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

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Goals of the plattform

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

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

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

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

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

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

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

The reform of AMNOG must be more than just an economic stopgap

Professor Jörg Ruof

Dear readers

Adaptability is a central feature of healthy organisations and functioning healthcare systems. The term „change management", which is frequently used in business jargon, goes far beyond the passive, reactive ability to adapt to new conditions and rather takes a strategic, formative and proactive perspective.

In this sense, the AMNOG is also constantly challenged to deal with changing framework conditions. This includes, among other things, political adjustments after the German parliamentary elections last fall or the paradigm shift in clinical research towards increasingly specific, genetically determined treatment options and smoother transition between clinical research and health services research in daily clinical practice. Strategic benchmarks in dealing with these dynamic conditions involve evidence and a sense of proportion:

- **Evidence** - because all participants in the Platform on Benefit Assessment consider evidence-based medicine as a relevant benchmark,
- **A sense of proportion** – because the interpretation of evidence that is available in each case requires a very subtle ability to make judgements, especially in view of the high relevance of the respective decisions for everyday healthcare.

The Spring 2022 meeting of the Interdisciplinary Platform on Benefit Assessment and the associated publication cover both the changing policy environment and the dynamic developments surrounding post-market data collection.

Political considerations for the further development of AMNOG: The first articles take a look at the political framework from different perspectives. The considerations of the coalition are described by Ms Stamm-Fibich, the opposition is represented by Mr Pilsinger, and Mr Storm presents the view of the health insurances – among other things with recourse to the current DAK AMNOG Report. Mr Steutel represents the perspective of the research industry.

There is consensus that AMNOG is a success story ensuring rapid access for patients to innovative treatments, implementing necessary savings for the German healthcare system and strengthening Germany as a business and science location. There is also widespread agreement on the selection of controversial issues to be addressed in the further development of AMNOG. For example, rare diseases (orphan diseases), novel therapies such as single-dose gene therapies, and the consideration of data from health services research are repeatedly addressed in the articles.

However, the respective priority areas and approaches differ significantly. On the one hand, reference is made to the enormous savings potential of AMNOG, which has already been realised, and it is shown that structural problems of the SHI system cannot be solved by savings in the pharmaceutical sector alone. On the other hand, pharmaceuticals for the treatment of rare diseases or oncology products or corresponding combination therapies have a very high cost dynamics in relation to the frequency of prescription.

Perspectives on post-marketing data collection in AMNOG: It was possible to establish a dialogue between the different positions on the second conference focus. In the individual contributions, the positions of the regulatory authorities (Ms Naumann-Winter & Mr Broich), Institute for Quality and Efficiency in Health Care (IQWiG) (Mr Lange), Statutory Health Insurance Physicians (KBV) (Ms Bickel & Mr Jantschak), National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) (Mr Mayer, Mr Hastedt & Ms Göppel), registry (Ms Dörnbrack, Ms Pechmann,

Mr Kirschner), as well as the industry (Mr Leverkus & Mr Rauchensteiner) are presented.

From the point of view of regulatory affairs, first of all the mostly insufficient data for many rare diseases is mentioned and the threefold relevance of registries i) for the preparation of clinical studies, ii) as external control, and iii) after approval is discussed.

The IQWIG refers to the overview of study designs for the generation of healthcare data from the corresponding IQWIG report and warns against a „lose-lose situation" with higher costs and high uncertainty regarding comparative evidence.

KBV and GKV-Spitzenverband see post-marketing data collection as an emergency solution in individual cases but point out the considerable procedural effort and the delays in the availability of evidence. However, the GKV-Spitzenverband sees potential in post-marketing data collection, especially in view of the increase in highly specialised therapies for rare diseases - ultimately a promotion of scientific excellence and evidence-based healthcare.

On the example of the timely generation of healthcare data in the context of the COVID pandemic, this potential is also emphasised in the industry's contribution. On the industry side, the possibilities of digitisation are listed as another focus.

The article of the team of the University Hospital Freiburg on the SMArtCARE registry is certainly of special importance. It is the first registry that has been commissioned with post-market data collection by the Federal Joint Committee. Moreover, SMArtCARE as a disease registry now includes several innovative therapeutic procedures in the serious disease of spinal muscular atrophy – it is therefore the first practical experience base in dealing with the new tool of post-market data collection.

Dear Readers, Health economist Uwe Reinhardt, one of the leading US healthcare experts, who died in 2017, once accurately described Obamacare as an „unglued patch on an ugly overall system of healthcare financing". In contrast – and despite all criticism – I believe that in Germany we have the privilege of a healthcare system that is solidly financed overall and functions very well for the entire population.

The success of the further development of AMNOG will be measured by whether it continues to promote the cornerstones of i) rapid patient access to evidence-based innovative procedures, ii) solid financing with a sense of proportion, and iii) strengthening Germany as a science and business location, and thus brings about an overall additional benefit – and does not become a purely economic stopgap, an „unglued patch".

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AMNOG 2.0: Reform needs & planning: What will the new legislature bring?

Martina Stamm-Fibich (MdB) | Jonas Wolframm

AMNOG is a proven system whose basic principles should not be compromised by the coalition. However, it is necessary to react to current developments in the pharmaceutical market to get the prevailing price dynamics under control. The reform measures outlined in this article can ensure the supply of innovative pharmaceuticals and keep spending dynamics within reasonable limits. Nevertheless, some questions remain regarding the medium- to long-term development of AMNOG. This refers in particular to the trend towards single-dose therapies and personalised medicine, and the associated evidence problems.

The good news first: In global comparison, in Germany the supply of medicines to citizens in the statutory health insurance system is at a top level. The fact that new active ingredients are reimbursed by the statutory health insurance system immediately after their approval and market entry is the exception, even in other European countries. AMNOG ensures that patients benefit immediately from new active ingredients, because the benefit assessment and subsequent price negotiations take place only after market entry.

The current legal situation ensures that patients do not have to wait for vital therapies for bureaucratic reasons. Many other countries have a cost-benefit assessment or „fourth hurdle" as a prerequisite for market launch or reimbursement. This hurdle does not exist in Germany. As a result, innovative pharmaceuticals are available much faster in Germany than elsewhere. On average, newly approved pharmaceuticals are available to patients just 133 days after their approval.[1] By comparison: In Austria, it takes an average of 315 days, in Italy 429 days, in Spain 517 days and in France 497 days for pharmaceuticals to reach the supply. In Germany, new oncology products are even available after an average of just 82 days[2] while the EU average is 445 days before insured patients can get these therapies.

At the same time, AMNOG saves the statutory health insurance system around 3.9 billion Euros[3] in pharmaceutical expenditures every year. AMNOG enables reimbursement amounts that are based on the quality and performance of the respective active ingredient. Despite all detailed criticism, the way in which active ingredients are evaluated and priced in Germany is only fundamentally questioned by a very small number of stakeholders more than ten years after the introduction of AMNOG. In addition to the rapid availability of pharmaceuticals, AMNOG also contribu-

ted significantly to cost containment in the pharmaceutical sector.

Despite all this success, there is still a need for action. In the discussion about AMNOG, it is often referred to as a „learning system". This ability to learn is important, because new innovations in the fields of ATMPs, oncology products and orphan drugs are major challenges for the AMNOG due to their high spending dynamics. A look at the figures illustrates the imperative need for reform. The annual treatment costs of new pharmaceuticals have risen significantly in recent years. On average, the annual treatment costs for a new pharmaceutical introduced between 2011 and 2020 amount to approximately 126,000 Euros.[4] For orphan drugs that have been newly approved in the same period, the annual treatment costs even average 295,000 Euros.[5]

If the costs are considered in relation to the prescription volume, the following picture results. In 2020, orphan drugs accounted for only 0.06% of the prescription volume.6 At the same time, however, these low prescription numbers generated 11.6%[7] of the gross sales of the pharmaceutical market of the statutory health insurance system. Oncology products accounted for only 1.2% of the prescription volume in the same year, but the resulting expenditures were 20.5%[8] of total pharmaceutical expenditures. This means that 1.26% of prescriptions account for 32.1% of pharmaceutical expenditures.

The price development described above is taking place in the context of a structurally induced financial imbalance of the statutory health insurance system. The financial situation of the statutory health insurance system will remain problematic for years to come. On the one hand, the pandemic has placed a heavy burden on the health insurances. On the other hand, demographic change will further

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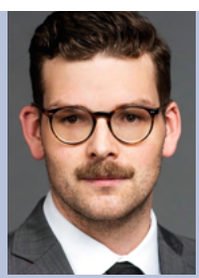

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exacerbate the imbalance between revenues from contributions and expenditures of the statutory health insurance system in the coming years. This development is forcing politics to look everywhere in the statutory health insurance system for potential savings. AMNOG is no exception. On the contrary, AMNOG is one of the areas where savings can be made without compromising the quality of patient care.

In addition to limiting the expenditure dynamics described above, the aim of the reforms must be to ensure that access to and availability of active medical ingredients is not jeopardised because of new AMNOG reforms. Therefore, we do not support the introduction of a cost-benefit assessment, as called for by some experts. Instead, there is a need for selective reform, which must be addressed now.

Validity of the reimbursement amount according to § 130b SGB V from the seventh month after market entry

Unlike many other countries, Germany does not have a „fourth hurdle" that regulates pricing even before the pharmaceutical enters the market. This exception – colloquially known as the „first year of free pricing" – means that very high prices are often paid for new active ingredients that enter the market before the benefit assessment and subsequent price negotiations and without any proven additional benefit. The reimbursement price based on the available evidence is only adjusted one year after market entry. This is too late and contradicts the principle of evidence-based pricing.

While the regulation was feasible at the time AMNOG was introduced, as there were considerable uncertainties regarding the appropriate comparative treatment (ACT) and the expected results of the benefit assessment, it is now outdated. In the meantime, the G-BA has established a well-established decision-making practice and, as a rule, the ACT can also be determined with relative certainty. The problem of provisions to cover potential rebates for the retroactive reimbursement amount has thus been resolved. To partially rectify this, the coalition agreement provides for the restriction of the „first year of free pricing". Specifically, we are talking about a retroactive reimbursement amount that applies from the seventh month after market entry.

Reform of the orphan drug regulation

As already pointed out above in the text, we currently observe that there is a growing spending dynamic in the field of orphan drugs that is often not associated with the actual available evidence. When granting the orphan drug status, the European Medicines Agency (EMA) does not differentiate whether there are already other therapies with orphan drug status in the identical indication. This means that several active substances are available for the same indication, for each of which a fictitious additional benefit must be assumed by the G-BA. The current legal regulations have thus led to a situation that is no longer in line with the original objectives of orphan drug regulation. Instead of accelerating research and development of true „soloists" to address previously unmet medical needs, more and more second and third agents find their way onto the market. There is no justification for simply assuming an additional benefit for these active ingredients, irrespective of the market situation, within the framework of the privileged treatment under Section 35a of the German Social Code Book V (SGB V).

As soon as therapy alternatives are available, new active substances must also be evaluated for the indication in relation to existing therapies. Against this background, a mere lowering of the 50-million Euros threshold does not

seem to be reasonable since the focus is only on reducing costs and no further steering effects are to be expected. The regulation should therefore be supplemented to the effect that in future second and third active ingredients must also undergo a regular benefit assessment.

Introduction of combination discounts

If an active ingredient is used in addition to, rather than as a substitute for, a combination, Section 130b SGB V does not include any functioning regulation for negotiating a reimbursement amount. This results in enormous cost increases that are often out of all proportion to the actual additional benefit of the combination compared with the respective individual active ingredient. One task will therefore be to create the possibility of negotiating new reimbursement amounts for such combinations, which will then allow a reasonable price for the entire combination. The introduction of a combination discount seems to be a suitable means for this.

Avoidable discarding of finished pharmaceuticals

In the past, some pharmaceutical companies used strategies to maximise their profits by offering only excessively large package sizes, especially for orphan drugs. In contrast to the inpatient sector, where only the quantity of active ingredient used is paid for, in the outpatient sector the statutory health insurance system must pay for the entire package. This affects e.g. the active ingredients patisiran, givosiran, and lumasiran. These are used on a weight-adapted basis, which means that in some cases up to two-thirds of the active ingredient is discarded. This avoidable discarding and the resulting additional costs of three to four times the amount should be stopped. Pharmaceutical companies should be obliged to adapt the package size to the dose used.

VAT reduction

One point that is only indirectly related to the AMNOG reform but has a positive effect on reducing pharmaceutical expenditures in the statutory health insurance system, is the reduction of the value-added tax on pharmaceuticals. It is not feasible that the statutory health insurance system financially supports the federal budget in the context of pharmaceutical spending. Calculations show that reducing VAT on pharmaceuticals to 7% would result in savings of around six billion Euros.[9] This relief is more sustainable than refinancing via the federal subsidy, since a one-time decision would result in permanent relief at this point. The measure would also be justifiable in view of our neighbouring countries: Most EU member states privilege pharmaceuticals in VAT.

Trend toward single-dose therapies and associated evidence problems

The trend toward stratified medicine is a major problem for AMNOG in its current version. This is especially true for the benefit assessment and subsequent price negotiation for expensive cell and gene therapies. Because such therapies often enter the market as single-dose treatments with a weak evidence base, alternative reimbursement models are needed that also consider the long-term effects of the active ingredients. It must be reflected in reimbursement practice that data on the efficacy of such therapies are subject to great uncertainty at the time of benefit assessment. At this point, however, the discussion is not yet over. What is clear, is that politics will have to act sooner or later in this area as well.

Conclusion

AMNOG is a proven system whose basic principles should not be compromised by the Ampel coalition. However, it is

necessary to react to current developments in the pharmaceutical market to get the prevailing price dynamics under control. The reform measures outlined in this article can ensure the supply of innovative pharmaceuticals and keep spending dynamics within reasonable limits. Nevertheless, some questions remain regarding the medium- to long-term development of AMNOG. This refers in particular to the trend towards single-dose therapies and personalised medicine, and the associated evidence problems.

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Guidelines of evidence-based pharmaceutical policy: The view of the opposition

Stephan Pilsinger, MdB | Spokesman for Health Policy of the CSU State Group

The AMNOG has been a success story for more than ten years, according to Stephan Pilsinger, spokesman for health policy in the CSU parliamentary group. According to the CSU politician, it not only strengthens Germany's position as a business and science location, but also ensures that innovative, highly effective pharmaceuticals are available to all patients fairly quickly. In addition, modalities of AMNOG brought annual savings of billions of Euros for the benefit of the German healthcare system. In his article, the CSU health expert describes why and with which set screws AMNOG should be further developed with a sense of proportion and evidence-based.

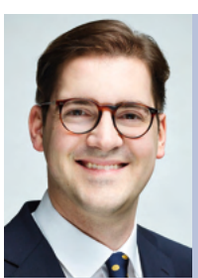
In the expectation of the media and the political establishment, the „view of the opposition" does not seem to know or does not want to know terms like „sense of proportion" or „evidence-based". Quickly and loudly, the opposition usually requests the big and fast throw; „far-reaching reforms" are needed, everything must be turned upside down, evidence and efficiency are not so important if only the media effect is achieved. I am not playing this game, and neither is the CDU/CSU parliamentary group, which is the largest opposition group in the 20th parliamentary term of the German Bundestag. A „sense of proportion" and „evidence" remain reliable parameters of our healthcare policy and thus also – and even more so – in pharmaceutical policy.

The German Pharmaceutical Market Reorganisation Act, the AMNOG, which came into force in 2011, is and remains a success story that does not have to be revolutionised but further developed „with a sense of proportion" and „evidence-based". With the AMNOG process, politics, the pharmaceutical industry, and self-administration have done much good for the insured community as well as for Germany as a research and business location: With the AMNOG, we created transparency and certainty for both patients and prescribers as to the actual added value of new active ingredients. This added value creates a scientifically sound basis for price negotiations between manufacturers and the health insurers.

As a result, the AMNOG saved more than three billion Euros in 2019, 2020 and 2021 for the benefit of the statutory health insurance (SHI) - around two billion Euros in annual savings had been forecast by the legislature in 2010. In 2021 alone, AMNOG-based savings of 5.9 billion Euros were achieved. For 2022, the IGES Institute forecasts record savings of as much as 8.4 billion Euros. And all of this is without the market valuation, a tool which was still being di-

scussed at the time. Thus, AMNOG contributes significantly to the stability of pharmaceutical spending - year after year.

In this context, a big thanks goes to the Federal Joint Committee (G-BA), the Institute for Quality and Efficiency in Health Care (IQWiG), the Federal Institute for Drugs and Medical Devices (BfArM), and the Paul Ehrlich Institute. According to the DAK-AMNOG Report 2022, 291 pharmaceuticals were subjected to an early benefit assessment within the scope of 527 procedures by the end of 2020; in 58 percent of all procedures, an additional benefit was proven. This is – despite the Corona pandemic – once again a significant increase as compared to 2019, when 265 new active substances were subjected to 439 early benefit assessments by the G-BA. In addition, there are the numerous consultation meetings for pharmaceutical companies at the highest scientific level.



Stephan Pilsinger *was born in 1987 and studied human medicine at the LMU Munich 2007-2015. Afterwards, he worked as a physician in internal medicine at a municipal hospital. In 2017, he was elected to the German Bundestag as a directly elected representative. After his part-time distance learning in business administration, he graduated as Master of Health Business Administration (MHBA). In 2021, he was re-elected to the German Bundestag.*

With their precise, committed and evidence-based work, the above-mentioned institutions ensure that the German AMNOG procedure is regarded as the „gold standard" worldwide and that the AMNOG procedure – even with the qua natura conflicting interests here – is not only accepted but highly recognised by all stakeholders. Representative surveys of the relevant stakeholders show that the procedure is perceived as scientifically sound, transparent, fair, plannable, and fast. As a result, Germany is now the country in Europe where new active ingredients are fastest on the market and thus available to patients. This applies both to regularly approved pharmaceuticals and high-priced orphan drugs.

Over the past eleven years, we have successfully completed almost all procedures on time within six months in accordance with the requirements of Section 35a of the German Social Code, Book V (SGB V). On average, it takes only 50 days for a new pharmaceutical to be available to patients after approval in Germany. That is number 1 in Europe! By comparison: In Switzerland, it takes 87 days, in England 297 days, and in France even 474 days. This reflects the excellent work of the G-BA and the participating institutes mentioned above.

We must not jeopardise the excellent system of supply of pharmaceuticals in Germany, of which the AMNOG procedure is an important part. Regarding innovative pharmacotherapies, which are often only intended for relatively small groups of patients but are very expensive – i.e. orphan drugs, biopharmaceuticals or gene therapies – but also in order to cap the costs in the healthcare system per se, it is often the pharmaceutical sector from the political side where the healthcare cost-cutting tool is first applied.

The recently published draft bill „for the financial stabilisation of the statutory health insurance system" with a „processing status" of 4 March 2022, which, according to

Federal Health Minister Lauterbach, comes „from the shoals“ of his ministry, shows that SPD Minister Lauterbach wants to curb costs in the SHI system primarily through savings in pharmaceuticals.

To absorb the deficit of 17 billion Euros in 2023 forecast by the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and to prevent an increase in additional contributions, as well as to keep the federal subsidy at a tolerable level, the BMG's draft bill is mainly at the cost of the pharmaceutical industry.

None of these are structural, well-thought-out measures. The Ampel coalition wants to venture more progress, but it is precisely this progress that is being thwarted. Instead of imposing heavy restrictions on our innovative pharmaceutical industry and only presenting short-term cost-cutting measures, we need to think about how we can keep pharmaceutical costs in line with intelligent, long-term measures and how we can further develop the AMNOG evidence-based and with a sense of proportion.

This is the only way to strengthen Germany as an innovative pharmaceutical and business location, ensure continued rapid access to high-quality pharmaceuticals, and at the same time keep costs under control.

Moreover, the assumption behind the above-mentioned draft bill that, with a singular view of expenditures in 2021, disproportionately rising pharmaceutical expenditures were mainly responsible for the SHI deficits is false for the following reasons:

- In the longer term, the share of pharmaceutical expenditures in SHI expenditures will remain stable at 16 percent.
- 75 percent of the increase in SHI spending can be attributed to increases in hospital and physician services. As a rule, absolute increases in pharmaceutical spending are caused by an increased number of prescriptions. By contrast, the average prices for pharmaceuticals have been decreasing for years, which is also due to the effectiveness of the AMNOG.
- The extensive regulation of the pharmaceutical market and the statutory and contractual rebates now contribute to considerable savings and ensure the fastest access to innovations throughout Europe.
- Through statutory and individual rebates, AMNOG, the reference price system, etc. the pharmaceutical industry already contributes significantly to the stability of SHI finances. Overall, the savings for the SHI funds in 2021 were around 21 billion Euros. In 2022, the amount is likely to be even higher.

The following points must be clear to politicians and pharmaceutical companies:

- Gene therapies as single-use treatments will gain in importance in healthcare. As personalised medicine, they place new demands on benefit assessment and reimbursement.
- There is an increasing number of antibiotic resistances. We need new reimbursement models to secure financing of reserve antibiotics and incentives for the development of new antibiotics.
- In an ageing society, the need for pharmacotherapies is increasing in terms of innovation and volume. The one-sided focus on pricing fails to recognise the increases in spending due to an increasing number of prescriptions.

The key political objective must be to further develop the AMNOG based on evidence and with a sense of proportion, not to deflate the pharmaceutical industry to account for the growing needs of patients, to prevent patients with rare diseases from being cut off from vital, yet expensive pharmaceuticals, to continue to guarantee rapid access to new active ingredients, and to retain innovation and economic strength in Germany. How can this be reali-

sed in practice? The following ideas should be discussed:

1) Strengthening new financing models such as pay-for-performance contracts: New gene therapies in particular, as the last hope for patients, enable a fair distribution of risk as success-based payment models. The prerequisites can be realised with collective (Section 130b SGB V) or selective (Section 130a Paragraph 8 and Section 130v SGB V) contractual arrangements. To make these contractual models attractive for health insurance funds, the morbidity-oriented risk structure compensation system needs to be adjusted. In this model, which is favoured by the author, e.g. four payments could be made in case of corresponding proven patient benefit.

2) Sustainable financing of ATMPs and reserve antibiotics in the inpatient sector: Advanced therapy medicinal products (ATMP) or reserve antibiotics are predominantly used in the inpatient sector. This practical application requires funding security for the clinics. The path taken by the CDU/CSU-led federal government at the end of the last legislative period in the context of the Health Care Development Act (GVWG) should be concluded with a further development of the AMNOG by closing the gap of new examination and treatment methods.

3) Requesting or requiring manufacturers to conduct more research on rare and previously untreatable diseases: Instead of debating on the purpose of spending money on a relatively small number of patients, we should focus on how to get private research activities to do more research on previously untreatable diseases. Where are the needs of the future? What role will demographic change, climate change or globalisation play, for example? Where do we have to start today to have the answers to the treatment questions in 10 or 20 years?

4) The concept of the Dynamic Evidence Award developed by the German Techniker Krankenkasse is very interesting and should be discussed: As is well known in expert circles, this concept targets gene therapies with little evidence at market entry and uniquely high costs, which cannot be adequately covered by the AMNOG in the opinion of the author. Gene therapies are not typical pharmaceuticals. Techniker Krankenkasse wants to see the concept of dynamic evidence pricing as a complement to the AMNOG process. This model should be seriously discussed and ultimately adopted in the SGB V.

5) Ensure reliability of the appropriate comparator therapy: Problems with the comparison with an appropriate comparator therapy (ACT) can arise if, due to a change in medical knowledge, the ACT is unilaterally changed by the G-BA during the evaluation process, which lasts only a few months. Such a change now occurs in one of six procedures.

In the worst case, the change of the ACT can lead to the studies that the company has collected to prove the additional benefit suddenly being worthless. In the past, various pharmaceuticals, including those for the treatment of melanoma and psoriasis, received an inferior benefit assessment as a result. Since the studies take several years to complete (the last phase III study alone took about 2.5 years), are cost-intensive, and the study design is often developed in consultation with the G-BA, the subsequent acceptance of the results should also be reliable. Otherwise, the procedure would be much like the race between the hare and the hedgehog.

The sudden change in ACT sends the wrong signal to attending physicians - after all, innovative drugs are tainted by the stigma of a supposedly low added benefit. In the end, patients are the ones who suffer: They might not re-

ceive certain pharmaceuticals. Investments by the manufacturer to provide appropriate studies that are made in reliance on the G-BA consultation, are not adequately rewarded by the change in the ACT, neither in the evaluation nor in the reimbursement situation.

A compromise between the problem of the need for a plannable study design and the consideration of new medical findings is required: The initial comparator therapy for which a clinical study was initiated must no longer be completely dropped from the assessment, but must be considered along with the new, modified ACT.

