INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

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# Adaptive Pathways – Opportunities and Risks

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# Contents

# Goals of the platform

In 2011, the legislator initiated a paradigm shift in the field of pharmaceutical supply in Germany, with far-reaching consequences. The principle, based on the AMNOG, provides that: for new active substances brought on the German market, the pharmaceutical company must prove an additional patient-relevant benefit compared to the available standard of treatment – the appropriate comparative therapy (ACT) – if a higher reimbursement price is sought than for the ACT.

The additional benefit is evaluated and determined by the Federal Joint Committee (Gemeinsamer Bundesausschuss), generally on the basis of proposals from the IQWiG. The pricing is determined largely by the result of this additional benefit assessment. In Germany the price is for the first time negotiated between the National Association of Health insurance Funds and the pharmaceutical company.

The assessment of the additional benefit by the G-BA is the result of expert work based on a law (AMNOG) and on procedural and methodical regulations (e.g. IQWiG methods). 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 (Medizinischer Dienst der Krankenkassen, MDK) 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 drugs, likewise classified and interest-based, are submitted by the pharmaceutical companies to the G-BA, 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 drug approval,
- Working towards international standards of evidence-based medicine and of health economy being adhered to and applied,
- Determining whether and to what extent actual 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,
- Identifying 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.

The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. The Advisory Council considers an interdisciplinary discussion regarding the results of the assessment and the applied benefit assessment methods to be essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new drugs for patients earlier than it was previously the case.

The interdisciplinary platform resulted from 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 Roche Pharma AG, DAK Gesundheit, Xcenda GmbH and Springer Medizin.

**The Advisory Council of the Interdisciplinary Platform on Benefit Assessment**

# Early approval with limited data: Do opportunities outweigh risks?

**By Dr. Pamela Aidelsburger und Dr. Jürgen Bausch**

*The early approval of a new active substance through the existing instruments of the EU regulatory authority EMA or through „adaptive pathways" can be indicated, especially in cases where the unmet medical need is particularly high. Early approval requires carefully weighing how much possible damage potential society is willing to accept in order to obtain what may be a final treatment option for a patient. In addition to ethical questions such as equity, adaptive pathways are also associated with challenges regarding the early assessment of benefits: As long as the definition of the unmet medical need is not clear, weighing the benefits and risks in the assessment process will generally be controversial.*

Pharmaceutical industry research is a high-performance field with the goal of meeting unmet patient needs. This unmet medical need has always been an important driving force among experts to „paw the ground" – even though this „need" was weighted differently by pharmaceutical companies and paying parties. New active substances with the potential to satisfy an urgent unmet medical need, for example in case of orphan drugs or oncology products, could be granted early approval through adaptive pathways even when only limited data about effectiveness and damage potential are available for decision making at the time of approval, primarily due to time constraints.

The existing instruments of the EU regulatory authority EMA are known: „accelerated access", „compassionate use", „conditional marketing authorisation" and „marketing authorisation under exceptional circumstances". One wonders why the European regulatory authorities are bringing further changes (such as adaptive pathways) into the discussion, especially when one notes that the use of the current possible pathways is very limited.

The approval of a new active substance in Germany is only one side of the coin. With the AMNOG (German Pharmaceutical Market Reorganisation Act), a newly approved pharmaceutical product is subject to a benefit assessment as the basis for subsequent pricing. Methods for the assessment of benefits in the course of approval and pricing are not uniform even for „normal" active substances. Every institution has its own peculiarities and perspectives. The discrepancy in the methodology approach for new active substances to cover a severe unmet medical need is likely to be even greater when the evaluation of benefits is performed based on limited data.

Let us discuss approval further for a moment. Not only „the industry" and by far not all experts at companies conducting research are „pawing the ground". Powerful politi-

cal forces dedicated to industrial policy are also at work, along with patient representatives criticising the conventional approval procedure that takes months or years.

Pronounced pressure aimed at shorter approval processes is applied primarily where satisfactory treatment options are not yet available for severe patient problems. This applies to a number of cancers and rare congenital, hereditary disorders. As soon as initial positive results regarding minor therapy progress are reported – usually in tiny subgroups only – journalistic pressure is applied by the media. This is perfectly understandable for oncology patients with progressive tumours as well as parents forced to helplessly watch the decline of their child with a genetic defect, unable to do anything.

But as long as there is no national and international consensus regarding the question of what an „unmet medical need" is, a discussion of the criteria for more relaxed approval practices in exceptional cases will always be controversial. The weighing of benefits and risks once again plays a key role in the assessment of benefits for reimbursement decisions. Here too the question is what probability of error a society is willing to accept in reimbursing the costs of a treatment when its benefits were not determined on the basis of sufficient data.

This suggests questions of equity: Is it ethically justifiable to reimburse the treatment costs for a small number of patients with a high unmet medical need, but not a large group with a lesser need? Who determines with what probability of error a patient receives treatment even though there may be serious side effects and this cannot be evaluated yet based on the available data? Especially from an ethical perspective, there will always be situations in exceptional cases where the persons in charge at the regulatory authorities can utilise the existing possibilities for accelerated approval.

Our existing conference proceedings for the third convention of the „Interdisciplinary Platform on Benefit Assessment" documents the current findings on the question of possible approval changes at the European level and their significance in the final assessment of benefits by the Federal Joint Committee from different perspectives.

The discussion revealed a need for action on two points in particular. A further development of fast approval pathways is going to widen the gap even more for the assessment of benefits in the context of price negotiations and reimbursement. Even now manufacturers are frequently having problems providing reliable data for all patient populations in the assessment of benefits. The participants agreed that uncertainty in regards to weighing the supposed benefits on one side and not yet reliably investigated damage potential on the other side constitutes a problem. How much possible damage potential is the patient, society or also the paying party willing to accept in order to obtain a possible benefit – even if the patient is merely grasping at straws?

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# Adaptive Pathway and PRIME Initiative – Trojan horses in the approval process?

**By Dr. Ansgar Schulte, Professor Dr. Karl Broich | Federal Institute for Drugs and Medical Devices**

*Innovative medicines for hitherto inadequately treatable diseases should reach the patient as quickly as possible. Existing procedures and processes such as early scientific advice, conditional approval or accelerated processing procedures shall therefore be optimised towards this goal in the European approval procedures. The European Medicines Agency (EMA) and the national regulatory authorities have supported this goal with the initiatives „Adaptive Pathway" and „Priority Medicines" („PRIME"). Principles and first experiences from this process and regulatory consequences are presented.*

There are always stronger efforts to make innovative medicines available to patients faster, as there are still many diseases for which there are no adequate treatment options.

This is the case for many oncology indications, but also for very rarely occurring diseases (orphan diseases). This is called a high „unmet medical need". When it comes to life-threatening diseases or when significant deterioration would be the outcome without treatment, it is also understandable that patients would wish to use new drugs as quickly as possible.

Here the current approval procedure takes too long and many development programmes in large populations also failed in the past due to an incorrectly selected study population or inadequate formulation of the research question.

Even today, many active ingredients have not proven effective in the development because they do not help all patients. Firstly, the patients are different, and on the other hand apparently phenotypically identical diseases often have different causes and outcomes. Statistically, sometimes no significant difference in favour of investigational treatment is then found and the development of such a drug is stopped.

The regulatory authorities have, however, learned that some of these active ingredients can nevertheless help certain subpopulations, although they are not suitable for wide application. If these patients could be identified beforehand by suitable markers, for example, through a genetic test or through detection of a particular molecule in the blood, the effectiveness of a drug could be demonstrated in a study and it could be made available to patients, rather than phased out as is the current practice.

For this reason the European Commission have taken up the cause to bring new and innovative medicines to patients faster in the expert group STAMP (Commission Expert

Group on Safe and Timely Access to Medicines for Patients) [1]) and the European regulatory authorities in their strategy paper (EU Medicines Agencies Network Strategy to 2020) [2].

The expert group STAMP was established to advise the departments of the European Commission in view of the implementation of EU pharmaceutical legislation and programmes and actions in this area. The group exchanges views on ways and initiatives in EU Member States on how to use existing regulatory measures even more efficient to ensure that patients have access to new drugs as early as possible.

The pharmaceutical regulatory preconditions for this has already existed under the „conditional approval" or in the potential for accelerated processing („accelerated assessment") for a long time, for example; they should now only be applied better and in a more flexible manner. The PRIME initiative [3] of the EMA is the most consistent in implementing this, comparable to the „Breakthrough Therapy Designation" programme of the American Food and Drug Administration.

PRIME is a programme that was initiated by the EMA and which can be used since March 2016. It aims to enhance the development of drugs against serious diseases for which there are no adequate treatment options. In the development of such drugs, the EMA is now offering support already at a very early stage and promotes this through specific means; for example, by reduced fee rates of the related scientific advisory procedure and the optimisation of development plans that it enables.

The primary objective is that in a positive benefit-risk ratio innovative drugs are available to patients as early as possible.

In addition, innovations nowadays often see the light of day in academic centres or small and medium-sized start-up businesses (SME). Scientists there have very good con-

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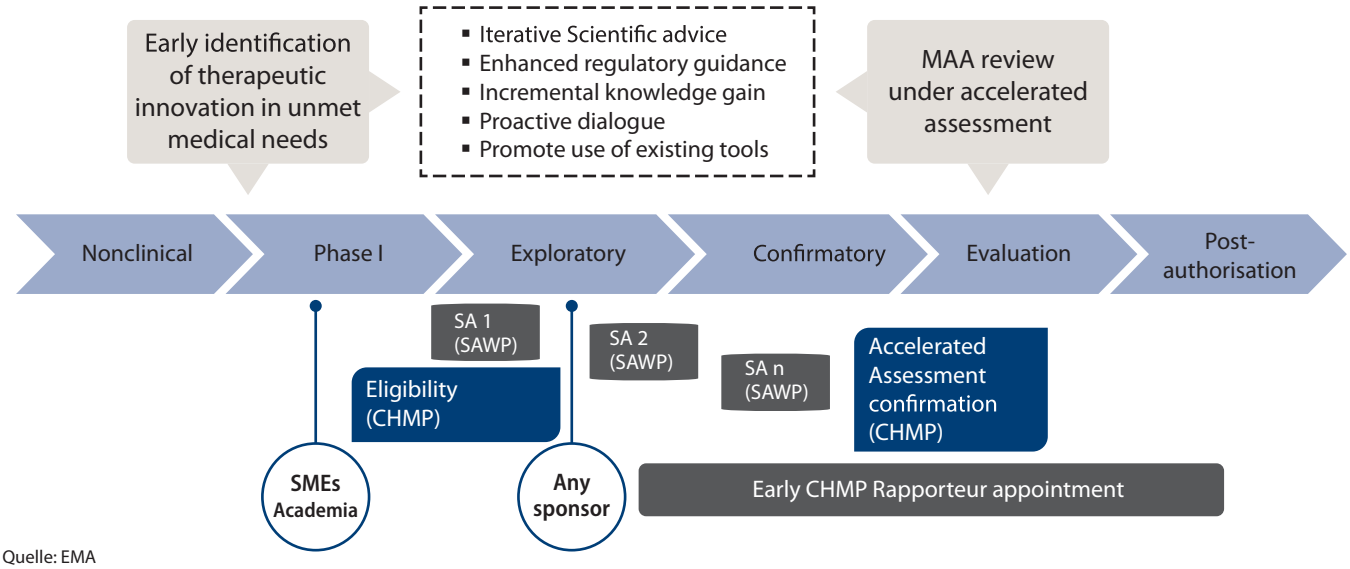
cepts, but are inexperienced in the regulatory decision-making processes, and so often make the wrong regulatory decisions. Not least many development programmes fail because of this. Such errors should be reduced by the PRIME initiative through the very early collaboration of a rapporteur team and experts of the regulatory authorities with applicants, ranging from early scientific advice to the final recommendation for approval in the European approval committee (see Figure).

The aim with these models is to find a way that satisfies both the demands as regulatory authority and the interest of the patients in question. One of the ideas is to not test the clinical trials directly in a large patient population, but to begin with the patients who could benefit the most from the new treatment (Adaptive Pathway concept) [4]. The concept of adaptive approval is based on three principles:

1. The iterative development, which means either:
   - Gradual approval, starting with a limited patient population, which can be extended to a larger population, or
   - The confirmation of a balanced risk-benefit ratio of a product after conditional approval based on early data with surrogate markers, which were examined as predictors of the important clinical outcomes.
2. Collecting evidence on health-care data („real-life use") to complement data from randomised clinical trials.
3. The early involvement of patients and evaluation panels

**Arzneimittelentwicklung im Rahmen der PRIME-Initiative**




Quelle: EMA

Figure 1: Drug development as part of the PRIME initiative: Early starting repeated scientific advice (SA) and early assignment of a rapporteur who oversees the development programme (lifecycle management of a product) and organises and makes the required regulatory expertise available. (Source: EMA)

in the discussion on the development of a drug. Characteristic of this development is the formulation of specific indications or the development of drugs for well-defined, mostly small groups of patients – without non-identifiable artificial entities being created in clinical practice, though. Associated with this shift away from the blockbuster principle of drug development, clearly differentiated regimens are often developed, including, where applicable, individual dose titration, so that the „one strength once daily for all" principle applies more rarely.

