



Publication series

INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

Volume 11
September 2020

European HTA Procedure: Advances and Pitfalls

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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,

- identifying possible undesirable developments, in particular with regard to supplying patients with new active substances,
- Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure, e. g. on the further development of the legal framework conditions of AMNOG.

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

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

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

„I am a firm believer in Europe – not just as our heritage, but as providing hope and vision for the future“

By Professor Dr Jörg Ruof

Dear readers, the title of this editorial is a quote from the speech by Federal Chancellor Angela Merkel to the European Parliament in Brussels on 8 July 2020 on the German Presidency of the Council of the EU. Health is a central theme of this speech which is, however, less dominated by the discussion about a consolidation of the fragmented European benefit assessment, but rather by the topic that overshadows everything else, i.e. the Corona pandemic.

Especially the pandemics and the often chaotic handling of this global health challenge demonstrate the significance of a pragmatic yet empathic approach to political leadership. While the USA terminate all kinds of international cooperation in the field of healthcare and leave the World Health Organisation (WHO) in light of the pandemics, Angela Merkel stands up for fundamental rights and cohesion.

The necessity for cohesion also applies to „European HTA Procedure – Advances and Pitfalls“, i.e. the topic of this publication. Thus, this publication is based on the „Vision of a convergent term for a benefit within the EU“.

- The first two articles illustrate the current parliamentary procedure. Due to his medical background and as spokesman of the EPP Group in the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament, Peter Liese is deeply familiar with the matter. Despite the regrettable delay, the concerns he expressed can be overcome and the parliamentary procedure will take its course.

Ministerial Counsellor Ortwin Schulte heads the Health Unit at the Permanent Representation of Germany to the European Union in Brussels. In his article, he provides a profound overview of the milestones and difficulties in the progress of negotiations in the trilogue between the EU

Commission, the European Council, and the European Parliament.

- The role model function of the regulations of the European Medicines Agency (EMA) for the proposal of a EU-HTA regulation is outlined in the article of Ortwin Schulte and subsequently presented from the BfArM's perspective by Sabine Mayrhofer and Harald Enzmann. Since 2018, Harald Enzmann has been Chair of the Committee for Proprietary Medicinal products for Human Use (CHMP) and thus been actively involved in the European approval process. Despite the differences between the consistent European assessment of benefit and risk and current national assessment of the (additional) benefit, However, it was necessary to approach or at least eliminate ambiguity of evidence requirements through intensive exchange with the various decision makers evidence.
- The Chief Operating Officers of the European Network for Health Technology Assessment, Marcus Guardian, provides and overview of the workflow and working fields of the EUnetHTA. At present, 83 HTA organisations from more than 30 countries cooperate within the scope of EUnetHTA.
- Edith Frénoy is responsible for the division Market Access at the European Federation of Pharmaceutical Industries and Associations and presents specific suggestions for improvement from the industry's perspective – like the common definition of requirements; participation rights of the industry; binding force of the reports, definition of a clear legal framework, and assurance of compatibility with the German AMNOG system.

The two subsequent articles reflect the perspective of major German stakeholders:

- In his „interjection“, Thomas Kaiser from the IQWiG refers to the need for completeness and transparency in the European benefit assessment procedure. Moreover, the

specific treatment situation of the member states and healthcare systems must be considered in the determination of the appropriate comparative treatment.

- From the G-BA's perspective, the Head of the Department Pharmaceuticals, Dr Antje Behring, reflects on developments related to the draft regulation. The long-term success of EUnetHTA will be determined by whether and to what extent the expected advantages can be achieved for the involved stakeholders.
- Finally, Stefan Huster reports about the arbitration board's work and points out that a potential Europeanisation of HTA might provide a solution for the German governance problem [National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) decides about the additional benefit and then negotiates the price], but does not seem to be helpful to address other fundamental problems of the AMNOG procedure (such as the determination of the appropriate comparative treatment or linking of pricing to the G-BA decision).

Especially in view of increasing autocratic tendencies in many countries, an open and controversial exchange remains a privilege that needs to be fostered and protected. The present publication provides an overview about the often conflicting perspectives on the Commission's draft regulation. Thus, the previously mentioned cohesion is the result of the common concern of all stakeholders to optimise and secure patient treatment over the long-term. With this in mind, I would like to thank all speakers and participants of the partly virtual event as well as the sponsors, because without their support the exchange would not be possible.

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European benefit assessment – from a European policy point of view

Dr Peter Liese | Member of the European Parliament

The establishment of a European HTA assessment is a lengthy process requiring complex coordination in particular with the large member states. The resulting delays are regrettable as the potential of an improved cooperation between regulatory authorities and HTA bodies are not yet sufficiently utilised. Parliamentary consultation so far has shown that all concerns can be overcome. This may also be taken account of through the stepwise introduction of a European benefit assessment which is currently being considered.

The procedure around the introduction of a European HTA assessment is one of the key and major procedures of European health policy. This process is very lengthy and characterised by an intense need for coordination. However, considerable progress was achieved in the past years. Thus, the European Parliament already addressed many of the concerns that the large member states brought forward regarding the subsidiarity objection in early 2019. Moreover, regular consultations are held in the working groups of the Council of Ministers.

The delayed or missing legislation, respectively, is regrettable and occasionally leads to problems:

- Thus, human and institutional resources are not used optimally. Highly-qualified scientists and the competent national institutions, e.g. IQWiG or G-BA, do the same work in different countries several times. Often, similar processes are repeated which leads to inefficiencies.
- This also results in multiple burdens for the companies. Documents must be submitted in every country, although the scientific assessment of e.g. a three months' survival benefit shouldn't be different in France as it is in Germany or The Netherlands.
- Moreover, potential areas for improvement regarding a better coordination of approval and HTA procedures across Europe. With a better interconnection between these two procedures, both efficiency and control of innovations could be optimised. Thus, companies could for example be informed at a very early stage which molecules represent feasible innovations or constitute a relevant added value and which are rather pseudo innovations.

The concerns regarding a standardised European HTA procedure are well-known and were already discussed in detail in the parliamentary procedure. Although they should

be taken seriously, they can be overcome. Considering e.g. the intensively discussed issue regarding the appropriate comparative treatment, there may be different standard treatments for an indication in Romania, Germany, or Portugal. This must be taken into consideration at European level and rather supports the case for an inclusive selection of the appropriate comparative treatment, i.e. with different possible comparators. In general, double or repeated European assessments by national HTA bodies could be prevented with such an approach. However, there may be exceptional circumstances. In these cases, an additional scientific analysis at national level could be feasible and necessary.

So far, a staged approach to the introduction of a Euro-

pean benefit assessment is becoming increasingly apparent. European HTA procedures could for instance initially focus on pharmaceuticals in the indication haemato-oncology. Due to the usually life threatening course of a disease, they should be addressed as a matter of urgency and delayed market entries that are often associated with national HTA procedures are deemed to be particularly problematic from the patient's perspective.

It is expected that a common position of the member states will be developed in the coming months that will be coordinated in trilogue with the Commission and Parliament and implemented in the legislative process by the end of 2020. Future approaches should be more binding than the previous Joint Action 3. It is not intended to put European HTA assessments under the umbrella of the European Medicines Agency EMA. In contrast, a close connection to the European Commission becomes apparent with a strong influence of the member states. Using the member states' high level of human and institutional expertise will be of great importance here.



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The interplay between registration and HTA procedure

Dr Sabine Mayrhofer, Dr Harald Enzmann | Federal Institute for Drugs and Medical Devices (BfArM), Bonn

During the approval of innovative pharmaceuticals in the European Union, the approval authority is one part of a decision chain, from the development decision taken by a company until the individual treatment decision by the respective physician. Differences between the uniform European benefit risk assessment for the approval and the (additional) benefit assessment of the different national Health Technology Assessment (HTA) bodies are unavoidable. An exchange between the different decision makers, including industry and patients, has shown to be helpful to approach the requirements of benefit assessment and approval or at least ensure a consistent process.

Registration is only one step in the introduction of innovative pharmaceuticals. The requirements regarding development, approval and marketing of innovative new pharmaceuticals have changed in recent years and will continue to change in future.¹ In particular, price and reimbursement decisions have proven to be an additional hurdle for a successful development.² Market authorisation is no longer considered to be the last and crucial objective in the development of a pharmaceutical. It does not necessarily make a medicine available for patients (as was the case for a long time in many parts of Europe) and is no longer a guarantee for economic success.

Other decision makers with different objectives, mandates and decision criteria build upon the benefit risk decisions and scientific justifications of the approval authorities. Market approval is only one of several steps on the way of a pharmaceutical to routine application in clinical practise.

From the patients' or the public's point of view it is rather irrelevant, which decision maker is ultimately responsible if access to an innovative pharmaceutical is impeded. Apparent or actual contradictions in the scientific justification of the different decision makers are difficult to explain and may lead to the whole system being questioned and considered inconsistent and not very helpful to meet the needs of patients.

A decision, e.g. taken by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) about the benefit risk ratio of an innovative pharmaceutical and its detailed scientific justification will be compared by patients, physicians and the interested public with other scientific assessments of this pharmaceutical performed by other institutions. We should not expect appreciation, if the alleged objective scientific evaluation by two scientific bodies arrives at completely diffe-

rent results, thus jeopardising the availability of the pharmaceutical for patients.

Supposed or actual contradictions in the scientific assessment of a new pharmaceutical by the different decision makers can occur at different levels: already within the system of European approval of pharmaceuticals by the EMA, the scientific committees might arrive at different results that appear to be or are in fact contradictory. The assessment by the CHMP, for example, might arrive at the conclusion that a „significant clinical benefit“ in the sense of Regulation (EC) 726/2004 was proven, while the Committee for Orphan Medicinal Products (COMP) – upon assessment of identical data – comes to the conclusion that there is no „significant benefit“ in the sense of Regulation (EC) 141/2000.

On a global scale, different assessment results of a phar-

maceutical obtained by different approval authorities may also be a potential source of insecurity among patients. Even if both EMA and Food and Drug Administration (FDA) come to comparable or even identical results in their assessment of the benefit risk ratio in the vast majority of the procedures³, these rare cases in which ultimately different approval decisions are taken why the benefit risk ratio should be positive on this side of the Atlantic while it is negative on the other side remain difficult to explain.

In contrast, different decision criteria and deviating decisions that might arise for the European approval of pharmaceuticals on one hand and questions of national pricing and reimbursement on the other hand are still rather explainable. Different assessments of the benefit risk ratio by the EMA's CHMP and the (additional) benefit of a pharmaceutical by HTA bodies can be presented clearly and un-



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Dr Sabine Mayrhofer works as a scientific associate at the Department EU and International Affairs of the BfArM. Since 2003, she has been engaged in the BfArM's cooperation with various national approval authorities in the European network of the EMA and the centralised European approval processes under the responsibility of the BfArM discussed by the Committee for Medicinal Products for Human Use (CHMP) of the EMA.

derstandably; thus, common approaches can be developed to capture both without duplicating work.⁴

With the awareness of this interdependence, approval authorities have increasingly developed their perception of being only one of several decision makers in a complex process that begins at the research stage and ends with a treatment decision taken by an individual physician for an individual patient.

This is accompanied by the awareness that pharmaceutical development will be impaired and patients' access to innovative pharmaceuticals delayed, if the decision criteria various decision makers apply for consecutive decisions differ widely and are partly conceived as mutually exclusive. Thus, a positive benefit risk ratio remains the basis for the marketing authorisation of pharmaceuticals, but it must be consistent as far as possible with preceding and subsequent decisions of others. Contradictory scientific assessments compromise the credibility of the whole system and can be avoided if all decision makers cooperate. Approval authorities are thus faced with new challenges in the scientific assessment of new pharmaceuticals and their communication with other decision makers and stakeholders.

2. The interaction of regulators with various decision makers

In the interests of patients and for the sake of the credibility of the whole system, European approval authorities seek the exchange with upstream and downstream decision makers (see figure 1). While the common goal is the best possible and successful treatment of patients, the criteria that are relevant for the decision depend on the objectives, the mandate, and the area responsibility of the respective decision maker.

Figure 2 provides an overview of these criteria within the

decision process for a pharmaceutical that shall be used for the treatment of patients in Germany.

It is the management of R&D-based pharmaceutical companies' responsibility to decide about the initiation or continuation of the usually global, clinical development. The key decision criterion will be the expected economic success of the respective pharmaceutical. The fact that the vast majority of clinical development projects fails in the end shows that this expectation is associated with a high level of uncertainty.⁵

The European Commission decides upon market authorisation for an innovative pharmaceutical based on the assessment of the benefit risk ratio by the EMA. A high level of transparency regarding which evidence is required to furnish proof for a positive benefit risk ratio contributes significantly to most pharmaceuticals that are submitted for approval being rated positively and subsequently approved. In Germany, the assessment of the additional benefit and decisions about price and reimbursability are taken on a national level and in other EU member states even on a regional level. The extent of the additional benefit is evaluated on the basis of predefined criteria. This might also comprise different assessments, e.g. by taking account of social values.⁶

It is important that the result of the benefit assessment and the justification are published. This transparency allows for a scientific discussion of the different HTA bodies about the respective methods and their further development making future decision predictable. In contrast, negotiations about and the reasons for the national decision about the reimbursable price are treated confidentially. The decision about the treatment of a patient with a certain pharmaceutical is taken on an individual basis and mainly depends on the expected treatment success for the respective patient, even though economic considerations

The interaction of regulators with various decision makers

Two way interaction of regulators with upstream decision makers

- Scientific advice for developers, pipeline information

Two way interaction of regulators with downstream decision makers

- Objective information for patients and physicians, patients' participation in assessmentg
- Transparent assessment for use by HTA, EMA/EUnetHTA joint work plan

Credibility of system depends on consistency in scientific assessment

- between regulators, e.g. EMA and FDA
- between HTA bodies (at least in the EU)
- between regulators and HTA bodies

most frequent differences: surrogate endpoints and subgroups

Source: Dr Enzmann, Dr Mayrhofer

Figure 1: For the sake of the credibility of the entire system, European approval authorities seek the exchange with upstream and downstream decision makers.

Decision makers in the approval of pharmaceuticals and their relevant criteria

| Decision | Clinical development | Market authorisation | Additional benefit | Pricing and reimbursement | Treatment decision |
|------------------------|------------------------------------|---------------------------|-------------------------|----------------------------|----------------------|
| Expansion | Global | European (EU) | National | National | Individual |
| Decision maker | Developer, pharmaceutical industry | EMA (European Commission) | HTA bodies, IQWiG, G-BA | Payers, GKV-Spitzenverband | Patients, physicians |
| Key decision criterion | Profit | Benefit-risk profile | Additional benefit | Cost efficiency | Treatment success |
| Strength of evidence | Expectation | Evidence | Evidence | Negotiation (non-public) | Expectation |

Source: Dr Enzmann, Dr Mayrhofer

Figure 2: Stakeholders at different levels take their decisions based on different criteria: From the global scale during the clinical development to the individual treatment decision taken by the physician.

can be incorporated into the decision.⁷

This expectation will usually not be based on the evidence for efficacy and safety of the pharmaceutical for that particular patient, but on the scientific assessment of approvability and additional benefit.

On European level and within the EU member states, convergence or at least compatibility of the different requirements are pursued by means of an intensified multilateral exchange between academic research institutes, pharmaceutical industry, approval authorities, HTA bodies, payers as well as physicians and patients to ultimately facilitate patients' access to innovative pharmaceuticals. Scientific consultations for the developers of pharmaceuticals, cooperation with HTA institutions and payers as well as exchange with patients are of particular importance for approval authorities.

