in relation to the equivalence range. It should be noted that coherence cannot be determined using the node splitting method in a network for a comparison pair where only either direct or indirect comparisons are available. In this case, only the global approach can be used, whereby CINeMA assumes significant or large inconsistency in this situation with an interaction test of $p < 0.10$.

A final evaluation of the validity of a network meta-analysis is carried out with a rating across all six domains. This is challenging and necessary as the individual domains are not independent of each other. High heterogeneity can make the determination or static force for measuring incoherence difficult or impossible, and high imprecision also has an influence on the extent of heterogeneity.

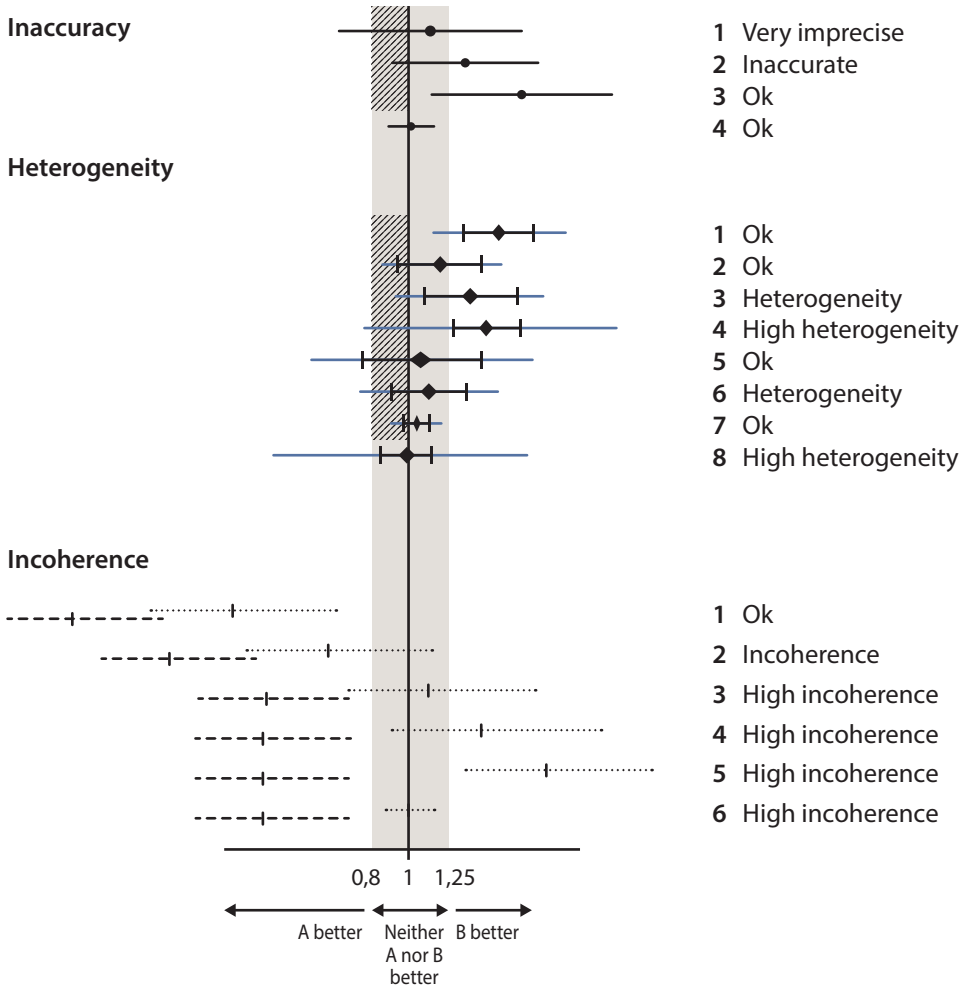
With the increasing use of the network meta-analysis technique, the use of rankings, particularly using Bayesian models, to recommend a „best" intervention has also increased. Practical Guideline D 4.3.1 also recommends rankings by means of so-called Surface Under the Cumulative RAnking Curves (SUCRA) and the indication of probabilities of best treatment, but rightly concedes that the classification systems are often interpreted incorrectly.[2] Nonetheless, there is a lack of guidance on how not to misinterpret them.

Better clarity can be achieved by means of a treatment hierarchy question defined in the study protocol, which describes the criteria according to which a hierarchy of treatments is created. The approach of Salanti et al, which will also be incorporated into CINeMA in the future, will be briefly presented here.[17] The criteria are based on questions relevant to decision-makers, such as which treatment is most likely to be associated with a median survival of at least two years or with the longest median survival. A recommendation is then made according to the treatment hierarchy question based on the maximisation process using ranking statistics. A ranking statistic represents a treatment-specific overarching probability distribution of absolute or relative treatment effects.

Since relative treatment effects compared in network meta-analyses are subject to a probability of error, a clear hierarchisation of multiple comparisons measured with error is difficult. A ranking of only point estimators answers the question of which treatment is associated with the greatest possible mean advantage over other comparator treatments, but only considers the respective uncertainty measure of each point estimator and not that of the entire network. This ranking is particularly unreliable for networks with small studies and numbers of cases.

In a Bayesian model, on the other hand, posterior averaged treatment effects are given with a credible interval for a range of possible values. Probability-based ranking answers the question of which treatment is most likely to have the best averaged outcome for the outcome of interest. Rankograms and cumulative ranking plots do not only consider mean values or ratios but calculate the probabilities for a ranking based on the overall distribution curves of effect estimates and are thus distribution curves of rankings. SUCRA determine a numerical summary of rankograms and answer the question of which treatment beats or outperforms the largest proportion of comparator treat-

CINeMA decision rules for assessing imprecision, heterogeneity and inconsistency in network meta-analyses



Key: Black lines: Confidence intervals, blue lines: Prediction intervals, grey area: Area of equivalence with odds ratio range from 0.8 to 1.25, dashed area: Interval between no effect and clinically relevant effect in the opposite direction from the observed effect. For coherence: dashed line: direct effect, dotted line: indirect effect.

Source: [9]

Figure 4: The precision of an effect estimator is classified as imprecise if the confidence interval extends into the equivalence range but does not extend beyond the equivalence range beyond the zero line (scenario 2).

ments. Compared to a simple ranking, SUCRA reflects the overlap of treatment comparisons.

The higher the overlap, the more similar SUCRA values are. High scatter values (variance) of effect estimates lead to a high overlap of the treatments investigated and can change positions in the ranking: I.e. high scatter values and lack of precision of an effect estimator of interest can lead to a lower ranking of the effect estimator of interest with smaller scatter values of competitive comparative treatments.

Due to these aspects, a „naïve" rating should be avoided, and a classification of therapies should be carried out considering all validity criteria of CINeMA and with special consideration of the extent of overlap of SUCRA values.[18] Nevill et al.[19] have developed an extended graphical method that allows a better interpretation of the SUCRA ranking depending on the network structure and precision of effect estimators.

Figure 5 shows an example of a SUCRA circular ranking plot of a network meta-analysis on weight-reducing pharmaceuticals, which allows a better interpretation of a ranking and combines the ranking with network characteristics. The development of methods for calculating and visualising rankings is in a state of flux, but guidelines for an improved interpretation of treatment rankings in network meta-analyses must be provided.

Discussion and conclusions

Indirect comparisons are becoming increasingly important in HTAs and the assessment of additional benefit, as the number of approvals based on pivotal trials by the EMA is increasing due to innovation in the life sciences. The Methodological Guidelines 4.3.21 and Practical Guideline D 4.3.1. on direct and indirect comparisons2 focus on network meta-analyses of randomised controlled trials based on aggregated data in the description of methodological procedures for indirect comparisons. In addition, so-called population-adjusted methods such as multilevel network meta-regression or matching-adjusted indirect comparisons are discussed. Analytical methods of studies based on prospective, standardised observational data are mentioned only cursorily. The methodological advantages of a target trial simulation and its importance of a standardised comparison including all known confounders and inverse probability-based adjustment procedures[6,20] are only mentioned cursorily in the Methodological Guidelines 4.3.2. Detailed information on the assessment of the validity of target trial simulations or propensity score matching is missing.

The present guideline thus represents a step backwards compared to the publication of the French Haute Autorité de Santé (HAS), which formulated its requirements regarding the use of target trial simulation for HTA reports that are not based on randomised controlled data and was also involved in the development of the present guidelines.[21]

Even if a broad overview of methodological indirect comparison procedures based on network meta-analyses is justified, the weighting of content in the guideline is at odds with the reality of HTA submission procedures. This is underlined by an analysis of the applications for benefit assessments on active substances based on indirect comparisons assessed by IQWIG from 2011 (introduction of the Act on the Reform of the Market for Medicinal Products (AMNOG)) to 2017.[22] During this period, 267 procedures were completed, of which 62 applications included indirect comparisons. These applications comprised a total of 111 indirect comparisons, of which 52% were based on meta-analyses using the Bucher method,[23] 5% on network meta-analyses, 41% on unadjusted indirect comparisons and 5% on adjusted indirect comparisons.

In total, 96% of the applications were rejected, with inappropriate comparative therapy (8.1%), incomplete study data (38.7%), inadequate study eligibility (47.7%), study similarity (39.6%), statistical procedures (25.2%), and lack of homogeneity (2.7%) being the main reasons for rejection. Of the accepted indirect comparisons, three were based on the Bucher method, whereby no additional benefit was attested in any case.

