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EU Pharma Regulation: Impulse for Germany

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Goals of the plattform

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

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

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

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

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

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

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

Pharmaceutical regulation in global competition: A test of mettle for the EU

Prof Dr Jörg Ruof

Dear readers,

There is no denying that the times are changing, and with them the political environment. One reads Angela Merkel's autobiography „Freiheit" with a touch of wistfulness – and realises at the end: the „Golden Angies" are now well and truly over. War in the East, „America First" in the West, and tectonic political shifts internally in almost all member states of the European Union.

The key question in this context is whether the post-war European structure – federal and liberal – that has been created will be strong and resilient enough to assert itself in an internationally highly competitive environment given the changed political framework. The efforts toward comprehensive EU pharmaceutical regulation are a fitting example of these challenges. The focus must lie in bringing together and consolidating evidence requirements within a global scientific context in order to maintain a seat at the table as Europeans, to preserve a critical industrial infrastructure in the pharmaceutical and medical technology sectors in Europe, and – most importantly (reference is made here to Mr Danner's article in this publication) – to promote European competence in „meaningful innovation" and „affordable, accessible and effective healthcare" through constant focus on patient benefit.

The difficulties that arise in this respect are already evident when looking at the much-cited PICO schemes (Population, Intervention, Comparator, Outcome) in the context of EU HTA procedures: For example, when it comes to anchoring European interests and evidence requirements (relative effectiveness) in the development programmes of globally operating companies within the EU HTA context, one is reminded of the famous quote by former US Secretary of State Henry Kissinger: „What is Europe's phone number?" The question now becomes: „What is Europe's PICO?" Demanding a multitude of comparators for a double-digit number of European PICO schemes per upcoming EU HTA procedure from the companies is certainly not a promising strategy in view of Europe's declining market share in the global environment.

This publication touches on various facets of the EU pharmaceutical agenda and the associated national impulses. The pharmaceutical policy priorities of the new legislative period are outlined by Dr Kippels. The subsequent report by Dr Steiners calls for reliable, predictable, and innovation-friendly framework conditions and concludes with the offer of a constructive integrative dialogue involving all stakeholders. Professor Broich compares the key aspects of authorisation procedures in Europe and America using specific examples. The articles from the G-BA and IQWIG provide an overview of the current state of European HTA regulation and compare the methodological foundations of HTA assessment in Europe and in Germany.

An overview of the diversity of European reform approaches in the pharmaceutical sector is provided from the perspective of the statutory health insurance funds by the GKV-Spitzenverband. Finally, Professor Ijzerman and the research group from the Erasmus School of Health Policy & Management describe the difficulties arising from the lack of a definition and the inconsistent handling of „unmet medical need" in benefit assessments in the European context.

At the beginning of each publication, the objectives of the platform for benefit assessment are reiterated. The focus is unmistakably on the scientific discussion surrounding the benefit or additional benefit of innovative pharmaceuticals.

The aspect of costs/prices/budgets, often dominant in day-to-day politics, is neither excluded in the publications nor in the platform meetings but is nevertheless treated as secondary.

This is not out of ignorance, but to ensure that, in view of drained public funds and overburdened budgets, the true focus on the ongoing need to optimise patient care is not lost. Thus, the priority of the present report lies primarily on the scientific and substantive aspects surrounding EU pharmaceutical regulation and the German AMNOG legislation.

As always, heartfelt thanks go to all participants of the meeting for their committed discussions, to the sponsors without whom the entire platform initiative would not be possible, and above all to the authors of this publication for their outstanding dedication.

We hope, dear readers, that this publication serve as inspiration for your own reflections and positions. We hope you enjoy the read.

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EU Pharmaceutical Agenda – Impulses for pharmaceutical provision in Germany from a patient perspective

Dr Martin Danner | BAG Selbsthilfe

The enhancement of patient involvement in European procedures for pharmaceutical authorisation and Health Technology Assessment (HTA) is a key concern of BAG Selbsthilfe. It is essential to clarify the methodological concept that should underpin the involvement of patients in EMA committees. In Germany, patient participation is seen less as a source of legitimation and more as a source of insight within scientific assessment. In the European context, there is currently a risk that patient involvement is conceived more as a tool for legitimisation rather than a source of knowledge. Accordingly, European umbrella organisations for patients, such as the European Patient Forum (EPF) and EURORDIS – Rare Diseases Europe, have advocated for strong and substantively meaningful patient involvement at the European level.

Part of the EU Pharmaceutical Agenda includes the enhancement of patient involvement in European procedures for pharmaceutical authorisation. For instance, in the future, representatives from patient organisations are to be included in the European Medicines Agency (EMA)'s Management Board, the Committee for Medicinal Products for Human Use (CHMP), and the Pharmacovigilance Risk Assessment Committee (PRAC).

It is a welcome development that Article 143, No. 4a of the Commission's proposal[1] has included the reimbursement of expenses for participating patient representatives. However, there remains disagreement regarding the extent of participation. While Articles 148 and 149 still refer to „voting rights", recent statements suggest only that patient votes are to be „taken into account".

Naturally, the European umbrella organisations EPF and EURORDIS have vocally opposed this downgrade.[2] Yet beyond the superficial issue of voting rights at the EMA lies the more fundamental question: what is the intended methodological approach for including patients in EMA committees?

The involvement might be interpreted as a form of citizen participation intended to provide reassurance at the EMA that a certain residual risk associated with authorisation, possibly based on less robust evidence, is still acceptable.

Patient representatives would then be expected to reflect on whether quicker access to innovation or the avoidance of residual risks should be the guiding principle in authorisation decisions. In Germany, patient participation is primarily valued as a contributor to scientific insight, rather than a tool of legitimation. The clarification of patient preferences, the differentiation of subpopulations, and the understanding of actual care practices are crucial

components of knowledge that must be methodologically integrated into every pharmaceutical assessment – including during the authorisation process.

In the area of pharmaceutical benefit assessment, it is well established that the patient perspective is not merely to determine whether an assessment outcome is „acceptable" or not. Rather, the aim is to enrich the process of knowledge generation in HTA procedures with the expertise of those affected. It is therefore consistent that training in HTA methodology is a standard offering for patient representatives at the G-BA in Germany. In such a context, a qualitative consultative role is by no means ineffective.

By contrast, patient representatives at France's Haute Autorité de Santé (HAS) possess voting rights as a matter of course but receive no specialist support. Regarding the EMA, it is therefore essential to ask: is there a methodological concept in place that explains why and for what purpose patient representatives are to be included?

The resolution of this question will also influence the future design of the European pharmaceutical benefit assessment procedure.

According to the European Commission's plans, the EMA database used for patient involvement is also to be used to identify patient representatives for the EU HTA process. The professional qualifications of these individuals seem to be of little concern. Nor is it acknowledged that participation in authorisation procedures cannot simply be equated with participation in benefit assessment processes. Training in HTA methodology is not currently foreseen.

This raises the suspicion that patient involvement is again being conceived primarily as a means of legitimisation, not as a source of expertise. At least there is the possibility of proposing qualified patient representatives from Germany to the secretariat of the coordination group for participation in the EU HTA procedure. This right is granted to national coordination bodies under Article 83 of Regulation (EU) No 536/2014.[3]

Curiously, this body is not the G-BA, but the Federal Institute for Drugs and Medical Devices (BfArM). Although BfArM is normally not involved in pharmaceutical benefit assessment, it would be highly beneficial if patient involvement from Germany could be strengthened at the European level via this route.

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Pharma agenda: Germany after the federal election

Dr Georg Kippels | Member of the German Bundestag, Parliamentary State Secretary to the Federal Minister of Health

Regarding the pharmaceutical market, the new government is clearly under pressure to act: supply security must be ensured, and it must be guaranteed that potential innovations continue to enter the market. This will only succeed if there is a corresponding level of remuneration available. A revision or further development of the AMNOG is therefore necessary. Another issue we need to address is the development of orphan drugs. In this context, the definition of rare diseases and hence orphan drugs needs to be reviewed. Furthermore, the BfArM list of currently about 500 supply-relevant pharmaceuticals that cannot readily be delivered is a significant concern. Additionally, everything relating to the existing stock must be scrutinised. An intensive debate – in the sense of a new Pharma Dialogue – must be conducted on these points.

Regarding the pharmaceutical market, the new government is clearly under pressure to act: on the one hand, it must ensure supply security and ensure that potential innovations continue to enter the market. But this will only succeed if, on the other hand, a remuneration volume is available to cover it. Supply security and cost-effectiveness are two sides of the same coin. However, it is becoming increasingly clear that the resources available cannot cover the expenditures. Contributory increases are the inevitable result. That is why cost regulation remains at the top of the agenda even in the new government.

Expenditure by the statutory health insurance (GKV) on pharmaceuticals (excluding vaccines) rose in 2024 by 9.7 % to 53.7 billion Euros. Previous years also saw significant increases that, from the insurers' perspective, cannot continue. In 2022, the GKV Financial Stabilisation Act (GKV Finanzstabilisierungsgesetz) introduced guidelines, combination discounts and a sales cap for orphan drugs, as a first attempt to curb cost increases and cap pharmaceutical spending. Unfortunately, this attempt failed, since it led only to marginal savings and, according to the pharmaceutical industry, had the unpleasant side-effect of some new innovative products not being brought to market in Germany. Although the number remains disputed, the fact remains that the measures legislated failed to achieve the intended purpose.

In the Medical Research Act, the Ampel coalition attempted another correction. However, even here, unfortunately, a bold step to abolish the guidelines entirely could not be agreed upon. Instead, a privilege was merely introduced, conditional on a certain proportion of study participants having been enrolled at specific trial sites in Germany. It remains unclear whether this will actually help. At the European level, we will also have to consider the EU

Pharmaceutical Strategy and the requirements of EU HTA.

The pressing question in this legislative term will therefore be: How can we continue to enable initiatives for new development and the German market launch of innovative pharmaceuticals? In my view, we will not succeed without further changes to our approval practices in connection with the AMNOG. As stated in the coalition agreement, we should therefore commence the revision or further development of the AMNOG.

New pharmaceuticals or precision medicine, due to their novel mechanisms of action (e. g. one-off applications), often do not meet the required study prerequisites and, on the other hand, drive costs ever higher. Therefore, we must move to a different remuneration structure characterised by „pay-for-performance", and develop more flexible early benefit assessment models, for example through real-world data collection during treatment, to demonstrate additional benefit in a patient-friendly manner over the course of therapy.

I've long advocated entering into a renewed Pharma Dialogue. Together, we could develop methods to determine added benefit and appropriate comparator therapy, to bring the speed of market entry into a justifiable harmony with the cost-effectiveness of the reimbursement price to be negotiated.

Another issue we must tackle is again the development of orphan drugs. There appear to be certain outliers in the application of the orphan drug privilege. Well-known diagnoses are being finely subdivided under therapeutic lines to fall under the orphan-drug approval privilege. We should therefore review the definition of rare diseases – and hence orphan drugs – once more, so that this does not become a loophole for privileged approval and hence higher-priced remuneration. These are immense challenges, and they concern only the market for innovative pharmaceuticals.

Furthermore, we must consider the far greater number of generics. We are particularly concerned about the BfArM list of currently around 500 supply-relevant but not readily deliverable pharmaceuticals. This problem arises from international markets, but it also plays a role regarding how large pharmaceutical companies operate in the European market and the establishment of new production sites in Europe. This must be supported by sensible, financially underpinned incentive policies – but to date no convincing measures or instruments are in place. We must address this issue during this legislative period.

Beyond quantifying which cost positions continue to grow over time, we can no longer afford to leave everyt-

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hing in the existing stock untouched. There are medical developments that may require a re-assessment of one or other pharmaceutical. To avoid benefit restrictions in the face of ever-ncreasing pharmaceutical costs, we will, in my view, have to review the entire pharmaceutical market for its evidential basis. Those pharmaceuticals that have entered the market since AMNOG's introduction meet these requirements. But prior to AMNOG, there were a number of pharmaceuticals that did not. Where analysis reveals a significant cost relevance, we should subject these to a critical review once more.

It was foreseeable that all these issues would not be found in great depth in the coalition document, but rather in the form of general programme points. It is clear, however, that an intensive debate must be conducted on all these points. Otherwise, in view of ever-rising social-insurance contributions, we will witness a very critical overall economic development. That is in the interest of neither economic growth nor the welfare of the insured and employees.

Pharmaceutical supply in Germany and the EU: status and outlook

Dr Daniel Steiners | General Manager, Roche Pharma AG

Ensuring high-quality pharmaceutical provision in Germany and the EU faces major challenges. While medical progress is opening up new therapeutic options, established framework conditions are eroding, increasingly impairing our capacity for innovation and supply security. This article examines current developments at EU level (EU HTA, EU pharmaceutical legislation) and in Germany (AMNOG). It highlights the critical importance of reliable, innovation-friendly framework conditions for research, development, and patient access. Particular attention is given to the need to further develop the AMNOG system in line with medical progress and to preserve value-based pricing. Possible solutions are outlined, and a call is made to strengthen reliable framework conditions so that, together, we can build future-proof supply systems.

Innovation requires reliable framework conditions

The pharmaceutical industry is a decisive driver of medical progress and improved provision of healthcare. New therapies help transform patients' lives and outlooks. Yet innovation does not arise in a vacuum: it needs an ecosystem that promotes research and development, offers planning certainty, and enables rapid access to new pharmaceuticals. We are currently witnessing a period of profound realignment.

The revision of EU pharmaceutical legislation and the implementation of the European Health Technology Assessment (EU HTA) are redefining the European framework; at the same time, Germany's established AMNOG system is increasingly reaching its limits and, especially since the introduction of the so-called „guard rails", can no longer fulfil its original purpose as a value-based pricing instrument. Against this background, this article examines the current situation and sets out the course corrections required to safeguard high-quality pharmaceutical provision in Germany for the future.

Setting the course through EU Pharmaceutical Legislation and EU HTA

The European Union is facing a rare but significant opportunity with the overhaul of its pharmaceutical legislation. The stated objectives – improved access to pharmaceuticals, more supply security, enhanced competitiveness, and sustainability – are highly relevant to us as a European community. However, the current proposals, especially those concerning adjustments to intellectual-property protection, also entail substantial risks. Given the long development cycles (10 to 15 years) and the high financial risks in research and development (only a fraction of active substances reaches the market), robust IP protection is indispensable. To secure research, production, and the best pos-

sible medical care in future, it is crucial that German policymakers play an active role – locally and at European level – in advocating reliable and resilient framework conditions.

In parallel, the joint European benefit assessment (EU HTA) aims to harmonise methods for evaluating healthcare technologies across member states, avoid redundancies and accelerate patient access. The potential for efficiency gains is undeniable. A key challenge, however, lies in integrating EU HTA effectively with national systems. Although the first steps are heading in the right direction, our AMNOG must align even more closely with EU HTA so that the results of the European assessments can be taken up and considered appropriately.