2.1 Scientific advice

The decision about the start or continuation of the development of a pharmaceutical by the respective pharmaceutical company is usually supported by a scientific consultation provided by the approval authorities. This provides a useful instrument to avoid misunderstandings and helps to better align the development of the pharmaceutical to the requirements of the approval authorities as early as in the planning phase. The considerable influence of the scientific consultation on the prospects of the development is well documented. The chances of a market authorisation was shown to be significantly higher, if the contents of the scientific consultation by the EMA were taken into consideration during the development (see figure 3).⁸

As the marketing authorisation does not at all guarantee patients' access to a pharmaceutical, if the assessment of HTA bodies and decisions of payers exclude reimbursement, the possibility of a common or parallel scientific con-

sultation by approval authorities and HTA bodies was established^{9,10} with the objective to make the requirements transparent and predictable and consistent with those approval authorities and HTA bodies apply. This does not mean that they must be identical. Different questions and decision criteria will often lead to different requirements.

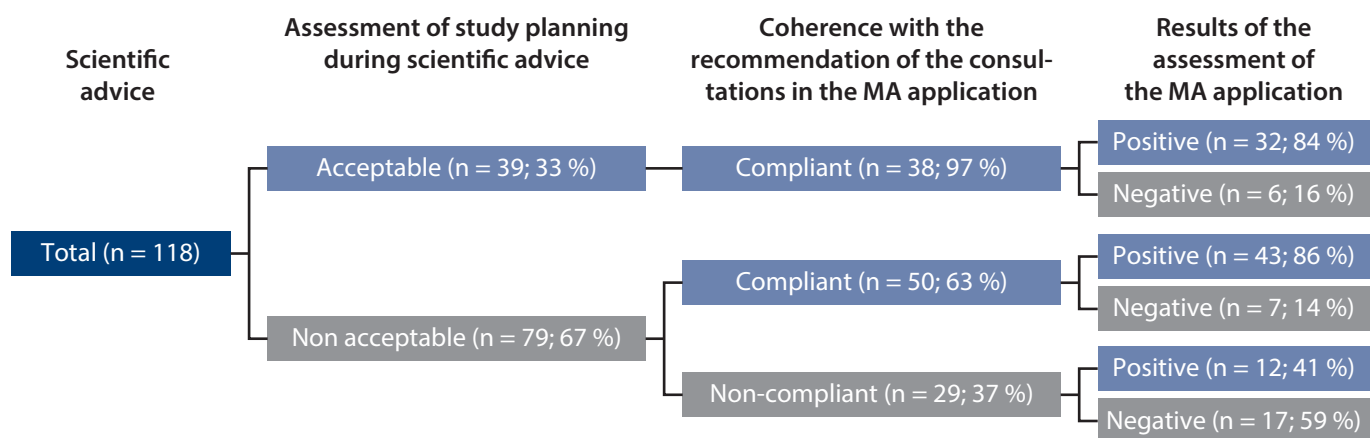
However, it may be attempted to enlarge the overlapping area as far as possible or incorporate the approval authority's requirements into the subsequent requirements of HTA bodies. This is often possible, if the data required by the approval authorities to furnish proof of a positive benefit risk ratio is less than the data expected by HTA bodies that shall also enable quantification of the benefit compared to other therapies.

2.2 Cooperation with HTA bodies

The well-established and continuous dialogue between approval authorities and HTA bodies – primarily between the EMA and the European Network for Health Technology Assessment (EUnetHTA) – helps to avoid double work, contradictions and subsequent delays. The common objective that has already been set out ten years ago is to integrate the assessment during the approval decision process into the subsequent assessment of the (additional) benefit thus making the best possible use of synergies and overlapping areas (see figure 4). HTA bodies communicate to approval authorities what is of special importance in the assessment reports of the approval from the HTA bodies' perspective so that the EMA can adjust the European Public Assessment Reports¹¹ accordingly.¹²

Conversely, the dialogue with the EUnetHTA gives the EMA the opportunity to explain the internal logic of the benefit risk assessment and provide support in the correct interpretation of the assessment reports (where necessary). It is essential to create the highest possible transparen-

Scientific advice increases the chance of a market authorisation



Source: Hofer MP et al: Impact of scientific advice from the European Medicines Agency. Nature Reviews Drug Discovery 2015; 14: 302–303

Figure 3: The considerable influence of the scientific consultation on the prospects of the development is well documented. Considering the contents of the scientific consultation by the EMA during the development increases the chances of a market authorisation.

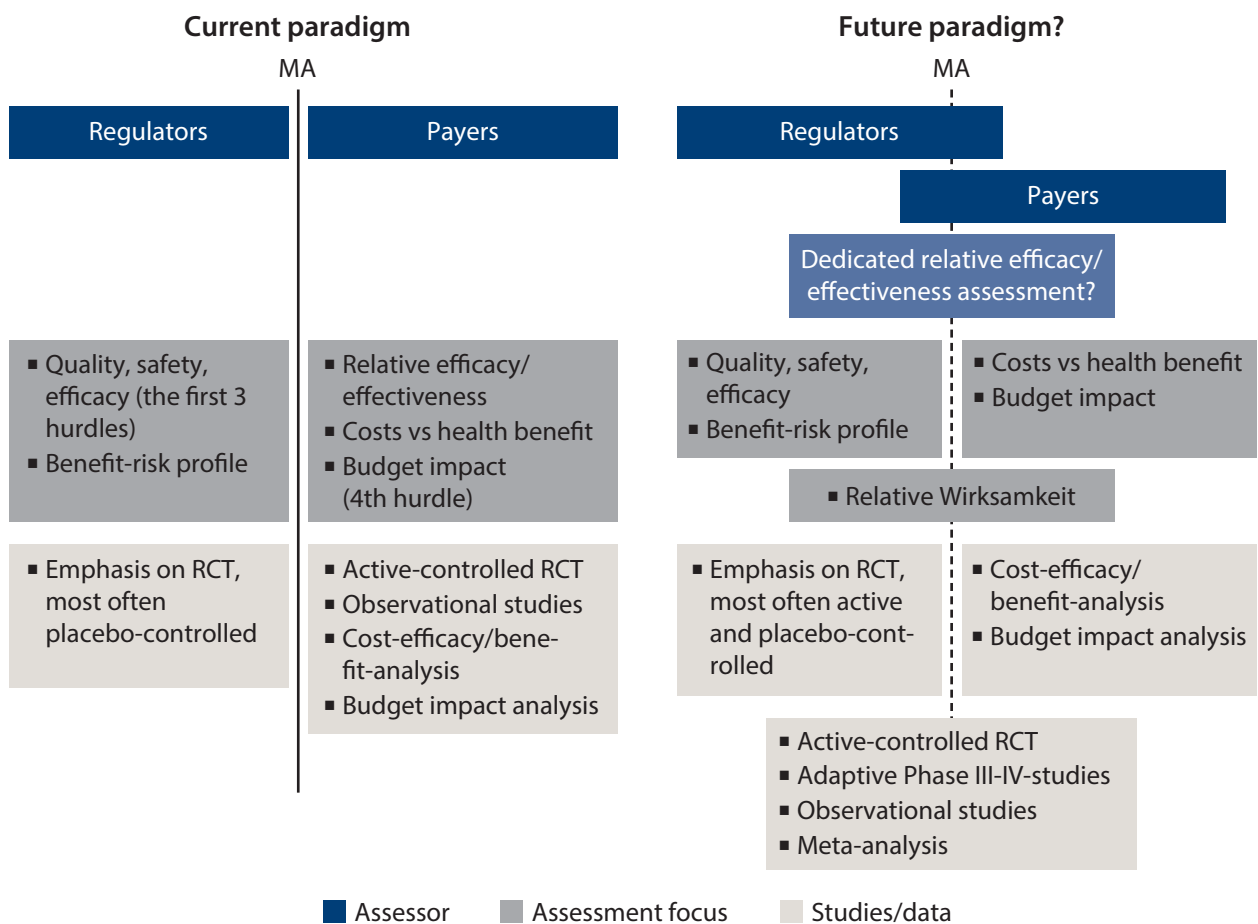
cy about this exchange towards other decision makers. For this purpose, the minutes of the common meetings are published.¹³

Besides an intensive exchange between EUnetHTA and EMA, there are numerous common activities between approval authorities and HTA bodies on national level. These parallel activities seem unavoidable as long as there are significant differences between assessments performed by national HTA bodies across the European Union. While national divergences, e.g. regarding an appropriate comparative treatment, will already be addressed in the approval process under the guidance of the EMA and combined to a joint European position, there is no necessity to determine a joint European position on the HTA bodies' side. With the establishment of the EMA, approval authorities were able

to find a way to a common European position despite the diversity of national pharmacological doctrines and different pharmaceutical and medical traditions in the member states. It is thus understandable that in case of different opinions as to which comparative treatment should be used as a control arm in the pivotal studies, the EMA's recommendations are followed more frequently than the heterogeneous positions of various HTA bodies.¹⁴

At present, neither the EUnetHTA nor smaller groups like FiNoSe¹⁵, a cooperation of HTA bodies of Fimea (Finland), NoMA (Norway), and TLV (Sweden) are able to take an equivalent role to EMA. Therefore, it would be beneficial to organise the different HTA bodies in one structure across Europe that is comparable with the European regulatory network under the leadership of the EMA.

Regulators and payers getting closer, but still different 10 years later



Source: Eichler, HG et al. Nat Rev Drug Disc, 2010, 277–291

Figure 4: The objective that has already been set out ten years ago is to incorporate the assessment within the scope of the approval decision into the corresponding assessment of the (additional) benefit.

Economic differences will probably be a hurdle for a uniform assessment of pricing and reimbursability in the foreseeable future. Nevertheless, such a European structure of the HTA bodies might promote convergence of benefit as-

essment and in the long-term perhaps even a uniform European assessment of the medical benefit and the medically reasonable application of a pharmaceutical.

2.3 Exchange with patients

The common goal of all decision makers involved in the development of new pharmaceuticals is the use of these pharmaceuticals by patients. Patients need to accept these pharmaceuticals and their perception and perspective must be taken into account. For pharmaceuticals that are approved in the European Union within the scope of a centralised procedure by the EMA, patient involvement has been established at various levels. In this process, patients – wherever possible patients with the corresponding disease – are involved in the scientific committees of the EMA.

However, via EMA's Scientific Advice Working Party patients are also involved in the scientific consultation, and via EMA's Scientific Advisory Groups in consultations of the clinical experts for the CHMP in consultations for the development of new pharmaceuticals, respectively. Since the EMA has launched a permanent working group for patient organisations (Patient & Consumer Working Party, PCWP)¹⁶ in 2006, a continuous cooperation with a broad range of patient organisations has been established.

Besides a regular exchange between the patient organisations and the EMA and its scientific committees in the PCWP, these organisations also ensure that affected patients with virtually any disease are involved into the decision making process. Moreover, patients have the opportunity to participate in the EMA's procedures, provided they register their interest with the EMA. In all cases, clearly defined and transparent criteria will be applied to maintain independence for patients and patient organisation, respectively, especially with regard to any financial influences from individual pharmaceutical companies.

3. Different assessments by HTA bodies and approval authorities

Approval authorities and HTA bodies might arrive at different assessments or decisions that appear to be contradictory. An early and repeated exchange between all stakeholders, the pharmaceutical industry, approval authorities, HTA bodies, payers, clinical experts are their professional associations and patients can help to avoid this wherever possible.

If this is not possible due to the different tasks and mandates of the decision makers, cooperation can help to make the reasons for these differences transparent thus encouraging acceptance of patients and the society. Different ways of thinking among HTA bodies and approval authorities are often reflected in the following topics:

3.1 Clinical inferiority versus non-inferiority

For a positive approval decision, non-inferiority against a generally accepted comparative treatment is sufficient. From the HTA bodies' and payers' perspective, the mere non-inferiority does not justify higher costs as compared to the established comparative treatment. However, the latter might be not be economically attractive for the developer of the new pharmaceutical. The resulting low price can even cause the marketing authorisation holder not to market an approved pharmaceutical.

To justify a higher price, HTA bodies and payers request solid proof of an additional benefit, preferably by means of direct comparison with the established standard therapy. These different requirements relating to the regulatory benefit risk assessment and HTA conclusions on price and reimbursability increase the complexity – and thus the corresponding effort – of the studies required for the development of a new pharmaceutical. If these different requirements are processed successively, several clinical studies

might be conducted thus increasing development costs and delaying patients' access to innovative products.

Studies that are designed to meet both approval authorities' and HTA bodies' expectations are in the interest of both patients and the pharmaceutical industry, as double work can be avoided and availability of a pharmaceutical can be accelerated through early price and reimbursement decisions. Since 2010, parallel scientific consultation by the EMA and HTA bodies has become an important driver for convergent requirements of European regulatory authorities and HTA bodies. At the same time, these joint or parallel consultations do not only reduce the different expectations of regulatory authorities and HTA bodies, but also promote the establishment of joint positions of the numerous European HTA bodies.

3.2 Disease-specific versus macro-social perspective

Approval authorities can quite easily approach the patients' perspective regarding the significance of benefits and risks or relevance of the endpoints in clinical studies. This is also driven by the fact that patients or patient representatives, respectively, are involved in regulatory considerations at various levels.¹⁸

Regulators can incorporate the patients' scale of values into their benefit-risk decisions, without the need to examine whether the weight patients suffering from this disease attribute to the specific benefits and risks of a certain pharmaceutical is equally important for patients with another disease. In contrast, payers must counterbalance the interests of various patient groups competing for limited resources. Therefore, clinical endpoints allowing a comparison between various diseases (e.g. mortality, hospitalisation, or ability to work) would be more useful for HTA bodies than endpoints in which patients' perception and their disease-specific preferences play a greater role.

3.3 Surrogate parameters versus „hard clinical“ endpoints

The above mentioned effort of HTA bodies to base their decisions on general endpoints, i.e. those that are applicable for virtually any disease that are directly perceptible for patients and can also be objectively measured, inevitably creates a conflict with the effort of approval authorities to promote an early availability of innovative pharmaceuticals. Inconsistent requirements of approval authorities and HTA bodies – but also promising approaches to overcome them become – particularly apparent on the example of adaptive licensing.¹⁹

It is one of the main features of adaptive licensing to introduce a pharmaceutical for a small group of patients in a first step as soon as possible for which it has shown the highest efficiency and safety. Only then the indication can be extended to further patients with the same disease and a less outstanding yet positive benefit risk ratio. Another principle of adaptive licensing is to enable an early approval on the basis of surrogate parameters and request subsequent confirmation by conventional „hard“ clinical endpoints, e.g. within the scope of a conditional marketing authorization.

Especially in case of pharmaceuticals that are expected to address a high unmet medical need, conditional marketing authorisation can be granted for a small subpopulation with the best benefit-risk profile based on surrogate endpoints with the obligation to subsequently furnish proof using conventional clinical endpoints. As soon as the positive benefit-risk profile has been confirmed by the clinical endpoints, the conditional marketing authorisation would be switched to full marketing authorisation. For the proof of the efficiency in another less ideal patient population, the same surrogate parameter can be used; especially as the positive benefit-risk profile that has been demon-

strated in the initial „ideal“ patient population for the conditional marketing authorisation was subsequently confirmed by means of conventional „hard“ clinical endpoints (also accepted by the HTA bodies) underlining the validity of the surrogate parameter. On the basis of this surrogate data, approval authorities can thus easily extend the indication to a larger patient population.

However, for an extension of an indication, there is no procedure that is similar to the „conditional“ approval, i.e. a later confirmation by means of hard clinical endpoints cannot be requested. This means that the results of the surrogate will most likely not be confirmed for the target population of the extended indication in a randomised study using conventional clinical endpoints. While this might be acceptable for the regulatory conclusion of a positive benefit ratio, it can create an unsatisfactory situation for HTA bodies.

For the assessment of a potential benefit of a certain pharmaceutical and the determination of an adequate price, HTA bodies prefer conventional „hard“ clinical endpoints; they often consider the surrogate parameters that were used as a basis for the initial approval inappropriate. The initial price for the pharmaceutical will therefore be determined on the basis of clinical endpoints rather than on surrogates, even if this leads to delays. Within the scope of an adaptive licensing, data on the conventional clinical endpoints is often only available from the confirmatory studies that made the switch from the conditional to full approval possible, i.e. only for the initially assessed subgroup with the highest efficiency and fewest adverse effects.