The data on IQWIG assessment procedures can certainly not be transferred in full to the practice of the HTA institutions of the other member states and information on trends in subsequent years is lacking. Nevertheless, it can be seen that meta-analyses with the simplest comparison pattern (triangular network AB versus BC versus AC) and small study pools in addition to indirect non-randomised comparisons are in the foreground for applications with indirect comparisons.

However, in network meta-analyses with a simple loop structure and a limited number of studies, validity problems are more frequent due to the lack of possibilities to prove transitivity and coherence. This raises fundamental questions about the weighting of evidence in HTA reports based on small network meta-analyses. However, both the Methodological Guidelines 4.3.21 and the Practical Guideline D 4.3.1. on direct and indirect comparisons[2] suggest in their structure and argumentation that indirect methods based on meta-analyses should be given a higher priority.

Too little weight is given to testing alternative approaches using standardised indirect comparisons with individual, prospectively collected, highly standardised patient data. This weighting contradicts empirical evidence, which shows a high degree of agreement between the results of selected randomised controlled studies and studies emulated based on observational data on the same study question.[24,25]

The constellation of the choice of methods for indirect comparisons in the AMNOG applications examined in the study by Werner et al[22] further underlines the urgency of expanding methodological aspects in HTA guidelines for indirect adjusted comparisons. The focus here is on the prospective standardised collection of real-world evidence, target trial simulation with target trial protocol development, the careful specification of confounding and effect modification with the aid of confounder diagrams (directed acyclic graphs (DAGs)) as well as statistical analyses using inverse probability weighting procedures.

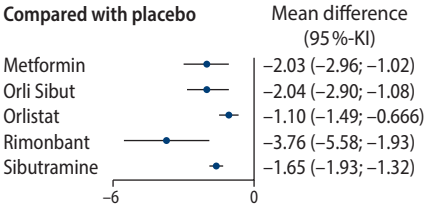
The EUnetHTA processes, which will soon come into force across member states, require not only guidelines that list and describe methodological procedures for HTAs, but also guidance on assessing the validity of HTA applications based in particular on indirect comparisons. Using the example of network meta-analysis, the innovative CINeMA approach to assessing the validity of network meta-analyses was presented.

Only the use of uniform standards to assess the validity of HTA reports with indirect comparisons allows a reduction of „elements of subjectivity in the assessment of many assumptions and that [this] decisions [may] vary between member states“ and thus a more uniform assessment and weighting of indirect evidence presented in HTA reports across member states.[2]

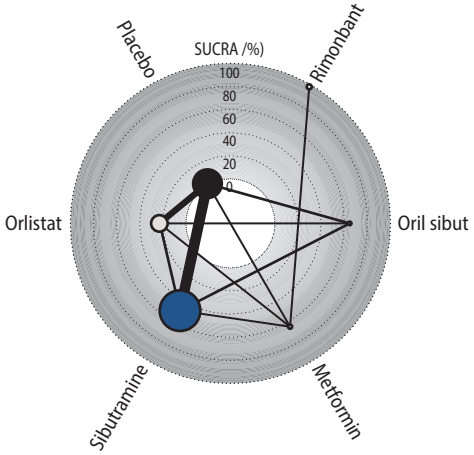
The current state of development of the Guidelines 4.3.2 on methodology1 and the Practical Guideline D 4.3.12 on direct and indirect comparisons give rise to justified fears that future submissions of HTA reports on innovative pharmaceuticals and therapies based on indirect comparisons within the framework of EUnetHTA will not benefit from simplified cross-Member State processes, but on the contrary will be confronted with higher hurdles due to insufficiently specified requirements. It remains to be seen whet-

Graphical representation of treatment effects and hierarchical classification using a SUCRA circle plots

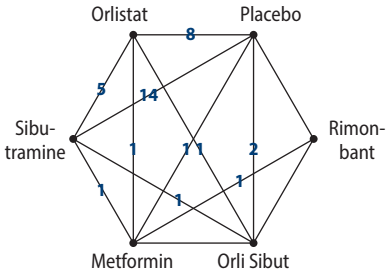
A. Relative effects of therapies to reduce body weight (body mass index)



B. Ranking results



C. Network of all included studies



Explanation: Figure B: The probability of a higher ranking increases from the centre to the periphery (range from 0 to 100%). The thickness of the bars corresponds to the number of comparative studies (number in figure C). The thickness of the nodes corresponds to the number of patients in the comparison. Sibutramine (blue node) has the highest rating and the higher number of patients, but in terms of direct comparisons with competing weight loss interventions, only orlistat has been investigated in more than one study

Source: [19]

Figure 5: Example of a SUCRA circular ranking plot of a network meta-analysis on weight-reducing pharmaceuticals, which allows a better interpretation of a ranking.

her and to what extent HTA applications based on optimal methodology and standardised high-quality data from indirect comparisons will be given a chance for market launch in the cross-member state HTA processes.

References

[1] EUnetHTA. Methods Guideline D4.3.2 DIRECT AND INDIRECT COMPARISONS. 29. 07. 2022(Version 1.0). https://go.sn.pub/pc2SCx. Accessed August 20, 2023.

[2] EUnetHTA Individual Practical Guideline Document D4.3.1: DIRECT AND INDIRECT COMPARISONS. 16.12.2022(Version 1.0). https://www.eunethta.eu/d4-3/. Accessed August 20, 2023.

[3] EUnetHTA. COMPARATORS & COMPARISONS: Direct and indirect comparisons. November 2015. https://go.sn.pub/BMu1Id. Accessed August 20, 2023.

[4] Bucher HC. Methoden für indirekte Behandlungsvergleiche – eine Fallanalyse. Interdisziplinäre Plattform zur Nutzenbewertung 2023 September (Auswirkungen von EU HTA auf das AMNOG-Verfahren) (in press);2023; 17:44-57.

[5] Bucher HC. Bemessung des Zusatznutzens von Arzneimitteln ohne RCT – ein Fallbeispiel. INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT AMNOG: Finanzstabilisierung – neue Behandlungsparadigmen. März 2023;16:48-59.

[6] Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-764.

[7] Hernan MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA. 2022;328(24):2446-2447.

[8] Agency EM. Exceptional circumstances. https://go.sn.pub/5JH8Zm Accessed 20.08., 2023.

[9] Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med. 2020;17(4):e1003082.

[10] Cochrane Collaboration Chapter 11: Undertaking network meta-analyses. 2023. https://go.sn.pub/7fppPN.
Accessed 20. August 2023.

[11] Papakonstantinou T, Nikolakopoulou A, Rucker G, et al. Estimating the contribution of studies in network meta-analysis: paths, flows and streams. F1000Res. 2018;7:610.

[12] Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. PLoS One. 2014;9(7):e99682.

[13] CINeMA Confidence in Network Meta-Analysis. Institute of Social and Preventive Medicine; University of Bern; 2020. https://cinema.ispm.unibe.ch/. Accessed August 20, 20234.

[14] Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making. 2013;33(5):641-656.

[15] Veroniki AA, Tsokani S, White IR, et al. Prevalence of evidence of inconsistency and its association with network structural characteristics in 201 published networks of interventions. BMC Med Res Methodol. 2021;21(1):224.

[16] Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 2018;93:36-44.

[17] Salanti G, Nikolakopoulou A, Efthimiou O, Mavridis D, Egger M, White IR. Introducing the Treatment Hierarchy Question in Network Meta-Analysis. Am J Epidemiol. 2022;191(5):930-938.

[18] Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Syst Rev. 2017;6(1):79.

[19] Nevill CR, Cooper NJ, Sutton AJ. A multifaceted graphical display, including treatment ranking, was developed to aid interpretation of network meta-analysis. J Clin Epidemiol. 2023;157:83-91.

[20] Hernán MA RJ. Causal Inference.: Boca Raton, FL: Chapman & Hall/CRC; 2016.

[21] Vanier A, Fernandez J, Kelley S, et al. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. BMJ Evid Based Med. 2023.

[22] Werner SL, L. Rasch, A. Merkesdal, S. Ruof, J. Untersuchung der Akzeptanz und der Ablehnungsgründe indirekter Vergleiche in IQWiG-Nutzenbewertungen. Gesundh ökon Qual manag. 2020;25((01)):24-36.

[23] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683-691.

[24] Wang SV, Schneeweiss S, Initiative R-D, et al. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. JAMA. 2023;329(16):1376-1385.

[25] Ewald H, Speich B, Ladanie A, Bucher HC, Ioannidis JPA, Hemkens LG. Marginal structural models and other analyses allow multiple estimates of treatment effects in randomized clinical trials: Meta-epidemiological analysis. J Clin Epidemiol. 2019;107:12-26.

