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AMNOG: Financial stabilisation – new treatment paradigms

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VOLUME 1
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VOLUME 3
Adaptive Pathways – Opportunities and risks

VOLUME 4
AMNOG 2.0 – Information problems

VOLUME 5
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VOLUME 6
Physician information via software – Ways and goals

VOLUME 7
Physician information via software – Orientation or control?

VOLUME 8
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VOLUME 11
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VOLUME 12
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VOLUME 13
Patients and medical societies: Additional expertise for AMNOG

VOLUME 14
Guidelines – their role in AMNOG and medical care

VOLUME 15
Further development of the AMNOG with a sense of proportion and evidence

VOLUME 16
AMNOG: Financial stabilisation – new treatment paradigms

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Volume 16
March 2023

Contents

Goals of the plattform

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

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

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

- Discussing the procedures for the assessment of the additional benefit, including in relation to approval of pharmaceuticals,
- Working towards international standards of evidence-based medicine and of health economy being adhered to as well as applied and further developed,
- Determining whether and to what extent patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life, are identified and which methodological problems occur during the process,
- dentifying possible undesirable developments, in particular with regard to supplying patients with new active substances,
- Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure, e. g. on the further development of the legal framework conditions of AMNOG.

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

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

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Quo vadis, AMNOG? Levelling of differentiating benefit categories

Professor Jörg Ruof

Dear readers

stable financial conditions are a „must" for an intact healthcare system: every hospital, every practice and every company needs financial stability. At the same time, it is undisputed that due to enormous progress in basic medical research, treatment paradigms are continuously specified and renewed.

The Autumn Meeting 2022 of the Platform for Benefit Assessment and this publication deal with the area of conflict that arises from these two aspects. In the first part, the law on the financial stabilization of statutory health insurance (GKV-FinStG) is reviewed from different perspectives. The subsequent articles focus on the generation of comparative evidence in rare diseases and in the increasingly specified and thus smaller patient populations of precision oncology.

A view on the GKV-FinStG

Despite the consensus that the AMNOG is a proven and well-established system, the speakers' assessments of the GKV-FinStG vary widely. From the G-BA's point of view, Professor Hecken points out the appropriateness of the intended savings in the pharmaceutical sector. However, he takes a very critical view of the so-called „benchmark provision" as well as on the categorical implementation of the combination discount. The two political articles from the SPD's (Ms Stamm-Fibich) and the CDU's (Mr Kippels) perspective, respectively, reflect the different views of the government and the opposition on the law.

The illustration of evidence gaps in the AMNOG procedures and the corresponding impulses from the law take a central position in Ms Stamm-Fibich's article. In contrast, Mr Kippels considers the law to be unsuitable to meet the requirements of the coalition agreement for a preventive, crisis-proof, and modern healthcare system. In particular, he questions the new regulations for pharmaceuticals with a low or non-quantifiable benefit.

This aspect is also the focus of Ms Friebertshäuser's article presenting the industry's perspective. In her view, the de facto devaluation of AMNOG procedures with these two benefit categories counteracts the principle of pricing based on additional benefit.

Evidence & treatment paradigms for rare diseases and in precision oncology

For many years, research and healthcare for patients with rare diseases have been a high priority at German and European level. The corresponding presentation from the Federal Ministry of Health states: „Due to the small markets for orphan drugs, it might not be very attractive for companies to develop pharmaceuticals for rare diseases under regular conditions, as research and development costs might not be amortised. Against this background, special facilitations have been created for the development of orphan drugs."[1]

The regulatory framework and the specifics of evidence generation for orphan drugs are described in the BfArM's article. The patients' concerns and issues are subject of the two articles by Ms Mann and Mr Hagedorn. Both in the case of pharmaceuticals for rare diseases and in precision oncology, situations repeatedly arise in which a randomised comparative study is not feasible.

Mr Bucher's article undertakes a detailed methodological analysis of the non-randomised evidence as discussed in the AMNOG procedure using the case study of amivantamab in lung cancer. Mr Schlomm illustrates an approach to optimised precision healthcare for patients with prostate cancer in the Berlin-Brandenburg region simultaneously developing high-quality real-world evidence (RWE) (Ge-

sundheitsplattform Deutsches Netzwerk für angewandte Präzisionsmedizin, DNA-Med).

The last article in the publication is by the statistician and clinician Bruno Falissard who is deeply familiar with the French assessment process from different perspectives. The challenges, questions and approaches he formulates are very similar to the situation in Germany. In the future, common European approaches, e.g. in the collection of RWE for rare diseases, will be inevitable.

Dear reader, the combination of the two topics „GKV-FinStG" and „Evidence & Treatment Paradigms for Rare Diseases" reflects the area of conflict the further development of the AMNOG will have to face. The significance of financial stability is undisputed. However, it is conceivably unfavourable that a central differentiation instrument of the G-BA is devalued by the de facto equation of the categories „low additional benefit" or „non-quantifiable additional benefit" with the comparative therapy.

In his speech in the Bundestag about the GKV-FinStG on 20 October 2022, Health Minister Lauterbach also consistently speaks of pharmaceuticals „with no or only very low additional benefit, but which cost significantly more than the comparative therapy".[2] This formulation is in clear contrast to the definition of „low" or „non-quantifiable" additional benefit in the Ordinance for the Benefit Assessment of Pharmaceuticals (AM-NutzenV). According to this definition, in both cases there is a patient-relevant additional benefit, which includes „a previously unachieved moderate and not only low" advantage for patients in the first case and which can even be substantial in the second case, but is not yet quantifiable due to the available data.

The implied broad limitation of the differentiating benefit gradations established in the AMNOG can impair the rapid and broad availability of newly approved active substances, especially for rare diseases, but also for rare subgroups such as cancer patients.

It can be assumed that in future manufacturers will examine in detail the development and offering of a pharmaceutical on the German market against the background of the structural levelling of a central element of AMNOG – the differentiating benefit assessment. The Platform for Benefit Assessment will continue to monitor this development and its effects very carefully.

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Law of the financial stabilisation of statutory health insurance: Perspectives of the further development of AMNOG

Professor Josef Hecken | Impartial chair of the Federal Joint Committee (G-BA)

The last decade of pharmaceutical supply was characterised by the successful introduction of the AMNOG procedure. In view of the current funding deficit in the statutory healthcare system, cost savings for pharmaceuticals as intended by the GKV-FinStG are appropriate and do not jeopardise the principles of appropriate pharmaceutical care. However, especially the intended guiding regulation, i.e. the pricing for pharmaceuticals with little or no quantifiable additional benefit based on the appropriate comparator therapy should be reviewed, as well as the categorical setting of the 20% combination discount. The lack of structural and _strategic orientation of the law should also be viewed critically. Far beyond the regulations in the pharmaceutical sector, the specified measures are exclusively based on an activation of existing reserves of the statutory healthcare system. There are no perspective approaches, for example, to prepare the statutory healthcare system for the upcoming demographic change.

The initial situation

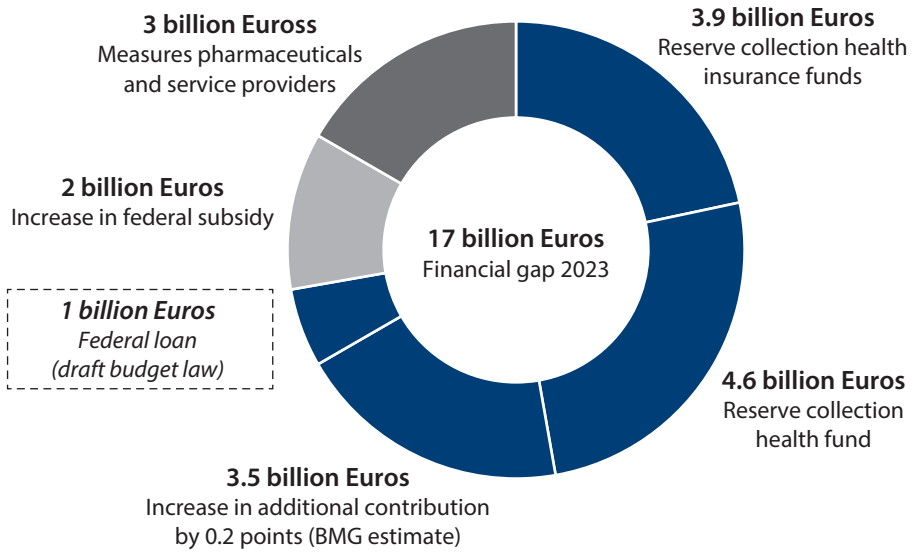
The further development of the German Pharmaceutical Market Reorganisation Act (AMNOG) is anchored in the coalition agreement of the coalition.[1] Strengthening the health insurance funds' ability to limit pharmaceutical prices is explicitly envisaged and is to be welcomed. The extremely precarious financial situation of the statutory healthcare system, partly due to the Corona pandemic, means additional pressure to take action. In the draft of the GKV-FinStG, it reads: „Due to the gap between revenues and expenditures, the average additional contribution in the statutory healthcare system would increase by around one percentage point in 2023 from currently 1.3 percent and subsequently by a further 0.2 to 0.3 percentage points each year without additional measures".[2] The financing gap in the statutory healthcare system is estimated at around 17 billion Euros in 2023. The GKV-FinStG specifies various measures to close this financial gap (figure 1). Measures in the area of pharmaceuticals account for approximately three billion Euros.

Savings in the pharmaceutical sector

The savings in the pharmaceutical sector as specified in the law are distributed among various subsectors (figure 2). Overall, these burdens are justifiable. For example, the increase in the pharmacy discount, the manufacturer's discount, or the reduction of the turnover threshold for orphan drugs are required to stabilise the financial situation in the statutory healthcare system. The necessity of discounts on uneconomical package sizes, for example in paediatrics, is also beyond question. Especially in case of high-priced pharmaceuticals it should be avoided that they have to be disposed of expensively.

Thus, the following measures should also be considered:

Overview of the measures in the GKV-FinStG



Source: Own presentation of the Techniker Krankenkasse (2022): TK position on the GKV-FinStG see: https://www.tk.de/presse/themen/gesundheitssystem/tk-position-gkv-finanzierung-2131180

Figure 1: The intended savings in the pharmaceutical sector as specified in the draft law add up to around three billion Euros.

Since July 2012, **Professor Josef Hecken** *has been Impartial Chairman of the Federal Joint Committee (G-BA). Prior to that he was engaged as State Secretary at the Federal Ministry for Family Affairs, Senior Citizens, Women and Youth. President of the Federal Insurance Office (2008-2009), Minister of Justice, Health and Social Affairs and, from 2008, also Labour of the Saarland.*

- Mandatory price-quantity agreements basically make sense. For example, in individual cases within the scope of indication extensions, there is a clear increase in patient numbers without a change in the reimbursement amount (figure 3). However, the question is why existing possibilities to terminate existing contracts and conduct renegotiations in case of volume expansion of individual pharmaceuticals have not been exhausted so far.
- The retroactive effect of the reimbursement amount is well justifiable and even required. The fact that it refers to the date of the assessment by the G-BA (i.e. six months after market launch) is also to be welcomed, because only after this official assessment a potential

Savings through the GKV-FinStG in the pharmaceutical sector

Measure	Savings in 2023 (estimated)
Increase in pharmacy discount	0.17 billion €
Manufacturer discount	1 billion €
Retroactive effect of AMNOG reimbursement amount	0.15 billion €
Deductions for pharmaceuticals with/without minor additional benefit and calculated deduction on the basis of a patent-protected appropriate comparative treatment	0.25–0.3 billion €
Compulsory price-volume agreements	0.05–0.1 billion €
Discounts for uneconomical package sizes ("discarding")	0.05 billion €
Discounts on pharmaceutical combinations	0.185 billion €
Reduction of the sales threshold for orphan drugs from 50 million to 20 million €	0.1 billion €
Additional reserve of influenza vaccines	-0.075 billion €
Total savings	**1.88–1.98 billion €**

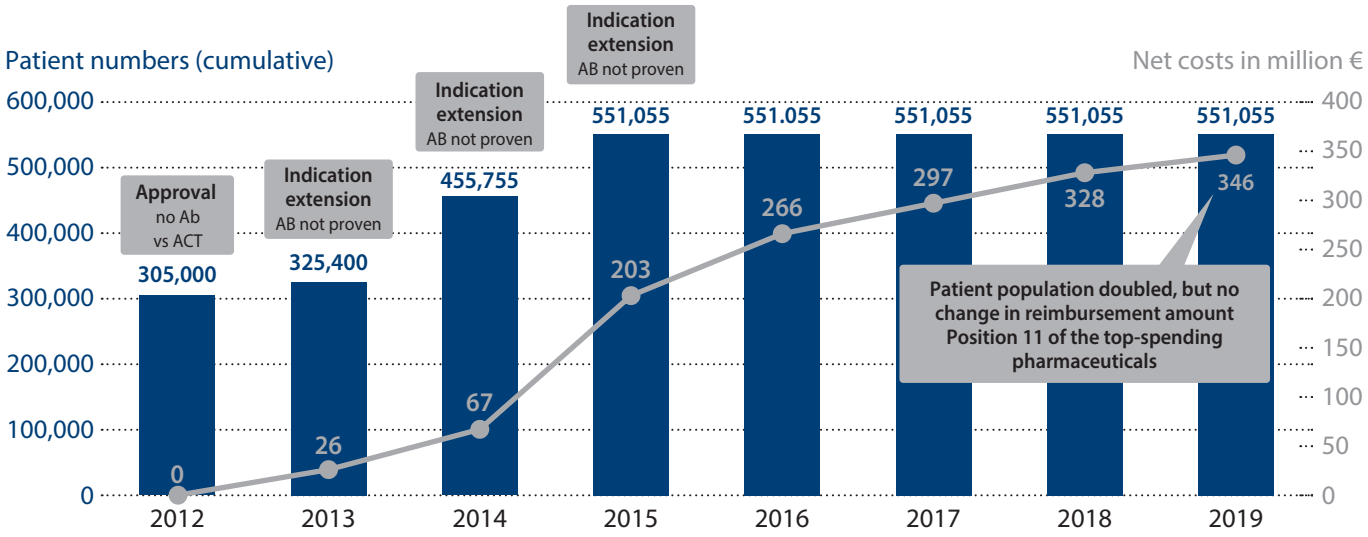
Source: Own presentation based on the draft of the GKV-FinStG, BT-Drs. 20/3448

Figure 2: The savings contained in the draft law result in an overall justifiable burden.

therapeutic added value can be determined as compared to the appropriate comparative therapy.

- The idea behind the planned reductions for pharmaceuticals with a non-quantifiable or low additional benefit is to strengthen the negotiating position of the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband). However, the explicit exclusion of a negotiation of higher reimbursement amounts for active substances with a low or non-quantifiable additional benefits is associated with systematic and legal concerns. As stated in the statement of the impartial members of the G-BA on the GKV-FinStG, the determination of a low or non-quantifiable additional benefit is by no means only based on a marginal added value of the pharmaceutical in the respective indication: The additional benefit – provided it is not based solely on an orphan privilege – was determined on the basis of patient-relevant endpoints in clinical studies suitable for the benefit assessment and was quantified in accordance with the requirements of Section 5 of the AM-NutzenV.[3] Contrary to the mandatory requirements for the reimbursement amount negotiations, we therefore suggested to include a flexible directory provision in Section 130b of the German Social Code, Book V (SGB V), which allows exceptions in the context of price negotiations. In addition, it must be considered with this regulation that the orphan privilege would be obsolete in this case, because many orphan drugs are initially as-

Volume expansion in the context of indication extensions



Source: Own representation according to Schröder M, Lohmüller J, Telschow C, Niepraschk-von Dollen K, Zawinell A, Bauckmann J. (2020): Der GKV-Arzneimittelmarkt (The Pharmaceutical Market of the Statutory Healthcare System – Report 2020). Adapted version dated 3 September 2020. Berlin: WIdO

Figure 3: In individual cases, there is a significant increase in patient numbers in the context of indication extensions, whereas the reimbursement amount has not changed.

sessed as non-quantifiable, as the data situation does not permit a quantification of the additional benefit.

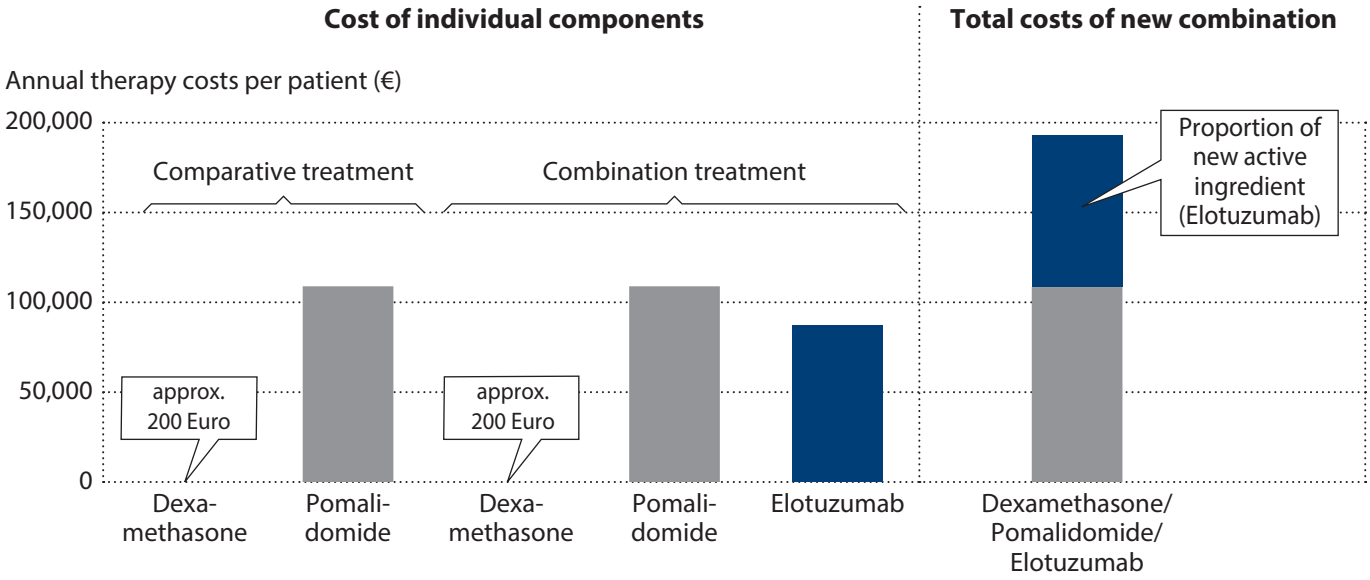
- Oncological combination therapies represent a major financial challenge for the statutory healthcare system. Figure 4 illustrates the cost dynamics on the example of multiple myeloma. Accordingly, the proposed regulation in Section 130e SGB V basically makes sense which provides for a discount on combination therapies. However, the 20% flat-rate discount without taking into account the additional benefit of this combination or the individual added value of the individual substances, should be viewed critically – especially since legal objections seem possible.

Conclusion

The last decade was marked by a successful introduction of the AMNOG procedure. In a European comparison, the German system has a role model function. In Germany, the time until new pharmaceuticals are available to patients is only 133 days. Moreover, Germany takes a leading role in Europe in terms of the number of newly approved pharmaceuticals available on the market (figure 5). In addition, AMNOG achieves considerable savings of approximately three billion Euros annually.

Due to the current funding deficit in the statutory healthcare system, savings are also indispensable in the pharmaceutical sector. In view of the total annual expenditure

Costs of combination therapies in oncology on the example multiple myeloma



[1] Standardised calculation as in the decisions on the benefit assessment according to § 35a SGB V taking into account current reimbursement amounts

Source: own calculation G-BA

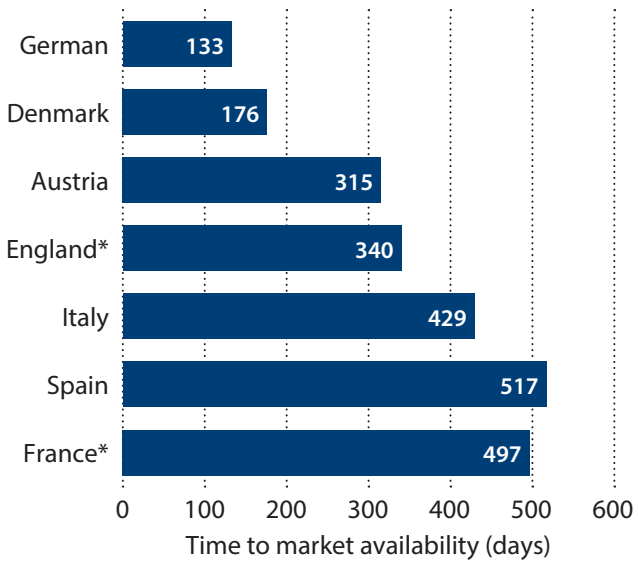
Figure 4: Since oncological combination therapies represent a major financial challenge for the statutory health system, a cost brake generally makes sense. However, the flat-rate discount must also be evaluated critically from a legal point of view.