As a consequence, the extended indication will probably include patient populations in which the benefit-risk ratio will probably be positive, but less outstanding as it was in the initial „ideal“ subgroup. The patient populations for

which the pharmaceutical is indicated will be enlarged by the extension of the indication. At the same time, it seems plausible that the average benefit per patient will be lower in this new and broad indication will be lower as compared to the initial „ideal“ subgroup. If the price of the pharmaceutical shall reflect its benefit, the extension of the indication would require an adjustment of the price.

However, there is no data about conventional clinical endpoints from randomised controlled studies for the new broader indication and approval authorities do not need and thus not request them for the determination of a positive benefit-risk profile. Although different approaches have been developed to address this predetermined breaking point between assessment of the benefit-risk profile and the (additional) benefit, this discrepancy often remains.^{20,21} However, it seems remarkable that for pharmaceuticals that have received particularly intensive scientific consultation by the EMA within the scope of the Priority Medicines-Program (PRIME), more (also) clinical endpoints and less frequently exclusively surrogate parameters were recorded.²²

4. Final remarks

The assessment of the benefit risk ratio of an innovative pharmaceutical by approval authorities cannot be identical with the quantification of its benefit or additional benefit by HTA bodies that must take their price and reimbursement decision on this basis. The risk of unnecessary double work can be addressed with a holistic development strategy incorporating an early and repeated exchange between the various decisions makers, joint work on the interfaces, and the willingness of all stakeholders to incorporate the assessment of others into the own assessment and decision-making process.

At present, the consistent and binding European assess-

ment of the benefit and risk ratio by the EMA has no equivalent on the side of HTA bodies. It is not foreseeable that the voluntary cooperation of small groups of HTA bodies in informal groups will create a consistent European perspective.²³ A European harmonisation of medical assessment of new pharmaceuticals by HTA bodies that is comparable to the EMA could help avoid contradictions and strengthen the overall credibility of the system. Although the European Commission has developed such an approach, it remains to be seen whether and when it can at least partly be implemented.²⁴

At present, the economic aspect seems to be too heterogeneous, i.e. there are too many differences in the individual member states for a uniform European decision making. However, a future strong European HTA body would promote the development of a consistent European perspective with regard to the scientific assessment of the medical benefit of innovative pharmaceuticals. A development towards „more Europe“ in benefit assessment like it has been catalysed for approval by establishing EMA, would also facilitate the coordination of European approval decisions and subsequent assessments by HTA bodies.

This article is based on a presentation held during the spring meeting of the „Interdisciplinary Platform on Benefit Assessment“ on 13 March 2020. The views expressed in this article represent those of the author and do not reflect the position of the Federal Institute for Drugs and Medical Devices (BfArM) or European Medicines Agency (EMA), respectively.

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Benefit Assessments and Early Advice of EUnetHTA

Marcus C. Guardian | Chief Operating Officer; European Network for Health Technology Assessment

Since 2005, the European Network for Health Technology Assessment (EUnetHTA) has gradually evolved throughout Joint Actions (JAs), namely JA1, JA2, and JA3. Currently, 83 HTA bodies from > 30 countries are collaborating under the umbrella of EUnetHTA. The EUnetHTA core model provides a methodological framework for Relative Effectiveness Assessment (REA) with the four clinical domains being included in EUnetHTA assessments. EUnetHTA aims to continuously engage in horizon scanning, topic identification, selection, and prioritisation. Within EUnetHTA, both French and German HTA bodies, Haute Autorité de Santé (HAS), and Gemeinsamer Bundesausschuss (G-BA) respectively, lead the activities around Early Dialogues. EUnetHTA, together with the European Medicines Agency (EMA), has created a single gateway for all pharmaceutical Early Dialogues involving HTA bodies. Until September 2019, a total of 80 letters of intent were received, resulting in a total of 56 Early Dialogues.

Within JA3, a total of 14 REAs have been initiated, with final reports already being published for eight of those REAs. Since JA3, EUnetHTA's methodological framework and working processes have been vastly improved and standardised, national uptake of EUnetHTA assessments has increased, and the recommendations within Early Dialogues have impacted the respective development programmes. EUnetHTA is ready to take the next step towards an integrated European Clinical HTA Assessment.

The starting point of EUnetHTA was in 2005, when a call by the European Commission was answered by 35 HTA organisations across Europe. In 2010, the 'Joint Action 1' (JA1) was set in motion, aiming for an effective and sustainable HTA collaboration across Europe. The first collaborative pharmaceutical assessment of Pazopanib was conducted at the end of JA1.¹ Building on those early collaborative experiences, JA2 was launched in 2012. Further strengthening cross-border HTA collaboration and development of practical tools and approaches were part of JA2.

The third period within EUnetHTA's history (JA3) started in 2016 and will conclude in 2021. The 'definition and implementation of a sustainable model for HTA collaboration across Europe' is the aim of this third period of Joint Action and joint funding. Currently, 83 HTA bodies from > 30 countries are collaborating under the umbrella of EUnetHTA (Figure 1).

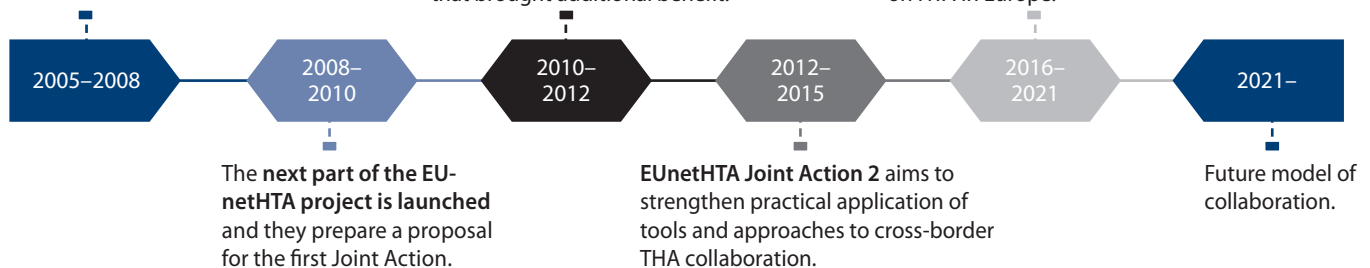
The EUnetHTA Core Model

In December 2012, EUnetHTA published its first methodological framework, version 1.0 of EUnetHTA's core model. The core model was further refined in the subsequent JA 2 and JA 3. The current version of the model consists of nine domains, further split into four clinical domains that are included in the 'Rapid REA' (Relative Effectiveness Analysis), and five non-clinical domains (i.e. costs & economic evaluation, ethical analysis, organisational aspects, patient and social aspects, and legal aspects) that remain within the national scope of each of the countries.

As EUnetHTA does not give recommendations on added value or reimbursement, its focus is restricted to the i) description of the health problem and the current use of technology, ii) description and technical characteristics of the intervention, iii) the comparative assessment of safety

The history of EUnetHTA

A commission call is answered by 35 organisations in Europe and the EUnetHTA project begins.



Source: EUnetHTA

Figure 1: In 2012, the first of three Joint Actions was launched building on previous collaborative experiences.



Marcus C. Guardian based on an educational background in international law (TU Dresden), business administration (Qingdao University), and diplomatic studies (University of Leicester) Marcus has forged a career in network development, strategic guidance, and policy management. In 2016, he accepted the challenge of steering EUnetHTA Joint Action 3 as its Chief Operating Officer (COO). In tandem with this, Marcus recently launched the International Horizon Scanning Initiative (IHSI) as General Manager, building a global stakeholder pool to adopt innovative data-driven tools that will significantly impact national healthcare product negotiation potential.

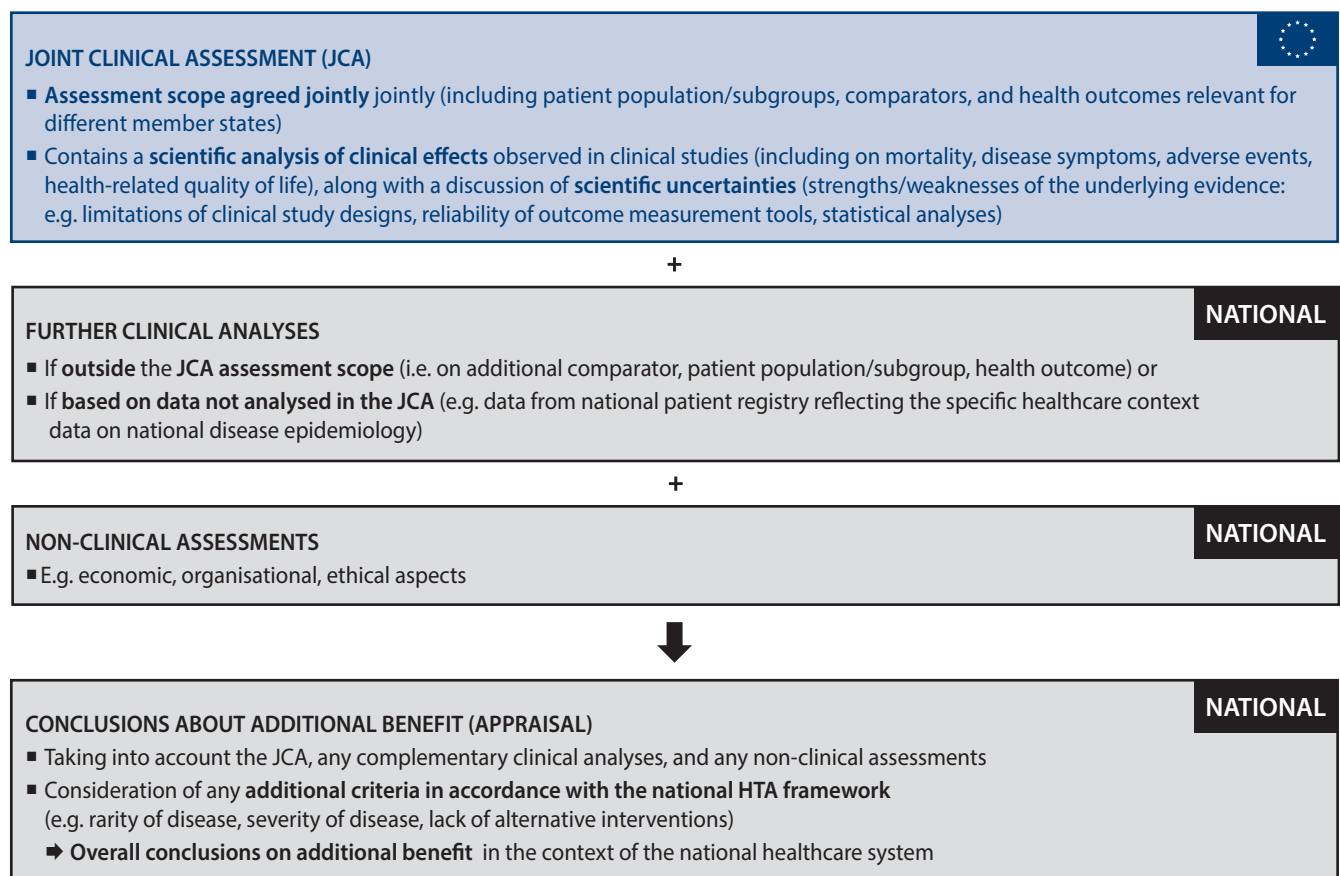
and iv) clinical effectiveness. The scope of the suggested European Joint Clinical Assessment and subsequent national responsibilities are displayed in figure 2. National activities may include complementary clinical analyses, assessments of the non-clinical components of the core model, and the final appraisal determining the 'added value' of the innovative medicine.

EUnetHTA's Product Lifecycle Elements

EUnetHTA aims to continuously engage in horizon scanning, topic identification, selection and prioritisation. A respective pilot project plan has been developed throughout EUnetHTA JA3 and was published in March 2019.³ Specific EUnetHTA activities spread throughout the lifecycle of a pharmaceutical product are:

- Early Dialogues with industry either in collaboration with the regulatory authorities ('Parallel Consultation') or a multi-HTA Early Dialogue may be conducted early on before a medicine has been introduced into the market.

Clinical assessments on European level and national responsibilities

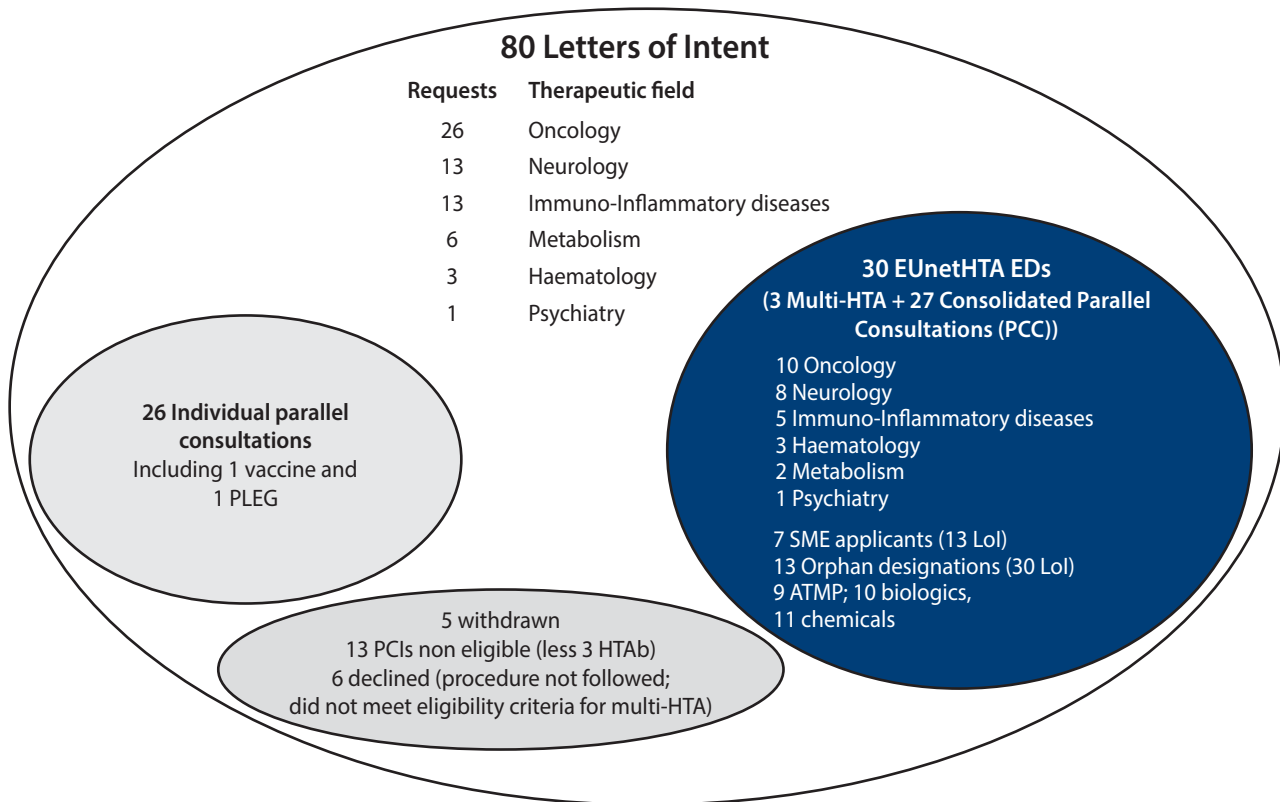


Source: EunetHTA

Figure 2: National activities building upon joint clinical assessments on European level can comprise additional clinical as well as non-clinical assessments.

- Joint Assessments covering both the determination of the scope of the assessment (Population/ Intervention/ Comparator/ Outcome) and the final assessments may be conducted in parallel with the regulatory process, and published shortly after the publication of the European Public Assessment Report (EPAR).
- Finally, additional data collection and Post-Licensing Evidence Generation (PLEG) may be discussed between the manufacturer and EunetHTA to determine data gaps and suggest pathways to address those gaps.