6) Improve post-marketing data collection: It is well known that complex clinical studies with many subjects take place to demonstrate an additional benefit. However, there are rare diseases for which a large number of subjects can hardly be determined. Accordingly, it is also difficult to collect sufficient data to determine the additional benefit. For these and similar cases, such as pharmaceuticals with special approval, we have the instrument of post-market data collection. It enables data to be collected while an approved pharmaceutical is already in use. In this way, an evidence-based additional benefit can be determined, which is also a good indicator of benefit in patients.

However, to furnish proof of an additional benefit, especially for rare diseases, and to fully exploit the advantages of post-market data collection, it must be made more practical and expanded. According to reliable reports from the pharmaceutical industry, the requirements of the G-BA regarding the data to be collected and the conduct of the study are often impossible to realise and exceed the scope of other healthcare studies.

For this reason, an early cooperative exchange between the G-BA and pharmaceutical manufacturers would be desirable, during which the manufacturer is informed as early as necessary about the necessity of post-market data collection and potential problems can be resolved. Moreover, a close coordination between the regulatory authorities and the G-BA should take place from the outset to coordinate study requirements.

Although healthcare data („real world data“) play an increasingly important role in medicine as digitisation and electronic networking advance, they are currently not considered in benefit assessments. To close data gaps and to provide more evidence, this should be done in the future.

7) Involvement of professional societies in defining endpoints: It is well known that the key starting point for the additional benefit assessment is the definition of endpoints, i.e. targets against which additional benefit is to be demonstrated in clinical studies (e.g. survival, cure, improvement of the medical condition, adverse drug reaction). Currently, the Federal Joint Committee (G-BA) advises pharmaceutical manufacturers on the choice of endpoints. In the subsequent benefit assessment, the recommended endpoints are generally decisive, even if they are often doubted by experts.

To adequately reflect the state of scientific knowledge and to make new therapies available to patients, medical societies should be taken into account to a greater extent in the definition of endpoints, as is already the case when defining ACTs.

Although professional societies bring together the experts in a specialist field and the physicians they represent are in daily contact with patients, their expertise is currently disregarded when it comes to advising the pharmaceutical company on endpoints.

Particularly for chronic diseases and cancer medicine, this leads to endpoints that professional societies consider relevant to patients are not considered, and innovative

pharmaceuticals thus receive a poor benefit assessment. In oncology, this procedure currently leads to a contradiction between additional benefit and therapy recommendation in 60 percent of cases so that benefit assessment and evidence-based guidelines increasingly drift apart.

For example, a pharmaceutical intended for the treatment of rare breast cancer recently had to be withdrawn from the market because the improvement in progression-free survival time was not assessed as a patient-relevant endpoint by the G-BA, contrary to the assessment of the professional societies. Something similar thing happened with diabetes pharmaceuticals, whose improvements in blood glucose lowering were not recognised. This is inefficient and even harmful in the patient's sense.

All these considerations show: AMNOG must be further developed in an evidence-based manner and with a sense of proportion by adjusting the above-mentioned and other parameters – this is the right way to ensure continued rapid access to new active ingredients or gene therapies for patients, to strengthen Germany as a research and business location, and at the same time to keep costs under control.

In contrast to the across-the-board cuts envisaged by the Federal Ministry of Health, which are only effective in the short term, this approach can set the long-term course for the goals to which all stakeholders in the healthcare system are ultimately committed.

Evidence-based pharmacotherapy: from a health insurer's perspective

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Pharmaceuticals that gain market access through the so-called accelerated approval procedure are increasingly in focus. They have particularly weak evidence base due to a mostly insufficient data base. The systematics of the evidence-based AMNOG procedure is ineffective for these therapies, which leads to uncertainty among prescribers and patients and cause exorbitant expenditures for pharmaceuticals without evidence-based additional benefits for the community of solidarity. Based on this, there is also still no satisfactory solution for the evaluation of combination therapies. The common goal of patients, physicians, and health insurers should therefore be to increase the evidence base for these therapies as much as possible.

One of the major advantages of the solidarity-based system of statutory health insurance is the coverage of treatment costs for every insured person who is ill or at risk of becoming ill, irrespective of age, wealth, status, therapy costs, or other criteria.

Thanks to medical progress, life expectancy in Germany rises continuously and many diseases that were considered incurable not so long ago can now be treated. This is also reflected in the ever-increasing number of newly approved pharmaceuticals. Between 2020 and 2023, 434 approvals of new pharmaceuticals or extensions of approval are planned[1] as compared to 244 from 2016 to 2019.[2] This is good news for patients. However, beyond the quantitative increase in new registrations, there are two crucial factors that must be considered regarding the reimbursement of pharmaceuticals both for affected patients and the statutory health insurance system as a solidarity-based community. Efficacy and safety for the insured on the one hand, and a benefit, if possible as an evidence-based added value to already existing therapies, on the other hand.[3]

While efficacy and safety of a pharmaceutical have also been assessed in addition to quality criteria in market approval procedures since the 1970s as prerequisites for market entry, pharmaceutical manufacturers were allowed to set prices for their products on the German market regardless of an additional value until the end of 2010. Since the mechanisms of a self-regulating free market are not effective in the German healthcare system, this circumstance has led to significant spending increases. To regulate this for new pharmaceuticals, the legislator created an instrument in 2011, i.e. the Pharmaceutical Market Reorganisation Act (AMNOG). It is a price regulative based on the proven benefit of a pharmaceutical as compared to existing therapies through reimbursement amount negotiations bet-

ween the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and the pharmaceutical manufacturer.

I. AMNOG effects

Thus, AMNOG first made an evidence-based benefit assessment possible as a starting point for subsequent pricing, which is valuable for the solidarity community. The AMNOG process thus paved the way for benefit-based pricing.

Patients still have unrestricted and rapid access to new pharmaceuticals and therapies, which still characterises the current German pharmaceutical system. In the statutory health insurance system, for example, new pharmaceuticals are available to patients less than three months after they have been approved. This is mainly due to the fact that in Germany there is still no so-called „fourth hurdle" after the approval in form of a price negotiation prior to market entry, as is the case in almost all other European countries (figure 1).

For the pharmaceutical industry, this means an unparalleled fast opportunity to bring their products to market within Europe. Moreover, free pricing for manufacturers in the first year after market launch has remained. The reimbursement price agreed during the AMNOG procedure or set by an arbitration court is valid only from the 13th month after market launch, which gives companies the additional advantage of setting a price anchor for subsequent reimbursement amount negotiations.

By 2020, savings for the solidarity-based community re-

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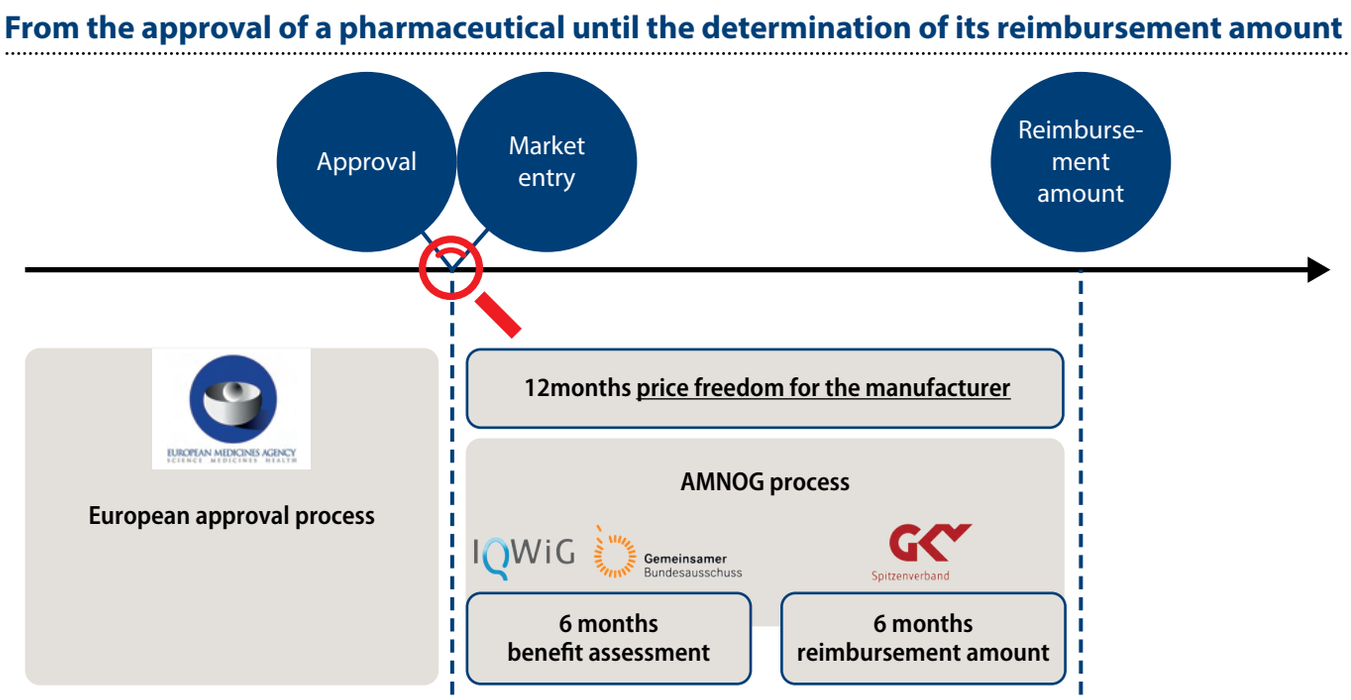


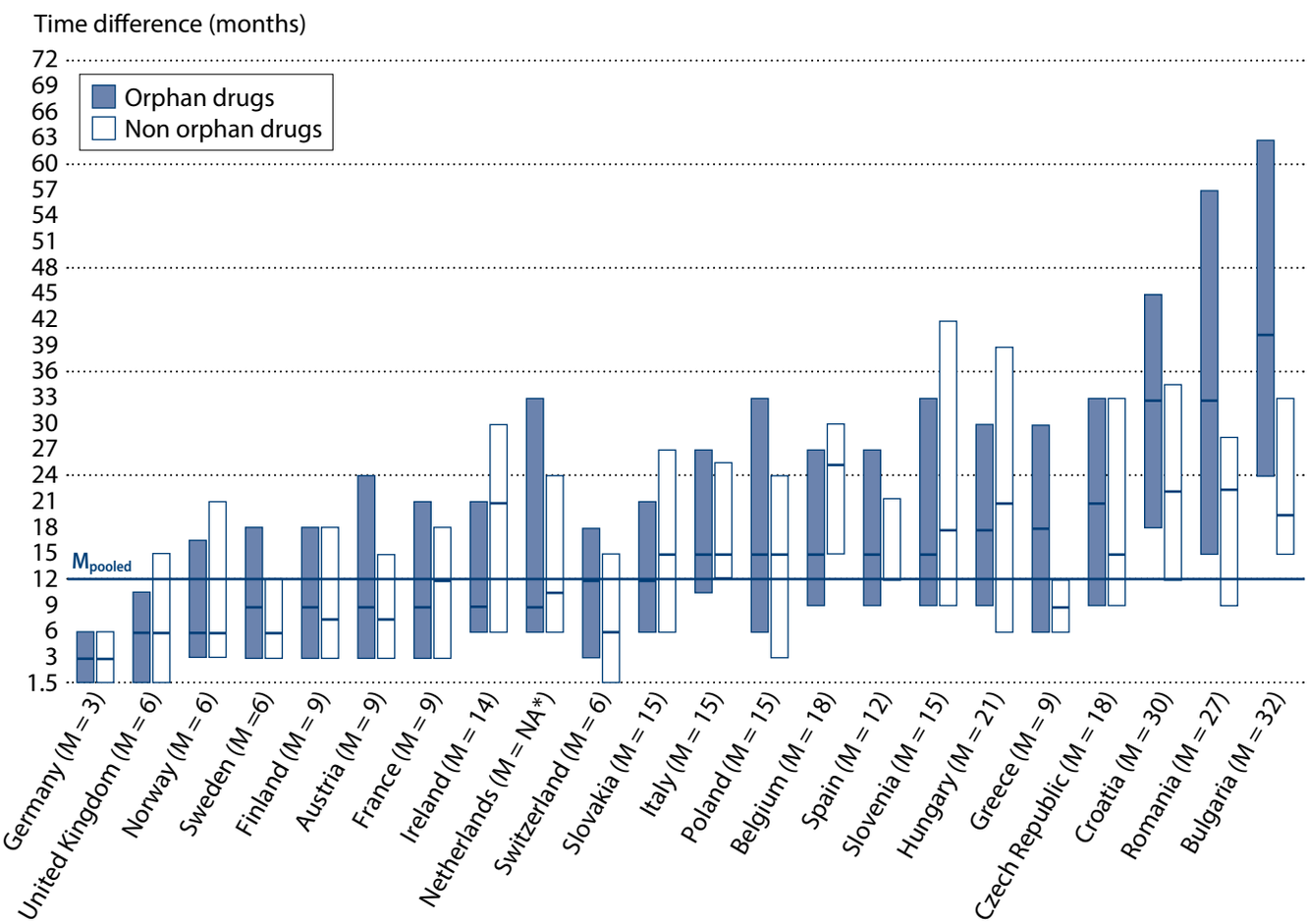
Figure 1: Unlike in many other European countries, there is no „fourth hurdle“ in Germany .

sulting from the AMNOG procedure are estimated at approximately 3.4 billion Euros.[4] This sum should, of course, be viewed against the background of free pricing by the pharmaceutical manufacturers upon market entry. Depending on the strategically set entry price level, we can therefore speak of more or less savings through AMNOG, regardless of whether the price at market entry follows a benefit at all.

II. Adjustment requirements

Despite AMNOG, prices for new pharmaceuticals have been developing rapidly, especially in recent years (figure 3). In 2021, the statutory health insurance system will already have spent over 46.7 billion Euros on pharmaceuticals.[5] This corresponds to an increase of approximately 7.8% on the previous year.[6] This figure already includes statutory rebates and rebate payments contractually agreed between health insurers and pharmaceutical companies. For the first time in 2019, the cost block for pharmaceuticals was the second largest in the statutory health insurance system after the costs for hospital treatments and has thus overtaken expenditures for outpatient healthcare.[7] In addition, the number of new approvals also increased, although a high therapeutic benefit could only be proven for

Mean time to market availability after approval of new pharmaceuticals in Europe

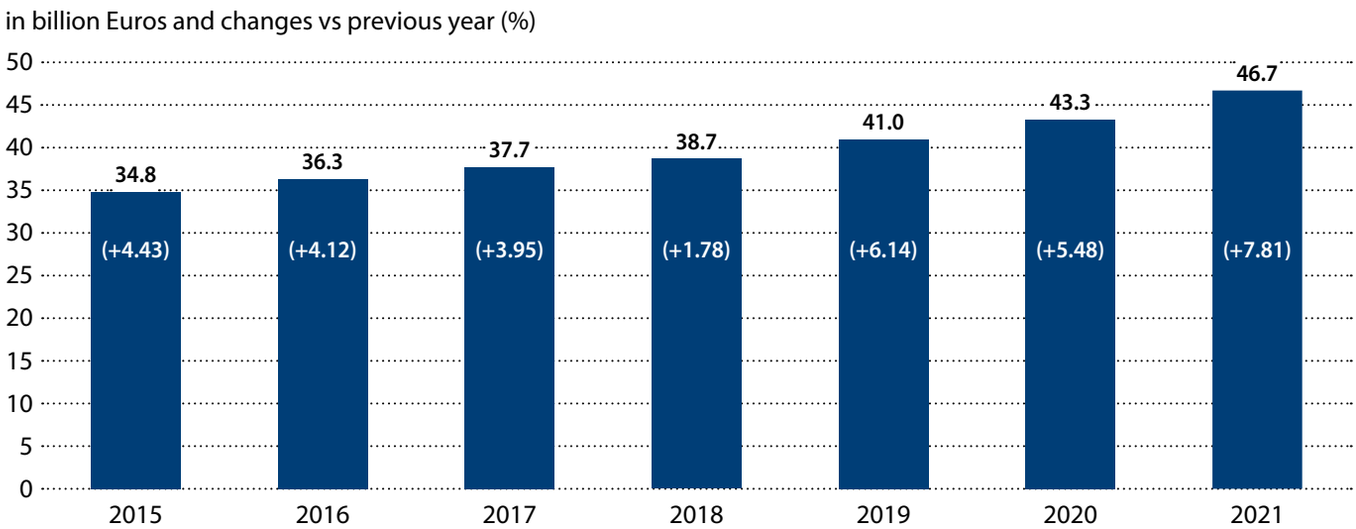


*Data in original source incorrect Source
Source: AMNOG-Report 2022

Figure 2: In Germany, new pharmaceuticals are available three months after their approval. In the majority of European countries, this is only the case after two to years.

one third of the new pharmaceuticals.[8] The discussion about the willingness to pay for new pharmaceuticals has now given way to a discussion about solvency.[9] The AMNOG-Report 2022 of DAK-Gesundheit shows that the cur-

Development of pharmaceutical spending in the statutory health insurance system without co-payments by the insured



Source: Own presentation on the basis of the Federal Ministry of Health (BMG); data for 2021 from KV45

Figure 3: For the first time, the cost block for pharmaceuticals is the second largest in the statutory healthcare system in 2019 after the costs for hospital treatments and has thus overtaken the expenditures for outpatient healthcare.

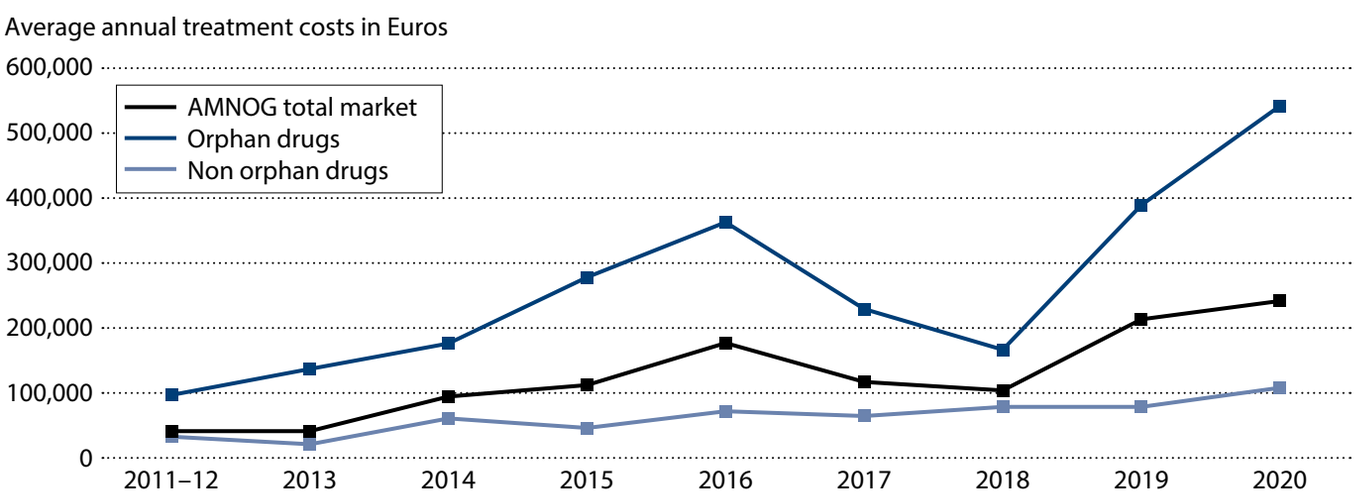
rent AMNOG process for achieving a balance between evidence-based patient benefit and reimbursement price reaches its limits, especially in case of pharmaceuticals that come onto the market through the so-called accelerated approval procedure, e.g. orphan drugs, as well as in case of single-dose and combination therapies.

1. Orphan drugs

The economic and regulatory incentives for the pharmaceutical industry introduced by European Regulation (EC) No. 141/2000 in 2000 have resulted in more than 180 orphan drugs being approved to date, as compared to only eight in the previous period.[10] Moreover, accelerated approval procedures[11] for orphan drugs by the European Medicines Agency (EMA) that have been continuously expanded have also resulted in a considerable increase in the total number of procedures. The economic incentives at European level are thus successfully leading to an increase in the development of own orphan drugs or the acquisition of small pharmaceutical manufacturers by large international groups. The economic success can also be justified by the exorbitant prices for orphan drugs (figure 4).

These incentives involve a certain potential for abuse, as the following trend in the pharmaceutical industry shows. Common disease patterns, as in oncology, are being „orphanised“ into ever smaller disease patterns through in-

Development of annual treatment costs of new pharmaceuticals at market entry depending on the approval status



AMNOG-Report 2022, data 2011-2020; data source: G-BA)

Figure 4: The annual treatment costs of orphan drugs approved in 2019 and 2020 have reached new levels with an average of 390,000 Euros (2019) and 540,000 Euros (2020), respectively.

creasing precision medicine (so-called slicing by biomarkers).[12] In Germany, Section 35a of Social Code Book Five (SGB V) legally presumes the additional benefit of a pharmaceutical that has been approved as an orphan drug. Within the scope of the benefit assessment procedure, only the extent of the additional benefit is determined. If the pharmaceutical manufacturer turns over more than 50 million Euros with the orphan drug within twelve months, the „orphan privilege" from Section 35a SGB V does not apply, and the pharmaceutical will be subject to a full benefit assessment process. 60% of all orphan drugs that have been evaluated in the benefit procedure did not show any quantifiable additional benefit, since – among other things – the medical relevance or the effects of a treatment for patients remained unclear.[13]

With regard to pure approval numbers of new orphan drugs, the incentives may not have missed their mark. However, this is also reflected in a price trend that represents a significant financial challenge for the solidarity community. For example, the annual treatment costs for orphan drugs that have been approved in 2019 and 2020 will reach new records, averaging 390,000 Euros in 2019 and 540,000 Euros in 2020, respectively. The average annual treatment costs for orphan drugs thus increased to an average of 295,000 Euros within the last ten years.[14] In 2010, orphan drugs accounted for less than 5% of the total net costs of the statutory health insurance market; by 2024, the share of expenditures for orphan drugs in the total

pharmaceutical expenditures of the statutory health insurance system is predicted to reach 18%.[15]

In addition to the ever-increasing financial challenges described above, there is a significant information deficit for physicians and patients regarding orphan drugs due to insufficient data at the time of approval. Weak evidence regarding efficacy and safety leads to uncertainties in the treatment decision.[16] The benefit assessment does not help here either. This shall also provide transparency about the therapeutic benefit for patients and their physicians.[17] As described, however, this benefit is determined by legal fiction without the need for actual evidence. In summary, the systematics of the evidence-based AMNOG procedure is not suitable for the evaluation of orphan drugs, which leads to uncertainties regarding these pharmaceuticals among physicians and patients and results in exorbitant expenditures for pharmaceuticals without any evidence-based additional benefit for the community.

2. Single-dose therapies

Another systemic weakness of the AMNOG procedure are pharmaceuticals whose promise of cure is based on a single dose rather than on a long-term treatment. These are usually gene therapy medicines, somatic cell therapy medicines, and biotechnologically processed tissue products, which, as novel therapies or so-called ATMPs (advanced therapy medicinal products), currently still cover indications that are considered to be rare conditions. This means that the challenges identified regarding evidence of efficacy and safety for patients and physicians and the principle of „no additional costs without additional benefits“[18] for the statutory health insurance system also apply here. By taking a curative approach to previously chronic diseases, manufacturers are condensing treatment costs that would otherwise have been incurred over a longer treatment cycle into a single payment, resulting in completely new price dimensions.[19] Moreover, the current process of benefit assessment and reimbursement system does not reflect the cure after a single dose of a small number of patients, since pricing according to benefit for the statutory health insurance system only takes effect from the 13th month after market entry (figure 1).[20] If the number of patients is too small, the majority of patients might already have completed treatment after 12 months and pricing according to benefit will not take effect from the 13th month (or only in rare cases).

3. Combination therapies

A third challenge is the use of patent-protected pharmaceuticals as combination therapies, which are quite common in the field of oncology. Approval of new pharmaceuticals that shall explicitly be combined with other therapeutics, whether two or more pharmaceuticals are used side by side (simultaneously) or one after the other (sequentially), increased by 32% from 2019 to 2020 in the outpatient setting alone.[21] The number of approved combinations of orphan drugs has recently increased by as much as 50%.[22] For patients and their physicians, these combination options represent a multiplication of therapeutic options. For the solidarity community, they also represent an increasing financing challenge, since the individual prices of high-priced mono- or add-on therapies add up when pharmaceuticals are combined, while the additional benefit only shows a comparatively slight increase. This is also due to the fact that at present only the pharmaceutical that includes the combination regimens in its marketing authorisation undergoes an additional benefit assessment for the combination. The other pharmaceutical/s in the combination is/are not assessed. Consequently, benefit-based prices for combination therapies cannot be achieved.