Here critics speak of a limited data base and the lowering of approval standards, impermissible concessions for the pharmaceutical industry, displacement of risks of the treatment to patients and attending physician – however, in our view this is not true.

The evidence for the effectiveness of a new treatment in such a better defined patient group usually is even higher.

More comprehensive efficacy and safety data have to be generated for the wider use of a drug after first closer approval. Here, the regulatory authorities now gain experience how much additional evidence must come from traditional randomised controlled trials and to what extent so-called „real-world" or health-care data can be taken into account. How the product develops and what indications can still be added then shows up over time. Furthermore, this also does not become the „control method" of the approval, but remains limited to specific, well-defined cases. So the majority of applications for a PRIME process are also

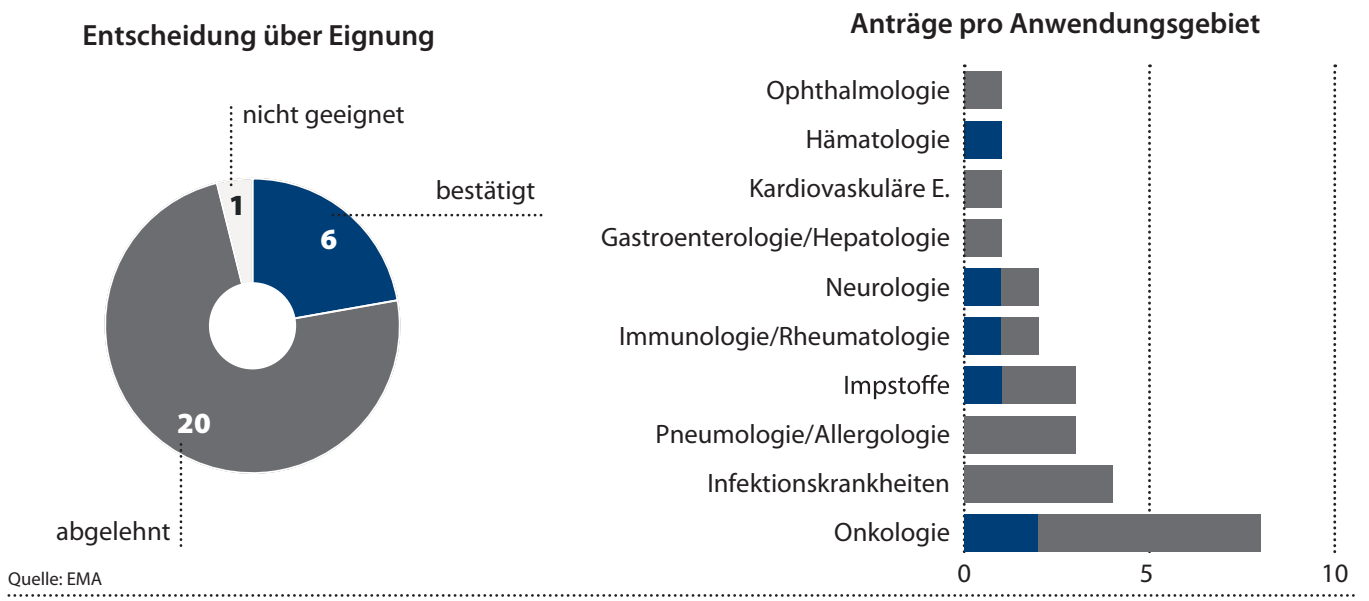



Figure 2: First experience with an application under the PRIME initiative, in terms of which only six out of 27 applications were accepted, the majority of applications was found in oncology indications.

rejected after experiences in the first few months (see Figure).

Early involvement of the Health Technology Assessment authorities (HTA), in other words the authorities that are responsible for assessing health-related technologies, is essential here: With the further development of a product and the possible future expansion or specification of the application areas, adapted updated assessments on the additional benefits of a drug are also carried out. Concretely, one will thus see more conditional approval decisions with conditions which must be met in specific time slots. Accordingly, there might be limited assessments of additional benefits in the future.

We want to use the pilot phase of Adaptive Pathway and PRIME for their further development and as the Federal Institute for Drugs and Medical Devices (BfArM) we are actively engaged in it.

The biggest challenge for pharmaceutical companies today, however, is to design clinical trials in such a way that they meet the requirements of the regulatory authorities in the different markets, while at the same time meeting the requirements of the Federal Joint Committee (G-BA) for early additional benefit assessment.

As other countries have also implemented complex health technology assessment processes, most multinational studies must also meet their requirements. Here the early scientific advice by the participating institutions is of increasing importance since. The assessors already gain critical business insights into the benefits of new drugs in the approval process. As a rule, the benefits of a drug is examined within the framework of controlled clinical trials. Here the efficacy and side-effect profile of the drug to be tested are compared with either an established comparative treatment (comparator) or with a placebo. In most cases, the application of the comparator takes place in Germany according to the specifications of the approval text.

The regulatory authorities in the EU also accept an active comparator when it is listed in the corresponding dosage in the guidelines of the scientific associations of at least one member state. This allows pharmaceutical companies to carry out large multinational clinical trials, even when approval texts and treatment standards vary in different countries. The results of the drug approval procedure are then also instrumental for the additional benefit assessment, because the clearly defined indication in the approval process creates the basis for an assessment of the additional benefits by the Federal Joint Committee (G-BA).

The additional benefit is a benefit that is quantitatively or qualitatively higher than the benefit of the appropriate comparative treatment. The appropriate comparative treatment must also be approved in the indication and dosage used in Germany. This means the appropriate comparative treatment is more narrowly defined than the comparative treatment, which can be used for registration purposes. In this respect the Federal Institute for Drugs and Medical Devices (BfArM) can make an early contribution: The relevant outcomes and comparative treatments in this regard are known, which means the applicant can be given valuable information in the scientific consultation.

In the cooperation with the Federal Joint Committee, however, points of discussion about the issue of appropriate comparative treatment or the relevant outcomes of clinical trials always come up again. This was also a topic of discussion of the dialogue event „Creating Health Together – BfArM Strategy 2025“. Pharmaceutical companies pointed out that the regulatory authorities sometimes have different requirements than the Health Technology Assessment agencies. While the BfArM assesses the risk-benefit ratio, the Federal Joint Committee is concerned about the question of whether the benefits of a drug is greater than

the benefit of a comparative treatment. There are reasons for this. The approval and the early benefit assessment of new drugs are regulated in several jurisdictions (AMG [Medicines Act] versus [Social Security Code Book V] SGB V) and have different aims and testing programmes.

However, without prejudice to the different task definitions, there is a justified question as to the possible convergence of the requirements. Many of the important parameters for early benefit assessment would already be possible to determine under clinical trials without much additional effort when the respective requirements are taken into account at an early stage. The outcomes selected for approval are not always accepted in the additional benefit assessment, such as the measurement of the progression free survival (PFS).

The discrepancies in the discussions between the Federal Joint Committee and the participating pharmaceutical companies therefore mostly concern the establishment of the appropriate comparative treatment, the definition of relevant subgroups, acceptance of patient-relevant outcomes or the classification and grading of side effects. This will only change when the pharmaceutical companies actually seek advice before the start of the Phase III studies and the possibility exists to jointly coordinate requirements both by the Health Technology Assessment institutions and the regulatory authorities.

Because of this need for coordination, the Federal Institute for Drugs and Medical Devices (BfArM), the Paul Ehrlich Institute (PEI) and the Federal Joint Committee have decided on the „structured cooperation between the Federal Joint Committee, the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute“ [5] to establish joint early consultation as a routine procedure. In addition, data exchange should be improved and dialogue between the participating institutions promoted. Assessors of the Federal Institute for Drugs and Medical Devices (BfArM) and consultants of the Federal Joint Committee now get the opportunity to work in the other institution for a certain period of time. The goal is to get to know the local structures and to gain a deeper insight into the work processes and assessment criteria. This approach is aimed at creating a network of contact points. The exchange so benefits the cost-effectiveness and promotion of innovation of both institutions as well as top-quality patient care.

In addition, the Federal Institute for Drugs and Medical Devices (BfArM) has entered into a more intensive and structured dialogue with the patient representatives to include their expectations and assessments.

In the context of central rapporteur processes, it is necessary to take patients‘ points of view with regard to questions about appropriate study outcomes or potential risks, for example, more strongly into account: What are appropriate patient-relevant outcomes? What side effects are still acceptable at a certain spectrum of effectiveness? Is there an „unmet medical need“?

If all these points are adequately considered and critically weighed in the early planning of clinical trials, many development programmes for drugs can be optimised; they lead to better results and give patients faster access to innovations. This goal is supported by programmes such as „Adaptive Pathway“ or PRIME and we as regulators are the last ones to have an interest in lowering approval standards.

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# Politics between industry and patient interests

**Michael Hennrich | Member of the German Parliament**

*Lawmakers face the challenge of ensuring patient access to a supply of high-quality pharmaceutical products along with planning and legal certainty for pharmaceutical companies, while simultaneously maintaining the ability to finance the healthcare system. The German Pharmaceutical Market Reorganisation Act (AMNOG) in 2010 marked a watershed in these efforts. Overall the law has proven itself. Existing conflicts in assessment procedures should be addressed through process changes initiated by self-administration. Many of the conflicts could be addressed with a doctor information system providing doctors with substantiated information about the AMNOG assessments. Here quality and additional benefits should play an essential role.*

While a bold title was specified for me here, I believe the role played by health insurers in the system needs to be questioned in particular. Ultimately it is often the health insurers who enforce patient interests. Here I am assuming that the interests of the health insurers should largely be identical to those of the patients.

Demands of the industry: Generating healthy sales and profits is naturally the primary focus. Access to skilled workers and an intact infrastructure are required as well. Furthermore, there is an interest in innovations and in bringing them to market. Politics however must in particular guarantee planning reliability and legal certainty in the approval and assessment process in order to support long-term, costly measures and research by the manufacturers. Pharmaceutical companies play an active role in the healthcare system and need to rely on stable basic condition in order to live up to this expectation.

Demands of the patient: For patients the most important goal is access to a high-quality supply of medications. Affordability must be guaranteed at the same time. The justified demand for fast access to innovative products at times encounters various patient care realities in practice. For instance, the „arrival" of the new medication in the healthcare system sometimes still depends on the health insurer and region. Progress in the development of medications for previously incurable diseases represents a tremendous gain for patients. However, the distribution of costs is very unequal here. Given the great diversity of around 120,000 products, 86,000 items and 13,500 brands, there are a mere 2,750 active ingredients of which only 500 account for about 95 percent of sales. However, treatment alternatives are demanded and also required, especially for serious illnesses. Mistrust towards new preparations can

however be noted as well, especially since a lack of evidence, intolerance or ineffectiveness reduce confidence at times.

**What does the reality look like?**
Rebate agreements, the reference price system, the right of the patient to care pursuant to Section 2 SGB V and the efficiency principle according to Section 12 SGB V (including the jurisprudence of the Federal Constitutional Court, see so-called „Nikolaus verdict") form the legal framework for day-to-day healthcare.

A quick check of the reference price system and the rebate agreements: reference pricing and rebate agreements have largely proven themselves. One problem is that adjustments in the reference price system do not reach doctors and patients quickly enough (high additional payments in the pharmacy). The issue of rebate agreements and delivery bottlenecks is another important aspect that we will keep an eye on. In principle however, affordability is guaranteed by all the established measures; they have resulted in significant price reductions already.

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***I think it is important to leave some leeway in the reference price system and implement therapeutic progress more effectively.***

Therapeutic diversity needs to be maintained at the same time. The possibilities of the aut-idem rule, pharmaceutical concerns, the substitution exclusion list and the additional cost rule (with the patient paying the surcharge out of pocket) are named here as examples. I think it is important to leave some leeway in the reference price system and implement therapeutic progress more effectively. Conclusion: There is little need for changes in this area.

**Rebate agreements and delivery bottlenecks:**
Delivery bottlenecks for pharmaceutical products, especially in the areas of oncology products and antibiotics, affect day-to-day healthcare negatively. Delivery bottlenecks have multi-factorial causes in the international context that can be preceded by market developments over many years as well as government intervention, such as the design of rebate agreements. This means there cannot be a single way to prevent delivery bottlenecks. However, the Federal Ministry of Health and the manufacturer associations are already in contact regarding this issue. It would not

have been possible to finance the old system much longer: Until 2010 we had the problem with patented pharmaceutical products that the costs were getting out of control while no therapeutic progress was evident in many cases. It was essential to ensure that the supply of patients with patented products added value for the patients. What was the situation in Europe? Germany was one of the last countries that did not yet have market access restrictions. We remember the discussion about bogus innovations and me-too preparations with a high financial burden for health insurers and therefore patients.

**AMNOG:**

Here the German Pharmaceutical Market Reorganisation Act can be considered an essential watershed. The early assessment of benefits and subsequent price negotiations for new pharmaceutical products brought pricing and the benefits of medications closer together.

There were three basic defining concepts:

- Faster access to innovations (unrestricted pricing, no fourth hurdle)
- Planning reliability and legal certainty for companies
- Affordability

However, many small and detailed rules were negotiated and discussed in controversial debates: Among these were the fundamental question of who plays what role in the system, or what the role of the industry should be in the assessment procedure (scoping process as in Scotland). Very different interests also became apparent regarding the question of who negotiates the price when and at what point in time, or whether centralised or decentralised control would be best for doing justice to the various players.