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This concerns, first, adapting methodological evaluation principles to the European framework to avoid fragmentation and conflicting outcomes, e.g. in the acceptance of endpoints. Second, at procedural level it must be ensured that the European report (Joint Clinical Assessment, JCA) can be taken into account early and adequately in the national benefit assessment, even in the event of delays. Unfortunately, this is currently not fully guaranteed and thus contradicts a core idea of the joint European assessment. Adjustments are therefore needed.

The situation in Germany: AMNOG at a crossroads

Germany was long regarded as a frontrunner in the rapid availability of new pharmaceuticals, mainly due to the AMNOG procedure introduced in 2011 to encourage innovation while balancing the interests of payers and manufacturers. The system is intended to provide swift market access following authorisation, coupled with a structured additional-benefit assessment and subsequent price negotiation.

Yet these once-reliable framework conditions are increasingly eroding. In particular, the GKV Financial Stabilisation Act has led to a significant tightening that goes beyond short-term savings measures. The combination of increased pressure in price negotiations – through rigid „guard rails" that contradict value-based pricing – and the combination discount massively increases complexity and drastically reduces planning certainty. This devalues certain benefit categories (e.g. „non-quantifiable"), relativises value-based pricing and ignores the importance of incremental innovations.

Moreover, the established AMNOG logic is increasingly reaching its limits with certain therapeutic approaches and evidence situations, especially where justifiable evidence uncertainties exist at the time of market authorisation.

These situations arise not from shortcomings in study design but from the nature of the disease or the ethical framework of research:

- **Very small patient populations:** In rare diseases or specific sub-groups, large randomised controlled trials (RCTs) may simply be impracticable. Direct comparative data demanded by AMNOG cannot be generated in such therapy settings.
- **Ethical limitations:** In areas of high unmet medical need it may be ethically imperative to allow patients in the control arm an early cross-over to the potentially more effective study medication. As a result, long-term comparative data may no longer be derivable from an RCT.
- **Limitations in demonstrating long-term effects:** Evidence of cure (e.g. with one-off curative therapies) or sustained response often cannot be fully demonstrated within usual study durations; necessary evidence may emerge only many years later.

In these borderline areas, the rigid application of classical assessment criteria in AMNOG means that study data of a lower evidence tier (non-RCT evidence) are not considered and the true value of an innovation may be inadequately captured.

This increases complexity, undermines planning certainty, and can ultimately delay or prevent urgently needed therapies from reaching patients in Germany. At the same time, reliable framework conditions are the basis for entrepreneurial decisions on R & D investment, directly influencing our long-term pharmaceutical provision and site attractiveness.

Shaping the future of AMNOG together

To ensure that patients continue to gain access to innovative therapies, AMNOG must be developed further in a targeted manner. The focus should be on establishing a pragmatic and fair approach to justifiable evidence uncertainties arising from medical progress. For the reasons outlined, it may happen that no additional benefit can be determined for a new pharmaceutical under AMNOG despite its high relevance to patient care. The consequences for subsequent price negotiation can be significant.

To correct this imbalance, AMNOG should be further developed as follows:

1) If an additional benefit cannot be derived for formal reasons, but a pharmaceutical addresses a relevant and unmet medical need (drawing on expertise from clinical practice and the patient perspective), this must be adequately reflected through a more flexible negotiation framework during the price negotiation.

2) In particular therapy situations where it is impossible or inappropriate to conduct or demand studies of the highest level of evidence, the best available evidence must be used for the additional-benefit assessment; this presupposes a fundamentally higher acceptance of non-RCT evidence.

3) Evidence uncertainty (e.g. regarding long-term effects) should, in individual cases, be addressed through flexible, outcome-oriented reimbursement models (e.g. pay-for-performance). These, however, require pragmatic and mutually agreed arrangements between payer and manufacturer as well as the lowest possible bureaucratic burden. In this context it would be necessary to be able to establish performance-dependent reimbursement models as an optional element of the central § 130b negotiation.

These adjustments demand the courage to embrace flexibility and the willingness to challenge established assessment patterns without sacrificing scientific rigour. The aim is to create a framework that keeps pace with medical

progress and ensures that innovative pharmaceuticals continue to reach patients, even in particularly complex therapy situations.

Conclusion: Working together for future-proof provision

Pharmaceutical supply in Germany and the EU stands at a critical juncture. Key decisions at EU level and national challenges – especially in dealing with evidence uncertainties under AMNOG – require urgent action. As a research-based pharmaceutical industry, we are ready to play our part. But we need reliable and predictable framework conditions – free of innovation-hostile measures such as the guard rails and combination discount – that reflect scientific realities. These are not an end in themselves; they are the prerequisite for ensuring that medical progress continues to reach patients in future.

In order to achieve this goal, we need a constructive dialogue among all stakeholders in the healthcare system – payers, clinicians, patient representatives, policymakers and industry – so that we can continue to refine the framework conditions and ensure that Germany remains a frontrunner in sustainable, high-quality healthcare.

Trends in pharmaceutical authorisation in Germany/EU versus US FDA: Case studies

Prof Dr Karl Broich | Federal Institute for Drugs and Medical Devices (BfArM)

The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) reach concordant decisions on the market authorisation of new pharmaceuticals in more than 90 per cent of cases.[1] This high degree of alignment is the result of intensified collaboration between the two authorities since 2003, which has strengthened the convergence of authorisation decisions, even though both authorities evaluate applications independently and operate under different systems that can lead to differences in assessment practice and timelines.[2]

The federally conceived European Medicines Agency and the more centrally structured US Food and Drug Administration exhibit significant structural and procedural differences.

The duration of EMA authorisation procedures exceeds that of FDA procedures on average. Marketing-authorisation dossiers are almost invariably submitted earlier in the USA than in Europe.[3] Three case studies illustrate a trend towards (i) narrower indications (lecanemab), (ii) lower acceptance of surrogate endpoints (pegcetacoplan) and (iii) greater reluctance to accept single-arm study designs (mobocertinib) in Europe. In response, numerous measures and activities have been initiated at national and European level to strengthen Germany and Europe as locations for research and for the pharmaceutical industry.

EMA versus FDA – structural and procedural characteristics

Both the European centralised authorisation process and the FDA procedure assess the following parameters:

- Quality
- Efficacy
- Safety.

Both take an evidence-based approach to the evaluation of clinical studies. The EMA focuses on a „positive benefit-risk balance"; uncertainties can be discussed but a complete data package from randomised clinical trials is generally preferred. The FDA focuses on „substantial evidence of effectiveness" and safety based on clear study data, but also accepts data from, for example, single-arm study designs that must later be supplemented. Marked structural and procedural differences exist between the authorities.

Key structural characteristics of both authorities are juxtaposed in table 1. As with the EU HTA Regulation (EU HTAR),[4] the European authorisation process reflects the federal, decentralised structure of the European Union (EU) and recognises the diversity of the Member States (e.g. healthcare systems, languages, expertise), whereas the FDA is a tightly centralised agency. Responsibilities, staffing, budgetary framework, etc. differ considerably between the FDA and the EMA.

Significant procedural differences are also apparent (table 2). The FDA is usually involved very early, from the approval of clinical trials onwards. In addition, the clinical and pre-clinical data available to industry are transparent to the FDA. By contrast, the EMA is often involved later and sometimes only with partial data transparency.

Conversely, there is high transparency regarding EMA work products, whereas the FDA publishes only a summary of each authorisation.

Authorisation times differ markedly between the FDA and the EMA; in 2023 the median time to authorisation (i.e. days from dossier submission to authorisation) for a new active substance (NAS) was 453 days in the EU and 333 days in the USA. It should be borne in mind that in Europe the scientific evaluation and subsequent authorisation recommendation are issued by the EMA, but the actual authorisation decision is then taken by the European Commission; in the USA, authorisation coincides with completion of the scientific review. The median time to completion of the scientific review is 378 days (EMA) and 333 days (FDA).[5] EMA and FDA share incentive schemes designed to enable earlier market entry. Both authorities offer incentive pathways for earlier market entry: Orphan Designation and Breakthrough Therapy Designation, PRIME and Priority Review, Conditional Approval and Accelerated Approval.

Both FDA and EMA face significant internal and external challenges. The impact of current changes in the US political environment on the FDA's operation and functionality is not yet fully foreseeable. The EMA's objectives are to adhere to the highest scientific and regulatory standards in the interests of patients, to support innovative therapies, to ensure comprehensive transparency and to limit review time to 210 days.

A central challenge in achieving these ambitious goals is the continual increase in workload against limited resources. The expertise and number of experts within the authorisation authorities are finite. The increasingly strict interpretation of conflict-of-interest rules further limits the use of expertise from academia in authorisation procedures.

Another major challenge for the EMA's procedures is uncertainty in planning. Of all authorisation applications announced with a Letter of Intent for 2021, only 46 per cent were initiated on time; 21 per cent were delayed, 14 per cent slipped into 2022 and 1 per cent into 2023. In addition, 18 per cent of applications were withdrawn, in some cases after lengthy delays.[6]

The following three case studies illustrate differences between EMA and FDA authorisation procedures; the findings are not universally generalisable.

Case study 1: Lecanemab

:Lecanemab is a humanised monoclonal IgG1 antibody that prevents beta-amyloid deposition in patients with Alzheimer's disease. The assessment is based on phase II study 201 and the phase III „CLARITY" study. Study 201 enrolled 854 patients. The primary endpoint (Alzheimer's Disease Composite Score, ADCOMS) at 12 months was not met, but there was a reduction in amyloid deposition in the brain and corresponding trends towards less clinical deterioration.[7] The randomised, controlled, double-blind phase III CLARITY study in 1795 patients showed a moderate slowing of cognitive and functional decline but revealed an increase in relevant adverse events.[8]

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Marketing-authorisation authorities compared – structural characteristics

EMA/EU	FDA/US
■ Operational leadership by an Executive Director elected by the EMA Management Board (MB) ■ Strategic leadership by the EMA MB, which has 35 members representing EU Member States, European Commission, European Parliament, and patient, physician and veterinarian organisations	■ Operational and strategic leadership by a Commissioner appointed by the U.S. President
■ Decentralised EU agency (for centralised marketing authorisations); EMA acts mainly as a coordinating body	■ Central U.S. agency
■ Scope: pharmaceuticals (human & veterinary)	■ Scope: from food, pharmaceuticals and medical devices to cosmetics and cigarette
■ 1 office in Amsterdam	■ > 200 domestic offices and 7 international sites
■ ≈ 900 staff; external assessment via a unique network of ≈ 5,000 experts from national competent authorities (NCAs) sitting on multinational scientific committees, e.g. CHMP (Committee for Medicinal Products for Human Use)	■ ≈ 19 000 staff; in-house assessment
■ Annual budget ≈ € 600 million (91 % from fees)	■ Annual budget US $ 7.2 billion in 2024 (US $ 3.96 billion federal funding and US $ 3.3 billion ≈ 45 % from fees)
■ Marketing-authorisation decision at the highest level by the European Commission on the basis of a Community opinion of the CHMP	■ Marketing-authorisation decision at lower level, normally by the Director of the Center for Drug Evaluation and Research (CDER)
■ Growing public/patient involvement, e.g. public hearings and stakeholder dialogues	■ FDA more frequently uses public Advisory Committee meetings
■ 24 official languages	■ 1 language
■ European Economic Area (27 EU countries + 3 EFTA states: Norway, Iceland, Liechtenstein)	■ 1 country

EU: European Union; EFTA: European Free Trade Association

Source: BfArM

Table 1: The authorisation authorities EMA and FDA differ in many structural characteristics: the EMA reflects the EU's decentralised structure, whereas the FDA is a tightly centralised agency.

Marketing-authorisation authorities compared – procedural characteristics

EMA/EU	FDA/US
■ Member States apply to perform the assessment; EMA selects according to "best available expertise"	■ In-house assessment
■ Rapporteur & co-rapporteur	■ Primary & secondary reviewer
■ Clinical trial centrally applied for in CTIS, authorised decentrally	■ Early involvement through approval of clinical trials
■ Assessing experts are deliberately rotated (scientific advice coordinators are routinely barred from serving as rapporteurs)	■ Assessing experts remain the same throughout the product life-cycle – from advice through clinical trial to authorisation – wherever possible
■ Clock-stop for amendments	■ No clock-stop; procedure must be re-submitted
■ Fee-based scientific advice	■ Free scientific advice
■ Lower fees for MAA & maintenance	■ Higher fees for MAA & maintenance
■ Formal refusal ("Refusal" by the European Commission following a negative CHMP opinion) ■ Withdrawal of application must be timely	■ Informal refusal (FDA Complete Response Letter is not a formal refusal) ■ Withdrawal of application possible after CRL
■ Very high transparency (EPAR is automatically published after both positive and negative opinions)	■ Summary is published upon approval; CRL is not automatically published

CTIS: Clinical Trial Information System; MAA: Marketing Authorisation Application; EPAR: European Public Assessment Report

Source: BfArM

Table 2: The two authorities exhibit major procedural differences: the FDA is usually involved very early in development programmes, the EMA much later.

A tabular overview of the timelines of the two authorisation procedures is provided in table 3. Each took roughly two years, but the EMA process started significantly later owing to later dossier submission. An accelerated procedure was supported by the FDA but rejected by the EMA. The FDA's accelerated approval was based on the surrogate endpoint of reduced amyloid plaques observed in the phase II study; conversion to traditional approval with a broad indication followed availability of CLARITY data.

European authorisation, unlike that in the USA, is restricted to patients who do not express apolipoprotein E 4 (APOE4) or are heterozygous. This restriction is based on safety, not efficacy:

- During the EMA re-examination process – when the

CHMP recommendation switched from negative to positive – the rapporteur and co-rapporteur considered efficacy demonstrated for the entire population. The primary endpoint was met (-0.45; 95 % CI: -0.67; -0.23; p<0.001). Progressor and time-saved analyses confirmed these advantages in the overall population. Additional clinical benefits were observed in APOE4 non-carriers/heterozygotes:

Clinical Dementia Rating (Sum of Boxes); CDR-SB:

- -0.58 (95% CI: -0.81, -0.35)
- Alzheimer 's Disease Assessment Scale (Cognitive Subscale); ADAS-Cog14:
- -1.63 (95% CI: -2.56, -0.71)
- Activities of Daily Living for Mild Cognitive Impairment; ADCS-MCI-ADL:
- 2.23 (95% CI: 1.34, 3.13)

- However, examination of the current safety data revealed stronger signals on several safety endpoints – specifically ARIA (amyloid-related imaging abnormalities) and intracerebral haemorrhage (ICH) – in APOE4-homozygous patients, and these patients were therefore excluded from the marketing authorisation. In the USA, the labelling contains only a warning.[10]

Case study 2: Pegcetacoplan

Pegcetacoplan is a C3 complement inhibitor that slows the death of retinal cells in geographic atrophy (GA), i.e. the irreversible and progressive thinning and loss of the retinal pigment epithelium, resulting from age-related macular degeneration (AMD).