Early consultation from July 2017 through September 2019



Source: EunetHTA

Figure 3: On the basis of 80 Letters of Intent (LoI) Early Dialogues were initiated in 56 cases. As a consequence, changes were then implemented in the early development plan in 69 percent.

EUnetHTA Early Dialogues

The French and German HTA bodies, Haute Autorité de Santé (HAS), and Gemeinsamer Bundesausschuss (GBA) respectively, act as the gateway for all pharmaceutical early dialogues involving HTA bodies. The Early Dialogue Working Party (EDWP) prioritises respective requests and coordinates the interaction with the relevant volunteering national HTA bodies.

Between July 2017 and September 2019, a total of 80 Letters of Intent (LoI) were received with haematology/oncology, neurologic conditions, and immune-inflammatory conditions covering most of the submissions. Some of those LoIs were withdrawn, were ineligible, or declined, resulting in a total of 56 Early Dialogues. About half of the Early Dialogues were considered high priority (multi-HTA or consolidated parallel consultations, PCC (n =30)) vs. low priori-

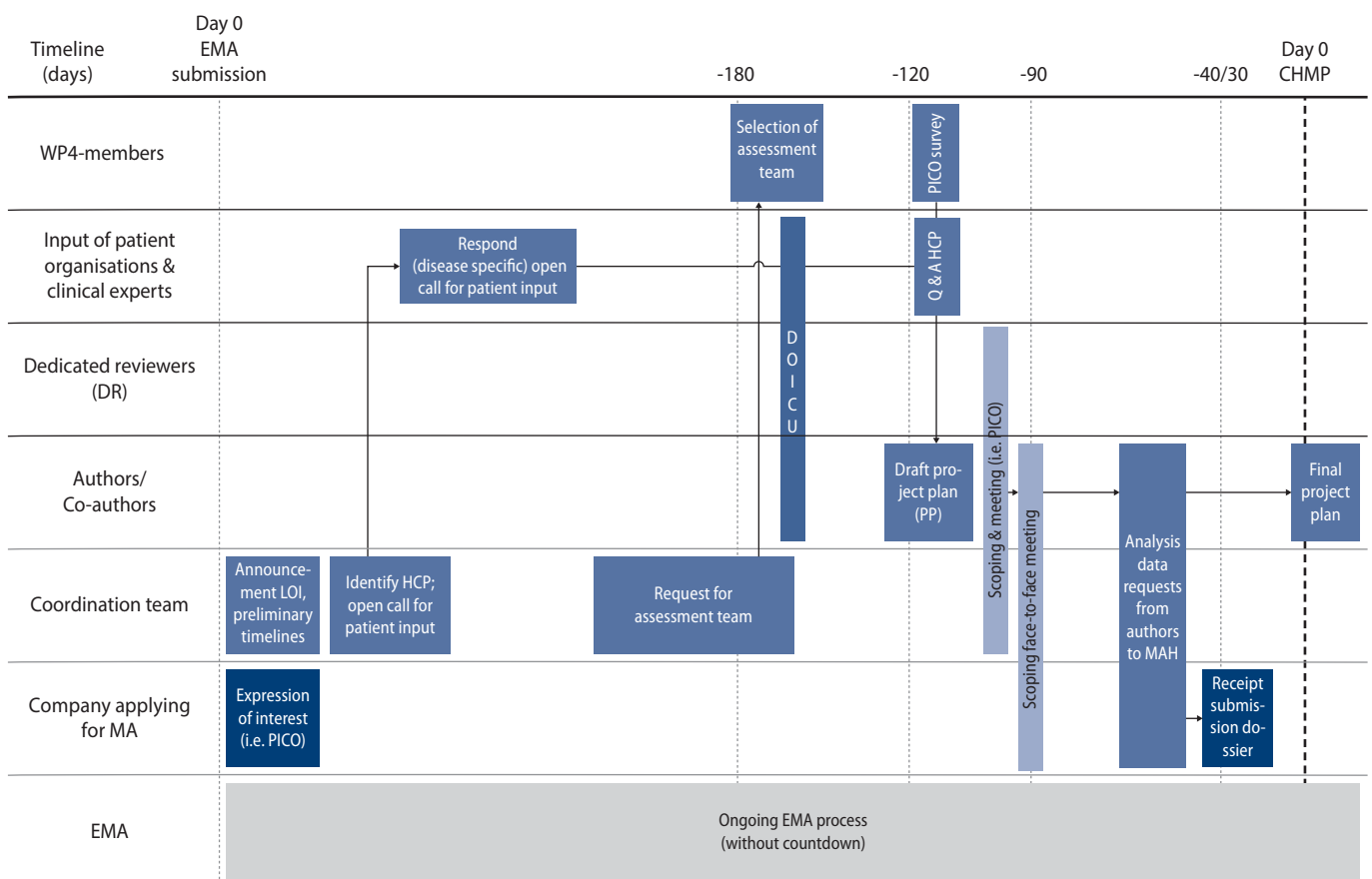
ty (n=26 individual parallel consultations, PCI). In 69% of those 56 processes, changes were implemented in the early development plan (Figure 3).

Pharma Joint Assessment

Currently, EUnetHTA conducts only selective assessments

of innovative pharmaceuticals. Topics for Joint Assessments are prioritised based on four criteria: i) whether the topic is of inter/sub/national interest, ii) the uptake, iii) whether EUnetHTA's national partners are interested in being part of the authoring team for a specific compound and iv) feasibility in relation to timelines. Timelines and ac-

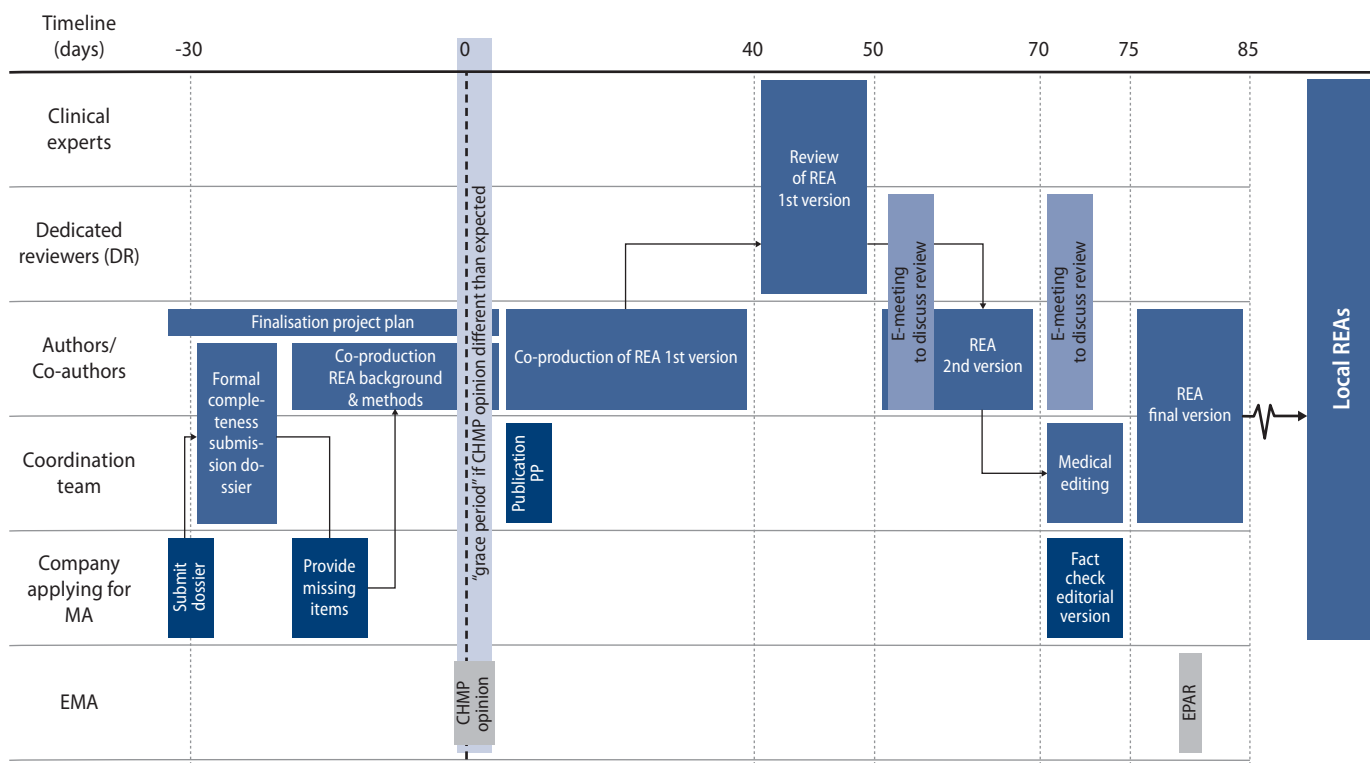
Process flows and activities in the scoping phase



Source: EunetHTA

Figure 4: Scoping phase for EUnetHTA Relative Effectiveness Analyses (REA): This phase comprises the submission of Lol by the company until the preparation of the final project plan by EUnetHTA

Process flows and activities in the assessment phase



Source: EunethTA

Figure 5: Assessment phase for EUnetHTA Relative Effectiveness Analyses (REA): This phase comprises the finalised project plan by EUnetHTA until the finalisation of the definitive REA.

tivities covering the two phases of the pharmaceutical REA, the scoping phase and the assessment phase, are displayed in figures 4 & 5.

Within JA3, a total of 14 REAs have been started, with final reports being published already for eight of those REAs. One additional REA (Enasidenib in Acute Myeloid Leukemia) was terminated due to the product being withdrawn from the market. Within the previous funding periods, one (JA1) and six (JA2) REAs were published respecti-

vely. A recent review of published EUnetHTA REAs revealed that, since JA3, time intervals between EMA approval and EUnetHTA assessment were < 80 days, number of (co-)authoring HTA bodies ranged between two (in six REAs) and > 10 (Pazopanib), and EUnetHTA did consider non-RCT evidence in seven procedures.⁴

Furthermore, Implementation of Pharma Joint Assessments increased considerably since JA3, indicating an improved national uptake of Joint Assessments (Figure 6). In

conclusion, EUnetHTA's methodological framework and working processes have been vastly improved and standardised since JA3, national uptake of EUnetHTA assessments has increased, and the recommendations within the Early Dialogues have been well received by manufacturers resulting in changes in the respective development programmes. EUnetHTA is ready to take the next step towards an integrated European Clinical HTA Assessment.

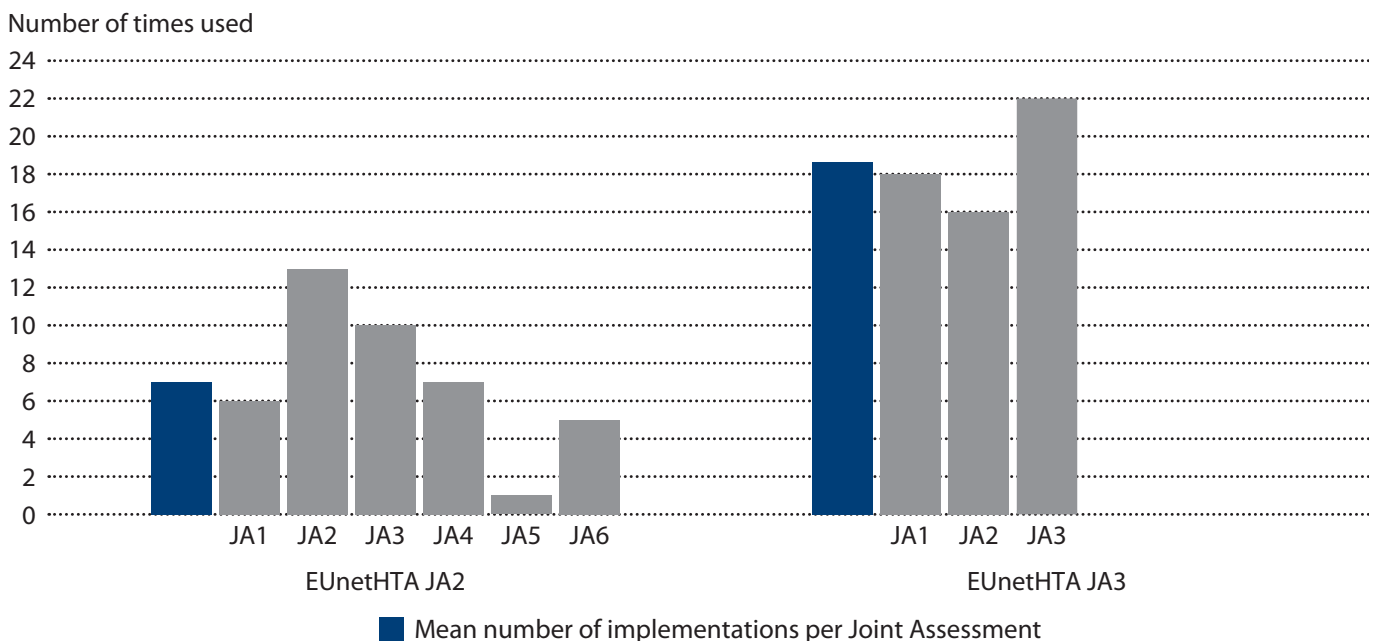
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Implementation of Joint Assessment



Source: EunetHTA

Figure 6: The implementation of joint assessments of pharmaceuticals has increased significantly with the Joint Action program 3. This indicates a stronger national consideration of joint assessments.

Prospects for negotiations on the EU-HTA regulation

Ministerial Counsellor Ortwin Schulte | Head of the Health Unit at the Permanent Representation of Germany to the European Union in Brussels, Belgium

The starting position is a very lengthy process with tension lines across the EU Commission, the Council of the European Union, and the European Parliament (EP). The division of powers between the European Union and the member states in the area of pharmaceuticals and medical devices is very complex. Thus, the proposal for a EU-HTA regulation is aimed at harmonising the process of benefit assessment of pharmaceuticals and medical devices on the model of regulatory approval. Any concerns regarding the principle of subsidiarity should be addressed with a legally sound specification of EU-HTA assessment process. Moreover, the coordination during decision making constitutes another topic of intense debate. Due to the outbreak of the COVID-19 crisis, the ongoing legislative process has been discontinued in an unforeseeable manner. The limited capacities of European health policy must now be reassigned on the basis of current priorities. Potential positive effects of a EU regulation that incorporates the HTA bodies' expertise in the member states on the efficiency of national healthcare systems must be taken into account.

S **tarting position**
The proposal for a EU-HTA regulation which has been presented after an – even for European Commission standards – exceptionally lengthy preparation process has been negotiated by the two EU co-legislators since January 2018. While the European Parliament – at first with the Spanish Socialist Soledad Cabezon-Ruiz as rapporteur, followed by the German Social Democrat Tiemo Wölken in the current term of the European Parliament – adopted its opinion in 2018 and confirmed it for the new term of the European Parliament after the European elections, the Council has not yet adopted a formal position.

Under five Presidencies so far (Bulgaria, Austria, Romania, Finland and Croatia) intensive negotiations have taken place in the Working Group Pharma, but no formal position was adopted nor a common position or general direction determined. Although two years of negotiations in the Council without any formal approach of a position are not unusual in the legislative process of the European Union in politically complex areas, it is still remarkable that nearly the only comprehensive legislative proposal by the European Commission in the area of European health policy is making such a slow progress.

Inter-institutionally, the slow negotiation process causes tensions, i.e. the European Commission complains about the Council blocking the process, and the European Parliament accuses the Council of delaying tactics. The reasons for this state of negotiations will be outlined in the following section and an outlook provided on the COVID-19 crisis and its potential influence on the ongoing EU-HTA legislation (see figure 1).

Milestones of the negotiation progress

| Time | Activity |
|-----------------|---|
| February 2018 | Subsidiarity objections by national parliaments |
| June 2018 | Political debate at the EPSCO Council |
| since July 2018 | Joint papers GER/FRA |
| December 2018 | Joint letter of the Health Ministers of GER, FRA, SP, POL, CZE, and BGR |

Figure 1: Political orientation guidelines from the member states' perspective. A formal position on the EU-HT regulation has still not been established.