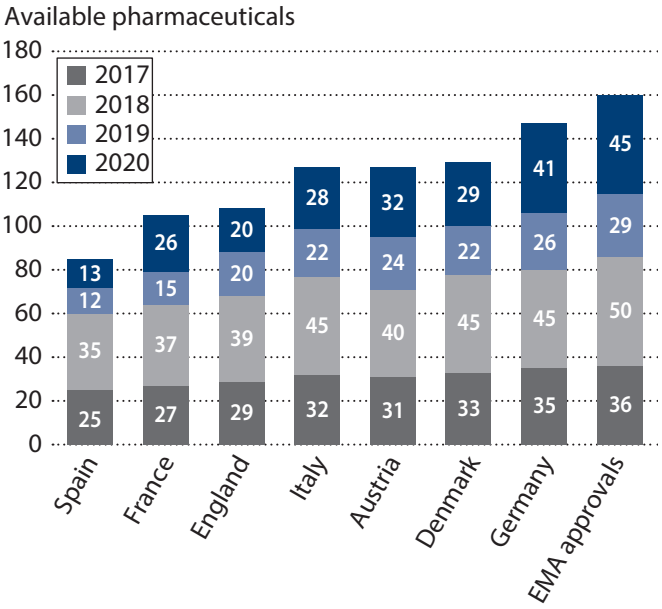
on pharmaceuticals of approx. 50 billion Euros, the planned savings on pharmaceuticals within the framework of the GKV-FinStG are appropriate and do not call into question the foundations of an appropriate pharmaceutical supply.

However, the lack of structural and strategic orientation of the law must be viewed critically. Far beyond the regulations in the pharmaceutical sector, the specified measures are primarily based on an activation of existing reserves of the statutory healthcare system. Perspective approaches to prepare the statutory healthcare system for the upcoming demographic change are missing. Structural weaknesses such as the realignment of the hospital landscape are completely left out.

The review requests of the government parliamentary groups include, in particular, the „benchmark regulation" for pharmaceuticals with a low or non-quantifiable additional benefit, which is also classified as problematic from the perspective of the G-BA, as well as the categorical setting of the 20% combination discount.

Access to pharmaceuticals across Europe





* excluding special programmes such as Temporary Authorisations and Early Access.

Source: Own presentation based on IQVIA (2022): EFPIA Patient W.A.I.T. Indicator 2021 survey

Figure 5: In a European comparison, Germany plays a leading role both in the speed of access to new pharmaceuticals and in the number of new pharmaceuticals available.

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How can we ensure innovation without sacrificing good evidence?

Martina Stamm-Fibich, Member of the German Bundestag | Jonas Wolframm

The task of the Federal Joint Committee (G-BA) is to make decisions on the medical benefit of a pharmaceutical based on the criteria of evidence-based medicine. The decisions made by the G-BA within the framework of the benefit assessment must subsequently be considered in the negotiations on reimbursement amounts between the pharmaceutical manufacturer and the health insurance funds. Ideally, the price of a pharmaceutical is based on its medical benefit. Recently, however, the evaluation of the benefit was made more difficult by the fact that the clinical evidence provided for the evaluation is weak and does not allow any conclusions about the actual benefit of the respective pharmaceutical. This article points out these so-called „evidence gaps" and proposes solutions, especially the proposed measures introduced in the law on the financial stabilization of statutory health insurance (GKV-FinStG).

The primary goal of our healthcare system is to provide good medical care for our citizens. This also includes ensuring that patients have access to medical innovations as quickly as possible. Unfortunately, medical innovations are often very expensive. Due to the high prices, a conflict of interest initially arises between the financial stability of the healthcare system and the broad application of expensive medical innovations. At the same time, however, even very expensive innovations can still be economical, if it is evident that the additional benefit for those affected justifies a higher price as compared to the therapies that are currently available on the market.

In this context, it must also be taken into account to what extent expensive secondary diseases or disabilities for patients can be prevented through medical innovations. The obligation to furnish proof that medical innovations actually deliver what they promise lies with the pharmaceutical industry. It is the task of the manufacturers to present the corresponding evidence for the efficacy of an active substance in a quality that also allows valid conclusions to be drawn about the advantages of an active substance over other therapies on the market.

It is in the nature of things that the generation of this evidence takes time – time that patients often do not have. Decisions on the reimbursement of pharmaceuticals are made in a conflict between speed and thoroughness. The fundamental question is therefore: How much evidence is sufficient to be able to negotiate an economical reimbursement price and at the same time prevent patients from having to wait an unnecessarily long time for the desired therapy?

To answer this question systematically, the legislator introduced the Pharmaceutical Market Reorganisation Act (AMNOG). Within the framework of the early benefit

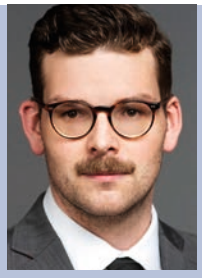
assessment, new active substances are compared with the specified comparative therapy. The evidence generated in this manner about the „additional benefit" of an active substance serves as a decisive instrument for pricing. The basic operating principle of AMNOG is: The statutory healthcare system pays for medical innovation in cases where it is evident that the patients actually benefit from it.

However, the prerequisite for an assessment is that the evidence is of high quality and actually allows statements about the additional benefit as compared to other therapies. Currently, this is not always the case. At present, there are some „evidence gaps" that make it difficult for those responsible to apply the guiding principle of the AMNOG.

Especially in the areas of orphan drugs as well as conditional or accelerated marketing authorisations, free combinations and advanced therapy medicinal products (ATMPs) and single-use therapies, the evidence is often weak for a variety of reasons. From our point of view, the existing „evidence gaps" mean that the original idea of the AMNOG, i.e. the link between evidence and reimbursement price, is increasingly being undermined. Instead, high reimbursement amounts have been paid for active substances whose additional benefit has often not been sufficiently proven.

The AMNOG was designed as a „learning system" and has already proven its ability to learn. An example of this is the introduction of post-marketing data collection to improve the evidence for orphan drugs. The problems are, however, more profound., For this reason, the legislator has implemented some reform proposals within the framework of the GKV-FinStG to enhance the balance between innovation and evidence. Unfortunately, the law does not address all these challenges, e.g. the „evidence gap" for single-use therapies remains.

Martina Stamm-Fibich *is Chairwoman of the Petitions Committee in the German Bundestag, a full member of the Health Committee and Patients' Representative of the SPD parliamentary group. Her topics in the Health Committee are pharmaceuticals, medical devices, remedies and aids, patients' rights, and the G-BA reform. Before joining the Bundestag, she was an independent works council member at Siemens AG Healthcare Sector. She represents the constituency of Erlangen (242).*



Jonas Wolframm *studied political science and Japanese studies in Tübingen, Kyoto and Trier. After his engagement in political consulting, he has been a research assistant in the office of Bundestag member Martina Stamm-Fibich (SPD) since 2019. There, he is responsible for the content of the topics pharmaceuticals, medical devices, remedies and aids, patients' rights as well as for the reform of the G-BA.*

Facts and figures on the quality of evidence

To assess the current quality of evidence, it is worth taking a closer look at the decision-making practice in the context of early benefit assessment. It is noticeable that the number of benefit assessments with a so-called „non-quantifiable additional benefit" has been increasing for some time. In the early years of the AMNOG, decisions of this type were predominantly found for orphan drugs. By the end of 2017, 80% of all procedures with „non-quantifiable additional benefit" were still orphan drugs.[1] In recent years, however, the additional benefit of active substances without an orphan drug status were also increasingly rated as „non-quantifiable". In the years between 2018 and 2020, the proportion of orphan drugs among all active substances with a „non-quantifiable" additional benefit was only 66%. About half of the decisions were due to the fact that the data provided were not suitable for benefit assessment.

Another notable development is that the proportion of first-assessed active substances that were approved in an alternative approval procedure, e.g. through conditional or accelerated approvals, increased from 30% in 2015 to 46% in 2020.[2] This trend towards weaker evidence is alarming. Unfortunately, national legislators' hands are tied when it comes to the authorisation practices of European medicines agencies. For this reason, national countermeasures must be taken that demand the necessary evidence as a prerequisite, at least in the course of pricing.

Evidence gaps in the AMNOG - room for improvement

The discrepancy between the speed of market access and the available evidence that can be used for pricing is particularly large in case of orphan drugs. The current orphan drug legislation means that orphan drugs approved by the EU Commission are awarded a „fictitious" additional benefit in the benefit assessment irrespective of the evidence. Until now, a full evaluation of the active substance was only required when the 50 million Euros limit was exceeded.

On the one hand, this procedure has the advantage that the approved orphan drugs are available for patients extremely quickly. At the same time, however, the regulation does not create incentives for conducting studies with high evidence quality. Overall, we believe that the approval of orphan drug is handled very loosely by the EU. As a result, approvals are very often granted on the basis of very weak data. This may be medically justifiable, but it presents the G-BA with major problems when it comes to pricing.

Politicians are also aware that the field of orphan drugs presents special challenges for the implementation of clinical studies. Yet the impression often arises that some manufacturers are not very interested in high-quality data, since poor data will not necessarily be reflected in low reimbursement amounts. The consequence of this practice is that the balance between evidence and reimbursement price is not right in many cases. This is where the AMNOG must intervene as a corrective tool. However, this is not yet sufficiently the case, as the 50 million Euro limit is set relatively high. At the same time, the current regulation does not provide for a full benefit assessment even for active substances with already existing therapy alternatives. Pricing on the basis of comparative evidence is thus not possible in most cases.

Another challenging area regarding the balance between evidence and innovation are the so-called free combination therapies in oncology. They are now widespread in healthcare practice and account for 44% or about half of all combination therapies used.[3] In general, they rely on the additive effect of complementary mechanisms of

action. The advantages are obvious: There are more treatment options and patients benefit from the synergistic effects of both active substances if they are successful. On the other hand, however, the high costs of the system are a substantial financial challenge.

The combination of two pharmaceuticals results in a linear price increase in the current reimbursement regime, which is offset by a non-linear increase in benefit as compared to the monotherapy. The consequence is that the price is to be assessed as unjustifiably high. In addition, the additional benefit of combination therapies compared to monotherapy is often unknown, as free combinations are usually not systematically evaluated. Thus, at present the AMNOG does not sufficiently cover combination therapies. Due to the high innovation density in the area of oncology products and the associated cost leaps, the reform pressure is particularly pronounced in this area.

Finally, ATMPs should not remain unmentioned, because they are also associated with evidence gaps that make evidence-based pricing considerably more difficult. The G-BA has made ATMPs subject to the AMNOG in the Fair Health Insurance Competition Act (GKV-FKG). However, the increasing availability of ATMPs, especially single-use therapies, poses considerable problems for the benefit assessment and the associated pricing process, as ATMPs are often approved in an accelerated procedure and questions about long-term effects cannot (yet) be answered at the time of the early benefit assessment.

At this point, long-term promises of a cure collide with comparatively short data collection periods in the studies that are submitted. Due to the often very high prices and simultaneously low level of evidence, the evidence gap for ATMPs and single-use therapies is currently particularly large. Because the current reimbursement and pricing mechanisms have not yet been designed for single-use therapies, the legislator has introduced post-market data collection as well as requirements for the quality of the application (quality asurrance guideline) to improve the evidence. These measures can generate better evidence over time. However, questions regarding the pricing of single-use therapies in particular at the time of market launch remain unresolved.

Excursus: Discussion on the relevant endpoints for early benefit assessment

In the past, there have always been discussions about the methodology used by the G-BA and IQWiG for the early benefit assessment of pharmaceuticals. The G-BA decides which endpoints it considers relevant for the assessment of the additional benefit. This is followed by the obligation of the manufacturers to provide high-quality data on the defined endpoints for the benefit assessment. Because the questions of pharmaceutical approval and benefit assessment differ considerably, surrogate endpoints used for the approval often do not play a major role in the benefit assessment.

In contrast, the focus is on endpoints such as quality of life or symptoms. Thus, pharmaceutical companies must ensure during study planning, that both patient selection and the choice of comparators and endpoints are carried out in such a way that the studies provide relevant evidence for benefit assessment. In this context, the consultation on clinical studies at the G-BA plays an important role. It should be claimed by the pharmaceutical companies. If, despite these measures, the pharmaceutical company does not fulfil its obligation at this point and delivers poor evidence, this should also have financial consequences during of price negotiations.

Suggested solutions

How can the problems described above be solved? The goal must be to strengthen the evidence base as a whole. For this purpose, the legislator has already taken a first step with the introduction of post-market data collection. In our opinion, the right way to get good data is to sanction bad data. At present, the statutory healthcare system pays enormous prices for pharmaceuticals with very weak evidence, thus providing an incentive for bad data.

This contradicts the guiding principle of evidence-based medicine – pharmaceutical companies who bring active substances with good evidence onto the market should also be rewarded for this. In case of pharmaceuticals with poor evidence, on the other hand, the inadequate proof of efficacy should also be reflected in the reimbursement price. The AMNOG reform measures in the GKV-FinStG are based on this principle. For example, lowering of the turnover threshold for orphan drugs that has been decided will probably ensure that evidence will also play a more central role again for this group of active substances, since active substances will be subjected to a full benefit assessment earlier.

Through the newly introduced benchmarks for reimbursement amounts, evidence is taking a more important role in the context of price negotiations. The retroactive reimbursement amounts from the seventh month onwards will ensure that evidence plays a leading role in pricing earlier than has been the case to date. In areas where no better evidence is provided in the medium term, the law provides for changes in pricing taking into account the lack of evidence. This includes, above all, the combination discount that has now been introduced for free combinations. The problem regarding the lack of evidence for single-use therapies at the time of the early benefit assessment remains unresolved. Subsequently, a more in-depth discussion on innovative reimbursement models should be conducted.

Conclusion

The basic principles that have applied so far for the benefit assessment of pharmaceuticals in the AMNOG must be strengthened: Evidence must play a greater role in the context of price negotiations. The measures that have now been adopted in the GKV-FinStG are a step in the right direction. At the same time, however, we need a new approach regarding the level of authorisation. The trend towards accelerated and conditional approvals should not continue to intensify. Moreover, patient-relevant endpoints such as quality of life and symptoms should also be given more attention in the clinical studies.

In general, clinical studies need to focus more on the relevant research questions of benefit assessment. This lies within the responsibility of pharmaceutical companies. Existing advisory services offered by the relevant authorities must be used consistently by the industry. High reimbursement amounts that cannot be justified by corresponding evidence should belong to the past. This is also in the interest of insured persons whose contributions must be handled responsibly and sustainably.

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Optimising the supply of pharmaceuticals – suggestions from the opposition

Dr Georg Kippels | Member of the German Bundestag

The current health policy discussion is marked by a special challenge of the regulatory dimension. The financial requirements of approximately 17 to 26 billion Euros annually – depending on estimates and considerations – are immense. Unfortunately, the law on the financial stabilization of statutory health insurance (GKV-Finanzstabilisierungsgesetz, GKV-FinStG) does not take a systematic approach, but attempts to reduce the financial requirements in the short term through a series of unsustainable individual measures to avoid an increase in contributions in 2023. As far as the planned „further development" of the AMNOG is concerned, the GKV-FinStG presented by the government is considered crucial for the future healthcare situation in Germany. Even pharmaceuticals with a low or non-quantifiable additional benefit present enormous advantages for patients. In the coalition agreement, the coalition mentions „a preventive, crisis-proof and modern healthcare system" to fight rare diseases as a central future field. The GKV-FinStG is not suitable to meet this requirement.

The current health policy discussion is marked by a special challenge of the regulatory dimension. On the one hand, there is the financial dimension and, on the other hand, the structural dimension with the associated question of which areas should be addressed at this point in time. These topics were already emerging abstractly at the time the coalition agreement was concluded and are also mentioned there in various places. However, the coincidence of the consequences of the Corona pandemic, the progress of demographic change and the required structural changes in the healthcare system now lead to a special kind of cumulation.

Both the current and the medium-term financial needs, ranging from 17 to 26 billion Euros annually – depending on estimates and considerations – are immense This calls for a big throw which can turn out to be a curse or a blessing. I do not want to address all fields of action, although it is not possible to completely separate them. As the opposition, however, we are not surprised that the AMNOG is also mentioned. Let me anticipate the conclusion of my analysis: I am not convinced that the GKV-FinStG will lead to a financially more sustainable healthcare system and solve the existing problems.

The „further development" of the AMNOG announced in the coalition agreement is reflected in the GKV-FinStG. The current law contains a series of measures intended to close the financial gap in statutory health insurance. Unfortunately, the law does not use a systematic approach, but rather attempts to reduce the financial requirement in the short term through a series of not really sustainable individual measures in order to avoid an increase in contributions in the coming year. This is not completely successful and and affects particularly strongly the area of pharmaceuticals, which actually account for only 16 percent of the

costs in the statutory healthcare system. However, the decisive factor is that the law specifies minimal changes in many different areas although a solid consideration would require fundamental and sustainable changes. Here again, the coalition obviously lacks the ability to make decisions.

As far as the planned „further development" of the AMNOG is concerned, the GKV-FinStG is considered crucial for the future healthcare situation in Germany. As a political party in the succession of our former chancellor Ludwig Erhard and the principles of the social market economy, we consider the AMNOG procedure which was established in 2011 a success, as it controls the reimbursement for innovations without interfering with a free market introduction. This means that German patients have access to innovations and thus receive best possible healthcare immediately upon approval.

Dr Georg Kippels *studied law in Cologne and Düsseldorf and subsequently worked as a self-employed lawyer in Bedburg. He has been a member of the CDU since 1980. He was mayor of Bedburg-Mitte from 2000 to 2020. He has been a member of the German Bundestag since 2013 and a full member of the Committee on Health since 2015. In the current 20th legislative period of the German Bundestag, he is the representative of the CDU/CSU on both the Committee on Health and the Subcommittee on Global Health.*

In my opinion, the success of the AMNOG process lies in the examination of the added value that the innovation brings as compared to existing pharmaceuticals that are already on the market. I also consider the categories of low and non-quantifiable additional benefit to be particularly important. As a health politician and elected representative, I try to put myself in the situation of the affected patient and evaluate the intended changes of the AMNOG from his or her point of view. When it comes to the financial equivalence of a new pharmaceutical with a low or non-quantifiable additional benefit and the appropriate comparative therapy, I wonder whether it is then still profitable for companies to launch such products on the German market.

Thus, in terms of the GKV-FinStG I see the potential danger of major market exits. By changing the existing AMNOG regulation, Federal Health Minister Lauterbach intervenes in a proven system that enjoys a high international reputation. This intervention does not represent a further development, as it only introduces higher flat-rate reductions without considering the assessment of the new ones. Even pharmaceuticals with a low or non-quantifiable additional benefit provide tremendous advantages for patients, e.g. delay of disease progression, tolerability, or improved quality of life.

With his law, Federal Health Minister Lauterbach deliberately risks potential market withdrawals and jeopardises the introduction of new pharmaceuticals. I consider this a potential problem for patient care in Germany. The long-term deterioration of innovative treatments which will be the likely consequence will inevitably be fed back to politicians when physicians and patients ask why a new better pharmaceutical is not available for them in Germany.

I would also like to mention the aspect of the constitutionality of the proposed regulation. The system of benefit

assessment with a corresponding scaling of prices in the negotiation is flexible and adapted to the situation.

The law gives up this flexibility and operates with rigid discounts or limits in the additional benefit categories of no additional benefit, non-quantifiable or low additional benefit. This affects areas of property protection (Article 14 German Basic Law), freedom of occupation (Article 12 German Basic Law) and the principle of equality (Article 3 German Basic Law).

This would make the current AMNOG process – which is independent of politics and has proven itself – a political issue. In my opinion, this is not a forward-looking policy. Above all, a careful discussion process is needed to identify all effects of the changes and take informed decisions. This is certainly not guaranteed at present.

From the opposition's point of view, a further development of the AMNOG should not only focus on price cuts with the associated danger of reduced availability, but rather on mechanisms that lead to a qualitatively better assessment of the benefits of pharmaceuticals.

Research and business location & orphan drugs

Let us take a look at the example of drugs for rare diseases (orphan drugs). Page 68 of the coalition agreement of the coalition states: „We will ensure the supply of innovative medicines and vaccines."[1] However, the proposed cuts in the GKV-FinStG have exactly the opposite effect. Approximately four million people in Germany live with a rare disease. So far, approximately 8,000 different rare diseases are known. However, we only have 138 pharmaceuticals to treat these diseases, because research is difficult and costly. It therefore seems all too logical that rare diseases are the so-called „orphans" of medicine.

In the European Union (EU), a disease is considered rare if it affects no more than five in 10,000 people in the EU. Although the total number of people affected is high, the individual patient group is small, which makes studies more difficult and therefore the pharmaceutical can only be sold in small numbers. Orphan drugs are expensive and sometimes do not deliver what we expected in the development phase. But research funding is essential for the affected patients and can lead to an enormous improvement in these diseases.

Since the evidence for orphan drugs is particularly difficult, but their value is recognised, the instrument of „post-marketing data collection" was introduced by the then Federal Health Minister Spahn. This was a correct and important signal. In 2011, orphan drugs – which were defined by the EU 20 years ago – were granted an exemption in the early benefit assessment in order to adequately consider all special features. In the AMNOG, they are certified as having a so-called fictitious additional benefit. This marked the start of a promising improvement in the supply situation in Germany, which has become exemplary throughout Europe. Briefly: Orphan drugs simply do not fit into the systematics of the AMNOG, but are now being unnecessarily forced into the regulation. Above all, the AMNOG is structurally changed which should be carefully prepared and does not belong in the context of a short-term financial support measure.