This leads to enormous price increases in the already high-priced field of oncology, as exemplified by a combination therapy for the treatment of multiple myeloma[23] or – in extreme cases – combinations of ATMPs with a promise of cure after a single dose with a permanent therapy, as in the field of therapy for spinal muscular atrophy (SMA).[24]

III. Approaches

The challenges described in the AMNOG-Report 2022 of DAK-Gesundheit and briefly outlined here show that „innovation" does not have to go hand in hand with additional benefits for patients. Due to the separation of treatment decision-making and cost coverage, German manufacturers of patent-protected pharmaceuticals have a market advantage as compared to other industries. In addition, the incentive of accelerated approval for market entry and fictitious additional benefit in the calculation of the reimbursement price shifts further entrepreneurial risk to the cost covering solidarity community.[25] Due to weak evidence regarding efficacy, safety or additional benefit, the risk of treatment failure of some pharmacotherapies is significantly increased for the insured. It makes no sense that especially pharmaceuticals for rare and often severe diseases do not undergo adequate benefit assessments, and thus there is no transparency for particularly vulnerable patient groups.[26] Furthermore, it is grotesque that the financial risk of failure of pharmacotherapies with weak evidence-based data, but absurdly exorbitant prices is borne by the health insurers alone.

In recent years, AMNOG has proven to be a learning and flexible system and has undergone several adjustments. Due to the change in therapies, an adjustment is more urgent than ever needed to ensure a sustainable and financially viable healthcare system. The link between the price and the benefit of the therapy must be brought back into focus, without creating a fourth hurdle.

1. Measures to increase evidence

Against the background of the low patient numbers for orphan conditions, it is understandable that the so-called „gold standard" presents a challenge for pharmaceutical manufacturers during pivotal clinical trials in the development of orphan drugs. This makes it all the more necessary for regulatory authorities to oblige manufacturers to design broad international studies to obtain the largest possible number of patients for data generation.[27] To obtain further results for increasing evidence on efficacy and safety after accelerated approval, the competent authorities should impose strict conditions on approvals for further data collection and also closely monitor these conditions and, if necessary, impose severe sanctions.[28]

At the level of benefit assessment in Germany, the possibility for the G-BA to oblige pharmaceutical manufacturers to conduct so-called post-market data collection, which was already created by the Act for Greater Safety in the Supply of Medicines (GSAV) in 2019, can be seen as progress for further evidence generation. The resulting early involvement and consultation of the G-BA is certainly an advantage. However, to be able to conduct an additional benefit assessment based on a comparative evaluation, indication registries are also important. In a registry, data from everyday clinical practice can be collected in a structured and standardised manner. Evaluation of these data can be used not only epidemiologically, but also in clinical research to generate evidence for a pharmaceutical for which a randomised controlled intervention trial (RCT) is not indicated.

Nevertheless, not all evidence problems can be solved by this means.[29] Pharmaceutical manufacturers should involve registries already during the development of a phar-

maceutical for an accelerated approval, in which the results are later included[30] or make sure to consider this criterion during the usual buyout of smaller pharmaceutical manufacturers engaged in the development. Since especially the prices for orphan drugs and ATMPs with low evidence are non-transparent and seem to be arbitrary, the obligation for more evidence could at the same time provide more price transparency.

2. Introduction of an interim price and abolition of the orphan privilege

Patients with rare diseases have the same right to efficacy, safety, quality, and information about the therapeutic benefits of their pharmaceuticals as other patients. To provide for an increase in evidence in addition to the regulatory measures recommended above, the fictitious additional benefit according to section 35a SGB V, which is granted with approval as an orphan drug, should be abolished to pave the way for a comprehensive benefit assessment not only from sales of more than 50 million Euros.

Due to the above-mentioned challenges in evidence generation, sufficient data will probably not always be available for a benefit assessment that does justice to the claim of an assessment of an additional benefit. For this case, an interim price is proposed in various degrees which will be replaced by an evidence-based reimbursement price from market entry until the end of a benefit assessment procedure, i.e. when sufficient data are available.

To ensure that this interim price is an incentive for the pharmaceutical manufacturer to generate evidence as quickly as possible without delaying market entry significantly, it should fulfil two minimum requirements. On the one hand, it should be as far below the manufacturer's target price as possible. On the other hand, the interim price should not be the subject of negotiations but should be as comprehensible as possible.[31] Whether the calculation is based on a comparison of pharmaceuticals within the relevant indication, a model considering research costs, or other criteria[32] will not be discussed conclusively here.

However, it seems important that the interim price for pharmaceuticals with weak evidence provides an incentive for the pharmaceutical company to conduct studies, collect data, and share and reduce the risk of the insured and the solidarity community. In contrast to the proposal[33] of an interim price for regularly approved pharmaceuticals, which is also worth mentioning, it could be discussed not to retroactively replace the interim price for pharmaceuticals that have come onto the market through accelerated approval by the reimbursement price. The discussion is important because of the restitution problems that would otherwise arise for the statutory health insurance system.[34]

However, a maximum period should apply for retroactive reimbursement of the interim price for pharmaceuticals with weak evidence, for example 24 months, so that provisions in the statutory health insurance system are manageable and the pharmaceutical manufacturer is nevertheless encouraged to furnish proof of benefit within this period. In addition, the price would always follow the currently available evidence.[35]

3. Introduction of a success price for single-dose therapies.

An interim price could also be agreed for ATMPs whose single administration is associated with a hope of subsequent cure until the actual promise of success has been proven. The reimbursement price procedure for Zynteglo (betibeglogene autotemcel), which belongs to the group of ATMPs and orphan drugs and was launched on the market by accelerated approval procedure, is a good example for determining the interim price for single-dose therapies.

After the GKV-SV and the manufacturer could not reach an agreement in the reimbursement negotiations, the arbitration board set a reimbursement price that would apply provided that 100% of the efficacy of Zynteglo was proven. This success price accounted for the saved costs for long-term therapy as well as other factors. As long as this success could not be proven by the manufacturer, an interim price applied which was based on the efficacy proven from studies up to the time of the arbitration proceedings (in this case 80%).

In addition to this example, the interim price for single-dose therapies did not apply retroactively but was to be paid as a one-time payment at the point of proof of success by the respective health insurance. Thus, the reimbursement price is prospectively directed into the future and can be adjusted upward or downward for future cases, depending on the evidence, and there should be no repayments to the manufacturer or the health insurance.[36] This model is a good starting point for the design of an innovative reimbursement pathway for single-dose therapies. For a general transferability, further clarifications in detail are required.[37]

4. Manufacturer discounts for combination therapies[38]

New high-priced pharmaceuticals, especially in oncological indications but also for the treatment of rare diseases, are increasingly being approved for combined use. In these cases, the particular challenge is that there are several types of combination therapies that need to be differentiated. Different regulatory requirements apply in each case for the use of mono therapies without corresponding combination approval or approved combinations from the same or different manufacturers. The uniform, cross-indication reimbursement amount is based on a single active ingredient. Single-agent or continuous therapies with only one pharmaceutical should thus be assessed differently than their use in combinations. To date, the reimbursement amount for simultaneous or sequential combinations can neither be agreed upon by the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) and the pharmaceutical company in the reimbursement amount negotiations, nor set by the AMNOG Arbitration Board. It requires a corresponding legal mandate for negotiation. It is important here that, depending on the combination, the corresponding additional benefit becomes apparent to patients considering the side effects, and pricing of all individual pharmaceuticals in the combination is not added up, but based on the additional benefit.

At least for the containment of the extremely increasing costs for combination therapies, a simple control can be achieved quickly by creating a special „combination manufacturer's discount". This should be applied additionally whenever pharmaceuticals are used in combinations. However, such combination therapies would then also have to be identifiable without doubt in the accounting data of statutory health insurances.

5. Performance-based contracts as a solution?

Voices are becoming louder that see pay-for-performance (P4P) or risk-share contracts as a solution for financing therapies for which no adequate price can be expected from the AMNOG process based on the proven additional benefit due to evidence gaps or therapy durations. These performance-based contracts are complex contractual arrangements that must be tailored to the respective framework conditions of pharmacotherapy. Moreover, a clear definition and measurable criteria for therapeutic success or failure are required. Particularly important here is the availability of corresponding data, which must be processed in compliance with data protection regulations. In theory,

these contracts offer payers the possibility of sharing the risk of therapy failure with the manufacturer. Due to the complexity, the data problems, and the lack of compulsory contracting, however, one should not expect effective contracts on a broad scale. Finally, even an optimally designed performance-based contract cannot reflect the exorbitant prices that are currently being charged and are rarely in relation to the evidence-based benefits of the respective pharmaceutical.

Most importantly, patients do not benefit from these contracts. They, as well as physicians, will continue to be deprived of the additional therapeutic benefit and the effort to obtain further data on the efficacy and safety of some therapies, unless AMNOG is adapted.

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[33] Richard et al. ibid, which would also solve the problem of setting anchor prices

[34] DAK AMNOG-Report 2022, chapter 1.2.3, p. 14.

[35] BKK-Dachverband, Ansätze für eine patientenorientierte und wirtschaftliche Versorgung 2022 (Federal Association of Company Health Insurance Funds (BKK-Bundesverband), Approaches for patient-oriented and economical care) (BKK-DV 2022), p. 2.

[36] Cf. on the total reimbursement amount applicable prospectively: BKK-DV (Federal Association of Company Health Insurance Funds), pp. 4-5; on the Zynteglo case of Bluebird bio: DAK AMNOG-Report 2022, chapter 1.2.3, p. 16.

[37] Wasem J, Hüer T, Abels C. AK 2021, chapter 2.2, p 25-26.

[38] Also see: Parow et al. DAK AMNOG-Report 2022, chapter 4.3, p. 99-106; BKK-DV 2022, p. 5.

AMNOG 2.0 – a comment from the industry's perspective

Han Steutel | President of the Association of Research-Based Pharmaceutical Companies in Germany (vfa)

With the AMNOG, a well-balanced system was successfully implemented that ensures high-quality medical care and positive research incentives, as well as rapid availability of pharmaceuticals. By saving billions of Euros, the AMNOG has contributed to ensure that the percentage of SHI spending accounted for by pharmaceuticals has remained stable. The AMNOG should be strengthened to make Germany attractive in global competition as a pharmaceutical location with technological leadership. Any further additional statutory price regulation measures are neither necessary nor effective. Instead, the AMNOG process could be optimised to enhance the framework conditions for innovation.

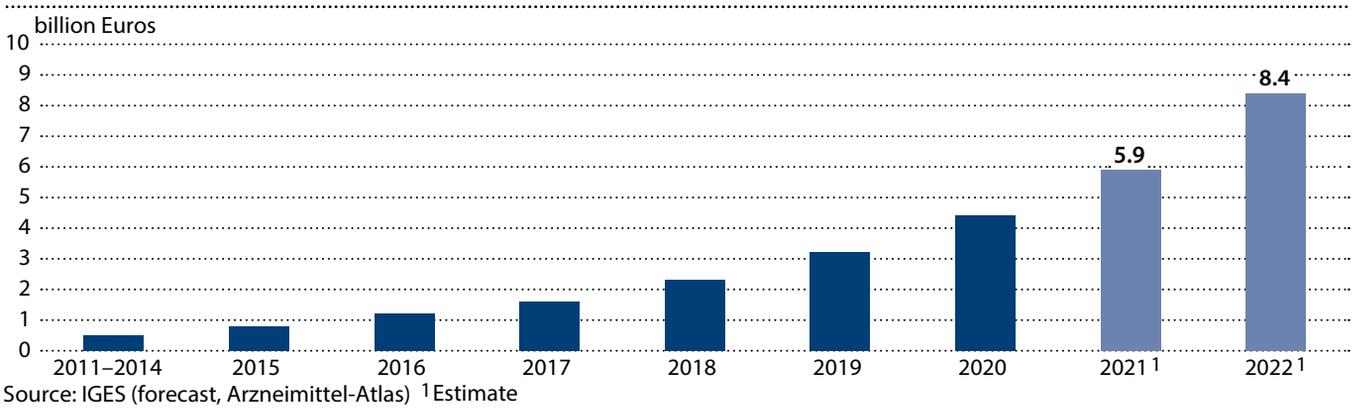
The German Pharmaceutical Market Reorganisation Act (AMNOG), which came into force 11 years ago, is now an integral part of the pharmaceutical regulation in Germany. It has been legally incorporated with the aim of ensuring that the statutory health insurance system pays only as much for a pharmaceutical as is feasible based on its identified additional benefit as compared to standard therapy. This has laid down the framework for fair, value-based pricing.

After initial problems, the AMNOG has become established in recent years. Germany has thus successfully implemented a well-balanced system of benefit assessment with subsequent negotiations. Overall, it ensures high-quality medical care while still setting positive incentives for the research and development of innovative pharmaceuticals. At the same time, it considers the interest of payers in keeping expenditures for pharmaceuticals stable and innovations affordable.

The AMNOG now makes a significant contribution to stabilising pharmaceutical expenditures. Savings from negotiated reimbursement amounts are expected to reach 8.4 billion Euros in 2022 (figure 1). Over the past ten years, the share of pharmaceutical expenditures in SHI expenditures has always been around 16 percent. It is also remarkable that, in most cases, negotiated solutions were found that were appropriate for individual cases, so that the number of market withdrawals has remained low to date. In this respect, the AMNOG ensures a high-quality supply of pharmaceuticals in Germany.

Against this background, it is even more surprising that extensive legal price regulation measures are once again being discussed, such as additional manufacturer discounts or interventions in the AMNOG regulations themselves. These measures massively jeopardise the pharmaceutical loca-

Estimated savings through AMNOG reimbursement amounts



Source: IGES (forecast, Arzneimittel-Atlas) 1 Estimate

Figure 1: In recent years, AMNOG has generated increasing savings. In the previous year, the figure was 5.9 billion Euros, and in the current year it is estimated at 8.4 billion Euros.

tion and, as has already been observed in the past, are a devastating signal to the international investor scene. The German pharmaceutical industry has attracted worldwide attention due to its technological leadership, for example in the mRNA approach, and has positioned itself at the forefront of global competition. Politicians should be aware that countries like the USA, France and China are currently placing massive emphasis on the pharmaceutical industry – a move that is understandable from an economic point of view, as the research industry is one of the most important private investors in research and development. This does not only enable top-quality medical care, but also generates strong exports, well-paid jobs, industrial infrastructure, and ultimately high tax revenues for the state.

It is incomprehensible that in Germany the structural financing problems of the SHI system shall be solved by savings in pharmaceuticals that regularly only account for one-sixth of expenditures. Instead, we need sustainable structural measures on the revenue and expenditure side and not short-sighted, anti-innovative ad hoc measures at the one-sided expense of the research-based pharmaceutical industry.

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In particular, the immediate availability of pharmaceuticals for patients is a great asset of the German healthcare system. The current reimbursement rules provide positive incentives for the rapid market launch and supply of innovative pharmaceuticals. So far, Germany has been a first launch country in Europe for research-based pharmaceutical companies. Once they have received European approval, they can market their new pharmaceuticals directly in Germany because reimbursement is guaranteed here from the beginning. This design of the AMNOG is perceived as a crucial factor at company headquarters. On average, new pharmaceuticals reach the German market just 50 days after EU approval; in France, for example, patients must wait 472 days. Germany also ranks first in Europe in terms of the availability of innovative pharmaceuticals.

Potential reforms should focus on AMNOG's procedural processes to improve the framework conditions for innovations and their evaluation. Planning security for research-based companies, for example, is a key success factor and still needs to be improved in the AMNOG. The G-BA guidelines must be reliable for the conduct of studies, the preparation of dossiers, and for the benefit assessment itself. In this connection, the possibility of consultation with the G-BA is indispensable. Although improvements have been made here in the past, consultations cannot regularly take place in a timely manner. This is not favourable for the extremely fast-moving process of study planning.

There is a further need for optimisation, for example, in determining the appropriate comparator therapy. In recent years, changes were made at short notice in every sixth study because the G-BA identified a change in the state of medical knowledge. In certain cases, clinical studies of the pharmaceutical companies that were designed according to the specifications of the

G-BA consultations were devalued for the benefit assessment, and an additional benefit could no longer be proven. Investments made by the manufacturer in a suitable study situation in reliance on the G-BA advice, even in the case of a special study set up specifically for the German evaluation system, are not rewarded in this way.

When determining the comparator therapy, the manufacturer's studies should therefore be better taken into account if it was generated based on a G-BA consultation. The previously advised comparator therapy for which a clinical study has been initiated should also be considered in the selection of comparator therapies if the G-BA deems changes to the comparator therapy appropriate. This approach may serve as a bridging provision for the manufacturer's study position, in situations where the state of medical knowledge changes gradually.

It is also important that the expertise of the medical scientific societies is taken into account in the G-BA deliberations on benefit assessment. Important progress has been made in this area over the past two years. The cooperation should be expanded even further into an early structured dialogue.

Since the introduction of the AMNOG, the preparation of dossiers has been associated with an enormous amount of work for the pharmaceutical companies. This is because the G-BA set high data standards right from the start, so that the dossiers achieved a level of transparency of study data that had not been achieved before. Most recently, the G-BA has once again significantly extended its requirements. The extension of the obligations led to an extreme increase in the number of evaluations, which caused the average size of the dossier to increase by a factor of 4 to 5 from approx. 750 to approx. 3,500 pages. In individual cases, 20,000 to 40,000 pages are necessary to meet the requirements of the G-BA. Finally, the analyses show that only 23 percent of the evaluations presented therein are con-

sidered by the G-BA or IQWiG in the benefit assessment. This suggests that large parts of the requirements are not recognisably necessary and that an adjustment of the current dossier submissions is called for.

In light of the current discussions, it should also be mentioned that the promotion of research and development of orphan drugs is a common success story. Since the EU Orphan Drug Regulation came into force, 200 orphan drugs have been approved. Some 25 percent of the pharmaceuticals in the AMNOG are orphan drugs. However, the need for new treatment options remains very high, as for about 98 percent of such diseases there are still no approved pharmaceuticals. Germany also ranks first in Europe in terms of the availability of innovative pharmaceuticals. This is no coincidence, because in the benefit assessment in Germany, the need to recognise the special status of orphan drugs was seen by the legislator from the very beginning. The additional benefit is initially considered to be proven, and the G-BA determines how high the added benefit is based on the documents to be submitted. This is a logical implementation of the EU regulation and at the same time ensures smooth and fast access for patients to important pharmaceuticals, often the only treatment option.

It is important to note that the generation of evidence for rare diseases is a major challenge for all stakeholders. Due to the rarity of the disease, clinical studies are often not possible to the same extent as in other disease areas. The methodological requirements of the additional benefit assessment should therefore be adapted to the special therapy situations. So far, they tended to focus on more common diseases with larger studies. It is important to maintain a balance between the goal of rapid patient access to urgently needed therapies on the one hand, and the formulation of meaningful assessment benchmarks and, if necessary, the acceptance of a higher degree of data uncertainty due to the special characteristics of orphan drugs and the rarity of the diseases on the other. In addition, innovative reimbursement models (e.g. pay-for-performance approaches) can be suitable in individual cases to make important therapies quickly available to patients and at the same time ensure the economic stability of the health insurers.

Taking more account of healthcare data presents new opportunities for benefit assessment. For example, the first procedures for post-market data collection were recently initiated. For the first time, healthcare data will be systematically collected for the purpose of benefit assessment. Initial experience is still disillusioning. On the one hand, part of the current methodological requirements is too strict and impractical. At the same time, the G-BA's criteria for initiating the procedure are unclear and can hardly be anticipated. This lack of planning certainty can predominantly be counteracted by early and binding consultations with the Federal Joint Committee.

To make the best possible use of healthcare data, the acceptance of real-world evidence should be improved. The potential of healthcare data became especially apparent in the last two years of the COVID-19 pandemic, as such data and existing structures enable rapid analyses (e.g. in Israel). One success factor from the perspective of the research companies would be equal access to this data.

We should not allow AMNOG to become unbalanced, but all stakeholders should further develop it with a sense of proportion. Above all, it is necessary to strengthen the innovative strength and the supply orientation and to further improve the processes.

Registries for rare diseases

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

The development of pharmaceuticals for rare diseases, especially for very rare and unknown diseases, is a major challenge. Research-oriented registries with a systematic and full monitoring of the daily treatment of patients with rare diseases could contribute to improving the efficiency of pharmaceutical development at several levels: as a preparation for study planning, as external control and after approval to address remaining uncertainties. It remains a case-by-case decision for which purpose a certain registry is suitable. In addition to the nature of the diseases and the quality of data collection, the depth of detail regarding basic information and the course of the disease is also essential. Especially for very rare diseases with complex treatments or pharmacodynamic endpoints in the pivotal study, it is recommended to plan a registry at an early stage – and in consultation with patients, developers, regulators, and HTA organisations.

Internationally, the development of pharmaceuticals for rare diseases is supported because such developments face unique challenges.[1,2] Besides rarity, the greater hurdle to the successful development of a pharmaceutical is probably the lack of understanding of the disease itself. Once a pharmaceutical is approved, other pharmaceuticals for the same underlying disease often follow.[3] A common feature of many rare diseases is that clinical events occur late or infrequently in the course of the disease. The geographic distribution of the small number of patients represents another challenge for research. The population may be further fragmented if the disease course is significantly different in the subgroups (e.g. children of different age groups) that separate clinical studies must be set up for different subgroups.

The same applies to the approval of orphan drugs as to pharmaceuticals for common diseases.[4] The majority of orphan approvals in the EU is based on the results of randomised controlled studies.[5] However, study designs may also be accepted, such as single-arm studies with external control where appropriate, or intra individual controlled studies. Any deviation from the gold standard usually requires a good knowledge of the pathophysiology and mechanism of action of the requested compound and may be justified by the rarity of the disease or poor prognosis.[6] In case of orphan drugs, greater uncertainty at the time of approval must be accepted; rare side effects in particular simply cannot be determined in development programs with only few patients.

The great unmet medical need for a large number of diseases for which there is still no treatment option makes it necessary to increase efficiency of pharmaceutical development. Research-oriented registries with a systematic and complete monitoring of the daily treatment of patients with rare diseases could contribute at several levels: as

a preparation for study planning, as external control and after approval to address remaining uncertainties.

The spectrum of registries with health data is very broad and ranges from purely epidemiological to clinical registries.[7] Basically to mention are disease or exposure registries, whereby disease registries also allow statements on the natural course of disease, whereas exposure registries only collect information on selected treatments (e.g. stem cell transplant registries, product registries) or specific conditions (pregnancy). The depth of detail regarding basic information and disease progression of selectively included patients may differ considerably, so that it must always remain a case-by-case decision whether registries are suitable for answering a particular research question.

In general, registries should be modularly expandable, so that newly gained knowledge can be taken account of. Moreover, linking different data sources with disease registries (tissue bank, molecular characterisation) could significantly improve the understanding of the respective disease. However, the quality requirements for a registry suitable for knowledge gain are remarkably high, especially the comparison of treatment alternatives with respect to efficacy and safety is subject to a multitude of methodological uncertainties.[8,9]

Registries for the preparation of efficient clinical studies

From a regulatory perspective, information on the natural history of disease can be used to define operationalisable endpoints and determine appropriate data collection dates. Patients with rare diseases or their families are very engaged and should definitely be involved in the selection or prioritisation of endpoints so that events relevant to everyday life are represented in registries or studies.[10] Building on experience from registries, case numbers or necessary study durations can also be better planned.[11] Com-

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mon prescription patterns may promote the design of combination treatment studies when untreated patients represent a minority of the patient population. Critical concomitant medications could be identified in advance and prepared or prioritised with interaction studies, if necessary.

As in clinical studies, longitudinal registries can capture the patients' medical history and determine relevant factors that influence the disease progression (if applicable). Knowledge about the course of the disease in separate groups can either define an appropriate study population or serve as a basis for extrapolation of results. The effects of specific inclusion and exclusion criteria on the representativeness of a (planned) patient population can also be tested.

Pre-approval experience from the treatment of a specific disease can be systematically incorporated into the planning of clinical studies, also regarding expected treatment effects in everyday care. This may have to be limited to so-called hard endpoints, since in everyday care many endpoints for determining the efficacy quantifying treatment response, e.g., tumour volume reduction, muscle function test etc., are often not collected or not sufficiently valid due to the lack of standardisation regarding the methodology of data collection.

In addition to mortality and morbidity endpoints, intermediate endpoints, e.g. pharmacodynamic effects, are sometimes used for rare diseases if clinical endpoints are not collected in a sufficiently robust manner e.g. due to low event rates coupled with the rarity of the disease in time-limited studies. Registries can also help to shed light on the surrogate nature of such endpoints.

If the characteristics of a disease allow it, patients can also be recruited directly from a registry for a clinical study, and the data collected can also be used in a study analogous to a run-in phase. However, not all prevalent patients are always suitable for a treatment approach to be evaluated, or all questions can be addressed with an intra individual controlled study design.

Registries as external controls

External controls are accepted for regulatory purposes only in well-justified exceptional cases.[12] The possibility is usually limited to severe diseases that are considered deterministic and is reserved for substances that have already shown particularly promising (and biologically plausible) treatment effects. This approach requires high transparency and stability regarding diagnostic and prognostic criteria or the definition of preferred hard endpoints. If no standard of care can be defined for the study population, but therapeutic alternatives are still available, external controls – usually actively controlled studies with investigators' best choice – are preferred. High-quality data collection and valid statistical methodology are also required when adjusting for known prognostic factors.