Ministerial Counsellor Ortwin Schulte is Head of the Unit Health Policy at the Permanent Representation of Germany to the European Union in Brussels, Belgium. After his law studies, he started his career 1992 at the German Ministry of Health. From 2001 to 2005 he worked as Head of the Health Unit in the Federal Chancellor's Office in Berlin. From 2005 to 2007, he also chaired the EU Presidency Task Force in the German Ministry of Health before he took over the Bilateral Relations Unit from 2008 to 2016. Since 2011, he is also Associate Professor at the Medical and Pharmaceutical University in Chisinau/ Republic of Moldova.

2. Division of powers between EU and the member states in health policy

The division of powers between the European Union and the member states in the area of pharmaceuticals and medical devices is very complex and based on a basic principle that has been established for decades: quality and safety requirements will be almost entirely harmonised in the comprehensive secondary EU legislation. The latest highlight of this development was the foundation of the European Medicines Agency (EMA) which recently moved from London to Amsterdam. It is responsible for the majority of regulatory approval processes of pharmaceuticals. This is by no means a monolithic process, but it is based on a well-balanced division of powers between the EMA as the key coordination instance and national approval authorities. In each approval procedure, a national authority is appointed as rapporteur and co-rapporteur.

This procedure specified in the EMA regulation can be legally protected at the European Court of Justice in case of dispute and produces internationally recognised and in many cases globally groundbreaking results. However, the procedure only relates to quality and safety, the price of the product and cost-benefit ratio are not subject of the procedure.

The proposal for a EU-HTA regulation is aimed at harmonising the process of benefit assessment of pharmaceuticals and medical devices while taking major parts of the approval process as a model; no separate agency will be founded, but a Secretariat at the European Commission entrusted with HTA tasks. This material yet not organisational alignment is a logical extension of the existing EMA procedure and the basic principle of the EMA – the systematic consideration of 27 national authorities for an administrative decision at EU level – also applies for benefit assessment.

One argument against this approach, however, is that the extension of the EU responsibility affects a very sensible policy area that has been resolutely defended by many member states for decades: The EU-HTA regulation produces procedural results that are important preliminary decisions for both cost control and resource allocation in the national healthcare system.

Supporters of the EU-HTA idea like to point out that the mere sacrosanct area of controlling the national healthcare system, i.e. price determination and design of the catalogue of services, are not subject of the EU decision. In principle this is correct, but it does not reduce common concerns, as the EU benefit assessment is considered prejudice that is difficult to overcome for the question of reimbursement and price determination at national level.

Against this background, such a prejudice is inconsistent with the guaranteed autonomy of national healthcare systems according to Article 168 Para. 7 AEUV. Routine verification of EU legislative initiatives by national parliaments has led to formal subsidiarity objections in four cases (Germany, France, Czech Republic, Poland); although they cannot stop the legislative process as the quorum of eleven national parliaments required for a so-called „yellow card“ cannot be reached, it represents a politically effective indicator for the deeply fundamental basic concerns in these four member states.

The European Union is characterised by the principle of conferred powers. It only has the responsibilities that have been granted by the primary legislator in the European treaties. Therefore, the decision about the quoted legal basis is not a formality for a secondary legal regulation; instead, the course is set and the framework for action defined. Unsurprisingly, the European Commission has chosen a legal basis which grants the EU an extensive freedom of action: Article 114 AEUV that refers to the provisions for the

assurance of a single market and applies horizontally in all policy areas that are relevant the single market, i.e. also health policy.

In contrast, the sceptical member states point out that in a secondary legal regulation with direct relevance for the control of healthcare systems, one provision of the EU treaty regulates healthcare policy that only creates a very limited framework for action: Art. 168 TFEU.

Mediating views – including those of the European Parliament – quote both legal bases. Experiences with complex legislative projects in the EU show that the legal basis should only be discussed after the contents of the EU regulation have somewhat been established. After two years of negotiations it is quite obvious that a cautious regulation emphasising national scopes for action will be more compatible with Article 168 AEUV while a common final benefit assessment at EU level is more compatible with Article 114 AEUV.

3. Judicial legal protection

The question of whether the working results of EU-HTA processes are binding for national healthcare systems is certainly the political core of the discussion in the Council of the EU. This is closely (and in the public discussion of the previous months sometimes indistinguishably) related to the question of legal protection. But when it comes to the competences of national or European courts, it seems important that another – from some member states' point of view – significant aspect becomes relevant: An imminent overlapping of national legal protection systems by legal protection in the jurisdiction of the European Union (see figure 2).

At first, it is evident that benefit assessment decisions of public authorities or (after appropriate delegation of the decision-making authority by national courts) institutions

of self-government constitute administrative acts which usually regulate legal relationships that have at least an effect for the applicant and can thus contain detrimental regulations. According to Article 19 Para. 4 of the German Basic Law (Grundgesetz), administrative acts are subject to judicial control by the courts. Legal protection designs of many EU member states are highly sophisticated and differentiate between private and public interests, e.g. regarding the implementation of a preliminary procedure, granting of scope for judgement evaluation to the acting institutions, suspensive effect of appeals and claims as well as cost implications.

In case of judicial legal protection against procedural results of EU-HTA assessment, these national legal protection systems might be overlapped. Prior to European benefit assessment, a national benefit assessment (or – depending on the member state – cost/benefit assessment) is performed and of course this temporal precedence is also provided when judicial legal protection is claimed against the final decision at national level. It is or might not be legally impe-

rative to suspend national legal protection procedures until European jurisdiction has taken a decision; pragmatically it seems, however, quite reasonable. Therefore, judicial legal protection must always be taken into consideration when it comes to the assessment of the extent of intervention into national governance of healthcare systems.

In order to preserve the member states’ competences in the design of the joint secondary legislation on EU-HTA, a precise description of the legal character of EU-HTA assessment is imperative. Both European and most national administrative regulations of the member states distinguish between decision-preparing acts without any external legal effect and independent administrative decisions with a self-contained regulation that can be appealed against at least by the applicant (depending on the procedural status of third institutions and companies but also by other stakeholders). An incontestable characterisation of EU-HTA assessment as decision-preparing measure would thus be important to rule out existing concerns regarding the principle of subsidiarity.

Positions on the legal protection

| Legal protection | Proposal of the European Commission | Idea Germany/ France |
|-----------------------------|---|---|
| European Court (Luxembourg) | Yes, all stakeholders regarding scientific assessment | No, risk of overlapping of national legal proceedings |
| National legal remedies | Yes, regarding the overall HTA decision | Yes, regarding all aspects and national legislation |

Figure 2: Proposal of the Commission and Germany/France on legal protection within the scope of the EU-HTA procedure.

4. Coordinated decision-making

For a long time, decisions regarding the single market and also for health-related regulations have not been taken based on the principle of unanimity in the Council to secure the EU’s capacity to act and encourage member states with deviating opinions to seriously consider compromises and form alliances in case of need.

The EU-HTA regulation must also be adopted by 55 percent of the member state in the EU Council representing 65 percent of the EU population. Conversely, at least four member states representing 35 percent of the EU population can prevent the adoption of a decision.

This basic principle for regulations of the secondary community legislation also applies for many implementing

decisions of the so-called tertiary community legislation. In many sectors, decision-making based on the principle of comitology also requires a qualified majority of the member states. However, in the EU-HTA regulation, the European Commission stipulated that voting decisions in the Coordination Group of the member states only require the simple majority of the non-weighted votes of the member states.

This is opposed by a remarkably large group of member states for two reasons: Firstly, many member states consider this a misconception of the principles of scientific work, if scientifically sound assessments can be voted about. Thus, scientific assessments are not subject to voting and potential conflicts in the assessment must be taken into account by including them in the assessment report and must not be determined by means of an administrative decision.

Secondly, for non-scientific implementation decisions, it is doubted whether votes by simple majority of the non-weighted votes are acceptable. It is not surprising that larger member states stand up for the qualified majority option with weighted voting, while smaller member states favour the one country, one vote principle.

Issues of majority are issues of power distribution that might only be solved in the late stage of an agreement. Suffice it to say that this should also be a reassurance option in case of emergency that provides a precautionary measure for the unlikely event of fundamental undesirable developments in HTA practice. If the qualified majority applies, member states with sufficient personnel HTA resources can coordinate their efforts and formally intervene according to the form that has been defined in the EU Treaty. It is also part of the overall assessment to determine to what extent national scopes for action can be secured (see figure 3).

5. Perspectives in light of the COVID-19 crisis

The COVID-19 crisis has affected the ongoing legislative process in an unforeseeable manner and has interrupted EU-HTA negotiations in the Council for several months. Even compared to other recent legislative projects of European healthcare politics, this is an exceptionally complex legislative project with a tremendous impact on the healthcare systems regulated at member state level.

From an organizational point of view, it is not sure whether working groups will be able to meet and subsequent inter-institutional dialogues – with experts arriving from the member states – can take place in Brussels in the coming months. Although virtual video conferences are possible, these are associated with a substantial loss of the negotiating dynamics; in addition, complex issues arise in terms of transparency, procedural correctness, and assurance of confidentiality.

As far as the content is concerned, it should be clear af-

Dispute resolution procedures

| Category | Proposal of the European Commission | Idea Germany/ France |
|--------------------------|--|--|
| Scientific questions | Efforts to achieve consensus – otherwise votes by simple majority of the non-weighted votes | Consensus principle , no voting, reflect minority opinions |
| Organisational questions | Simple majority of the non-weighted votes | Qualified majority of the weighted votes (55 % MS with 65 % pop.) |

Figure 3: Several member states consider scientific assessments not to be subject to voting. They request that potential conflicts are reflected in the assessment report.

ter two years of negotiations that significant changes are required before the European Commission's proposal – which is very much based on the single market principle – can be adopted in the Council with a qualified majority. Thus, the question will be whether the inner logic of the proposal that has been established in 2017 is still in line with the completely changed political landscape of a health crisis that presents an extreme burden and significantly affecting the total economic activity in the EU. However, it may be stated that a regulation adopted at EU level incorporating the expertise of all HTA bodies in the member states can improve the efficiency of national healthcare systems.

This however seems to be contradicted by the enormous pressure of expectations towards the EU legislator regarding an appropriate reaction to the COVID-19 crisis, i.e. regarding supply shortages, cross-border solidarity of the systems and digital solutions for contact tracing. At present, limited capacities of the European healthcare politics must be allocated according to the priorities of the EU institutions.

Disclaimer

The views expressed in this article represent those of the author.

Benefit assessment in the European context – the G-BA's perspective

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In the past two years, the European Commission's draft regulation of 31 January 2018 for the promotion of European cooperation on Health Technology Assessment (HTA) has been subject to fierce controversies. These led to the further development of the regulation within the scope of parliamentary discussion and discussions in the Council working groups, but from the G-BA's perspective, key questions remain open and problems unsolved. The clarification and agreement on key topics before the EU-HTA regulation enters into force is an essential requirement for the acceptance of the regulation by the individual member states. Within the scope of the EUnetHTA project, the G-BA has been continuously involved in a structured and sustained cooperation of HTA bodies in Europe. After expiry of Joint Action 3¹ and in the context of the management of the current SARS-CoV-2 pandemics it will become apparent how solid this concept of the previous project-based voluntary cooperation is. It will ultimately be judged by whether and to what extent the expected advantages can be realised for HTA institutions, pharmaceutical companies and decision-makers in the member states.

Further development of the draft regulation of 31 January 2018

From the G-BA's perspective, the following aspects of the European Commission's draft regulation of 31 January 2018 should be subject to critical evaluation (see ²).

1. Legal basis Article 114 of the Treaty on the Functioning of the European Union (TFEU)
2. Binding adoption of the European benefit assessment (Joint Clinical Assessments, JCA)
3. Competences of the European Commission (EC)
4. Process flow and requirements with respect to quality and transparency.

Another main point of criticism is the unclear distinction between legal binding force of a European assessment and the remaining scope of discretion for national decisions (appraisal). With a binding adoption of the EU-HTA report, an adjustment of this report to a decision for national healthcare systems is only partly possible and relevant questions regarding the specific treatment situation remained unsolved. These question could refer to all aspects of the clinical study, such as whether the patient populations that are significant for the treatment context have been evaluated, whether the respective treatments are compliant with the treatment standard (both comparative treatment or appropriate use of the respective pharmaceutical), or whether the respective endpoints are conform with the system of values of the respective healthcare system.

In its first hearing in February 2019, the European Parliament has adopted its position on the draft regulation which was confirmed in October 2019 by the newly elected European Parliament.

The European Parliament emphasized that greater account must be taken of the requirements of the national healthcare systems thus providing more flexibility for the

application of EU-HTA assessments. Moreover, the European Parliament took a clear position regarding the legal basis (amendment of Article 168 Paragraph 4 AEUV), the role of the EU Commission, the majorities in voting procedures and for scientific evidence-based practices. In addition, it was recommended to provide the possibility of a complementary national assessment, provided that certain aspects were not included in the joint European assessment.

Consultations in the Council were continued during the Bulgarian, Austrian and Romanian Presidency addressing the tasks and the composition of the coordination group, procedural issues of joint clinical assessments, and scientific consultations. During the Finnish Presidency, a progress report was published at the meeting of the Council of the European Union (Employment, Social policy, Health and Consumer Affairs) on 9/10 December 2019. During the Finnish Presidency, views were primarily exchanged about the fact that the European assessments should gradually be-



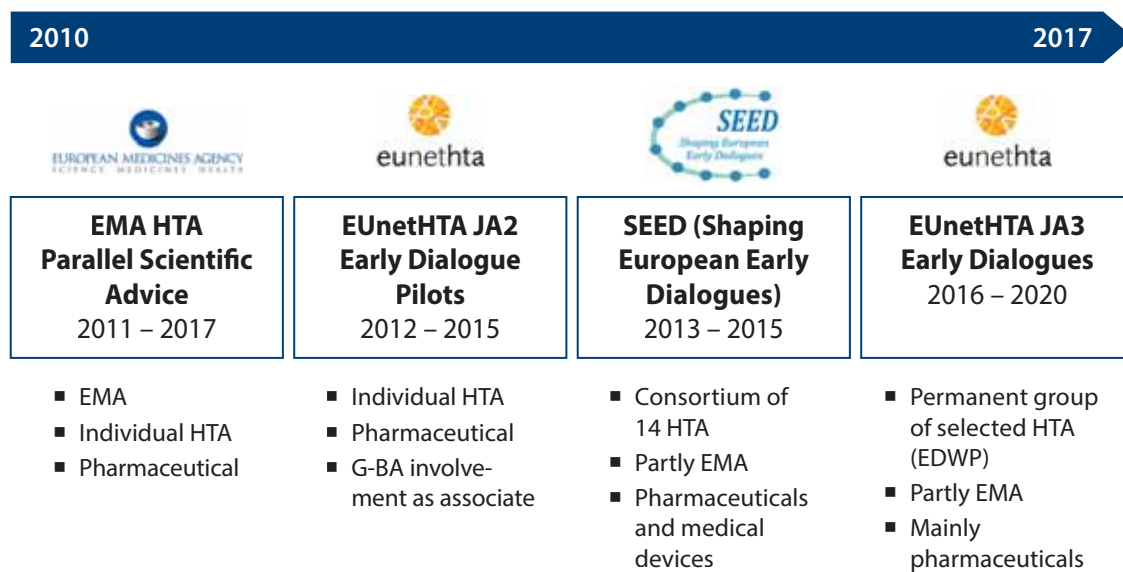
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gin, which and how many health technologies should be subject to mandatory Joint clinical assessments (JCA), how JCAs should be implemented, updated and approved, as well as which obligations should be imposed on pharmaceutical companies and the member states. In particular, it should be discussed critically which consequences result from an official listing of the assessed health technologies. Despite all efforts to achieve an agreement and common understanding regarding the formulation of the regulation, finalisation of relevant preparatory work would be neglected from the G-BA's perspective: The results of the EUnetHTA Joint Action 3 (JA 3) had not been summarised in a final report and could thus not be considered in the discussion. However, it is obvious that the difficulties of EUnetHTA JA 3 lie in the missing binding legal basis for the conduction of European benefit assessments. Thus, start-up problems might be attributable to the „recruitment“ of pharmaceutical companies providing their products and the respective data for EUnetHTA benefit assessment on a voluntary basis. Other aspects, such as agreement on documents that need to be submitted, content, statement and format of benefit assessments, process flows, interaction with previous steps within the scope of a life cycle approach of a health technology (scientific consultations or horizon scanning, etc.) must be prepared independently of the submission of benefit assessment dossier. These procedures provide an essential basis for the formulation of the regulation.