AMNOG 2.0 – on the path to an efficient system? Main topics of discussion with the speakers

Dr Harald Herholz, MPH | Department of Medicines, Remedies and Aids of the KV Hessen, Frankfurt am Main

Against the background of the Financial Stabilization of Statutory Health Insurance (GKV-Finanzstabilisierungsgesetz, GKV-FinStG) and the three presentations by Dr Georg Kippels, MP, on „Innovation and efficiency – synergy or contradiction?", Mr Olaf Weppner on „Efficiency of the AMNOG process – the industry perspective", and Dr Antje Haas on „Efficient pricing concepts with gene therapies", the panel discussion reflected on the following topics:

- *According to initial analyses by various institutes, the expected savings targets of the GKV-FinStG will not be achieved by a long way. Health insurances are warning that the reins should be pulled tightened. What can be done?*

- *Several speakers proposed a reform of the citizens' benefit (formerly unemployment benefit II) and a reduction in VAT from 19 to 7% for pharmaceuticals. Both points would lead to major relief. It would be wrong to expect effective short-term savings from the tools mentioned in the GKV-FinStG. Only the compulsory discount shows immediate savings, and at 1.3 billion euros it is higher than expected.*

Dr Harald Herholz, *MPH, completed his studies in human medicine at the Johann Wolfgang Goethe University in Frankfurt am Main. He earned his doctorate in the Department of Cardiology and engaged in clinical work in rheumatology. Dr Herholz pursued studies in public health at the Hannover Medical School under the guidance of Professor F. W. Schwartz. During a research stay he served as a research assistant at the Department of Epidemiology within the School of Public Health at the University of Texas Health Science Centre in Houston. He then worked at the Association of Statutory Health Insurance Physicians in Hesse, Frankfurt am Main where he initially served as a personal advisor to the Board of Directors and later took on the role of Quality Assurance Officer. Since 2012, he has been associated with the Department of Medicines, Remedies & Aids of the KV Hessen.*

- *Evidence assessment should not be made even more complex. The feasibility of implementation by the Federal Joint Committee (G-BA) and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) must be kept in mind. While industry representatives clearly reject the new pricing guidelines, particularly in connection with the 20% combination discount, representatives of health insurances are satisfied with the new differentiation between patent-protected and non-patent-protected comparative treatments. Too often, therapies have benefited from expensive comparators. In addition, in recent years there have often been large price jumps, even with small innovation steps by medicines. This was now different:*

- *The technical design of the combination discount was criticised. It should be clear from the legal text when a combination exists and in what time frame - but this basis was lacking, said several lawyers.*

- *From the industry's point of view, the combination discount in conjunction with the pricing guidelines would lead to prices being too low, resulting in therapies no longer being introduced in Germany. For this reason, a constitutional complaint has been filed.*

- *The fact that individual health insurances rejected this tool because its implementation was a lot of work was disputed in the discussion. After all, there were enormous potential savings to be made here. It also made sense to focus on the free combinations. However, there was a lack of implementation by the G-BA. The lists drawn up there were too time-consuming. It would be much more pragmatic to require physicians to use simple coding on the prescription when combining pharmaceuticals.*

Innovation and efficiency – synergy or contradiction?

**Dr Georg Kippels | Member of the German Bundestag,
Chairman of the CDU/CSU Parliamentary Group in the Health Committee**

The German healthcare system is one of the most efficient, yet one of the most expensive in the world. The synergy of innovation and efficiency is required to pursue a „healthy" further development of the system both in terms of content and finances. Innovation – with a view to continuously improving treatment options; efficiency – with a view to optimising processes and saving resources. Innovations are often characterised by limited predictability. Particularly in case of long-term cell and gene therapies, the players in the healthcare system must first learn how to deal with uncertainties. It should also be noted that it is not always only leap innovations that can bring about relevant improvements for patients, but also step-by-step innovations. Criticism of the Financial Stabilisation of the Statutory Health Insurance (GKV-FinStG) and the „guidelines" points to a lack of balance and a one-sided weakening of the incentive to innovate.

The German healthcare system is one of the most efficient, yet one of the most expensive healthcare systems in the world. Our aim is to provide patients with the best possible and, above all, the most innovative care. This claim is in constant competition with the financial viability of this healthcare system.

The competition between these interests can be described very well with the terms innovation on the one hand and efficiency on the other. In fact, the question arises as to whether synergy effects can be leveraged from this or whether this represents a contradiction, possibly even an insoluble contradiction.

In my opinion, there is much to be said for looking at this pair of terms as a partnership and using it as a basis for further development of the German healthcare system both in terms of content and finances. On page 87 of its coalition agreement, the current German government initially called for the supply of innovative pharmaceuticals and vaccines to be ensured. Bottlenecks should be addressed, and the production of pharmaceuticals brought back to Germany.

However, in speeches made last year by Federal Health Minister Karl Lauterbach, it was also pointed out that efficiency reserves should be raised to ensure the long-term financial viability of our healthcare system and – in his opinion – can apparently be raised.

At this point, the question arises as to whether it is not precisely innovations that can create and constantly improve efficiency. Let us first look back at the actual meanings of these two terms. We use innovation to describe the constant search for improvement and new processes to solve existing or newly emerging issues. It is therefore a constant process of change with a positive orientation in order to find answers to questions that were previously

unanswered or at least could not be answered satisfactorily. In contrast, efficiency is oriented towards process improvement, i.e. existing processes are examined with a view to optimisation, whereby they can be made faster, cheaper, and often also more cost-effective in a way that conserves and saves resources. This definition alone shows that the individual objectives can interlock very well, even if they may initially trigger contradictions with regard to the economic situation. To this end, however, it is necessary to define a corresponding timeline on which the individual advances can be weighed up against each other.

As mentioned at the beginning, the German healthcare system is under permanent financial pressure. Major reforms in recent decades, such as in 2004, changed remuneration structures, for example through the introduction of flat rates per case. The German Pharmaceutical Market Reorganisation Act (AMNOG), which came into force on 1 January 2011, intended to create incentives for improvements in patient care by regulating the prices of innovative pharmaceuticals, while only the creation of equivalent alternatives should not trigger a remuneration incentive.

Although these processes have proven their worth over the past decades, they are also subject to constant pressure to adapt to changing conditions. Both the patient structure as a result of demographic change and the emergence of new medical technologies are leading to a recognisable increase in efficiency, although at the same time the cost burden is also increasing. This was one of the reasons for the German so called traffic light coalition (Ampelkoalition) to introduce the GKV-FinStG last year in order to reduce the significantly increasing cost burden caused by innovations, but also to create an incentive to reward far-reaching innovations as opposed to incremental innovations.

The review of the GKV-FinStG and the assessment of the points of criticism raised in the legislative debate show, however, that although innovations are a constant goal of research and development, they can only be subject to planning to a very limited extent. If we therefore evaluate the innovations in the field of individualised medicine, cell and gene therapies, very costly one-off therapies or so-called combination products, the efficiency effect is primarily characterized by the fact that the intensity or duration of treatment is significantly reduced. Although the short-term cost burden is high with the improved success of a partially possible full recovery, the long-term economic view leads to a positive balance.

However, the analysis of the change in development processes and development content also shows that it is not always only leap innovations, but also so-called step innovations in change processes that lead to an efficient

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increase in supply per se, although the timing of the occurrence of such efficiency increases can vary greatly.

There is little doubt that, in view of the capacity of the citizens to bear financial burdens through contribution payments, we must take a much longer-term view of efficiency than may have been practiced or undertaken in the past. It should also not be overlooked that there is a subjective efficiency component in healthcare in particular, namely in the sense that patients are quite willing and able or prepared to incur higher costs at an early stage in order to restore or improve their quality of life and thus lead a longer, unimpaired life. From my point of view, there is much to suggest that innovation on the one hand and efficiency on the other are a pair of interests characterised by synergy effects, although the respective advances do not necessarily have to be made in parallel but can also be made in alternative directions. If, after research and development has been completed, an innovation result is available that cannot be further developed, at least for a foreseeable period of time, there are certainly opportunities to optimise the content of this stage of innovation as part of an efficiency development process. However, the result of such an efficiency improvement process can then in turn represent a switch to a corresponding innovation process because the findings from the efficiency optimisation led to a conceptual and structural change triggering a new innovation.

German legislators now face the particular challenge of ensuring that, despite all efforts to limit costs (and therefore also increase efficiency), the environment of economic activity is not innovation-hampering and thus inhibits innovation. Criticism of the GKV-FinStG and its regulations on the so-called guidelines indicates that the Act has triggered this effect. Innovation incentives are now so difficult to calculate or are so low that they can no longer be brought into a justifiable balance with the economic risks and preliminary investments and can thus no longer be weighed up in an economically reasonable manner.

According to the latest analyses by the German Association of Research-Based Pharmaceutical Companies (vfa) on the effects of the GKV-FinStG and the German Act to Combat and Improve the Supply of Medicines (Arzneimittel-Lieferengpassbekämpfungs- und Versorgungsverbesserungsgesetz, ALBVVG), they acknowledge the need and necessity of research and development to achieve innovation. However, pharmaceutical companies are too heavily burdened with bureaucratic framework conditions that are only or only too one-sidedly dedicated to possible efficiency improvements. However, innovation needs the environment of development spaces and experimental activities with the simultaneous prospect of actually being able to establish the measurable benefits and additional benefit in the system.

I am convinced that these steps will have to be fundamentally analysed in the coming weeks and months, as we will also have to redescribe and redefine the incentive factor of pricing and price regulation for innovative pharmaceuticals and, to this end, examine the system for its efficiency reserves on a permanent and intensive basis.

Let us thus consider the conceptual pair of innovation and efficiency as a mutually enriching competitive situation and in no way as a mutually beneficial dynamic. This should not be perceived as a contradiction, but rather as a desirable synergy.

AMNOG 2.0 – on the path to an efficient system?

Olaf Weppner | Vice President, General Manager, Managing Director AbbVie Deutschland GmbH & Co. KG

The AMNOG, i.e. the combination of benefit assessment and subsequent price negotiation, is at a crossroads. Despite ongoing intense discussion and some criticism, not only from the industry, it has not been optimally efficient over the past ten years but has at least ensured massive savings for payers without major incidents, without losing sight of providing patients in Germany with the latest and most innovative pharmaceuticals. At the end of 2022, politicians decided to make far-reaching and small-scale interventions in the AMNOG system with the aim of achieving further savings in the pharmaceutical sector which call into question not only the efficiency of the system, but also its ability to function as a whole. This article aims to shed light on why the current legislation is heading in the wrong direction and what concrete steps are needed to continue to reconcile cost-effectiveness and quality of care in Germany.