Post-approval registries

If a favourable risk-benefit ratio is assumed for a rare disease, but the evidence presented is judged to be incomplete, further data collection from registries may be requested or recommended.[13] Compared with conventional pharmaceuticals, orphan drugs are frequently represented in the special forms of approval, which are generally associated with certain conditions. In general, the specific question regarding the benefit-risk ratio determines which design is chosen for data collection after approval.[14] Generally, interventional studies and/or non-interventional studies, also in the form of a registry, are possible. Open questions at the time of approval often refer to safety aspects but may also concern the (durability of the) efficacy of a substance.

The effort for the establishment of a registry or even the planning of an efficient registry study to address any existing uncertainty should not be underestimated, as many aspects from data protection and quality assurance to basic responsibilities and deadlines must be considered. At present, the inherently valuable time between publication of study results and commercialisation is lost in planning data collections, whereas with an existing infrastructure, new data could be collected continuously and used directly to improve medical care.

Outlook

Patients with rare and usually complex diseases are often treated at university-affiliated specialty outpatient clinics, where good conditions prevail for innovative pharmaceuticals.[15] The diseases, which are often still misunderstood, are studied in detail by experts, even before treatment standards or guidelines exist. The establishment of the European Reference Networks that pools expertise for specific therapeutic areas, also involves the implementation of data platforms to provide long-term access to thoroughly collected data.[11]

In future, especially with the currently known challenges between approval and HTA (small, single-arm studies, external controls, pharmacodynamic endpoints), it is advisable to start interacting with regulators and HTA institutions at an early stage within the scope of parallel consultations.[16] Prospectively planned data collection from everyday care can also be conducted concurrently with studies and can thus support subsequent regulatory decisions meaningfully.[17] The potential of high-quality and standardised data collection for knowledge gain and efficient development of orphan drugs is enormous.

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Principles and methods of healthcare-related data collection

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Data collection within the scope of post-marketing data collection can be conducted according to the same principles as a common clinical study. This also means that established scientific standards are adhered to with regard to the design of the study. In principle, data collection without the intention of a comparison is meaningless for the benefit assessment. Data collection can be done on a study-by-study basis or on the basis of routine data or registries. Non randomised studies require special efforts to reduce the inherent potential for bias. This applies primarily to the identification of relevant confounders, their complete collection, as well as statistical methods to control their influence on the study outcome as much as possible. Moreover, data must be of sufficient quality. Healthcare-related data collection should not result in a „light" study. Healthcare-related data collection can be a useful addition to strictly controlled clinical studies, which e.g. are often characterised by very narrowly defined inclusion and exclusion criteria. For incomprehensible reasons, the legislator has excluded randomised studies for post-marketing data collection. This results in an intrinsically increased uncertainty in the interpretation of study results as well as an increased effort for the conduct of the study, i.e. in a „lose-lose situation".

Introduction

With the Act for Greater Safety in the Supply of Medicines (GSAV)[1] dated 9 August 2019, the legislator granted the Federal Joint Committee (G-BA) the right to request pharmaceutical companies to conduct so-called post-marketing data collection for certain pharmaceuticals (and for which only a limited evidence base is available at the time of market entry) in order to improve the data basis for the benefit assessment. However, this basically sensible regulation is limited by the fact that such data collection may not take place within the framework of a randomised controlled trial (RCT). The legislator justified this by stating that the application should be accompanying the application,[2] but left open why this would argue against an RCT.

After the law came into force, the G-BA commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to develop concepts for the generation of healthcare-related data and their evaluation for the purpose of the benefit assessment of pharmaceuticals in accordance with Section 35a of the German Social Code, Book V (SGB V). The related report A19-43 was completed in January 2020 and submitted to the G-BA.[3] The report first explains basic principles from which further methodological considerations are derived. Although the report primarily addresses non randomised studies in accordance with the legal basis for post-marketing data collection, RCTs are also addressed as an option for healthcare-related data collection.

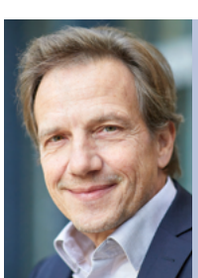
Comparison

It cannot be repeated often enough that a comparison is needed to determine the actual effects of a (medical) intervention. It is irrelevant whether one speaks of efficacy, (additional) benefit, side effects or harm in this context. Stephen Senn put it this way: „The effect of any treatment for

a given patient is the difference between what happened to the patient as a result of giving him the treatment and what would have happened had treatment been denied."[4]

Since „would have happened" is not experiential, this means that in addition to a group of people receiving a particular intervention, a control group receiving a different intervention or no intervention must be observed. Thus, there is a need to compare groups with respect to outcomes over time.[5] Special situations in which different treatment phases for the same person are compared rather than different groups of persons are not considered.

In this respect, single-arm studies, such as those listed as an alleged alternative to an RCT in the explanatory memorandum to the GSAV – which refers to „application observations" – are obsolete, at least as long as a comparison with an expectation is not made. The famous parachute situation is a good example: Falling from high altitudes means certain death – this is the explicit expectation. But if a person uses a parachute when jumping out of an air plane at a very high altitude and thus glides safely to earth, the benefit of the parachute is proven. However, such parachute situations or even approximations of them are very rare in medicine.[6] But when a new parachute enters the market, it must of course compete against the old one in an appropriate study and not only against the expectation.[7]



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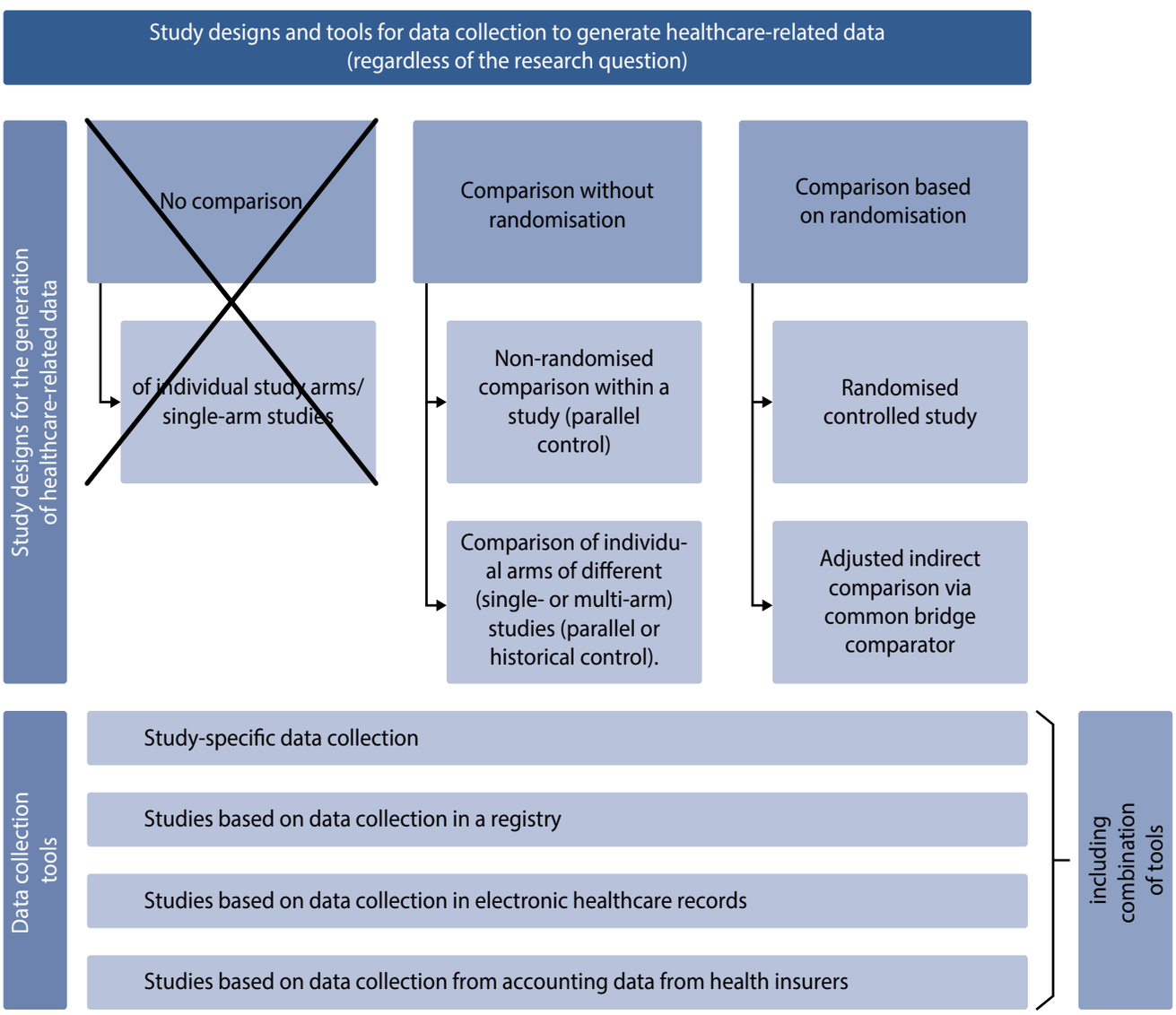
Methods and instruments

The first step is to consider potential designs for a comparative study. A general distinction can be made between designs with and without a randomised group allocation and further between direct comparative studies and indirect comparisons (figure 1). Studies without randomisation also include those in which individual arms of different studies are compared with each other; the latter are either conducted in parallel (more or less) over time, or a so-called historical comparison is made. If only studies comparing A vs B and B vs C are available, but the research question refers to the comparison A vs C, then this comparison can also be made „indirectly" via the bridge comparator B without requiring a new study.[8] A prerequisite for this, however, is that the two studies (A vs B or B vs C) are sufficiently similar.

Next, the data collection instrument must be selected. Should data be collected on a study-by-study basis, on the basis of a registry, using electronic healthcare records or billing data, or using a combination of these tools? In the A19-43 report, it is very clearly formulated and justified that currently – apart from study-specific data collection –

Study designs and tools for data collection to generate healthcare-related data



Source: Adapted from Report A19-43 [3]

Figure 1: In addition to study-specific data collection, data collection in the context of a registry is currently the only viable option for post-market data collection.

the only usable option for a post-market data collection is data collection within the framework of a registry, i.e. a registry-based study.[3] It is important to distinguish between a registry as infrastructure and a registry-based study.[9]

The starting point and thus crucial for the benefit assessment is the clearest possible definition of a PICO scheme, i.e. the definition of the population to be evaluated (in the sense of an indication), the test and comparator intervention, and the relevant outcomes. Thus, this information must be available in a registry in order to be usable for post-market data collection. This applies in particular to patient-reported outcomes (PRO) on symptoms and health-related quality of life. The opposite approach – i.e. adapting the question to the available data – is not an option.

In addition, data must be of sufficient quality. Healthcare-related data collection should not result in a „light" study. This applies in particular to post-market data collection according to the GSAV, since the results of the corresponding studies are relevant for the assessment of the additional benefit by the G-BA (Section 7 (1) AM-NutzenV).[10] As a consequence, a registry must e.g. maintain a set of measures to ensure the accuracy of the data collected. This includes, among other things, a source data check, the conduct of audits and IT-supported checks (cross-reference checks). Detailed information on pharmacotherapy must also be available in order to assess its use in compliance with the approval. With regard to endpoints, standard classifications and valid standard survey instruments must be used. Moreover, measures must be taken to enable a fair comparison.[5] A comparison is considered fair, if the baseline conditions for patients are the same in the intervention and control groups, and patients have the same conditions during the course of the study. Only in this way can the differences that have been observed between the intervention and control group be interpreted as caused by the intervention (causal relationship). The usual and at the same time simplest tools to ensure equal baseline and follow-up conditions are randomisation (for structural equality), blinding (for observational equality), and the intention-to-treat (ITT) principle, i.e. that all patients included in the study will also be evaluated, according to the original group allocation.

If no randomisation is or can be used (-> GSAV), structural similarity can only be achieved approximately with the methods currently available, since all these methods are based on assumptions, the main ones of which are not verifiable. Moreover, they are designed to achieve structural equality or structural similarity, retrospectively, in the course of statistical analysis. Moreover, blinding and in non-randomised studies the ITT principle can either not be realised at all or at best to a limited extent. In this case, a non-randomised study should be conducted, including all essential aspects like a randomised one – only without randomisation. This idea is described as „emulation of a target study". [11] At this point, it should be emphasised that maybe for pragmatic reasons, deterministic allocation mechanisms alternative to randomisation, such as allocation alternating by days of the week in the context of the legal regulation on post-market data collection, fail for the same reasons as randomisation.

Confounders play a significant role in statistical methods to achieve structural equality or similarity, respectively. Confounders are those characteristics-typically patient characteristics, but not exclusively-that are associated with both therapy and outcome. For example, because of a person's age, he or she is less likely to receive a more aggressive intervention due to safety considerations (-> association with therapy). At the same time, increasing age increases the probability of death (-> association with outcome). The comparison of a more aggressive intervention with a less

aggressive one would thus be biased if this circumstance were not adequately taken into account.

There are three main approaches:

- Direct adjustment for the relevant confounders using appropriate regression models. The disadvantage of this method is that only a rather narrowly defined number of confounders can be included in the corresponding models. Otherwise, the results are unreliable.
- The propensity score method: The probability that a patient receives therapy A (and not alternative B) is estimated on the basis of the relevant confounders, again using a suitable regression model. In case of a 1:1 randomisation, this probability would be exactly 0.5. A score, i.e. the propensity score (PS), can then be calculated from the parameter estimates based on the model for the individual confounding variables. Finally, the actual statistical analysis for the group comparisons is designed to align the treatment groups with respect to the PS score, mainly by matching, weighting, stratification, or adjustment. More confounders can be included in the PS method than in direct adjustment. Moreover, the evaluation can (and should) be limited to those patients who have a certain probability of being eligible for the respective therapeutic procedures. However, this in turn may be associated with severely limited generalisability.
- The instrument variable (IV) method searches for a characteristic(s) that is associated with therapy but not with outcome (except via association with therapy). In randomisation, there would be a „perfect" association (correlation = 1) for obvious reasons; this is also true for deterministic allocation mechanisms such as the alternating allocation mentioned above. At first, the IV method seems very elegant and attractive – theoretically, it should be possible to take unknown confounding variables into account with its help, similar to randomisation. Unfortunately, it has a crucial practical disadvantage: the assumption of non-association with outcome will usually not be justifiable with sufficient certainty. Moreover, for IVs with only a moderate or even weak association, the population about which conclusions can be drawn will also be severely limited.[12]

Based on the aforementioned advantages and disadvantages, it can be justified that for post-market data collection within the scope of benefit assessment according to the GSAV, the PS method can most likely be applied. For this purpose, three key requirements have to be fulfilled: Positivity, sufficient overlap, and balance. Positivity means that the interventions to be compared represent a realistic treatment option for patients. Thus, there must be no contraindications for any of the interventions to be compared in the respective population. PS scores must overlap sufficiently between the treatment groups. If this is not the case, then a statement can only be made for a very limited population, which is contradictory to the actual goal of a post-market data collection. Finally, it must be ensured that, despite comparable PS scores, there is also sufficient similarity in the individual relevant confounding variables (balancing).

Studies conducted for post-market data collection for the purpose of benefit assessment must also adhere to established scientific standards regarding study design. This means that a study protocol must be prepared that, among other things, specifies the research question (PICO). All relevant confounding variables must be identified systemically in advance and specified in the protocol. Once again, the principle applies that not only those confounding variables that are e.g. routinely collected in the context of a registry may be taken into account, but in fact all

relevant confounding variables. This means that data collection in a registry may have to be extended to include these confounding variables.

The PS model must be described in the study protocol as well as any decision criteria (e.g. the matching algorithm or thresholds for [insufficient] balance). In addition, planned sensitivity analyses must be specified. These are of particular importance for assessing the reliability of the results. In addition to the study protocol, a statistical analysis plan (SAP) must be drawn up. Last but not least, there should be a publication plan that also includes the protocol and the SAP and the study should of course be registered.

Conclusion

Healthcare-related data collection can be a useful complement to more tightly controlled clinical studies, which are often characterised e.g. by very narrowly defined inclusion and exclusion criteria.[13] Against the background of a weak evidence base at the time of approval of certain pharmaceuticals, it was recently implemented in the SGB V as „post-marketing data collection" with a thus a slightly different focus. For incomprehensible reasons, the legislator has excluded randomised studies for post-marketing data collection. This exclusion means an increased effort for the conduct of a post-marketing data collection. Since the post-marketing data collection is intended to generate findings for the purpose of benefit assessment, it must not be of inferior scientific quality compared with the clinical studies that otherwise justify approval.

The exclusion of randomised studies results in an intrinsically increased uncertainty in the interpretation of study results as well as an increased effort for the conduct of the study, thus in a „lose-lose situation". In this context, a methodological-interpretative problem that has not yet really been solved satisfactorily is how to deal with results that show no difference. While the observation of a clear difference from the null effect allows the conclusion with good precision that some difference exists even from a methodologically uncertain study (e.g. so-called dramatic effect[14]), this cannot be true for the reverse case.

Outlook

Current implementation difficulties with the first requests for post-marketing data collection by the G-BA also indicate that the initiation of a study after approval or after market entry is actually too late. It would make more sense for pharmaceutical companies to document the treatment of patients in indication-based registries at a very early stage in the clinical development phase of pharmaceuticals. However, the corresponding legal basis would have to be established at European level.

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Significance of Post-Market Data Collection for the KBV

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With the GSAV, the G-BA was given another tool within the scope of early benefit assessment. In order to improve the evidence especially on orphan drugs, post-market data collection can now be requested. In addition to the generation of evidence, the changes in the SGB V shall also address the high treatment costs. The G-BA can restrict coverage to those physicians in the statutory health insurance system who participate in a post-market data collection. Since post-market data collection is associated with the high administrative costs and the risk of recourse, a distortion in prescribing behaviour cannot be ruled out, especially if an existing treatment alternative is not subject to any restriction. Against the background of the methodological preconditions, post-market data collection will not be sensitive enough to detect small effect differences in the context of benefit assessment. For active ingredients without therapeutic alternatives or ultra-orphans, post-market data collection is not a suitable tool. From the point of view of the KBV, post-market data collection can only be an emergency solution for individual cases.

Introduction

On 16 August 2019, the Act for Greater Safety in the Supply of Medicines (GSAV) came into force. Adjustments were made to Section 35a and Section 130b of the German Social Code, Book V (SGB V) extending the range of tools for the Federal Joint Committee (G-BA) in the context of early benefit assessment.

The G-BA was given the opportunity to request the pharmaceutical company to submit data from a post-market data collection and evaluations for the purpose of the benefit assessment of pharmaceuticals used for the treatment of an orphan condition (orphan drug), pharmaceuticals with a conditional marketing authorisation (CMA) and pharmaceuticals with a marketing authorisation under exceptional circumstances (MAEC).[1]

The focus is on observational studies, case-control studies and registry studies while randomised controlled trials (RCT) are excluded.[2] This created a new assessment situation within the framework of the established AMNOG procedure, which regularly prescribes the consideration of data of an evidence level below the gold standard RCT.

Orphan drugs as the primary target of the new post-market data collection regulations

The focus of post-market data collection is on pharmaceuticals that have been approved on the basis of weak evidence and launched on the German market. In case of orphan drugs, the additional benefit is already considered proven by law (Section 35a (1) sentence 11 SGB V). In contrast to the regular benefit assessments according to Section 35a SGB V, the pharmaceutical company does not have to prove the additional benefit of an orphan drug as compared to an appropriate comparator therapy. On the basis of this legal additional benefit fiction, an additional benefit is thus frequently determined even without proof of a me-

dical improvement. This is then regularly classified as non-quantifiable „because the scientific data basis does not permit this" (Section 5 (8) AM-NutzenV). This „fictitious" additional benefit can become permanent after expiry of the document protection period if the sales threshold of 50 million Euros is not exceeded.

The IQWiG's working paper „Evidence on Orphan Drugs" revealed that establishing a „fictitious" additional benefit when orphan drugs enter the market is misleading in more than half of the cases, as no evidence of an additional benefit is determined in subsequent regular benefit assessments. These findings were based on analyses of orphan drugs that had undergone a benefit assessment under facilitated conditions as well as a regular benefit assessment after exceeding the sales threshold.[3]

Primarily orphan drugs are covered by the new regulations in Section 35a paragraph 3b SGB V on post-market data collection. Pharmaceuticals with a sole CMA or MAEC only play a minor role, as these two types of approval are often associated with an orphan drug status.[4]

Since orphan drugs are pharmaceuticals with a relatively small target population, the G-BA can restrict the authority to prescribe such a pharmaceutical at the expense of the statutory health insurance to those physicians in the statutory health insurance or approved hospitals that participate in the requested post-market data collection. This is

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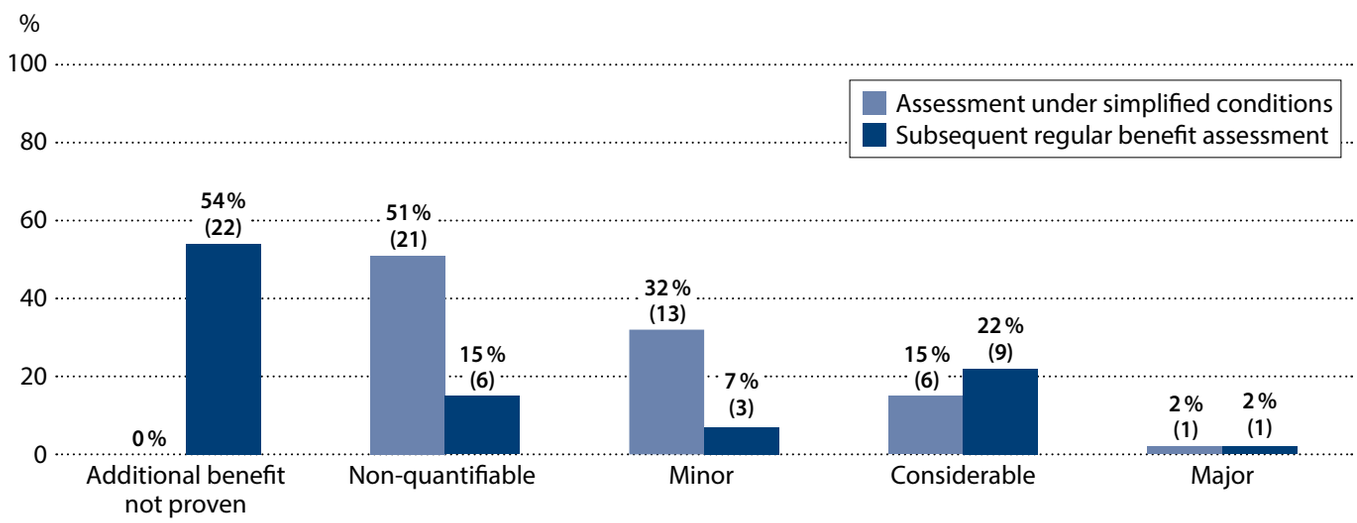
Results of additional benefit assessments of orphan drugs



Source: KBV, Interdisciplinary Platform on Benefit Assessment Spring Meeting 2022; data from IQWiG's working paper "Evidence on Orphan Drugs"

Figure 1: Establishing a „fictitious" additional benefit when orphan drugs enter the market is misleading in more than half of the cases, as no evidence of an additional benefit is determined in subsequent regular benefit assessments.

intended to ensure the collection of complete and validated treatment data of insured persons and prevent only fragmentary data collection (Section 60 (2) of the G-BA Regulation).

Post-market data collection as a tool for evidence generation and cost containment

The GSAV also created a provision in Section 130b SGB V, corresponding to the one in Section 35a, paragraph 3b. If the additional benefit of an orphan drug still cannot be quantified after a post-market data collection has been conducted, the German National Association of Health Insurance Funds (GKV-SV) must agree on a discount on the reimbursement amount negotiated in the initial assessment.

Pharmaceuticals with a CMA or MAEC without orphan drug status would also be subject to a comprehensive re-evaluation. However, these were already evaluated against an ACT in the initial evaluation after they enter the market and would not have been granted an additional benefit on the basis of inconclusive evidence. In these cases, the reimbursement amount should not lead to higher annual treatment costs than ACT.

The legislator specifies the following goals for this amendment: Pharmaceuticals that have been granted approval on the basis of weak evidence, in particular orphan drugs, shall (still) be made available to patients in the statutory health insurance system without delay and, at the same time, a better data basis is to be created for (re)assessing the additional benefit. The aim is to create an incen-

tive to perform post-market data collection while avoiding that the reimbursement amount remains the same although there is no sufficient evidence for an additional benefit.[2] Thus, post-market data collection is to be understood both to create a better evidence base and as a tool for price regulation. Conflicting goals between individual stakeholders cannot be ruled out.