Assessment is based on the randomised, double-blind, sham-controlled studies OAKS (n = 637) and DERBY (n = 621).[11] The primary endpoint in both studies was total GA lesion area; various functional vision parameters were secondary endpoints. After 24 months, monthly intravitreal pegcetacoplan injections slowed GA lesion growth by 22% (OAKS) and 19% (DERBY).

Key procedural differences concerned acceptance of endpoints. In the USA, a traditional authorisation was granted on the anatomical endpoint, deemed a „reasonably likely" surrogate for Fast Track designation; the EMA requires functional endpoints such as improved visual function. Within the CHMP, use of microperimetry as an intermediate endpoint was controversial. In BfArM' s view, this would have been sufficient to justify a Conditional Marketing Authorisation (CMA); however, the position failed to secure a majority within the CHMP.

Looking beyond the EMA/FDA comparison also confirms the particular challenges of this case: the UK Medicines & Healthcare Products Regulatory Agency (MHRA) issued a negative opinion in November 2024. Australia's TGA granted approval with a restricted indication in January 2024.

It should be noted in this context that the Fast-Track procedure in the USA took approximately 3.5 years to reach a positive decision, whereas the highly complex European procedure required only two years to reach the CHMP's negative opinion. Once again, the dossier for the European authorisation procedure was submitted with a delay, after the FDA process had already begun.

Case study 3: Mobocertinib

Mobocertinib is a tyrosine-kinase inhibitor that selectively inhibits EGFR and was developed for EGFR exon 20 insertion-positive non-small-cell lung cancer in later-line therapy. The FDA granted accelerated approval in September 2021; on FDA advice, the company withdrew the product in March 2024 after the required phase III study failed to confirm benefit. Mobocertinib was never authorised in Europe. The application for a conditional marketing authorisation (CMA) was withdrawn by the company in July 2022.

Indication and authorisation timeline: Lecanemab EMA vs FDA

EMA/EU	FDA/US
Indication: Leqembi is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology.	Indikation: LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.
Jan `23: Start of centralised procedure; accelerated assessment refused	Sep `21: Rolling submission initiated (accelerated-approval pathway)
Jul `24: CHMP negative opinion	Jan `21: Lecanemab receives FDA Fast Track designation
Sep `24: Start of re-examination process Nov `24: CHMP positive opinion	Jan `23: Accelerated approval based on biomarker and early/immature efficacy data
Jan `25: European Commission requests review/consideration of new safety data	Jun '23: Traditional approval based on the results of the CLARITY study
Feb `25: CHMP positive recommendation maintained Apr `25: Marketing authorisation granted by the European Commission	

CHMP: Committee for Medicinal Products for Human Use

Source: BfArM

Table 3: Timeline of the two authorisation procedures for lecanemab – each required roughly two years, but the EMA process began significantly later owing to later dossier submission.

The decision was based on a post-hoc-defined subpopulation of the single-arm study AP32788-15-101, which showed an ORR of 28%.[12] The randomised phase III EXCLAIM-2 first-line study was stopped at a pre-specified interim analysis in July 2023 owing to lack of superiority over platinum therapy.[13]

The case studies show that each system and approach has advantages and disadvantages. In the case of mobocertinib, the EMA's more conservative approach protected EU patients from an ineffective therapy, but it is also one reason why many companies – especially multinationals – prioritise the FDA. The aim of the revision of EU pharmaceutical legislation, presented by the European Commission in April 2023 as part of the Pharmaceutical Strategy for Europe, is to comprehensively modernise and simplify the existing legal framework for human pharmaceuticals, in order to make the European market attractive again and accelerate authorisation procedures. The planned reform represents the largest overhaul in 20 years.

Against this background, the question arises how Germany, as a leading location within European regulation, can help ensure both regulatory excellence and an innova-

Indication and authorisation timeline: Pegcetacoplan EMA vs FDA

EMA/EU	FDA/US
Intended indication: Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) Delete and replace with: intended indication: Treatment of geographic atrophy secondary to age-related macular degeneration	Indication: Geographic Atrophy (GA) secondary to age-related macular degeneration
Dec `22: Submission of marketing-authorisation application Jan `23: Procedure start / appointment of rapporteurs Convening of an AHEG Jan `24: Negative CHMP opinion Jun `24: ■ Procedure reset on the basis of the CJEU Hopveus ruling, exclusion for conflict of interest; ■ AHEG reconstituted with new experts ■ Negative CHMP opinion Jul `24: Re-examination: request for re-assessment; rapporteurs disagree and propose CMA Sep `24: Negative CHMP opinion: rapporteur recommendation for CMA not adopted	Jul `18: Fast-Track designation for treatment of GA Feb `23: Approval for treatment of GA

AHEG: Ad Hoc Expert Group; CHMP: Committee for Medicinal Products for Human Use; CMA: Conditional Marketing Authorization; EuGH: Court of Justice of the European Union

Source: BfArM

Table 4: Major procedural differences between FDA and EMA for pegcetacoplan concerned acceptance of study endpoints.

tion-friendly environment. The following measures show how BfArM, in close cooperation with the Paul-Ehrlich-Institut (PEI), is providing impetus at national level, in concert with European initiatives, to strengthen Germany as a pharmaceutical location.

Measures to strengthen Germany as a pharmaceutical location

Strengthening Germany and Europe in the international environment – while ensuring a supply of high-quality, safe pharmaceuticals – is a central concern of BfArM. Within the developed pharmaceutical strategy, and now in the Medical Research Act, a whole package of interlocking measures is embedded that serve this objective, and

BfArM is centrally involved in their implementation and execution. Examples include:

- Process optimisation, acceleration and debureaucratisation is the shared goal of both federal higher authorities, BfArM and PEI. A number of measures have already been taken to implement this objective:
  - BfArM has assumed the role of single-entry point for coordinating and managing authorisation procedures and clinical-trial applications (including ethics vote and radiation protection) for all pharmaceuticals.
  - A single gate procedure has also been implemented for scientific advice. Application forms have been digitalised, processes adapted, and faster processing times realised. The full utilisation of the specialist expertise of both authorities has been ensured.
  - Establishment of a specialised ethics committee pursuant to § 41c of the German Medicines Act (AMG):[14] The aim of this initiative is to pool expert competence for particularly urgent and complex authorisation procedures. From 1 July 2025 the remit of the ethics committee will include, among other things, studies handled by the EMA Emergency Task Force, complex master-protocol studies, first-in-human studies, and ATMP studies. The more than 100 members were appointed following a call for applications issued by the Federal Ministry of Health; the committee's secretariat is based at BfArM.
  - Strengthening digitalisation in healthcare: numerous legislative and subordinate initiatives (e.g. the Digital Act, the Health Data Use Act, the Regulation on a European Health Data Space, the European Medicines Agencies Network Strategy to 2028, etc.) are aimed at promoting digitalisation in healthcare and within authorisation processes. Just as with its support for Digital Health Applications (DiGA[15]), BfArM is taking a pioneering role in implementing these projects.
  - Clinical evidence 2030: The paradigm shift in basic clinical research towards increasingly targeted pharmaceuticals is also having far-reaching effects on the collection and interpretation of clinical evidence. A vision for „Clinical Evidence 2030" has recently been developed by regulatory experts within the European network. According to this vision, the patient perspective will in future serve far more strongly as both the starting point and the end point of clinical research. Increasingly efficient and meaningful study designs will be aligned with the specific research questions; the development of real-world evidence (RWE) will be further promoted; together with clinical trials, this will enhance both the external and the internal validity of study programmes, and highly transparent procedures and processes will improve the quality of cooperation and mutual trust.[16]

In summary, it should be emphasised that, in keeping with the federal structure of the European Union, significant structural differences exist between the EMA and the more centrally organised FDA. Overall, the duration of EMA authorisation procedures exceeds that of FDA procedures, largely owing to the formal „clock-stop" and the multi-step decision process, which entails a loss of time between the CHMP recommendation and the EU Commission's authorisation. In addition, the submission of the authorisation dossier – and thus the start of the procedure – almost invariably takes place earlier in the USA than in Europe, so that the European authorisation decision can often be taken on the basis of a broader body of data.

The case studies presented illustrate the European trend towards (i) more narrowly defined indications (lecanemab), (ii) lower acceptance of surrogate parameters (pegcetacoplan) and (iii) greater caution with single-arm study designs (mobocertinib). At national and European level, a wide range of measures and activities has been initiated (new EU legislation, Medical Research Act) that, in addition to ensuring a high-quality, safe pharmaceutical supply, aim to strengthen Germany as a location for research and the pharmaceutical industry. In this context, BfArM, together with PEI, is actively involved and plays a leading role.

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Status of the European HTA Regulation

Dr Stephanie Said | Federal Joint Committee (G-BA)

The European HTA Regulation (EU HTAR) entered into force at the beginning of January 2022. During a multi-year preparatory phase, structures were established and key documents for carrying out the Joint Clinical Assessments (JCA) and Joint Scientific Consultations (JSC) were developed. In January 2025, the implementation phase of the EU HTAR for pharmaceuticals began. The first European HTA procedures have already started. Capacity for the JCA and JSC procedures is being provided by the member states. The core functionality of the IT platform is in place and funding is secured based on the recently signed Framework Contract. An evaluation of the EU HTAR is planned for 2028, at which optimisation proposals can be submitted.

Introduction

The European HTA Regulation (EU HTAR), which covers both pharmaceuticals and medical devices, pursues key objectives: accelerating Europe-wide access to innovative pharmaceuticals and medical devices, consolidating European cooperation on Health Technology Assessment (HTA) and reducing the administrative burden on pharmaceutical companies.[1]

Adopted in December 2021, the EU HTAR entered into force at the beginning of January 2022. Its implementation is divided into several phases:

- From 2022 to 2024, essential structural, procedural, and methodological foundations were laid down in so-alled Implementing Acts and guidance documents.
- From January 2025, Joint Scientific Consultations (JSC) and Joint Clinical Assessments (JCA) will be initiated and carried out. The rollout of JCAs will be gradual, so that procedures on oncology pharmaceuticals and Advanced Therapy Medicinal Products (ATMPs) take priority at first. From 2028 the focus will expand to all orphan drugs, and from 2030 all newly centrally authorised pharmaceuticals will be covered. Joint Scientific Consultations (JSC) can be applied for in two application windows starting in February 2025.
- The European JCA procedures comprise only the joint clinical assessment; appraisal of the additional benefit continues to take place at national level.
- Introduction of the European HTA procedure for medical devices and in-vitro diagnostics (IVDs) will be staggered, starting in 2026.

The EU HTA governance structure is shown in figure 1. The overall process is coordinated by the Coordination Group established by the Member States and by its four associated sub-groups: one sub-group for developing methodological and procedural guidance, one for conducting the

JCAs, one for conducting the JSCs, and one for identifying emerging health technologies (horizon scanning). The G-BA, together with the Spanish agency AEMPS, chairs the JSC sub-group. IQWiG, with the Portuguese agency INFARMED, co-chairs the Methodology sub-group. The European Commission provides administrative and technical support. An IT platform with differentiated access areas underpins cooperation. The network of interest groups and experts (stakeholder network) supports the implementation of the EU HTAR. Its members include patient organisations, associations of health-technology developers, professional healthcare organisations and other non-governmental organisations from the health sector. Key information sources on the state of implementation are the European Commission website[2], the Coordination Group work programme[3] and the Implementation Rolling Plan[4].


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Joint Scientific Consultation (JSC)

Details of the JSC procedure are set out in several Implementing Acts and in guidance on the process, the selection of health technologies and the appointment of (co-)assessors. In addition, the Coordination Group and the responsible sub-group have finalised a wide range of document templates that are available for the required submissions and for the outcome document.

In 2025, a maximum of ten JSC procedures are planned (five – seven for pharmaceuticals and one – three for medical devices). Two application windows are available (3 February to 3 March and 2 to 30 June). Applications undergo a stepwise selection by the JSC sub-group:

- Check of eligibility criteria under the EU HTAR, e.g. development stage of the health technology or alignment with a planned JCA procedure;
- Check of selection criteria under the EU HTAR, such as unmet medical need, first product in a new product category, potential impact on patients, public health, or healthcare systems, etc.;
- Alignment with the current work programme.

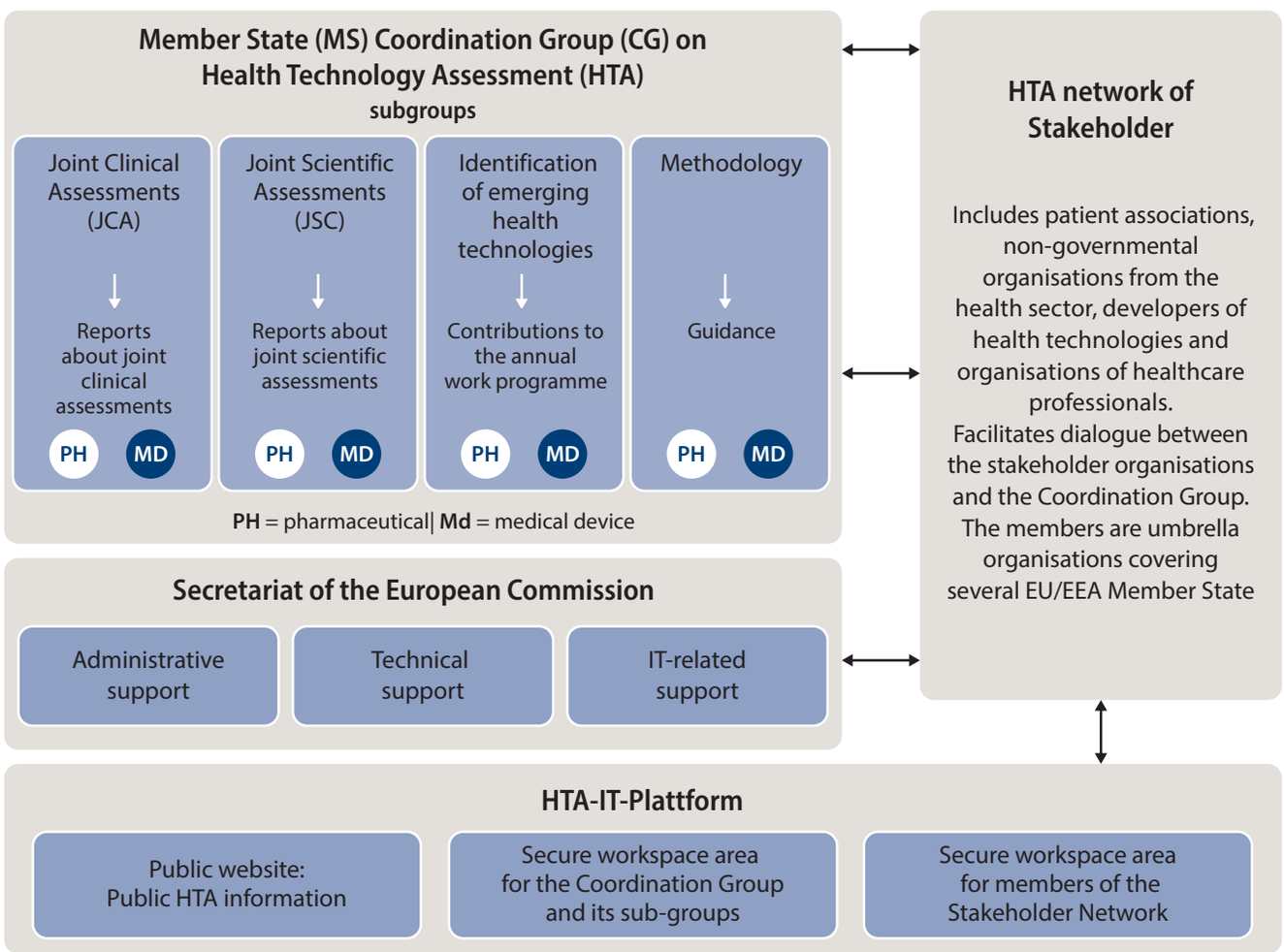
Consultation capacity will increase significantly in the coming years, and the 2028 evaluation of the EU HTAR will examine the possible introduction of a fee mechanism.