The coalition agreement already mentioned „We will ensure the supply of innovative pharmaceuticals and vaccines. We will resolutely combat any bottlenecks in the supply. We will take measures to relocate the manufacture of pharmaceuticals back to Germany or the EU, including the production of active ingredients and excipients. This includes reduction of bureaucracy, identification of potential investment grants for production facilities as well as grants to ensure security of supply."

Looking at the intended reform of the AMNOG, the

Ampel coalition replaces entrepreneurial freedom with state guidance. Instead of allowing companies to make a profit with innovative pharmaceuticals, which is then reinvested in Germany which in turn strengthens Germany as a research location, Minister Lauterbach is trying to reduce the profit margin to the maximum. However, no information is given on the means with which the Ampel coalition wants to ensure the supply of innovative pharmaceuticals.

In the coalition agreement, the Ampel coalition mentions „a preventive, crisis-proof and modern healthcare system" to fight rare diseases as a central future field. However, the lowering of the turnover threshold for orphan drugs from 50 to 30 million Euros will only lead to a faster application of the additional benefit assessment procedure of the AMNOG, which is unlikely to be successful due to the special study situation of orphan drugs. It is therefore to be expected that the supply of pharmaceuticals for rare diseases in Germany will deteriorate sooner or later as pharmaceuticals will disappear from the market or research will not even begin. People hoping for a cure will be bitterly disappointed.

Moreover, orphan drugs are negatively affected by the law through the compulsory discount for combination therapies, through the requirements for additional benefits when negotiating the reimbursement amount and – in case of discards – through uneconomical package sizes. These effects can accumulate unfavourably. The savings effect for the statutory healthcare system is negligible in view of the overall dimension of pharmaceutical costs, but the damage to the treatment of patients in particularly difficult and often life-threatening health situations is enormous.

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Innovation and evidence – trends from the industry's perspective

Chantal Friebertshäuser, until 31 December 2022 Managing Director MSD Deutschland | Member of the Board of the vfa

At present, we are at a crossroads in health policy: The AMNOG has proven its worth. It has (1) stabilised pharmaceutical expenditures in the long term, (2) promoted innovation, and (3) shown itself to be open enough for technically sound further development. On the other hand, the planned measures of the law on the financial stabilisation of statutory health insurance (GKV-Finanzstabilisierungsgesetz, GKV-FinStG) would be a fundamental deviation from the basic principles of the AMNOG. By devaluing the low and non-quantifiable additional benefit and lowering the orphan threshold, we will see many later applications for marketing authorisation. Benchmark, lump-sum discounts, special termination rights and the retroactive effect of the negotiated price even for new indications counteract the principle of benefit-based pricing through negotiation. Therefore, it is crucial not to pass the currently planned AMNOG measures with a savings law only because we think that we are under time pressure. It is important to promote the necessary restructuring and expansion of our benefit assessment system in a joint dialogue.

Since the Act on the Reorganisation of the Pharmaceutical Market (AMNOG) came into force on 1 January 2011, the share of pharmaceuticals in the total expenditure of statutory health insurance has remained stable for many years at around 16%, of which only 11.1% is accounted for by pharmaceuticals after deducting wholesale and pharmacy margins. In the meantime, pharmaceutical companies annually contribute 21 billion Euros to the stabilisation of statutory health insurance through discounts and rebates.

I would like to illustrate this with an example from my company: In 2015, we introduced an immuno-oncology pharmaceutical to the German market that was generally perceived as groundbreaking. Since then, in the course of the repeated extension of the approval to include further indications, the negotiated price has fallen by around one third, and this despite the fact that we have even been able to prove a considerable additional benefit in almost half of all new indications.

In total, 319 innovative pharmaceuticals were newly launched in Germany in the first ten years of the AMNOG. By comparison, 282 pharmaceuticals were launched in the previous ten years (figure 1). The cleverly balanced evidence- and benefit-based incentive system not only continues to ensure the development of new active substances, but also ensures rapid access to newly approved therapy options for patients in our country. Nowhere else in Europe are new active substances available as quickly as in Germany: 133 days against an EU average of 511 days, but also compared to, for example, 497 days in France, which is also a large market.

Accordingly, many countries reference the reimbursement amount negotiated in Germany in their national pricing. If legislative interventions lead to misaligned incentives and dysfunctionalities in the German benefit

Research-based industry continues to be highly innovative

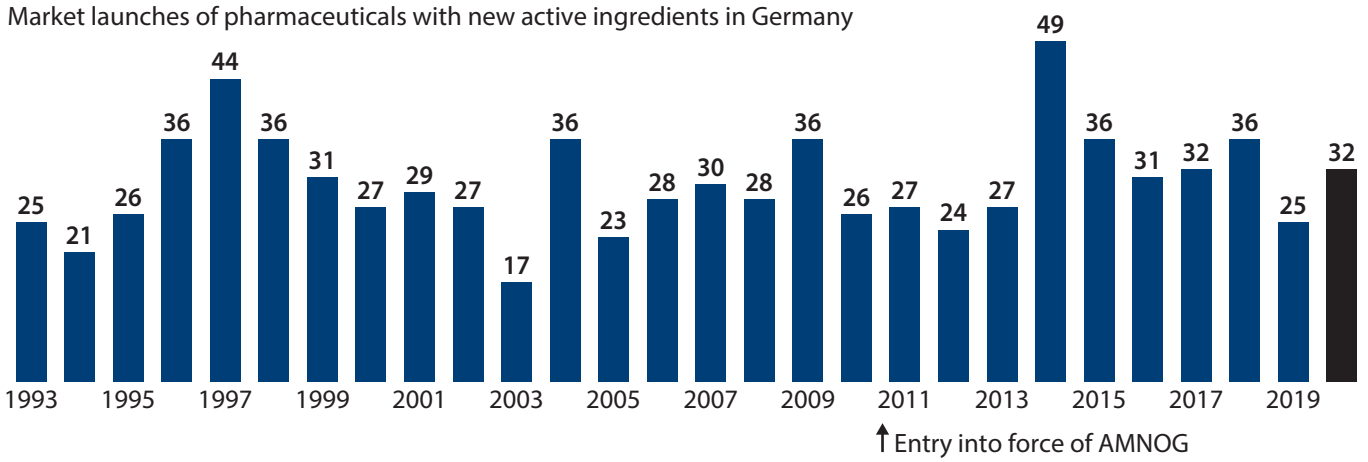


Figure 1: In the first ten years after the AMNOG came into force, 310 new pharmaceuticals entered the market in Germany. By comparison, 282 pharmaceuticals were launched in the previous ten years.

Chantal Friebertshäuser *was until 31 December 2022 Senior Vice President and Managing Director of MSD Germany. For more than 130 years, the company, known in the USA and Canada as Merck & Co., Inc. and based in Rahway, New Jersey (USA), has been researching pharmaceuticals, vaccines, and biologicals. Chantal Friebertshäuser is a board member of the Association of Research-Based Pharmaceutical Companies (vfa) and the Board of Directors of the German-American Chamber of Commerce (AmCham).*

assessment and price negotiations, this will have considerable consequences for patients throughout Europe and also worldwide.

Of course, this does not mean that we should regard the AMNOG framework as a rigid framework to which we adhere unalterably, until its supporting elements corrode at some point and must be replaced. In fact, already in the first decade of its existence, the AMNOG has shown itself to be a learning system that can adapt to its changing environment with due flexibility: Orphan drugs and reserve antibiotics are well-known examples. But, and this is crucial: The changes made by the legislator were preceded by expert discussion. The basic principles of benefit-based pricing in the negotiated procedure were always preserved.

It has also been common sense in the best sense not to overburden all parties involved in the benefit assessment procedure. For example, the original plan to also have the

AMNOG contributes to stabilising pharmaceutical expenditures

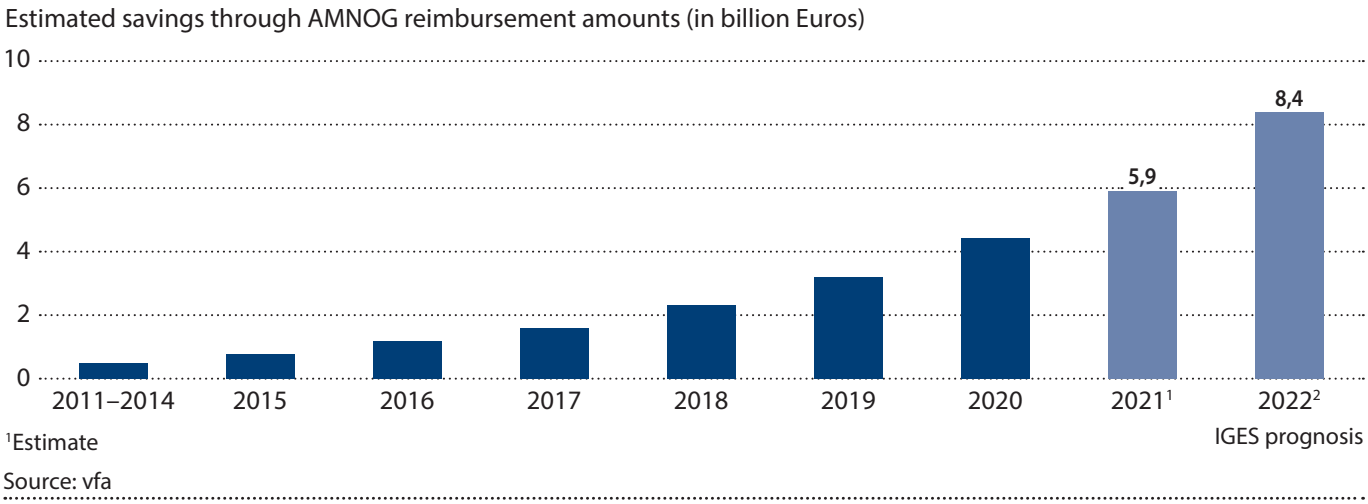


Figure 2: Since the AMNOG came into force, it has increasingly generated savings for the statutory healthcare system – in 2022, these are expected to amount to 8.4 billion Euros.

existing market subsequently undergo a benefit assessment within the AMNOG was consensually overruled with the 14th Act amending the 5th German Social Codebook (SGB V) with effect from 1 January 2014. With this regulation, the legal basis for the benefit assessment of pharmaceuticals in the existing market has been eliminated. Instead, it was agreed on a lump-sum compensation of the presumed price adjustments.

The special right of termination for existing reimbursement amounts now envisaged in the draft law for the GKV-FinStG submitted by the Federal Government, on the other hand, would not only undermine the principle of trust and interfere with ongoing fair and evidence-based negotiated agreements, but would also exhaust the negotiating partners for months, if not years, slowing down the benefit assessment for new pharmaceuticals. Healthcare providers as well as payers, and thus ultimately also the budget legislator, would have to face considerable planning uncertainties.

The individual interventions in the finely balanced and globally praised assessment and pricing system of the AMNOG as intended in the draft law would actually trigger considerable distortions in several dimensions:

The new so-called „benchmarks“ in the price negotiations are actually price determinations of a public medicine. There is simply nothing left to negotiate. In future, superior pharmaceuticals with a low or non-quantifiable additional benefit would automatically be granted the maximum price level of the inferior product. Instead of the fair initial assessment of the additional benefit of the new pharmaceutical at the time of approval, there would be a de facto devaluation of the additional benefit.

The principle of „equal prices for equally good products“ and „slightly higher prices for slightly better products“ is

broken. This may mean the end for many stepwise innovations, which in the past have gradually provided gains in the patients' survival time for types of cancers that have a particularly poor prognosis at advanced stages. Together with the new mandatory rule on the consideration of volume and volume-related aspects in the price negotiations, the evidence-based incentive model of the AMNOG with its functioning gradual price degression would be replaced by a steep political price slide.

An additional discount on the reimbursement amount of patent-protected pharmaceuticals used in combination shall be introduced, although the combination administration is already taken into account in the price negotiations. As soon as only one pharmaceutical company carries the combination in its label, the costs of the combination are taken into account in the price negotiations by comparing it with the appropriate comparative therapy. Anyway, combinations are normally labelled by both manufacturers. Not only is there no regulatory gap for the legislator, but the amount of the proposed discount is obviously arbitrarily chosen for purely fiscal reasons: 20%.

The federal government has failed to provide a technical justification for the increase of this malus regulation for combination therapies, nor has it provided a comprehensible explanation which effects this will have on healthcare.

This constellation shows how absurd the combination discount is in the context of the other planned measures: If one of the two combination partners is the most economical appropriate comparative therapy of the other pharmaceutical, this will result in a calculated reimbursement amount of zero Euros in the future. Unlike the previous negotiated solution, the combination discount also has a considerable third-party effect. There is also a lack of possibilities to differentiate between the combination partners according to their contribution to the overall benefit. An exception clause limited to the individual case will not be sufficient to eliminate these fundamentally existing legal uncertainties, also with regard to the lack of necessity of the measure.

The privileged treatment of orphan diseases has so far also enabled companies to develop innovative therapies economically in indications with small case numbers and to launch them on the market promptly. In future, if the relevant threshold value is lowered from 50 to 20 million Euros in sales, studies that are difficult to recruit would have to be continued on a regular basis due to the distribution of patients until sufficient data is available in the German benefit assessment. Otherwise, pharmaceuticals without a quantifiable additional benefit risks economic failure. For patients, this would mean that they would possibly have to wait another few years for the therapy. The system of early benefit assessment would be turned into its opposite.

It is therefore incorrect to say that the law in this form would not lead to any restrictions in patient care. The opposite is the case. The cumulative effect of the planned measures is nothing less than an attack on modern oncology. Let me illustrate this once again with the anti-cancer drug mentioned above: Since its initial market launch in 2015, we have been able to approve it for 15 different indications and thus fundamentally help more than 30,000 patients in Germany alone. By 2025, we want to approve the pharmaceutical for further indications and thus make it possible to treat twice as many cancer patients. In addition to new tumour entities, we are now also moving increasingly into early stages and curative settings.

Even today, this considerable expansion of the contribution to care and the number of patients treated is only matched by a moderate increase in turnover. According to our assumptions, eight out of ten new patients would receive the pharmaceutical „free of charge". This proves it:

AMNOG works. Pharmaceutical expenditures remains effectively limited even with the increased use of particularly successful new treatment options.

Under the now planned provisions of the GKV-FinStG, however, things would look quite different: Despite a doubling of the number of patients treated, there would now even be a decline in turnover. Or in other words: we would treat all additional patients for free and even put money on top! It is obvious that this is not compatible with rational action and the responsibilities a management has towards its investors. The result: certain innovations fail to materialise and patients in small indications with a high unmet medical need are not treated as well as they could be.

Instead of legally discrediting the linguistically rather unfortunate categories of a low or non-quantifiable additional benefit, which keep the wheel of medical progress turning, we should rather ask ourselves how it is that so many promising therapy innovations find themselves in these benefit categories. In fact, there is a very different and urgent need for further development of the AMNOG: We regularly fail to adequately consider existing evidence within the framework of our early benefit assessment system (figure 3).

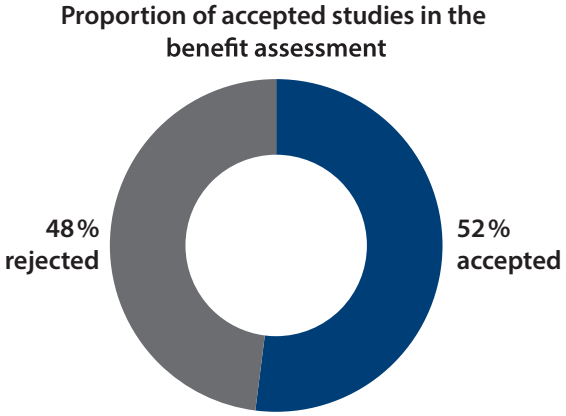
Today, 48% of the clinically available evidence is not accepted in the AMNOG. Some of the reasons for this are home-made. The threat of a late change of the appropriate comparative therapy hangs like a sword of Damocles over pharmaceutical companies. Moreover, increasingly targeted approaches also mean increasingly smaller patient groups. Nevertheless, we allow ourselves the luxury of breaking down basket studies into individual indications within the framework of the benefit assessment. Modern therapies are often based on active principles that are not limited to one organ system.

Moreover, it is not uncommon for patient-relevant benefits to become apparent early in studies. However, the ethically required switch from the control arm to the intervention group in these cases makes it difficult to reach late endpoints such as „overall survival“ in a meaningful way. We could effectively fill these gaps with registry data. Federal Minister Lauterbach also recently praised „digital twins“ generated from healthcare data and virtual control arms in clinical studies, on the example of Israel. In Germany, however, such study designs are not acknowledged in the benefit assessment! Just recently, a company had to withdraw a pharmaceutical from the market due to the lack of acceptance of a registry study. But it is also clear: the described path to more evidence from real-life healthcare is not a one-way street. For years we have been talking about bringing innovative, data-based reimbursement models (pay for performance) together. It is time to take the next steps here.

At present, we are at a crossroads in health policy: The AMNOG has proven its worth. It has (1) stabilised pharmaceutical expenditure in the long term, (2) promoted innovation and (3) shown itself to be open enough for technically sound further development. The planned measures of the GKV-FinStG, on the other hand, would be a fundamental deviation from the basic principles of the AMNOG.

By devaluing the low and non-quantifiable additional benefit and lowering the orphan threshold, we will see much later applications for marketing authorisation. Benchmarks, flat-rate discounts, special termination rights and the retroactive effect of the negotiated price even for new indications counteract the principle of benefit-based pricing through negotiation. As a result, safety, efficacy and quality are no longer sufficient for market availability. Patient care is in danger of being disconnected from the progress of medical knowledge.

Consideration of available evidence needs to be improved



- **48 %** of the **approval studies** submitted for benefit assessment were rejected **by the G-BA**
- Submitted evidence is classified as irrelevant if e.g. the comparative treatment does not correspond to the G-BA's specifications.
- Without harmonisation of the study guidelines, a fair benefit assessment is not possible.

Source: vfa

Figure 3: Only 52% of the evidence presented in approval studies is accepted by the G-BA in the early benefit assessment procedure.

Therefore, it is crucial not to pass the currently planned AMNOG measures with a savings law only because we think that we are under time pressure. Responsible policy-makers must not wait to act and correct themselves until the negative effects described have actually materialised. Adjustments to curricula and research programmes will mostly only be seen at a point in time that is difficult to operationalise for a policy that thinks in four-year cycles. Long-term innovation processes cannot be switched on and off depending on the budget situation. It is important to promote the necessary restructuring and expansion of our system of benefit assessment in a joint dialogue, instead of shaking its pillars only to be surprised later that the system as a whole begins to falter.

Rare diseases: guidelines for evidence requirements from a regulatory perspective

Dr Frauke Naumann-Winter, Dr Wiebke Löbker and Professor Karl Broich | Federal Institute for Drugs and Medical Devices (BfArM)

In 2000, the Regulation on Orphan Medicinal Products was adopted to improve access to effective and adequately tested pharmaceuticals for about 35 million patients with an orphan disease in the EU. In our article, we provide an overview of the experiences with this regulation and present the regulatory requirements, which can vary significantly depending on the therapeutic setting and the individual therapeutic intervention. Especially in case of particularly rare diseases or complex interventions, prospective data collection over the entire lifecycle of an orphan drug is particularly significant. The dialogue between patients and physicians as well as manufacturers, regulatory authorities and HTA institutions should be intensified at national and European level to ensure that conclusive data are collected for all stakeholders within the scope of a usually global development programme. Various initiatives and platforms aim to increase the visibility of rare diseases to improve healthcare for these patients in the long term.

Historical background and criteria of the orphan drug regulation

In the discussion about the development of an EU programme for the promotion of drug developments for rare diseases at the end of the 1990s, mainly so-called „blockbusters" were approved that had been developed for the treatment of large patient groups. Even if evidence for the relevant clinical efficacy for treatment in rare diseases was available during their development, these were often not taken up in regulatory terms, and if the corresponding active substances came onto the market at all and then for other diseases, they were often used off-label for rare diseases.[1]

To improve access to effective and adequately tested pharmaceuticals for approximately 35 million people with an orphan disease in the EU, the Regulation on Orphan Medicinal Products came into force in 2000.[2] Under this process, promising active substances are granted a so-called orphan designation (OD) so that they benefit from certain administrative or financial advantages.[3] The criteria for initial designation include a threshold for rarity of a disease (as a postulated cause for lack of profitability) and require initial evidence regarding the scientific rationale for the use of the researched compound in the respective rare disease.

The criteria for initial orphan designation allow easy and broad access to the incentive programme. Unless they are the first drugs developed for the diagnosis, prevention, or treatment of a rare and serious or even life-threatening disease, candidates must demonstrate so-called substantial benefit over existing, a so-called satisfactory methods.[4]

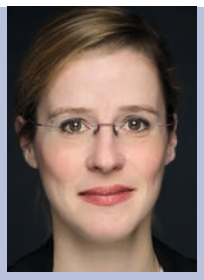
This substantial benefit can either be based on a so-called clinically relevant advantage or a significant contribution to patient care.[5] A clinically relevant advantage exists if better efficacy or a more favourable safety profile are

documented, or the new drugs can be used, e.g. for a different disease stage or after failure of standard therapy. A significant contribution to patient care can be demonstrated, e.g. on the basis of improvements in quality of life achieved through simplified administration.