AMNOG: not always optimal, but plannable and functional at the bottom line

Since the introduction of the German Pharmaceutical Market Reorganisation Act (AMNOG) in 2011, pharmaceutical companies have had to prove whether and to what extent a new pharmaceutical provides an additional benefit as compared to the standard therapy (the so-called appropriate comparative therapy) when launching a pharmaceutical on the market. A price negotiation then takes place on the basis of this assessment.

With the core principle of the AMNOG – a price negotiation that is orientated towards the additional benefit assessment and the value of the product – a generally accepted balance between three important pillars has been maintained in Germany for several years:

I. Innovations were quickly available to patients in Germany.

II. The prices for innovative pharmaceuticals were orientated towards the value of the innovation and were economical.

III. The attractiveness of the location was ensured by reliable framework conditions for patient care, innovation, and jobs in the innovation-driven pharmaceutical industry.

The AMNOG was not always optimal with regard to various aspects. From the industry's perspective, the methodological corset in particular – such as the definition of so-called patient-relevant endpoints, dealing with indirect comparisons or additional benefits that only materialise in the long-term – posed major challenges for some therapies. The AMNOG has also become increasingly bureaucratic with regard to the „technical" requirements relating to the module templates for the dossiers and has become out of hand in some cases. According to empirical studies, the requirements for dossiers have increased by a factor of 4 to

5 over the years from an average of approx. 750 to 3,500 pages for modules 1-4 alone[1], whereby the added value of some of this additional information, e.g. on subgroup analyses, for decision-making in the AMNOG appears unclear to say the least.[2, 3]

On a positive note, however:

- Germany is the European leader in terms of pharmaceutical availability: according to statistics, 92% of the pharmaceuticals approved between 2017 and 2020 were available to patients in Germany.[4]
- The AMNOG has provided a lot of impetus, e.g. improving evidence. In particular, patient-reported endpoints on morbidity and quality of life have become established in study design.[5, 6]

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- In most cases, the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and the pharmaceutical companies were obviously able to agree on the price. The process is also having a financial impact – the savings for statutory health insurance are estimated to be around 8.3 billion euros for 2023.[7]
- Last but not least, the specifications and framework conditions set by the system were largely predictable for health insurances and the pharmaceutical industry.

GKV-FinStG as a system break with harmful long-term consequences

The Financial Stabilisation of the Statutory Health Insurance (GKV-FinStG)[8] passed at the end of 2022 made far-reaching changes to the basic concept and practice of the AMNOG. The law adopted a series of rules that met with great resistance from almost all stakeholders in the healthcare system. Among other things, this criticism centred on the fact that such massive interventions in the existing system and the logic of the AMNOG, which had not been fully thought through in several places, were harmful to the care of patients in Germany and the innovative pharmaceutical industry. The Bundesrat (Federal council) stated that the law jeopardised the innovative strength and performance of the pharmaceutical industry in Germany.[9,10]

Until recently, the AMNOG applied the following principle: pharmaceuticals with a proven additional benefit (categories low, considerable, substantial, unquantifiable) may cost more than the appropriate comparative therapy. With the GKV-FinStG, this principle has now been discarded – in future, minimum discounts will apply in case of minor or non-quantifiable additional benefit, despite patient-relevant therapeutic progress. In addition, the degree of complexity of many regulations has reached a level that even experts can barely comprehend, e.g. the combination dis-

counts, which have still not been finalised around a year after the law was passed. Instead of modernising methods, strengthening the principle of negotiation, and reducing bureaucracy, the AMNOG, the hallmark of the German healthcare system in an international context, introduces regulations that slow down innovation and thus moves further away from a more efficient system.

Although the planned interventions are aimed at making savings, they are unnecessary. If you look at the dynamics of expenditure, it becomes clear that pharmaceuticals are not the main driver of expenditure in the statutory health insurance system. Pharmaceutical expenditure accounts for around 12%[11] of expenditure in the statutory health insurance system and has remained constant for many years.[10] In addition, pharmaceutical prices have been falling for several years, in contrast to general consumer prices.[12, 13]

Devaluation of the additional benefit and the significance of step innovations for those affected

The so-called „guidelines" formulate specifications for the AMNOG price negotiations between the GKV-Spitzenverband and pharmaceutical companies. They regulate small-scale price caps for innovative pharmaceuticals depending on the patent and document protection of the appropriate comparative therapy and the extent of the additional benefit. With the introduction of the „guidelines", the previously valid and proven basic principle of „higher prices for products with additional benefit" and „same price for the same benefit" has been destroyed. Instead, the following now applies in many cases: „at most the same price despite proven additional benefit" (for minor or unquantifiable additional benefit) and also „at least 10% lower price, although the benefit is not less" (for unproven additional benefit).

This new rule devalues and ignores the significance of the „minor" additional benefit (according to the Pharmaceutical Products Benefit Assessment Ordinance (AM-NutzenV), a „not only minor improvement in the therapy-relevant benefit") and the non-quantifiable additional benefit (which cannot be reliably categorised between minor and significant) as well as the significance of the proven progress in therapy for those affected.

The following example is an impressive illustration of how important step innovations are for patients and society: The fatal infectious disease HIV has now become a chronic disease thanks to 33 new active substances from seven classes (as of 2021).[14] The development took place in numerous small steps – steps that would not have been recognisable progress according to the GKV-FinStG and would not have justified a higher price for a pharmaceutical. If we no longer honour the individual steps in future, then we will lose these steps and innovations for German healthcare.

The devaluation of the additional benefit goes hand in hand with a whole series of other new savings regulations in the „guidelines", which define discounts for a wide variety of case constellations: Discounts for patent-protected comparator therapies, discounts for comparable pharmaceuticals that have not yet undergone the AMNOG, discounts for combination therapies, etc. The fact that these discounts add up when several case constellations coincide has particularly drastic effects. The result is absurd total discounts, which in individual cases leave the negotiating parties with hardly any room for manoeuvre to reach an agreement on the reimbursement amount.

Overall, Germany is losing a great deal of flexibility – meaningful negotiation solutions are made impossible by the prescribed regulations. The system takes away the room for manoeuvre for special therapy situations that had

only been achieved in the past with several amendments to the law.

Combination discount: an inefficient set of rules

In future, a so-called combination discount of 20% will apply to pharmaceuticals with new active substances that are used in a combination previously specified by the Federal Joint Committee (G-BA) and are given in free combinations, unless the combination can demonstrate at least a considerable additional benefit.

It is also important to note that combinations form the backbone of medical progress in many therapeutic areas, including combinations with an additional benefit below considerable. As a result, therapeutic successes can now be recorded for a whole range of diseases, e.g. in the treatment of oncological diseases. These therapeutic successes were often inconceivable just a few years ago.

Even before the GKV-FinStG, pharmaceutical combinations were already subject to evaluation and negotiation of their total price based on their overall benefit. A special discount can therefore not be justified in terms of content. Even the GKV-Spitzenverband considers the savings potential to be very limited.[15] The implementation of the combination discount by naming the combination partners or processing the combination discount has also raised questions for almost a year and is difficult from many perspectives. The combination discount has not created a savings measure, but another bureaucratic monster.

GKV-FinStG has negative consequences for those affected and for Germany as a centre of innovation

Due to the previously existing framework conditions, German subsidiaries of internationally operating companies have acquired an important role. In the past, companies have conducted studies that were explicitly planned for the German market or adapted global study programmes to German HTA requirements. Poorer reimbursement conditions mean that global companies are looking more critically at the German market.

On the one hand, the clinical studies will then be less and less adapted to the German healthcare context, and on the other hand, fewer German centres will participate in the clinical studies. This will counteract the expected incentive for more evidence generation in Germany. Overall, access to new pharmaceuticals in Germany will become more difficult and innovations will not reach patients.

Solution approach

It is beyond debate that further development and improvement of efficiencies in the AMNOG are necessary. However, this further development requires sensible and well-thought-out measures for the long-term stabilisation and modernisation of the benefit assessment and reimbursement rules. This is the only way that innovations in Germany can reach those affected in the future. In addition to the correction of the GKV-FinStG and the abolition of the introduced rules, there are a number of measures that the pharmaceutical industry considers to be absolutely necessary and for which it encourages a joint dialogue.[16]

- **Strengthening the AMNOG principle and value-based price negotiation, freedom for new contract models:** The core principle of benefit-based pricing for innovative pharmaceuticals has always been: Statutory health insurance funds are allowed to pay more if there is an improvement over the previous standard therapy. The significance of the additional benefit must be restored by abolishing the „guidelines". In addition, it is necessary to strengthen the negotiation principle of the AMNOG, the basic idea of which is that the negotiating

partners – the GKV-Spitzenverband and the pharmaceutical company – agree on a common perspective on the value of a pharmaceutical. The negotiating partners do not need micromanagement, but rather the necessary leeway to recognise therapy improvements in special therapy situations and to take the respective market situation into account.