Topics in a JSC may include PICO questions (patient, intervention, comparator, outcomes), post-licensing evidence generation (PLEG) and, where applicable, health-economic issues. The latter are addressed only by those Member States that routinely perform economic evaluations. The procedure is illustrated in figure 2.

Joint Clinical Assessments (JCA)

Implementing Acts and guidance for JCAs cover process flow, selection of (co-)assessors, evidence preparation,

EU HTA governance structure

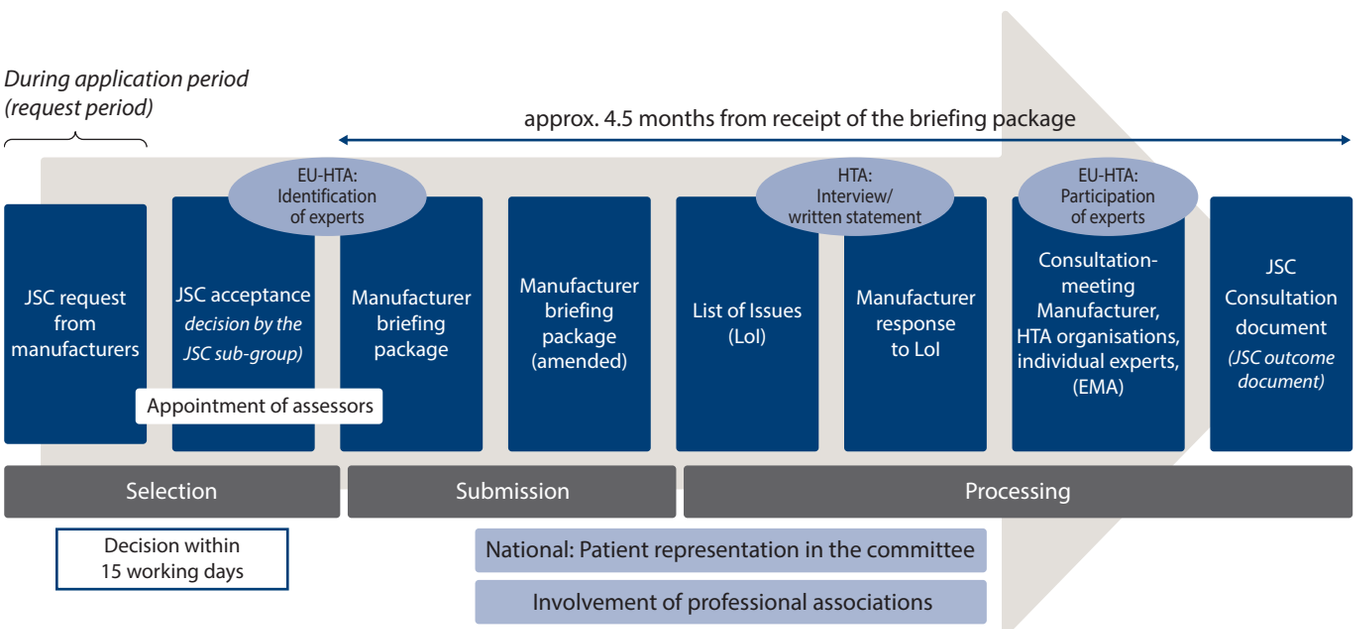


Source: Factsheet Implementing the EU Health Technology Assessment Regulation

Figure 1: The overall HTA process (EU HTAR) is coordinated by the Coordination Group established by the Member States and its four sub-groups.

endpoints, statistical aspects (multiplicity, subgroups, post-hoc analyses), validity of study designs and the use of templates. A central element is scoping. According to Article 8(6) of EU HTAR[1], the scope must be inclusive and meet Member-State needs regarding parameters, data, and evidence. These requirements are operationalised

Procedural Flow – Joint Scientific Consultation



Source: G-BA

Figure 2: Details of the JSC procedure are set out in several Implementing Acts and in guidance on the process, the selection of health technologies and the appointment of (co-)assessors.

using the PICO framework (figure 3).

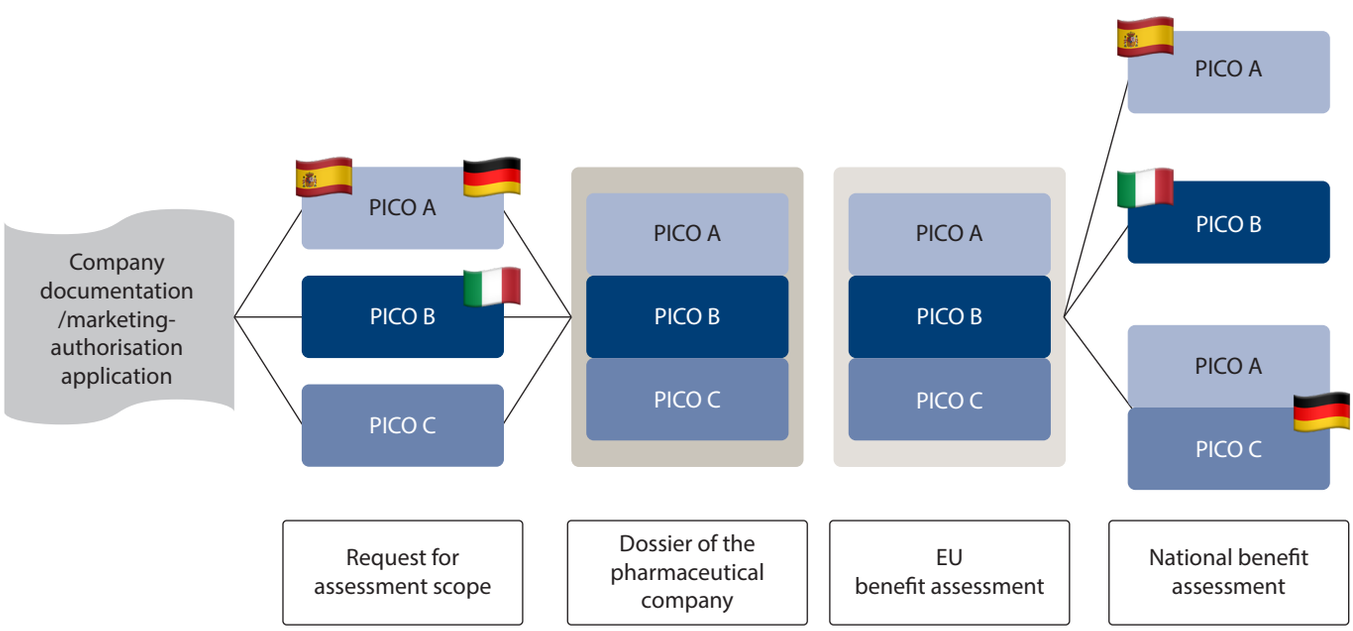
At the beginning, the requirements of the Member States regarding the assessment scope are requested; these are based on the documentation submitted by the pharmaceutical company and are supported by a PICO proposal from the assessors. The PICOs submitted by the Member States are then consolidated in a time-consuming process and communicated to the pharmaceutical company. In the PC's dossier, the data must be prepared in accordance with the consolidated PICO schemes. At EU level, the results for all required PICO schemes are subjected to a scientific evaluation. The subsequent national processes are based on the data and analyses presented in the European dossier that are relevant to their needs and may be supplemented by specific requirements at national level.

In three published pilot exercises of the JCA sub-group, determination of the assessment scope was simulated. This resulted in 7 to 13 required PICO schemes for the selected indications.[5]

Interaction with the German AMNOG procedure

The first ordinance amending the Pharmaceutical Benefit Assessment Ordinance entered into force on 8 March 2025.[6] It refers to the EU HTAR in several places:

Definition of the Joint Clinical Assessment (JCA) and of the assessment scope (scoping)



Source: G-BA

Figure 3: At the start of a JCA, Member-State requirements for the assessment scope are gathered; the PICOs submitted by the Member States are then consolidated in a time-consuming process and communicated to the pharmaceutical company.

- Paragraph 7(1) specifies the EU dossier, the JCA report (if available) and other information on the IT platform as important foundations for the national benefit assessment.
- .Paragraph 7(4) sets out the possibility that the JCA report may not be available at the start of the AMNOG procedure. In that case, any JCA report that becomes available after the relevant national dossier-submission date must be submitted to consultation by the G-BA.
- Paragraph 9(3) contains requirements for the G-BA regarding publication of the EU dossier and for the pharmaceutical company (PC) regarding transmission of the EU dossier if, at the time the benefit assessment is published, it is not yet publicly accessible at European level.

In summary, it should be emphasised that the adoption of all guidance documents and templates in accordance with the work programme has been successful. The first JCA and JSC procedures have already started. Capacity for the procedures is being provided by the Member States, and various European agencies have already assumed (co-)assessor roles in the current procedures. The basic functionality of the IT platform is in place and funding is secured based on the recently signed Framework Contract (FWC).[7]

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IQWiG Methods Paper and EU Guidances: A comparison

Dr. Barbara Spix, Dr. Daniela Preukschat | Department of Pharmaceutical Assessment at IQWiG

The first Joint Clinical Assessments (JCAs) began in spring 2025. In preparation for this, various methodological and procedural guidances were developed and published by upstream subgroups of the HTA Coordination Group. These now serve as a basis and support for the procedures and the stakeholders involved (manufacturers, assessors, member states).

The development of the EU guidances can be viewed from two perspectives: on the one hand, they reflect the current common understanding of EU HTA among the 27 member states; on the other, they also reveal the differing needs of the member states for their national assessment procedures. IQWiG played a key role in the drafting of the guidances through its active involvement in the work of the subgroups.

There are consistencies between IQWiG's methodology and the content of the EU guidances in essential aspects.

In 2021, the European legislator adopted a regulation introducing joint health technology assessments (HTAs) at European level (EU Regulation 2021/2282).[1] Assessments already started on 12 January 2025 for pharmaceuticals containing new active substances for the treatment of oncological diseases and for advanced therapy medicinal products (ATMPs). The basis for the Joint Clinical Assessments (JCAs) is an assessment scope defined specifically for each procedure, which includes the questions of the various member states in the form of PICO(s). The PICO is intended to reflect the research question within the respective member state. The legal context, care practices and availability of comparator therapies all influence the determination of the PICO.

Although the aim of the regulation is to harmonise the scientific basis of HTA assessment, it must be acknowledged that there is currently no uniform clinical practice within the EU. The member states' research questions are consolidated as far as possible and determine which data the manufacturer must submit with the European dossier. The European assessment report, based on this, includes a description of the relative effects of a new pharmaceutical and the certainty of those effects in relation to the research questions. This serves as a body of evidence available to all member states and is intended to provide a basis for national assessment and decision-making.

However, the assessment of the extent and probability of added benefit – in Germany according to the PICO required by the G-BA and pursuant to Section 35a SGB V – and pricing remain within national competence (figure 1). Member states must „duly consider" the JCA report in their national reimbursement decisions. To ensure this, an optimal integration of the European process with the German benefit assessment system (AMNOG process) is also required.

Development of European guidances

As part of the preparation for the European assessments, various methodological and procedural guidances were developed within the subgroups and adopted by the HTA Coordination Group. These include, among others, the process for determining the assessors for a JCA procedure, the scoping process, the handling of endpoints, the methodology for comparisons and evidence synthesis, requirements for the European dossier as well as requirements for the JCA report. The development of these guidances must be viewed against the background of differences between the assessment procedures within the national healthcare systems of the member states (figure 2).

There are member states where decision-making and pricing are based on clinical added benefit (e.g. Germany), whereas in other member states, such as the Netherlands or Ireland, decisions are based on cost-effectiveness analyses. This has implications for the endpoints required in the PICO as well as for the evaluation of the relevance of endpoints in national assessments. Another aspect in which national decision-making processes differ among the member states concerns the population(s) to be assessed within the indication. Unlike, for example, in Germany, where the reimbursement and assessment of a pharmaceutical is generally tied to the entire approved indication, other countries allow for restricted reimbursement for specific patient groups.

This is expected to result in different definitions regarding the patient population(s) within the PICO determination of the individual member states. Furthermore, differences exist in the availability of pharmaceuticals, particularly new or high-priced ones, across member states. Depending on this, some member states may consider certain pharmaceuticals as a comparator in a PICO, even if this comparator is not included in the PICO of other member states. These different requirements regarding endpoints, population and comparator must be taken into account in the European assess-

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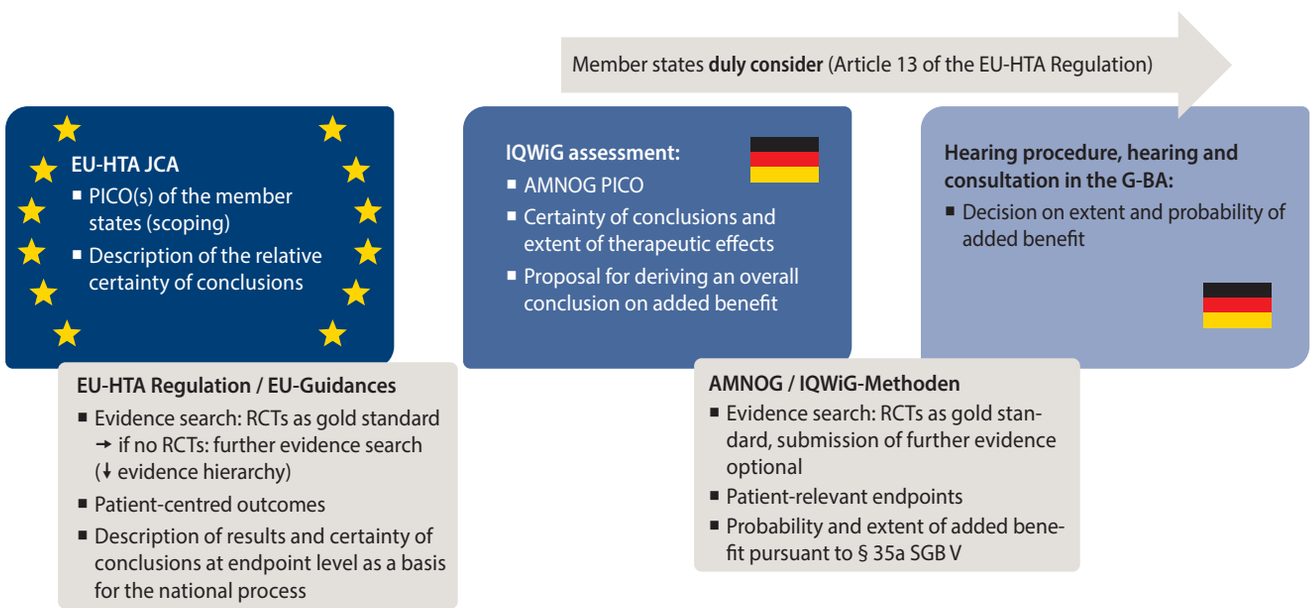
Transfer of the JCA report from the European level to the national level of benefit assessment



Source: IQWiG

Figure 1: The European assessment report includes a description of the relative effects of a new pharmaceutical and the certainty of those effects in relation to the research questions. The assessment of the extent of added benefit and pricing remain within national competence.