The orphan drug status must be confirmed at the time of approval to gain access to orphan market exclusivity. Here, the so-called orphan medicinal product (OMP) is granted market exclusivity over similar drugs such as generics or direct derivatives. During the period of market exclusivity (e.g. ten or even up to twelve years for pharmaceuticals that have been developed for children in accordance with the EU Children's Medicines Regulation), the pharmaceutical companies do not have to fear direct competition, as a possible breach of market exclusivity is associated with high requirements. However, since the definition of similar products is rather narrow, innovative research activity even in the same therapeutic area is usually not slowed down even by approval of a pharmaceutical with active market exclusivity.[6]

Overview of OMPs

More than 230 OMPs have been approved in the last 20 years, and market exclusivity is still in effect for approximately 150 OMPs.[7] Contrary to the initial expectations, OMPs are mainly new substances, often even innovative approaches such as gene therapy or anti-sense technology. While a few indication areas (e.g. adult haematooncology) have



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Professor Karl Broich, *is a physician (approbation in 1985, doctorate in 1986) with a degree in (neurology in 1993); additional qualification in psychotherapy with emphasis on behavioural therapy (1999). 2000 to 2009 initially Department Chair Neurology/Psychiatry, then Head of Approval Department 4 at the BfArM; from 2009 Vice President, since 2014 President of the BfArM.*

benefited from very dynamic and also successful drug development, the majority of the 6,000 to 8,000 rare diseases remain without treatment.[8]

This is also and especially true for paediatric pharmaceuticals despite the high unmet medical need and the anticipated synergies between the EU regulations for rare diseases and for paediatric pharmaceuticals. The experience of the orphan regulation with regard to known active substances shows that both well-established-use and repurposing continue to be rarely pursued and off-label use for rare diseases remains widespread (e.g. indications of drugs and actual recommendations in guidelines). There have also been some poor experiences with orphan approval of known agents, which have been accompanied by significant price increases.[9]

In the EU, orphan drugs are generally approved by the European regulatory authority and are thus immediately marketable throughout the EU. Unfortunately, however, actual access to orphan drugs in the EU is very unevenly distributed.8 This is related to both the marketing and pricing strategy of pharmaceutical companies and national rules of reimbursement through the nationally regulated healthcare system. Orphan drugs, especially for extremely rare diseases, are often associated with very high costs.

The therapeutic spectrum of orphan drugs is very broad, with a particularly large number of orphan drugs developed to date for oncology, metabolic diseases and neurology. In terms of disease prevalence, orphan drugs represent the entire spectrum from extremely rare to just below the 5 in 10,000 threshold.[7]

Regulatory requirements

The development of orphan drugs is particularly challenging, and many years may pass from the discovery of a treatment approach to the marketing of a finished pharmaceutical.10 Many rare diseases are also progressive with late or infrequent clinical events. Therefore, in addition to mortality and morbidity endpoints, intermediate endpoints, e.g., pharmacodynamic effects, are sometimes used for rare diseases when clinical endpoints cannot be collected in a sufficiently robust manner in time-limited studies, e.g. due to low event rates coupled with the rarity of the disease.

The prognosis for heterogeneous disease courses is often poorly predictable, in part because many of these serious diseases are still poorly understood. Depending on the particular therapeutic setting and the specific benefit/risk ratio for a product to be approved, the indication may initially be limited to a specific population that is clearly defined due to its high unmet medical need. This resulting niche means that even in case of approved pharmaceuticals, there is still an unmet need for additional patients with the same underlying condition. The regulatory requirements as well as the data submitted for approval vary significantly depending on the respective therapeutic setting and the therapeutic intervention. In addition to controlling the quality of the clinical studies submitted and their potential for bias, orphan drugs place particular emphasis on the consistency of the data in the overall setting, which should fit well within the relevant scientific context.[11] A large proportion of orphan approvals in the EU are based on the results of randomised controlled studies.[12,13]

However, study designs may also be accepted, such as single-arm studies with external control or intra individual controlled studies. Deviation from the gold standard requires a good knowledge of the pathophysiology and mechanism of action of the respective substance and should be agreed in advance with regulatory authorities. For some diseases, there are also regulatory guidelines describing appropriate study designs or endpoints for the clinical

development of orphan drugs.[14] Both national regulatory authorities and the EMA offer several platforms for a regulatory/scientific dialogue, especially SME and Academia, which are very important for rare diseases.[15]

In recent years, study designs in which early clinical phases (exploratory) and later phases (confirmatory) merge have become increasingly important. Approvals can be granted based on interim evaluations of ongoing studies.

Moreover, the pharmaceutical industry often interconnects study programmes across several, different patient populations so that information from ongoing, parallel studies can also be for the approval decision. If a favourable benefit/risk ratio is seen in a rare disease, but the evidence presented is not considered complete, a special form of approval can also be granted (conditional approval, approval under exceptional circumstances). Compared with conventional pharmaceuticals, orphan drugs are frequently represented in these special forms of approval.[16]

Data collection throughout the life cycle

The funding programme for orphan drugs does not fundamentally lower the requirements for approval, but in fact, agents for rare diseases often must accept more uncertainty at the time of approval. In purely numerical terms, it is simply not possible to capture rare or even very rare side effects of many orphan drugs in small populations prior to approval. In the so-called risk management plan for the period after the approval, the information that is still missing and the information to be provided subsequently are clearly specified and are binding.[17] This relates primarily to safety aspects, but can also affect the (durability of the) efficacy of a substance. If the approval is based on an interim evaluation, later data sections of the pivotal studies or results of further studies must be provided.

In general, the specific question regarding the benefit/risk ratio determines which design is selected for data collection after approval; in principle, interventional studies and/or non-interventional studies are possible.[17,18] Registry studies from existing or planned registries can also be commissioned to provide data from everyday healthcare. Here, collection in disease registries is recommended. The effort required to establish a registry or even to plan an efficient study to address the existing uncertainty should not be underestimated. However, the quality requirements for a registry suitable for knowledge gain are very high, especially the comparison of therapy alternatives with regard to efficacy and safety is subject to a large number of methodological uncertainties.[19]

A particularly valuable time for gaining knowledge is when the first translatable approaches for the treatment of a disease have been found, i.e. often before the actual clinical development of certain substances. The prospect that a pharmaceutical may soon be available puts a spotlight on further research into the underlying disease.

Here, prompt interaction between developers, regulators, HTA institutions, patient organisations, but also registry holders, would be essential to enhance the planning of the entire life cycle of a pharmaceutical, starting with timely preparation for more efficient trials and, where appropriate, joint planning of long-term follow-up of patients in day-to-day healthcare after approval. There is much potential to improve the quality of a data collection effort if the procedure is planned prospectively.[13]

Dialogue for efficiency

An early exchange between patients and physicians as well as manufacturers, regulatory authorities and HTA institutions at European and national level is of particular importance to ensure that meaningful data are collected for all stakeholders in a typically global development program-

me. The dialogue between regulators and HTA has also already been initiated in the parallel consultations at the EMA and should be further intensified in the interest of efficient development of pharmaceuticals.[20] Exchanges between regulators and the Federal Joint Committee (G-BA) are already taking place at national level: The Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI), together with the G-BA, which is responsible for the early benefit assessment of pharmaceuticals in accordance with Section 35a of the German Social Code, Book V, have established a procedure for the early interaction in the form of joint consultations.[21]

In the future, the EU HTA Regulation 2282/2021 will ensure a further harmonisation.[22] Here, the joint scientific analysis of clinical data by the HTA institutions of the EU member states is planned, starting in 2025 initially for oncology products and ATMPs, and from 2028 for all OMPs. This aims at greater transparency and consistency regarding the scientific basis of HTA decisions for reimbursement and pricing, which continue to be regulated nationally.

Conclusion

In principle, the funding programmes for orphan drugs have been successful: For the EU alone, over 200 orphan drugs have been brought to market. For many rare diseases, a dynamic of drug developments can be observed that would have been unthinkable without the scientific progress of the last 20 years.[10]

In parallel with the revision of the pharmaceutical strategy by the European Commission, the submission of the draft orphan regulation is expected in early 2023. Here, the weaknesses identified in advance should be addressed; for example, better approach to actually neglected therapeutic areas without a functioning study landscape and without an established clinical research base would be desirable. The regulation should also be better adapted to current scientific and regulatory circumstances.

Internationally, there are several efforts to improve the basic prerequisite for innovative and efficient drug development, e.g. also European research alliances and registries with different rare diseases of one specialty in focus, such as the European Reference Networks.[23] Standardisation of data, improvement of data quality and sustainability of data access are on everyone's lips. Various initiatives and platforms aim to improve the visibility of rare diseases, among other things,[24] to improve healthcare for patients in the long term. Here, it is important to identify potential synergies to optimise joint efforts for promotion and collaboration for orphan drugs.

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Orphan drugs in the AMNOG procedure – a patient perspective

Mirjam Mann | Executive Director of the Alliance of Chronic Rare Diseases (ACHSE) e. V.

In Germany, about four million people live with one of the approximately 8,000 rare diseases. People with rare diseases wait longer than average for the right diagnosis, and quite a few never receive it. There are only few experts for their individual diseases, most of whom are not easy to find and are often not sufficiently networked with other care providers. Knowledge about the different diseases is still very incomplete. Causal treatments are only available for a few of them. People with rare diseases are ill for life.

Since there is no fourth hurdle in Germany – unlike in other European countries – affected patients are in the fortunate position that they can actually obtain almost all pharmaceuticals within a few weeks of their approval. This also applies to orphan drugs and it is important to maintain this rapid access.

At the same time, there are only approximately 200 pharmaceuticals that are or were classified as orphan drugs. Viewed globally, there is still no causative or disease-slowing therapy at all for many millions of people living with one of the approximately 8,000 rare diseases. We therefore need more orphan drugs, not fewer. Research and pharmaceutical development must therefore be driven forward and not inhibited. We do not only need achievements of university research, but also the know-how and commitment of the pharmaceutical industry. To this end, it must be economically interesting for them to develop pharmaceuticals for these diseases.

At the same time, it is essential for affected patients that sufficient funds are available for other, extremely important elements of healthcare, such as networking of centres, high-quality care, specialised rehabilitation, and good case management. Excessive prices for pharmaceuticals use up funds that could be used for these services. Thus, what is needed are pharmaceuticals that are „worth the price". Pharmaceuticals that are worth their price does not necessarily mean that they are cheap.

Concerns and fears of affected patients

While we are already facing the statutory health insurance deficit with the proposed repair measures, affected patients are already worried. The COVID-19 pandemic presented and continues to present major challenges to all chronically ill people. As often, people with rare diseases have faced and continue to face very specific burdens and problems. Additionally, they are now facing new challenges as a consequence of the horrible war against the Ukraine and the resulting energy crisis.

It had long been clear to all professional stakeholders in the healthcare sector that the statutory health insurance system would be facing a larger deficit in 2023 as a result of these crises and previous political decisions. Even before this draft law, people with rare diseases were therefore worried that they would again be forgotten under these general conditions. The mingle-mangle of measures in the area of pharmaceutical supply that is now being proposed makes us fear that the development and marketing of orphan drugs will once again become unattractive. In particular, the plan to regulate pricing using benchmarks is not only an intervention in self-administration, but also poses a major threat to the timely availability of orphan drugs.

Demands of ACHSE – also topical in the current discussion

Several general demands of ACHSE, which improvements in the healthcare system are urgently needed, have also become relevant again when we discuss the new developments in the field of pharmaceuticals, especially advanced therapy medicinal products (ATMPs):

1. Structured patient pathways should be described and published so that non-specialist physicians know what their next steps are to provide optimal care and to whom they shall refer affected patients.

2. Promote networking of the centres: Financial resources must be made available to strengthen and extend the network among German centres for rare diseases as well as with the European Reference Networks (ERN) and with the supply of the individual location.

3. Funding of the centres is based on a complicated mix. Surcharges must be negotiated individually. In the further development of centre financing, ACHSE would prefer to have regulations that do not have to be negotiated in competition with the financing of other healthcare services.

Mirjam Mann *has been Managing Director of the Alliance of Chronic Rare Diseases (ACHSE) since its foundation in 2004. ACHSE is a network of more than 130 patient organisations of people with rare diseases and advocates for the interests of affected people. In addition to managing the office and financing the work of ACHSE, Mirjam Mann is particularly responsible for networking and political advocacy.*

4. We need certified centres to make expertise transparent.

5. Complex healthcare should only be administered by experts. In the interest of patients, not all physicians should do everything.

6. We need to generate significantly more evidence before and after the approval of a pharmaceutical. For this purpose, a national strategy for patient registries is needed. The Federal Government should develop a national strategy for the establishment, expansion, maintenance and care of rare disease registries, ensuring communication, interoperability and networking between the different stakeholders and between the registries. We need a registry landscape based on patient registries, not product registries.

7. Affected people should be viewed holistically and supported in the same way. Every chronically ill person should be entitled to an independent, system-competent case manager „on prescription“: „MyCaseManager“. This person stands by the affected person, helps them apply for the benefits they are entitled to, helps them overcome the bureaucratic hurdles and takes care of all necessary support options, thus ensuring the best possible care for them and not leaving them alone in our healthcare and social benefit system.

8. ACHSE requests a reliable and sufficient funding for self-help, not only in the form of project funding. Self-help takes on the tasks of counselling, improving information and guidelines, educating people about diseases and treatment options, providing psychosocial support for those affected by the same disease, and driving improvements in healthcare. It contributes knowledge and expe-

rience to the healthcare system, research and society and should therefore also be supported by the society in a sustainable and predictable way. This also applies to the umbrella organisations, such as ACHSE or BAG SELBSTHILFE. This support ensures that self-help can be an independent and critical voice, also towards the pharmaceutical industry.

Reasonable prices are in everyone's interest

In the development of orphan drugs, there is a tension between the enormous need for therapies for diseases that are not yet (well) treatable and the related desire to ensure access of patients to the new pharmaceutical as quickly as possible, even beyond clinical studies, on the one hand, and the need to have validated data on the quality, safety, efficacy and benefit of a pharmaceutical to enable proper treatment decisions and negotiate an appropriate price, on the other.

Just like other patients, people with rare diseases have a right to and a need for safe, high-quality and effective pharmaceuticals that also provide additional benefits as compared to existing care options. ACHSE therefore strongly supports the demands and efforts to obtain evidence on the added benefit of orphan drugs both in clinical studies and subsequently through post-market data collection.

In the European Union, a pharmaceutical is approved as a pharmaceutical for rare diseases (orphan drug), if the pharmaceutical company can demonstrate that no satisfactory method for the diagnosis, prevention or treatment of the condition in question has been approved so far in the EU, or that the respective pharmaceutical – if such a method exists – will be of significant benefit to people affected by that condition. Whether the additional benefit of orphan drugs is sufficiently proven with the „significant benefit" as determined by the EMA is apparently viewed differently by European HTA authorities. The regulatory and HTA authorities must reach a consensus with the pharmaceutical industry and patient representatives on how and when the evidence required for the right treatment decision can and should be collected for orphan drugs. From ACHSE's point of view, it makes sense to collect as much evidence as possible already in the registration studies, which also takes into account the questions of HTA authorities.

To ensure that people with rare diseases receive the appropriate pharmaceuticals, the price must also be right. A fair price rewards the risk and know-how invested by the manufacturer, is paid for a product that has proven its added value and can be borne by the solidarity community. Pharmaceuticals for very small populations will never be cheap, but they should be worth the price. At the same time, sufficient incentives should be provided to the pharmaceutical industry to develop new products for the vast majority of people affected, for whom there's no pharmacotherapy available at present.

ACHSE supports measures to prevent excessive prices. However, as both the pharmaceutical industry's development and manufacturing costs and the price negotiations are non-transparent or confidential, ACHSE cannot take a position on the integrity of current prices. Especially because price negotiations are secret, the Federal Ministry of Health has a great responsibility to ensure that changes in the legal regulations remain without negative consequences for the availability of orphan drugs in Germany.

But the negotiating parties – GKV Spitzenverband and the pharmaceutical company that wants to bring a certain product to market, as well as the pharmaceutical industry as a community – must also contribute to ensuring that

treatment of people with rare diseases does not deteriorate in Germany and that the costs remain manageable. Negotiation guidelines that restrict the possibilities to flexibly search for solutions together are not helpful in this context.

Do benefit assessments for orphan drugs have an image problem?

Tobias S. Hagedorn | Executive Director of the German Interest Group for Phenylketonuria and Related Inborn Errors of Metabolism (DIG PKU) e.V.

Despite early diagnosis and available therapy options, daily burdens of patients show that the rare metabolic disorder phenylketonuria (PKU) still presents a problem in paediatrics. Orphan drugs can help to meet many lifelong and insufficiently fulfilled healthcare needs. In the increasing controversy about the evidence of benefits and the costs of orphan drugs, the people concerned feel inadequately perceived and feel like they have become a plaything in the system. They are worried that their access to good and innovative healthcare might be restricted in future. The process of benefit assessment is also about trust in a healthcare system that leaves no one behind.

The everyday lives of people with phenylketonuria and their inadequately met care needs

With a frequency of about 1:10,000, phenylketonuria (PKU) is one of the rare diseases. PKU is a genetic disorder of the phenylalanine metabolism. Phenylalanine is an amino acid that is normally broken down to tyrosine. If left untreated, PKU leads to severe mental and physical disabilities. This is caused, on the one hand, by a structural brain damage due to permanent poisoning of the brain with phenylalanine and, on the other hand, by functional deficits as a consequence of the neurotransmitter deficiency.[1] In Germany, the disease is diagnosed reliably and early enough through newborn screening in order to avoid the serious consequences by means of nutritional therapy.[2] This distinguishes PKU from many other rare diseases with long diagnostic odysseys.

The standard treatment of PKU – and thus also the appropriate comparative therapy – is a nutritional therapy that essentially consists of two pillars: Firstly, the intake of natural protein is massively restricted so that patients consume as little as possible of the phenylalanine that is dangerous for them. Secondly, all other protein components as well as vitamins, trace elements, micro- and macronutrients are substituted to prevent malnutrition.[3]

This so-called „PKU diet“ has nothing to do with fad diets. It is medically necessary and has a massive impact on the daily lives of those affected. Many foods are not suitable for the diet at all. While metabolically healthy people enjoy sausage or cheese sandwiches for breakfast, the only thing left for PKU patients is the butter in between. Meat, fish, dairy products, pasta, and the majority of pulses – all are not allowed.[4] Low-phenylalanine pasta, bread or flour are only available in specialised shops and are very expensive. People with phenylalanine spend a lot of time baking

their own bread and preparing other meals – time that they lack elsewhere. Other foods have to be weighed and their phenylalanine content calculated. Two medium-sized cooked potatoes are equivalent to about 150 mg of phenylalanine. The daily tolerance of many patients is 300 to 400 mg. A scale, a calculator and a nutritional table are the daily companions of these patients.

Everything must be planned. When visiting friends, PKUers – as they call themselves – bring their own salad. Spontaneous restaurant visits usually no longer fit into the daily diet plan.[5] In the days before and after a scheduled restaurant visit, they calculate what they can eat to make up for the „diet mistake" associated with it. Sometimes there are also bizarre restaurant situations when, for example, „roast beef without roast beef" is ordered, because the side dishes are quite suitable. Of course, this leads to queries and constant pressure to explain themselves, even though the patients usually don't want this at all, e.g. from customers or suppliers at a business lunch. PKUers just want to be accepted normally, like everyone else.

PKU does not only affect the patients, but also their environment. Elevated phenylalanine levels often initially manifests in adults through headaches, lack of concentration, irritability and thus also influence professional performance, family and social environment, and mental or spiritual health.[6,7]

This short journey into the everyday life of patients makes it clear that PKU – despite early diagnosis and available treatment options – is not a solved problem in paediatrics, but that those affected have a multitude of lifelong care needs that are inadequately met in our healthcare system, some of which can also be covered by innovative pharmaceuticals. And it gives an idea of how important access to new pharmaceuticals and therapies is for PKU patients, but all the more for people with many other rare diseases who have gone through a long diagnostic odyssey and for whom there are no treatment options so far.

Yet PKU patients can look to the future with optimism. For some years now, cofactor therapy has been available for some patients, and the first PKU patients already receive treatment with an innovative enzyme replacement therapy. Research is currently being conducted on a large number of potential innovative therapies, some of which are preclinical and some of which have already been evaluated within the scope of clinical studies.[8] Not all of them will make it to a marketable pharmaceutical, but there is hope that life will be easier – yet not carefree – for future generations of patients. And one day there may also be a curative gene therapy, but it will probably be very expensive.