Surely the classification of the various additional benefit levels can be considered to be in the interest of the industry as well. The definition of the additional benefit however was a key point of conflict, for instance since the IQWiG imposed very restrictive requirements here and the quality of life was difficult to measure with the applied methods. Patient interests clearly need to be the focus here, but this can be highly subjective on occasion.

*The AMNOG has largely proven itself in practice and is not being fundamentally questioned.*

The debate surrounding orphan drugs also posed the challenge that the interests of patients and the industry aligned here on the one hand – researching rare diseases and the accompanying, desirable establishment of innovations – but, on the other hand, the health insurers and therefore also the patients had an interest in affordability. We also faced the challenge of how the role of the industry in the system could be strengthened (Section 130c – contracts and partners in integrated care).

**Where do we stand today?**

The AMNOG has largely proven itself in practice and is not being fundamentally questioned. It is largely accepted by health insurers and by the industry. Patients are relatively unaware of it. In my opinion, we did quite well in attaining the objective of achieving a balance between fair prices for the industry and affordable prices for the health insurers. While there are still scattered discussions about a positive list and a fourth hurdle, I believe by and large that this is not going to happen.

Too much focus on cost effectiveness, not enough on quality: The core of the AMNOG is to make every medicati-

on available on principle, especially innovations, and to provide fast access for patients. Free market access and free pricing directly follow approval under pharmaceutical products law. A preparation is available to patients after just two months. That is much faster than in Great Britain, Spain, France or Italy. The early benefit assessment and subsequent pricing take place in parallel. This does not break any taboos in the international comparison, nor does it contradict approval under pharmaceutical products law. Safety, effectiveness and quality were already confirmed with the approval. Only the added value compared to other treatment options is determined by the G-BA in the subsequent benefit assessment, separate from approval. Ensuring high-quality care in the medium and long term is the primary objective.

Ensuring affordability: As mentioned however, it is necessary to weigh the various interests in order to ensure affordability. We have recently seen the potential cost risks with the hepatitis C example. That is also why topics such as the retroactive reimbursement amount, an upper limit for sales or greater contractual freedom in terms of upstream rebate agreements in the system are being seriously discussed.

Structured dialogue between the regulatory authorities and G-BA with the involvement of the IQWiG: The coordination problems repeatedly criticised in this context caused by the different requirements for study design and so on in the context of approval and the assessment of benefits are increasingly being resolved. Optimising cooperation between the regulatory authorities and G-BA is under way and a common approach has been agreed upon. In particular, this makes planning easier for the manufacturers.

The assessment procedure: We have a reasonable distribution of duties between the IQWiG and G-BA. However, equitable participation rights of the pharmaceutical products commission and the professional associations in this process are important to me. Here I also consider adequate participation for patients and the strengthening of procedural rights to be relevant. This cannot and does not have to be resolved by lawmakers. Here I count on process changes initiated through self-administration.

**Chronic illnesses/surrogate parameters:**
The question of how we deal with chronic illnesses and endpoints relevant for patients remains to be clarified. This is also an essential topic in the pharmaceuticals dialogue. The problem lies on the one hand in the debate about the surrogate parameters, since the strict methodology of the IQWiG does not work here. On the other hand, it should be clear that patients cannot wait ten years or more until survival evidence is proven. Improving the quality of life also constitutes an endpoint relevant for patients.

Especially with chronic illnesses, problems occur with the assessment since an additional benefit is not attested for new products relatively often here and there are also assignment difficulties related to multi-morbidity. This leads to recurring complaints from the professional associations and providers. Often the additional benefit is also rejected for formal reasons, for instance in diabetes. But insofar as insurers are not willing to make concessions on the reimbursement side, there is even the threat of a market withdrawal in Germany in such cases which results in a worsening of care. A reassessment is in fact quite possible. But according to the AMNOG, this can only take place after one year pursuant to Section 35a, Paragraph 5 SGB V. That does not help the affected patients! Therefore we have to ask ourselves whether there is any room to manoeuvre in regards to evidence here. We need a bit more flexibility in the system for such cases. Here a right for the G-BA to ma-

ke corrections would be conceivable; whether legal clarification would be required in this case needs to be resolved.

**Products with recognised additional benefits:**
In principle it can be noted that the assessment procedures are working quite well and an additional benefit was attested in the majority of AMNOG processes that were completed. However, the G-BA not only evaluates the fundamental fields of application but also breaks down the indications to sub-populations. The trend that no additional benefit is being determined for numerous sub-populations has intensified in recent years. I also believe it is meaningful to examine the individual patient groups in evaluating the benefit of a medication. Therefore patient segmentation is also part of the dossiers that have to be submitted in the course of the AMNOG review.

***After an early approval, the state of knowledge does not yet correspond to the previous standard and there is not enough information from scientific studies.***

Genetic particularities, age, gender and the embodiment of the illness can for example cause a medication to work well for one patient, while it does not work at all or only with significant side effects for another. That is why the IQWiG (independently) forms several sub-groups in most procedures. However, the G-BA does not perform this process known as slicing and is more reserved in its approach. Sub-group analyses do not however meet the high standard of clinical studies and, in addition to other methodology inaccuracies, do not have the statistical significance since some of the sub-groups are very small.

**Adaptive pathways and conditional approval:**
Another change is currently under way at the European level. Through adaptive pathways, new medications are intended to achieve accelerated market readiness in the future on the basis of smaller studies and gradually submitted evidence. Small indication groups are intended to be gradually expanded and the significance of surrogate parameters versus clinical endpoints is to be increased again along with observation studies, pharmacovigilance instruments and post-marketing studies versus prospective randomised intervention studies. Earlier patient access to urgently needed treatments is the goal. Of course the risk of bringing products to market earlier is readily apparent and has to be weighed against the patient benefits of this principle.

It is clear that the state of knowledge does not yet correspond to the past standard after early approval and that there is not enough information from scientific studies. Handling such preparations requires a tremendous amount of training at the very highest level. The conditional approval of the EMA could be combined with constraints on prescriptions, for instance only in certain centres. If for example one were to conduct comprehensive treatment studies after approval, the pharmaceutical companies would also have an additional tool for documenting the effectiveness of the pharmaceutical product according to the G-BA criteria. The possibilities mentioned above for bringing pharmaceutical products into the healthcare system faster ultimately have little to do with the requirements of the AMNOG procedure. In contrast to approval, this is about determining the additional benefit compared to conventional therapies. This is difficult when the corre-

sponding application data are lacking, so greater flexibility would be needed here.

**Efficiency of the mixed price:**
After the benefit assessment, all sub-groups are currently being included in price negotiations in order to form a uniform mixed price that represents all patient groups. Pricing is being repeatedly criticised by the industry. This is because the prescriptions for patient groups with a minor additional benefit would thus be branded as „uneconomical" by the health insurers and associations of statutory health insurance physicians, making it unlikely they would reach the patient in the healthcare system. This quasi results in a quantity limitation, since billing for the sub-groups with a great additional benefit is at the (comparatively) „too low" reimbursement price while the reimbursement price for the sub-groups with a minor additional benefit is comparatively „too high", causing a sort of quantity limitation at the regional level.

While I see this difficulty, it must be noted that the concrete pricing rules were not developed by the lawmakers. The resulting dispute about the policy for setting the mixed price has occupied us for some time already.

**Efficiency of the reimbursement amount:**
The efficiency of the reimbursement amount is therefore at the core of the discussion. From the industry's perspective, a prescription for AMNOG products is always efficient since the negotiated mixed price explicitly included all sub-groups in pricing – those assessed as very good and those assessed as less good. This logic is comprehensible. Health insurers on the other hand argue that prescribing a pharmaceutical product in a sub-group assessed as less good – where the mixed price that was established is too high – violates the efficiency principle of Section 12 SGB V. So the question we face is how to solve this problem.

We need to ask whether to distance ourselves from the mixed price due to the problems described above and take a different approach, even though this is certain to pose considerable difficulties in the process. I do not believe that rules related to the particularities of a practice are a solution. We are therefore discussing ideas such as a (partial) reimbursement exclusion by request of the manufacturer or a user-oriented reimbursement price according to the model proposed by Ms. Haas of the National Association of Statutory Health Insurance Funds. A price/quantity model is being discussed as well.

**Review of efficiency:**
In practice the dispute leads to warnings from the associations of statutory health insurance physicians against use in sub-groups with no additional benefit. Regional agreements stating that a prescription is only permitted when there is a recognised additional benefit also cause innovations not to reach the patient in some cases. Against this background, we are also aware that merely the risk of a prescription defined as uneconomical leads to pronounced prescription restraint by doctors. Here our fundamental approach of „consultation before recourse" should be put into practice; only very few cases of recourse are in fact known.

Nationwide rules are fading into the background: Due to the different perspectives and procedures mentioned above, prescription practices and patient access to innovations are no longer consistent throughout the federal territory. We need a discussion about framework specifications for regional agreements: Uniform rules are needed for more affordable original products, AMNOG products and their cost effectiveness, biosimilars and possible quotas. While we would have liked to address these issues in the Statut-

ory Health Insurance Care Strengthening Act (GKV-Versorgungsstärkungsgesetz), this was not possible due to time constraints in the legislative procedure. Essentially the issue is how to deal with the problem that products partly have an additional benefit and partly not. The cost-benefit assessment according to Section 35b SGB V has not played a role so far. While it is this consideration in particular that represents the social – that is to say economic – benefit, it would consume a lot of time and cannot be realised with the current methodology requirements for classic evidence.

**Doctor information system:**

A uniform, well thought out doctor information system that provides doctors with substantiated information about the AMNOG assessments would be a good way to counteract many of the problems identified above. Here quality and additional benefits should play an essential role.

AMNOG assessments for medications are not reflected by doctors' prescriptions. IT-supported registers, for instance for oncology products and diabetes, would make it possible to obtain more detailed insights and conduct long-term, systematic observations. AMNOG information should be incorporated in the doctors' software as well. In the end, a doctor should know how economical his prescription is but does not need to know what the medication costs. I see great opportunities in registers and general patient care research in order to use expensive preparations even more purposefully, for example in combination therapies.

# Principle of hope vs. principle of risk: Consequences of accelerated market access

**Dr. Annette Zentner, MPH and Dr. Antje Haas | National Association of Statutory Health Insurance Funds**

*The objective of adaptive pathways is to speed up the approval and reimbursement of new pharmaceutical products. It shifts the burden of proof for a positive benefit-risk ratio from the pre to the post-marketing phase without ensuring that the required data are also generated after approval. Consequently the increased treatment risk is shifted to patients and the medical profession, while the responsibility for financing is borne by the healthcare system and paying parties. Early approvals of pharmaceutical products must remain limited to duly justified exceptional cases where there is an urgent unmet medical need. The standards of the AMNOG additional benefit assessment must not be lowered. Repeated additional benefit assessments that remain under national responsibility and a reimbursement amount adapted to the respective state of knowledge are needed. The fictitious additional benefit of orphan drugs and free pricing in the first year are no longer tenable.*

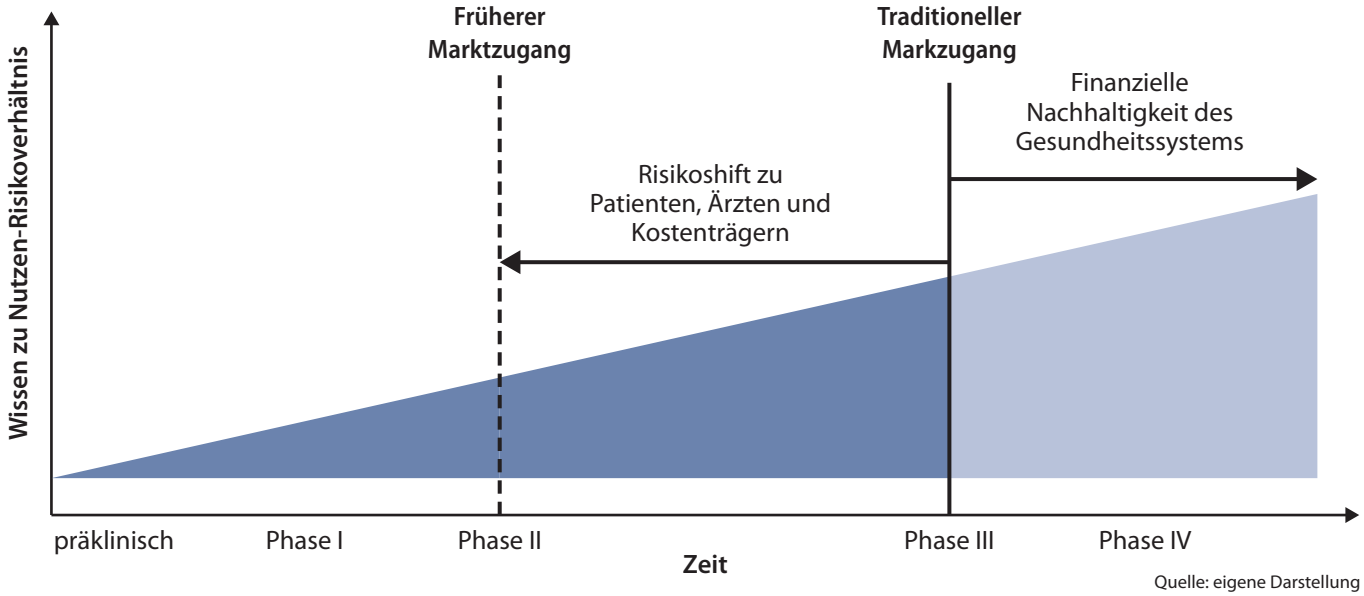
Adaptive pathways are aimed at achieving earlier patient access to new pharmaceutical products through accelerated approval and reimbursement. Notwithstanding the limited availability of data about benefits and risks, approval is to be issued for select patient groups, followed by the subsequent „adaptive" expansion of market access – meaning step-by-step on the basis of a prospective development plan.(1, 2) The concept is based on existing European tools and processes such as the conditional marketing authorisation and marketing authorisation under exceptional circumstances as special approval procedures, compassionate use programs, scientific advice from public authorities for manufacturers and pharmacovigilance procedures, but intends to optimise these and make them more flexible.