- **Consideration of special therapy situations in the early benefit assessment:** New therapies are becoming increasingly targeted and the group of patients to be treated is becoming smaller. Scientific progress is thus becoming a challenge for benefit assessments within the existing AMNOG corset because effects in AMNOG-compliant patient-relevant endpoints are difficult or impossible to prove. Even if randomised controlled trials continue to be the standard, conducting them is not always sensible. Here, the AMNOG can learn a lot from the regulatory authorities, which decide on a case-by-case basis what are adequate study designs. The German HTA system must learn to deal methodically with such situations and allow more flexibility in dealing with uncertainty in the data situation.
- **Special provision for therapeutic soloists:** In therapeutic situations where no adequate treatment option exists to date, particularly for rare conditions, every new treatment option is of great importance and value to those affected. All new therapies that cover a situation without sufficient treatment options and that have already demonstrated an improvement in the treatment situation with positive clinical studies should be recognised per se as having at least an additional benefit relevant to negotiations. They will then be price-regulated under these initial conditions in the AMNOG.
- **Critical review and adjustment of the national requirements to the decision-relevant measure:** Not only should the methods evolve, but the AMNOG must become less bureaucratic overall. The technical requirements relating to the early benefit assessment, in particular the dossier requirements, e.g. relating to subgroups or side effects, must be scrutinised for their necessity and reduced to the relevant level. This will contribute to efficiency for the entire process and for all those involved.
- Priority regulation for EU HTA: From 2025, new pharmaceuticals and their indication extensions will gradually be subjected to a joint European benefit assessment. The AMNOG must utilise the momentum here to learn from other European HTA systems and further develop local methods. Taking into account the current results from EUnetHTA21, there is a risk that we will initially have to carry out the European assessment separately and then go through additional extensive processes in Germany. Here we need a clear priority regulation for EU HTA.3

Conclusion

In an attempt to generate savings, the GKV-FinStG introduced a series of regulations relating to innovative pharmaceuticals and the AMNOG that are neither effective nor efficient and also jeopardise the care of patients in Germany and the innovation location as such. They devalue incremental innovations and weaken previously reliable framework conditions for the care of the insured as well as the business location.

A correction of the GKV-FinStG and the abolition of these regulations is imperative in this context. Although further development of the AMNOG is necessary, this should take place in dialogue with the pharmaceutical industry. The following principles should be anchored at the core of this further development:

- Strengthening the AMNOG principle and value-based price negotiation, freedom for new contract models,
- Consideration of special therapy situations in the early benefit assessment,
- Special provision for therapeutic soloists,
- Critical review of the national requirements, e.g. relating to module templates or the complexity of data collection accompanying the application,
- Priority regulation for EU HTA: Further development of German methods and greater utilisation of synergies with the introduction of the EU HTA.

References

[1] Association of Research-Based Pharmaceutical Companies (vfa) AMNOG dossier templates: Reduzierung nötig 2022. (Reduction necessary 2022.) Available at: https://go.sn.pub/TkzkPn.. [accessed: 22 November 2023].

[2] Schweitzer MK, Dold MN, et al. Auswirkungen der neuen Dossieranforderungen auf Nutzendossiers und Bewertungen durch das IQWiG des G-BA. (Effects of the new dossier requirements on benefit dossiers and assessments by the IQWiG of the G-BA.) Monitor Health Services Research. 2023;03/23:40-4.

[3] Schweitzer MK, Dold MN, et al. Shaping a suitable EU HTA dossier template: why the German template is not fit for purpose. The European journal of health economics. 2023.

[4] European Federation of Pharmaceutical Industries and Associations (EFPIA). EFPIA Patients W.A.I.T. Indicator 2021 Survey 2022. Available at: https://go.sn.pub/chWcjU. [accessed: 27 November 2023]

[5] Association of German Substitute Health Insurance Funds. „Mehr Daten allein reichen nicht" („More data alone is not enough" (Interview with Dr Thomas Kaiser, Director of the Institute for Quality and Efficiency in Health Care (IQWiG)) 2022.) Available at: https://go.sn.pub/tVmdba. [accessed: 11 December 2023].

[6] Federal Joint Committee (G-BA). Seit 10 Jahren als lernendes System etabliert: (Established as a learning system for 10 years:) Nutzenbewertung von neuen Arzneimitteln 2021. (Benefit assessment of new pharmaceuticals 2021.) Available at: https://go.sn.pub/wEB811. [accessed: 11 December 2023].

[7] IGES. AMNOG-Rabatte: (AMNOG rebates) Einsparungen von 8,3 Milliarden Euro in 2023 erwartet. (Savings of 8.3 billion euros expected in 2023.) Available at: https://go.sn.pub/s2yNtx. [accessed: 27 November 2023].

[8] Federal Law Gazette. Financial Stabilization of Statutory Health Insurance (GKV-Finanzstabilisierungsgesetz, GKV-FinStG) dated 7 November 2022, 07 November 2022. Available at: https://go.sn.pub/9cb8OL. [accessed: 22 November 2023].

[9] Federal Association of Self-Help for People with Disabilities and Chronic Illnesses and their Relatives (BAG SELBSTHILFE e. V.). Statement of the Federal Association of Self-Help for People with Disabilities and Chronic Illnesses and their Relatives (BAG SELBSTHILFE) on the draft bill of the SPD, Alliance 90/The Greens and FDP parliamentary groups Draft Act on the Financial Stabilisation of Statutory Health Insurance (GKV-Finanzstabilisierungsgesetz - GKVFinStG) 2022. Available at: https://go.sn.pub/gKQwE2. [accessed: 27 November 2023].

[10] Bundesrat (Federal council). Statement of the Federal Council Draft Act on the Financial Stabilisation of Statutory Health Insurance (GKV Financial Stabilisation Act - GKVFinStG) 2022. Available at: https://go.sn.pub/Xo9aaV. [accessed: 27 November 2023].

[11] Association of Research-Based Pharmaceutical Companies (vfa) Pharmaceutical expenditure quickly explained 2023. Available at: https://go.sn.pub/c3kmXG. [accessed: 27 November 2023].

[12] Federal Union of German Pharmacists' Associations (ABDA). The pharmacy. Figures. Data. Facts. 2023. Available at: https://go.sn.pub/YjFYVb. [accessed: 22 November 2023].

[13] Association of Research-Based Pharmaceutical Companies (vfa) Statement Evaluation of the effects of the Financial Stabilisation of Statutory Health Insurance (GKV Financial Stabilisation Act - GKVFinStG) on healthcare and the business location 2023. Available at: https://go.sn.pub/RjxAbZ. [accessed: 01 December 2023].

[14] Association of Research-Based Pharmaceutical Companies (vfa) Individual-Kombis: (Individualised combos:) In der HIV-Therapie ein Muss 2022. (A must in HIV therapy 2022.) Available at: https://go.sn.pub/rJcHfx. [accessed: 11 December 2023].

[15] National Association of Health Insurance Funds (GKV-SV) Statement of the National Association of Statutory Health Insurance Funds of 23 September 2022 on the draft law on the financial stabilisation of statutory health insurance (GKV Financial Stabilisation Act) of 19 September 2022, Bundestag printed paper 20/3448 2022. Available at: https://go.sn.pub/ghJ0T5. [accessed: 22 November 2023].

[16] Association of Research-Based Pharmaceutical Companies (vfa) AMNOG 2025 – current fields of action 2023. Available at: https://go.sn.pub/269M2K. [accessed: 22 November 2023].

Efficient pricing for gene therapies

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Gene therapies have considerable potential in the treatment of diseases. It is expected that by 2030 more and more of these therapies are available with an increasing focus on common diseases. The pricing of gene therapy products continues to show a considerable discrepancy to the available evidence. It is questionable whether the introduction of performance-based remuneration systems can be part of an efficient solution. This would require extensive legal and technical changes and the elimination of existing data gaps, which is currently not foreseeable.

The importance of gene therapies in the past and future

The status

Gene therapy has made great progress in recent years and offers promising possibilities for the treatment of various diseases. Since 2017, the momentum in this field has begun to increase significantly. In Germany, 14 gene therapies were already available in 2022.[1] At European level, 18 therapies had been approved by this time.[1] 95% of the gene therapies were orphan drugs.[2] In Germany, they therefore benefit from the privilege of the legal fiction of additional benefit and thus also the opportunity to achieve high prices in reimbursement negotiations.

Outlook for 2030

A forecast by the MIT Center for Biomedical Innovation (CBI) assumes that a median of 63 approved gene therapies will be available by the turn of the decade in the USA.[3] These cover various indication areas. It is striking that half of the gene therapies shall be approved in the oncological field, which is primarily targeted at haematological cancers (figure 1).

This shows that the research and development of gene therapies is focussed on common diseases. However, if there is a perception that the probability of success is higher for rare diseases, the perception of frequency and rarity in relation to diseases may differ depending on the region. While some diseases are considered rare in Germany, they are widespread in other parts of the world. Thalassaemia for example is rare in Germany, but more common in the Mediterranean region. Overall, the proportion of more common diseases accounts for the largest share of clinical research projects in gene therapies. Gene therapies for Alzheimer's dementia and Parkinson's disease are being researched just as

much as for coronary heart disease or diabetes.[4]

Based on estimated list prices, the MIT CBI has estimated that the projected 63 approved gene therapies will generate sales of around 24.4 billion US dollars in the USA in 2030 (figure 2).[3] If this figure is converted to Germany on the basis of population figures, this results in a turnover, and therefore costs, of around six billion euros. In relation to the current AMNOG market, this would be a share of around 25% – for gene therapies alone.

2. Pricing and evidence

There is still a considerable discrepancy between pricing and available evidence in the development of gene therapy products. Of the 18 approved gene therapies, only one therapy, i.e. Talimogen, has included an active comparator group in its clinical study. Although this comparison was made with an off-label drug, it is a notable exception. In contrast, all other previously approved gene therapies lacked an active comparison group.