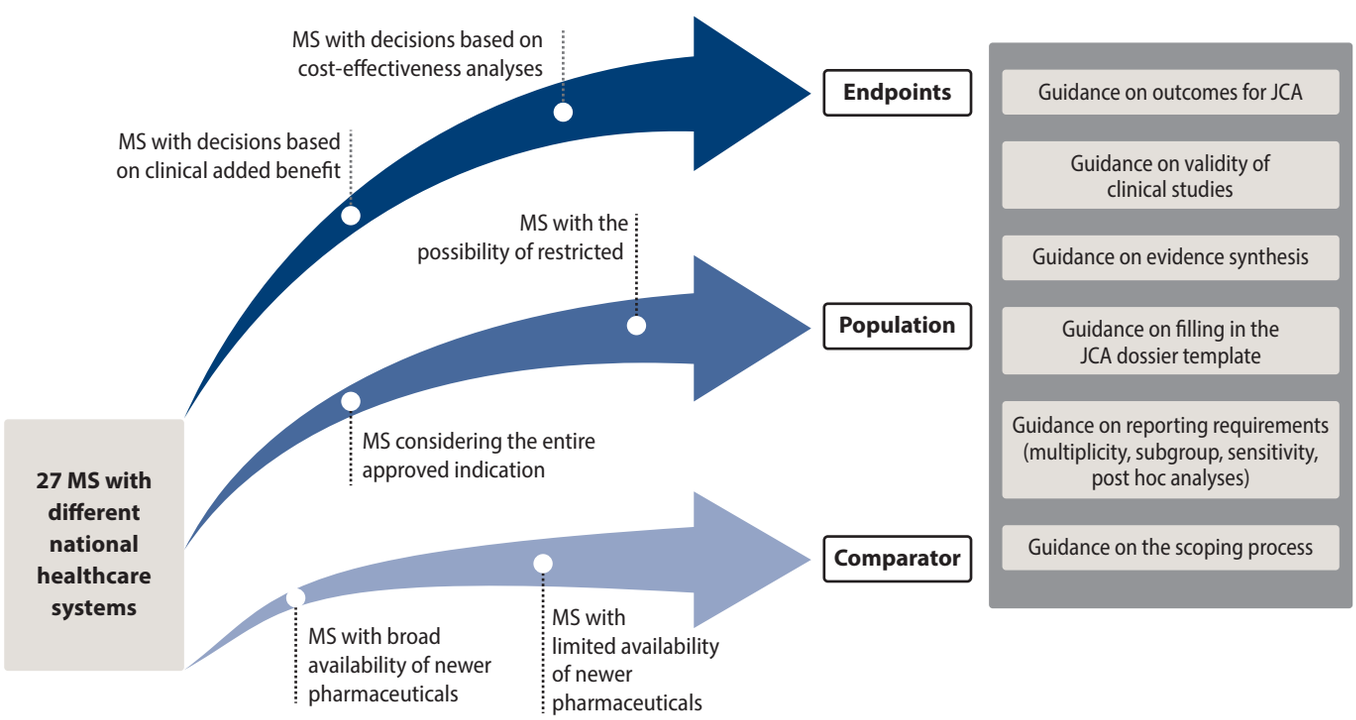
ment process. This is achieved through the assessment scope, which, according to the HTA regulation, must be inclusive and must meet the needs of the member states. In the development of the corresponding guidances, e.g. for the scoping process and endpoints, these varying requirements were taken into account. The Scoping Guidance[2] therefore defines various possible scenarios for the designation of comparators for a PICO; the Outcome Guidance[3] describes definitions of a wide range of endpoints that may be relevant to member states, as well as possible uncertainties regarding their certainty or measurement.

Evidence search and selection

For the preparation of the dossier within the framework of a European benefit assessment, the manufacturer must conduct a systematic literature search for each PICO of the assessment scope.[4] Based on the results of the literature search and the complete list of available studies, the manufacturer subsequently selects the study or studies relevant for the respective PICO. This selection takes place in a multi-step process and depends on the comparator scenario of the respective PICO.

A fundamental difference compared to the AMNOG pro-

Development of the EU HTA guidances against the background of differences between the member states



AWG: Indication; MS: Member state

Source: IQWiG

Figure 2: In Germany, decision-making and pricing are based on clinical added benefit, while other member states make decisions on the basis of cost-effectiveness analyses.

cedure is that, in order to address each PICO in the European dossier, the manufacturer must consider additional evidence – even of lower certainty – such as indirect comparisons or non-randomised comparative studies, if directly comparative RCTs are not available.

According to the AMNOG procedure, the benefit assessment primarily relies on RCTs (evidence levels Ia/Ib).[5] If no directly comparative RCTs with the appropriate comparator therapy (ACT) are available or if these do not allow sufficiently reliable conclusions about added benefit, the manufacturer may optionally submit RCTs for an indirect comparison with the ACT or non-randomised comparative

studies. According to the IQWiG Methods Paper[6], the latter are only considered in the benefit assessment if a sufficient level of result certainty can be demonstrated through adequate adjustment, or if a dramatic effect is present.

If the assessment scope for a patient population, e.g. specifies only a single PICO with one comparator (so-called unique comparator scenario), the manufacturer must first search for directly comparative RCTs. If one or more directly comparative RCTs are available for the required comparator, the study selection is complete, and no further evidence needs to be considered. Provided that there is no evidence from directly comparative RCTs, the manufacturer is required to include, at the second level, RCTs for an adjusted indirect comparison (comparison with a bridge comparator) with the comparator. If these are also not available, the third level involves selecting non-randomised directly comparative studies or indirect comparisons without a bridge comparator. In contrast, the requirements under AMNOG are already met at the first level, i.e. with the selection of directly comparative RCTs. Submission of additional evidence, e.g. due to lack of availability of directly comparative RCTs, is not mandatory.

In situations with ≥ 2 treatment options as comparator for the same population (resulting in several PICOs with ≥ 2 comparators in total), all available RCTs with direct comparisons against the respective comparators, as well as further RCTs that link the intervention to the comparators within a network, should be considered at EU level.[4] These specifications particularly address the needs of those member states that use network meta-analyses (NMA) in their national procedures.

In contrast, under the AMNOG procedure, the evidence search and selection does not require the presentation of connected networks for NMAs. In the case of multiple comparators, the manufacturer may always select one comparator deemed relevant for assessment and restrict the evidence synthesis in the AMNOG dossier to that comparator.[7] The approach to study selection under EU HTA in a situation with multiple „or"-linked treatment options as comparator is illustrated in Figure 4 of the Dossier Template Guidance.[4]

Methodology for comparisons

The guidelines on evidence synthesis[8,9] describe the available methods for direct and indirect comparisons of treatments, including the underlying assumptions, strengths and limitations. According to these guidelines, well-designed and well-conducted RCTs are considered the gold standard for estimating a treatment effect and should be prioritised in evidence synthesis. If no evidence from direct comparative studies is available or if multiple treatments are to be compared simultaneously, indirect comparisons may alternatively be used. In this case, adjusted indirect comparisons that account for randomisation are considered appropriate, for example using the Bucher method or frequentist and Bayesian methods for NMAs.

The guidelines on evidence synthesis also mention another category of studies: non-randomised studies, such as single-arm studies, cohort studies, case-control studies, use of historical controls, and unadjusted indirect comparisons. However, estimating relative treatment effects based on such studies carries a very high risk of fundamental bias due to the lack of randomisation. The levels of evidence described above for comparisons generally align with IQWiG's methodology.[6]

For indirect comparisons (as well as for direct comparisons), three key assumptions should apply. First, the underlying studies should be similar in terms of potential effect modifiers (e.g. patient characteristics) – this is the similarity assumption. Second, there should be no significant

differences between the study results – this is the homogeneity assumption. Third, there should be no inconsistencies between evidence from direct and indirect comparisons – this is the consistency assumption. These aspects must be examined when assessing evidence from indirect comparisons. If the similarity assumption cannot be upheld between the studies in an indirect comparison, further methods to adjust for these factors may be considered. Both the IQWiG Methods Paper[6] and the EU Guidelines[8,9] mention in this context the possibility of applying matching- adjusted indirect comparisons (MAIC) or propensity scores.

IQWiG states in its Methods Paper that MAIC analyses without a bridge comparator are generally not an adequate method for confounder adjustment. For non-randomised comparisons without a bridge comparator, only those comparisons that use individual patient data and differ from MAIC analyses without a bridge comparator are generally considered appropriate for confounder adjustment. Consistent with this, the EU guidelines also address these limitations and uncertainties in the use of MAIC analyses without a bridge comparator.

For appropriate adjustment, it is necessary that all relevant confounders and effect modifiers are accounted for in the statistical model. The propensity score method can adjust for such known and actually measured confounders in non-randomised comparisons. However, a relevant uncertainty arises in relation to potentially existing but unknown confounders, which can only be evenly distributed between treatment arms through randomisation. The uncertainties associated with non-randomised data require a sufficiently large treatment effect that is assumed not to result solely from bias due to unknown confounders. To examine this, a statistical test against a „shifted null hypothesis“ (hypothesis shift) can be conducted, in which the statistical significance of the treatment effect is tested against a threshold that deviates from the original null hypothesis („no effect“). Overall, with regard to comparison methodology and the description of uncertainties, such as in the application of MAIC and propensity scores, there is substantial alignment between the EU guidelines on evidence synthesis and the IQWiG methods.

In the context of a European assessment with potentially numerous PICOs, for which direct comparative study data will not always be available, and based on the different needs of the member states for which the JCA report must be useful, it is to be expected that indirect comparisons will increasingly be submitted and assessed. In the JCA report, the certainty of the data submitted by the manufacturer regarding the treatment effect is to be described. The strengths and weaknesses of the data should be presented. This ultimately forms the basis for the member states‘ decisions on reimbursement and pricing at national level. The member states decide at the national level which uncertainties they accept in their respective decision-making contexts and which they do not.

Endpoints

Endpoints have a central importance for the assessment of new health technologies. In the European benefit assessment process, endpoints are defined during the scoping process within the framework of the determination and feedback of the national PICOs by the member states. The JCA report presents the results regarding the required endpoints as well as potential uncertainties of the results (figure 1). The Outcome Guidance[3] supports, on the one hand, the member states in the definition of relevant endpoints during the scoping process, and, on the other hand, the assessors in reporting the endpoints in the JCA report.

A central difference between the AMNOG procedure and

the EU HTA procedure arises from the fact that, according to AMNutzenV[7] and the IQWiG Methods Paper[6], the therapeutic benefit is assessed on the basis of patient-relevant endpoints, in particular morbidity, mortality and quality of life. This includes, e.g. very specifically the improvement of the health status or quality of life of patients, the shortening of disease duration, the prolongation of survival, or the reduction of side effects.

Within the AMNOG procedure, the manufacturer presents the results on all patient-relevant endpoints in Module 4 of the dossier[5] and justifies why the endpoint is classified as patient-relevant. The patient relevance of the endpoints is assessed by IQWiG. The extent of the added benefit of the intervention is then assessed at the level of each patient-relevant endpoint as well as in the overall view. In the JCA report, however, results are presented for all those endpoints required by the member states via the national PICOs and represented in the assessment scope. A selection of endpoints, for example depending on patient relevance, does not take place at EU level. The HTA regulation explicitly points out that the assessment should not contain a ranking of endpoints. The evaluation of the relevance of an endpoint and the consideration of the corresponding results in the national decision-making process is the responsibility of the member states.

In the HTA regulation[1] and in the Outcome Guidance[3], endpoints are described as „health-related" or „patient-centred". Patient-centred endpoints include endpoints relating to mortality, morbidity and endpoints that are connected to the feelings, beliefs, preferences, needs and functions of the patients (e.g. the ability to participate in activities of daily living). Ideally, when deciding what constitutes a patient-centred endpoint for a PICO, patients affected by the disease itself or individuals with knowledge of it (e.g. patient representatives), as well as clinical experts experienced in the disease area, should be involved. This is ensured both in the AMNOG procedure and in the EU HTA procedure, as involvement of such external experts takes place or is foreseen at various stages of the respective procedures.

Another topic addressed by the Outcome Guidance, which has been the subject of intensive discussion for several years, concerns surrogate endpoints. A surrogate is considered a substitute endpoint for the actual patient-centred or patient-relevant event of interest and is often used in studies when the patient-relevant event only occurs with a time delay (e.g. progression-free survival as a surrogate for overall survival). However, the reliability of surrogate endpoints is often reduced.

Both the IQWiG Methods Paper[6] and the Outcome Guidance[3] therefore require validation using appropriate statistical methods. The Outcome Guidance describes correlation-based approaches to surrogate validation, whereby the strength of the association between the surrogate and the endpoint of interest (correlation measure at patient level) as well as between the treatment effects on the surrogate and on the endpoint of interest (correlation measure at study level) should be demonstrated, the latter on the basis of meta-analyses of several RCTs.

In addition, the guidance describes, based on available literature[10], a threshold value of at least 0.85 for the correlation measure as high, which can thus be used as a criterion for surrogate validation. IQWiG also describes in its Methods Paper primarily correlation-based approaches to surrogate validation, ideally based on a meta-analysis of several RCTs.

As an alternative, the application of the concept of a surrogate threshold effect (STE) is also mentioned, in which the magnitude of the effect on the surrogate in the studies for benefit assessment is compared with the STE. Due to

the increased uncertainties associated with the use of surrogate endpoints within an assessment procedure, the Outcome Guidance emphasises that patient-centred endpoints (e.g. mortality, morbidity, quality of life) should preferably be required by the member states during the scoping process. Validated surrogate endpoints may be required in addition to patient-centred endpoints if a member state considers this relevant.