**Early access versus evidence and financial sustainability**

The adaptive pathways approach is subject to the well-known conflict of weighing demand for the earliest possible access to new pharmaceutical products against the need for valid evidence about benefits and risks as well as ensuring the financial sustainability of the healthcare system.(6) Figure 1 illustrates this schematically according to the pharmaceutical product development phases. Early market access shifts treatment risk to patients and doctors, and the risk of bad investments to the paying parties and the healthcare system.

From the EMA's perspective, the demand for early access to new pharmaceutical products relates primarily to seriously ill patients and those with an unmet medical need. This medical care gap supposedly justifies accepting greater uncertainty regarding the risk -benefit- ratio at the time of initial approval. Furthermore, proponents of the concept

## Adaptive Pathways: Risikoshift zu Patienten, Ärzten und Kostenträgern




Quelle: eigene Darstellung

Figure 1: Early market access shifts treatment risk to patients and doctors, and the risk of bad investments to the paying parties and the healthcare system.

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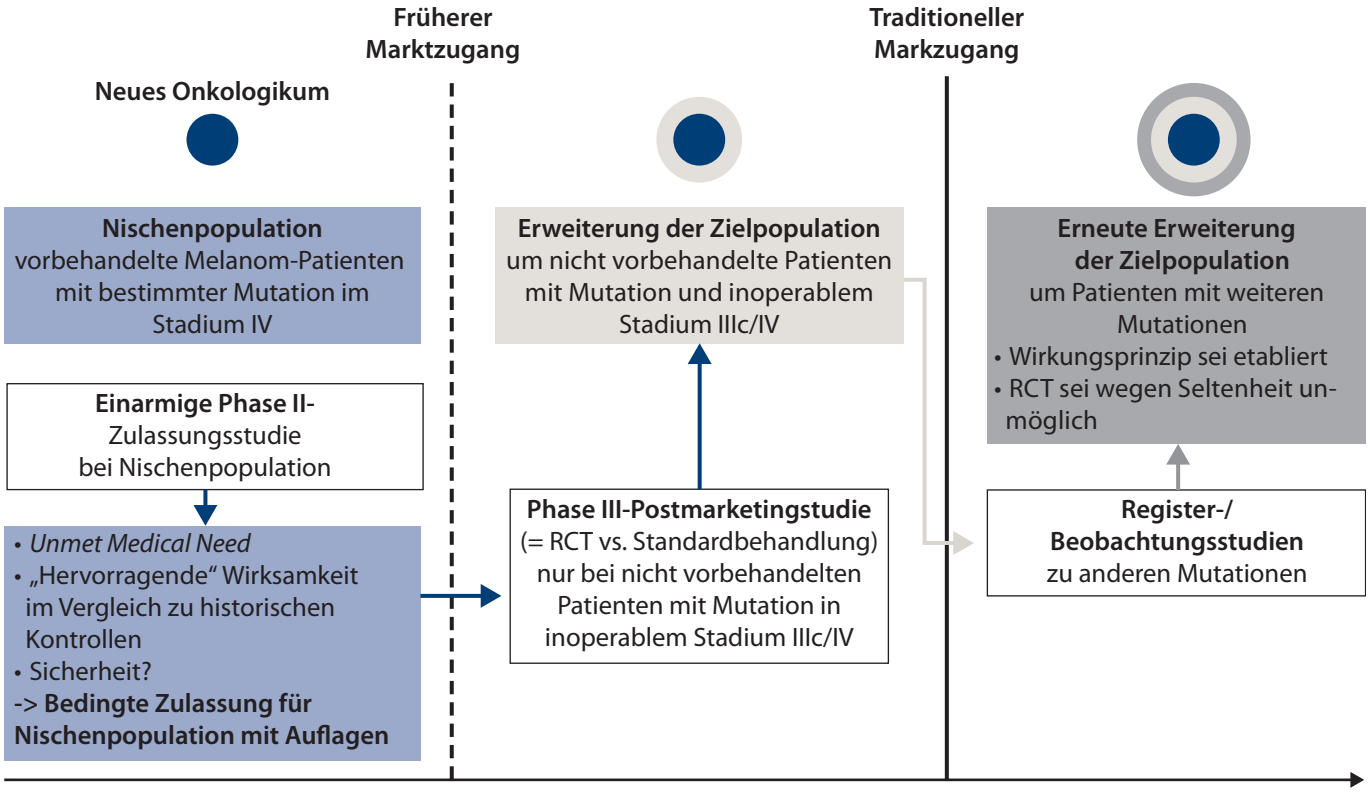
argue that faster access to promising treatments is equally urgent regardless of the type of illness due to what is called a treatment window of opportunity, and that adaptive pathways therefore constitute the approach to market access for pharmaceutical products that should be preferred in the future.(7)

Adaptive pathways appear to meet industry demands to reduce regulatory barriers and requirements for the generation of evidence prior to approval, since postulated benefits are that pharmaceutical companies would benefit from earlier earnings and less expensive and/or shorter clinical studies.(8)

For quality of care reasons and to maintain the financial sustainability of the healthcare system, paying parties on

## Fallbeispiel der EMA: Adaptive Pathways-Szenario für Onkologikum




Quelle: eigene Grafik nach Angaben der EMA

Figure 2: Case study for the „indication expansion" scenario.

the other hand argue that coverage should only be mandatory if the (additional) benefit of a new pharmaceutical product is proven.

**Adaptive pathways scenarios with EMA case studies**

According to the EMA, there would be two scenarios for adaptive pathways: (A) Initial approval for a narrowly defined patient (sub)group with an unmet medical need (niche indication) and planned, subsequent indication expansion with approval for additional patient groups or (B) initial, conditional approval on the basis of uncertain data (surrogate endpoints for instance) with planned, subsequent full approval while reducing uncertainty through the collection of post-marketing data.(1)

When the first case study published by the EMA for the „indication expansion" scenario with malignant melanoma is analysed, it becomes clear that the new pharmaceutical product adaptively receives full approval for a broad population, that is for previously treated and not previously treated patients with various mutations – without ever investigating the effectiveness and safety or the benefits and risks relevant for patients compared to the previous standard therapy in all patient groups by means of comparative phase III studies (see Figure 2). This is further complicated by the fact that no additional evidence is generated after approval for the initial niche population with an unmet medical need in order to support the initial assessment of a positive benefit-risk ratio.

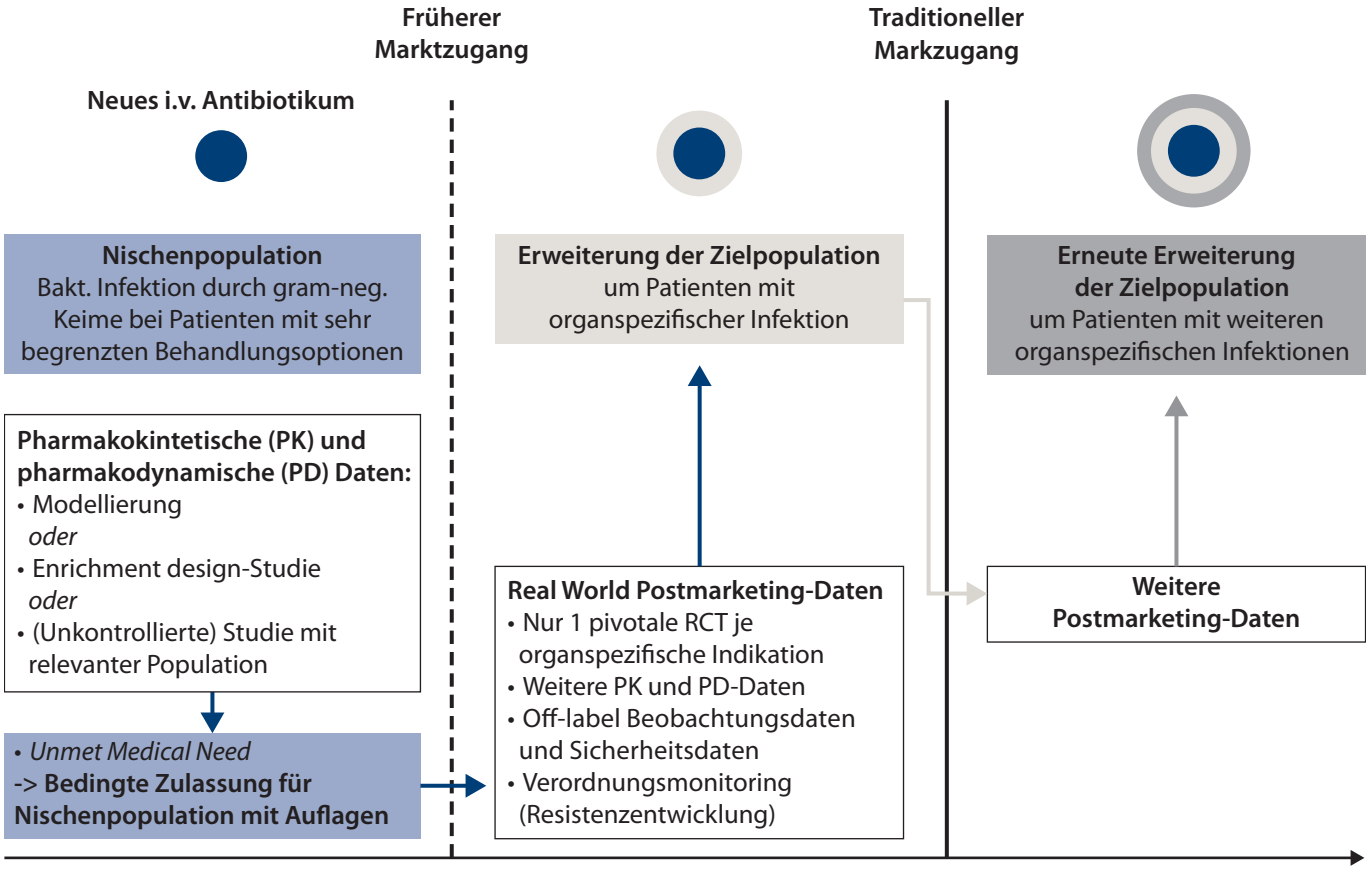
The second EMA case study for an intravenous antibiotic against gram-negative microbes also makes it clear that the evidence standards are lowered with the adaptive pathways concept, not only initially but also in the post-marketing phase (see Figure 3). For the initial niche indication with an unmet medical need in the form of treating bacterial infections in patients with very limited antibiotic treatment options, the evidence requirements are much lower compared to traditional approvals in terms of pharmacokinetics, pharmacodynamic data and modelling.. Since real-world healthcare data would be generated after approval, a pivotal study instead of two double blinded, actively monitored RCTs would be sufficient for each additional significant organ manifestation of the infection.

In the third EMA case study (see Figure 4) on genetically modified, autologous cells similar to chondroblasts for cartilage healing and repair, a pharmaceutical product for novel treatments (ATMP)(d), approval is issued on the basis of a surrogate endpoint as the primary endpoint (structural restoration) notwithstanding its limited informative value.(b) The case study makes three things clear: The idea of the adaptive pathways concept is by no means limited to situations with an urgent unmet medical need; the „reduction of uncertainty" scenario is directly and simultaneously linked to the „indication expansion" scenario and the requirements to record endpoints relevant to patients after approval remain vague.