The question arises as to why there is a lack of active comparison groups in most approval studies of gene therapies. This is a cause for concern when it comes to therapies that can potentially be compared with existing, well-established treatments. An example of this is the situ-

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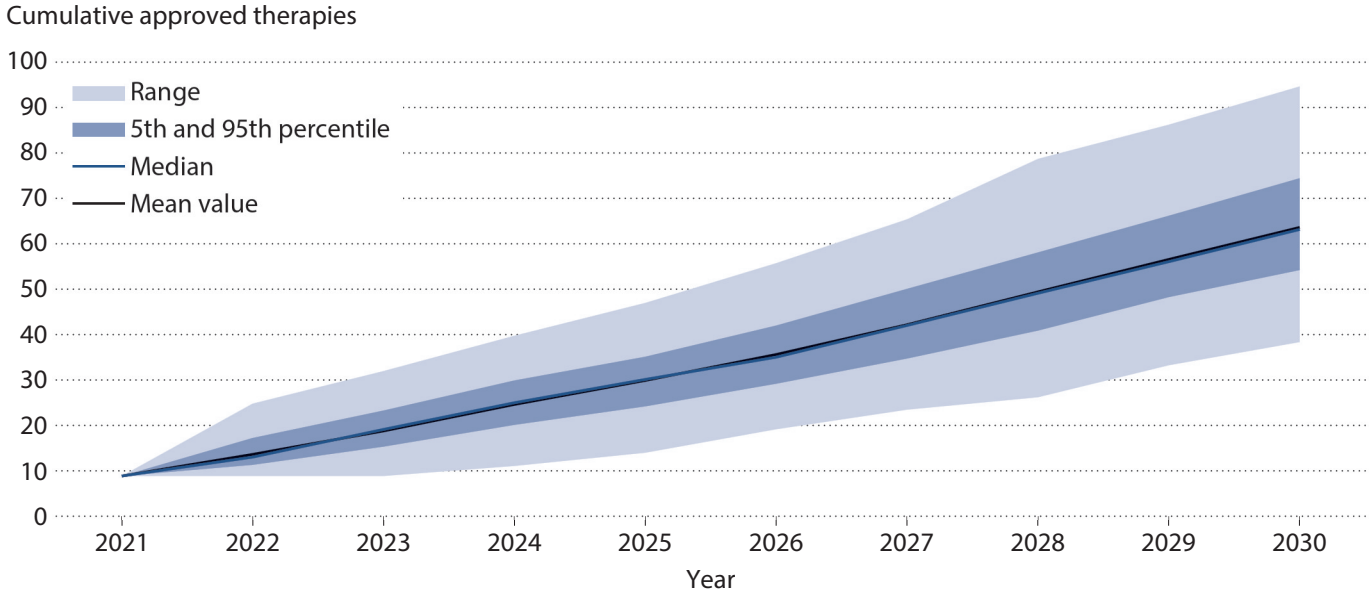
Projected cumulative US approvals for gene therapies



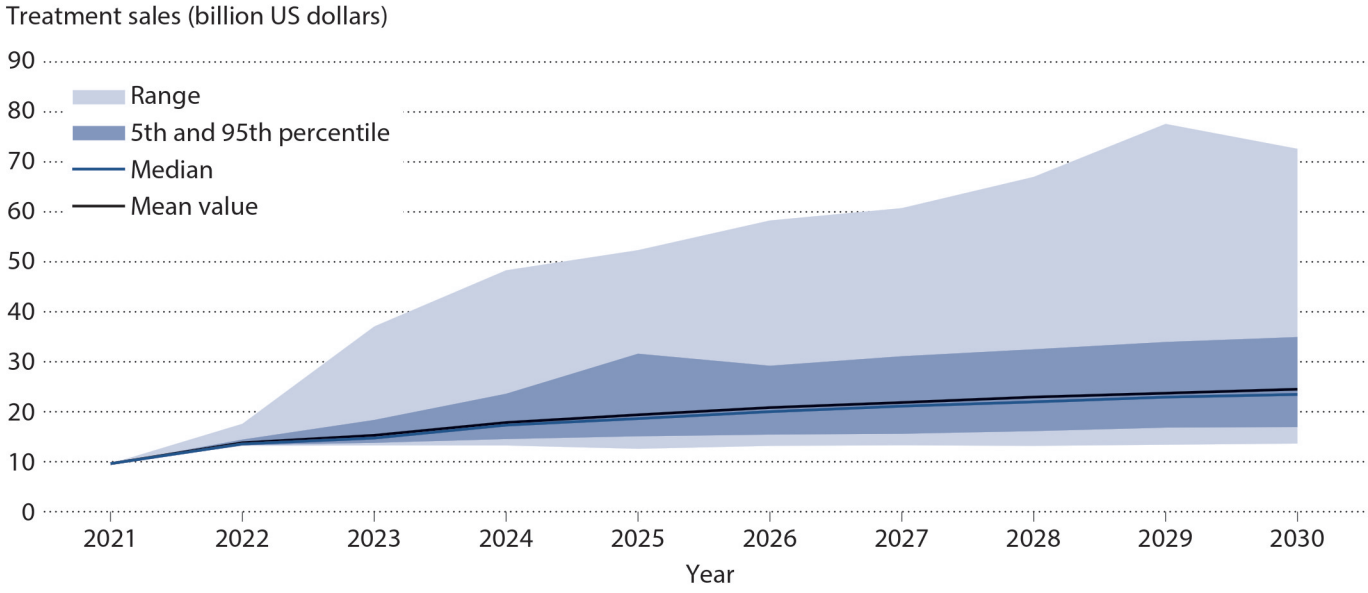
	2021	2022	2023	2024	2025	2030
Cancer, haematological	6.0	6.8	8.0	9.8	11.7	31.6
Cancer, solid tumour	0.0	0.4	0.9	1.4	2.0	4.1
Cardiovascular	0.0	0.0	0.0	0.0	0.0	0.2
Haematological	0.0	1.6	2.9	4.2	5.2	9.1
Immunological	0.0	0.1	0.3	0.5	0.6	1.4
Metabolic	0.0	0.2	0.5	0.6	0.9	3.1
Musculoskeletal	0.0	0.1	0.2	0.2	0.4	1.0
Neurological	1.0	1.3	1.8	2.2	2.5	3.7
Ophthalmological	2.0	2.8	3.3	4.1	4.5	6.2
Others	0.0	0.4	0.9	1.6	1.9	3.1
Total	**9.0**	**13.6**	**18.7**	**24.7**	**29.7**	**63.5**

Source: [3]

Figure 1: The MIT Center for Biomedical Innovation predicts that around half of gene therapies will be approved in the oncological field.

ation in the field of haemophilia. The gene therapies Zynteglo® and Zolgensma® could also be compared with established treatment standards. This discrepancy between the possibilities for comparative studies for around two thirds of the authorised gene therapies and the actual implementation sheds a clear light on the deficit in relation

Projected annual sales of gene therapies for the US market



	2021	2022	2023	2024	2025	2030
Mean value (billion US dollars)	**9.3**	**13.6**	**15.2**	**17.9**	**19.4**	**24.4**

Source: [3]

Figure 2: Based on estimated list prices, the MIT CBI forecasts sales of the 63 approved gene therapies in the USA at around 24.4 billion US dollars in 2030.

to the evidence base. In addition, the typically short duration of studies for the approval of gene therapies should be noted. The evidence presented is limited to one to a few years. However, the hopeful outlook and the associated price expectations of the manufacturers extend to a potentially lifelong effect and the associated savings in other treatment costs. The prices charged and the available evidence are completely decoupled.

With the Act for More Safety in the Supply of Pharmaceuticals (GSAV) in 2019, the legislator created an incentive for the industry to close these evidence gaps by means of post-market data collection. However, the first post-market data collections have shown that the process is extremely complex. Many formal and technical hurdles tie up resources, making it impossible to generate evidence efficiently and promptly using post-market data collection. One example of this is Zolgensma® which was launched in Germany in July 2020 and will not provide data from the post-market data collection until July 2027.[5] Only then will the next benefit assessment follow, which will lead to a new price negotiation.

3. Remuneration approaches and contract options

The discussion about the remuneration of healthcare services is a key issue in the healthcare sector. In the field of gene therapy, we are faced with specific challenges as we are dealing with the payment of a single therapy. Performance-oriented remuneration systems are being discussed as a solution for the pricing of gene therapy products. These models are based on the idea that payment for therapies is linked to their actual success. This means that payments are linked to the actual effectiveness of the therapy for all patients in real-life care, instead of setting a fixed price based on scientific study results . The introduction of performance-based remuneration systems in gene therapy involves various contract models that need to be carefully evaluated.

One model that has been discussed intensively for haemophilia this year is the model of instalment payments. In this model, e.g. an annual payment is made by the health insurances to the pharmaceutical company until a therapy failure is detected or the contractually agreed end of payment is reached. However, this model is associated with considerable challenges.

Its implementation requires a great deal of administrative effort and can thus only be realised by the health insurances based on selective contracts. It does not appear realistic to oblige health insurances to use standardised models on a selective contractual basis in the form of reimbursement amounts. Data availability, monitoring of individual data collection efforts and the competitive interests of the health insurances are not compatible here. Long-term instalment models are currently neither legally nor technically compatible with the morbidity-oriented risk structure compensation system (Morbi-RSA) and the risk pool. It is important to note that reimbursement agreements do not only affect statutory health insurances, but also private health insurances, hospital supervisory authorities, correctional institutions, aid organisations and even foreign self-payers, for whom different price levels may arise.