Only if absolutely necessary should a member state require a validated surrogate endpoint in place of a patient-centred endpoint. If the manufacturer submits a surrogate endpoint, including its validation evidence, in the European dossier, the validation of the surrogate is reviewed by the assessors and addressed in the JCA report. This includes a description of the strength of the association between surrogate and patient-centred endpoint as well as between treatment effect on the surrogate and patient-centred endpoint, a description of the level of evidence, and the uncertainties and limitations regarding the use of this surrogate. The final assessment of the validity of a surrogate and the decision on whether to consider such an endpoint in the national assessment procedure is the responsibility of the member states.

Endpoints on health-related quality of life as well as other patient-reported endpoints are often collected using validated questionnaires and the scales contained therein. Of interest here is the assessment of the relevance of the observed effects of the pharmaceutical under investigation, i.e. whether the difference between the intervention and control groups of a study is perceptible to patients. According to the IQWiG Methods Paper[6], the assessment of relevance can basically be carried out on the basis of mean differences and responder analyses.

As a plausible threshold for a perceptible change, a response criterion of at least 15 per cent of the scale range (if pre-specified) or exactly 15 per cent of the scale range (if defined post hoc) is applied. If no responder analyses are available or if these are not suitable, analyses of the continuous data can be used, with standardised mean difference (SMD, in the form of Hedges' g) and a non-relevance threshold of 0.2 for the assessment of relevance. At European level, analyses of continuous data should always be presented (e.g. change in values over time).[3] These can, however, be supplemented by analyses on the categorical scale, i.e. using a responder definition. The JCA report should also indicate which of the two effect measures were pre-defined as the primary analysis in the study protocol. Furthermore, if the manufacturer submits responder analyses, the methodology and rationale for the definition of the response criterion should be presented.

Unlike in the IQWiG Methods Paper, no specific value for defining a response criterion is currently mentioned in the Outcome Guidance. Instead, different methods for estimating the minimal (clinically) important difference (MID, MICD) are described (anchor-based or distribution-based methods), which can be used as a criterion for a meaningful change in the patient and thus as a response criterion. The consideration of results according to continuous scale and/or based on a responder definition lies with the individual member states within the framework of the national decision-making process.

Handling of data cut-offs

The issue of data cut-offs is addressed in two different EU guidances, the Reporting Guidance[11] and the Dossier Template Guidance.[4] As a rule, where several data cut-offs are available, the results for the last pre-specified data cut-off must be submitted by the manufacturer in the EU dossier and presented by the assessors in the JCA report, in each case for all endpoints. In cases where the data quality of

the last pre-specified cut-off is not sufficient, for example due to a high proportion of missing values, results from earlier cut-offs may also be reported. In order to meet the needs of all member states regarding necessary data cut-offs, two additional requirements are also formulated. For multiplicity-controlled endpoints, often the primary endpoint of a study, in addition to the last pre-specified cut-off, the results of the cut-off at which the null hypothesis was rejected should be reported. For member states where the national assessment only takes place several years after the European benefit assessment, the last available cut-off for the endpoint overall survival is particularly relevant. The results for overall survival for this cut-off must therefore also be submitted in the EU dossier and presented in the JCA report.

In the dossier for the AMNOG procedure, the manufacturer must state which data cut-offs were carried out, whether they were planned a priori, and whether any further cut-offs are planned.[5] As a rule, analogous to the EU HTA procedure, the results of the last pre-specified cut-off are relevant here, and possibly also data cut-offs required by the EMA.

Conclusion

- The guidances for EU HTA contain comprehensive information on the scoping process, evidence synthesis, endpoints and provide detailed analytical recommendations for manufacturers and assessors.
- There are substantial consistencies between the methodological guidances for EU HTA and IQWiG methodology (e.g. systematic evidence search, high-quality RCTs as gold standard, uncertainties regarding non-randomised comparisons and surrogate endpoints).
- In the JCA report, available evidence of varying quality is presented, including its uncertainties. The decision on whether to take this evidence into account, e.g. for reimbursement decisions or price negotiations, is made by the member states at national level.

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Pharmaceutical supply in the EU: Status and outlook from the perspective of Germany's Statutory Health Insurance Funds

Robert Pecak | Maximilian Blindzellner | Dr Antje Haas | National Association of Statutory Health Insurance Funds (GKV-Spitzenverband)

The reform of European pharmaceutical legislation is in full swing. It aims to address current European challenges. In addition to the so-called „Pharma Legislation", the European Commission has already presented the first draft regulation of the „Critical Medicines Act". This law is intended to ensure that pharmaceuticals approved in the EU are available for supply within the EU. From the perspective of statutory health insurance, many aspects relevant to the German pharmaceutical supply can be found in the ongoing European legislative processes.

The most important aspects of the Pharma Legislation Reform of data exclusivity and implications for statutory health insurance finances

A particularly important provision to be reformed by the legislative package is the timeframe for data exclusivity for newly marketed pharmaceuticals. Under the existing regulation, a maximum combined protection period through data exclusivity and market exclusivity of eleven years is permitted. According to the plans of the EU Commission, the period would be extended to a maximum of twelve years, while the plans of the EU Parliament envisage a period of eleven and a half years.[1] Both reform proposals share the goal of making the protection period more modular depending on certain criteria (figure 1).

By extending data exclusivity or market exclusivity, the entry of generic competition is delayed. According to calculations by the German Social Insurance Representation in Europe (DSV), each additional year of regulatory protection results in extra expenditure for statutory health insurance of more than one billion Euros. Considering the entire European market over the same period, the additional costs amount to more than three billion Euros.[2] These figures clearly illustrate the significant impact this provision can have not only on the financial viability of the German healthcare system, but also on the healthcare systems of other EU Member States (figure2).

Expansion of the „Bolar Exemption"

Regulatory data protection and patent protection grant companies a time limited monopoly. This is intended to allow companies to recoup their research and development expenses. However, once the protection periods have expired, market competition should be able to begin

as quickly as possible, causing prices to fall and freeing up resources for further innovation.

The aim of the so called „Bolar Exemption" is to ensure that this generic competition can begin on day one after the expiry of any protection periods. Generic and biosimilar pharmaceutical companies should be able to conduct studies with the reference pharmaceutical. These studies are often necessary for the approval of the generic pharmaceutical. The position of the EU Parliament calls for a broad interpretation and legal clarification. These studies for approval and reimbursement decisions, as well as for health technology assessment (HTA) procedures, should be possible during the ongoing patent protection of the reference pharmaceutical. This includes all related activities. In addition, the EU Parliament's proposal clarifies in a separate article that patent protection must not influence decisions on approval, HTA and reimbursement (prohibition of so-called „patent linkage"). This provision could lead to earlier price competition. Such price competition is particularly important for the diversity and financial viability of German pharmaceutical supply.

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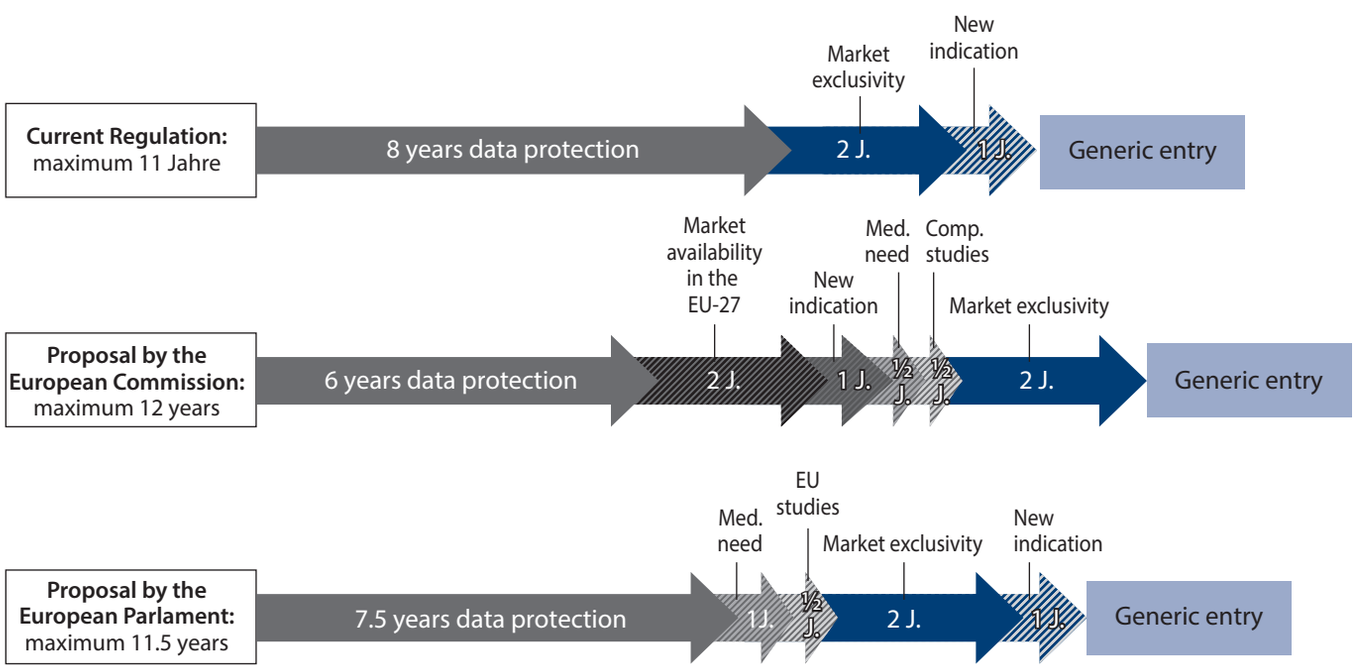
Planned measures for regulatory data protection



Source: GKV-Spitzenverband, own illustration based on "Reform of the EU pharmaceutical legislation – European Commission"

Figure 1: According to the plans of the EU Commission, the market protection period would be extended to a maximum of twelve years, while the plans of the EU Parliament envisage a maximum period of eleven and a half years.

The problem of antimicrobial resistance

Resistant pathogens do not stop at national borders. The increasing number of microbial resistances is thus a common European challenge. Figures provided by the Scientific Institute of Local Health Insurance Funds (WIdO) on antibiotic prescription in Germany showed a significant increase in prescriptions of reserved antibiotics. The number of prescriptions of these sparingly used pharmaceuticals increased by 18.4% in 2023 compared with the previous year.[3] With the rising number of prescriptions of reserve antibiotics, the risk of resistance also increases. It is particularly important to prevent the development of serious or resistant infections in advance and to limit the use of reserve antibiotics in human and veterinary pharmaceuticals to what is necessary.

Furthermore, additional research into antimicrobial therapies is also needed for pathogens with critical resistance situations. The EU Commission and the EU Parliament wish to introduce transferable vouchers – so-called „vouchers" – as an incentive for the development of a phar-

Financial impact of regulatory data protection

Figures from the DSV:

Every additional year that the entry of generic competition is delayed costs the Statutory Health Insurance (GKV) in **Germany** more than **1 billion Euros**.

Across the EU, each additional year of regulatory data protection results in extra costs of more than **3 billion Euros**.

U Pharmaceutical Reform:
The cost of one additional year of regulatory data protection

Every additional year that the entry of generic competition is delayed costs the Statutory Health Insurance (GKV) in Germany more than **1 billion Euros**.

Across the EU, each additional year of regulatory data protection results in extra costs of more than **3 billion Euros**.

The following figures and assumptions form the basis of these calculations:

GKV turnover for non-generic pharmaceuticals in 2023 (projection):	29.1 billion Euros
Average effective protection period:	13 years
Lifecycle factor:	1.4
Share of pharmaceuticals benefiting from extended regulatory data protection:	46.5 %
Factor for average extension of effective protection period:	Factor 0.92
Average price reduction through generic competition:	75 %
Germany's share of EU pharmaceutical market revenue:	25 %

Source: German Social Insurance – European

Figure 2: Extended data exclusivity or market exclusivity delays the entry of generic competition. Each additional year of protection means extra expenditure for statutory health insurance of more than one billion euros.

maceutical against such priority pathogens. After the pharmaceutical has been approved, the pharmaceutical company receives a voucher for up to twelve months' additional data exclusivity. This voucher can be sold once. It is thus to be expected that these vouchers will be acquired by pharmaceutical companies that wish to apply them to high-turnover pharmaceuticals. This forecast is supported by the EU Commission's impact assessment report.[4] As a result, it is not primarily the companies that developed the antibiotic that will benefit, but the companies that purchased the voucher for particularly high-turnover pharmaceuticals.

These so-called „windfall profits" could impose a disproportionate financial burden on the German healthcare system without delivering effective or targeted benefits to the companies actually conducting the research. In the critical phase of drug development, vouchers also do not offer assistance to the researching companies. Alternatives that support companies already during the research phase are so-called „push & pull incentives". A proposal for this incentive system is set out in the EU Parliament's position. Under a „milestone payment programme", certain milestones such as the completion of clinical phase I would be

rewarded during the research phase with grant payments. While these grants are considered „push incentives", guaranteed purchase volumes of the often low-turnover pharmaceuticals are classic „pull incentives".

The problem cannot be solved by developing new active substances alone; the existing ones must also be used rationally and sparingly.

Hesitant reforms for orphan drugs

Similar to the current situation with reserve antibiotics, special provisions for pharmaceuticals for rare diseases (orphan drugs) were originally justified as a remedy for market failure. For diseases affecting fewer than 5 in 10,000 people in the EU, it was assumed that therapies would not be economically developed without further incentives. In view of the developments over the past 25 years, this general thesis can no longer be maintained. On one hand, many very rare diseases remain under-researched; on the other, some relatively common chronic orphan diseases have experienced dynamic markets with high profits (clustering). To place the promotion of therapies for rare diseases on a stable footing over the next 25 years, a refocusing of incentives on genuine cases of market failure in ultra-rare diseases and on real therapeutic breakthroughs is urgently needed.

The draft Critical Medicines Act

With the COVID pandemic and the associated turmoil in world trade, the security of pharmaceutical supply has entered the political agenda. Pharmaceutical companies and wholesalers are obligated, within their areas of responsibility, to ensure an adequate and continuous supply of the relevant pharmaceutical so that patient needs are met (section 52b (1) of the German Medicinal Products Act or article 81 of Directive 2001/83/EC). With the draft Critical Medicines Act, the question now arises how this obligation can be supported by supplementary provisions to ensure pharmaceutical supply.

Various, complex causes of supply bottlenecks

Pharmaceutical supply shortages can have diverse causes: problems may arise even during the production of an active substance. A prominent past example is the nitrosamine contamination in the production of sartans. If the production of the active substance cannot be offset by other manufacturers, widespread supply and shortage issues can result.

After the active substance is produced, it is often transported to Europe for secondary production of the pharmaceutical. Transport problems may occur, e. g. a blockage of important supply routes. One such incident was the blockage of the Suez Canal by a cargo ship about four years ago. Even if the pharmaceuticals have already been produced, inventory miscalculations can still occur – especially when stock-checking processes are not fully digitised.