Tobias S. Hagedorn *has a commercial education and is married to a phenylketonuria patient. This is how he came to patient self-help in 1997. For 25 years, he was a member of the Board of the German Interest Group for Phenylketonuria and Related Inborn Errors of Metabolism (DIG PKU) as a volunteer. Since August 2022, he has been the full-time executive director of the self-help organisation. Since 2001, he has been executive director of the European PKU Society ESPKU as a volunteer and since 2018, he has been a member of the executive committee of the PKU World Association GAP.*

Patient concerns

The German Interest Group for Phenylketonuria and Related Congenital Metabolic Disorders (Deutsche Interessengemeinschaft für Phenylketonurie und verwandte angeborene Stoffwechselstörungen, DIG PKU) is the national self-help organisation that has been independently representing the interests and needs of patients and their relatives against political decision-makers and stakeholders involved in the healthcare system since 1975.[9] The interest of DIG PKU is neither the shareholder value of the pharmaceutical industry nor the deficit of the statutory health insurances. The purpose of the association is the development of innovative pharmaceuticals that have been proven to be safe and effective and therapies and the rapid access of patients to them.

DIG PKU and its members observe with concern that more and more major hurdles can or will make access to orphan drugs more difficult. These include the revision of the European framework for orphan drugs and the German law on the financial stabilization of statutory health insurance (GKV-Finanzstabilisierungsgesetz, GKV-FinStG) with the changes to some key AMNOG regulations. DIG PKU is concerned how it will be ensured that the content of both laws is coordinated in such a way that there is no undesirable collateral damage from their combined effect.

The European Commission wants to focus the development incentives for orphan drugs more strongly on the area of so-called „unmet medical needs".[10] But what are unmet medical needs? Is PKU, for which there is early diagnosis, nutritional therapy, enzyme replacement therapy and cofactor therapy, still a condition with „unmet medical needs"? After the previously described impact of nutritional therapy on their daily lives, the patients' answer is obvious. Others, however, such as the impartial chairman of the Federal Joint Committee (G-BA) Professor Hecken, would like to grant orphan status only to true soloists, i.e. only to the first therapies for diseases for which there have been no pharmaceuticals so far.[11] And they also put forward good arguments for this. However, affected patients fear that significantly fewer innovative pharmaceuticals can be developed for them as a result and that they may be cut off from scientific progress.

The criteria for the benefit assessment of innovative orphan drugs also include the so-called patient-relevant endpoints. But what is patient-relevant? Measuring the phenylalanine level in the brain, i.e. where the damage occurs, is technically possible, but neither patients want to undergo this procedure on a regular basis nor do health insurers want to pay for it on a permanent basis. Instead, the comparatively easily measurable phenylalanine level in the blood has been the scientifically recognised surrogate parameter used in everyday life for decades to monitor and predict the treatment success.

The extent to which the everyday life of PKU patients is shaped by the massive restrictions on natural protein intake has already been explained. And of all things, these two endpoints – reduction of the natural protein intake and regular control measurement of the phenylalanine level in the blood – were assessed as not patient-relevant in the early benefit assessment of an innovative enzyme replacement therapy not so long ago.[12] PKU patients reflexively feel let down due to the fact that their experiences of daily living and their needs have not been taken into account in a benefit assessment. Upon closer inspection, however, we must also hold pharmaceutical companies accountable for ensuring the informative value of their dossiers regarding such endpoints with an appropriate study quality, also methodologically.

It is not only the low patient numbers that make registration studies with high informative value difficult. It is

also the disease-specific characteristics that need to be taken into account. There are over 6,000 rare diseases,[13] and all of them have their own unique challenges. It is thus not surprising that no added benefit has been identified for more than half of the orphan drugs for DIG PKU that have crossed the sales threshold and undergone regular assessment since 2011. For another 15 percent, the added benefit could not be quantified.[14] In order to determine whether the added benefit of an innovative pharmaceutical for a rare disease is only fiction or how great it actually is, a flexibilisation of the procedure regarding study quality, data sources and patient-relevant endpoints and also in terms of the underlying comparative therapy is, in our view, just as essential as the consideration of our special needs in a constructive exchange between pharmaceutical companies, the regulatory authorities, and patient organisations.

According to the European Health Technology Assessment (HTA) Regulation, orphan drugs will also be subject to a European benefit assessment procedure from 2028, in addition to the benefit assessment in Germany.[15] Patients fear that this may become another hurdle to their access to such pharmaceuticals. In order to prevent this, they need the support of the G-BA and the Institute for Quality and Efficiency in Health Care (IQWiG), which are working on the basics for the implementation of the European HTA Regulation.[16]

Patients with PKU and other rare metabolic diseases want to have access to pharmaceuticals and therapies that are not only safe and effective, but also meet their needs and are thus better than existing therapies. Therefore, the DIG PKU also has a natural interest in ensuring that the benefits of these pharmaceuticals are evaluated objectively. However, newspaper headlines from the beginning of 2022 upset patients: These headlines refer to „moon prices" for orphan drugs,[17] „unjustified privilege of a fictitious additional benefit",[14] „mismanagement",[18] and „rare diseases targeted by austerity policies"[19] to name but a few. These headlines have a different effect on patients than they do on representatives of health insurers, regulatory authorities, or the pharmaceutical industry.

DIG PKU observes with concern that patients deliberately underdose their amino acid mixtures because they are concerned about the costs. Others do not dare to discuss their interest in cofactor therapy or enzyme replacement therapy with their physicians as they are afraid that the health insurer will not pay for the more expensive pharmaceutical for long anyway. Headlines like these make patients feel insecure and fearful about their future care as the increasingly feel like petitioners or even social parasites. They certainly do not feel privileged.

It is about money

The discussion about the benefit assessment of orphan drugs is mainly characterised by evidence. In reality, however, it is also about the costs of these pharmaceuticals. This becomes obvious by the GKV-FinStG,[20] with which politicians intervene in the otherwise holy grail of self-administration and negotiation autonomy and prescribe legal benchmarks for price negotiations on pharmaceuticals that were assessed to have no, a not proven, a not quantifiable or low additional benefit. How loud would the outcry have been if the Minister of Health, for example to give new impetus to the development of new orphan drugs, had raised the sales threshold for the full benefit assessment and cut rebates?

Patients also want that their healthcare system remains financeable and that sufficient funds are available for the many other aspects of healthcare: inadequate care of adult patients and the development of structures for the transition to geriatrics, expansion of diagnostic possibilities

through genomic newborn screening, implementation of centres and their networking in German reference networks, patient registers, pilots, good care, rehabilitation – there is enough room for both the development and optimisation that will cost money. In view of these challenges, everything that can lead to a loss of confidence of people with rare diseases like PKU in their access to therapy should be avoided. Therefore, benefit assessments should not only be used as an instrument to raise financial efficiency reserves.

When benefit assessments compare different therapies and their prices, all costs should be taken into account. Therapy-relevant special foods for the PKU diet are extremely expensive. 750 g of bread costs about 5 Euros, 500 g of pasta about 4 Euros, 500 g of flour about 3 to 3.50 Euros. According to a publication of the German professional journal Ernährungsumschau, the additional costs for these special foodstuffs amounted to up to 165 Euros per patient and month[21] in 2018, depending on age. Against the background of the current inflation, they are probably significantly higher today. These prices are not covered by the health insurers, and must be borne by the patients themselves. In Germany, there are currently about 5,000 people diagnosed early with PKU. With their contribution, they subsidise our healthcare system with about ten million Euros annually. For a long time now, many patients can no longer afford these important products, they neglect their treatment – with all the health consequences that this also entails for our healthcare system.

Another approximately 3,000 patients were born before the introduction of newborn screening. Many of the late-diagnosed and usually correspondingly handicapped patients are not treated at all for their underlying disease PKU. For a long time, no medical benefit was seen in this that would justify the significant therapy expenditure – this is also a kind of benefit assessment. Today we know that even a very late initiation of treatment can have a positive influence on the quality of life of these patients.[22, 23] Nevertheless, most of these patients remain without nutritional therapy. No amino acid mixtures, no low-protein diet. Savings for the healthcare system: Approximately 80 million Euros.

These total savings of some 90 million Euros annually are only due to the non-priced low-protein foods and non-prescribed amino acid mixtures. To talk about the massive undersupply of adult patients and the need for investment to build up urgently needed treatment capacities would go beyond the scope of this article. The price for these savings and the structural undersupply is borne by patients with phenylketonuria and related congenital metabolic disease with their money and – much worse – with their health. How high the social costs are will only become clear in the next few decades.

Are patient concerns unjustified?

Also in conjunction with the revision of the European framework for orphan drugs, patients with phenylketonuria and related metabolic disorders perceive the lowering of the turnover threshold and, above all, the legal benefit-based benchmarks for price negotiations through the GKV-FinStG as a considerable threat to their previously good access to innovative therapies. And they ask themselves whether they will also pay the price by being cut off from scientific progress? Some say so, others say so. The DIG PKU does not know the answer, but is afraid that this might be the case. The AWMF is also worried about the availability of effective new pharmaceuticals as it reports in its statement on the draft law.[24] In the public hearing of the Health Committee, the expert Professor Günter Neubauer called the lowering of the sales threshold dispropor-

tionate and arbitrary and criticised that it hits a small and sensitive group of patients relatively hard with comparatively low yield.[25, 26]

The Member of the Bundestag, Dr Georg Kippels (MdB, CDU), devoted his entire speaking time to this topic during the first reading of the GKV-FinStG, thus giving his voice to people with rare diseases in the chorus of physicians, hospitals, pharmacies, and health insurers.[27]

We consider it a partial success of our political work that the law was improved in the parliamentary procedure. We welcome the fact that the sales threshold for the benefit assessment was lowered less drastically than originally planned, and that the consequences of the law explicitly for people with rare diseases are to be evaluated in a year's time.[28] Whether this is sufficient to maintain patients' good access to innovative pharmaceuticals remains to be seen.

DIG PKU is not asking for even better and faster access to innovative pharmaceuticals for its members, but wants to avoid that it gets worse, not for PKU patients and certainly not for patients with many other rare diseases for whom there is no therapy yet. And in this conviction the rare disease community is united, those with more or less unmet medical needs and those with and without available therapies and treatments.[29]

However, part of the truth is also that patients must also recognise that in a resource-limited healthcare system not everyone can get everything at any price. Without going into the necessary framework conditions for innovations, one thing is clear: Fair prices are needed so that as many people as possible can have access to orphan drugs and innovative therapies as quickly and extensively as possible. Professor Hecken is right when he says that it is „worth all the effort to open the black box of pricing" and to create more transparency.[26] Without this transparency, no one can really assess whether the pharmaceutical industry's price expectations are justified, fair or outrageous. More transparency also makes it possible to discourage pharmaceutical companies, service providers and other stakeholders from abusing regulations that are supposed to benefit the better care of patients for unreasonably high profits.

However, appropriate prices for pharmaceuticals and therapies for rare diseases cannot only be found through benefit assessments directly after approval. We need continuous evidence generation before and after approval, a kind of reverse translation, i.e. the structured and continuous improvement of pharmaceuticals based on post-market data. We need insights into research, development, and manufacturing costs. Just looking at the benefits of a product with a snapshot cannot be enough to achieve the goal. The pharmaceutical industry should earn good, but not antisocially high profits with orphan drugs.

Conclusion

Patients currently feel like the ball in a roulette game. They are exposed to high centrifugal forces in a rapidly spinning system with many simultaneous legislative and policy initiatives, and do not know where they will fall. Does it even mean „rien ne va plus" for PKU patients in the end? Benefit assessments do not have an image problem, but they are increasingly the focus of critical attention among self-help organisations like the DIG PKU. Affected patients are happy about the scientific progress and the possibilities it will bring for future generations of patients.

Earlier diagnosis, better, and individualised therapies for more patients are promising opportunities, but also present challenges and responsibilities. We need to talk about the concerns of health insurers as well as the concerns of the research-based pharmaceutical industry and, of course, the concerns of patients. We also need to talk about how ATMPs and orphan drugs can develop their opti-

mal benefit. We must take care that parallel European and German legislations do not produce undesirable collateral damage.

We need to talk about solutions that will make our care better and that will continue to give us access to innovation in medicine, access to a better future.

If we succeed in this, we will preserve the most important asset that sustains our healthcare system: The legitimate trust of patients that no one will be left behind.

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Assessment of the added benefit of pharmaceuticals without RCT – a case study

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Study registry-based comparative trials are becoming increasingly important during the approval and benefit assessment of new pharmaceuticals, especially for rare diseases where randomised studies are difficult or impossible to conduct. In a rapid report, the IQWIG published an overview of potential concepts to generate and evaluate healthcare-related data which also considers non-randomised controlled studies. Based on a current case study on the AMNOG dossier for the early benefit assessment of amivantamab in adult patients with advanced non-small cell lung cancer, a critical evaluation of the application and the dossier assessment is provided. Due to the complexity of the application, the methodological critique is limited to the endpoint overall survival.

Introduction

After the Act for Greater Safety in the Provision of Medicines (GSAV) came into force on 9 August 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to prepare a concept for the generation of healthcare-related data and their evaluation for the purpose of benefit assessment of pharmaceuticals according to Section 35a of the German Social Code, Book V (SGB V). One of the objectives of the law and the concept is the so-called post-marketing data collection to improve the benefit assessment of pharmaceuticals for which only a limited evidence base is available at the time of market entry.

The IQWIG concept was published as a rapid report for healthcare-related data for benefit assessment on 13 May 2020, and provides an overview of potential concepts to generate and evaluate healthcare-related data.[1] The report emphasises that „... in particular, data collection that cannot be assigned to the category „randomised controlled trial (RCT)" will also be considered."[1] The focus is on methods for data collection and analysis of studies by means of study registries. In September 2020, the European Medicines Agency (EMA) also published a draft on the use of registry data.[2]

The purpose of this article is to outline and analyse the methodological challenges and conditions of a preferably bias-free collection and analysis of data for the benefit assessment of pharmaceuticals in cases where a randomised comparative design is missing or impossible on the example of a specific study submission. In this respect, we focus the data-analytical aspects of confounder control and statistical model selection on the example of the application for the early benefit assessment of amivantamab in adult patients with advanced non-small cell lung cancer (NSCLC).[3] The application was submitted by the pharma-

ceutical company on 14 January 2022. In the dossier assessment of 13 April 2022, the IQWIG classified the added benefit of amivantamab in this indication compared to a comparator therapy as not given.[4] The decision was then substantiated by the G-BA on 7 July 2022.[5] Due to the complexity of the request, the critical evaluation of the application and the dossier assessment is limited to the endpoint overall survival.

Requirements for the generation and analysis of healthcare data for benefit assessment in non-randomised studies

In its rapid report, the IQWIG states that data collection from individual studies, registries or electronic patient records can be used for comparative studies without randomisation for benefit assessment, provided that „data relevant to the specific research question are available in such a quality that the analyses can be interpreted with sufficient certainty in the context of a registry study".[1] Consequently, a detailed study protocol and analysis plan are required for data analysis, including a systematic identification of relevant confounders (e.g. using scientific literature with involvement of experts). With regard to statistical models for confounder control or adjustment, the IQWIG makes few concrete specifications and is open to various methods. They mention propensity scores and meeting important modelling criteria such as positivity, overlap, and balance.

The EMA is more explicit in its guidance regarding the analysis of comparative non-randomised registry-based studies.[2] For example, the agency requires a comparison of the registry-based study population with the remaining registry population and patients who were not included in the study. This criterion provides more insights regarding the representativeness of the study population with the entire patient population for which the respective treatment would be considered.

Furthermore, the EMA requires the specification and handling of missing data in the analysis plan, as well as an explanation of the assumptions regarding the distribution frequency of missing variables, the reasons for their not being included, and temporal reference values for missing data. Similarly, specifications and assumptions on imputation techniques in the absence of data are required.

Particularly useful is the guidance on general analytic problems of observational comparative studies.[2] For example, the EMA emphasises that treatment decisions are influenced by various factors, such as disease stage and comorbidity, which may also be correlated with the relevant endpoint. Even if such factors are known in detail – and if

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measured – can be adjusted for in multivariate models, this does not guarantee a bias-free analysis. Therefore, the EMA requires extensive sensitivity analyses. Consequently, it is emphasised that for longer observation periods, adjustment for confounders at baseline is not sufficient and models must be taken into consideration that allow adjustment for time-dependent confounding.

Patient registries allow the comparison of patients who have received the investigational product over a longer period of time (so-called prevalently treated) with patients who have received a different therapy. This constellation is susceptible to two forms of biases. Prevalently treated patients are survivors of an early treatment strategy and their inclusion in the analysis may be subject to selection bias. Covariates relevant to treatment receipt at baseline may be influenced by previous treatments, or may be influenced by e.g. different patient behaviour (compliance) (healthy user effect). This bias can only be avoided if patients with new treatment are included (incidence treated). However, this is usually associated with a loss of the number of available patients.

If the patient observation starts long before the start of treatment with the therapy of interest, an immortal time bias can be the consequence, because this observation time is logically free of disease events of interest. Therefore, a time-dependent definition of exposure status is mandatory to define the relevant observation time („when does the clock start ticking and when is it stopped“) and to include different exposure statuses in the analysis.

Time-related and information bias may arise when comparing an intervention group with historical control patients whose data were collected at an earlier time point. Because diagnosis, treatment, and prognosis of historical control patients may differ from current patient cohorts, these differences must be carefully considered and included in the analysis. The same applies when e.g. patients from other countries or regions serve as controls where the therapy of interest is not available at all. In these cases, careful analysis of differences in the respective patient population and comprehensive confounder analysis and modelling are mandatory.

In their comments, both institutions emphasise the need for early consultation of applicants with review authorities regarding the feasibility of a benefit assessment based on non-randomised data.

Example of a benefit assessment based on non-randomised comparison groups

As mentioned above, the medical benefit and added value for the active substance amivantamab (Rybrevant®) as monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) and activating exon 20 insertion mutations of the epidermal growth factor receptor (EGFR) after failure of platinum-based therapy versus the appropriate comparator therapy (ACT) as defined by the G-BA shall be determined in the application with regard to the endpoint survival.[3]

- **Inconsistencies in patient selection and comparative therapies**

In our analysis we focus on the subindication in patients for whom further treatment is indicated. According to the guidelines of the G-BA, the pharmaceutical company selects a treatment with docetaxel or docetaxel in combination with nintedanib, or pemetrexed as comparator therapy.

Since no evidence is available from randomised controlled studies for the present therapy comparison, the company compares a patient subpopulation (including inclusion criteria) from the phase I CHRYSALIS study[6] with patients who received one of the substances of the comparati-

ve therapy in two German study registries. For this purpose, the company „entered into a cooperation with the CRISP registry (Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients (CRISP))[7-9] and the research platform NGM (Network Genomic Medicine)[10,11] to perform comparative analyses with data from the actual German medical care environment."3

In its unfavourable assessment, the IQWIG criticises that patients of the comparator therapy were included in the

Patient characteristics after failure of platinum-based therapy with treatment with amivantamab (CHRYSALIS study) and comparative treatments in the CRISP and NGM registry studies

	CRYSALIS	CRISP	NGM
Age	N 114	N 7	N 27
Mean value (SD)	61.8 (10.0)	58.6 (12.6)	63.1 (12.2)
Median	62.0	57	64
Range	(36; 84)	(46; 79)	(34; 79)
n	114	7	27
Male	44 (38.6%)	2 (28.6%)	14 (51.9%)
Initial tumour stage	114	7	27
IIIA	6 (5.3%)	0	
IIIB	4 (3.5%)	0	5 (18.5%)
IV	90 (78.9%)	6 (85.7%)	20 (74.1%)
Brain metastases	29 (25.4%)/114	3 (42.9%)/7	10 (37%)/27
Cancer diagnosis until the first dose (months)	N 114	N 7	N 27
Mean value (SD)	22.3 (20.0)	11.8 (4.3)	21.1 (22.6)
Median	17.5	13.6	14.2
Range	(1.4; 130.1)	(2.9; 15.3)	(3.5; 110.6)
Number of previous treatment lines	N 114	N 7	N 27
1	48 (42.1%)	4 (57.1%)	15 (55.6%)
2	34 (29.8%)	3 (42.9%)	6 (22.2%)
3	15 (13.2%)	0	5 (18.5%)
4+	17 (14.9%)	–	1 (3.7%)
Previous immunotherapy	N 114	N 7	N 27
Previous immunotherapy yes	50 (43.9%)	6 (85.7%)	9 (33.3%)

Quelle: J-C. Janssen GmbH, Zusatzanalysen Teil 2. 2022

Table 1: When comparing the studies, it is noticeable that the number of available patients in the control group from the two registries is much smaller. Age and gender are also different between the groups.

study several times due to multiple receipt of one of the available therapies. In addition, the IQWIG criticises that several international study registries, where additional available patients could have been recruited, were not considered by the pharmaceutical company.

On the other hand, the pharmaceutical company reports that only 33.3% and 24.7% of patients with advanced NSCLC identified in the CRISP and NGM registries, respectively, received one of the comparator treatments as specified by the G-BA. This raises the question of whether the selection of study populations and comparator treatments could not have been better coordinated in a hearing.

- **Different baseline characteristics of the comparison groups**

Table 1 shows the number of patients treated with amivantamab and the comparator therapies with selected patient and treatment characteristics at the time of study inclusion. It is notable that the number of available control group patients from the two registries is much smaller. Age and gender between the comparison groups are different. While the number of patients with stage IV tumours is about the same between the groups, a higher percentage of patients in the comparison arms suffer from brain metastases.