Affection of physicians in the statutory health insurance system

Due to the planned restriction of the authority to provide care, physicians in the statutory health insurance system may be directly affected by a decision to request post-market data collection. So far (as of: April 2022), the G-BA has only passed a resolution to request a post-market data collection for the active ingredient onasemnogen abeparvovec (Zolgensma®),[5] a gene therapy for the treatment of spinal muscular atrophy (SMA). However, physicians in the statutory health insurance system are not directly affected by the restriction of supply authorisation and the associated mandatory participation in the post-market data collection, which was also decided.[6]

Zolgensma® is infused once in an inpatient setting. Due to a decision of the Federal Joint Committee on Quality Assurance Measures for Advanced Therapy Medicinal Products (ATMP) and the associated high demands, this gene therapy can only be administered at specialised treatment centres.[7] The follow-up treatment provided after the inpatient stay is also performed at these centres in most cases.

Unclear risks of recourse

For a future post-market data collection of an active ingredient that can also be used in an outpatient setting, the resolution to restrict the supply authority must clarify how the intended participation in a post-market data collection is to be proven. So far, the law does not provide any information on this.

Proof can be furnished in different levels of intensity. In the opinion of the KBV, written proof of participation in a corresponding indication registry is generally considered appropriate and sufficient. However, the KBV sees the proof of full data collection at the individual patient level critically. Here, a risk of recourse for physicians in the statutory health insurance system cannot be ruled out, e.g. if only individual data sets are not completely available for data evaluation.

Most active ingredients eligible for post-market data collection will be high-priced pharmaceuticals, so that prescribers must be protected against recourses. In the event of high hurdles and procedural risks, negative effects on the implementation of a post-market data collection can be expected.

High administrative effort

The administrative burden associated with a post-market data collection is considered high. Although the legislator specifies that data collection should accompany the application and that there are no restrictions for the prescribing physicians with regard to the provision of medicinal products (e.g. no randomisation or study specifications), it should be noted that the post-market data collection should be carried out „for the purpose of benefit assessment".2 Post-market data collection can thus be distinguished from documentation in the context of routine care and even from a pure observational study.

To demonstrate an additional benefit during benefit assessment according to Section 35a SGB V, an improvement in the influence of accepted patient-relevant endpoints must be shown as compared to the current treatment standard (Section 5 (5) AM-NutzenV). For this purpose,

complex measurement tools must be used, especially for the collection of data on the patients' quality of life or disease symptomatology, respectively. Although data are probably collected by the patients themselves in the majority of cases, intensive training is necessary in advance to instruct them in the correct implementation and use of the tools. Continuous patient motivation is also necessary, as well as the coordination of data provision for the registry.

If a post-market data collection has been decided for an active ingredient for which an alternative treatment is available but whose prescription is not restricted, this could have an influence on prescribing behaviour. Due to the high administrative effort involved in collecting data during post-market data collection, a switch to this alternative therapy cannot be ruled out. Data for the target active ingredient would thus be collected to a lesser extent. This could have a particularly negative impact on the duration and feasibility of data collection.

Contracts and remuneration

Up to now, the remuneration of services related to a post-market data collection is also unclear. „The addressee [...] is the pharmaceutical company, who must either conduct post-market data collection [...] himself or have it conducted by third parties at his own expense".[2] How this will be implemented in concrete terms in the context of statutory healthcare remains to be seen.

Here, both reporting lump sums from the registry as well as the remuneration of individual services directly from the pharmaceutical company to the physicians are possible. In particular, the amount of remuneration remains unclear. Relevant parts of the services to be provided are probably not yet included in the uniform assessment scale (EBM) or the medical fee schedule (GOÄ). The number of services should be based on the actual effort.

In order to participate in a post-market data collection, specific contracts must be concluded between registries, pharmaceutical companies, hospitals and physicians in the statutory healthcare system. Disagreement about the content of the contracts would have a direct impact on healthcare. The key question is who will negotiate and structure these contracts and the remuneration of the services they cover for physicians in the statutory healthcare system. Whether such a contract can also include mandatory regulations on the provision of comparative data is also still unclear.

Difficult to implement without an existing indication registry

For the implementation of a post-market data collection, an existing indication-specific registry is desirable, which already collects patient-relevant endpoints and covers a substantial proportion of patients in the respective target population. The further a registry deviates from the high requirements of IQWiG, the more difficult a potential implementation of a post-market data collection will be. A usable dataset that can be used as a historical comparison is of high value.

It is unrealistic to completely rebuild an indication registry in a time frame that is reasonable for post-market data collection. Without an existing registry, by the time a post-market data collection is successfully completed, document protection may already be nearly expired.

Product registries are not eligible for post-market data collection, as comparative data on treatment alternatives in the indication are required. In fact, collection of control data must be cross-financed by the pharmaceutical company. Alternatively, an established registry has a usable retrospective database. It is also conceivable that comparative data are collected via research questions of the registry

that have to be answered in parallel. Ultimately, it must be clarified to what extent the company will have access to third-party data or who will compile these data sets, respectively. Ideally, two or more active ingredients would be subjected to post-market data collection and the data collected in an indication registry. Each active ingredient then serves both as a research question and comparative treatment (ACT).

Difficult to implement in the absence of alternative therapies

The orphan drug status is granted by the EMA in particular to pharmaceuticals for the treatment of a rare life-threatening or severe chronic disease with high unmet medical need.[8] According to the decision criteria of the regulatory authority, there is a lack of treatment alternatives in the indication and only a few patients suffer from such a disease.

However, the EMA's procedural practice has shown that the orphan drug status is also granted if current active ingredients have already been approved and treatment alternatives exist. A large number of new active ingredients are now available for the treatment of multiple myeloma or chronic lymphocytic leukaemia. However, the high medical need can also extend to partial areas of the indication.

The feasibility of a post-market data collection is questionable, especially in the absence of treatment alternatives in the indication. It seems unrealistic that patients with a serious or even life-threatening disease voluntarily forego treatment with a promising new active ingredient simply because the evidence of benefits has not been provided based on the patient-relevant endpoints that have been considered by the G-BA.

The higher the medical need in the indication, the more difficult it becomes to collect data on an earlier treatment standard after the general market availability of an active ingredient. In such situations, retrospective data prior to approval of the new active ingredient could be used. However, this requires an established registry that has a usable data set.

Difficult to implement with ultra-orphans

For ultra-orphans or indications with small heterogeneous patient collectives, post-market data collection is – in the opinion of the KBV – difficult to implement in practice, as the number of patients required for a methodologically adequate confounder adjustment cannot be recruited within a reasonable period of time.

In case of significant treatment effects that cannot be explained by possible bias alone, it is possible to dispense with a confounder adjustment. However, in such a situation, the need for post-market data collection may be fundamentally questioned and additional benefit may be inferred based on either a known deterministic trend or available historical data.

It should also be discussed whether, in case of ultra-orphans, it would not be more feasible to organise data collection at European level. However, a mandatory full and not only fragmentary data collection can only be implemented within the German legal framework, since the authority to provide care for physicians can be restricted here. It is also questionable whether the standard of care in other European countries is comparable to that in Germany and whether suitable European registries exist that can answer a question that is only relevant to the German statutory healthcare context. Therefore, data collection in German-speaking countries (DACH region) seems more realistic.

Feasibility and proportionality

In the past, the EMA has increasingly pursued the principle of adaptive marketing authorisations. An active ingredient is initially conditionally approved for a limited patient population with a high unmet medical need based on initially available clinical data. A phase III RCT in an earlier line of treatment is ongoing and the compound will position itself in this new therapeutic setting in the foreseeable future.[9] Thus, the question arises as to how relevant data from a post-market data collection that address the initially „adaptively" approved indication are for healthcare. This question must be asked all the more critically if post-market data collection is expected to be terminated after the availability of higher-quality evidence in this earlier line of treatment.

In methodologically adequate comparative studies without randomisation, the IQWiG assumes that statements on the benefit or harm of an intervention are only possible if the confidence interval for an observed effect for endpoints in the category of serious/severe subsequent complications exceeds a threshold of 2-5 for the relative risk.[10] Given these methodological preconditions, post-market data collection is not sensitive enough to detect small effect differences on patient-relevant outcomes within the scope of a benefit assessment. The expected gain in knowledge through post-market data collection for a comparison of two active ingredients of a pharmaceutical class (parallel developments) is therefore unclear.

Long procedures

In addition, the duration of the procedure is expected to be long and significantly longer than the time limits previously imposed in the AMNOG procedure. For post-market data collection for Zolgensma®, data for the achievable motor development up to month 36 have been requested. In order to estimate the sustainability of the achieved development, data up to month 60 are required. Evaluations shall be submitted by 1 July 2027 for a new benefit assessment.[11] For Zolgensma®, the sales threshold of 50 million Euros was already exceeded during the ongoing benefit assessment. The procedure under simplified conditions was initially suspended and a regular benefit assessment was subsequently conducted. No additional benefit could be derived for any of the subpopulations defined by the G-BA.[12] A discontinuation of the post-market data collection was not planned, as the identified evidence gaps still exist and the orphan drug status also endures.

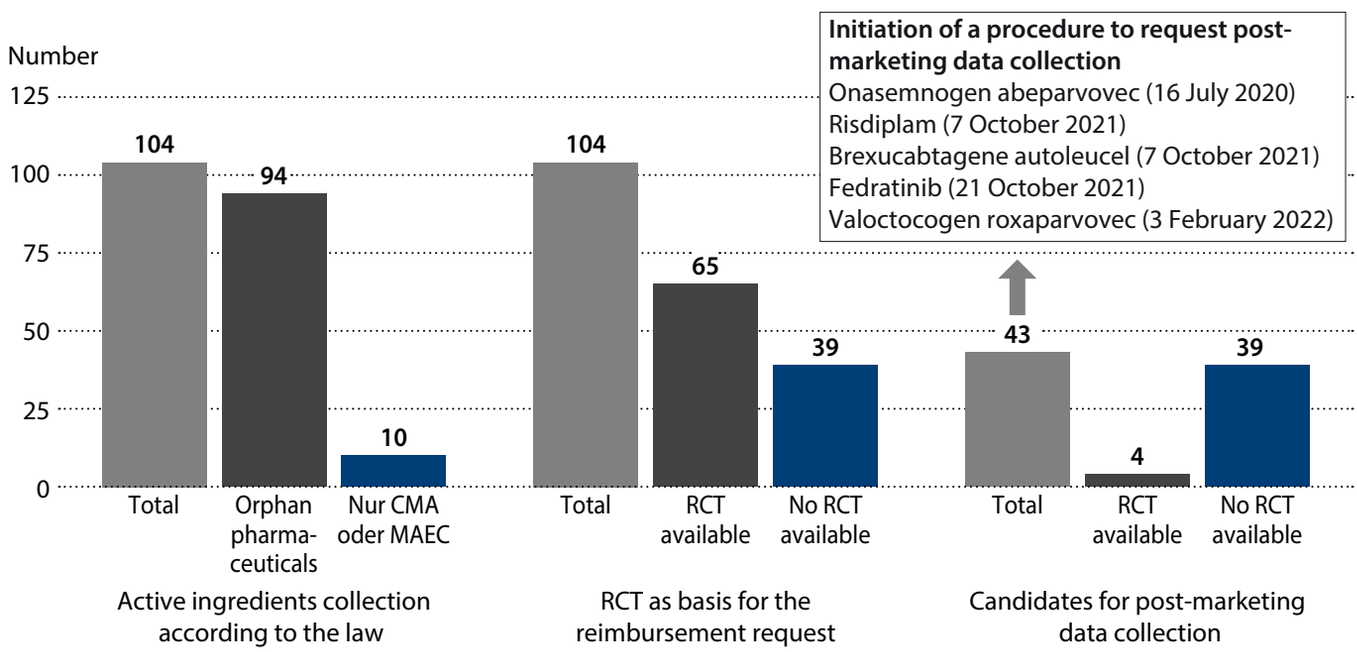
Monitoring of approval procedures (from January 2020 to March 2022).

The G-BA has reviewed all approval procedures that have been initiated since January 2020 regarding the suitability of the respective active ingredients for a post-market data collection, in consideration of the legal requirements. In principle, an approval procedure without data from an RCT is assumed to lack meaningful evidence for the benefit assessment. Data from publicly available sources were used for the initial screening.

A total of 104 compounds were considered eligible for post-market data collection, of which 94 were orphan drugs. For 10 compounds, only a CMA or MAEC was available. For 65 of these 104 compounds, an RCT formed the basis for the respective marketing authorisation application. All 39 active ingredients with regulatory evidence without RCT were generally considered potential candidates for post-market data collection. In addition, there were four further candidates with RCTs, but in therapy situations that were considered unsuitable in relation to the expected context of use (figure 2).

The results of this screening confirm the IQWiG's wor-

Approval procedures EMA from January 2020 to March 2022



Source: KBV, Interdisciplinary Platform on Benefit Assessment Spring Meeting 2022; status of consultations; April 2022

Figure 2: All 39 active ingredients with regulatory evidence without RCT were generally considered candidates for post-market data collection. In addition, there were four additional candidates with RCT in inappropriate therapy situations.

king paper „Evidence on Orphan Drugs" and even extend its key statement. For a relevant proportion of orphan drugs in the approval process, the evidence base is considered insufficient for a future benefit assessment. For only five active substances has it been decided to initiate a procedure to request post-market data collection and IQWiG has been commissioned to prepare a concept. Post-market data collection for the active ingredient Zolgensma® was started on 1 February 2022.

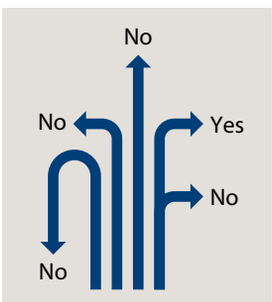
A post-market data collection as an emergency solution in individual cases

Closing existing evidence gaps after approval with a post-market data collection is generally associated with high hurdles. In most cases, once a new active ingredient is available on the market, the required evidence can probably no longer be provided subsequently to furnish proof for an additional benefit or to quantify the extent of the additional benefit, taking into account the still existing additional benefit fiction.

The legislator assumed that approximately nine to ten

Post-marketing data collection is an emergency solution for individual cases

- Complex procedure with high administrative effort and risk of recourse for physicians in the statutory health insurance system
- Creation of treatment-relevant evidence questionable in many case
- Difficult to implement in the absence of treatment alternative, for ultra-orphans, without existing indication registry
- Only minor savings potential to be expected in relation to the overall process (AMNOG)



Source: KBV, Interdisciplinary Platform on Benefit Assessment Spring Meeting 2022

Figure 3: Due to the long duration of the procedure and the relatively small number of suitable candidates, the savings potential through post-market data collection in relation to the overall AMNOG procedure is to be considered low.

post-market data collection would be requested by the G-BA every year.[2] However, initial practical experience shows that significantly fewer procedures can be expected, as the feasibility of post-market data collection can be questioned in advance in many cases. Overall, this is a complex procedure with high administrative and personnel costs, both for the G-BA and during concept development and acceptance of the study protocol and statistical analysis plan by the IQWiG. Since the data generated by the company have to be considered, a high level of evaluation is necessary to avoid wrong decisions.

Due to the long duration of the procedure and the relatively small number of suitable candidates, the savings potential through post-market data collection is to be assessed as low in relation to the AMNOG overall procedure. Against the background of the rapid innovation cycles in the pharmaceutical industry, creation of treatment-relevant evidence is also questionable in many cases. Post-market data collection is ultimately only an emergency solution in individual cases.

Outlook

From the point of view of the KBV, RCTs remain the gold standard in benefit assessment. In the past, numerous evaluation procedures have demonstrated the feasibility of RCTs, even for orphan drugs. Examples include the active ingredients nusinersen (Spinraza®) and blinatumomab (Blincyto®). Both were granted a significant additional benefit in the benefit assessment on the basis of small, well-planned RCTs in paediatric indications.[13,14]

Advantages of an RCT in orphan indications can include that the number of patients requested can be lower than in a post-market data collection, as no confounder adjustment is required. Moreover, an RCT may be the more appropriate tool if low to moderate effect sizes are expected. Conducting an RCT as part of the approval programme may appear to be less expensive and simpler than an expensive post-market data collection after the approval with an uncertain outcome.

If RCTs cannot be conducted, it is advisable to collect data on the natural history of the disease or on the current

treatment standard in parallel conducting the pivotal trial with the new active ingredient to be able to present an indirect comparison already in the benefit assessment. For the active ingredient atidarsagen autotemcel (Libmeldy®) for the treatment of metachromatic leukodystrophy, a rare metabolic disease, a significant additional benefit could be derived on the basis of an indirect comparison with historical sibling data.[15]

In order to address the previously poor evidence base for a relevant proportion of approved orphan drugs, taking into account the costs incurred, further development of the legal basis in Section 35a SGB V should be considered. Especially as the new regulations on post-market data collection created with the GSAV can only insufficiently address this problem.

In individual cases, the G-BA should e.g. be authorised to decide on an RCT as a sanctioned time limit requirement within the framework of the benefit assessment of orphan drugs. If effective therapy alternatives are available, an RCT can also be ethically justifiable after the approval of an active ingredient. Fedratinib (Inrebic®) for the treatment of myelofibrosis was approved based on an RCT versus best-supportive-care. However, since the initiation of the study, the standard of care has changed. Ruxolitinib (Jakavi®), also a JAK inhibitor, is now available as a treatment alternative for patients in this indication.[16] An RCT investigating ruxolitinib versus fedratinib could answer open questions regarding the tolerability or even better efficacy better than a post-market data collection.

In addition, from the point of view of the KBV, it would make sense to maintain the additional benefit fiction only for ultra-orphans. Based on the current orphan drug regulation, diseases are considered rare in the EU, if no more than 5 in 10,000 inhabitants suffer from them. In Germany alone, this could theoretically include up to 40,000 patients for every orphan drug. However, in case of a large patient population, an RCT could also be conducted, especially within the framework of international study programmes. The orphan drug status in the indications chronic lymphocytic leukaemia and multiple myeloma has been subject of frequent critical discussions in the past. As a definition for an ultra orphan, a limit of 1 to 50,000 is discussed by the Scottish Medicines Consortium.[17]

Merely lowering the sales threshold of orphan drugs from 50 million Euros to 20 million Euros – as discussed by politicians[18] – is not very effective. Initially, a benefit assessment would begin under facilitated conditions, as has been the case to date. However, if a lower sales threshold is quickly exceeded, there is then the risk of having to frequently suspend procedures that are already ongoing to then continue them after the determination of an ACT and resubmission of a complete dossier by the pharmaceutical company.

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Post-market data collection – emergency solution with potential?

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With the law for more safety in drug supply (GSAV), the legislator has created the basis for the conduct of „post-market data collection" and provided the opportunity for the G-BA to request comparative, mostly registry-based data collection after approval in case of relevant evidence gaps. However, there is a need for further legal and structural development, especially in the area of registry culture to make post-market data collection an effective tool for improving the evidence situation in accelerated approval procedures. A registry agency should be established to serve as a communication interface to provide effective incentives for quality assurance, and to drive harmonisation in areas such as data protection, data collection and data use.

Increasing importance of pharmaceuticals with accelerated approval

With accelerated approvals, a change in the regulation of market access for pharmaceuticals can be observed worldwide representing a significant challenge for benefit assessment and reimbursement of pharmaceuticals.[1]

A crucial part of the evidence generation is thereby shifted from the pre-approval phase to the post-approval phase – for more than half of all pharmaceuticals, comparative data against treatment alternatives are not available at the time of approval.[2] Accelerated approvals are mainly used for pharmaceuticals for the treatment of an orphan condition (i.e. orphan drugs)[3] which generally enjoy extensive privileges in the approval and evaluation process, but also pharmaceuticals for more common diseases that receive conditional approval[4] or approval under special conditions.[5] Subject to the condition of a high „unmet medical need", accelerated approvals aim to ensure rapid access to new pharmacotherapy for patients.

While accelerated approvals played virtually no role in the EU at the turn of the millennium, in 2021, they will account for around 31 percent of all approvals for new pharmaceuticals – this a new record.[6]

Thus, accelerated approvals must be viewed with caution, especially from the aspects of physician decision-making reliability and treatment quality. Pivotal studies often have significant evidence gaps. While in the past approval was normally only granted after completion of phase III studies, approval is nowadays often based on phase II trials only with a comparatively small number of patients. Study populations in phase II studies are partly „specially" customised and only partially represent the target population as defined by the approval in many cases. They are often single-arm studies, i.e. studies without a comparison group. The risk from these study deficits is ultimately borne by the

patient, but also by the insured community.

And these risks do not only include unknown side effects of the active ingredients, but also deficits in the efficacy. Taking an insufficiently effective pharmaceutical can cause indirect harm, e.g. in cancer therapy, because it leads to uncontrolled tumour growth, or because irreparable damage is caused by the progression of the disease. Due to the substantial evidence gaps for accelerated approved pharmaceuticals, the „principle of hope" – hope for efficacy and safety – is often the main focus.

Orphan drugs

Consequently, a closer look at the group of drugs known as orphan drugs reveals the extent of the evidence gaps. Orphan drugs and their manufacturers enjoy the legal privilege of the undeniable fiction of an additional benefit without the obligation to undergo comparative benefit assessment against an appropriate comparator therapy (ACT). This means that they also benefit during reimbursement negotiations, as they can achieve higher prices.[1]

Only when an annual sales threshold of 50 million Euros in Germany is exceeded within twelve calendar months, a full evaluation will be initiated. In 2021, only 23% of the benefit assessments of orphan drugs by the Federal Joint Committee (G-BA)[7] identified an evidence base on which the additional benefit could be quantified (n=75 patient groups/assessed indications). In 37% of the cases, an additional benefit that could not be quantified was identified, and in 40% of the cases, full evaluations led to an unproven additional benefit. This means that in more than three

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quarters of the evaluated indications there were relevant evidence gaps or no possibility to determine an additional benefit, respectively.

The Institute for Quality and Efficiency in Health Care (IQWiG) evaluated whether the evidence gaps that exist for orphan drugs at the time of approval will be closed in the period after approval. For this purpose, the Institute reviewed all full evaluations from 1 January 2011 to 30 September 2021, which followed an initial evaluation with orphan privilege. The result is disillusioning: in more than half of the cases, the full evaluation did not reveal an additional benefit (54%). IQWiG concludes: „Ten years after the Early Benefit Assessment Act came into force, it is time to abolish the privilege of additional benefit for orphan drugs."[8]

Thus, for the steadily growing number of pharmaceuticals with accelerated approval, substantial evidence gaps are often not closed even in the post-approval phase. HTA reports based on qualitative study data neither fulfil an end in themselves nor do they serve to determine an appropriate price. They mainly support patients and physicians to take an individual, informed decision between alternative therapies. Patients, physicians, HTA institutes and thus society as a whole face the challenge of obtaining the information they need as quickly as possible.[2,10]

Post-market data collection

The necessary incentives for the industry to close evidence gaps after approval were lacking for a long time. On 15 August 2019, the Act for Greater Safety in the Provision of Medicines (GSAV) was published in the Federal Law Gazette.[11] The legislator created the basis for post-market data collection and provided the opportunity for the G-BA to close evidence gaps by requesting a comparative, mostly register-based data collection after the approval of a pharmaceutical. According to Section 35a (3b) SGB V, the pharmaceutical company can be obliged to plan and conduct a comparative (e.g. register-based) study. The G-BA itself engages in the planning of the study. The results of the study will then be evaluated within the scope of a renewed benefit assessment according to Section 35a (3) SGB V.[12] Unfortunately, the legislator has not explicitly provided for the possibility of requiring randomised (registry) studies, which means that the advantages of RCTs regarding the superior data quality and lower numbers of required study subjects cannot be fully exploited.

The aim of post-market data collection is thus to close evidence gaps and to generate data that allow an adequate assessment and quantification of the additional benefit. Depending on the outcome of the benefit assessment after post-market data collection, deductions from or additions to the initially determined reimbursement amount will be implemented.[13]

Obstacles to the implementation of post-market data collection.

In February 2021, the G-BA obliged a pharmaceutical company for the first time to create the basis for a new benefit assessment by means of a post-market data collection and evaluations. For Zolgensma® (active ingredient: onasemnogen abeparvovec), a gene therapy for the treatment of spinal muscular atrophy in children, a registry study shall be conducted, based on which statements can be made on the therapeutic status in comparison to other available treatments for this disease. For this purpose, all physicians who intend to use Zolgensma® must participate in the data collection.