Moreover, an unpredictable surge in demand due to seasonal morbidity patterns can also cause supply shortages. Because the causes of supply bottlenecks are so varied, suitable measures are also varied. It is important that these are evidence-based and transparent. Isolated price increases without associated obligations are therefore unsuitable. One suitable instrument is the diversification of suppliers in production and supply chains. This is intended to make Europe less dependent on individual producers from third countries. Appropriate stockpiling, supported by digital recording systems, can mitigate transport and logistics problems. In times of seasonally increased demand for certain pharmaceuticals, improved digital demand planning can help (figure 3).

Proposed measures

The now-published draft Critical Medicines Act must be sensibly linked with the pharmaceutical reform. The interplay of the legal acts could, e. g. be used to set up an EU-wide early warning system for supply shortages. This could serve as a valuable tool for preventing shortages. To avoid future bottlenecks, marketing approval holders should be required to report impending shortages in good time.

In addition to priority treatment for so-called „strategic projects", the draft calls for priority supply to EU Member States for pharmaceuticals that have benefited from state aid. It also provides for new mandatory procurement criteria for „critical pharmaceuticals" and „pharmaceuticals of common interest".[5] Such mandatory inclusion would constitute a significant intervention in German pharmaceutical supply and the freedom to negotiate rebate contracts. The bureaucratic effort would also be immense. Furthermore, the proposed regulation gives rise to legal uncertainties regarding the treatment of EEA contracting states and other agreements. These legal uncertainties must be resolved before the Critical Medicines Act is incorporated into existing EU law.

Enforcement of manufacturer responsibility

Under existing law, marketing approval holders are already obliged to ensure adequate and continuous availability of their products within their responsibility. As long as these regulations are neither sanctioned nor enforced, there is an incentive to implement cost-cutting measures that increase the vulnerability of the supply chain. Only through appropriate sanctions does the competitive environment create an incentive to accept higher production costs in order to avoid potential penalties. Without sanctions, new regulations that merely encourage „maximum efforts" will probably remain ineffective.

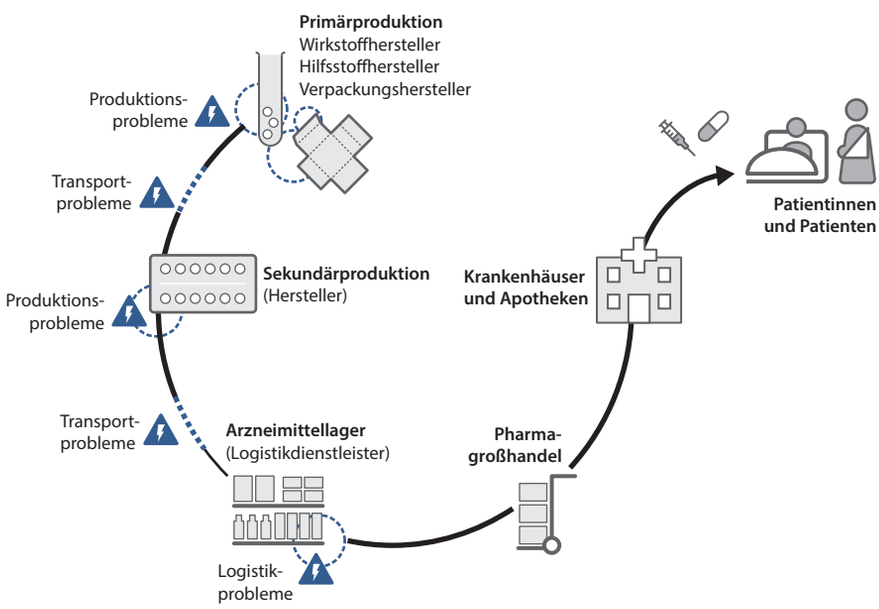
Stockpiling

German law already includes extensive regulations on pharmaceutical stockpiling. For example, pharmaceuticals subject to a rebate contract must be kept readily available for six months. In addition to the German regulations, voluntary use of the EU solidarity mechanism for pharmaceuticals under European coordination could be used in crisis situations. Often, supply shortages are caused by problems in the supply of the active substance. Therefore, the Critical Medicines Act could consider whether stockpiling of active substances as a strategic EU reserve would be sensible. Effective stockpiling of pharmaceuticals and efficient coordination in crisis situations requires that stocks be digitally and in real-time recorded and tracked.

Outlook

2025 is undoubtedly an exciting year for European pharmaceutical legislation. Especially in view of geopolitical and trade-policy tensions today, common European solutions and efficient, agile supply structures are needed. Above all, innovative solutions are required that on the one hand enable efficient and high-quality pharmaceutical supply and on the other ensure the long-term financial sustainability of public healthcare systems.

Various causes of supply bottlenecks



Various causes of supply bottlenecks:

- **Production** issues
  - e. g. contamination, such as with sartans in 2018
- **Transport** disruptions
  - e.g. Suez canal blockage
- **Logistical** problems
  - e.g. miscalculations in pharmaceutical inventory
- **Illness-related Demand Spikes**
  - e.g. unexpected increase in demand due to illness outbreaks

Source: GKV-Spitzenverband, own illustration

Figure 3: It is important that instruments to counter supply shortages are evidence-based and transparent. One suitable instrument is the diversification of suppliers in production and supply chains.

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Unmet need in healthcare: ambiguity in the definition does not help setting priorities

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The term „Unmet Need" is used multiple times in European Union (EU) Health Technology Assessment (HTA) regulations, the EU pharmaceutical legislation and in HTA guidelines in member states (MS). There is no consensus about the definition of unmet need, yet in most guidance documents it refers to the unavailability of treatment options for patients with severe conditions or for patients suffering from significant residual disease. Examples are orphan or neurodegenerative diseases like Alzheimer. Proxies or determinants of unmet need, referred to as decision modifiers, may be also considered to inform payment decisions in MS. Amongst others, they include rarity, disease severity, intended treatment aim, innovative treatments or cross-sector benefits. Others have argued to include other value components in the appraisal, such as the value of knowing or value of hope. However, these terms are ambiguous and not actionable. For many treatments, a cascade of factors ultimately determines if medical products will be available to patients in MS and, hence, interpreting unmet need as a binary outcome is not appropriate. Concerns have been raised that prioritising R&D efforts to areas of unmet need should be aligned with the right incentives to mitigate commercial risks, e.g. by (financial) protection measures.

Background

The European Regulatory Framework for Health Technology Assessment (HTA) came into effect in January 2025.[1] This regulation presents guidance for Joint Clinical Assessments across Member States (MS) which is considered a step forward in harmonising HTA across the the European Union (EU). In the regulations reference is made to medical products that address unmet needs, particularly to define exemptions for MS to make independent national assessments. The rationale for this exception is that, while evidence generation may be transferrable across health settings, the assessment of relative effectiveness and/or the availability of treatment options is context dependent. Also, early access to medicines in circumstance of high unmet need may be subject to decisions of individual MS. While these exemptions are guided by „unmet needs", no clear definition of unmet needs is provided nor implemented across regulations or MS.

In addition, a large literature exists that aims to define priorities for reimbursement (and accelerated approval) based on unmet needs identified by eliciting (patient) preferences. Most of this work is done within the jurisdiction of individual MS. One of the very first examples in Germany was the IQWiG pilot, testing multiple methodologies to prioritise patient-relevant endpoints for anti-depressive medication (Danner et al, 2011). The study, employing Multi-Criteria Decision Analysis, aimed to prioritise treatment- related outcomes and adverse events. The notion that patient preferences and other non-clinical value components played an important role in national coverage decisions has grown since then, with pivotal studies reviewing and validating prioritisation or preference elicitation methodologies (Thokala et al, 2016; Soekhai et al, 2019; Whichello et al, 2020), the qualification

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of the PREFER framework on when and how to elicit preferences by European Medicines Agency (EMA) (PREFER consortium, 2022) and the development of the ISPOR Value Flower concept in 2018 (Neumann et al, 2022).

With reference to these methodological and conceptual developments, this paper aims to provide some backgrounds into the definition and assessment of unmet needs and how this could facilitate European and national priorities for medical product development, reimbursement and healthcare delivery.

How is Unmet Need defined in European and National guidelines

European guidelines: unmet need refers to availability

The term „unmet medical need" appeared explicitly in 2006,[2] where it was defined as „… a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those aFected". The previously introduced EU regulation on HTA refers to unmet need, specifically as a criterion to define exemptions for joint assessments and to expedite assessment within the MS for medical products addressing a high unmet need (e.g. Article 7:4). No definition of unmet need was provided in the regulation.

Further, in 2023, the European Commission (EC) proposed a new pharmaceutical legislative framework[3] for the EU to replace the existing framework that has been in place for over 20 years. The definition used in the framework states that „… a new medical product is addressing an unmet need if (1) there is no medical product authorised or when there is still significant morbidity and mortality and (2) the medical product is for a designated orphan indication".

While the recent HTA regulations do not explicitly define unmet need, other EU regulations do. They typically refer to the limited availability of treatment options, either because they are not on the market, not supplied, or if there is significant residual morbidity or mortality in specific patient groups. Examples of diseases with (high) unmet need are neurodegenerative disorders like Alzheimer's disease or Multiple Sclerosis, many orphan diseases and rare cancers (Scavone et al, 2019).

However, although there is appreciation for the attempts to present a universal definition of unmet need, a widely accepted definition should also address the underlying causes that have hindered innovation in these areas. As such, a definition should also include principles like fairness, flexibility, feasibility and sensitivity to risk (which is when unmet need becomes more important than confirmed clinical benefit) (Bloem et al, 2025).

National guidelines: unmet need used as (reimbursement) decision modifiers

National guidelines also explicitly address medical products addressing unmet need. But this consistently is linked to national reimbursement and coverage decisions, something that EU regulators explicitly leave to national jurisdictions. Further, the emphasis on unmet need in National guidelines appears to be primarily used to accelerate access or differentiate market access pathways and payment schemes. Without intending to be complete, we reviewed the methodological guidelines for preparing and submission of value dossiers in four countries.

The Netherlands Pharmacoeconomic Guidelines (Zorginstituut[12]) do not explicitly mention unmet needs in their methodological guidance for preparing value dossiers. The dossiers follow a „reference case" format with a preferred methodology to define comparator(s), relevant

costs and outcomes, and modelling. The Advisory Committee in their appraisal phase, however, does explicitly consider „necessity" and „feasibility" in addition to clinical effectiveness and cost-effectiveness as presented in the value dossier. These additional criteria explicitly make a connection to the „availability" of treatment options in terms of unmet need, supply, and access.

The Australian guidelines (those of the Medical Services Advisory Committee or MSAC[8]) do explicitly mention unmet need and particularly point at equity and access to new medical devices and procedures. This obviously is a critical piece of deliberation with an emphasis on rural and disadvantaged or First Nation populations, including the barriers and restrictions to access health services.

Pharmaceutical Benefits Advisory Committee (PBAC) guidelines, unmet need is mentioned as an eligibility criterion for the early resubmission pathway for High-Added Therapeutic Value (HATV) medicines. However, the recent review of the HTA policies and guidelines recommends that criteria of importance to patients and clinicians (e.g. for high added therapeutic value (HATV) that addresses high unmet clinical need (HUCN)) are appropriately included and considered. From personal experience, MSAC does also explicitly discuss „feasibility" of implementation to ensure equal access across the Medicare population in both public and private hospitals.

The German Social Codebook[10] does not explicitly mention unmet need in their appraisal process, nor is it used by AMNOG. However, in their 2023 position paper, the Verband forschender Arzneimittelhersteller (vfa) states that unmet needs to be defined as „Ein ungedeckter medizinischen Bedarf ist ein Zustand, der durch zugelassene Medikamente und Methoden nicht angemessen verhindert, behandelt oder diagnostiziert wird". This aligns with earlier definitions of unmet need emphasising the unavailability of appropriate treatment options. Further, concerns have been raised in Germany that unmet needs should align with incentivising new developments. However, there remains uncertainty around what the right incentives are to ensure medical products are developed for those with unmet need.

The National Institute for Health and Care Excellence (NICE[9]) in the United Kingdom, in their guidance, is probably the only institute who make explicit mention of „unmet need" by stating that „the extent of unmet need is reflected within the severity definition". Unmet need or severity of the disease in this definition is considered a decision modifier (article 6.2.12), with severity of the disease determined by future health lost by people living with the disease with standard care in the NHS. This includes the availability of other treatments, diagnostics, and best supportive care.

From these four examples, it can be concluded that if a reference to „unmet need" is made, it is predominantly interpreted as either the lack of availability of treatment options and/or significant residual disease for which additional treatments should become available. If „unmet need" is not explicitly covered in the guidance documents for submission of value dossiers, agencies will likely consider and include this additional criterion in the appraisal phase.

A broader definition of unmet need to include appropriate and efficient care?

From the quick scan of European and selected National guidelines and policy documents, we find unmet need to be relatively narrowly defined as „availability of treatment" with some implicit conditional relation to disease severity. But a more detailed review of the literature should be undertaken, particularly to understand how and when

unmet need is placed in the broader context of social welfare and health. A very comprehensive and detailed description of the different perspectives of unmet needs can be found in the NEED Framework (Maertens de Noordhout et al, 2024). From their work it is concluded that there currently is no consensus on the definition of unmet needs. They state that „Needs can be defined as the essential elements that are necessary for human survival, well-being, and development. They are the basic conditions that individuals must fulfil to sustain their physical, psychological, and social welfare".

If we were to take this approach, it is inevitable to refer to the different theories of need that exist, including the theory of Human Need by Gough and Doyal (1984) and the social need taxonomy by Bradshaw (1972). Gough and Doyal argue that human needs can be categorised into eleven core categories, with healthcare (i.e. the need for access to quality healthcare services to promote and maintain good health) one of them. Bradshaw introduces the concept of social need and four definitions of need, including normative, felt, expressed and comparative need (Bradshaw, 1972).

A helpful approach presented by Stevens and Gillam (1998) provides a broader and comprehensive definition of unmet need by stating that „unmet need is the capacity to benefit from healthcare". This implies that the different phases from market approval and authorisation until the actual delivery of care are necessary to be included in determining unmet need. According to Stevens and Gillam, unmet needs may also be considered assuming some finite resources, thereby explicitly linking unmet need to scarcity and resource allocation. They suggest that the definition of unmet need requires a measure of epidemiology (how many) and a measure of effectiveness (how good) and distinguish four types of unmet need:

- Non-recipients of beneficial healthcare interventions, implying that patients have no access to care which is referred to as unmet need in its original form.
- Recipients of ineffective health care, implying resources are available to deliver care and that they should be released to do so.
- Recipients of inefficient health care, meaning that despite the treatment being effective, other, less expensive, options are available.
- Recipients of inappropriate health care, implying better treatment or care options are available.