The use of instalment models or classic reimbursement amounts for different insurance groups in parallel is difficult to imagine. Other existing challenges are manifold. The reporting requirements for the price and product information of such contracts have not yet been resolved by IFA GmbH, and regulations in connection with the reference base for manufacturer discounts, VAT and trade surcharges are also unclear both legally and technically.

The interactions with orphan drug monitoring in the Federal Joint Committee (G-BA) for the sales threshold prior to a full evaluation within the framework of Section 35a SGB V also raise questions. Inefficiencies in contract design are also relevant, including the situation of health insurance changers, for which no viable solutions have yet been proposed.

An important ethical aspect concerns the distribution of the return on innovation in gene therapies. The question arises as to whether it is appropriate to include all costs saved in the price of gene therapy, which would mean that the pharmaceutical company alone would receive the entire return on innovation, or how the return on innovation should be divided between the insured community and the pharmaceutical company. Finally, a rate model also raises questions about the efficiency audits of physicians, which is impossible if the actual price is unknown. Overall, this is a model that cannot be implemented under the current legal and technical conditions.

The reimbursement model is another performance-based remuneration model. The problems here are comparable to instalment payments. The payment method is fundamentally different, as the total reimbursement amount to be agreed is paid directly upon treatment. This shifts the

burden of proof and the risk of overpayment to the health insurances.

Another model is the prospective cohort model. It is based on a transparent, prospectively adjustable reimbursement amount. The experience gained from the treatment of all patients within the treatment cohort is collected from year to year. This also includes the follow-up of previously treated cohorts. The first reimbursement amount is initially a provisional price based on the data from the authorisation studies in the G-BA decision. This data usually covers a period of one to three years. Subsequently, the reimbursement amount depends on the treatment results within the observed cohort in accordance with the contractual conditions, including the success criteria. The advantage of this model is that it does not include any additional payment flows such as repayments or instalments and ensures a transparent reimbursement amount that is always forward-looking (figure 3).

Data collection is the subject of the contractual agreement and can be based on registry or billing data, for example. The data collection and analysis does not have to be carried out by each health insurance individually, as is the case with the other models. Data collection and the corresponding adjustment of the reimbursement amount is carried out by the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband).

Another disadvantage of this model is the at least temporary decoupling from the benefit assessment of the G-BA. This can be countered by using the results of the post-market data collection instead of independent analyses of treatment success within the cohort model. The interim results of the post-market data collection could be analysed e.g. at annual or multi-year intervals and transferred to the model for adjusting the reimbursement amount. A pay-for-performance model is thus transformed into a pay-for-evidence model. The new reimbursement amount can be agreed in negotiations but can also be the result of an agreed calculation methodology according to the success criteria.

Nevertheless, the advantage of this model is a transparent reimbursement amount based on the actual treatment results in the treated cohort. It combines the concept of scientific study data on the probability of success with systematic evidence from the G-BA's post-market data collection for all treated patients. It is therefore a way of incorporating the growing evidence into remuneration.

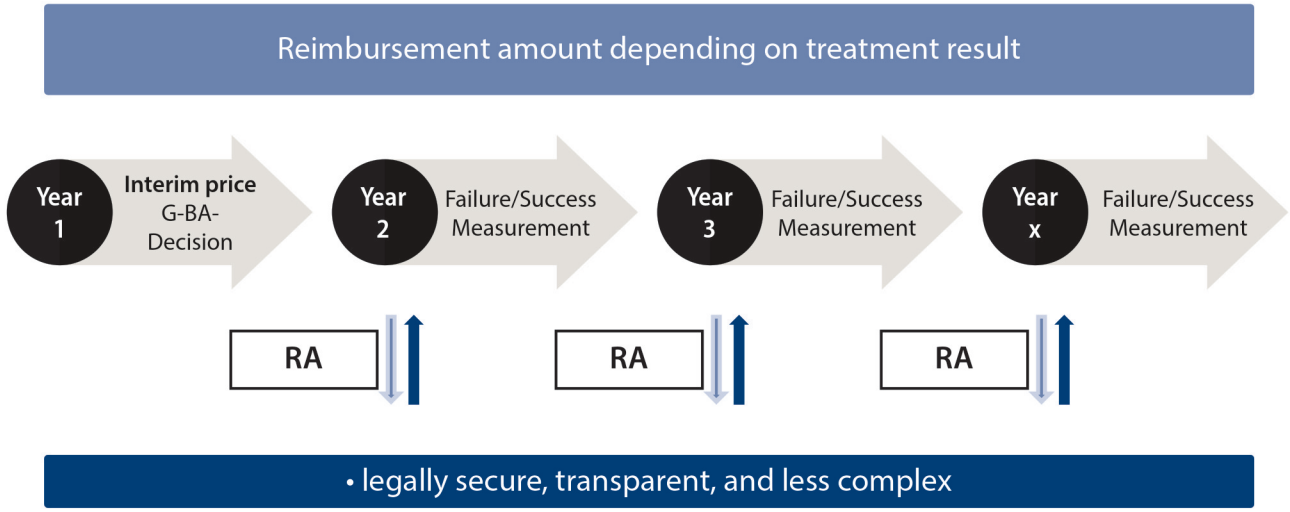
4. Lack of basic data

The problem inherent in all performance-related remuneration concepts is the incomplete or missing data base in Germany. To ensure efficient feasibility, the first step would be to ensure that suitable data can be analysed over a longer period of time and with a shorter time lag than it is currently possible. Currently, data availability for reimbursement negotiations is as follows. Data from the outpatient sector either have no reference to insured persons (data in accordance with Section 84 (5) SGB V – GAMSI data), or if they do have a reference to insured persons, they only have a maximum observation period of two years and a time lag of up to 21 months (data in accordance with Section 217f SGB V).

Data from the hospital sector also have a long delay and only a case reference. Even more fundamental, however, are the difficulties arising from the lack of a link between inpatient and outpatient data. A patient who is treated with a gene therapy in hospital „disappears" in terms of data after leaving the hospital. It is therefore impossible to track the further development of the patient's disease and any treatment that may be required on an outpatient basis.

The data gaps affect not only gene therapies, but also other medical treatments. A technical solution would be a

Collective cohort model



Source: Own presentation

Figure 3: The advantage of the collective cohort model is that it does not include any additional payment flows and ensures a transparent reimbursement amount that is always forward-looking.

standardised, cross-sectoral pseudonym for insured persons without a time limit, or at least with a significantly longer time span to ensure the tracking of (gene therapy) treatment over time and thus identify repeated therapies, follow-up therapies or hospitalisations.

5. Conclusions

To summarise, it is currently unclear whether and to what extent performance-based contract levels can provide an answer to the financing risks of the statutory health insurance system in connection with highly expensive gene therapies. None of the contract models presented can be regarded as efficient. The prospective cohort model would be legally secure, transparent, and low-cost. The technical and data-related deficits presented do not only affect gene therapies but have an impact on all areas of medicine and require urgent solutions.

References

[1] CAT quarterly highlights and approved ATMPs. EMA/CAT/247792/2023

[2] Union Register of medicinal products – Public health – European Commission Community Register of orphan medicinal products 10/10/2023

[3] Young CM, Quinn C, Trusheim MR. Durable cell and gene therapy potential patient and financial impact: US projections of product approvals, patients treated, and product revenues. Drug Discov Today. 2022 Jan;27(1):17-30

[4] IQVIA Blog Piping Hot: A look at the state of cell, gene and RNA therapies in early 2023. Stefan Lutzmayer, Consultant, EMEA Thought Leadership, Aaron Wright, Analyst, EMEA Thought Leadership, 2 May 2023

[5] Press release Federal Joint Committee according to § 91 SGB V; No. 05 / 2022, Registerstudie zur Gentherapie mit Zolgensma® startet. (Registry study on gene therapy with Zolgensma® starts)

Regulatory „guidelines“ for an AMNOG update: Consensus is still rare

Dr Florian Staeck

Despite the most recent legislative efforts of the German government through the Financial Stabilisation of Statutory Health Insurance (GKV-FinStG), a clear reform path for the benefit assessment procedure according to the AMNOG has yet to emerge. The latest legislative interventions have not met expectations in terms of the anticipated savings effects. Additionally, measures such as the discount for combination therapies or the price-range regulation have posed unresolved methodological implementation issues until fall 2023.

Against this backdrop, participants at the 18th Interdisciplinary Platform on Benefit Assessment overwhelmingly agreed that an update of evidence-based strategies in benefit assessment would be the most promising approach. The tools required for this and the necessary intermediate steps to maintain a balance between innovation and the financial viability of the statutory health insurance system were the subject of controversial debates at the platform conference on 29/30 September 2023 in Berlin. The event was entitled „AMNOG 2.0 – on the way to an efficient system?“

and discussions were driven by various health economic, methodological, and financial considerations regarding the future of the AMNOG system. Participants emphasised that this begins with the question of how the procedure should be improved regarding which efficiency indicators – allocative efficiency must be brought into agreement with issues such as the availability of pharmaceuticals. When focusing on economic productivity in terms of additional years of life gained, external effects such as the financial stability of the statutory health insurance system should always be considered. Finally, any planned refinement of the AMNOG regulation would also have to consider the resulting additional transaction costs.

Two fundamental positions were advocated:
Plea for a return to a stronger focus on evidence: Representatives of this position take the view that the GKV-FinStG has destabilised a previously functioning benefit assessment procedure by introducing elements that contradict the original principle of pricing based on evidence.

Plea for the necessary supplementation of the AMNOG procedure with accompanying cost-reducing tools: In its ten-year history, the AMNOG has struggled to maintain the balance between innovation and financial viability. Although every second new active ingredient remains without a proven additional benefit, expenditure in significant sub-segments of the patent-protected pharmaceutical market has increased disproportionately. Alternatives to value-based pricing alone are needed.