For the post-market data collection of Zolgensma®, the IQWiG has developed the guidelines for study planning on behalf of the G-BA. Based on this and with the involvement of experts, e.g. the Drug Commission of the German Medi-

cal Association (AkdÄ), the G-BA specified the type, duration, and scope of data collection as well as the analyses of the pharmaceutical company (Novartis Gene Therapies) in a demand resolution of 4 February 2021. According to these requirements, the pharmaceutical manufacturer should prepare the exact study protocol including the statistical analysis plan (SAP) and submit it to the G-BA for review. Due to multiple adjustment requirements regarding the study protocol and SAP, data collection in the registry study could not begin until February 2021. Not surprisingly, the pharmaceutical exceeded the sales threshold of 50 million Euros even before the start of the post-market data collection. This led to a full evaluation (benefit assessment without orphan privilege) with the result that an additional benefit could not be proven. The new benefit assessment according to the post-market data collection is planned for 2027.[14]

The first procedure illustrates a series of problems with the commissioning and implementation of post-market data collection. For example, the timelines until the actual start of data collection are exceptionally long. In addition to the correspondingly late benefit assessment after post-market data collection, this often leads to problems regarding case number planning and recruitability for the (registry) study. Especially in case of gene therapies for rare diseases with a high medical need for new therapeutic options, there is often widespread use immediately after approval. If data collection has not started at this point, the data might be lost. This can be relevant when it comes to including enough subjects for the registry study, especially in case of rare diseases.

The lack of suitable registries can also be a limiting factor. To conduct a post-market data collection a timely manner, an indication registry is needed that can provide the necessary data of sufficient quality.[15] However, these are not available for all indications or must be modified regarding the collection of relevant endpoints. Corresponding evaluations, modifications and contractual regulations for data use are time-consuming and can only be partially influenced by the G-BA.

Completeness and comprehensiveness of data collection are crucial factors, especially in post-market data collection for orphan drugs. It must be ensured that healthcare providers provide the data of every patient providing their full consent to the registry and thus to post-market data collection. Although the G-BA can restrict the authority to provide care to those providers who participate in data collection, there are no effective control mechanisms.[16] At this point, both willingness and interest of care providers to participate are particularly important. Therefore, data collection and provision should be as easy and standardised as possible.

An overriding problem is the selection of candidates, i.e. the decision for which pharmaceuticals post-market data collection is deemed necessary and for which it is not. In addition to the main criterion of currently insufficient evidence, the G-BA's rules of procedure contains the following aspects as essential criteria for assessing the necessity of post-market data collection: a) informative value of existing data on patient-relevant outcomes, b) consideration of ongoing studies, and c) feasibility and appropriateness of data collection.[17]

In the early benefit assessment, evidence gaps become particular apparent in the result categories „additional benefit is not proven" or „non-quantifiable additional benefit". Legally prescribed automatic mechanisms that would induce the elaboration of a post-market data collection concept (feasibility assessment by IQWiG; or corresponding elaboration/testing by the pharmaceutical entrepreneur) including comments procedure in the case of accele-

rated approved pharmaceuticals with obvious evidence gaps and/or the aforementioned assessment results at initial assessment could accelerate the process of candidate selection, make it fairer, and standardise it.

The first post-market data collection thus shows that the procedure is time-consuming, contains many formal-technical hurdles, and will remain limited to individual cases under the current framework conditions. In addition to simplifying the procedure for post-market data collection through structural adjustments, the registry culture in the healthcare system must also be improved step-by-step to get the most out of the scientific potential of registries and thus ensure the generation of follow-up evidence as quickly as possible. Initiatives at European level to establish an EU Health Data Space must be taken up and complemented by national efforts. Thus, the patchwork-like registries should be harmonised, and mandatory quality-assured indication registers should be established and networked under the umbrella of a national (or, in the future, European) registry agency.

Outlook and need for action

On 29 October 2021, the „Expert Opinion on the Further Development of Medical Registries to Improve Data Feeding and Connectivity", commissioned by the German Federal Ministry of Health (BMG), was presented by the BQS (Institut für Qualität und Patientensicherheit GmbH) and the TMF (Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.).[18] This should be seen in the light of the Register and Health Data Usage Act planned in the coalition agreement of the current federal government.[19] This report identifies a number of key opportunities for further development in the area of registry data collection, quality assurance, and use:

Implementation of a registry agency

A key point in the recommendations of the report is the implementation of a registry agency under the supervision of the BMG or a delegated body (figure 1). Registry operators could apply to have their registries included in the agency's inventory. Auditing and evaluation based on quality levels would take place via an independent scientific advisory board, thereby creating incentives for quality assurance and improvement. Further harmonisation could be achieved through requirements and legal regulations defined within the framework of the register agency, e.g. in the areas of data protection, data collection, IT systems, quality management, and data access rights/use. At present, the legal basis for the operation, design, use, etc. of German registries resembles a patchwork quilt, not least because data protection and other regulatory areas are primarily regulated by the federal states.

Beyond harmonisation, such a registry agency should also function as a communication interface between registry operators, the scientific community, the industry, and governmental and self-governing institutions. Data should be made linkable across registries or studies. Institutions such as the G-BA, or pharmaceutical companies contracted by it, should be given the necessary data access rights.

The G-BA should also be given the opportunity to establish new registries or to adapt existing registries, especially for post-market data collection, to benefit from the German registry landscape on a regulatory basis.[18]

„Research readiness"

The goal must be to be able to access registry data more quickly than before within the framework of post-market data collection. The classification into quality levels by the registry agency should take into account and reflect the requirements for a post-market data collection. The time-

consuming adjustment of registries before the start of data collection must be eliminated. Moreover, for high-quality registries, retrospective data could be used for a registry study in the context of post-market data collection even without costly testing and adjustment. Networking among registries could increase the number of cases of study participants. If a registry agency acts as a communication interface, arrangements, requirements, user agreements, etc. could be made in a standardised way, saving time and effort.

A registry agency can also support IT standards that do not include data from different sources, but may also allow data to be fed directly from, e.g. the electronic health record (ePA) or practice software.

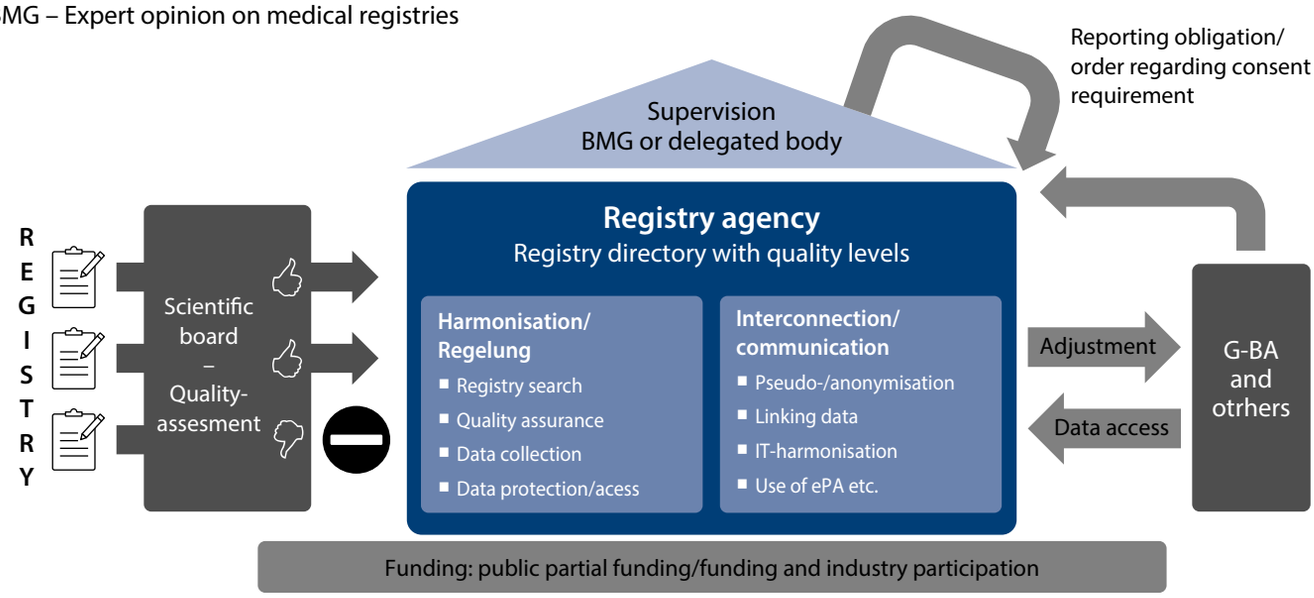
The registry centre would provide a point of reference to establish legal (cross-national) regulations regarding, in particular, data protection, collection, and access. Research readiness is a central issue for the success of post-market data collection – the structural prerequisites regarding the registry landscape and registry data use must be in place to be able to conduct post-market data collection at all within a reasonable period.

Feasibility

Most accelerated approvals are granted for orphan drugs for the treatment of diseases with a low prevalence. The

Implementation of a registry agency

BMG – Expert opinion on medical registries



Quelle: Dr. Thomas Mayer, GKV-Spitzenverband

Figure 1: Overview of potential tasks and functions of a registry agency – adapted from „Expert opinion on the further development of medical registries to improve data feed-in and connectivity“.[18]

rarer a disease is, the more difficult it is to recruit enough subjects for a registry study. To ensure an adequate data pool for post-market data collection, sufficient valid and complete patient data must be collected. Accordingly, the completeness of the data collection is important. If possible, data on every patient treated should be collected and fed into the registry. Both feasibility and duration of post-market data collection are directly dependent on this factor. Weighing up the privacy interests of patients and the therapeutic advances to be expected for them using data, an expansion/legal opening towards the consent-free use of (care) data – e.g. directly from IT primary systems such as the ePA – must be discussed – wherever sensible and appropriate.

Furthermore, a nationwide registry landscape is a basic prerequisite for the feasibility of post-market data collection. Currently, the German registry landscape is extremely inhomogeneous – there are numerous indications for which registries of sufficient quality are lacking. On the other hand, there are clustered registries in certain areas, which may be associated with a certain competition for data or duplication of data and may jeopardise the completeness of the individual registries. Finally, the G-BA should be given more extensive powers by law to adapt and initiate essential indication registries.

Interim pricing model

To effectively address the problem of inadequate data in accelerated approvals, the GKV-Spitzenverband proposes the introduction of an interim price model (figure 2). Only for pharmaceuticals with uncertain data would a lower interim price initially be determined based on evidence-independent criteria instead of the reimbursement amount.

Only when the data situation is sufficient for a complete benefit assessment could a reimbursement amount be agreed, which would then replace the (lower) interim price. The proposed interim price model establishes a good balance between price and evidence. Manufacturers with early meaningful data are rewarded. Thus, incentives are maximised to generate early evidence to prove the additional benefit.

Conclusion

The post-market data collection procedure initiated by the legislature is an emergency solution with potential. In its current form and under the given conditions, the procedure is too costly and will remain limited to individual cases. Through structural-legal adjustments (criteria-based candidate selection, predefined timelines, low-effort through direct IT-supported use of healthcare data) as well as a systematic improvement of the registry culture (registry agency, research readiness, feasibility), post-market data collection can be a gentle and effective tool that helps to minimise evidence gaps and associated patient risks in accelerated approvals – at least in the follow-up – for the benefit of patients.

Low-effort generation of post-approval evidence via post-market data collection can help ensure the permanent maintenance of direct market access without a fourth hurdle. In view of a trend towards more high-priced pharmacotherapies, such as advanced therapy medicinal products (ATMPs) no longer only for rare diseases or also combination therapies with patent-protected drugs with increasingly weaker evidence overall, it is necessary to establish a pricing model that also links a correspondingly high reimbursement amount to the prior submission of meaningful evidence.

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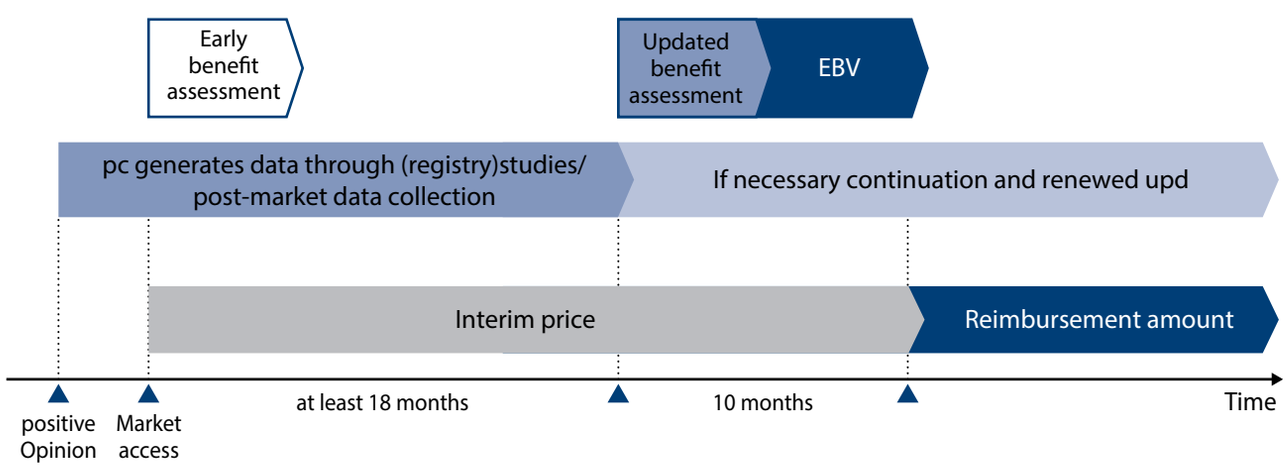
Interim price model: From small to big price



EBV = reimbursement amount negotiations, pc = pharmaceutical company
Source: GKV-Spitzenverband, Position paper Patent pharmaceuticals

Figure 2: Interim price model of the GKV-Spitzenverband for pharmaceuticals with accelerated approval.

[16] § 35a Paragraph 3b Sentence 2 SGB V

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The industry's view on registry data

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COVID-19 revealed how disadvantaged Germany is in the area of documentation of care-related data for important healthcare decisions. However, several initiatives have shown that healthcare-related data from registries do have potential for e.g. approval processes or HTA evaluations. With the concept of „post-marketing data collection", especially for rare diseases, Germany is now also dealing with the topic for the AMNOG benefit assessment process. However, the ideal concept of collecting and analysing such data for treatment comparisons from mainly indication registries seems to be difficult to implement in practice. Beyond the benefit assessment, there are already interesting opportunities for generating and analysing healthcare data for other purposes that could be driven by digitisation and linked to interoperable registries and other systems (e.g. ePA, research data centre, HIS, point-of-sale data, wearables, etc.).

COVID-19 and the data crisis: we need a better data infrastructure

In Germany, digitisation and amount of structured healthcare data lags far behind other countries. The Covid-19 pandemic in Germany, for example, revealed serious deficits in the data infrastructure in healthcare and research. So far, standardised treatment data are not collected in a structured way throughout Germany. This situation, understood as a „missing data" crisis, has painfully shown that Germany does not have enough infrastructure to acquire important data on testing and infections and on the effectiveness of containment and treatment measures during a pandemic and to make them available in a timely manner.

The positive effects that the collection and provision of substantial amounts of data can have on healthcare were impressively demonstrated during the Covid 19 pandemic in Israel. Many people there even consider it a duty and an honour to pass on the collected information in anonymised form and take it for granted that the entire world benefits from the accumulated knowledge.[1]

Several expert groups, such as the German Council of Science and Humanities, the German Working Group on Statistics, and the German Council of Economic Experts on Healthcare Development (SVR), see a need for action to establish well-connected structures in healthcare research for a crisis situation, recommend a national strategy for collecting and processing data and establishing an appropriate research data infrastructure toward a digital, systematic learning healthcare system.[2-4] The coalition agreement gives us hope. Digital infrastructure and digital innovations have a strong position in the paper. The section on „Digitisation in the healthcare sector" holds out the prospect of accelerated introduction of the electronic patient record (ePA) and e-prescription. A registry law and a Registry and

Health Data Usage Act for better scientific should be established and the decentralised research data infrastructure shall be expanded.[5]

Trends in the use of routine data: Real World Evidence (RWE) in the regulatory process

Regulatory agencies are increasingly incorporating RWE to demonstrate efficacy for approvals or marketing authorisation extensions.

The passage of the 21st Century Cures Act by the U.S. Congress in 2016 included testing for the utility of RWE with the goal of advancing pharmaceutical development as well as approval of innovative products.[6] In 2018, the U.S. Food and Drug Administration (FDA) submitted a programme for the evaluation of the potential use of RWE as outlined in the 21st Century Cures Act to support, among other things, indication expansions of already approved pharmaceuticals or post-marketing surveillance.[7] Similarly, the European Medicines Agency (EMA) is addressing this issue on RWE. The Patient Registry Initiative, which has been established more than a decade ago, and its workshops addressed the topic of using data from registries for the regulatory process, especially for rare diseases, resulting in a final version of the EMA Guideline for Registry-Ba-

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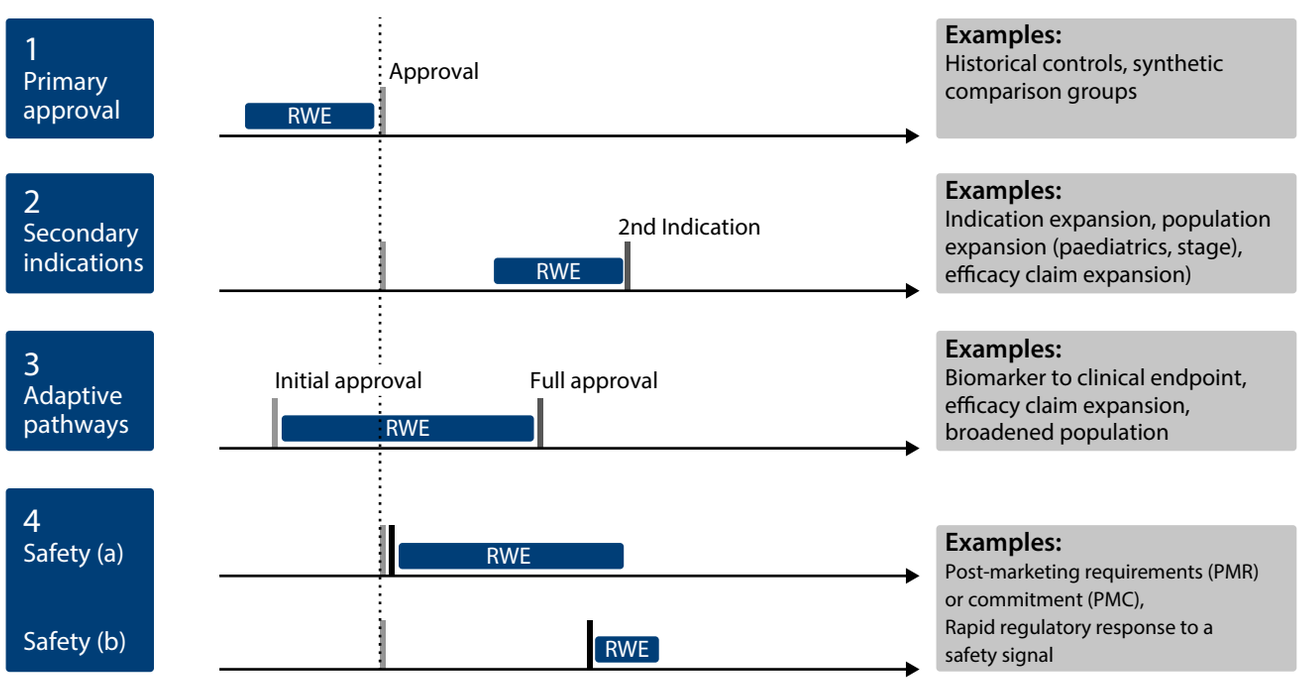
Dr Stephan Rauchensteiner *holds a degree in Psychology (2004) and did his PhD as a scholarship holder of the Ernst Schering Foundation in Global HEOR at Bayer during the postgraduate study programme „Consumer-Health-Care" at Charité (2008). From 2007, he worked as a clinical study manager at PAREXEL in Berlin and from 2010 in the Global Medical Affairs Haemophilia Region Europe department at Bayer in Berlin and Basel with focus on registries, NIS, investigator-initiated research, and phase IV studies. Since 2019 he is employed at Pfizer Pharma GmbH in Berlin in the Health Technology Assessment & Outcomes Research department, focusing among others on post-market data collection and registries.*

sed Study in October 2021.[8] Among other things, the distinction between registries and registry-based studies is described more clearly than ever before and specifications are made with feasibility assessments and checklists, how the quality of registries can be assessed by the pharmaceutical companies on the basis of individual criteria, how advice can be provided by EMA to the companies, and further elements for the collaboration of registries with pharmaceutical companies for registration studies and pharmacovigilance by means of registry-based studies are outlined in more detail. Another initiative led by Arlett et al. describes that the EMA has a vision to further integrate RWE into its approval processes with the scope of the DARWIN project.[9]

Franklin et al.[10] illustrate the potential use of RWE in regulatory decision making with a couple of use cases (figure 1). In the first case, RWE is used to support the initial approval of a new pharmaceutical. Particularly for orphan drugs or approvals in exceptional circumstances, an RCT might not be possible. Here, evidence from single-arm studies can be enriched with RWE, e.g. by performing indirect comparisons with historical controls or synthetic control

Real world evidence in the regulatory decision-making process – main use cases



Source: Adapted from Franklin et al. 2019 (10)

Figure 1: The use of real-world evidence in the regulatory decision-making process focusses on four use cases. In addition to the initial approval, these are indication extensions, adaptive pathways, and pharmacovigilance.

arms (external control arms, ECAs) from another registry.

The second example are indication extensions. Knowledge from the previous RCT can be used and extended with RWD, e.g. ECA or even observational studies might be sufficient in some cases. The third example are adaptive pathways. This is an approval pathway described by Mr Eichler from the EMA, where starting from a core indication with an RCT, a stepwise extension with RWE is conducted to expand the indication. The fourth area of application is in pharmacovigilance where it is a frequently used method as a requirement after a conditional approval or to verify certain safety signals; nicely seen with one of the COVID-19 vaccines how a signal could be proven.

Post-marketing data collection

In Germany, every new pharmaceutical must undergo the benefit assessment process, during which the Federal Joint Committee (G-BA) determines the additional benefit compared to an appropriate comparator therapy (ACT). Since 2020, the G-BA can request the pharmaceutical company to collect and evaluate post-market data collection for the purpose of benefit assessment.[11-14] Here, the focus is on orphan drugs and pharmaceuticals with a conditional marketing authorisation or marketing authorisation granted under exceptional circumstances. The G-BA can initiate a post-marketing data collection if, in its opinion, there are evidence gaps. There may also be a restriction on the authority to provide care, thereby only centres participating in the post-marketing data collection will be authorised to prescribe the pharmaceutical under investigation.[13]

According to European legislation, orphan drugs are defined as pharmaceuticals used for a rare, life-threatening disease, or a disease that may result in chronic disability. Further criteria of the European regulatory authority EMA for orphan drug status are, on the one hand, the rarity of the disease (5 out of 10,000 people in Europe have the disease), lack of appropriate treatment options, or in case there are other treatment options, the new therapy must represent a significant benefit.[15]

Another important procedure is conditional marketing approval.[16] Because of a significant medical need, such conditional approval may be granted before comprehensive clinical data are available; these data must be provided subsequently. In a procedure under exceptional circumstances, it is not possible to generate complete data for safety or efficacy, for example, because the condition is extremely rare, or data generation might be unethical.[17]

In its January 2020 Rapid Report, „Concept for the generation of healthcare-related data and its evaluation for benefit assessment, „14 the IQWiG defined requirements for the type and methodology of data collection. The IQWiG calls for an indication registry on which a post-marketing data collection is to be based by means of a register-based study and defines the requirements for quality criteria. Moreover, the conditions for data quality are defined. In addition, inclusion and exclusion criteria, requirements for confounder identification are defined, which among other things should take place in a systematic literature search. In a detailed statistical analysis plan (SAP), the analysis methodology, including confounder control and sensitivity analyses, should be prespecified.