Involvement of the G-BA in EUnetHTA

The EU promotes the cooperation in the assessment of health technologies by supporting the joint actions „EUnetHTA“ to establish a sustained European network for the assessment of health technologies (HTA) supporting evidence-based, sustained and appropriate decisions in the

European consultation process – involvement of the G-BA



Source: own presentation

Figure 1: The G-BA has been involved in European consultation procedures for several years. But only with the Joint Action program 3 (JA 3), a stable procedure for the cooperation of HTA agencies and EMA could be established.

healthcare systems of the member states. 81 partner institutions are involved in the third funding period of the EUnetHTA Joint Action (JA3) appointed by the respective authorities of the member states and assigned to different work packages (WP). The G-BA is involved as co-lead in WP5: „Evidence Generation – Early Dialogues“ that organises and conducts consultations for pharmaceutical companies regarding clinical study planning. The HAS (Haute Autorité de Santé, France) is the lead partner.

With the introduction of the German Pharmaceutical Market Reorganisation Act (AMNOG) in 2011, the G-BA and the office were given the task to consult pharmaceutical companies. Thus, the G-BA has been involved in various pi-

lot projects of European consultations since 2011. Preceding projects of the current project within the scope of EUnetHTA JA 3 are EUnetHTA JA2 and the SEED project (Shaping European Early Dialogues) during which pilots of European consultations (Early Dialogue Pilots) were conducted (see figure 1).

During EUnetHTA JA 3, a stable procedure has been established for the cooperation of the various HTA agencies involved and the European Medicines Agency (EMA) and a permanent core working group installed to design the consultation and coordination process efficiently and consistently. In Joint Action 3, the G-BA participated in more than 30 European consultations.

Besides the various work packages, EUnetHTA is committed to a transparent and close cooperation with the EMA. Regular meetings of all involved institutions take place to create a better mutual understanding for the issues of HTA institutions and approval authorities across Europe. Thus, one sub-project in which the G-BA is also involved addresses the challenges the formulation of an approved indication of a pharmaceutical presents for the HTA processes. The exchange about the genesis of an indication and its significance of the clearly defined and approved patient population for HTA assessments resulted in a better understanding of each other's problems.

Differences EUnetHTA – Benefit assessment and AMNOG Benefit assessment

The procedures of benefit assessment conducted within the scope of EUnetHTA and AMNOG differ in certain key aspects, but have certain steps in common.

Determination of the underlying question(s) for benefit assessment

For the benefit assessment in Germany, the research question that shall be evaluated has already been defined in Section 35a of the 5th German Social Codebook (Sozialgesetzbuch V, SGB V), the Pharmaceutical Products Benefit Assessment Ordinance (AM-NutzenV) as well as in the Rule of Procedures of the Federal Joint Committee (G-BA) and the corresponding module templates: the evaluation of the extent of the additional benefit the pharmaceutical provides as compared to the appropriate comparative treatment and its therapeutic significance in the context of the German healthcare system. The definition of the benefit and additional benefit also includes which patient-relevant therapeutic effects (prolongation of survival time, improvement of the physical condition, reduction of the di-

sease duration, improvement of the quality of life, reduction of side-effects) must be taken into consideration, especially for an additional benefit. The patient population to be evaluated is defined according to the indication.

Orphan drugs present an exception, as the assessment shall not be based on a appropriate comparative treatment, because an additional benefit has already been proven upon approval and the assessment shall be performed on the basis of the approval studies.

In Germany, pharmaceutical companies have usually (in more than 96 percent of the procedures) been advised by the G-BA prior to the benefit assessment regarding the comparative treatment to be used, endpoints and assessment instruments, the data to be used and other methodological or procedural issues. The transcript of the consultation protocol must be enclosed to the dossier to be submitted and is available to the assessing institutions. The determination of the appropriate comparative treatment is usually based on a systematic evidence synopsis.

Contrary to this procedure, the key parameters of the European benefit assessment are determined during a so-called scoping meeting of the assessing institutions and the pharmaceutical company. Prior to the scoping meeting, the institutions that are responsible in the European countries answer a query (scoping survey) regarding patient groups, comparators and endpoints (equivalent PICO process) that are relevant for the assessment so that the different national questions of the European assessment can be taken into consideration. This procedural step is outlined in the project plans of the respective assessment.

In the European assessment reports, either more than one research question must be answered or a compromise made between the different requirements. Consequently, it is only logical that the benefit assessment cannot be tailored to the individual healthcare system. Nevertheless, any

information that is relevant for the individual nation must not be missing. However, it would still be interesting for the learning process within the development phase of European assessments, if joint assessments by the EUnetHTA were more transparent as to which requirements form the basis of the final question of benefit assessment and the result of the survey among institutions was comprehensible.

The research question that shall be used as a basis for the benefit assessment has direct consequences on the assessment report. This is particularly apparent in the example of the assessment reports on polatuzumab vedotin in the indication „relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL)“. For this active ingredient, both a EUnetHTA assessment report³ (main author: Institute for Quality and Efficiency in Healthcare [IQWiG], co-author: Haute Autorité de santé [HAS]) and a benefit assessment by the G-BA⁴ (performed by the Department Medical Consultancy of the G-BA's office) are available.

European benefit assessment distinguishes between two patient populations, i.e. one patient group with failure of first-line treatment and another one with failure of two or more previous treatment options. This is due to the fact that these populations differ both in terms of their prognosis and well-established and approved treatment options and thus relating to the comparison to be made.

As polatuzumab vedotin is an orphan drug, a differentiation of the research question is not possible in Germany due to the different comparators to be used and the study population that was evaluated during the approval study must be considered in its entirety. In the European benefit assessment, the results of the overall study are also presented.

Requirements regarding the documents to be submitted

Due to the mandatory benefit assessment in Germany, every new pharmaceutical and subsequently every new indication of the new pharmaceutical must undergo early benefit assessment. Any non-submission or incomplete dossier submission has immediate consequences for the subsequent reimbursement negotiations. Within the scope of the EUnetHTA project, submission is voluntary for the companies. Due to this non-systematic selection of products, previously performed European assessments represent a non-representative assessment result of the approved pharmaceuticals. Thus, companies with outstanding positive study results might come forward.

Moreover, companies are not obliged to submit comprehensive documents and conduct systematic bibliographic literature or study research and update the data at regular intervals, even if this is recommended in the EUnetHTA submission template. In this template, concrete (methodological and structural) specifications regarding evaluation, methodology and presentation of the clinical endpoints and their results are partially missing. Consequently, information that is required for the evaluation is not always available as compared to the clear specification in the AMNOG dossiers.

However, the data basis of the two above mentioned assessment reports on polatuzumab vedotin was almost identical. In both cases, the approval study GO29365 was used with study arms C and D (data cut-offs 30 April 2018 and 11 October 2018) as well as study arm G (data cut-off: 15 March 2019). However, in the European procedure, only mortality data were reported for the data cut-off date of 11 October 2018, while data on adverse events were missing. These were included in the AMNOG procedure and could be presented in the dossier assessment. It has been clearly

specified for the early benefit assessment by the Pharmaceutical Products Benefit Assessment Ordinance (AM-NutzenV) and the Rule of Procedures (module templates) which documentation must be submitted. This documentation comprises all documents that were available for approval and documents that have been prepared by the approval authorities, such as preliminary assessment reports. Consequently, the G-BA has all relevant documents available.

Course of the procedure

Polatuzumab vedotin was approved on 2 January 2020. The European assessment report was published on the EU-netHTA website on 14 February 2020 together with the dossier of the pharmaceutical company, the project plan, and the Factual Accuracy Check. In Germany, polatuzumab was placed on the market and listed in the official price list (Lauer-Taxe) on 15 February 2020. The respective dossier assessment of the G-BA was published on the G-BA website three months later together with the documents submitted by the pharmaceutical company providing the opportunity to submit comments.

One of the major challenges of European benefit assessment is that the preparation of the assessment must be conducted almost in parallel with the assessment of the approval authorities. According to the process flow, very little time remains after the positive opinion to prepare the report and coordinate it with the HTA bodies (see figure 2). Any changes of the intended indication, dosage or notes in the summary of product characteristics must be taken into account in the short term. This is especially relevant for the German decision-making, as the limit of reimbursability is restricted by the approval thus defining the population to be assessed. Moreover, further data can be available until market entry, as studies and study reports may have been finalised in the meantime. For polatuzumab, this was not

the case and the data basis is the same.

Another aspect of European assessments is the process step of the so-called Factual Accuracy Check (Fact-Check) which is performed by the pharmaceutical company prior to the publication of the benefit assessment; this step does not exist in the AMNOG dossier assessment. During the Fact-Check, the pharmaceutical company can report back obvious errors or inconsistencies. In previous procedures, it was apparent which influence companies exerted on the content of the final report. Thus, during the benefit assessment of alectinib, entire passages of suggested changes by the pharmaceutical company were incorporated into the benefit assessment. This was not the case with polatuzumab, which is understandable in light of the currently practised process flow due to the transparent presentation of the Fact Check in a separate document. This represents a major further development, previously it could hardly be revealed where the changes in these reports came from.

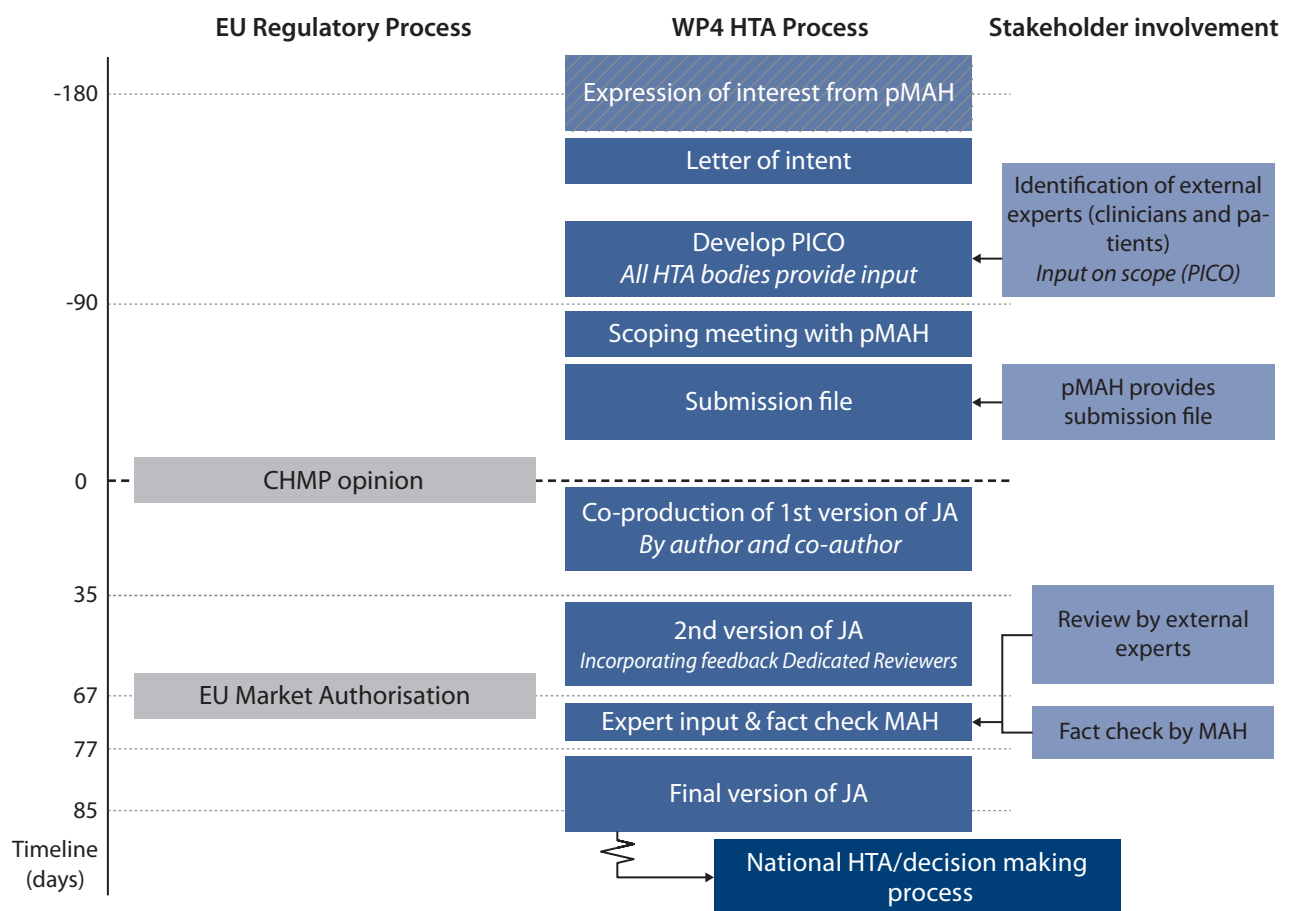
In the AMNOG procedure, the public hearing procedure allows for a transparent discussion of the pharmaceutical company's notes, but simultaneously an exchange with the statements of professional experts and patient organisation.

In the European benefit assessment, the experts and patient representatives were involved in writing before the report was published (in case of polatuzumab, six patient organisations responded to the open call, in case of alectinib only one single patient was involved!).

Contents of the assessment report

In both benefit assessments, both the European and the G-BA's, only the indication that was finally approved (diffuse large B-cell lymphoma [DLBCL]) was considered, despite the fact that during the approval study also patients with follicular lymphoma were included. Moreover, in both be-

Course of the EUnetHTA benefit assessment



CHMP = Committee for Medicinal Products for Human Use; pMAH = (pharma) marketing authorisation holder; PICO = model in evidence-based medicine: P = patient, I = intervention, C = comparison and O = outcome; JA = joint assessment

Source: EUnetHTA <https://eunetha.eu/services/submission-guidelines/pharmaceutical-submission/>

Figure 2: One of the major challenges of European benefit assessment is that the preparation of the assessment must almost take place parallel to the work of the approval authorities.

nefit assessments, the results of a non-comparative study arms were also presented in which the active ingredient in the finally approved lyophilised formulation was assessed

for pharmacokinetics and safety.

The points of criticism and addressed insecurities of the study were similar, i.e. in both assessments, critical emphasis

was placed on the fact that a detailed statistical analysis plan (SAP) or data regarding quality of life were missing in the GO29365 study or insecurities were due to an incomplete presentation of adverse events at certain data cut-offs.

The descriptive result presentation in the specific procedure on the different research questions in the European benefit assessment did not reflect the assessment of the additional benefit in advance, even though certain (surrogate) end points were (also) presented that would not have been considered patient relevant and thus not have been included in the assessment in the AMNOG procedure. In summary, the discussion about the endpoints or the subgroup analyses of the pharmaceutical company is differentiated and more detailed in the German assessment process.

Overall, an evolution of European assessments can be observed, so that the European benefit assessment can be integrated into the AMNOG assessment if certain procedural specifications are observed, such as transparent handling of submitted documents and comments as well as careful evaluation of evidence and notes on missing evidence. In the present case, the main stakeholder (IQWiG) was, however, familiar with the German processes and thus the assessment report was similar to the already known assessment reports and comparable to the methodological standards of the AMNOG benefit assessment. However, the previously published European assessment reports are not in a quality that makes them suitable for further use in the AMNOG process.