**Trend towards an approval strategy supported by the EMA**

What are the implications of the adaptive pathways concept for the pharmaceutical supply in Germany? One can expect early, accelerated approvals for niche indications on the basis of incomplete evidence and therefore with an uncertain risk -benefit- ratio to increase significantly. The industry has abandoned the former business model of a blockbuster strategy with full approval for what are called widespread diseases with large patient populations, such as diabetes mellitus and COPD, in favour of the niche buster model with accelerated approval of usually high-priced pharmaceutical products for small populations with niche indications, especially for rare illnesses or those redefined

## Fallbeispiel der EMA: Adaptive Pathways-Szenario für Antibiotikum




früher und wiederholter Dialog des pharmazeutischen Unternehmers mit Zulassungsbehörde während des Entwicklungsprozesses

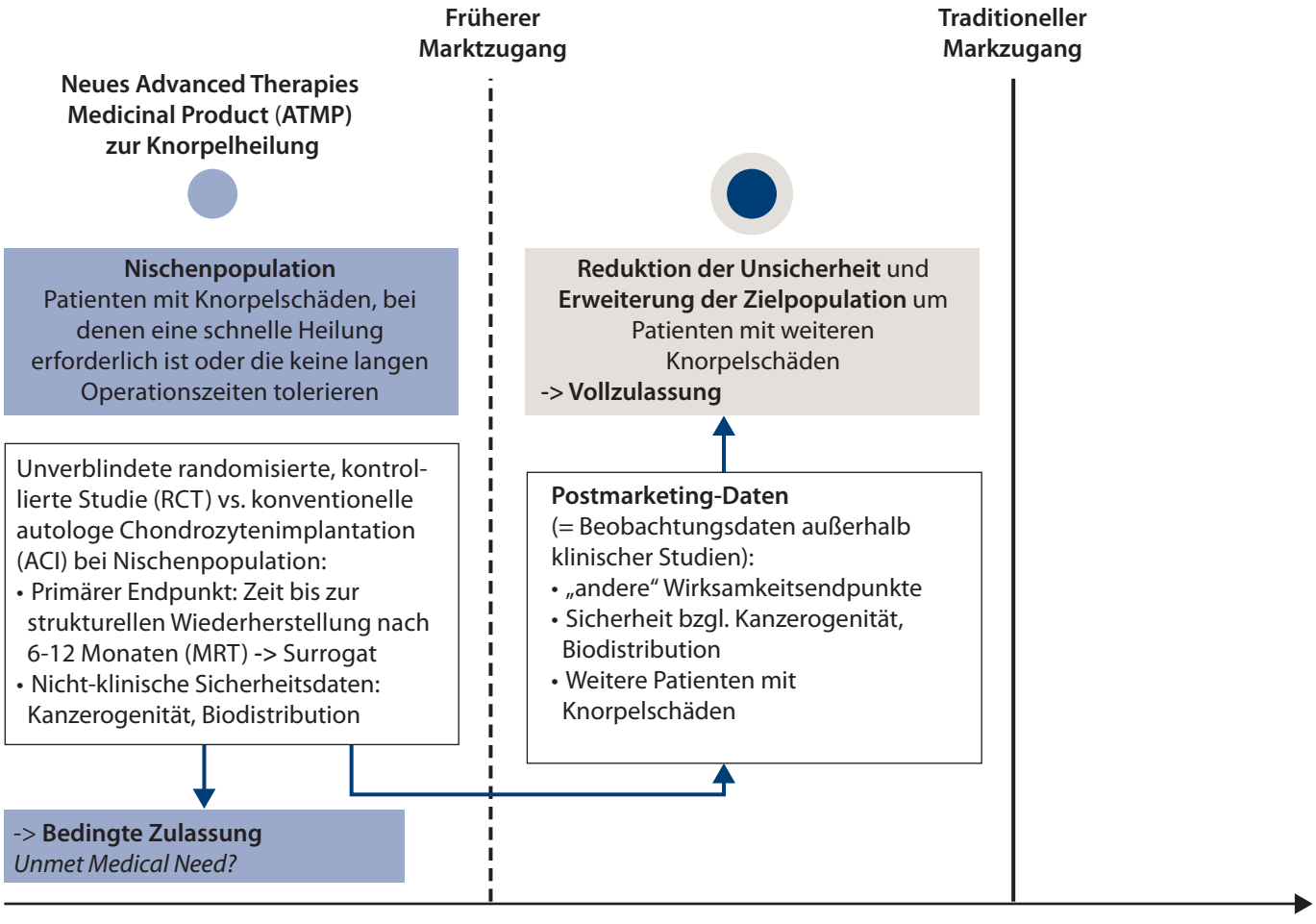
Quelle: eigene Grafik nach Angaben der EMA

Figure 3: The evidence standards are lowered with the adaptive pathways concept.

as such with an unmet medical need. (9, 10, 11) Even now 45 percent of pharmaceutical products with a conditional marketing authorisation or around one third (29 percent) of pharmaceutical products with a marketing authorisation under exceptional circumstances are orphan drugs. (b ,c)

This trend is now transforming into a strategy that is welcomed and supported by the authorities, namely by the EMA, as a so-called paradigm shift. Here the problem of the unmet medical need approach is that such an unmet need can hardly be defined using purely scientific criteria and it is easy to make the ethical argument that increased

## Fallbeispiel der EMA: Adaptive Pathways für ATMP




Früher und wiederholter Dialog des pharmazeutischen Unternehmers mit Zulassungsbehörde während des Entwicklungsprozesses

Quelle: eigene Grafik nach Angaben der EMA

Figure 4: With an ATMP, approval is issued based on a surrogate endpoint – even though the unmet medical need is questionable.

treatment risk should be accepted.

Experiences from the USA and Canada show that these are not merely theoretical considerations. Since the introduction of the four expedited programs by the FDA at the end of the 1980s, there has been a statistically significant increase in the proportion of accelerated approvals driven by non-first in class products that are less likely to offer clinically significant benefits.(12) The correlation between ac-

celerated approval procedures and the therapeutic value of a pharmaceutical product is weak in Canada as well.(13) Pharmaceutical products for less serious diseases such as Bimatoprost (LatisseTM) for the treatment of hypotrichosis (lack of hair) of the eyelid are also receiving expedited approval from the FDA.(12)

**Adaptive pathways shift the burden of proof to the post-marketing phase**

Adaptive pathways shift the burden of proof for a positive benefit-risk ratio from the pre to the post-marketing phase, but without ensuring that the required data are generated after approval. Consequently adaptive pathways gradually expand the fields of application for a new pharmaceutical product while the uncertainties of the underlying scientific data and therefore the risk -benefit- ratio permanently remain. Experience has shown that it is much more difficult to produce high-quality RCTs as the most valid evidence compared to other data following market approval (for example due to the lower acceptance of randomisation and/or blinding). Less evidence and incomplete data increase uncertainty and therefore the risk of incorrect decisions for patients, insured persons and the healthcare system. There is no incentive for pharmaceutical companies to conduct studies that could show that the pharmaceutical product is less effective or more harmful than originally expected.(14) Scheduling or content deviations from the original EMA requirements are common; experience has shown approvals are not revoked in such cases and other sanctions are not imposed.(11, 16)

Delays and/or failures to complete requested post-approval studies are not being sanctioned by the FDA in the USA either.(17) Monitoring and reporting by the regulatory authorities are especially essential in case of accelerated approvals so that a possibly higher, previously unidentified damage potential is recorded early on, and in order to inform decision-makers and the public regarding safety concerns and compliance of the manufacturers with the post-marketing requirements. However, the US Government Accountability Office notes that the FDA fails to meet its systematic review and reporting obligations for the expedited programs and finds fault with the integrity, timeliness and credibility of data following market approval.(18)

With adaptive pathways, the study requirements for approval are moving away from rather than towards the standards of the AMNOG additional benefit assessment based on endpoints relevant for patients.(6) That is a misdirected incentive. None of the pharmaceutical products with a conditional marketing authorisation or marketing authorisation under exceptional circumstances that fall within the scope of the German Pharmaceutical Market Reorganisation Act (AMNOG) changed their approval status by the end of 2015, which means the EMA requirements were not met up to five years after approval (as of January 2016).(6) This will result in growing, long-term uncertainty for decision makers in evaluating the additional benefit and value of a new pharmaceutical product. Political pressure on the Federal Joint Committee (G-BA) to nevertheless attest an additional benefit with approval can be expected to increase at the same time.

**Adaptive pathways shift the treatment risk to patients and doctors**

Adaptive pathways increase the risk of approving pharmaceutical products that have no benefit for patients or are actually harmful. The principle of hope for an effective treatment is supposed to justify the principle of immature data, and therefore leads to a principle of risk with high uncertainty in healthcare. The basis of guideline recommen-

dations and therapeutic advices will be less scientifically based as well. Here it is important not to forget that, notwithstanding mandatory pharmaceutical product approval testing which was introduced in the EU in 1965 as a result of the Thalidomid (Contergan) scandal, numerous products subsequently had to be taken off the market because of serious safety concerns.(11, 16, 19). Warnings regarding serious side effects are more likely in the USA and Canada for pharmaceutical products with conditional or accelerated approval than those with regular approval.(20, 13). The example of Bevacizumab (Avastin®) for the treatment of metastasised breast cancer, which was granted accelerated approval based on surrogate parameters, shows that the revocation of FDA approval is protracted and difficult to enforce even if a lack of patient benefits is proven. Some US insurers are covering the costs for this off-label indication to this day because of intense public pressure.(21). As a further complication, proponents of the adaptive pathways concept are proposing a modification to the point of excluding product liability by the manufacturer in the phase following initial approval.(8) Others – patients, doctors, the healthcare system or taxpayers – would then be responsible for claims. This is quite simply unacceptable. Unlike voluntary participants in approval studies, patients would neither be regularly informed of their participation in scientific studies after approval nor compensated by the manufacturer in case of damage.

**Adaptive pathways shift the financing risk to the paying parties**

Accelerated market access and therefore earlier inclusion in standard care with uncertainty regarding patient benefits and the value of the pharmaceutical product shifts responsibility for financing and the risk of bad investments from the manufacturer to the healthcare system and paying parties. This applies not only to added costs for the often high-priced, patented pharmaceutical products themselves – with a longer patent protection period following market access. Additional costs are also incurred for possible off-label uses, among other things in areas of anticipated additional indications, and expenditures for the collection of post-marketing data in the patient care routine and the required reassessment by the Institute for Quality and Efficiency in Health Care (IQWiG) and the G-BA. The effect of possible implications from the accelerated market approval of pharmaceutical products on the German healthcare system is particularly severe since, in contrast to most European countries, eligibility for reimbursement and availability are generally given directly with market approval or market access. Germany has the fastest access to publicly financed pharmaceutical products in an European comparison (22).

**Significant impact on the sovereignty of the EU member states**

Numerous current European activities show that the concept of accelerated approval for pharmaceutical products is already being implemented. The EMA with the revision of its Guidelines for Conditional Marketing Authorisation and Accelerated Assessment made changes to what is known as the optimisation of the early assessment tools and established the PRIME (PRIority MEdicines) schema, thereby offering additional regulatory and scientific advice to companies in very early development phases for products to satisfy unmet medical needs (23, 24, 25). Furthermore, the EMA is participating in ADAPT SMART, a three-year project financed in equal parts by taxpayer money and the industry under the Innovative Medicines Initiative 2 (IMI 2) subsidy program that serves to coordinate and support „Medicines Adaptive Pathways to Patients“

(MAPPs).(26, 27)

The adaptive pathways concept directly affects regulatory issues such as eligibility for reimbursement and pricing for pharmaceutical products under the national authority of EU member states. The latest legislative initiative of the European Parliament to transfer the comparative benefit assessment of new pharmaceutical products compared to the therapy standard to the EMA and to make it the binding basis for reimbursement and pricing decisions in national healthcare systems is a clear expression of the currently planned, serious encroachment on the jurisdiction of the EU member states. (28).

**Conclusion and demands**

From the perspective of the National Association of Statutory Health Insurance Funds, maintaining a solid basis of scientific evidence with proof of effectiveness and the assessment of risk prior to the approval of new pharmaceutical products must be the top priority. Accelerated approvals of pharmaceutical products must remain limited to duly justified exceptional cases with a genuine, urgent unmet medical need where it is possible to justify that earlier market access outweighs the danger of misjudging the risk- benefit- ratio.

The regulations introduced in the past decades, such as the conditional marketing authorisation, marketing authorisation under exceptional circumstances, compassionate use programs and framework conditions for orphan drugs already ensure that patients obtain timely access to new pharmaceutical products. The European regulatory authority should consistently make use of the option to revoke an approval or special status if the requirements are not met by the manufacturer or when a superior additional product for the same indication is approved.

The standards for suitable study criteria of the AMNOG benefit assessment anchored in social law must not be lowered. Instead one must strive for evidence to not only be generated in view of approval, but for the study requirements of the G-BA to be met more effectively and for pharmaceutical companies to receive corresponding timely advice. The direct responsibility of the EU member states in the additional benefit assessment for the sovereign design of healthcare systems and maintaining independence from industrial influence for all participating institutions must remain top priorities.

The adaptive market approval concept requires an adaptive additional benefit assessment and an adaptive reimbursement amount adjusted to the respective state of knowledge. The one-time assessment with re-evaluation as needed must be transferred to a regular process of mandatory data generation with recurring additional benefit assessments to verify or overturn the previous decisions. From the perspective of the National Association of Statutory Health Insurance Funds, the fictitious additional benefit of orphan drugs as an irrefutable general postulate and free pricing in the first year after market access are no longer tenable.