The first procedure of a post-marketing data collection has been applied to gene therapy onasemnogene abeparvovec for spinal muscular atrophy (SMA)[18,19]. The G-BA specifies the requirements for the PICO criteria, e.g. which population must be considered, what is a suitable intervention group, what is a suitable comparator, which endpoints are measured? Relevant points for data collection and analysis, such as the type and duration of collection, questions, endpoints, methodology of collection and analysis were

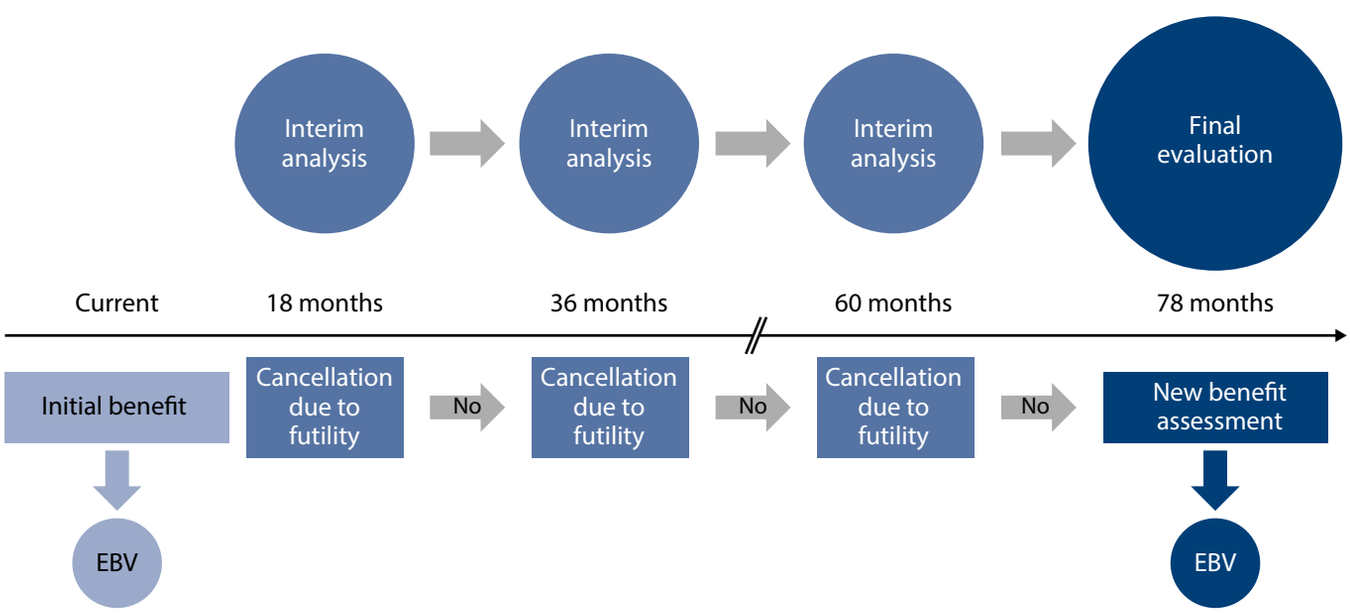
defined by the G-BA. In order to obtain complete and appropriate data, the procedure was conducted with restriction of supply authority.[20]

Status reports shall be provided every 18 months, with interim analyses for the first time after 36 months. In these interim analyses, post-market data collection may be cancelled due to futility if e.g. the required number of cases or effects cannot be achieved. The final evaluation should take place after 78 months. This should be followed by a new benefit assessment with a reimbursement amount negotiation (figure 2).

Several challenges arise from post-marketing data collection

The first challenge is that the required data quality is difficult to achieve. This is because registries pursue different goals than benefit assessment procedures and can only comply with practical requirements. A study conducted by the IGES Institute for the vfa concludes that only one registry fully meets IQWIG requirements.[21] The other twelve registries studied do not meet the requirements at all, or only partially. The register survey[22] conducted for the BMG by TMF covering 365 registries came to a similar conclusion.

Schematic representation of the anticipated post-marketing data collection process for onasemnogen-abeparvovec gene therapy for spinal muscular atrophy (SMA)



Source: Adapted from information in the G-BA decision on post-marketing data collection for onasemnogen-abeparvovec (19)

Figure 2: Schematic representation of the anticipated post-market data collection process for onasemnogene abeparvovec gene therapy for spinal muscular atrophy (SMA).

It reflects the very heterogeneous landscape. While some model registries are good, there are major difficulties with many others. However, these registries were of course not set up for benefit assessment, but to serve other purposes. This shows that further development of existing registries is a prerequisite for further work in AMNOG with these registries. As an industry, we are used to ensuring high data quality and interpretability in our studies, which are strongly regulated according to Good Clinical Practice (GCP). This is also a crucial point for us in post-marketing data collection to be able to show differences robustly and validly. However, the question arises here for registries whether such high requirements cannot be waived for post-marketing data collection.

Another challenge is the governance structures of the registries, which need to be reconsidered. Today, we often still work with a model in which only the registry operator has access to the registry data. In this model, a pharmaceutical company only receives an evaluation of the data, i.e. for example, a report on the number of patients included. The patient can apply for a special evaluation, on which the registry operator makes the final decision. The request can be rejected, or additional statistical tables can be provided.

According to the requirements of IQWiG and the G-BA, the pharmaceutical company must submit a study protocol and analysis plan and coordinate them with IQWiG and the G-BA. It is important to distinguish between a registry, which is the platform on which the data are collected, and a registry study or registry-based study. In a registry study, different parameters may be collected that are not present in the registry. In addition, a registry study may have different quality criteria and its own protocol and analysis plan.

It must be ensured that the pharmaceutical company can also perform the analyses as outlined in the protocol and SAP at the specified times in the post-market data collection process and AMNOG in a timely manner, for which it needs the constructive cooperation of the registry operator.

The knowledge of the registry operators about their own data is valuable here and must be considered in any case. One possibility would be e.g. an advisory board consisting of treatment providers, statisticians and data scientists of the registry operator. The input of this board can be important for protocol and analysis plan planning as well as for publication and results. This could be an approach that redefines the form of collaboration and opens up the possibility of accessing essential data to conduct the studies (figure 3).

An additional challenge is the question of a similar comparison cohort in observational studies as a prerequisite to draw a causal conclusion. In epidemiological research, propensity scores are the standard to adjust for the influence of possible confounders,[23] but nevertheless both groups should still be sufficiently similar.[24,25]

In situations where randomisation is not possible for ethical reasons, often even an observational study cannot provide a valid comparison. In the extreme case, we are dealing with two different deterministic populations that do not overlap.[25] A comparison also works best if the physicians consider the therapy options to be equivalent. Or the therapy option may be assigned based on a criterion that is not associated with an outcome variable (instrument variable).

In case of orphan drugs and especially „soloists", where there is only a symptomatic-effective therapy at the given time, a new pharmaceutical that offers a causal therapeutic option will make a critical difference in the therapeutic landscape. If the pharmaceutical is approved, most physicians and patients will then use it. Patients who cannot, will

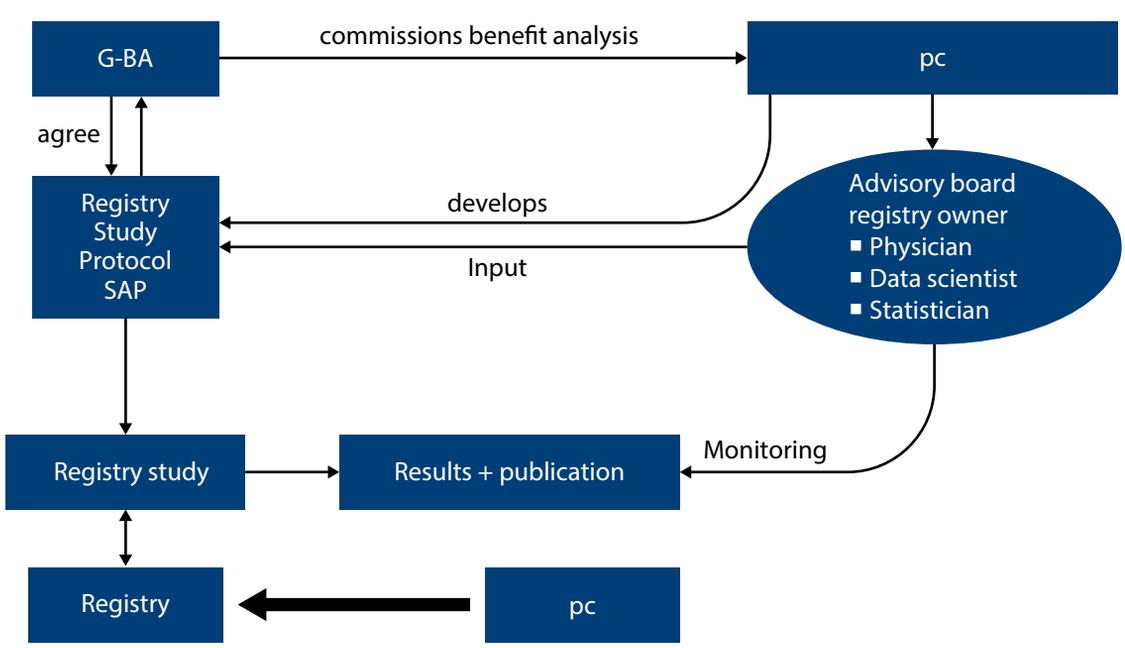
not or should not receive the new therapy are certainly different patients than those who do. Particularly for pharmaceuticals that would fall within the post-market data collection scope of use, it may be difficult to find an adequate, sufficiently similar comparison group.

As described above, in situations where a randomised controlled trial (RCT) is not feasible, an ECA may be used in the approval process. Prior to the approval, the pharmaceutical is not yet available, i.e. there are still similar patients as in the verum group who receive the old therapies in clinical practice, so these could be collected prospectively, in parallel, or taken from historical data collections. These ECAs are also observational studies and should have similar measurement intervals and endpoints as the single-arm study. We should try to make this part of the evidence from the approval fit for the benefit assessment, as some problems do not occur or do not occur in the intensity as in late post-marketing data collection after approval.

The IQWIG's requirement for „dramatic effects" with a relative risk (RR) of the treatment effect at RR>10 is particu-

Benefit assessment with registry

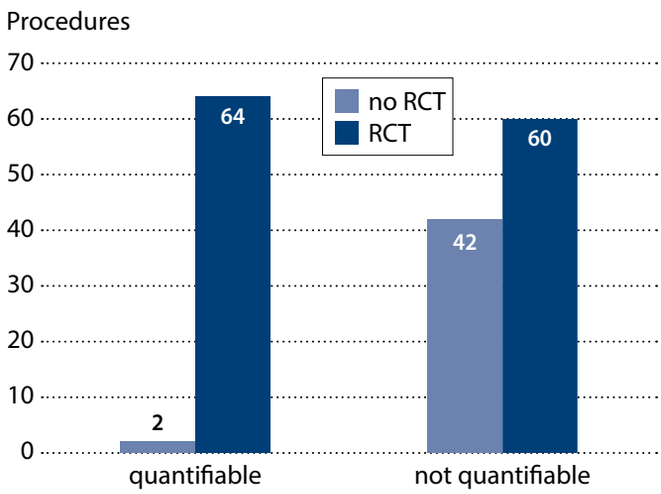
Post-marketing data collection:
The pharmaceutical company has to prepare a study protocol and a statistical analysis plan in advance



Source: Own presentation

Figure 3: Necessary governance structures of medical-scientific registries to enable registry-based studies for approval and benefit assessment.

Hardly any orphan drug without RCT so far



Source: vfa data base, March 2022

Figure 4a: Proportion of orphans with and without RCT studies and their level of additional benefit „quantifiable" or „non-quantifiable" in the German AMNOG benefit assessment process.

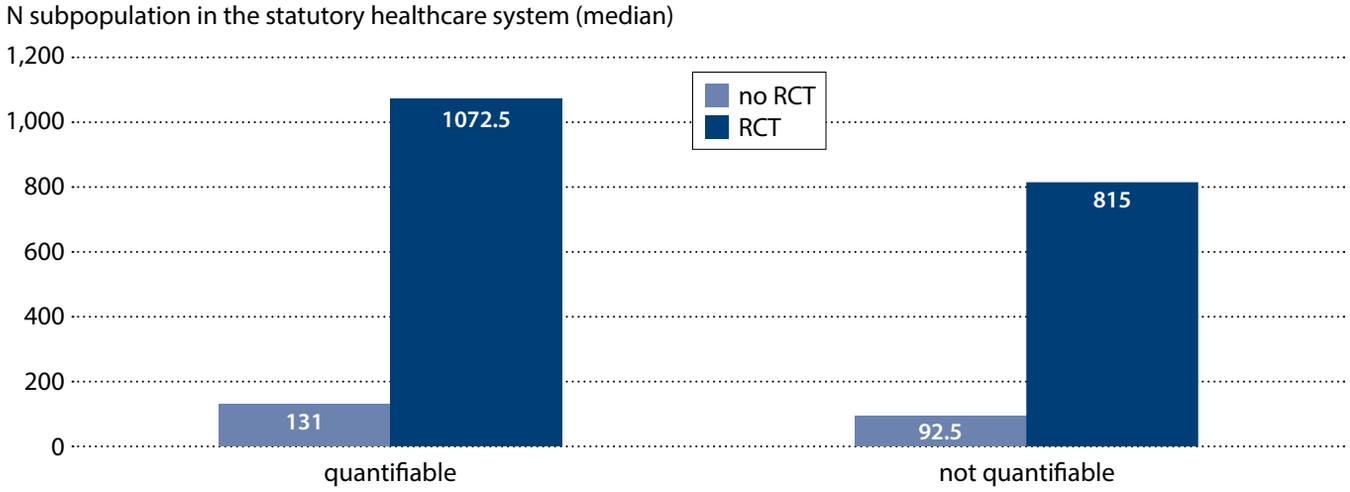
larly challenging. „Dramatic effects" are difficult to establish with small numbers of cases. In principle, an observational study has a higher potential for bias than an RCT. This finding comes from Glasziou et al,[26] in which cases an RCT can be dispensed with. However, they determine this based on indications more from the medical device field. The Rapid Report on healthcare-related data[14] states that a statement on benefit or harm would result if the confidence interval for the observed effect was above a threshold to be defined. The minimum therapy effect of RR is then reduced to RR=2 to 5, the concrete threshold would result from the quality of the data in the individual case. However, the lower limit of the confidence interval would then have to exceed this threshold for an additional benefit to be recognised. According to research by the vfa, most methods then nevertheless remain at a necessary point estimate of RR≥10, because with small case numbers the confidence intervals are exceptionally large. Thus, even a lowering of the limit is no relief. We are in the rare disease area with post-marketing data collection, which was not the case with Glasziou et al. According to the IQWiG paper,[14] a confounder adjustment should take place according to the highest scientific standards. In the examples of Glasziou et al. no confounder adjustment had to be performed. Post-marketing data collection comprises orphan drugs with conditional approvals and procedures in exceptional circumstances. Therefore, due to the large medical need and the small case numbers, the EMA accepts a greater uncertainty here and sometimes also waives comparative data precisely for this reason. If the „dramatic effects" are now demanded, this procedure of the EMA for this type of product is undermined. The same conditions are required in Germany as for any other disease with much larger patient numbers. It therefore seems more appropriate to follow the proposed methods of the 2017 InSPiRE project on new methods for clinical trials in rare diseases.[27]

However, the small case numbers are also a challenge in general. Clinical studies with randomisation have been conducted for about two-thirds of orphan drugs (figure 4), meaning the issue is not as extreme as often described. Approximately half of the orphan drugs with RCTs receive a quantifiable additional benefit, the other half a non-quantifiable additional benefit, because requirements of the G-BA rules of procedure may not be fulfilled, e.g. there may be no patient-relevant endpoints, the study duration was too short, no adequate control group was available, or the data were not transferable to German healthcare practice.

The other 42 procedures, approximately one-third of all

Evidence base (RCT/no RCT)

Number of patients in the subpopulation in the statutory healthcare system (median) by Evidence base (RCT/no RCT) orphan drug additional benefit and evidence base (RCT/no RCT)



Source: vfa data base, March 2022

Figure 4b: The median number of patients in the subpopulation in the statutory healthcare system for RCTs with quantifiable additional benefit is 1,072. When there is an RCT, but the additional benefit is not quantifiable, the median is 815. In contrast, patient numbers are significantly lower with a median of 92.5 when there was no RCT, and an additional benefit was not quantifiable.

procedures that do not have a comparison group, are usually granted a non-quantifiable additional benefit, predominantly due to the orphan regulation in the AMNOG. Looking at the patient numbers of the GKV target population shows: The median of the subpopulation in the statutory healthcare system for RCTs with quantifiable additional benefit is 1,072. When there is an RCT, but the additional benefit is not quantifiable, the median is 815. In contrast, the patient numbers are significantly lower with a median of 92.5 patients p.a. for those procedures where only a single-arm study is available (figure 4b). These small numbers of cases (also split into verum vs control group) make it difficult to show an effect statistically at all, even if an effect is present. An unequal ratio of control to verum can lead to a further reduction in power here. In these situations of small case numbers, pay-for-performance approaches may be more appropriate.

In these situations of small case numbers, pay-for-performance approaches might be more appropriate. In an interview in the German TV broadcast „Tagesspiegel", Professor Hecken mentioned that pay-for-performance is the contract of the future, at least for gene therapies, to ensure in-

dication and diagnosis-appropriate use.[29] In our opinion, this would be reasonable, especially for procedures with few patients. Here, these few patients can be tracked and counted, which is associated with less effort and cost than having to go through elaborate detours with newly designed studies with external registries not set up for benefit assessment.

One step further: Utilisation of digital possibilities. Medical progress is also based on care data from prevention, screening, diagnostics, and therapy

In addition to the highly regulated use of healthcare data by means of registries in the approval and HTA process, increasing digitisation offers further opportunities for a more reasonable use of registries and healthcare data than for pricing in the AMNOG process. The Federation of German Industries (BDI) has outlined the concept of the „Digital Patient Journey" (figure 5).[30] Starting with the patient as the central actor, data are not only collected once and then forwarded to research and development but can also flow back to other stations in a circular fashion, as will be illustrated below.

Medical HIS data or similar could, in addition to registers, the electronic patient file, e-prescriptions, cash register data, the research data centre, also be supported and networked with wearables via e.g. smart watches, etc. and serve to adapt preventive measures, quality assurance measures or guidelines, etc. For example, screening data on blood pressure, blood glucose and heart rate offer the possibility of classification into risk classes for prevention. With artificial intelligence (AI), abnormalities can be detected more reliably. Digital RWD evaluations offer enormous potential for personalised healthcare. RWD generated in the context of follow-up care can also be significant both in prevention and in the treatment of recurrences. If healthcare data from prevention, screening, diagnostics and therapy are combined with high-quality digital applications and regulated access is granted for meaningful research evaluations, redundant, manual multiple entries in different systems and registers could be avoided and each area would benefit in particular from the use of RWD and the improvement of the treatment landscape.[30]

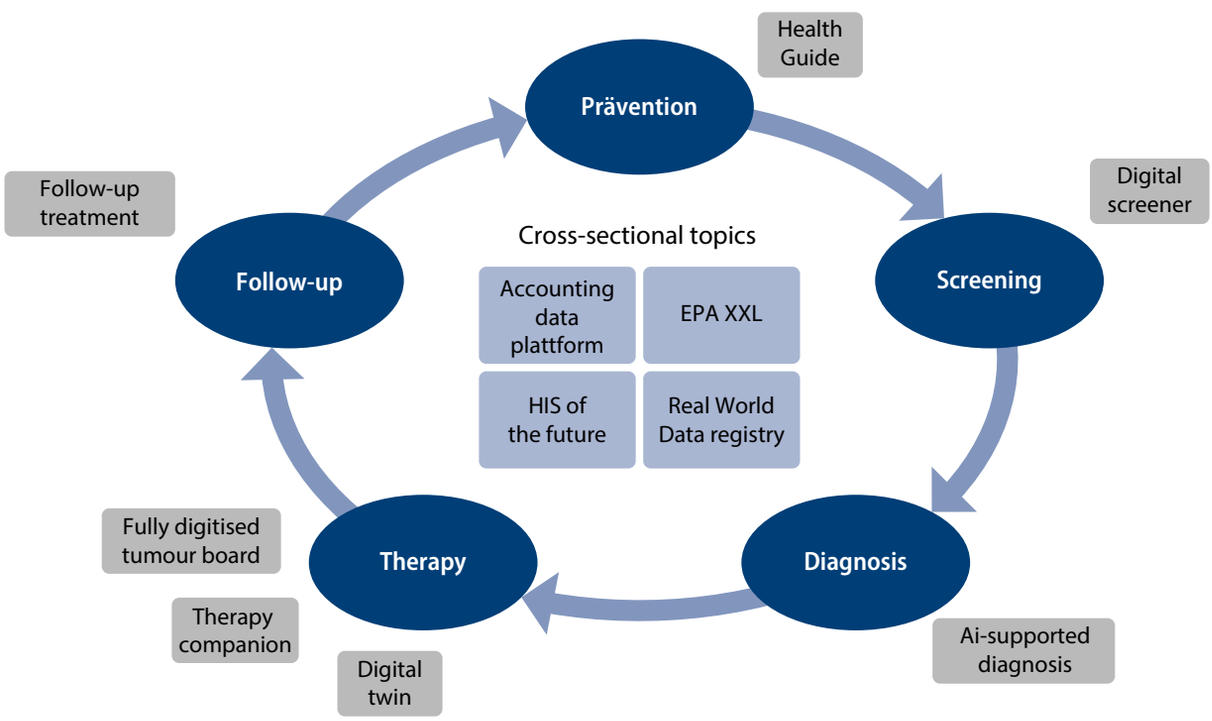
Conclusions

Post-marketing data collection: Planning security is important for the companies, i.e. we need an early involvement and early information on post-marketing data collection. Already during the early consultation, when we present our phase III programmes to the G-BA, post-marketing data collection should be discussed, if not even the first planning steps for it should be envisaged. We need a practical design and flexibility to even have a chance to show additional benefit. The scientific criteria are certainly helpful. However, not everything can be implemented in the way that makes sense, and therefore flexibility in design must be possible.

There are some methodological challenges with post-market data collection: We are dealing with small numbers of cases. On median, for the group of pharmaceuticals that would fall within the scope of a post-market data collection, the subpopulation in the statutory healthcare system is only about 100 patients annually – that is exceptionally low. In addition, there is a requirement for „dramatic" effects, which is difficult to achieve with these small case numbers. On the other hand, we are required to eliminate confounders with adjustments such as propensity score methods. But in this situation, is it even necessary to show effects above such stringent thresholds?

For soloists, once the pharmaceutical is approved, we have the problem of finding a comparable comparison

Digital approaches in the stages of the patient journey oncology – an overview



HIS = Hospital Information System

Source: BDI initiative Digital Health. Digital Patient Journey Oncology (30)

Figure 5: In the digital patient journey, data are collected only once, then forwarded to research, and can also flow back to the other stations in a circular fashion.

group in the healthcare setting. Since the patients who do not get the pharmaceutical are usually different from those who get the new pharmaceutical. If randomisation is not possible for ethical reasons, it is questionable whether a comparison that allows causal inferences can be made at all. What would be suggestions to meet these challenges?

For example, an ECA, e.g. also from a registry, could be defined before the approval and subsequently perform a comparison of the single-arm study with the ECA. This can be done using the same methodology as described in the IQWIG paper.[14] Finally, however, the question remains whether post-market data collection is the right model for pricing. After all, we conduct benefit assessment to have an anchor for pricing. Particularly in case of small case numbers with a full survey in a potential post-market data collection, pay-for-performance models may make more

sense and be more appropriate than a post-market data collection.

Healthcare data – dare more progress: With the new coalition agreement, we have a good chance of expanding the data infrastructure and reaching a level that is already common in other European countries. On the one hand, healthcare-related data can improve patient care, because the attending physician has the relevant information for the treatment decision immediately available. Relevant research questions can also be answered with healthcare-related data. We are getting a little closer to the vision of evidence-based medicine; i.e. that the physician and patient take the treatment decision based on data can become a reality with healthcare-related data.

However, we see the main benefit outside of AMNOG, not in pricing, but precisely to improve patient care and address relevant research questions. Important points of the current discussion, we from the industry support, is the creation of a central office for registers, in the sense of a meta-register, in which all German registers are listed with their information. We need improved interfaces and quality standards for registries. DNVF and TMF e.V. have already done some preparatory work. It is important that we as an industry are perceived as a healthcare researcher and that there is a regulation, in compliance with all data protection and compliance standards, on how we can access data for meaningful evaluation purposes. In other countries, it is common for the research-based pharmaceutical industry to have access to this data and conduct relevant research.

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Experiences of the SMArtCARE Registry with the G-BA's requirements

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Spinal muscular atrophy (SMA) is a rare, progredient motor neuron disease with many distinct levels of severity. At present, there are three approved pharmaceuticals for the treatment of SMA: nusinersen, risdiplam, and the gene therapy onasemnogene abeparvovec. Due to the rarity of the disease, the available evidence on these therapies is still very limited and there are no direct comparative studies. In 2017, the disease-specific SMArtCARE registry was established with the aim of collecting long-term routine clinical data of SMA patients from German-speaking countries as comprehensively and systematically as possible. Since then, far over 15,000 medical and physiotherapy visits of patients with SMA have been documented. Data sovereignty lies with the SMArtCARE network and data are analysed under the supervision of a steering committee independently of pharmaceutical companies. As the first German registry, the SMArtCARE database is now being used for a post-market data collection commissioned by the G-BA for the active substance onasemnogene abeparvovec.

Spinal muscular atrophy (SMA) is a rare neuromuscular disease with the leading symptoms of progressive muscular weakness and hypotension. Clinical symptoms include a wide spectrum ranging from symptom onset in infancy with marked muscular weakness and involvement of the bulbar and respiratory muscles (SMA type 1) to milder manifestations with symptom onset in adolescence (SMA type 3). The life expectancy of very severely affected infants with SMA type 1 is less than two years if they do not get pharmacotherapy and respiratory support.