It remains to be seen how other countries will deal with the assessment of polatuzumab vedotin.

Conclusion and outlook

Even if the first draft regulation on the European benefit assessment will be further discussed and main levers still

require fine-tuning, a final version is not yet in sight. Much will depend on how successful the Joint Action 3 of the EUnetHTA project will be, to which extent methodological cornerstones and standards can be agreed upon, how process steps will be optimised and coordinated and how confidence in each other's work has grown. The most recent publications of a Joint Assessments show that – under certain conditions – relevant information can be derived for the benefit assessment.

This presupposes that there are no relevant changes in the approval process, the individual research questions are clearly defined and represented, the assessment is methodologically robust without any influence of the pharmaceutical company and the pharmaceutical is placed on the German market shortly after the European assessment. The methodological discussion will not be over after EUnetHTA JA 3, just like it is not over in the AMNOG procedure. The national procedure is constantly evolving, adjustments made and new processes are added.

This is shown impressively by the most recent legal specifications, e.g. the possibility to request post-market data collection, taking particular account of the resistance issue of antibiotics, or specific requirements for the application of ATMPs. It remains to be seen to what extent these national regulations can be integrated into a European process. One significant positive development within the scope of the EUnetHTA project is that the cooperation between approval authorities and HTA institutions has improved significantly. Due to the mutual understanding for the different tasks, the need for an early exchange and supporting each other in the request for better evidence is seen on both sides.

The current pandemic situation shows that a European cooperation in the field of evidence-based medicine is important. Research activities by individual stakeholders wit-

hout a solid methodological planning of the evaluations, partly hasty and not quality-secured data communication, lack of central coordination of scientific questions and activities create uncertainty among decision-makers and lead to contradictory regulations in the member states. A valid data generation and assessment of evidence – even if this seems to take more time in the first step – finally leads to a better and more effective patient-relevant healthcare for patients in a shorter time.

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European benefit assessment: The industry's perspective

Edith Frénoy | Director Market Access, HTA policy lead at the European Federation of Pharmaceutical Industries and Associations

The voluntary cooperation of national HTA bodies within the scope of EUnetHTA has reached its limits: a legal framework with clearly defined participation rights and obligations for all stakeholders is now required to ensure an effective and sustainable cooperation and faster access to innovative pharmaceuticals. EFPIA – as the European association of the pharmaceutical industry – appreciates the European Commission's draft law coordinating the cooperation of national bodies across Europe in a well-structured procedure while making use of all skills and experiences to achieve the highest quality standards. Specific suggestions for improvement include i) common definition of requirements in the scoping phase; ii) participation rights of the industry; iii) binding force of the European reports; iv) definition of a clear legal framework; and v) assurance of compatibility with the German AMNOG system.

E **FP**IA, as the European association of the pharmaceutical industry, has supported HTA cooperation across Europe since the foundation of EUnetHTA in 2006-07. EFPIA members have participated in various pilot projects on the evaluation of clinical evidence and were able to implement them successfully together with the EUnetHTA. However, after many years of voluntary cooperation it became obvious that the potential of temporarily funded EUnetHTA projects has reached its limits: a legal framework with clearly defined participation rights and obligations for all stakeholders is now required to ensure an effective and sustainable cooperation and faster access to innovative pharmaceuticals at national and regional level.

In 2018, EFPIA advocated the European Commission's draft law coordinating the cooperation of national bodies across Europe in a well-structured procedure while making use of all skills and experiences of national HTA bodies to achieve the highest quality standards at European level. Although the draft law is widely supported, there are, however, certain suggestions for improvement. These mainly result from the experiences that EFPIA members and other stakeholders have gained within the scope of the many years of EUnetHTA cooperation.¹

Common definition of requirements

The possibility of a common definition of the key assessment elements during the scoping phase – comprising endpoints, determination of patient groups and appropriate comparative treatment – is of central importance. Thus, it seems neither rational nor reasonable to display the different national clinical HTA assessment processes cumulatively in the European assessment process in their current form. In particular, the joint early scientific consultation

provided by the EMA and EUnetHTA involving key stakeholders including the EMA shall set the course for a joint EU assessment that can be used at national level.

Participation rights of the industry

Based upon previous experiences of the industry with EUnetHTA, pharmaceutical companies should have the possibility for transparent exchange with the responsible HTA bodies during the assessment process to be able to address questions directly. Moreover, a mechanism for conflict resolution shall be implemented to ensure a smooth integration of the European report into national systems and give the pharmaceutical company the opportunity to indicate formal errors and perceived divergences in the in-



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terpretations at the end of the assessment process to the conducting HTA bodies.

Binding force of European reports

From the industry's perspective, it is also of central importance that the results of the European benefit assessment can be used for subsequent national assessment decisions and member states do not re-evaluate the evidence base that has been established at EU level. A flexible design that would allow for a deviation from the European assessment process and a free re-interpretation of the results would ultimately lead to a lack of incentives for the stakeholders of the EU process for a joint assessment of the clinical evidence and thus for a European decision-making process. Therefore, the draft regulation deliberately requests the systematic involvement of member states in the design of the joint assessment processes.

Legal framework

A clearly defined legal framework is required to ensure transparent procedures, while ruling out potential conflicts of interests e.g. regarding confidentiality of submitted data. The commission can monitor compliance with the procedural steps in the European process and establish the basis for a process, in which the involved stakeholders and the general European public can place trust.

Compatibility with the German AMNOG

In concrete terms, for Germany a European benefit assessment would mean that the G-BA as the highest body of self-government in the health care sector would keep its central function and still take a decision about the extent of the additional benefit of new pharmaceuticals on the basis of the European report that has been prepared under German participation. Similarly, subsequent negotiations

Industry recommendations for future joint assessments (1)

Recommendations regarding the process of joint assessments

Recommendation 1: An experienced author involved to each assessment team

To ensure a high-level quality of the joint assessments, an experienced author should be involved in each assessment. This would guarantee an appropriate level of confidence and expertise in utilising the advanced REA methodologies developed by EUnetHTA. The assessment team should consistently commit adequate resources throughout the whole process.

Recommendation 2: The systematic involvement of patient organisations and external clinical experts

Patient organisations and external clinical experts should systematically be involved in all the joint assessments. Their input should be considered in both the scoping and the assessment phase in order to maximise the quality of the joint assessments. There should be transparency on the criteria for their selection and on how their input is considered in all the steps of the process.

Recommendation 3: A consistent approach across scoping meetings

There should be a consistent approach to the scoping meeting, with the possibility for the manufacturers to discuss with the authors the elements of the PICO and the best methodology for the assessment. It should be responsibility of the authors to ensure that the resulting PICO is supported by strong scientific evidence and any decisions taken in the scoping phase should be taken forward throughout the assessment process. More facilitated communication between the manufacturer and the assessment team would help to expedite the process.

Recommendation 4: Introduction of a review meeting

There should be a review meeting for manufacturers, patient organisations and clinical experts to discuss the draft report with the assessment team. The factual accuracy check process should be a mandatory process step in all future assessments.

Recommendations regarding the confidentiality of joint assessments

Recommendation 5: Setting up a EUnetHTA framework for confidentiality

There should be a framework regarding confidentiality before the assessments start. This would ensure that the best and most relevant evidence is included in the final joint assessment, increasing their quality and reducing the need for subsequent integration of evidence (and, ultimately, maximising their use).

Source: EFPIA, An industry perspective on the current EUnetHTA process for harmonized assessment – real world evidence.

of an economic reimbursement amount would still be conducted between the National Association of Statutory Health Insurance Funds (GKV-SV) and the pharmaceutical company.

The IQWiG that currently assesses the clinical data on behalf of the G-BA as a basis for a recommendation regarding the additional benefit would then be involved in the benefit assessment process at European level. The framework conditions of AMNOG, e.g. determination of an ap-

propriate comparative treatment that is suitable for the German treatment context, can be integrated into the European process within the scope of the so called scoping phase, discussed with HTA experts of other member states, and then applied at national level. Analogous to the early consultation which is experiencing increased demand at national level, aspects such as study design and endpoints can be discussed at an early stage of the development of pharmaceuticals and study planning with all stakeholders

Industry recommendations for future joint assessments (2)

Recommendations regarding the resolution of issues in the assessment phase

Recommendation 6: Introduction of an issues resolution mechanism

The introduction of a systematic mechanism for issues resolution should be considered (as last-resort) to increase the rigour of the assessment phase and its outcome whilst demonstrating that the process is impartial and that the assessment team is accountable.

Recommendations regarding governance

Recommendation 7: Adoption of a consistent approach across all the assessments

A consistent approach should be used for all the assessments: this should be based on an agreed European approach based on EUnetHTA methodologies capable to adapt to the scientific challenges posed by different technologies. Different national authors should be able to come to the same conclusions.

Recommendation 8: Consensual agreement to changes to the EUnetHTA process

If there is a need to adapt approaches, this should be agreed prior to starting the assessment based on discussions with the industry and agreed with the manufacturer participating to the assessment.

Recommendation 9: Resources allocation and EUnetHTA timeline prioritising high-quality joint assessment reports

The timeline and resource allocation for the joint assessments should allow for a high-quality report. The industry shares the objective to have timely publication that is aligned to the regulatory process. The process timeline should automatically adapt to changes in the timeline of the regulatory process. There should be a facilitated discussion with the assessment team about the circumstances where flexibility in the timeline could increase the quality of the report: this would ultimately benefit the overall quality of the final assessments and support their use in national settings.

Recommendation 10: A clearly defined process for escalation of process issues

A clear set of rules to escalate and resolve process issues would be beneficial to all the stakeholders.

Source: EFPIA, An industry perspective on the current EUnetHTA process for harmonized assessment – real world evidence.

within the scope of the European joint scientific consultations and implemented accordingly. As both G-BA and IQWiG already play a major role in the development of methodology, quality assurance and generation of evidence by the EUnetHTA, they wouldn't lose much of their importance during benefit assessment.

EFPIA now hopes that the current deadlock in the negotiations of the Council of the EU will be overcome and that a solution will be found in the best interests of patients, healthcare systems and industry. For Europe and Germany

this provides the opportunity to align divergences in the assessment of the clinical benefit and integrate innovative therapies into the national healthcare systems without sacrificing the national sovereignty with regard to reimbursement or compromising the highly valued timely patient access to innovative pharmaceuticals in Germany.

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Short interjection on the IQWiG's perspective on European benefit assessment

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During the Platform Meeting in March 2020, the IQWiG had the chance to give a short „interjection“ on the IQWiG's perspective on European benefit assessment addressing the following topics: 1. European benefit assessment requires completeness and transparency. 2. European benefit assessment must take the specific treatment situation of the individual countries or healthcare systems, respectively, into consideration.

This article outlines the information gain achieved through statutory completeness and transparency requirements for study results in the AMNOG procedure and the differences across Europe. Regarding the 2. point, the example of the comparative treatment shows why European benefit assessment must consider the treatment situations in the individual countries, if it is supposed to be what the EU Commission wants it to be, i.e. the scientific basis for reimbursement decisions in the individual EU countries.

Background
Most of the approval process for new pharmaceuticals has been harmonised within the European Union (EU). The majority of approvals are granted centrally on the basis of the assessment of the European Medicines Agency (EMA). The approval itself is granted by the European Commission which operates a central registry of all pharmaceuticals that have been approved in the EU.¹

All subsequent decisions on whether and under what conditions new pharmaceuticals are prescribable (e.g. at which price, with or without restrictions against the approved field of application) will be taken at country level. These decisions are usually based on national benefit assessments by national HTA (Health Technology Assessment) agencies. In Germany, the early benefit assessment has been particularly decisive since 2011 according to the German Pharmaceutical Market Reorganisation Act (AMNOG).² Most of the reports on the early benefit assessment are prepared by the Institute for Quality and Efficiency in Healthcare (IQWiG), while decisions on the benefit assessment are taken by the Federal Joint Committee (G-BA).

Many national HTA agencies, including the IQWiG, joined a network of European HTA agencies that was founded in 2009 (EUnetHTA). The goals of this network which is currently already in an extended third project phase funded by the EU (Joint Action 3)³ are to establish a sustainable network for the exchange of knowledge between HTA agencies and the promotion of a good practice of HTA methods and processes ensure a more efficient use of HTA resources.⁴ The exchange within the EUnetHTA has contributed immensely to a mutual understanding of common features and differences between the agencies and the individual requirements and legal framework conditions in the national healthcare systems.

One subject of the cooperation in the EUnetHTA is the consultation of pharmaceutical companies together with the EMA prior to the benefit assessment and approval as well as common benefit assessment on a voluntary basis. In 2018, the discussion about a common benefit assessment gained substantial pace with the EU Commission's draft regulation.⁵ This draft regulation was discussed critically in many European countries including Germany. Many of the discussion points were addressed during the Platform Meeting in March 2019 and are outlined in the conference transcript.⁶ More than two years after the publication of the draft regulation there is still no consensus on a common benefit assessment at European level and the Corona pandemic has led to a shift of priorities in European health policy.⁷ Nevertheless, it makes sense to outline the main principles for a common European benefit assessment from the IQWiG's perspective as they are also useful for vo-



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luntary common assessments within the scope of EUnetHTA.

During the Platform Meeting in March 2020, the IQWiG had the chance to give a short interjection on this topic. However, due to the time limitation, not all principles could be presented. Therefore, only the following two major topics were presented:

1. European benefit assessment requires completeness and transparency.
2. European benefit assessment must take the specific treatment situation of the individual countries or healthcare systems, respectively, into consideration.

European benefit assessment requires completeness and transparency

From the IQWiG's perspective, data completeness and transparency of the procedure are indispensable prerequisites for an appropriate benefit assessment. This applies both at national and European level. Only if all (relevant) data are available, the result of the benefit assessment can be unbiased. And only if the benefit assessment itself is transparent, it can be understood, discussed and properly implemented in decisions and daily practice. The example AMNOG in Germany demonstrates that completeness and transparency are possible and result in a significant knowledge gain for informed decisions in the whole healthcare system as well as concrete treatment decisions.

Completeness and transparency are possible:

The example of AMNOG

The legal framework conditions for benefit assessment according to AMNOG are outlined in Section 35a of the 5th German Social Codebook (Sozialgesetzbuch V, SGB V) and the corresponding Pharmaceutical Products Benefit Assessment Ordinance.^{8,9} They also include provisions on the

requirements as to which data the pharmaceutical company has to submit as well as on the transparency of the procedure. Here, two aspects are vital:

1. The pharmaceutical company „[submits] all results, study reports and study protocols of studies on the pharmaceutical [...], for which the company acted as sponsor as well as all available information about ongoing or discontinued studies with the pharmaceutical, for which the company acts as sponsor or has been financially involved otherwise, and relevant information on studies of third parties, where these are available“.⁹

2. The pharmaceutical company „shall label trade and business secrets as such in the dossier. This labelling shall not conflict with the obligation for the disclosure of study results“.⁹

The legislator has thereby recognised that both components are required for an appropriate benefit assessment: Neither an incomplete but transparent benefit assessment nor an incomplete, but intransparent benefit assessment provides a sound basis for decision-making. If the pharmaceutical company does not comply with one of these provisions, the respective pharmaceutical cannot be granted an additional benefit. On the basis of these clear specifications and sanctions, pharmaceutical companies only refused to comply with the completeness or transparency provision with the respective consequences in a few individual cases (e.g. ^{10,11}).

In 2015, an analysis of the IQWiG of all early benefit assessments completed so far showed that these requirements regarding completeness and transparency are associated with a significant knowledge gain.¹²

Figure 1 illustrates this knowledge gain on study results as compared to other publicly accessible sources. Publications in scientific journals, publicly accessible approval reports of the EMA, and study registries only contain signifi-

cantly less than half of the actually available information on study results.