The concern is that the time from tumour diagnosis until a comparator therapy to be examined is longer in patients treated with amivantamab than in patients in the CRISP cohort, making the analysis susceptible to immortal time bias. The number of previous treatment lines is higher for amivantamab-treated patients.

- **Confounder identification and selection**

The pharmaceutical company describes 17 confounders in 171 constellations, which were identified by literature search and expert interview. The variables age, number of metastases, number of treatment lines, baseline anaemia, the 5-stage ECOG activity status (5= unrestricted activity, 0= death), brain metastases, disease stage, renal insufficiency were defined as a minimal set for the confounder adjustment.

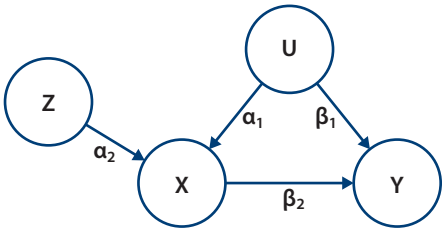
However, for the final propensity score model, only the number of treatment lines and brain metastases, location of metastases, age, and sex were considered, but the rationale for the final selection of confounder variables is missing. Thus, the IQWIG rightfully criticised the selection of confounders as inadequate, particularly as ECOG activity status was not measured at baseline and follow-up based on the selection criteria for the CHRYSALIS study. In the control data, any information on ECOG activity status is also missing. The pharmaceutical company argues that an equivalent ECOG activity status may be assumed for patients in the control groups, as they would otherwise not have been eligible for therapy based on clinical judgement.

The handling of the selection of confounders by both the IQWIG and the pharmaceutical company is insufficient and unsatisfactory. Formalistically, the IQWIG criticises the insufficient literature search for the identification of confounders to prepare a list of all confounders that is as complete as possible. However, the possibilities for confounder control are limited, especially in small patient populations and with a limited number of endpoints. In many cases, so-called „statistically non-significant" confounding variables associated with the model are removed by means of elimination procedures and not taken into account. A clinically and expert opinion based variable selection can be more purposeful.

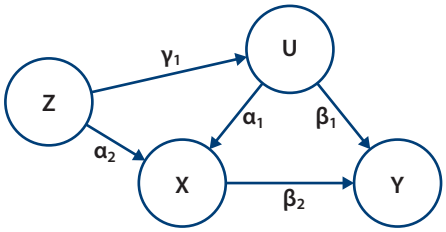
It should also be considered that confounders may be correlated with each other (e.g. cumulative cis-platinum

Causal chart with an instrumental variable Z and confounder U

1a Causal diagram with an instrumental variable Z and confounder U



1b There is an association between instrumental variable Z and the confounder U



Z Instrument variable, U Confounder, X Exposure (therapy yes/no) Y Endpoint.

Source: Am J Epidemiol. 2011;174(11):1213–1222

Table 1: When comparing the studies, it is noticeable that the number of available patients in the control group from the two registries is much smaller. Age and gender are also different between the groups.

dose and chronic renal failure). Inclusion of two or more highly correlated confounders may lead to model degradation due to overfitting. Furthermore, the distinction should be made between instrumental variables associated with exposure (relevant therapy) but not with the endpoint and confounders associated with exposure and endpoint. Figure 1A represents a causal diagram (Directed Acyclic Graph, DAG) that illustrates the relationship between an instrumental variable Z and an exposure. Figure 1B illustrates the relationship between an instrumental variable Z for which there is an association with the confounder U. Adjustment of instrumental variables can result in a worse model.[1,2] Therefore, model specification and its justification are very important. Models can be tested for robustness in sensitivity analyses and should be listed with predefined specifications recorded in the protocol. These points are neither mentioned nor duly considered in IQWIG's rapid report nor in the application of the pharmaceutical company.

- **Choice of statistical model and data analysis**

For the statistical analysis of the overall survival endpoint, the pharmaceutical company chooses a Cox proportional hazard model with treatment group as the only explanatory variable. Median overall survival is determined using the Kaplan-Meier method. The pharmaceutical company uses the propensity score (PS) method to calculate the adjusted treatment effect: „The PS for a study participant is derived from the probability of this study participant to belong to the treatment arm or the control arm. The probability is estimated for each study participant using logistic regression based on the available covariates (...)."[3]

For the adjustment, the pharmaceutical company chooses an IPW approach (Inverse Probability Weighting), „in which each observation, i.e. each included patient, is weighted according to the individual PS".[3] In this way, a pseudo population is generated that is well-balanced regarding the available covariates in the comparison

groups.[13] The treatment effect is estimated in the weighted population by means of a regression model with the variable treatment effect as the sole predictor. Since patients with multiple treatment lines are included in the analysis, a robust „sandwich method" is used for the estimation of the covariance matrix to obtain conservative estimators for standard errors and confidence intervals based on the correlated data.[14] The evaluation of the overlap of PS in the treatment groups of amivantamab and control treatments is performed using diagnostic plots.

When using this method, proper specification of the PS model is critical.13 The inclusion and exclusion of risk factors and predictors (instrumental variables) is important and was not carried out in sufficient detail by the pharmaceutical company. Due to the lack of model specification, there is a higher risk of bias, especially with the approach chosen by the pharmaceutical using the PS directly for weighting by means of Inverse Probability Weighting.[13,15] However, analysis and reporting of the balance of covariates in the comparison groups are sufficient[13] presenting graphical representations of the overlap of scores (figure 2). Similarly, standardised mean differences are presented for the confounders selected in the final model. However, there is no indication e.g. of a summary measure (C-statistic) regarding the agreement of the covariates.

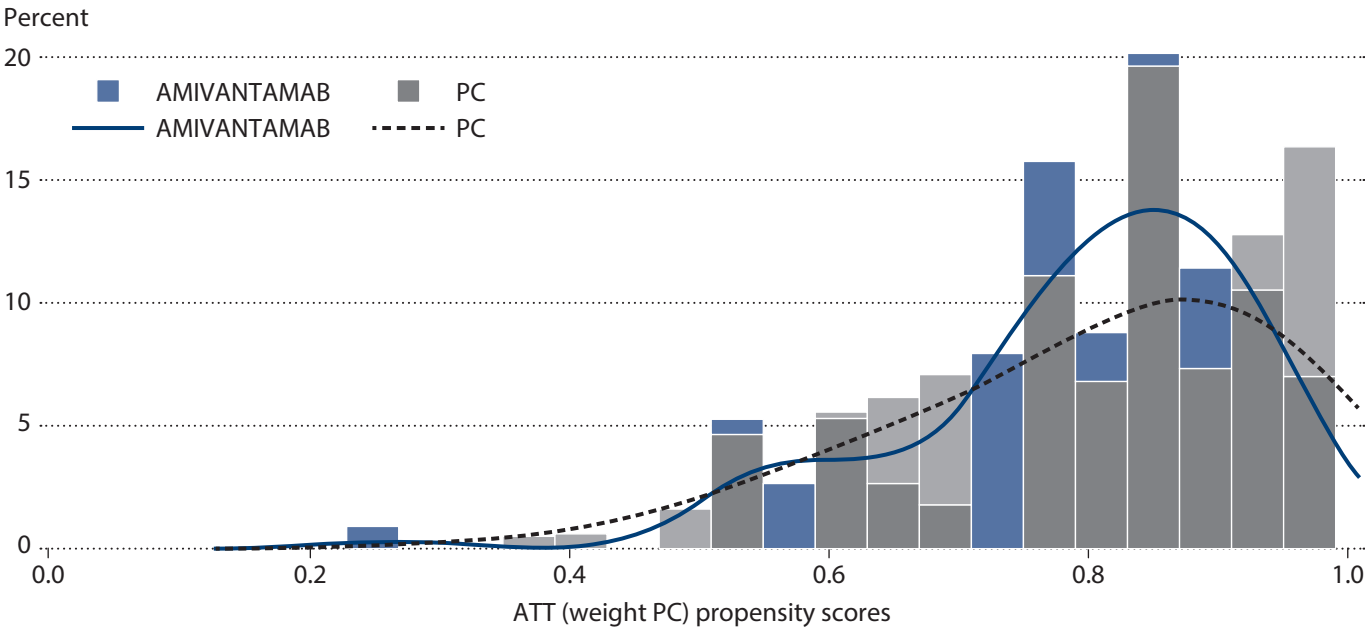
Evaluation of the propensity score distribution between the intervention and control groups is another important step of the analysis with the PS method. A high overlap of the propensity score distribution is an important indication for clinical equipoise and comparability of the selection of a treatment between groups. The question here is to what extent regions without overlap should be excluded (so-called trimmed) to exclude patients who had a probability close to 0 of receiving a particular treatment. Probability scores close to 0 or 1 result in large weighting factors, which can lead to bias and overrepresentation of patients who, based on clinical circumstances, would be very certain to receive either of the two eligible therapies.

In the report, the pharmaceutical company assesses that „sufficient overlap exists. In both the control and treatment groups, the propensity score obtained is between 0.8 and 0.9 in a large proportion of patients".[3] However, the diagram shows that propensity scores are close to 1 exclusively in the control group, raising questions regarding trimming and weighting. The pharmaceutical company does not evaluate different weighting methods available, nor does it provide any information on the trimming methods with exclusion of certain patients. The weighting method the pharmaceutical company uses, in which patients in the treatment group receive a weighting factor of 1 and patients in the control group are weighted with a probability of treatment of (propensity score / 1-propensity score), is very susceptible to bias due to extreme weightings, which makes the lack of detailed information on weightings all the more serious. Moreover, there isn't any information about the weighting limits used (weight truncation) and any limits used to avoid extreme variance values.

- **Results for the endpoint overall survival**

As mentioned above, we will only describe the main analysis for the overall survival endpoint. Table 2 shows the results for the pooled analysis of the comparison groups. It shows a reduced hazard ratio for overall survival of 0.43 [95% confidence interval CI 0.25; 0.74] and 0.39 [95% CI 0.22; 0.70], respectively, in the propensity score-adjusted, as well as in a simple multivariate model. These estimates are based on 40 event cases in 114 patients treated with amivantamab (median observation time 22.7 months) and 25 event cases in 34 patients in the multicomparator control arm (median observation time 12.3 months). The pro-

Overlap of propensity scores between CHRYSALIS studies and the pooled CRISP/NGM study comparison groups (main analysis set)



Average treatment effect of the treated, PC: Multi comparator, appropriate comparative treatment for all patients with a documented or assumed ECOG status of 0 or 1 (main analysis set).

Source: J-C. Janssen Additional Analyses Part 2. 2022

Figure 2: Appropriate analysis and reporting for balance of covariates in comparison groups. Therefore, the overlap of the scores is shown graphically.

pensity score model yields a rather conservative estimator. The confidence intervals for both estimators are quite wide but statistically significant.

Discussion

This critical assessment of an AMNOG application based on data from non-randomised controlled studies is limited to the methodological and analytical aspects of one endpoint, i.e. overall survival. An overall assessment of the evidence, in particular on side effect data presented by the applicant – which were not assessed here – is not the aim of the present analysis. Therefore, we do not take a position on the decision of the G-BA on the request for benefit assessment of amivantamab.

Nevertheless, the limited assessment allows some conclusions. The points criticised by the IQWIG regarding the choice of patient population and comparator therapy suggest a lack of coordination between the pharmaceutical company and the G-BA. The methodology and data analysis chosen by the applicant lacks a sufficient description of

the procedure for model specification and selection of confounders to be included in the model. The pharmaceutical company fails to demonstrate the robustness of the analysis using propensity scores through various statistical approaches. It is interesting that the IQWIG does not at all address the analytical aspects and deficits of the application in its assessment.

In terms of improved efficiency for future applications with observational data analyses, improved specifications on statistical and analytical aspects by IQWIG would be desirable. In addition, the template for this specific form of submission should be specified and simplified. An enhanced reporting of the selection criteria of patients included in observational studies, as well as an enhanced description of the methodology of the statistical analysis – in particular on variable and method selection – as well as information on the robustness of the results by means of sensitivity analyses are mandatory. Specifications on these methodological points, as formulated in the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology),[16] have been available since 2007, but still seem to have not yet been sufficiently disseminated in the AMNOG application system.

The propensity score methodology is a standard method for observational data analysis that has evolved over more than three decades.[13,17] It is difficult to understand why neither the IQWIG nor the applicant follow useful guidelines regarding the specifications and execution of observational data analyses using propensity scores that could allow experts to understand the chosen approach of the analysis and the validity of the results with the necessary statistical details.

The application form for AMNOG submissions based on observational data should be improved and tailored to the specific methodological aspects of this application and analysis. For example, it does not makes sense to include

Overall survival of patients treated with amivantamab after failure of a platinum-based therapy and patients treated with comparative treatments

	Amivantamab		Multi comparator		Amivantamab vs. multi comparator		
	Overall survival n/N (%)	Median (M) [95 % CI]	Overall survival n/N (%)	Median (M) [95 % CI]	Naiv HR [95 % CI] unadj.	HR PSM ATT [95 % CI]	HR adj. [95 % CI]
CHRYSALIS vs. pooled CRISP/NGM	40/114 (35.1 %)	22.77 [17; 48]	25/34 (73.5 %)	12.35 [6.28; 15.61]	0.36 [0.22; 0.58]	0.43 [0.25; 0.74]	0.39 [0.22; 0.70]

Key: M Months, HR Hazard ratio, CI Confidence interval, PSM Propensity score matching, ATT Average treatment effect among the treated population, unadj. unadjusted, adj adjusted.

Regression analysis with adjusted number of previous treatment lines, brain metastases, age.

Source: https://www.g-bade/bewertungsverfahren/nutzenbewertung/783/#dossier

Table 2: Results for the pooled analysis of the comparison groups show a reduced hazard ratio for overall survival of 0.43 [95% confidence interval CI 0.25; 0.74] and 0.39 [95%CI 0.22; 0.70], respectively.

specifications regarding indirect comparisons referring to randomised controlled studies in the application form. In addition, the application dossier must be streamlined. The present application dossier of the pharmaceutical company comprises 1,053 pages! It is not understandable why such a report with appendix cannot be condensed to 250 pages.

Due to the ongoing development of personalised medicine and the difficulty to conduct randomised controlled studies efficiently and timely, future clinical research will develop towards real world data (RWD) and real world evidence (RWE). In this changing clinical research landscape, randomised controlled studies will still be of importance, but they will not remain the only form of evidence for approval studies and benefit assessment studies for pharmaceuticals that are subject to compulsory health insurance.18 Besides well-conducted cohort studies, hybrid forms of studies and platform studies tested in cohort studies will become standard practices for approval and benefit assessment, especially for rare diseases.[18,19,20] In the United States, the 21st Century Cure Act of 2016 laid the foundation to accelerate the development of innovative medical products and introduction into healthcare, also based on RWE.21 Meanwhile, the Food and Drug Administration (FDA) has published initial drafts of detailed guidance on the use of RWE and RWD. Prominent examples of FDA approval of substances based on non-randomised studies underscore the importance of these developments.[22,18]

It remains to be hoped that the rules in the AMNOG process for the generation of evidence for the eligibility of innovative pharmaceuticals, which have not been evaluated by randomised trials, will be improved to allow for a more efficient use of regulatory and PU resources and to continue to provide patients access to new medical innovation within a reasonable time.

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DNA-Med as a model for nationwide precision medicine

Rafael Riedel, DNA-Med gGmbH | Professor Thorsten Schlomm, Charité – Universitätsmedizin Berlin, Clinic for Urology | Tim Rödiger, Die Brückenköpfe GmbH

The health platform DNA-Med connects patients with metastatic prostate cancer from Berlin-Brandenburg and their attending physicians with the Urological Cancer Centre of the Charité. Through the platform, patients – regardless of their place of residence – receive the same information, access to current clinical studies and new therapies through their attending physician as they do at the Charité. For this purpose, the clinical data of all patients registered in the DNA-Med network are constantly analysed in a central database by specialised physicians at the Charité. With the DNA-Med concept, we are developing a unique data ecosystem as the basis for a new type of patient-centred network medicine, and a high-quality real-world evidence (RWE) platform is being created at the same time. For this purpose, data is collected according to the Good Medical Practice standard (GCP) and processed for research questions.

Background and approach of DNA-Med

The widespread adoption of precision medicine requires a fundamental change in the care and research infrastructure. Our conventional system is designed for „one size fits all" therapies (e.g. chemotherapy) that can be prescribed by any practitioner for all patients in the appropriate indications.

Precision medicine fundamentally turns this decentralised system upside down by using complex, individual characteristics of individual patients to identify the appropriate treatment, which can only be measured and evaluated at specialised centres. For example, in precision oncology, the molecular structure of cancer tissue is studied prior to treatment to make causal predictions about the active ingredients that have the highest probability of efficacy for the individual patient. This is necessary because therapeutic approaches are becoming ever more precise and therefore apply to ever smaller patient groups.

Many new precision therapies enter the market and healthcare quite rapidly. This gives rise to the fundamental allocation problem of modern medicine: How do increasingly precise therapies find the right patients? After all, the high standards of evidence-based medicine must apply against the background of sharply rising treatment prices, especially in times of precision medicine. With increasing precision and an ever more dynamically changing standard of care, especially in oncology, this fundamental assignment problem is becoming increasingly difficult to solve for physicians, and thus the requirements for proof of benefit are also becoming ever higher. But how can we nevertheless offer precision medicine with central connection of individual patients to specialised centres nationwide in the future?

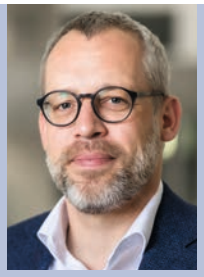
The DNA-Med model is an approach to answer these questions on the example of prostate cancer. Prostate can-

cer is the most common type of cancer in men. Approximately 70,000 new cases are registered every year throughout Germany. There are various treatment options available in Germany. However, these therapies do not provide the desired treatment success for all patients. After unsuccessful first and second-line treatment, individualised medicine gives patients with metastatic prostate cancer the option of gene-based „precision medicine".

The decoding of the human genome has led to major advances in medical research, particularly in precision oncology. After a prolonged implementation phase, the research-based pharmaceutical industry is now producing new, high-cost therapeutic approaches for precision oncology at a high rate. At the same time, the increasing number of new therapeutic options speeds up the demand for innovative and high-priced therapies considerably. Despite numerous and theoretically highly effective therapeutic approaches, precision oncology is not yet contributing to more effective healthcare in practice, as both costly and complicated molecular diagnostics and therapies are not always used in a targeted and effective manner.

Patients have predominantly been enrolled in precision therapy programmes only at the end of their cancer after the standard therapy options have been exhausted. Their health condition is often already precarious. In addition, molecular testing of their tumour tissue often takes an unreasonably long time because processes and regulations have not yet been established and standardised.

Furthermore, there is a lack of widespread knowledge about the benefits, the right timing and the choice of the



Rafael Riedel *has been CEO at DNA-Med since September 2022. After studying law and informatics, he held various positions in consulting and industry in the field of business development, project development, and digital consulting, including at Wunderman, K-MB, and TLGG.*

Professor Thorsten Schlomm *has been Head of the Department of Urology, Charité, Berlin since 2018. After studying medicine at the University of Göttingen, he completed his residency and was appointed Professor of Urology at the University Medical Centre Hamburg Eppendorf. Since 2016, he works as adjunct professor at the University of Bergen, Norway. He stayed in the USA (Colorado/ Denver/ Cleveland Clinic/ New York) several times and is the founder of DNA-Med.*

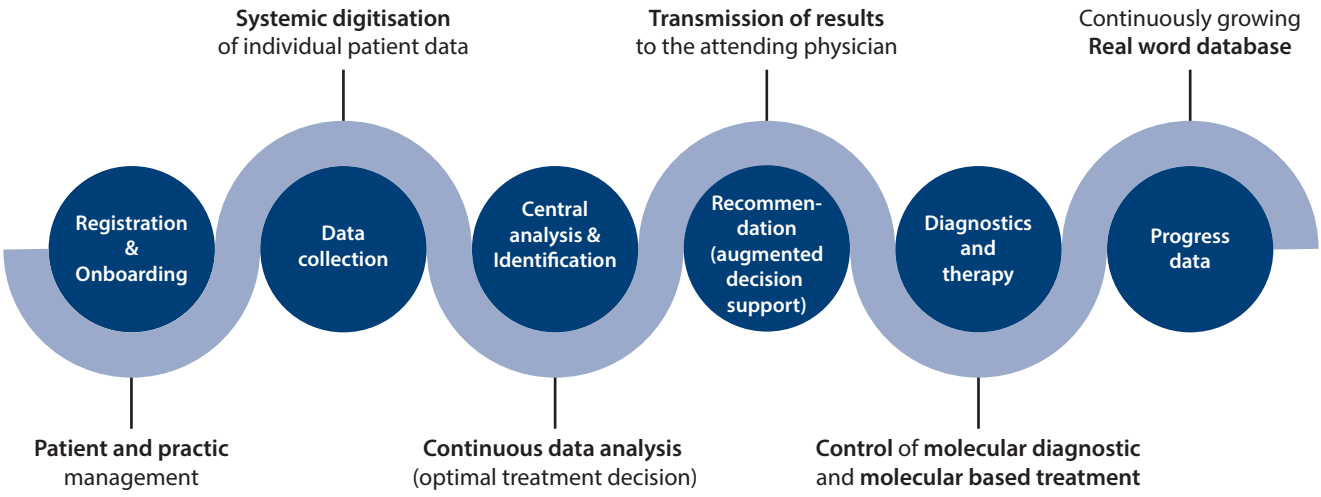
Tim Rödiger *worked at BARMER headquarters, first as a corporate and healthcare policy officer and later as head of risk management. In 2008, he moved to the AOK-Bundesverband and took over the department for corporate development. In 2016, he co-founded Lieblingsköder GmbH, where he continues to work as the managing partner. He has been a partner at Die Brückenköpfe GmbH since 2017.*

appropriate procedure of molecular diagnostics, because results, diagnostics and therapy are not systematically networked. As a result, the costs in oncology care are rising rapidly, but the quality of care is not improving nationwide at the same pace. The result is a nationwide overuse, underuse and misuse of healthcare, which will continue to increase in the future due to the high dynamics, growing complexity and expansion of indications as well as even more specific approaches.