**Footnotes**

a. Special form of a conditional marketing authorisation with reduced data requirements compared to full approval; may be considered for pharmaceutical products if they can cover an unmet medical need or when this is in the interest of public health. This applies for pharmaceutical products that are to be used (1) for the treatment, prevention or diagnosis of illnesses that lead to severe disabilities or are life-threatening, (2) against a threat to public health in crisis situations determined by the World Health Organisation or EU, or (3) for the treatment of rare diseases (orphan drugs)(3). The orphan drug status alone therefore opens up this special approval path. A marketing authorisation under exceptional circumstances may be issued if the applicant can prove that it is unable to submit complete data about the effectiveness and safety of the pharmaceutical product. This is the case (1) for indications that are so rare that the applicant cannot be justly expected to submit complete data, (2) when the applicant given the respective state of science is not able to provide complete information or (3) when the generally accepted principles of professional medical ethics do not permit procuring this information (4). Both special approvals are linked to specific requirements for pharmaceutical companies, which include generating missing evidence to confirm the positive benefit-risk ratio after approval is issued (5).

b. Updated research according to Zentner and Haas (2016) 6.

c. Pursuant to Section 35a SGB V, the medical additional benefit for pharmaceutical products to treat a rare disease is deemed to be attested with approval up to a sales limit of EUR 50 million per year. Proof of additional benefits compared to an appropriate comparative treatment does not have to be submitted by the pharmaceutical company. A fictitious additional benefit is therefore established by law. Only the extent of the additional benefit must be proven and is evaluated by the Federal Joint Committee (G-BA).

d. Pursuant to Regulation (EC) No. 1394/2007, the term ATMP (advanced therapies medicinal products) includes gene therapies, somatic cell therapies and modified biotechnology tissue products.

e. In the AMNOG procedure, all new active substances and active substance combinations are subject to an assessment of the additional benefit by the G-BA in comparison to the appropriate comparative treatment as the therapy standard since 2011.

f. The renaming of the EMA pilot project „Adaptive Licensing" launched in March of 2014 to „Adaptive Pathways" highlights the intended broad scope of the concept: This approach is intended to encompass the entire lifespan of a new pharmaceutical product from clinical development and approval to reimbursement, use and monitoring in clinical practice.

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# Benefit assessment after accelerated approval: experiences and perspectives

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*Within the framework of the adaptive pathways approval concept, an increase can be expected in the number of pharmaceutical products that are brought to market on the basis of little evidence with a conditional marketing authorisation or a marketing authorisation under exceptional circumstances. Pharmaceutical products with an „atypical" approval status have played a subordinate role in the AMNOG procedure to date. A relevant proportion of these products benefited from the existing special provisions for orphan drugs. How the European Medicines Agency will implement adaptive pathways in concrete terms is unclear. However, it is likely that no additional benefit can initially be derived in the subsequent benefit assessment in many cases due to the limited availability of data. Legal regulations are needed to ensure care in specialised centres and the comprehensive collection of missing evidence after market entry.*

With the adaptive pathways concept, the European Medicines Agency (EMA) pursues the goal of allowing patients to access new pharmaceutical products faster in the future. Step-by-step approval, initially based on little evidence, is intended to shorten the time to market entry. Two different models are being discussed [1, 2, 3]:

(1) Starting with early approval for a narrowly defined sub-population based on the results of initial clinical studies, the field of application is to be expanded in stages.

(2) Early (conditional) approval is initially issued based on early data from an ongoing clinical study using surrogate endpoints. Regular approval is to be issued as soon as convincing results for clinical endpoints are on hand.

After market access, additional study results and the collection of data from clinical use in practice, known as real-world data, is to establish a body of evidence that justifies regular approval.

Adaptive pathways are intended to use the existing EU legal framework for the approval of pharmaceutical products and provide an additional market access option, initially in areas with a high medical need [1, 4].

11 products were selected by the EMA for a possible pilot project. They include three oncology products, a pharmaceutical product for novel treatments (ATMP) and five orphan drugs [5].

In addition to proper prescription behaviour, the adaptive pathways concept presumes the systematic collection of treatment data. However, the legal framework that would be necessary to ensure the setup of the required, indication-specific registers and the mandatory inclusion of exposed patients is currently lacking in Germany. In particular, who will cover the resulting costs needs to be clarified. Having the generation of evidence financed solely by

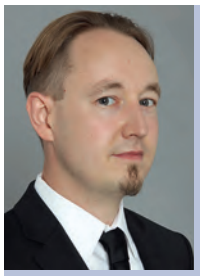
the insured community does not appear justified.

It is also necessary to discuss the extent to which register data can meet the requirements of the G-BA for comparative evidence in reference to an appropriate comparative treatment. Only when it is impossible or unreasonable to conduct studies at the highest evidence level is the recognition of an additional benefit based on data of a lower evidence level justifiable (Chapter 5, Section 5, Paragraph 3 of the G-BA code of procedure). From a methodology perspective, non-adjusted indirect comparisons with historical control groups will only be productive in isolated cases. The IQWiG has generally viewed such an approach critically to date [6].

In addition to the collection of treatment data, randomised clinical studies should also be conducted after market entry in order to generate the body of evidence required for regular approval. However, it is not highly realistic to expect statistically significant results for hard clinical endpoints when the pharmaceutical product being studied is generally available. For ethical reasons, one could not forbid a study participant in the control group from switching to treatment with an available, effective and approved therapy option if the (oncological) illness progresses. The pragmatic use of register data by the G-BA also appears necessary under consideration of future pharmaceutical product developments and further therapy trials in subsequent treatment lines.

Data collection for oncology products is intended as part of the nationwide clinical cancer registers planned according to the KFRG (law for the further development of early cancer detection and quality assurance through clinical cancer registers). On a critical note, data on the quality of life and morbidity relevant for a benefit assessment are not collected with the current, uniform basic oncology dataset [7].

Medical progress, in particular the growing importance of „personalised medicine", has to be considered in a clinical register established for future data collection. The G-BA has already conducted numerous benefit assessments to date where the previous genetic classification of the tumour was a prerequisite for the use of the corresponding pharmaceutical product. Afatinib (Giotrif), an active substance for the treatment of the non-small cell lung carcinoma (NSCLC) with activated EGFR mutation, showed a significant additional benefit (highest additional benefit category) in the patient group with the EGFR mutation Del19. On the other hand, no additional benefit could be noted for the patient group with an EGFR mutation L858R [8]. Crizotinib (Xalkori) is approved for the treatment of the ALK-positive NSCLC, but is also used off-label for the treatment of ROS1-positive NSCLC [9]. Neither in the current basic oncology dataset nor in the supplementary organ-specific



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modules is a comprehensive documentation of existing genome data intended [7].

**A summary of decisions to date**

Since the adaptive pathways concept is to be realised based on existing laws and does not constitute a fundamentally new approval process, one can mainly expect an increase in pharmaceutical products that are brought to market with a conditional marketing authorisation (CMA) or a marketing authorisation under exceptional circums-

**Positive Opinion der Europäischen Arzneimittelagentur (EMA) für eine „atypische" Zulassung seit Beginn des AMNOG-Verfahrens (Stand: 1. März 2016)**

| Wirkstoff | Conditional (CMA) | Exceptional (MAEC) | Orphan Drug | Keine Nutzenbewertung Ausnahmefälle |
|---|---|---|---|---|
| Fampridin (Fampyra) | Ja | Nein | Nein | |
| Vandetanib (Caprelsa) | Ja | Nein | Nein | |
| Pixantron (Pixuvri) | Ja | Nein | Nein | |
| Crizotinib (Xalkori) | Ja | Nein | Nein | |
| Brentuximab (Adcetris) | Ja | Nein | Ja | |
| Bosutinib (Bosulif) | Ja | Nein | Ja | |
| Vismodegib (Erivedge) | Ja | Nein | Nein | |
| Bedaquilin (Sirturo) | Ja | Nein | Ja | Packungsgröße |
| Cabozantinib (Cometriq) | Ja | Nein | Ja | |
| Delamanid (Deltyba) | Ja | Nein | Ja | Freistellung |
| Ataluren (Translarna) | Ja | Nein | Ja | |
| Stammzellpräparat (Holoclar) | Ja | Nein | Ja | ATMP: § 135, § 137c |
| Ceritinib (Zykadia) | Ja | Nein | Nein | |
| Blinatumomab (Blincyto) | Ja | Nein | Ja | |
| Vintafolid (Vynfinit) | Ja | Nein | Ja | Keine Zulassung |
| Osimertinib (Tagrisso) | Ja | Nein | Nein | |
| Alipogentiparvovec (Glybera) | Nein | Ja | Ja | |
| Lomitapid (Lojuxta) | Nein | Ja | Nein | |
| Cholsäure (Orphacol) | Nein | Ja | Ja | |
| Defibrotid (Defitelio) | Nein | Ja | Ja | Freistellung |
| Afamelanotid (Scenesse) | Nein | Ja | Ja | |
| Susoctocog alfa (Obizur) | Nein | Ja | Nein | Direktbezug für KVA |
| Asfotase alfa (Strensiq) | Nein | Ja | Ja | |
| Idebenon (Raxone) | Nein | Ja | Ja | |
| Tafamidis (Vyndaqel) | Nein | Ja | Ja | |

Figure 1: Since 2011 the EMA has issued 25 recommendations for granting an „atypical" approval.

tances (MAEC). Patients with statutory insurance are fundamentally entitled to being supplied with pharmaceutical products that require a prescription (Section 31 of the Social Security Code (SGB) V). The type of approval and the extent of the existing evidence have no direct influence on eligibility for reimbursement to date.

At the time they are first brought to market in Germany, products with a CMA or MAEC are also subjected on principle to a benefit assessment pursuant to Section 35a SGB V. The G-BA evaluates the additional benefit compared to an appropriate comparative treatment. Only for pharmaceutical products simultaneously approved for the treatment of a rare ailment as well (orphan drugs) is the medical additional benefit considered proven by the approval. Since the introduction of the AMNOG in January of 2011, the EMA issued 25 recommendations (positive opinions) for granting an „atypical" approval (CMA or MAEC) (excluding vaccines).

Delamanid (Deltyba) and Defibrotid (Defitelio) are exempt from the benefit assessment based on expected annual sales of less than one million Euros. Susoctocog alfa (Obizur) is only available through a direct purchase for pharmacies that supply clinics and from hospital pharmacies. As an advanced therapy medicinal product (ATMP), a stem cell preparation for the treatment of eye injuries (Holoclar) is subject to a methodology assessment pursuant to Section 135 and Section 137c SGB V [10].

The market entry of Bedaquilin (Sirturo) was realised with a package size not eligible for reimbursement (ambulatory), and the benefit assessment was therefore suspended [11]. Vintafolid (Vynfinit) was not brought to market after the application for approval was retracted [12]. For Afamelanotid (Scenesse), Osimertinib (Tagrisso) and Blinatumomab (Blincyto), the procedures have not yet been completed. Benefit assessments pursuant to Section 35a SGB V were carried out for the remaining 16 pharmaceutical products. However, nine active substances among these were simultaneously approved for the treatment of a rare illness as well; here the additional benefit is considered (notionally) proven (see Figure 1).

A mere seven active substances have been subjected to a regular benefit assessment to date. No additional benefit could be found in four cases. With Lomitapid (Lojuxta) and Ceritinib (Zykadia), this was because the data were unsuitable for a benefit assessment. The approval recommendations were based on the results of single-arm studies with no comparator. While the results of randomised, controlled phase III studies were on hand for the evaluation of Fampridin (Fampyra) and Pixantron (Pixuvri), the German standard of care was not adequately met here, especially in regards to the comparative arm. A market withdrawal took place only for Lomitapid following the assessment of benefits (see Figure 2).

The G-BA primarily considers direct comparative studies with endpoints relevant for patients. Non-comparative studies are also accepted as proof of an additional benefit in exceptional cases (Chapter 5, Section 5, Paragraph 3 of the G-BA code of procedure). An additional benefit could therefore be attested for Vismodegib (Erivedge) on the basis of the one-armed phase II approval study. Patients with advanced basal cell carcinomas for whom no more treatment alternatives were available benefited from a significant reduction of disfiguring tumours in the head and neck region [13].

Among the seven evaluated pharmaceutical products without orphan drug status, Crizotinib constitutes an anomaly. Approval was issued based on a one-armed phase I study. However, relevant interim results became available from an ongoing randomised, controlled phase III study between the beginning of the approval procedure and the beginning of the benefit assessment, which served as the

basis for the G-BA to determine a „significant additional benefit" [14, 15]. The attestation of an additional benefit based on the approval data is doubtful.

A „minor additional benefit" was attested for Vandetanib (Caprelsa), approved for the treatment of thyroid carcinoma, after comparing the positive effects (delaying the progression of pain) and relevant side effects [16].

For the four orphan drugs Brentuximab (Adcetris), Bosutinib (Bosulif), cholic acid (Orphacol) and Alipogentipavovec (Glybera), the respective positive opinion was issued on the basis of one-armed studies. In all cases the G-BA noted a „non-quantifiable additional benefit", primarily to satisfy the legal additional benefit requirement. The limited availability of data was mentioned in the reasons supporting the respective decisions. While Idebenon (Raxone), an active substance for the treatment of vision disturbances with Leber's hereditary optic neuropathy, was compared to a placebo in a randomised clinical study, a benefit regarding endpoints relevant for patients (improvement/change in visual acuity) could not be demonstrated.