With an incidence of 1:10,000, SMA belongs to the group of rare diseases. It is caused by mutations in the survival motor neuron (SMN) 1 gene on chromosome 5. Thus, the disease is also known as 5q-SMA. SMN2 is a predominantly homologous gene near the SMN1 gene. It is present in different copy numbers and SMN2 copy number is the most important predictor of disease severity.

Treatment of patients with SMA has changed significantly in recent years due to the development of various pharmacotherapies. In Germany, three different pharmaceuticals (nusinersen, onasemnogene abeparvovec, and risdiplam) are now available for the treatment of SMA. Onasemnogene abeparvovec was approved in May 2020 as the first gene therapy for the treatment of patients with clinical SMA type 1 or with up to three SMN2 copies. For all three therapies, current knowledge suggests that starting therapy as early as possible is crucial for the treatment response. Infants treated immediately after birth often show approximately age-appropriate motor development, which contrasts strongly with early death in the natural history of the disease. Consequently, SMA has been included in the new-born screening in Germany in October 2021.

To date, only limited data are available on the efficacy

and safety of these pharmaceuticals from clinical studies with predominantly paediatric patients. In order to assess treatment effects in a large cohort as well as treatment response over time, real-world data from untreated and treated patients must be systematically collected and evaluated. Under the leadership of Professor Janbernd Kirschner (Department of Neuropaediatrics and Muscle Diseases, University Hospital Freiburg), SMArtCARE[1,2] was already established in 2017 as a disease-specific registry in German-speaking countries. SMArtCARE is a joint initiative of neuropaediatricians, neurologists, and the patient organisation „Initiative SMA" of the German Society for Muscular Diseases (DGM). Meanwhile, more than 60 centres with data from more than 1,500 patients with an observation period of up to four years participate in the registry. At present, the SMArtCARE registry represents the largest data collection for SMA patients worldwide.

Although SMArtCARE is currently financially supported by the pharmaceutical industry (Biogen, Novartis Gene Therapy), full data sovereignty lies with the SMArtCARE network. The pharmaceutical industry does not have an influence on the design of the registry or the analysis and interpretation of the data. To ensure the scientific independence of the SMArtCARE registry, no data are shared directly with pharmaceutical companies for regulatory requirements but are sent to independent EU-based institutions for the prior evaluation of the statistical analysis plan (SAP) by the head of data collection and the steering committee.

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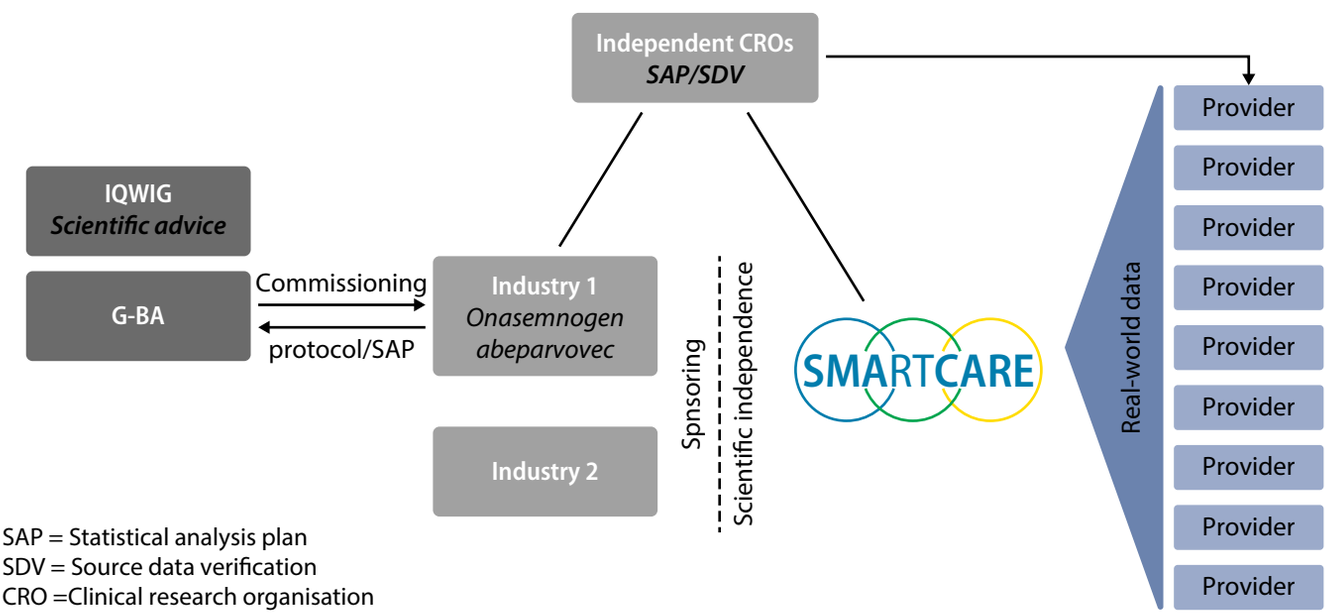
Implementation of a post-marketing data collection with the SMArtCARE registry

For the first time, the Federal Joint Committee (G-BA) has obliged a pharmaceutical company to collect real-world data in cooperation with indication registries for the therapy with onasemnogene abeparvovec and to evaluate them for an additional benefit assessment (G-BA decision of 4 February 2021). Data from routine clinical practice are to be collected over a period of five years as part of the so-called post-marketing data collection in accordance with Section 35a (3b) of the German Social Code, Book V (SGB V) to assess the long-term additional benefit as compared to the comparator therapy nusinersen in a renewed appraisal. Because the interventional studies conducted to date and the associated extension studies of onasemnogene abeparvovec only cover part of the patient population that is relevant to post-market data collection and are thus not suitable as a data source, the Institute for Quality and Efficiency in Health Care (IQWiG) mentioned the SMArtCARE registry as the primary data source in its Rapid Report of 1 October 2020.[3]

Post-markeingt data collection is designed as a sub-study within the SMArtCARE registry. All neuropaediatric centres in Germany and Austria that meet the quality guidelines (see below) for gene therapy or have treated

Collaboration of the SMArtCARE Registry with the various cooperation partners during post-marketing data collection



SAP = Statistical analysis plan
SDV = Source data verification
CRO =Clinical research organisation

Source: Professor Kirschner

Figure 1: Post-market data collection is designed as a sub-study within the SMArtCARE registry. All neuropaediatric centres in Germany and Austria that meet the quality guidelines for gene therapy will participate.

enough patients with nusinersen and are part of the SMArtCARE registry. Currently, these are 22 centres in Germany and Austria.

The five-year post-market data collection commissioned by the G-BA for the active substance onasemnogene abeparvovec has been running since 1 February 2022. The scientifically independent SMArtCARE registry was proposed by the IQWIG as the primary data source. The protocol that has been confirmed by the G-BA subject to conditions and the statistical analysis plan (SAP) were prepared based on patient-relevant outcomes derived from the SMArtCARE data collection forms. The SMA routine data documented by the providers (German and Austrian neuropaediatric centres) in the SMArtCARE registry will be transmitted in pseudonymised form to a clinical research organisation (CRO) based in Germany for post-market data collection according to the SAP. Source data verification (SDV) of the centres is also performed by an independent CRO

. In its decision of 20 November 2020, the G-BA stipulated that the use of onasemnogene abeparvovec must be associated with high quality standards (section 136a paragraph 5 SGB V, update 4 November 2021). These relate, among other things, to the infrastructure of the medical facility and its care and professional competence. Onasemnogene abeparvovec may only be used by specialists in paediatrics and adolescent medicine with a focus on neuropaediatrics. Institutions must prove their experience in the treatment of SMA with case numbers. Institutions that want to treat infants and young children with 5q-associated SMA with onasemnogene abeparvovec must participate in the registry study and collect the required routine data for the SMArtCARE registry.

What do the G-BA's requirements mean for the SMArtCARE registry?

From a regulatory and organisational point of view, the requirements of the G-BA present major challenges for the SMArtCARE registry in some cases. Despite the real-world data approach of the SMArtCARE registry, there are high-quality requirements for post-market data collection. Among other things, the G-BA requires source data verification, which is performed by an independent CRO. Moreover, post-market data collection within the registry must be reported to the ethics committees as a non-interventional (NIS) observational study. The requirements of the G-BA for the documentation of side effects made adjustments and extensions in the documentation forms of the database necessary. The considerable organisational effort for the participating centres for the documentation of the data in the context of post-market data collection – which can still not be adequately remunerated – was also much discussed.

Conclusion

As an indication registry, the SMArtCARE registry for patients with spinal muscular atrophy provides a good framework for the collection of comparative real-world evidence. The commissioned post-market data collection for the evaluation of an additional benefit of gene therapy sets high quality standards, which the registry must ensure in collaboration with independent CROs. For the participating treatment centres, participation in the study is associated with considerable effort both for patient care and documentation, for which adequate remuneration models must be established. Since the SMArtCARE registry was already established in 2017, it could rely on existing structures for the post-market data collection, thus considerably shortening the period from the definition of the protocol until the start of the study.

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Balanced reform cocktail for AMNOG: The search has only just begun

Dr Florian Staeck

At the end of 2021, the coalition announced a further development of AMNOG, some eleven years after it come into force. However, in spring of 2022, the focus and direction of this reform project were only vaguely recognisable. On the one hand, individual planned reform steps are driven by the effort to contain the dynamics of pharmaceutical expenditures in the statutory healthcare system in the short term to reduce the double-digit billion deficit in the statutory healthcare system looming for 2023. Since March 2022, this has triggered a fierce backlash from those primarily affected, i.e. the research-based pharmaceutical industry.

On the other hand, an attempt is made to address weaknesses of the existing AMNOG that have been identified as systemic. In particular, a more evidence-based pricing of new pharmaceuticals is claimed to establish a rational balance between the additional benefit of a pharmaceuticals and pricing. However, many stakeholders consider the tool of post-marketing data collection, which was created in 2019 with the Act for Greater Safety in the Provision of Medicines (GSAV), to be too costly, lengthy and associated with high methodological challenges.

In this area of conflict, the participants of the 15th meeting of the Interdisciplinary Platform for Benefit Assessment discussed perspectives for further development of the AMNOG in Berlin from 1 to 2 April 2022. The first part of the meeting was dedicated to the political debate about the share the pharmaceutical sector should bear in the required cost containment of the statutory healthcare system. On the second day, the participants discussed the possibilities and limits of post-marketing data collection. But what exactly the event title – a reform „with a sense of proportion and evidence-based" – means in this context was the subject of controversial debates.

The direction of the reform steps as they have become apparent in the draft bill for a financial stabilisation of statutory health insurance (GKV-FinStG) which has not been agreed upon within the coalition and has meanwhile been withdrawn was also heavily discussed.

The coalition sees a need for action, e.g. regarding the reimbursement amounts for orphan drugs. In view of the billions in deficits looming in the statutory healthcare system, waiting is not an option, they said. Opposition politicians, on the other hand, stressed that a one-sided focus on pricing would be wrong. Thus, the AMNOG continuously generated higher savings year after year – in 2022 alone, savings of 8.4 billion Euros would be realised, i.e. an increase of 2.5 billion Euros as compared to 2021.

This was countered by the view that the savings would be significantly lower if the newly approved pharmaceuticals came onto the market at prices according to the principle of revenue-oriented expenditure policy in the statutory healthcare system. Other participants emphasised that the share of pharmaceutical expenditures in the overall statutory healthcare system expenditures had remained largely constant at around 16 percent over the past ten years. Participants argued that structural reforms were therefore required to reasonably develop the AMNOG, which was considered the HTA „gold standard" in other countries.

They controversially discussed these aspects or reform proposals in particular:

- **Cost-benefit assessment:** The possibility AMNOG provided of initiating a cost-benefit assessment (CBA) in addition to the early benefit assessment in certain constellations was assessed very heterogeneously. On the one hand, this tool was rejected in order to avoid decreasing patients' accessibility to new pharmaceuticals. They argued that after all, the AMNOG process was working, so that there was

no need to initiate a CBA, which would be associated with a fourth hurdle. This was countered by the argument that a CBA did not automatically represent an additional reimbursement hurdle.

Instead, this tool could be helpful in pricing due to the additional information generated during a CBA. It was also pointed out that in several EU countries, e.g. France, Spain and the Netherlands, a cost-benefit analysis was conducted for every new vaccine. In addition, much relevant information had not yet been collected during the early benefit assessment and could thus not be used for pricing. In addition, the consideration of the economic long-term treatment effects could illustrate that reimbursement amounts originally criticised as „too high" were put into perspective in the overall view of a CBA. Sofosbuvir was cited as an admittedly rare and exceptional example. In this case, a cost-benefit analysis that takes into account the macroeconomic benefits of the therapy could broaden a view that is limited to the cost effects in the shielded area of the statutory healthcare system. According to the criticism, the results of a scientifically precise benefit assessment had so far been sacrificed „on the altar of a bazaar" in price negotiations. Here, a CBA could help to clarify the grey area between benefit and price.

- **Pay-for-Performance-agreements (P4P):** Some participants in the discussion spoke out in favour of strengthening P4P contracts, hoping that this would lead to a fair distribution of risk between payers and pharmaceutical companies. This position was underlined with the suggestion that to make such contract models attractive, an adjustment of the morbidity-oriented risk structure compensation would be necessary. This proposal was countered by both systematic and pragmatic considerations: P4P would have the consequence, on the one hand, that confidential prices would have to be agreed in the statutory healthcare system which would lead to physicians no longer having any information on the cost-effectiveness of their prescriptions.

Other participants were convinced that P4P agreements were too costly requiring a high level of personnel input on the part of the health insurance funds, so that they could not be used on a broad scale. It was argued that there were probably not enough human resources in the statutory healthcare system to be able to manage several dozen contracts for individual gene therapies at the same time. Against this background, P4P would continue to play a role only in selective contracts and in exceptional cases.

- **Markdowns in the context of combination therapies:** The draft bill for a financial stabilisation of statutory health insurance calls for a flat-rate discount on the reimbursement price if a new active ingredient does not replace another pharmaceutical but complements it reasonably, resulting in more effective combination therapies. Although this only applied to a few therapies so far, the number would increase in future. Participants noted that there was a need for action e.g. in oncology, but also in other chronic diseases, since newly approved active ingredients already lead to increases in expenditure in monotherapy. Similar issues arose in the context of single-use therapies, for which the AMNOG would not yet provide any useful pricing tool to implement the revenue-oriented expenditure policy anchored in SGB V.

The proposal of a flat discount was met with scepticism by several participants. Combination therapies occurred in very diverse constellations, so that it was questionable whether a rigid discount, e.g. 15 % on the reimbursement amount as mentioned in the draft bill, could be the right answer. Moreover, this would neither be a „learning sys-

tem“ under the AMNOG, nor could a rigid discount be well justified with reference to the principle of evidence-based pricing.

Participants argued that there were also practical procedural concerns: For example, a discount would presumably be priced into the introductory price called by the pharmaceutical company in the event of its legislative implementation. In addition, the question arose as to which treatment combinations should be covered by such a procedural requirement at all. It was argued that delimitation problems as to whether it was a combination therapy or merely a change in therapy were foreseeable.

- **Interim prices or shortening of the phase of free pricing from the previous twelve months after approval:** Participants lively discussed the extent to which orphan drugs promoted decoupling of price development from the additional benefits of new pharmaceuticals. In the draft of the financial stabilisation of statutory health insurance act, it was planned to shorten the free pricing phase from twelve to seven months which had already been criticised as an inadequate compromise in the past. Instead, representatives of the payers had proposed an interim price instead of the free pricing immediately after approval. This tool which was declared to be merely a calculation parameter to create new incentives for manufacturers to generate further evidence for the additional benefit of the new therapy even after approval.

It was countered that the interim price would de facto be a fourth hurdle in the reimbursement process, as – in an international comparison – no case was known in which the introductory price subsequently increased. This was contradicted using SGLT2 inhibitors as an example, where prices had also been raised because of a superior data situation. Participants complained that the answer to uncertainties in the evidence assessment could not be a purely selected price and the proponents of this idea had so far failed to provide methodological indications of how such a price could be appropriately formed. On the other hand, it would be more promising to further develop instruments in the statutory healthcare system that had so far not been running smoothly. Representatives of this position referred e.g. to managed entry concepts or pay-for-performance agreements, respectively.

AMNOG was facing high pressure to change in view of high and short-term deficits in the statutory healthcare system, was one of the conclusions of the debate. At the meeting of the Interdisciplinary Platform, a standardised reform concept combining short-term and long-term aspects of further development, was at best only recognisable in rudimentary form. In the discussion, the positions along the aforementioned points proved to be predominantly hardened: It was pointed out that new incentives for generating evidence were needed if the principle of early reimbursement of new pharmaceuticals in the statutory healthcare system was to be maintained. Germany had a special position in this respect as compared to other European countries. Orphan drugs were available in the statutory healthcare system on average 55 days after market approval, while in Italy this process took around one year and in Spain an average of 620 days. The reason for the dynamic development of pharmaceutical expenditure was the high launch prices of the manufacturers, i.e. an average discount of 22 % during the negotiated reimbursement price could no longer sufficiently slow down this dynamic, they outlined. This was because it could be assumed that this discount had already been considered when setting the list price.

Other participants warned against cumulative burdens on the research-based pharmaceutical industry, as set out

in the draft of the financial stabilisation of statutory health insurance act. In addition to the average 22 % discount in the early benefit assessment, there could be an incremental manufacturer discount for patent-protected pharmaceuticals, which was set at 19 % in the draft for 2023, a discount of 15 % on combination therapies, and the consequences of an interim price demanded by the health insurance funds. But all of this overlooked the fact that Germany was the reference price country in Europe for global companies.

In contrast to 2011, when the AMNOG came into force, the weighting of global sales markets had shifted strongly to the detriment of Germany and in favour of China; Germany now accounted for only 1 to 2% of global sales. And in contrast to the situation ten years ago, manufacturers could now refrain from launching a new active ingredient in Germany in future when political decisions were taken presenting a burden Germany as a pharmaceutical location. All this should be weighed against the AMNOG of the past: The argument was that AMNOG generated ever increasing savings for the statutory healthcare system and offered reliable framework conditions for companies.

Post-marketing data collection: Challenges and limitations

The second part of the meeting dealt with the pros and cons of post-marketing data collection. With the GSAV, the legislator allowed the Federal Joint Committee (G-BA) to oblige the manufacturer of a new active ingredient to conduct a post-marketing data collection within a reasonable period of time. The aim of this provision was to set incentives to ensure that reimbursement rates did not remain permanently high despite insufficient evidence. In 2021, around one-third of newly approved active ingredients were subject to accelerated approval.

The challenges were high: The European Medicines Agency (EMA) was increasingly granting approvals based on phase Ia/IIb studies as well as for single-arm studies. However, participants noted, that the FDA practised this approach much more aggressively and extensively than the EMA, so that approval times on both sides of the Atlantic were increasingly diverging. Participants argued that there was an increased risk that physicians would take treatment decisions based on insufficient data, because there were few data on efficacy and potential harms at this early stage and certainly not about the long-term efficacy of a pharmaceutical. However, most participants were sceptical about whether the concept of post-market data collection in its current form was suitable for closing evidence gaps to a sufficient extent and for promoting pricing that was more strongly oriented toward evidence. The debates focused in particular on these aspects:

- **Methodological challenges for non-randomized studies:** With the GSAV, the legislator had explicitly excluded randomised, blinded studies from the scope of post-market data collection. However, the text of the law mentioned, among other things, observational studies, case-control studies, or prospective comparative cohort studies in the sense of a registry study. However, participants emphasised that a post-market data collection could not be a „benefit assessment light". Rather, the legislator's waiver of randomisation – which was worth criticising – placed special demands on the study design.

  In this context, the principle applies that the smaller the expected differences in therapy effects were, the more urgent the fair comparison was. Comparisons were only meaningful if the starting conditions for different patient groups were fair. In fact, a post-market data collection would have to be planned like a randomised study – only

without randomisation, it was emphasised. For example, as in an RCT, there would have to be a standardised data collection, and valid survey instruments for patient-reported outcomes would have to be used. Particular attention would have to be paid to systematically identifying and collecting data on the relevant confounders. On the other hand, it was pointed out that for new, increasingly personalised pharmaceuticals, new methodological approaches would also have to be developed taking into account the specific requirements of new therapeutic approaches.

Overall, waiving of randomisation in a post-market data collection would be bought with a higher effort compared to an RCT. In addition to the question of study design, problems of the ethical justifiability of a post-market data collection would also arise in individual cases, e.g. if the active substance concerned was a therapy soloist and patients had so far only been treated with best supportive care. All these challenges made it clear that the correct and appropriate handling of „uncertainty" was of great and ever-increasing importance in view of the new therapeutic procedures undergoing the AMNOG.

- **Temporal challenges:** From the perspective of several participants, the timing of the first post-market data collection as decided by the G-BA for the active substance onasemnogene abeparvovec (Zolgensma®) highlighted the high time requirement of this tool. The gene therapy medicine for the treatment of spinal muscular atrophy (SMA) in children under two years of age had received conditional approval in the EU in May 2020 and could be used in Germany since 1 July 2020. In February 2021, the G-BA decided to request a post-market data collection from the manufacturer.

Finally, in January 2022, the study protocol submitted by the manufacturer and the statistical analysis plan were formally confirmed in a further G-BA decision. According to the current status of the procedure, statements on the long-term benefit should be available in summer 2027 as a result of the post-market data collection. This timeline made it clear that data collection for a post-market data collection should have begun well before the intended approval. It was recalled in this context that the first patient had already been treated with the gene therapy agent in 2012.

- **Challenges regarding data generation:** It was emphasised that it was advisable to generate network structures already in the run-up to the decision on a post-marketing data collection. In many cases, it would not be possible to recruit patients only nationally. The central goal would have to be to derive the required data from the treatment files with as little effort as possible. It was warned that the manpower in the healthcare sector alone would not be able to cope with the additional documentation effort. Although documentation was not a mandatory medical task, it would have to be financed. Other participants countered that a prospective study design was indispensable for registries because bias factors cannot be sufficiently identified retrospectively. This was because confounders were not documented in hospital databases, they said.

According to the participants, remuneration for documentation was another potential bottleneck in data generation. This was because centres participating in a registry should only be reimbursed for the administrative effort involved, so as not to create an incentive for a specific prescription. But this effort was high, participants recalled, referring to the post-marketing data collection concept for onasemnogene abeparvovec. In this specific case, they said, complex endpoints would have been established that required physicians to be trained on the measurement

tools. Against this background, nine to ten post-market data collections per year, which the legislator still assumed in the GSAV, would have to be considered unrealistic. Given the effort, there would rather be a maximum of four to five of these data collections per year in the future, participants predicted.

- **Infrastructural and regulatory challenges:** Given the multitude of problems that remained unresolved to date, the participants were convinced that post-marketing data collections could not be made successful without a previously established registry structure. However, there had been no clear statements from health policy makers as to what priority the project of a registry law would have in the current legislative period. A study commissioned by the German Federal Ministry of Health revealed a very heterogeneous registry structure among 356 registries in Germany. Participants argued that post-marketing data collection was associated with the need for completely new governance structures. The „old world" in which a registry owner received a request from a manufacturer and then provided specific data, no longer existed, they said. When a company was requested to conduct a post-marketing data collection by the G-BA, the company became the sponsor of a study and would have to seek appropriate cooperation agreements with the registry owner, they said. However, a central registry agency that could take on coordinating tasks in the registry landscape only existed on paper so far in the coalition agreement of the Ampel coalition.

In view of the unresolved regulatory challenges, individual participants argued that post-marketing data collection should be detached from early benefit assessment and instead be better and more reliably located in the approval of an active substance. They proposed to rather link the request for data collection to the award of the orphan drug designation. This step alone could then oblige manufacturers to enter data in registry studies. However, this step could only be taken at European level

Finally, the consequences of a post-marketing data collection for the pricing of a new active ingredient have not yet been clarified, participants pointed out. The legislator had provided for discounts on the reimbursement price if the evidence is unsatisfactory even after a post-marketing data collection. To this end, standards would have to be established at the level of self-governance in a framework agreement, but these did not yet exist, participants pointed out. Whatever possible reductions might look like here, the savings potential for the statutory healthcare system would be minor in view of the high time expenditure of a post-marketing data collection.

As a conclusion of the 15th meeting of the Interdisciplinary Platform for Benefit Assessment, the participants noted that the short-term threat of a high deficit in the statutory healthcare system required fast-acting cost-containment measures, but that these burdens would have to be distributed among the various players in the healthcare system with a sense of proportion. Separated from this was the further development of the AMNOG in the sense of a stronger evidence orientation, which was both necessary and difficult. It is true that the legislator sees post-marketingt data collection as a tool with high potential. In reality, however, post-marketing data collection is a very complex tool whose functionality is also associated with a wide range of prerequisites, such as an interoperable structure of registries. The search for new evidence-based reform approaches for the AMNOG that have a cost-containing effect and accounted for the increasingly targeted specifics of innovative therapeutic procedures has only just begun.

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INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

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

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