Adaptation of the healthcare process

The introduction of precision medicine and the associated multiplication of diagnosis and therapy options – some of which are very cost-intensive – requires a fundamental change in healthcare processes. At present, there is primarily a lack of an end-to-end process chain for precision medicine, since in medical practice both upstream diagnostics and downstream evidence are not aligned with the precision of innovative therapeutic approaches. There is a fundamental allocation problem of patients according to their individual disease manifestations and effective, diagnostic and therapeutic interventions depending on the cancer stage. In addition, numerous practical hurdles prevent the provision of the appropriate intervention. Together with the non-profit DNA-Med, the urological clinic of the Charité establishes the DNA-Med network as a pilot project with urologists in private practices in Berlin and Brandenburg: A patient-centred platform to make the latest findings and study options available to participating practices and patients in an individualised and process-optimised manner.

DNA-Med Care process precision medicine



Source: DNA-Med

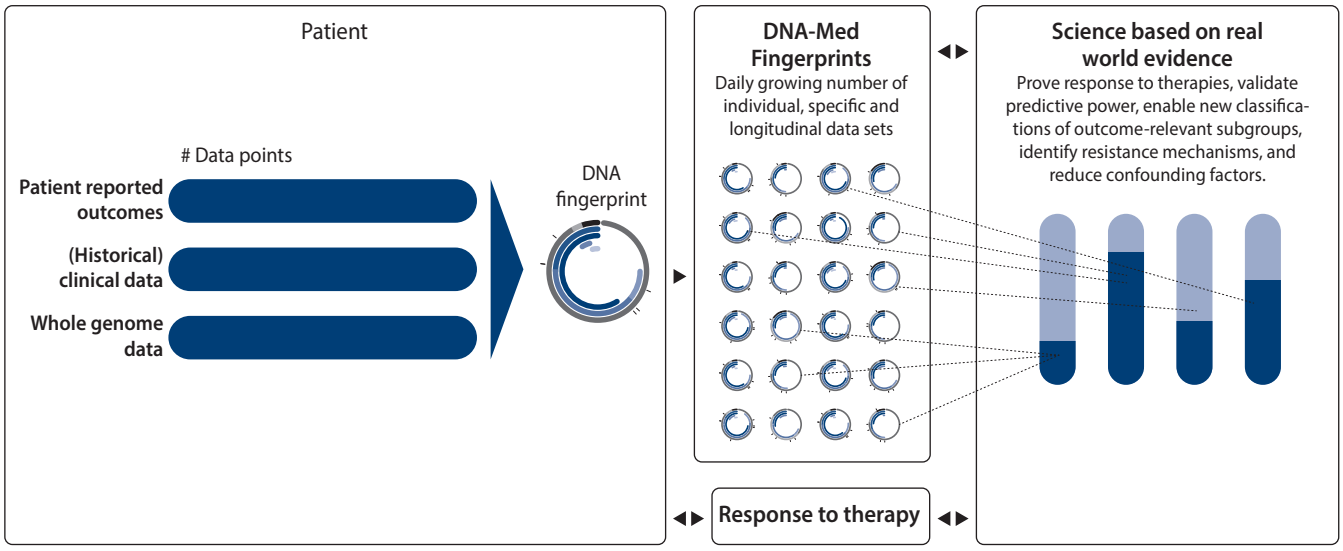
Figure 1: The idea behind the DNA-Med platform is to make top-quality university medicine available to all patients and physicians in a barrier-free manner and patients do not have to give up their familiar treatment environment.

The strategy here is to use an „augmented decision making" concept to make cutting-edge university medicine available to all patients and physicians in a barrier-free and customised manner, regardless of where they live, so that patients do not have to leave their familiar treatment environment (figure 1).

Patients have an active and central role in the entire treatment process by simply uploading their findings to the DNA-Med platform. In turn, anonymous data from the DNA-Med platform is available to the research community for the development of new therapeutic approaches. New research results can then in turn be made directly available to individual participants via the DNA-Med network. DNA-Med thus represents a first-of-its-kind scalable and population-based approach to the new challenges of precision medicine.

DNA-Med provides patient stratification for molecular diagnostics, quality-assured sequencing, and high-quality treatment recommendation (figure 2). These prerequisites for successful precision medicine cannot be taken for granted. This is shown by a breakdown of the current likelihood that patients for whom precision therapy is potentially available will receive it. If the individual stages of the process are followed from patient identification, through diagnosis and treatment recommendation, to monitoring, the probability is between 5 and 30 percent according to current studies (figure 3). At each individual stage, negative influences cause risks which can be described systemically

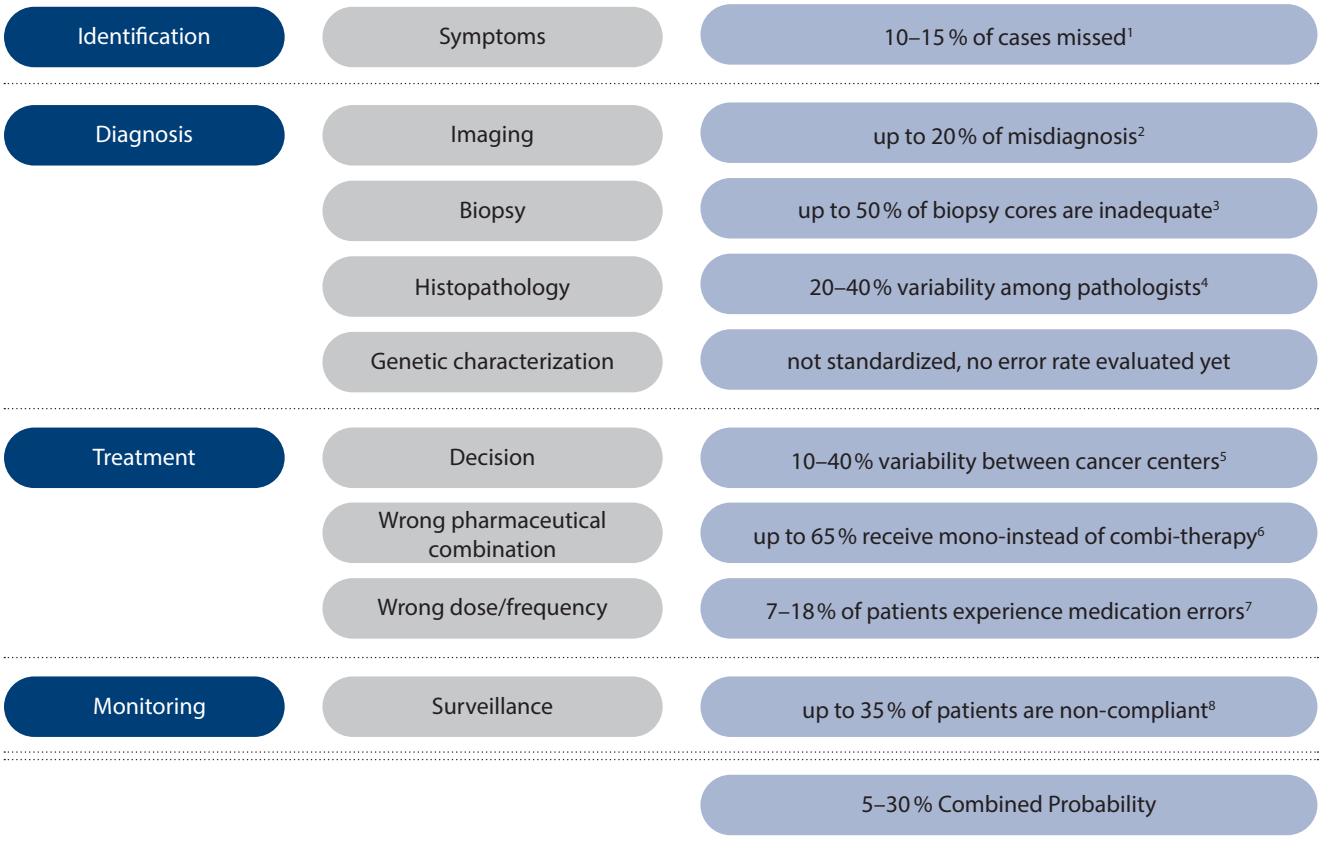
DNA-Med Data platform



Source: DNA-Med

Figure 2: DNA-Med offers patient stratification for molecular diagnostics, quality-assured sequencing, and high-quality treatment recommendation.

DNA-Med Statistics



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Source DNA-Med

Figure 3: Following all stages from patient identification, diagnosis and treatment recommendation to monitoring, the probability that a patient will also receive precision therapy is 5 to 30 percent.

as noise and bias, leading to less than optimal decisions in the course of the healthcare process.

Quality-assured end-to-end precision

The low likelihood of delivering advanced precision therapies diminishes the value of these therapies, as they oftepan do not reach the patients who are in fact suitable for them. For example, at the moment about 65 percent of patients for whom a guideline-based combination therapy has been shown to prolong survival are instead treated with monotherapy (Leith et al.).

The low precision in healthcare not only results in patients suffering from unnecessarily severe disease progression and side effects, but also leads to critical questioning of the pharmaceutical industry's innovation performance. This circumstance is problematic not because there is a lack of innovative therapies, but because there is a lack of effective provision of therapies via a modern and networked infrastructure. Unfortunately, the pharmaceutical industry has little influence on these deficits and can only compensate for them to a very limited extent.

These deficits can only be improved successfully, if – in addition to the innovative expansion of the range of therapies by the pharmaceutical industry – the necessary identification and stratification of potential patients can also be achieved.

This is based on high-quality data that is made available to the respective stakeholders via various information systems. DNA-Med has developed a comprehensive and quality-assured set of data points for its platform, which is collected for each patient to enable the best possible therapy decision and minimise potential sources of error. Data is collected for clinical studies in a GCP compliant manner to ensure a high level of acceptance in medical decision-making. This enables a profound integration into the recruitment of participants for clinical studies and, in perspective, FDA/EMA accepted simulation of studies, or retrospective modelling of additional treatment or control arms to completed or ongoing phase III studies.

Only this consistently high data quality will make it possible to noticeably improve the probability of providing precise therapies. Without a consistently high data quality, it will not be possible to automate individual process steps, improve predictive performance, or provide sufficient validation of diagnostic results and treatment recommendations.

Thus, a high-quality and comprehensive data set is a necessary prerequisite for the provision of high-performance precision medicine. In this context, it is essential to generate quality-assured data points along the entire process chain. Only in this way can the growing potential of effective precision medicine actually be used in daily practice.

Motivation of payers and relevance to patient care

Under Section 140a of the German Social Code, Book V (SGB V), the legislature grants the statutory health insurance funds the option of concluding contracts for special healthcare with approved service providers to improve the quality and efficiency of healthcare for the insured.

The conclusion of the healthcare contract between AOK Nordost and DNA-Med shall make precision oncology available in a barrier-free and systematic manner to all insured of AOK Nordost, thus significantly increasing the effectiveness of oncological therapies.

The approach of the DNA-Med platform is based on an integrated, digital and cross-sectoral networking of patients and physicians in private practices with a competence centre, which is currently located at the Charité, Universitätsmedizin Berlin. The connection of the competence centre and private practices via the DNA-Med platform allows

to provide the necessary expertise on target-oriented diagnostics and treatment options for an effective use of precision oncology in a comprehensive, timely and cost-effective manner. Patients are guided into standardised and quality-assured molecular diagnostics, on the basis of which their attending physician receives a well-founded treatment recommendation.

The non-profit DNA-Med platform acts as an intermediary, coordinating all stakeholders, from patients, attending physician, laboratories and pathologists, to the competence centre and health insurance companies, and operates the technical platform. From 2023, the platform and operator model can be offered throughout Germany and for other indicators. In this way, DNA-Med attempts to solve conceptual and practical problems of the complex process chain to make precision oncology available to every affected patient, thus making the approach relevant to healthcare.

During the trial run with AOK Nordost, it became evident that DNA-Med's role is key to success and thus feasibility and dissemination of precision oncology. Through a moderating function of this facilitator entity, different interests were balanced, intersections identified, common goals defined and numerous implementation problems solved. In this way, previous barriers to the widespread and quality-assured use of precision oncology were overcome.

The conceptual problems include, in particular, data protection and the (further) processing of data in compliance with data protection regulations. For this purpose, we developed a concept for a separate declaration of consent by patients for their participation in network medicine and studies. The problem of access authorisations to patient data to ensure consistent medical monitoring and evaluation across the individual sectors could also be solved.

One of the main tasks is to provide the participants with the necessary information for the respective process step and – within the scope of this use – to generate this information in anonymised form for research and further development. In this way, it could be legally ensured that data can also be made available to external partners.

In the course of collaboration with insurers, it has become clear that they would like to see quality assurance for molecular diagnostics to ensure effective use of resources.

Provision of data and optimisation of the patient care process

The provision of high-quality data not only lead to better results in terms of content, but also an optimisation of processes, compensation of structural deficits, and a reduction in the use of resources. Not least because the preparation and follow-up of medical decisions can be carried out via automated processes and algorithms, thereby relieving staff.

Increased effectiveness of healthcare is also necessary because more patients can and must benefit from the innovations of precise therapies that are coming to market at an ever faster pace. As a result, the patient population which places greater demands on medical infrastructure and care processes increases. In other words, at present there is simply a lack of human resources to handle the rapidly increasing number of eligible patients. This shortage of resource will intensify in our ageing society with rising incidence of cancer and an increasing shortage of specialists, which in turn increases the pressure to act.

For optimal scalability, initial automation steps and algorithms for decision preparation have been integrated into the application. The main focus here is on faster reporting in collaboration with molecular tumour boards and study inclusion. A visualisation summarises the previous treatment course of individual patients as well as the result of

molecular diagnostics. In this way, the molecular tumour board can make faster decisions and thus reduce the turnaround time for the preparation of the findings. For visualisation purposes, diagnostic and therapeutic subgroups were created, which are visualised via specific colour codes and representations.

For algorithm-based visualisation of patient history, the „DNA-Med Fingerprint" was developed summarising the entire data space of genetic, clinical, and later patient-reported data in a compressed form. The DNA-Med fingerprint allows for rapid, visual acquisition as well as the use of nearest neighbour algorithms and machine learning. Initial evaluations of this are very promising.

Processing and visualisation in the DNA-Med platform reduces the case review preparation time by approximately 40 minutes per patient. Post-processing time is reduced by 20 minutes per patient. Predefined algorithms reduce processing time by 45 to 90 minutes for 90 percent of patients. The main driver is the number of physicians involved.

A tumour conference often consists of more than ten physicians, while findings can be noted by a single physician using the DNA-Med algorithm-based platform. Overall, the physician processing time per patient is thus reduced by 85 to 135 minutes, thus contributing to a significant reduction in physician workload per patient as well as to an accelerated turnaround time.

Collaboration with stakeholders and provision of data

In addition to providing low-threshold access to precision medicine, the purpose of DNA-Med is to provide data for research and development. In particular, real-world data shall be used to improve indication quality, predictive performance on existing therapy alternatives, and the best possible therapy recommendation based on personal preferences. Care was thus taken from the beginning to facilitate an effective collaboration with all stakeholders in research and healthcare.

In this context, a data protection management system was established in collaboration with experts for pseudonymised and/or anonymised data transfer. The data protection management system includes requirement criteria for a real-world database, target dimensions of the data structure, and data security and protection. The DNA-Med database should be available to as many stakeholders as possible. To ensure proper handling of the data, data provision for different stakeholder groups was defined:

Data provision for healthcare research

- Analysis of treatment pathways and the efficacy of pharmaceuticals in everyday care in the sense of post-market data collection
- Dynamic review of guidelines with the help of real-world data as well as derivation of recommendations and necessary adjustments for a current „standard of care" on an increasingly small, precise subgroup level
- Complementation of other data repositories, such as the Research Data Centre or the GHGA
- Simple and rapid risk-benefit assessment.

Data provision for regulators

- Useful addition to the benefit assessment of medical devices, pharmaceuticals, or new treatment methods via IQWIG
- Enabling retrospective analyses, the results of clinical studies especially regarding the specification of a possible efficacy-effectiveness gap.

Data provision for payers

- Pseudonymised health and treatment data are central elements to identify and implement the potential of new

forms of healthcare
- Comparison of treatment relevance, quality and sequence of therapeutic procedures
- Real world data as a data source that depicts the actual healthcare situation as compared to clinical studies (see regulators).

Data provision for healthcare providers
- Benchmarking for quality management, process improvement and adaptation of SOCs and guidelines
- Comparison to similar patients for treatment recommendation.

Data provision for MedTech and pharmaceutical industry
- Generate RWE through RWE and use for benefit assessments
- Data base for the analysis of the market potential and the target population in the context of the early benefit assessment of new pharmaceuticals
- High-quality, post-market data collection for negotiations with payers and discussions with regulators and healthcare policy.

At present, the technical interfaces are being defined to automatically prepare and provide the possible data space for the purposes of use, depending on the respective stakeholder group. The goal is to develop real-world dashboards that can be used by stakeholders and data can be reused accordingly.

Integration of other regions and entities

The integration of the DNA-Med platform into other cancer centres is intended to provide patients with low-threshold access to gene sequencing and studies with simultaneous quality-assured stratification.

Patient access within the framework of the cancer centre strategy is planned for further urological tumours as well as initially in the indication areas of gastroenterology and gynaecology via the DNA-Med platform. In order to include further cancer centres and indication areas, the role and process model was expanded, which will also be used as the basis for the new platform as of 2023. The adaptation of the role and process models ensures conformity with legal requirements so that data can be used for research. In addition, with the conversion to a standardised database and integration of further cancer centres, the foundations have been laid for extending the approach of precision and network medicine to other sites and indications so that more patients benefit from comprehensive and structured access to precision medicine. At the same time, a consistently quality-assured and privacy-compliant data space for research and evidence generation can be established on this basis.

A French perspective on evidence standards and changing treatment paradigms

Professor Bruno Falissard | University of Paris-Saclay

The percentage of Growth Domestic Product (GDB) dedicated to health has changed substantially in the last years. In France, it was 5.4% in 1970 and rose to 11.1% by 2020. This figure is not expected to increase any further in the future. In parallel, the very nature of medications has also changed: from blockbusters to targeted biological treatments. Both of these changes induce an important tension in the evaluation process for pricing and reimbursement. Study designs and statistical methods have difficulty accounting for these tensions and some radical changes are probably needed to restabilise the system. For example, phase III studies could be replaced by pharmaco-epidemiological studies carried out at the European level.

Introduction

In my work, I face a certain conflict of interest. As a professor, I teach biostatistics, and as a clinician, I work as a child and adolescent psychiatrist. It usually takes me about an hour to admit a new patient. The health insurance company reimburses me for this with a fee of 46.70 Euros. In comparison, treatment with Zolgensma© in France is reimbursed at about two million Euros. So with the money we spend on treating one child, we could invest 40,000 hours in psychiatric consultations to treat the immense number of young patients who come to emergency rooms every day for suicide attempts or other serious psychiatric illnesses, and whom we are currently unable to treat due to a lack of resources. The point here is not to criticize the effectiveness of Zolgensma©, but only to compare it to the cost of psychiatric treatments, which sounds absurd.

Why did we get into such a situation? Because we are fascinated by high-tech medicine, because we believe that technology is stronger than death, which of course is not true. So I'm postulating here that the way we currently pay for healthcare is not based on a reasonable and just basis, and that we need to change that.

The percentage of gross domestic product spent on health has increased substantially in recent years. In France, it was 5.4 percent in 1970 and 11.1 percent in 2020. As a result, we had more and more money, and the new pharmaceuticals launched by the pharmaceutical companies were often commercially very successful. This was very interesting for the healthcare system, especially from an economic point of view, because it was quite easy to evaluate these treatments due to the large sample sizes that these pharmaceuticals allowed in randomised clinical studies. All the conditions were fulfilled for a quasi-systematic reimbursement of newly approved treatments.