**Ergebnisse regulärer Nutzenbewertungen von Arzneimitteln mit „atypischem" Zulassungsstatus**

| Arzneimittel | Zusatznutzen | Befristung | Datenbasis | Begründung |
|---|---|---|---|---|
| Crizotinib - CMA (Onkologie) | Beträchtlich, Anhaltspunkt | Ja | RCT Phase III | Vorteil Morbidität (Atemnot, Schmerz, Husten) und Lebensqualität |
| Vandetanib - CMA (Onkologie) | Gering, Anhaltspunkt | Ja | RCT Phase III | Vorteil Morbidität (Schmerz): beträchtlich Relevante Nebenwirkungen, deshalb Herabstufung des Zusatznutzens! |
| Vismodegib - CMA (Onkologie) | Gering, Anhaltspunkt | Ja | Einarmige Phase-II-Studie | Vorteil Morbidität (Ansprechrate) Relevante Reduktion sichtbarer Tumore |
| Fampridin - CMA (Multiple Sklerose) | ***Kein Zusatznutzen*** | – | RCT Phase III | Die zVT wurde nicht umgesetzt. Die Zulassungsstudien entsprechen nicht dem deutschen Versorgungskontext. |
| Pixantron - CMA (Onkologie) | ***Kein Zusatznutzen*** | – | RCT Phase III | Die zVT wurde nicht umgesetzt. Die Zulassungsstudien entsprechen nicht dem deutschen Versorgungskontext. |
| Ceritinib - CMA (Onkologie) | ***Kein Zusatznutzen*** | – | Einarmige Phase-II-Studie | Keine relevanten Daten |
| Lomitapid - MAEC (Stoffwechselerkrankung) | ***Kein Zusatznutzen*** | – | Einarmige Phase-III-Studie | Keine relevanten Daten |

Figure 2: A regular benefit assessment was performed for only seven „atypical" approved active substances.

In this case too the G-BA had to attest a „non-quantifiable additional benefit" for the pharmaceutical product [17]. For Asfotase alfa (Strensiq) on the other hand, a relevant reduction in mortality compared to a historical control was noted. Here the G-BA attested a „non-quantifiable additional benefit" since the intensity of the effect could only be estimated due to the lack of a direct comparative study [18]. For Carbozantinib (Cometriq), Ataluren (Trans-

**Ergebnisse der Nutzenbewertungen von Orphan Drugs mit „atypischem" Zulassungsstatus**

| Arzneimittel | Zusatznutzen | Befristung | Datenbasis | Begründung |
|---|---|---|---|---|
| Asfotase alfa - MAEC (Stoffwechselerkrankung) | **Nicht quantifizierbar** | Ja | Einarmige Phase-II-Studien | Reduktion der Mortalität gegenüber einer historischer Kontrollgruppe! |
| Brentuximab - CMA (Onkologie) | ***Nicht quantifizierbar*** | Nein | Einarmige Phase-II-Studie | Unzureichende Datenlage, Orphan Drug |
| Bosutinib - CMA (Onkologie) | ***Nicht quantifizierbar*** | Ja | Einarmige Phase-I/II-Studie | Unzureichende Datenlage, Orphan Drug |
| Cholsäure - MAEC (Stoffwechselerkrankung) | ***Nicht quantifizierbar*** | Nein | Fallberichte und Fallserien | Unzureichende Datenlage, Orphan Drug |
| Idebenon - MAEC (Augenerkrankungen) | ***Nicht quantifizierbar*** | Ja | RCT Phase II | ***Kein Vorteil gegenüber Placebo, Orphan Drug*** |
| Alipogen - MAEC (Stoffwechselerkrankung) | ***Nicht quantifizierbar*** | Ja | Einarmige Interventions-studien | ***Nutzen fraglich, Orphan Drug*** |
| Cabozantinib - CMA (Onkologie) | Gering | Ja | RCT Phase III | Vorteil Gesamtüberleben (nur bei Patienten mit RET-M918T Mutation, Mischpopulation nicht signifikant) |
| Ataluren - CMA (Muskeldystrophie) | Gering | Ja | RCT Phase IIb | Vorteil Morbidität (6-Minuten-Gehtest) Geringere Verschlechterung |
| Tafamidis - MAEC (Amyloidose) | Gering | Nein | RCT Phase II/III | Vorteil Morbidität (NIS-LL) Effekt auf die neuropathische Beeinträchtigung |

Figure 3: The additional benefit is considered proven for orphan drugs; at least a „non-quantifiable additional benefit" has to be attested.

larna) and Tafamidis (Vyndaqel), a minor additional benefit could be derived based on the results of randomised controlled studies (see Figure 3). Among the orphan drugs that received a positive opinion for a CMA or MAEC from the EMA, two pharmaceutical products deserve more in-depth discussion in order to illustrate the risks of premature approval on the basis of little evidence:

Vintafolid (Vynfinit) was intended for the treatment of patients with platinum-resistant ovary carcinomas and was to be administered in combination with an established chemotherapy. The EMA issued the positive opinion for a CMA on 20 March 2014 on the basis of a randomised, controlled phase II study. A moderate extension of progression-free survival was demonstrated in the study relevant for the approval. The G-BA would have had to attest an additional benefit for Vintafolid due to the orphan drug status. However, the interim analysis of an ongoing, randomised double blind phase III study was performed in the period between the positive opinion and the approval by the EU Commission. No benefit from a treatment with Vintafolid could be demonstrated here. Subsequently the company in question terminated the unsuccessful clinical study and retracted the approval application on 16 May 2014 [12, 19].

Only because the negative results of the phase III study were available in time was the pharmaceutical product not brought to market. While there were no relevant safety concerns for Vintafolid, the insured community would have been confronted with additional costs for no equivalent value in case of this add-on therapy (see Figure 4).

Alipogentiparvovec (Glybera) is an orphan drug for the treatment of familial lipoprotein lipase deficiency and the only gene therapy approved in Europe to date. The EMA rejected an initial approval application on 23 June 2011. A re-evaluation of the product with a restricted patient population was initiated by request of the EU Commission. On 19 July 2012 after the available data were re-evaluated, the EMA ultimately concluded that there actually is a positive benefit-risk ratio for Alipogentiparvovec and issued an approval recommendation for a MAEC. A requirement was imposed on the pharmaceutical company to regularly submit safety update reports [20].

The pharmaceutical product was not brought to market

**Vintafolid (Vynfinit) zur Behandlung des Platin-resistenten Ovarialkarzinoms**

| | |
|---|---|
| **20. März 2014** | **Positive Opinion der EMA für eine Conditional Marketing Authorisation**<br>• Verlängerung des PFS um 2,3 Monate in einer randomisierten, kontrollierten Phase-II-Studie (Vintafolid + Chemotherapie versus Chemotherapie) |
| **2. Mai 2014** | **Pressemitteilung zum Abbruch der laufenden Phase-III-Studie**<br>• In einer ersten Interimsanalyse konnte kein PFS-Vorteil mehr gezeigt werden |
| **16. Mai 2014** | **Der Zulassungsantrag wurde vor Erteilung der Zulassung durch den pharmazeutischen Unternehmer zurückgezogen** |

Keine Sicherheitsbedenken, aber *Mehrkosten ohne Gegenwert* (Add-on-Therapie)!

Figure 4: Only because relevant results of a phase III study were available in time did market entry not occur.

in Germany until 1 November 2014. The subsequent benefit assessment was performed on the basis of uncontrolled intervention studies and was intended to be concluded with a decision by the plenum of the G-BA on 16 April 2015. Based on the limited and not highly informative study data, it was not possible to quantify an additional benefit in this case; in fact it was questionable whether the administration of Alipogentiparvovec even leads to clinically relevant and lasting effects.

On 14 April 2015 the pharmaceutical company informed the G-BA that the responsible EMA rapporteur noted a negative benefit-risk ratio for the active substance following the evaluation of follow-up data. The G-BA then decided to temporarily suspend the decision in the benefit assessment procedure for Alipogentiparvovec, which caused the statutory evaluation period to be exceeded for the first time [21].

Notwithstanding the critical data, the EMA saw no cause to issue a recommendation to revoke the approval of Alipogentiparvovec. Finally the G-BA on 21 May 2015 was forced to attest an additional benefit for Alipogentiparvovec due to the legal provision that is binding for it, regardless of the information available to it in the course of the evaluation [22] (see Figure 5).

**Adaptive pathways and AMNOG**

In reference to the total number of procedures conducted according to Section 35a SGB V (161), pharmaceutical products with an „atypical" approval status (16) have played a subordinate role to date (as of: 17 March 2016). A relevant proportion of these products benefited from the existing special rules for orphan drugs. To date the results of benefit assessments for pharmaceutical products with an „atypical" approval status are poorer overall than the results of procedures after a „regular" approval, even though an additional benefit was attested more often for products with a CMA or MAEC (75 versus 55 percent).

No additional benefit could be derived for four active substances. In six cases the G-BA attested a „non-quantifiable additional benefit", but in five of these cases this was primarily to satisfy the legal additional benefit requirement. A „significant additional benefit" could only be attested once (see Figures 3 and 6). Of the twelve decisions where the G-BA attested an additional benefit, nine decisions were for limited periods.

It is not clear how the EMA will implement adaptive pathways in concrete terms and to what extent this concept will assert itself in practice. Fundamentally however, an increase in pharmaceutical products that are initially granted a CMA or MAEC based on the first clinical studies can be expected. If the current evaluation practices of the G-BA are maintained, deriving an additional benefit would likely not be possible in many cases due to the limited availability of data for market access, especially if comparison data from high-quality studies with an appropriate comparative treatment are (not yet) available or surrogate endpoints, from which the EMA derives indications of clinically relevant effects, cannot be considered in the course of the benefit assessment due to a lack of validation.

The approval of pharmaceutical products according to consumer protection law and the AMNOG for verification in keeping with social law build on each other. According to the Medicines Act, the approval of a pharmaceutical product is intended to ensure quality, effectiveness and harmlessness. Subsequently the AMNOG reviews the additional benefit according to social law compared to the appropriate comparative treatment as a prerequisite for a higher reimbursement amount and formulates requirements for quality assurance in the use of the pharmaceutical product. Given these prerequisites, insured persons ha-

**Alipogentiparvovec (Glybera) zur Gentherapie bei familiärer Lipoproteinlipase-Defizienz**

| | |
|---|---|
| **23. Juni 2011** | **Die EMA lehnt einen ersten Zulassungsantrag ab**<br>• EU-Kommission regt Neubewertung in einer eingegrenzten Patientenpopulation an |
| **19. Juli 2012** | **Positiv Opinion der EMA für eine Marketing Authorisation under Exceptional Circumstances nach erneuter Beurteilung der vorhandenen Daten** |
| **1. November 2014** | **Markteintritt in Deutschland und Beginn der Nutzenbewertung** |
| **14. April 2015** | **Der pharmazeutische Unternehmer informiert den G-BA über ein mögliches negatives Nutzen-Risiko-Verhältnis von Alipogentiparvovec**<br>• Der zuständige Rapporteur der EMA stellte dies nach Auswertung von aktuellen Follow-Up Daten fest |
| **16. April 2015** | **Der G-BA entscheidet, die Beschlussfassung vorläufig auszusetzen** |
| **April 2015** | **Keine Änderung der Zulassung durch die EMA nach Beratung über Follow-Up Daten** |
| **21. Mai 2015** | **Der G-BA stuft den Zusatznutzens als „nicht quantifizierbar" ein um der gesetzlichen Zusatznutzenfiktion von Orphan Drugs zu entsprechen** |

Ob Alipogentiparvovec zu klinisch relevanten Effekten führt *bleibt fraglich*!

Figure 5: Regardless of the available information, the G-BA had to assume an additional benefit.

ve a broad and general right to be supplied with approved medications.

Lawmakers have established evidence-based medicine and additional benefits relevant for patients as the standard within the scope of SGB V and the Pharmaceutical Products Benefit Assessment Ordinance (AM-NutzenV). Only in exceptional cases where it is impossible or unreasonable to conduct or demand studies at the highest level of evidence (randomised, controlled studies) is verification at lower evidence levels permissible for a benefit assessment (Section 5, Paragraph 3 AM-NutzenV). Since a benefit assessment is commonly conducted based on the studies underlying approval, the adaptive pathways concept causes a conflict in the interplay between the Medicines Act, SGB V and AM-NutzenV. Insofar it is questionable in particular how one can derive „appropriateness" or „efficiency" in terms of SGB V for pharmaceutical products such as Alipogentiparvovec or Idebenon with no proven effect on endpoints relevant to patients (effectiveness) (see Figure 3).