These tools and aspects were discussed at the conference:

Controversial assessment of the GKV-FinStG: Several participants at the conference described the law passed by the Bundestag in October 2022 as poorly crafted. Despite efforts to provide relief for the statutory health insurance system, such as through cost-covering contributions for recipients of (former) unemployment benefit 2, the coalition government instead opted for what were perceived as „filigree repairs“ in the AMNOG, leading to significant uncertainties. One example cited was the flat-rate discount of 20% for combination therapies, whose specifications were not adequately defined in the law. Consequently, implementation of this regulation failed by autumn 2023 due to a lack of legal concretisation.

Some attributed this to politicians‘ preference for budget impact instruments, aimed at reducing the financial burden on the statutory health insurance system rather

than incentivising evidence generation for new pharmaceuticals. E.g. the newly created obligation for price-volume regulations had nothing to do with evidence – the sole aim here is to achieve additional savings through economies of scale.

The lowering of the sales threshold for orphan drugs from 50 to 30 million Euros, above which a full benefit assessment is triggered, was also widely commented on. Given the limited savings effects observed, there were calls to abandon the special status for orphan drugs altogether and assess them „fairly and transparently" as part of a full benefit assessment procedure. They said that an incentivisation for research into rare diseases should take place elsewhere – a sales threshold was not a suitable criterion for determining whether a methodologically sound study can be set up or not. On the other hand, reference was made to the still very extensive – and in the European context leading – availability of pharmaceuticals for the treatment of patients with rare diseases.

Participants were critical of the combination discount and the price-range regulation, which defined rigid price caps for new pharmaceuticals with little or no quantifiable additional benefit compared to patent-protected comparative therapies. This departure from the old AMNOG logic was seen as devaluing incremental innovations. Some participants called for a return to negotiated solutions. Otherwise, situations would arise in which new active ingredients could no longer be introduced in Germany, they said. This could happen, e.g. if in the case of combination therapies with a low additional benefit determined by the G-BA, the combination partner would de facto receive the „zero price tag", they said.

This was countered with the argument that a system that always calls for higher prices, even in the case of low additional benefit compared to an already high-priced patent-protected combination therapy, was no longer justifiable. Pricing by manufacturers was increasingly based on expectations, but not on the data presented. It was therefore necessary to „tighten the reins a little", was the conclusion.

Critics highlighted legal uncertainties surrounding tools like the combination discount, with a constitutional complaint submitted to the Federal Constitutional Court – the complaining manufacturer sees the provisions of the GKV-FinStG as a violation of the principle of equal treatment. The court's decision, expected in 2024, would provide clarity on this matter. One proposed solution to methodological debates as to when a combination of active ingredients can actually be assumed to have been prescribed, recourse to the prescribing physician was suggested. Physicians could mark prescriptions for combination therapies, accordingly, signalling a conscious decision to prescribe them. This would then be a clear signal that the physician had made a conscious decision to prescribe the combination therapy, they explained.

While the „evidence machine" driving the AMNOG process was difficult to control, there was consensus on the need for smoother technology to support it. However, the optimal approach to achieving this goal remains a subject of controversy.

Pros and cons of a cost-benefit or cost-effectiveness assessment: The struggle for a realignment of the AMNOG procedure needed to be assessed against the background that Germany was the only country in Western Europe to forego information as a result of cost-benefit or cost-effectiveness assessments. This implies that potentially valuable information to complement value-based pricing was overlooked unnecessarily. One of the positions presented suggested that the ongoing failure to utilise such data would

strain the limits of the AMNOG procedure. Similarly criticised was the underutilisation of pay-for-performance contracts (P4P), which holds significant potential but has not been widely implemented. IQWiG's methodology for cost-benefit assessments was now much more elaborate than it was a few years ago.

This was countered by the fact that P4P contracts were enormously transaction-intensive and cannot be presented within the framework of collective agreements with all health insurances. The main issue at hand was that with P4P, the pharmaceutical ultimately ends up with a price that lacks transparency. It was emphasized that it is essential in the process for the negotiating partners to agree on parameters that they want to measure. However, it was argued that if the data basis were assessed inconsistently during that monitoring process, P4P could not become a viable model.

Some disagreement arose regarding whether, given the necessity for cost containment measures, it should not even be considered an ethical imperative to include cost-benefit information in the assessment. It was mentioned that the necessity of defining a frame of reference for the cost-benefit assessment (CBA), to which cost-benefit assessments are related – such as statutory health insurance or the national economy – was not a challenge that solely arises with the CBA tool originally. On the contrary, there was a high necessity to reach an agreement on what money should primarily be spent on in the statutory health insurance system.

It was pointed out that there was currently an assumption of a very high willingness to pay in an indication area like oncology, while the prices set for new antibiotics were relatively low. Against this background, the CBA could be a tool for obtaining indications for the monetisation of the additional benefit. Here too, the counter-argument was that the benefit assessment in the AMNOG had created a „value in itself". In contrast, the CBA would be a completely new tool for which it was uncertain how much additional „guidance" it could provide in the AMNOG procedure.

Challenges for alternative pricing models for gene therapies: Participants explored various strategies for efficiently pricing gene therapies and deliberated on which options could be implemented. There were currently around 2,600 ongoing studies with human cell and gene therapies worldwide. The focus was by no means only on rare diseases; a lot of research was also being carried out into diseases such as Alzheimer's dementia, Parkinson's, and arthritis. It was noted that among the 18 gene therapies approved in the EU so far, only one study included an active comparator group in the approval process, despite the potential for active comparators in many more cases.

A decoupling of pricing and the evidence presented could thus be observed. For the year 2030, expenditure projections suggested that a quarter of the AMNOG market would already have to be spent on gene therapies. It would not be possible to close this evidence gap with post-market data collection alone. In addition, an enormous time delay was to be expected with post-market data collection, e.g. the manufacturer of the active ingredient onasemnogen abeparvovec (Zolgensma) would not submit new data until 2027.

Various theoretical remuneration methods, including instalment or repayment models, were rendered infeasible due to a lack of price transparency, excessive monitoring costs or a lack of data availability. The sole viable option for legally secure implementation at present was a results-driven remuneration approach, exemplified by the prospective cohort model. This model would be accompanied by a transparent reimbursement amount. This would then be

constantly readjusted depending on the treatment outcome. This eliminated the need for continual negotiations between manufacturers and health insurance providers. However, for this to work effectively, it was essential that both partners have reached consensus on the rules governing price adjustments in advance. Additionally, it would also have to be accepted that the reimbursement amount may temporarily deviate from the G-BA's benefit assessment decision.

However, implementing this model also presents significant challenges, particularly regarding the monitoring of treatment outcomes. One notable issue was the changing pseudonym of the insured person after two years, making it difficult to track the progress of treatment. Moreover, it was not possible to track the course of treatment across sector boundaries – follow-up treatments or (re-)hospitalisations – with the available data in accordance with Section 217f social code book V. Against this background, it was not yet possible to say whether P4P contracts can provide a sufficient answer to the financing risks of single-use therapies in particular.

Indirect comparisons and their current consideration in the EUnetHTA guidance: Considering the impending joint European benefit assessment set to commence in January 2025, it's imperative to evaluate the level of methodological readiness of the joint clinical assessment (JCA) procedure, particularly in light of the increasing volume of clinical studies featuring immature evidence. The examination of two EUnetHTA guidelines in this context reveals a procedural status that fails to adequately address the challenges posed by the increasing number of clinical studies with immature evidence. This deficiency was problematic because it heightens the risk of subjective assessments within the framework of HTA procedures.

As a result, these EUnetHTA guidelines were currently sending out the wrong signal, as they undermine the principle of „best evidence for decision making" due to their lack of methodological rigor. One example cited was the inadequate consideration of indirect comparisons. There was also too little or no specification of when indirect comparisons of non-randomised evidence are valid and permissible. The lack of attention to validity criteria suggested that indirect comparisons could encounter increasing challenges in future JCAs.

Furthermore, since 2011, there hadn't been a single instance of an indirect comparison within an AMNOG procedure in Germany resulting in an attested additional benefit. In this respect, a harmonisation of the approval and HTA procedures was urgently required. On the contrary, in Germany, there hadn't been sufficient recognition of the consequences resulting from changes in the data bodies for the additional benefit assessment procedure.

As an interim conclusion, several participants asserted that perceiving innovation and efficiency as conflicting poles would impede the further advancement of the AMNOG. In contrast to the GKV-FinStG, any essential decisions should be prepared carefully and with sufficient time. Participants also cautioned against becoming overly immersed in minor, national reform debates.

Despite the calls for amendments to the AMNOG in Germany, research-based companies are heavily prioritising the upcoming joint European benefit assessment, scheduled to commence in January 2025. Research-based manufacturers wanted to know how the PICO will be defined at EU level in the future. It was suggested that a „lead PICO" would have to emerge in view of the possibility of up to ten PICOs in the EU procedure. For the other PICO elements, it would be necessary to acknowledge a higher level of uncertainty in the data provided by the manufacturers.

In the overall view of the 18th Platform Conference, regulatory approaches from the Netherlands and France provided a further source of information for the participants in the discussion. However, it is evident that achieving an „efficient" AMNOG 2.0 will require significant restructuring in numerous areas, particularly in aligning the assessment of patient-relevant benefits in clinical studies with the financial sustainability of the statutory health insurance system.

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INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

AMNOG 2.0: On the path to an efficient system

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