Since the beginning of the 20th century, and especially since 2010, the situation has changed fundamentally. There is a lack of money. In most cases, new pharmaceuticals are proposed for „targeted treatments", which means that sample sizes are much smaller, the evaluation process is more difficult, and the level of evidence is questionable. Let us look at this in more detail.

The level of evidence in drug evaluation has declined in recent years

A few decades ago, it was all about approval, and reimbursement was quite systematic. Today, that is completely different. Unfortunately, the evidence requirements in the approval process are completely different from those that are useful for pricing and reimbursement. Comparing a pharmaceutical to a placebo may be useful for approval, whereas it is not useful at all for pricing.

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Because studies in the past have been designed for approval, payers too often have to deal with data that are of limited interest. In particular, indirect comparisons must often be made, which significantly reduce the power of conclusions about the effectiveness of the products under evaluation. Because treatments are now „targeted", sample sizes in studies are small, risking low statistical power, which is generally counterbalanced by the use of surrogate endpoints.

Even more problematic, however, is that the mechanism of action of a new pharmaceutical intended for a small targeted population may now be known and a randomised controlled study may not even be necessary. In some circumstances, a single-arm study, e.g. with a comparison to historical controls, may be sufficient. Apparently, this is indeed the case, as many pharmaceuticals are approved in such a context.

After all, quality of life is an important endpoint for payers. Unfortunately, all too often these measurements are performed without precaution, much of the missing data is missing, and the results cannot be evaluated.

Because evaluation is more difficult, patient advocacy groups and companies sometimes believe payers are reluctant to reimburse new innovative pharmaceuticals that are of great interest. But is it true?

Are payers reluctant to reimburse new innovative pharmaceuticals?

Looking at the evaluation of Rybrevant© for the treatment of non-small cell lung cancer, this indeed seems to be the case. The pharmaceutical is promising, but the available data are only from a single-arm study. This was greatly regretted by the Transparency Committee: „It is not possible to determine the effect size of this treatment due to the

lack of a direct comparison and the methodological weakness of the indirect comparison, although a direct comparison with an available therapeutic alternative with a sound methodology would have been possible." The benefit – referred to in France as SMR (Service Médical Rendu) – was thus deemed insufficient and the drug was not reimbursed, representing a potential loss of opportunity for affected patients.

The situation of Yescarta© for the treatment of large B-cell lymphoma was quite different. The baseline data situation is quite similar: single arm study, historical controls. However, the Transparency Committee's decision is completely different and found a significant SMR and an ASMR 3 (Improved Medical Rendered Service) which allows a higher price level. A situation the CEESP (Committee on Public Health and Economic Evaluation) found embarrassing: „The estimated ICER* of 114,000 Euros/QALY** [and up to 372,081 Euros/QALY] is very high and raises questions about collective acceptability. Even for a small number of patients, it is important that the price of this drug reflect the general principle of fairness in pricing for all pharmaceuticals." [*Incremental cost effectiveness ratio (ICER), **Quality-adjusted life years (QALY)]

Why were these two pharmaceuticals evaluated so differently? Perhaps because Yescarta© is a cell therapy and cell therapy are fundamentally fascinating. Another reason could be that France feels obliged to reimburse high-tech products out of a kind of national ego. Perhaps, finally, because both drugs and societies have changed radically in the last few years, while the methods and statistics are almost unchanged and too often misused. This can make decisions seem incoherent from time to time.

Methods used to evaluate pharmaceuticals are not only scientifically based

To put it somewhat exaggeratedly: Our Western societies are experiencing a pruritus of postmodernity. With the enlightenment and modernity, universalism became a core value. Today, however, people are questioning universalism, because each person is a unique individual. There is something of a cult of uniqueness, as suggested by the title of Élisabeth Roudinesco's 2021 book Soi-même comme un roi (meaning „Be yourself like a king").[1]

Clinics reflect similar sentiments: Many patients believe that they are entitled to everything, they are customers, they pay their health insurance and are thus entitled to all new high-tech treatments and examinations. In reality, however, this is neither true nor possible. Patients are not customers. If this were the case, the price of a session with a child and adolescent psychiatrist in France would not be on the same level as a visit to a veterinarian treating a goldfish.

In this context, the terms „orphan" disease and „personalised medicine" are real marketing geniuses. For an orphan, we all feel plenty of emotions and have deep compassion. In the past, too little was invested in research for patients with very rare diseases, so there were no suitable treatments. Today, however, the situation is diametrically different: There is no limit to the funds spent on rare diseases; the price of Zolgensma© is a good example of this. Of course, this is a political decision, and in a democracy one has to respect this.

However, the consequence of this is that now all patients are likely to have a rare disease because medicine is personalised. In oncology in particular, the target group of patients has shrunk considerably as the genotyping of tumours has become more and more sophisticated: Most treatments then become orphan therapies, with all the

costs associated with an orphan therapy, and that is irresponsible for this situation.

Physicians also have their part of responsibility for this situation. It is boring and not fun to prescribe a blockbuster. However, it is all the more exciting and virtually sends you into a state of euphoria to prescribe a very expensive and sophisticated monoclonal antibody or cell therapy.

The growing importance of the terms „orphan disease" and „personalised medicine" also calls into question the process of claiming that a treatment is evidence-based. This is all the more problematic because this procedure is not based on a solid scientific theoretical foundation anyway. In his book „The progress of experiment: science and therapeutic reform in the United States", the author shows that in the 20th century there was a tension between efficacy demonstrated by a mechanism of action and efficacy demonstrated by a randomised controlled study. The rise of bio- and cell-therapies has put brought this tension back into focus.

The well-documented dispute between Fischer and Neymann & Pearson over the interpretation of the „p" value and type 1 and 2 errors shows that the sacralisation of randomisation and statistical testing is under scrutiny.[3] This is true of the concept of „evidence" embodied in the widely used term „evidence-based medicine". For some philosophers, evidence is only „that which justifies belief" and nothing more.[4]

Without being too provocative, we can conclude that the notion of „high standards of evidence" is mainly the rhetoric of a social ritual. We have to make decisions for or against the approval and reimbursement of treatments. Therefore, we call upon statistics or molecular biology, but none of the two can categorically reach such a conclusion. First, because statistics can never be categorical by nature, and second, because you cannot reduce patients to their biology.

Are innovative methods necessary to evaluate innovative treatments?

Recently, the French government agency Haute Autorité de Santé (HAS) has been accused of being too strict when evaluating innovative treatments. This led to: „On 4 October 2021, the Ministry of Solidarity and Health instructed the HAS to develop new methods for clinical research in order to provide practical benchmarks for industry in the face of an increasing number of pharmaceuticals innovations and marketing authorization applications at an ever earlier stage of clinical development." For this purpose, a committee on methodological issues was set up to do this work. Its conclusions were summarised in a publication.[5] They can be summarised in a few words: „There is no real way to change anything, because statistics are statistics: randomization is crucial to avoid bias, and a large sample size is needed in most cases for acceptable statistical power."

So, we are in a dead-end. On the one hand, pharmaceuticals are evolving by their very nature; on the other hand, statistical methods are blocked by their epistemology. This has very practical implications for public health: Zolgensma© is reimbursed at a price equivalent to the value of 40,000 hours of psychiatric consultations. This raises questions about the „principle of fairness", as CEESP points out. More generally, due to the methodological deficiencies in the evaluation process of new pharmaceuticals, we pay too much for high-tech pharmaceuticals.

Methodological deficiencies in the evaluation process of new pharmaceuticals

While phase III studies are undoubtedly useful, they usually have a poor cost-benefit ratio: they are very expensive (up to 300 million Euros) and are not suitable for evaluating side effects or targeting treatments to appropriate subpo-

pulations, nor for assessing benefits in „real life". And due to the proliferation of personalised or stratified medicine and the associated reduction in sample size of randomised clinical studies, it is becoming increasingly difficult to conduct correctly.

But then, why do we still conduct phase III studies? Mainly for dubious reasons: statisticians love them (their theoretical purity is fascinating, and there is money to be made from them once their secrets are understood), and big pharmaceutical companies love them too (smaller companies cannot afford the high cost of them, which in turn weakens competition). Moreover, health authorities are familiar with them and think that they do not have to pay for them (in fact, society pays for them through pharmaceutical prices).

What are the solutions?

As is so often the case with study designs: simple is better: solutions certainly cannot be found through sophisticated statistical methods. Instead, randomisation itself must be questioned. More and more voices are being raised that public health decisions will benefit from more large cohort studies than randomised clinical studies. It is likely that pharmaco-epidemiology will be the future (and already the present) in health technology assessment (HTA) reviews. Because real world data can be analysed, since large sample sizes are available and this makes it possible to do subgroup analyses. Of course, this will also be accompanied by difficulties. Mainly because of the ontological conflict of interest that pharmaceutical companies evaluate pharmaceuticals with which they will earn money. However, because of the simplicity of this design, this conflict is more or less offset in randomized clinical studies. Unfortunately, pharmaco-epidemiology requires the use of sophisticated statistical models that cannot be fully explained in a statistical analysis plan. The risk of customising these models to produce the expected results exists and is difficult to overcome.

One possible solution would be for the EMA to grant provisional approval already after a randomised clinical trial has positively passed phase II. The pharmaceuticals could then be used in Europe in special centres after approval and before marketing. In these centres, physicians would be allowed to prescribe these new pharmaceuticals in addition to already approved pharmaceuticals, with the requirement to use systematic and standardised data collection systems. Once sufficient data have been collected to provide reliable results on comparative effectiveness or efficacy, the EMA would decide on final approval and grant or deny market access at the national level.

Of course, this will continue to raise critical questions, but they will be less methodological in nature. At present, pharmaceutical companies bear the costs of phase III studies, which seems difficult in such a context. This saving for pharmaceutical companies should be compensated by a price reduction for newly launched pharmaceuticals. Who will take the economic risk of initiating a phase II study? If states bear the brunt of the costs, they should share in that risk; however, at present, they have little or no experience in that area.

Indeed, this proposal is currently quite utopian, but we need something like utopias to find a way out of this absurd situation of senseless redistribution of health care resources.

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Cost containment, method update: The AMNOG under reform pressure

By Dr Florian Staeck

The AMNOG system of early benefit assessment is facing major challenges. On the one hand, these challenges result from the need for stable finances for the statutory health insurance system. On the other hand – triggered by molecular biological research in the development of new pharmaceuticals – the necessity of refining the methodological arsenal used during benefit assessment is being discussed. Both topics were subject of the 16th meeting of the Interdisciplinary Platform for Benefit Assessment in Berlin on 7/8 October 2022. The title of the meeting was: „Paradigms of patient treatment in motion. A special challenge for the AMNOG". The participants discussed the draft of the GKV-Finanzstabilisierungs-Gesetz (GKV-FinStabG) presented by the Federal Government, which was then passed two weeks later in the Bundestag in a slightly modified version. The statutory healthcare system could only afford real innovative pharmaceuticals; with this thesis, individual participants in the discussion justified various readjustments in the AMNOG provided for in the draft law. In particular, these measures provided for in the GKV-FinStabG were discussed controversially:

Lowering of the sales threshold from which a complete early benefit assessment is required: The reduction from 50 to 20 million Euros as planned in the draft law was justified with frequently insufficient evidence, which was increasingly found in the past. Reference was made to the particularly large proportion of active substances with orphan approval, for which the Federal Joint Committee (G-BA) could often not determine a quantifiable additional benefit even after they were subjected to a complete AMNOG assessment. Critical comments were made about designs such as single-arm studies or very small patient populations, which make comparisons difficult. The way to good data should also be to sanction bad data, it was explained. The lowering of the sales threshold would enable an additional benefit assessment of about 20 more active substances as compared to an appropriate comparative therapy (ACT) – a considerable additional effort for the manufacturer.

It was countered that even if the sales threshold was lowered, there would still be a privileged treatment of orphan drugs in Germany, which did not exist in any other EU member state. On average, orphan drugs were already available for patients in Germany 102 days after their approval – and thus much faster than abroad. The value of 50 million Euros was set arbitrarily, it was emphasised.

Based on planned changes to the turnover threshold, more far-reaching demands were made among the participants. For example, there was a plea to limit the privilege to actual soloists for which there was no therapeutic alternative.

This had also been the assumption of the legislator at the time of the adoption of the AMNOG. It was countered by the fact that 20 years after the start of the orphan drug regulation at EU level, there were still only about 230 products for 8,000 rare diseases. This means that there was still an undersupply, it was emphasised. At EU level, pharmaceuticals are approved as orphan drugs if they are used to treat a serious or life-threatening disease affecting fewer than five in 10,000 people.

Notwithstanding this, a more far-reaching proposal was to eliminate the privileges for orphan drugs. Without this special regulation, manufacturers would have a stronger incentive to conduct more conclusive studies and, above all, submit patient-relevant clinical data, it was argued. The benefit assessment decision of the G-BA would also create more therapeutic safety for both physicians and patients.

Because part of the truth is also that the necessary evi-

dence is no longer generated once the medicinal products are available on the market, the participants outlined. This also applied if the additional benefit was limited or could not be proven at all.

Meanwhile, the EU Commission has announced a revision of the regulatory framework for orphan drugs and paediatric pharmaceuticals in November 2020. A public consultation of all stakeholders was completed end of July 2021. Unequal access to orphan drugs in the member states has been recognised as a weakness of the previous regulation. Another aim of the revision is to improve the management of previously neglected indications. A first draft by the EU Commission is expected in the first quarter of 2023.

Guidelines for the pricing of reimbursement amounts: For pharmaceuticals with a non-quantifiable additional benefit or a minor additional benefit, a reimbursement amount shall be agreed that does not lead to higher annual treatment costs than the appropriate patent-protected comparative therapy. Some participants described the goal of strengthening the negotiating position of the GKV-Spitzenverband as understandable, but the way of implementation as problematic. According to the AM-NutzenV, patient-relevant benefits were also required even if only a minor additional benefit was granted. It was criticised that this regulation represented a breach of the basic principles of the AMNOG, according to which an added benefit also justifies a higher price as compared to the appropriate comparative therapy.

This was contradicted with reference to the lack of effect of the price cap according to section 130b SGB V in the past years: For 71 percent of active substances without proven additional benefit, the price cap no longer generated a difference between active substances with or without additional benefit. The background to this was a „luxurious development" in the course of the AMNOG, through which a higher price was enforced in the reimbursement amount negotiations even with only a small additional benefit. As a consequence, the higher price level had become the new ACT, it was argued. Only against this background could the regulatory intention of the draft law be understood. However, the value of 71 percent was questioned in the discussion – this was only the result of „arbitrary interpretations" of the cheapest ACT in each case, it was criticised. According to other studies, 40 percent of these constellations resulted in a significantly lower reimbursement amount as compared to the price level of the ACT.

Irrespective of this controversy, it was pointed out that the government's planned „mandatory requirement" for a price anchor could have a negative effect, especially for new active substances for the treatment of patients with chronic diseases. In clinical studies, surrogate parameters were often used, which, at best, provided initial indications of additional benefits at the time of approval at best provide, as these might only become obvious after 10 or 15 years. As an example, the antidiabetic empagliflozin was mentioned, which had finally established itself in therapy despite sceptical benefit assessment results. Against this background, it was demanded that the legislator should design the reimbursement guidelines as a target regulation in order to be able to deviate from this in negotiations in justified cases.

Discount for combination therapies: The government draft provides that health insurance funds receive a discount of 20 percent of the reimbursement amount from the manufacturer if the pharmaceutical is used in a combination as specified by the G-BA. It was argued in the sense

of the proposed regulations that there was no linear price increase for combination therapies, which would be offset by a linear increase in the additional benefit. In this respect, costs add up, but the additional benefit was often smaller than the additional price in comparison.

However, legal concerns were raised in the discussion as to whether a discount was permissible without consideration of the extent of the added benefit. In this respect, for legal reasons, it would probably not be possible to avoid evaluating the added value of each individual product. In case of a flat discount, a pharmaceutical might have to be sold below its evaluated value. If pharmaceutical 1 of a combination was the most economical ACT, then the constellation could even occur that pharmaceutical 2 would be sold for a reimbursement amount of 0 Euros, they outlined. Some participants rated this as a concern that was far away from reality.

Other participants also warned against the across-the-board flat combination discount and appealed that it should be about taking up the virulent individual cases. One participant's suggestion that a discount could be replaced if the manufacturer submits convincing studies for the combination, which then have to prove themselves in the conventional AMNOG process, met with only limited approval. This option only partially solved the problem of cumulative costs, since in many cases it was a matter of approved components of the combination for which evidence exists. For free combinations without marketing authorisation, however, this proposal could be appropriate, they said.

The debate about the coupling of price and evidence was also associated with the fact that in benefit assessment procedures 48 percent of the evidence presented by the manufacturers was not recognised by the G-BA for methodological reasons. This applied e.g. for cases in which the comparative therapy selected in studies did not correspond to the specifications of the G-BA. In this respect, a harmonisation of the study specifications was called for, e.g. regarding the acceptance of registry data – as was the case in the USA, for example.

This demand led over to the second part of the conference, in which upcoming changes at EU level, such as the regulation on paediatric pharmaceuticals, the orphan drug regulation as well as the EU pharmaceutical strategy as a whole – were discussed regarding their connection with methodological challenges.

The example of the Orphan Drug Regulation of 2000 had made it clear that the multi-level incentive system had been functioning since then. So far, 230 orphan drug approvals had been granted with market exclusivity in about 150 of the cases. About two thirds of the successful study programmes were based on randomised controlled trials (RCTs), most of which were superiority studies, it was reported. Over the past years, the EMA granted an orphan designation because it recognised a clinically relevant advantage (significant benefit), e.g. due to a higher efficacy or a more favourable safety profile of the new active ingredient. In 2020/21, one third of the newly granted orphan designations related to ATMPs, i.e. mainly cell or gene therapeutics. This trend was expected to continue, they argued.

Especially in these cases, scientific advice in the run-up to study programmes was of very special importance. The number of so-called protocol assistance and scientific advice requests from manufacturers had recently increased from 630 in 2017 to 853 in 2021. In these consultations, RCTs remain the gold standard, but deviations are possible depending on the therapeutic context, e.g. regarding the design (e.g. single-arm studies), endpoints, or the establishment of a registry. Moreover, there was an ever increa-

sing demand in parallel consultations of EMA and HTA authorities by applicants.

In this way, potentially controversial issues between the authorisation and benefit assessment authorities could be identified at an early stage, they explained. This applied to the study design and the scope of data collection as well as to the clinical relevance of endpoints or treatment effects. The call to take the needs of HTA authorities into account already during the approval process received a heterogeneous response from the participants.

Reference was made to the still large differences in the assessment of active ingredients by the European approval authority on the one hand and German benefit assessment bodies on the other, despite using the same terminology („significant benefit"). These regulatory structures, which are still not harmonised, were the subject of fierce criticism from individual participants. The „postulate of methodological purity" or „methodological rigorism", respectively, was criticised, which did not contribute to doing justice to the existing evidence for new orphan drugs.

At the meeting, existing imbalances in the evaluation by the EMA and the G-BA were discussed on the example of the cancer drug amivantamab. The basis for the approval was a non-randomised study, whereas in the early benefit assessment data from two German lung cancer registries (CRISP and nNGM) was used. Irrespective of the fact that the indirect comparison showed almost a doubling of the median survival time, the registry comparison was not accepted as valid by the G-BA. In July 2022, the Federal Committee assessed the additional benefit for the pharmaceutical as not proven. The manufacturer then withdrew the active substance from the German market.

Conference participants saw the reason for this in methodological inadequacies both on the manufacturer side and at IQWiG. The instructions in the institute's Rapid Report were insufficient for complex analyses of real-world data, they said. The formalistic rejection justification in the benefit assessment procedure for amivantamab, together with the inadequate description of methodological issues in the IQWiG paper, had proved to be „an obstacle to the introduction of innovations into clinical care", was cited as a reason. In turn, the pharmaceutical applicant had chosen a methodology and data analysis in which the confounders used in the model were insufficiently described.

Against this background, participants derived the demand for greater methodological diversity in the benefit assessment in Germany, which should no longer be exclusively based on RCTs. The reason given was the development of more and more new targeted therapies. The progressive molecular characterisation of tumour entities „orphanised" cancer and at the same time heralded the departure from the paradigm of „watering can medicine", participants argued. This was because these molecular subgroups contained further predictive and prognostic markers. The continuously growing amounts of real-world data finally made it possible to model digital study arms and „match" them to an ongoing study. It would thus be crucial to standardise data collection.

Conventional randomised studies reached their limits when the recruitment of participants alone takes two years during which the standard of care had already changed. Large statistical comparisons could no longer be considered the sole standard in this environment, it was claimed. Manufacturers were thus dependent on coherent „guidance" from regulatory and HTA authorities, which ensures that the study data submitted were also accepted at the end of the day, was the demand. With a view to the joint benefit assessments starting in 2025 in the context of EU HTA regulation, it was disadvantageous if the methodological rigorisms in Germany spilled over to the EU level, it

was said. As a counter-position, it was pointed out that because of these methodological rigorism in Germany, every new pharmaceutical was available to the insured after approval without a fourth hurdle.

In view of the financial challenges of the statutory healthcare system and the methodological uncertainties in the AMNOG procedure, an „agility" in the actions of all stakeholders was required, in which the patient perspective must take a central position, it was concluded.

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