This definition clearly takes a wider health services perspective rather than a focus on the regulatory pathway as (understandably) presented in most of the EU regulations. In other words, in many studies unmet need not only concerns medical product development and market access, but merely also the mechanism of delivering (and releasing resources for) the medical products to those who need it.

This becomes very clear when reviewing the quickly evolving evidence base employing real-world data to determine actual use, real-world outcomes and identification of underserved populations. But it is also recognised in current work on de-escalation of cancer treatments. For instance, systemic cancer treatments may be de-escalated, avoiding excessive treatment while still preserving or improving outcomes (Soon et al, 2024). This could include treatments where patients are exposed to therapies with no notable benefits or with an unfavourable benefit-risk outcome. Alternatively, this also concerns adjustments in treatment pathways, such as a shorter neoadjuvant course of check-point inhibitor immunotherapy (CPI) rather than a longer adjuvant course in resectable stage III melanoma. Obviously, all these approaches to de-escalating therapy are proposed under the assumption that clinical outcomes

are preserved and simultaneously lead to a substantial decrease in resourcing requirements, including staffing, consumables, infrastructure and carbon footprint.

Elements of unmet need when allocating resources in national health systems

Stevens and Gillam explicitly include a measure of epidemiology (e.g. prevalence or severity) and a measure of effectiveness (e.g. benefit such as survival) in their approach to unmet need. While this is plausible, it immediately raises the question of what counts most: the relative benefit or the severity of the condition. And subsequently, a further question is what other factors (should) count and who will be making these judgments. Several studies have been addressing these questions, in terms of methods to define trade-offs (like Discrete-Choice Experiments, Multi-Criteria Decision Analysis or Multidimensional Thresholding) and which stakeholders to select, particularly the general public, payer or patients (Thokala et al, 2016; Soekhai et al, 2019).

In 2012, Linley and Hughes published the results of a cross-sectional survey in more than 4,000 people in the general population asking which factors are considered relevant when deciding about public funding for new medical services. Amongst other factors, like severity or disadvantaged populations, they also include „unmet need", which they defined as „no alternative treatments" or „significant unmet need". The results suggest that there is public support to include factors like severity of disease, treatments addressing an unmet need, innovative treatments or those with wider societal benefits in the resource allocation decisions by the National Health Service (NHS). However, there appeared no support for an end-of-life premium or for the prioritisation of children or disadvantaged populations like orphan diseases. In 2018, Bourke et al, confirmed this finding and concluded that the general public does not value rarity as a sufficient reason to justify special consideration for additional NHS funding of orphan drugs.

Since then, several studies have investigated which criteria should be included in reimbursement decisions, mostly at the level of individual MS. It is beyond the scope of this paper to go into further detail, but additional criteria considered are purpose of treatment (e.g. curative), equity, implications for workforce capacity, the carbon footprint and ambiguous factors like the value of hope or value of knowing. While the latter seem to address an element of value, it is controversial and questionable whether public resources should be allocated to pay for value without actually changing health outcomes. Similar, the carbon footprint and/or implications for our healthcare workforce (e.g. remote vs. hospitalised care) are critical for the efficiency and sustainability of our health service but it is not clear if and how these criteria should be incorporated in public funding decisions for new medical products.

Ambiguity and uncertainty: are we incentivising the right developments?

In this paper, we have elaborated on the definition of unmet need from the perspective of the EU regulators being focussed on the unavailability of medical products for patients with severe (residual) disease. Also, MS use a similar definition of unmet need in their national pharmacoeconomic guidelines and deliberative processes to inform reimbursement decisions.

The challenge though, arises when value judgments are to be made (e.g. benefits versus severity of the disease in one versus another population) or when taking a wider health services perspective in which unmet need is assessed in the context of either the delivery of care to patients or when making resource allocation decisions under

uncertainty. When making such trade-offs, our experiences demonstrate that neither the general population nor patients nor a group of experts find the definition of „unmet need" to be comprehendible as it aggregates several constructs into one.

This implies that „unmet need" as a criterion can be ranked low in prioritisation studies, simply because there is no clear normative framework. A further consequence is that while emphasising unmet need in EU regulations, industry is unexpectedly exposed to additional market uncertainty. Prioritising R&D investments for medical products that address (high) unmet needs does not at all ensure access nor inclusion in benefits packages in MS. Paradoxically, while „availability" of a treatment may unequivocally be determined at the EU level, this implementation is context specific in each individual MS.

The finding that several studies confirmed huge disparities between MSs regarding the availability of treatments, this is likely explained by features of the health system rather than those products not on the market. This uncertainty it creates should be recognised and anticipated on. Prioritising medical product development on the presumption of availability of (alternative) treatments alone may be a risky strategy when lack of availability is caused by inappropriate market incentives (e.g. small populations and hence market size in individual MS).

Rather, incentivising developments for populations with high unmet needs should first and foremost be based on strong evidence of improved clinical outcomes for those with diseased and confronted with healthy life years lost. Whether treatments will become available and hence, serve an unmet need, is a responsibility of MS. Fortunately, Research and Innovation, rather than healthcare per se, is funded, coordinated and regulated at the EU and thus provides opportunities to close the disparity gap.

Footnotes

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EU HTA, Pharmaceutical Strategy, AMNOG: Drivers of a mutual learning process

Florian Staeck

In the coming years, Germany's medicines and pharmaceutical policy agenda will be shaped even more strongly than before by the EU's current pharmaceutical agenda. At the same time, with the benefit assessment procedure at EU level (EU HTA), which began in January 2025, a mutual learning process has started. These developments in Germany are taking place against the background of increasing financial challenges for statutory health insurance (GKV).

With pharmaceutical expenditure in the GKV rising by almost ten per cent in 2024, calls for cost containment are growing louder – and at the same time the pressure to adapt AMNOG is also increasing. The new federal government has pledged to make Germany a more attractive location for clinical studies and thus intends to continue the political process launched through the Medical Research Act.

Against this interplay of impulses and framework conditions, the participants of the Platform on Benefit Assessment met in Berlin on 21/22 March 2025 under the heading: „EU- Pharmaceutical agenda: Impulses for the pharmaceutical supply in Germany". The discussions focused in particular on the following aspects:

Patient involvement in the context of the EU Pharmaceutical Strategy: The upgrading of patient involvement in European medicines authorisation under the EU's pharmaceutical agenda was discussed with mixed views at the meeting. For example, the degree of involvement of patient representatives has not yet been agreed: whereas initially there was talk of „voting rights", it was later stated only that patient votes should be „taken into account". The methodological concept behind this – whether it is intended as knowledge input from patients or as a form of citizen participation – was said still not to be clearly recognisable.

This heterogeneous structure is also reflected in the legal situation in the member states: in France, the voting right of patient representatives is already established practice. However, they receive practically no support from a „Patient involvement team". In Germany, by contrast, only a right of co-advisory participation has been established, while professional support for patient representatives is provided as a matter of course, it was argued. In the latter case, it would have to be taken into account that, with a co-advisory right, the pressure to reach consensus in decisions is usually high for patient representatives.

Different motivations for patient involvement would also have to be taken into account at EU level: in Germany, access to a new pharmaceutical is guaranteed by authorisation. By contrast, in many member states patient representatives might only hope through their engagement to gain access to new therapies. Furthermore, the indication-specific involvement of patients in EU HTA procedures creates the challenge that patient representatives would have to network across indications, it was said. This would be an undertaking that would not get off the ground by itself or without external expertise.

State of play of EU HTA: After a long preparation period, the European benefit assessment has now reached practical implementation: the first Joint Clinical Assessment (JCA) started in March 2025, followed in May by the first Joint Scientific Consultations (JSC). Extensive templates, guidances and workflows had been presented or set up in advance.

The current work plan envisages ten JSC – with hopes that this number could be increased significantly in the coming years. It had been possible in advance to recruit a sufficient number of qualified assessors and co-assessors, it was said. However, the ten JSC at EU level currently stand

against around 300 consultations per year by the Federal Joint Committee within the framework of AMNOG.

Key points in the national procedure, such as the completeness of the required data or the special status of orphan drugs, remain unchanged. Problems could, however, arise in the interaction between EU HTA and AMNOG if the JCA report were to be delayed, since suspension of the procedure is not envisaged. EU HTA was described as a „mutual learning process" in which attempts are being made to ensure maximum certainty for the parallel processes at EU and national level. National consultations of manufacturers by the G-BA on study planning and before dossier submission will also remain possible.

The discussion showed where processes are still running unevenly: if in more than half of cases the JCA cannot serve as the basis for the national benefit assessment, duplication of work arises which ought to be avoided, it was argued. Other participants warned that the unequal treatment of pharmaceutical manufacturers in view of limited advisory capacities at EU HTA should be viewed very critically.

It is not yet foreseeable whether, and to what extent, methodological differences between AMNOG and EU HTA will actually materialise in the procedures. For example, at EU level there is talk of „patient-centred outcomes", whereas in the AMNOG procedure the term is patient-relevant endpoints It was unclear, for instance, how in EU HTA, in oncological indications, the coexistence of the endpoints „overall survival" (OS) and „progression-free survival" (PFS) would be addressed. The principle here was said to be that the evaluation of a surrogate ultimately takes place at member state level, so that one would reserve the right to „question the decisions of other countries".

At present, one conclusion was that it is still unclear to what extent Germany will adapt the principles of assessment to the European framework, or whether the potential of a joint European assessment will instead be hampered by fragmentation – for example in the evaluation of endpoints.

Reform debate around AMNOG: The discussion on the need for reform of AMNOG focused in particular on how to handle gene therapies and ATMPs. Here, the principle of determining an additional-benefit-based price on the basis of a comparative therapy often reaches its limit.

There was therefore a vote for a „more flexible" AMNOG that would take the care perspective more into account and, for example, ask to what extent a previously unmet medical need is addressed by a new pharmaceutical. From the industry side, AMNOG was described as a „relevant locational factor", hence planning certainty with regard to the appropriate comparative therapy was said to be of great importance for companies. „Guardrails" and the combination discount introduced through the GKV Financial Stabilisation Act have further increased the complexity of AMNOG and contradict the principle of additional-benefit-based pricing, it was argued – a thesis that was not left unchallenged in the discussion.

The prospects for pay-for-performance (P4P) contracts were viewed sceptically. In principle, these could be an instrument to respond to uncertainty of outcomes (for example regarding long-term effects) with outcome-based reimbursement models. Especially in gene therapies, experience of how long an initial therapeutic success lasts could in principle be a starting point for fair P4P contracts.

However, such contracts were said to be very complex, very resource-intensive in monitoring, and still very much the exception in collective agreements. In addition, dissent between manufacturers and health insurance funds about the assessment of success or failure of a therapy often

leads to the breakdown of risk-sharing contracts. Moreover, problems were highlighted in using results from accompanying data collection in the context of such contracts. This could lead to a decoupling from the results of benefit assessments – and this was described as a development that was not welcomed. Overall, the potential for P4P agreements was therefore considered limited.

Impact on national medicines supply through EU pharmaceutical legislation: One important element of EU pharmaceutical legislation discussed was the impact on data protection and market exclusivity. The current protection extends to a maximum of eleven years. This period would have been extended to 12 years by proposals from the EU Commission. A compromise proposal from the European Parliament sets the maximum period before the start of generic competition at 11.5 years. It was highlighted that an additional year of data protection entails an extra cost of one billion Euros per year for the GKV.

Participants called for a re-examination of the core definition of rare diseases. There was said to be a need for a „more targeted" definition. In the past, the special rules for orphan drugs had been justified particularly by the diagnosis of a „market failure" – among other things as a result of insufficient research incentives. This claim could no longer be maintained in the light of recent market developments, it was argued. Instead, it was advocated that OD designation should focus only on cases of very rare diseases and therapeutic breakthroughs, and not on rare subgroups in known indications.

From different perspectives, participants discussed the measures proposed under the Critical Medicines Act (CMA) to prevent supply shortages. One view was that market-based instruments are needed to link supply responsibility and remuneration. Price increases alone would not suffice to achieve diversification of suppliers of active substances and excipients.

There is already a supply obligation in Section 52b of the Medicines Act, but this is not enforced. A regulation such as that proposed by the EU Commission, which provides for no sanctions in the case of failure to supply, creates incentives for cost-cutting that ultimately increase the vulnerability of supply chains.

One counter-argument was that stockpiling by manufacturers could sensibly be linked to purchase guarantees. It was also pointed out that stockpiling is associated with high costs, where a scaling factor would have to be taken into account for the duration of storage. Regardless of these different assessments, it was emphasised that digital recording systems could usefully support efficient stockpiling of medicines.

Trends in authorisation in the EU and USA: In the USA, new substances are authorised significantly faster than in Europe. In 2023, the median authorisation time at the FDA was 333 days, compared with 453 days at the EMA. One reason for this is the so-called clock-stop periods – the period during which the evaluation of a pharmaceutical is officially suspended while the applicant prepares answers to questions from the regulatory authority The FDA is a tightly managed authority, whereas the EMA was described as more of a large secretariat that coordinates the authorisation processes. The difference is also evident in the fact that the scientific assessment and authorisation of a new active substance are both carried out by the FDA. In Europe, however, the act of authorisation lies with the European Commission, which generally relies on the expertise of the EMA.

In addition to these different starting conditions, divergent developments can also be observed in Europe. For

example, in the Committee for Medicinal Products for Human Use (CHMP), fewer decisions than in the past are now taken by consensus. It is also becoming increasingly difficult to find the most suitable experts for individual assessments – the EMA draws from a pool of around 5,000 external specialists. Some slots repeatedly remain unfilled – it was reported that the absence of the United Kingdom from the EMA network is noticeable here. As a result, experts have to be recruited who are not regarded as opinion leaders. This problem is further exacerbated by the restrictive interpretation of the conflict-of-interest rules. Planning, and thus the provision of assessors, is also made more difficult by the fact that recently only about half of authorisation procedures could be started without delay.

Germany has also responded to the fact that recently only around one to three per cent of patients from Germany could be included in multicentric studies, through the Medical Research Act (MPG) passed last year. The MPG is a sensible step in this respect and enables the processing time for clinical trials to be shortened. Synergies also result from even closer cooperation between the teams at BfArM and PEI. Moreover, BfArM now serves as the starting point („single entry point“) for all procedures, the progress of which can also be tracked via a dashboard. In July 2025, the new Specialised Ethics Committee at BfArM will begin its work, particularly handling applications for complex (basket) trials – for this purpose almost 100 experts from various indication areas have been recruited.

A possible „game changer“ could be the Research Data Centre, which will start in summer 2025, it was emphasised. This could also apply to the question of the evaluation of endpoints in studies since digital apps are a valuable data source. Germany, it was said with reference to the prescription of around one million digital health applications (DiGA) last year, is in a good position internationally.

It was critically noted in the discussion that Germany is poorly prepared for new developments in authorisation when it comes to assessing additional benefit. This applies, for example, in the case of conditional authorisation – such authorisation cannot be revoked. Authorisation and HTA should move closer together at this point, it was demanded.

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