**Conclusion**

The fundamental concept of the AMNOG to provide patients and statutory health insurers with innovative pharmaceutical products quickly and at a reasonable price [23] should not be called into question by the adaptive pathways concept. However, possible risks of damage as well as the economic burdens of immature, incomplete pharmaceutical product development cannot be transferred unilaterally to the insured community. To date the G-BA

**Eine Bilanz bisheriger Nutzenbewertungen von Arzneimitteln mit „atypischem" Zulassungsstatus (höchste Zusatznutzenkategorie je Verfahren, Stand: 17. März 2016)**

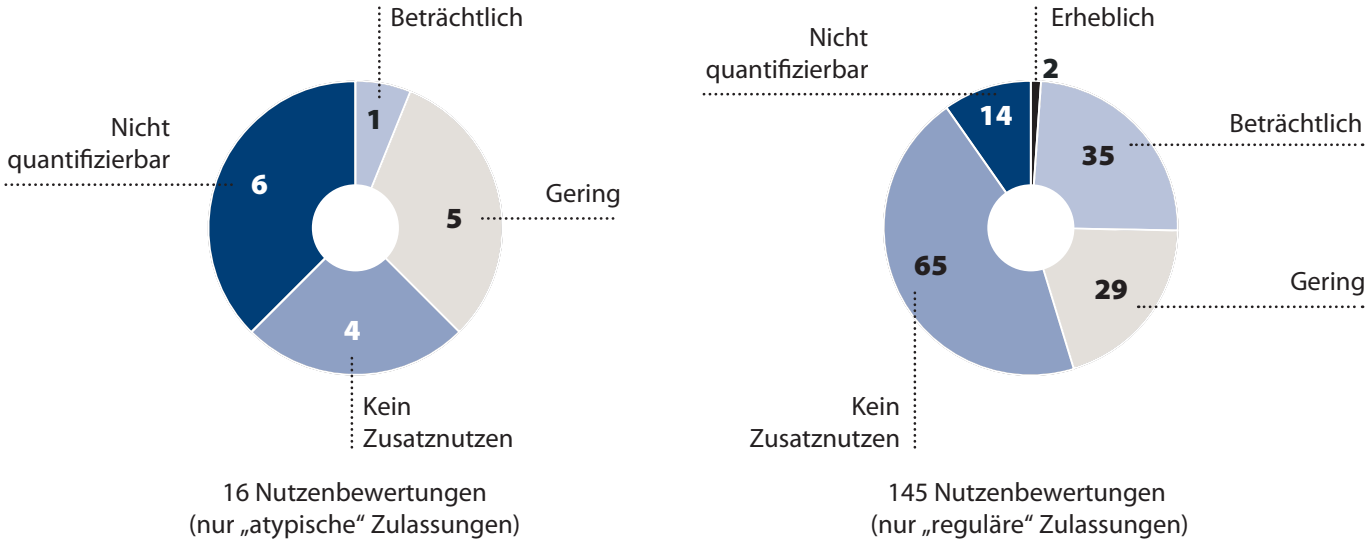


Figure 6: The additional benefit is low or not quantifiable more often compared to „regular" pharmaceutical products.

does not have any tools to respond adequately to an expected increase in „atypical" approvals. It is therefore necessary to account for the temporary nature of an approval under the adaptive pathways concept in social law.

If the standards for the approval of pharmaceutical products under the adaptive pathways concept are lowered, the eligibility for reimbursement must be made „adaptive" as well. For the active substances in question, it is therefore essential to guarantee controlled access in specialised centres within the scope of studies or an indication-specific register from the time of market entry in Germany in order to ensure proper prescription behaviour and the comprehensive collection of treatment data. Involving pharmaceutical companies is essential both from an organisational and from a financial perspective. Establishing alternative reimbursement regulations is required as well. Unrestricted pricing in the first year of market access is not justifiable for pharmaceutical products with an „atypical" approval status.

Once a body of evidence that justifies regular approval has been generated, existing restrictions on the eligibility for reimbursement can be lifted. On the other hand, the G-BA must also be able to determine that an additional benefit cannot be proven if the evidence requirements are not met or study results are negative.

Data collection within the framework of the planned nationwide clinical cancer registers has to be adapted to the requirements of the benefit assessment. A parallel generation of evidence for oncology products in dedicated, indication-specific registers would then be dispensable and duplicate structures could be avoided. Adaptive pathways should be used in areas with a high medical need. Howe-

ver, there is a high medical need for many oncological or neurological diseases and virtually every chronic illness fundamentally means there is an unmet need for new treatment options. A rational, consistent and sufficiently restrictive definition of this term is therefore of essential importance. Adaptive pathways must not be allowed to develop from a special provision for isolated cases to a regular procedure for the approval of pharmaceutical products.

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# Adaptive pathways: a useful tool or a „Trojan" – the controversy

**By Dr. Florian Staeck**

*Accelerated approval procedures for new medications are the subject of controversial discussions in view of the opportunities and risks. The consequences of an accelerated European approval procedure for market development in Germany must be thoroughly deliberated in view of the early benefit assessment according to the AMNOG. This became clear at the 3rd Convention of the Interdisciplinary Platform on Benefit Assessment on 4/5 March 2016 in Kelkheim, which dedicated itself to the topic of adaptive pathways.*

Participants intensively discussed whether the adaptive pathways concept is a „trojan horse" in the approval procedure or merely recombines and activates familiar steps already practised for many years in the approval procedure. Representatives of the latter positions argued that the concept is a toolkit attempting to address protracted approval procedures and failing development programs in large study populations. Under this accelerated procedure, approval is initially granted for a „restricted" indication – subject to the requirement to conduct further clinical studies and also generate real world data based on concrete patient care in the process.

Proponents of the adaptive pathways concept pointed out that lowering approval standards is by no means the goal. The possibilities of a conditional approval were for example opened up by the European regulatory authority EMA back in 2004. Although complete datasets from clinical studies are not yet available at the time of the conditional approval, the assessment of benefits and risks is already considered possible in suitable cases. In oncology studies in particular, sub-groups with greater efficacy compared to the overall population for a study are said to emerge. The proponents also referred to oncology products such as Ceritinib that do in fact address an unmet medical need in corresponding patient populations but are unable to exhibit an additional benefit since comparative studies according to the AMNOG procedure are currently lacking.

Accordingly the adaptive pathways concept is an attempt to define study populations earlier and more effectively – for instance by using bio-markers. Proponents of this approach emphasised that the same evidence is supposedly generated in the subsequent randomised study as with a

large study collective using heterogeneous populations – only in a shorter period. Adaptive pathways would also harbour the potential of developing a different study and assessment culture. It was said that studies are being conducted with a high internal but low external validity to date. The current approach to randomised clinical studies is said to be highly selective. As a rule, the study results cannot be transferred to other populations.

The adaptive pathways concept is not intended as a future standard approval procedure but remains tied in particular to the following initial criteria: The disease has to be life threatening, with no alternative treatment options, and the unmet medical need must be correspondingly great. A new lipid lowering agent would certainly not fall under this set of criteria; however, this would have to be assessed differently for certain oncology indications or diseases of the central nervous system. Here by the way it has proven itself to integrate patient representatives into the process in order to adequately assess the benefit-damage risk.

Sceptics and critics of accelerated approval on the other hand pointed out in the discussion that the risk of bad decisions to the detriment of patients and the healthcare system increases with a reduction of evidence. The adaptive pathways concept is said to increase the risk of expanding approvals while uncertainties may remain in the long term.

Numerous consequences are feared: For doctors this could mean that guideline recommendations and therapeutic advices would be based on much less certain data. Paying parties would have to fear higher expenditures due to the early market entry of a products, that may not be offset by an adequate additional benefit in the end. An increase in off-label use can be expected as well. Handling the required post-marketing data in regards to timely delivery and review by the regulatory authorities is a problem that has by no means been convincingly resolved. Sanctions are said to be difficult to enforce after approval.

Another weakness is that the term „unmet medical need" has not been defined anywhere to date. Experiences from the USA have shown that accelerated approval does not remain limited to serious diseases. Here one can also observe that there are no consequences for companies when data requested by the regulatory authorities are not supplied. Furthermore, one can assume that revoking the reimbursement eligibility for a product following accelerated approval is hardly feasible due to public pressure.

Overall the critics conclude that protecting patients from harm is of higher importance than the legitimate interests of the industry. They warned that adaptive pathways would fundamentally shift risk from the manufacturer to patients and paying parties. In their discussion, participants in the platform convention examined the following aspects of adaptive pathways in particular:

- Dealing with uncertainty: Accelerated approval goes hand in hand with a scientifically new procedure when extrapolating from a smaller to a larger population. Critics asked what scientific studies exist that clearly demonstrate the certainty with which this extrapolation is achieved. The response was that the adaptive pathways concept constitutes a learning process.

The pilot projects currently being implemented by the European Medicines Agency (EMA) under the „PRIME" (PRIority MEdicines) initiative are intended to gather insights into the methodology challenges of accelerated approval. Ex-

periences from the USA have shown that the proportion of products failing in the accelerated approval procedure is between five and ten percent. Numbers indicating that accelerated approval leads to more reports of adverse medical events have to be viewed with caution. Participants argued that it is not clear whether more side effects were actually reported for these medications, since quantitatively large studies where more adverse events could have occurred are lacking.

- Requesting additional study data, and sanctions in case of failure to deliver: Participants pointed out that there are virtually no possibilities today under the German social code book five to exclude a medication from reimbursement eligibility to the detriment of statutory health insurers. To date this is only possible if usefulness is lacking. If the requirements of the Federal Joint Committee for the subsequent delivery of data are not met, this could at the most have consequences in the assessment of the additional benefit. In the worst case for the company, the price level of the appropriate comparative treatment would then apply.

It was suggested that legal clarification could be meaningful at this point, giving the G-BA the authority to impose sanctions if new study data requested as a condition are not submitted within a defined term. In general, requiring additional studies has proven to be a blunt instrument so far. The requirement for a study with „hard" endpoints is hardly realisable when the active substance is already available in the market. If the manufacturer – as an additional option – is required to conduct a study proving usefulness, this would take another three years – making it an unsuitable process to achieve step-by-step, controlled prescription practices for new medications. It was once again noted that the AMNOG merely provides a starting point for reimbursement price negotiations but does not regulate the quality of care.

- Problem of tying approval to centres and specialists: The participants largely agreed that the „controlled" introduction – tied to especially qualified treatment centres – of new medications is difficult. This could not be done effectively in the approval process since such a rule would have to be based on national – German – patient care structures. Approval on the other hand always has to address an overall European context. At most the approval could note the need to tie prescriptions to centres in the dosage recommendations. But complying with these provisions could not be controlled by the BfArM. Participants were reminded that a new medication can be prescribed by any doctor as soon as it appears in the Lauertaxe. Intervention by the Federal Joint Committee comes very late as well, for example since a resolution pursuant to Section 35a SGB V is first needed in order to tie the prescription to centres.

With reference to proceedings negotiated in Karlsruhe at the end of 2015, it was said that the possibilities of the G-BA to restrict the prescription of an approved preparation are also being increasingly monitored by the Federal Constitutional Court in view of possible legitimation deficits of the Federal Joint Committee – although the court ultimately did not question the legitimation of the G-BA. Furthermore, participants warned against establishing rules aimed only at specific patient care sectors. It was suggested that expanding the reporting obligations in the cancer register law could constitute a practicable approach. That is because the law is designed to apply across sectors and offers the opportunity to monitor new approvals with the inclusion of hospitals.

With practically all new approvals in oncology for example, treatment starts on an inpatient basis and then continues in ambulatory care. In order to collect the most complete possible datasets against this background, one way could be to link the reimbursement of a prescription by the health insurer to mandatory reporting to the cancer register.

- Interference between the approval and benefit assessment due to adaptive pathways: Critics complain that accelerated procedures tend to move the standards for studies in the approval process further away from the data required by the G-BA in the early benefit assessment: Surrogate endpoints are said to be increasing and data on patient-related outcomes and quality of life are in part not highly reliable. This could result in approval studies being largely unsuited for decisions regarding the additional benefit. Political pressure on the G-BA to attest the additional benefit for products in adaptive pathways at the time of approval could increase as a result – similar to orphan drugs.

Others argued that this feared trend is by no means inevitable. They say it is important for the development of a medication to be supported by expert teams from regulatory and HTA authorities. This could contribute to converging the requirements. While congruence of the different requirement systems – approval and SGB V – will not be achieved, it was argued that the different requirements could be integrated into the study designs so that they at least do not impede each other. Timely dialogue between the BfArM, G-BA and IQWiG is important against this background. More in-depth cooperation agreed between the three institutions was expressly welcomed by all participants.

In this context the establishment of a new additional benefit category was suggested, with an additional benefit being attested conditionally and subject to further requirements. Such a category de facto already exists but not under this name. This was countered by the argument that such a new additional benefit category would remain without consequences as long as the remaining mechanisms for reimbursement price negotiations are not changed and enforcing requirements is not possible.

The discussions at the 3rd Platform Convention clearly showed that reconciling the opportunities and risks of adaptive pathways is a process that has only just begun, at least in Germany. On the one hand, participants demanded that a balance needs to be found between temporary data uncertainty and enabling accelerated market access for the company in question. Here the withheld benefit for patients due to delayed approval in the conventional procedure has to be weighed against potential harmful effects.

On the other hand, critics stressed that manufacturers in Germany at least have market access in any case. What they are hoping for from adaptive pathways is a price that is adequate from their perspective. Assurances from stakeholders in Germany that accelerated approval will always remain only a special procedure would have to be weighed against signals from some players at the EMA indicating that faster approval could in fact become a regular process. Whether adaptive pathways constitute useful tool or a trojan horse in the approval procedure is not yet clear for platform participants. The debaters agreed that much will depend on concrete application practices, especially by the EMA. After all, changing approval procedures with no verifiable benefit for patients does not make sense.

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