Considering these three sources together, all data is only available in approximately 50 percent of the study results and approximately 30 percent of the study results have not been reported in any of the three sources. Contrary to this, publicly accessible sources in the AMNOG procedure (Modules 1 to 4 of the dossier of the pharmaceutical company, benefit assessment of the IQWiG, decision of the G-BA) contain almost complete information on the study results.

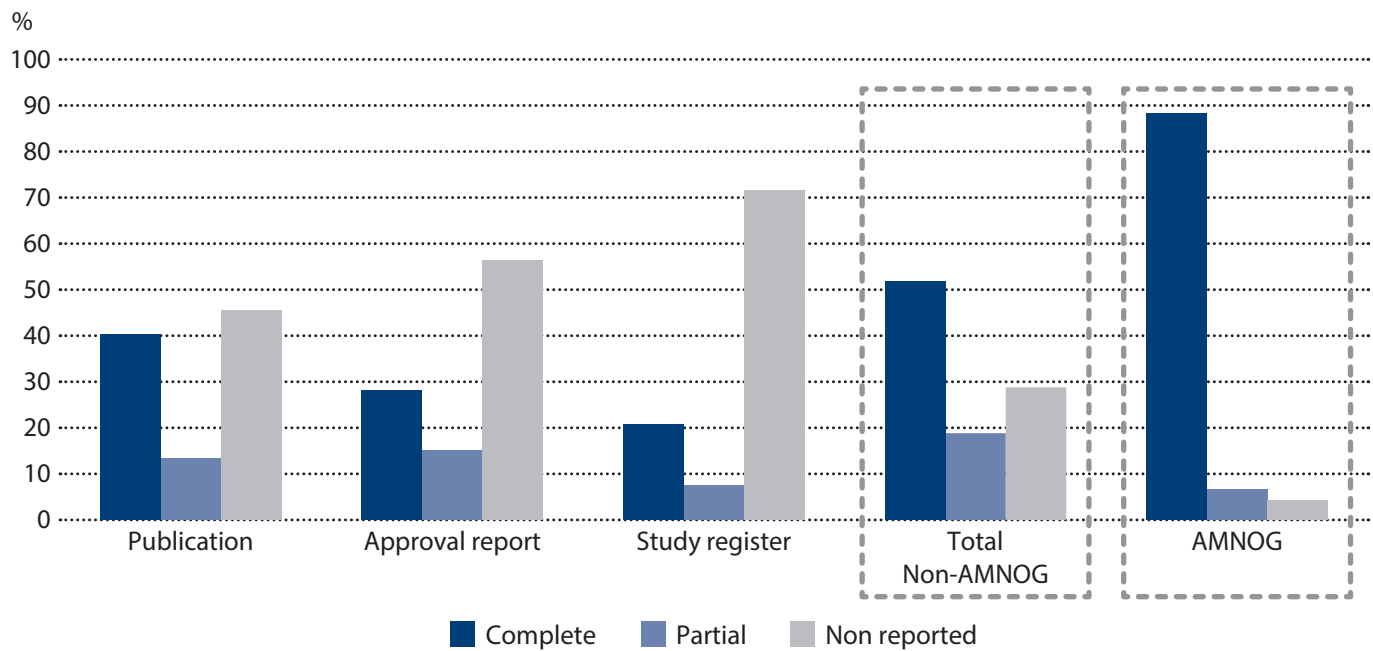
Completeness and transparency at European level: Room for improvement

A look at Europe shows: Completeness and transparency cannot be taken for granted, and the resulting information deficits are measurable.

This becomes quite apparent in the assessments HTA agencies perform as a basis for the decisions of the National Institute for Health and Care Excellence (NICE) in Great Britain. Large parts of the report are usually redacted and obviously the agencies do not have all data that needs to be submitted within the scope of the AMNOG process. This is subsequently illustrated by the example of the assessments on baricitinib for the treatment of rheumatoid arthritis or palbociclib for breast cancer:

- Baricitinib: In the RA-BEAM study, treatment with baricitinib was compared to treatment with adalimumab. Patients treated with baricitinib reported serious adverse events more frequently and the result was statistically significant. These results were compared in the AMNOG procedure.¹³ Obviously the competent British HTA agency also had this information, but the results were redacted in the NICE report.¹⁴
- Palbociclib: There are two studies comparing palbociclib + letrozole with letrozole: PALOMA-1 and PALOMA-2.

Availability of study results in various sources



Source: Köhler 2015 [12]

Figure 1: Publications in scientific journals, study registries and publicly accessible approval reports of the EMA only contain less than half of the actually available information on study results.

With approximately four times as many patients, PALOMA-2 represents the large majority of the body of information. Both studies show no significant difference in terms of overall mortality between the treatment arms. In the small PALOMA-1 study, the directions of effects favoured palbociclib + letrozole while they objected palbociclib + letrozole in the larger PALOMA-2 study. These results were published in the AMNOG procedure.¹⁵ However, the assessment of NICE states: „No OS data were available from PALOMA-2 ...“¹⁶

In the assessments of the EUnetHTA group, completeness

and transparency can also not be taken for granted at present. An example from the ongoing project phase of Joint Action 3 shows: In the PTJA04 report, the new active ingredient sotagliflozin for the treatment of type 1 diabetes patients was evaluated.¹⁷

During a so-called „fact check“ the pharmaceutical company was given the opportunity to make comments before the report is published. During this „fact check“, the pharmaceutical company objected the publication of the study results which the company had labelled as confidential in the dossier and the authors of the report drew the follo-

wing consequences:¹⁸ „The authors were not allowed to use the confidential information from the submission dossier attachments and have removed this information from the document upon request from the MAH.“

It is not known which information is meant and which consequences arise thereof. It is not really conceivable that such a report can provide the basis for national reimbursement decision or can be used to conduct an adequate hearing procedure.

The position of the pharmaceutical industry:

Back to the Stone Age of intransparency?

The example of EUnetHTA for the case of sotagliflozin shows that intransparency is the consequence of the requirements of the responsible pharmaceutical company. In general, intransparency of NICE assessments is also due to this fact. This and the position of NICE can be seen in the example of palbociclib. Besides the above mentioned lack of information on the overall mortality in the PALOMA-2 study, many study results were, as usual, redacted in the NICE report on palbociclib.¹⁶ With the aim of publication of this information, a Freedom of Information Act Procedure was initiated. This and the answer of NICE were published.²⁰ Among other things, NICE stipulates: „On balance, we therefore believe that protecting the commercial interests of Pfizer and of NICE outweighs the public interest in disclosure...“ and „The information is academic in confidence (AIC). It is the most recent overall survival (OS) data cut from the PALOMA-1 trial. It was marked AIC by the company, as it has not yet been published.“

What exactly does that mean?

1. The pharmaceutical company prohibits the publication of study results that are obviously relevant for the assessment for commercial reasons. From NICE's point of

view, commercial interests are more important than the public interest in the data.

2. The pharmaceutical company prohibits the publication of study results, also with the argument that these have not yet been published in a scientific journal. From NICE's point of view, the fact that the results have not yet been published in a scientific journal presents a valid argument to withhold information on the overall mortality from the public.

In Germany, the legislator decided to take the opposite way for a very good reason (see above mentioned details on the information content in scientific journals). However, major effort will be required to maintain this transparent and independent course at European level. This is not only shown by the example of sotagliflozin.

The objective of the pharmaceutical industry appears to take the course of intransparency that has been established with NICE across Europe as it becomes apparent in discussions between EUnetHTA and EFPIA (European Association of Pharmaceutical Industries and Associations).¹⁹

European benefit assessment must take the specific treatment situation of the individual countries or healthcare systems, respectively, into consideration

Understanding the term „European benefit assessment“ in the sense of the draft regulation of the EU Commission, this is associated with the following key objective: Preparation of a common assessment report that provides the basis for reimbursement decisions in the individual EU countries. The Commission distinguishes between clinical and non-clinical dimensions.⁵ The common assessment report shall be limited to the clinical dimensions, because reimbursement decisions lie within the responsibility of the national authority and also because from the EU Commission's point of view „non-clinical assessments are often more

Availability of oncological products recommended by the EMA in 2018 in selected

| Active ingredient | Indication | Availability | | | | | | |
|-------------------------|--|--------------|----|----|----|----|----|----|
| | | DE | NL | GB | FI | CH | BE | ES |
| Rucaparib | Ovarian cancer, fallopian tube cancer, primary peritoneal carcinomatosis | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ |
| Tisagenlecleucel | B-cell-lymphoma, acute lymphoblastic leukaemia | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✗ |
| Axicabtagene ciloleucel | B-cell-lymphoma | ✓ | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ |
| Neratinib | Hormone receptor positive breast cancer | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ | ✗ |
| Encorafenib | Malignant melanoma | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| Binimetinib | Malignant melanoma | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| Durvalumab | Non-small cell lung cancer | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Abemaciclib | Hormone receptor positive breast cancer | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| Brigatinib | Non-small cell lung cancer | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ |
| Apalutamid | Non-metastatic prostate cancer | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |

✓ Active ingredient available ✗ Active ingredient not available

Key: DE: Germany. NL: The Netherlands. GB: Great Britain. FI: Finland. CH: Switzerland. BE: Belgium. ES: Spain.

Source: All data according to analysis of WIP 1/2020 [21].

Figure 2: The varying availability of new oncology products demonstrate that uniform treatment standards cannot be assumed across Europe.

influenced by the respective national or regional context”⁵
 In a comment to the draft regulation, the German Medical Association criticises the classification of the assessment scope by the EU Commission:²⁰ „From a methodological point of view, the separation into clinical and non-clinical dimensions is artificial and ignores that HTA requires an overall concept in which the dimensions of the benefit assessment are clearly defined. This plays a significant role for both scope and content of the required literature and

evidence research, respectively.” In the next section it will be illustrated by the example of the comparative treatment why also the „clinical dimensions“, i.e. evaluation of the studies, can be significantly influenced by the respective national or regional context.
 From a pure German perspective (which is not the one of the IQWiG) it would be unproblematic if European evaluation reports corresponded exactly to the benefit assessments performed within the scope of the AMNOG proce-

ture. However, from the perspective of other countries it is not clear whether a specific AMNOG assessment can provide a suitable decision basis for local reimbursement decisions. Why is this the case and is necessarily different than it is handled during approval?

While the question „Can a pharmaceutical be used because it provides a larger benefit than it does harm?“ is addressed during approval, the question during benefit assessment is „(under what conditions) should the pharmaceutical be used, because a better treatment result can be expected as compared to the previous treatment options?“. Thus, the question of benefit assessment refers to the local (country-specific) situation. The consequences are obvious: An AMNOG assessment during which e.g. a new pharmaceutical with chemo-immunotherapy is compared, as it constitutes the present treatment standard in Germany, would be useless for countries, in which chemo-immunotherapy is not available.

Figure 2 illustrates the availability of oncology products recommended by the EMA in selected European countries in 2018 based on a current analysis of the Scientific Institute of Private Health Insurance (WIP).²¹ It is evident from this that across Europe uniform treatment standards cannot be taken for granted.

If the intention is to pursue the goal of using a common European assessment report as a basis for reimbursement decisions in the individual EU countries, this report must take local circumstances into consideration. Thus it is mandatory that such a report does not only cover one single question (comparison of a new pharmaceutical with any however selected comparative treatment), but also addresses the individual questions of all involved countries. And the result may be that comparative studies are available for the (common) question of some countries (because the comparative treatment selected by the pharmaceutical

country corresponds to the treatment standard in these countries), while no comparative studies are available for the (common) question of other countries. In these cases, it might thus be necessary to also provide indirect comparisons against the treatment standard of these countries.

But if European benefit assessment primarily implies – as sometimes noticeable – that dossier preparation shall be facilitated for the pharmaceutical company, the objective of a useful European benefit assessment is clearly missed.

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Current issues of the determination of reimbursement amounts

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The determination of reimbursement amounts by the arbitration board according to Section 130b Paragraph 5 SGB V is based on the (early) benefit assessment. Thus, for the arbitration board the question arises which consequences Europeanisation of Health Technology Assessments (HTA) would have on its work. Against this background, this article reflects ongoing arbitration and legal proceedings of the arbitration board.

According to Section 130b Paragraph 5 SGB V (5th German Social Codebook), the AMNOG Arbitration Board is not directly affected by the discussion about the potential Europeanisation of benefit assessments, because it only become active after the benefit assessment has been completed; moreover, it is generally bound to this assessment, thus does not perform a separate benefit assessment – at least not in a way as to correct an existing benefit assessment.

At the same time, certain competences of the arbitration board are unavoidable within the scope of pricing to specify benefit assessment decisions. This is particularly the case with inconsistent benefit assessment decisions or if the factual or legal situation has changed since the decision has been taken. Thus, the arbitration board is dependent on the benefit assessment decision and its transparency in various aspects.

For any considerations about a potential Europeanisation of benefit assessments it might therefore be interesting to take a closer look at the questions and problems that occur in the daily practice of the AMNOG Arbitration Board. For this purpose, we will subsequently outline the arbitration board's activities.

I. Organisation of the arbitration board

1. Composition of the arbitration board

With the Appointment Service and Care Act (TSVG) the recruitment mode of the arbitration board has changed since 2019: If pharmaceutical associations and the National Association of Statutory Health Insurance Funds (GKV Spitzenverband) cannot agree on an impartial chairman, he is no longer drawn by lot as in the past, but determined by the Federal Health Minister. However, the operators of the arbitration board did not want to show weakness that

would have resulted a further disempowerment of the self-administration by the Federal Ministry of Health and have thus appointed the author of this article as chairman

Organisation of the arbitration board

Composition of the arbitration board according to § 130b SGB V since 1 July 2019:

- Impartial Chairman: Huster (Kingreen) – previously Wasem (Rische)
- Impartial member: Fricke (Riederer – Nagels)
- Impartial member: Hansen (Kaesbach)
 - Note new regulation: in case of disagreement no longer drawn by lot as in the past, but determined by the FHM!

Source: Professor Stefan Huster



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of the arbitration board as of 1 July 2019 and Thorsten Kingreen – who is also professor at his Faculty of Law – as deputy. The other impartial members had already been active in the last term of office.

2. Update of the Rules of Procedure

One of the first acts of the arbitration board in the new term was to update the Rules of Procedure (GSchO). The impartial members who decide on the GSchO „in consultation“ with the operators of the arbitration board (Section 130b Para. 6 p. 2 SGB V) are responsible for this procedure. The update in autumn 2019 mainly included formal adjustments to take account of the changes in the legal framework conditions as well as practical requirements resulting from previous work and the office located at the GKV Spitzenverband; these were not controversial.

However, two particularities should be noted: On the one hand, the German Association of Pharmaceutical Importers (VAD e.V.) participated in the consultations of the GSchO for the first time as sponsoring organisation of the arbitration board. The VAD had enforced its role as of one of major national associations of pharmaceutical companies at federal level that have been established for the enhancement of the economic interests and thus one of the sponsoring organisations of the arbitration board (Section 130b Para. 5 p. 1 SGB V) before the Berlin-Brandenburg Superior State Social Court (LSG Berlin-Brandenburg). After the Federal Social Court had confirmed this decision, it was appropriate to involve the VAD, as there was a certain legal risk that – especially since the BSG decision – the arbitration board would no longer be able to take legitimate decisions without involving the VAD.

Meanwhile, the VAD has declared its consent to the BMG regarding the new composition of the arbitration board as of 1 July 2019 – which the VAD was not yet part of – so that

these legal concerns should have been dispelled now. At the next opportunity, the framework agreement according to Section 130b Para. 9 SGB V should be updated and re-adopted taking account of the VAD's involvement. The fact that other associations might represent non represented pharmaceutical companies and also seek the status of a „relevant major national association“, cannot be excluded, but is not apparent at present.

In addition, during the update of GSchO, a problem has been encountered that has been discussed over and over again within the scope of the AMNOG process, i.e. the question as to how confidential negotiations and results of the arbitration procedure can be. Although strict secrecy of the German reimbursement amounts would be favourable for all stakeholders, especially as these German prices serve as a global reference, it is difficult to ensure and would, however, present some kind of impurity in the self-administration of the GKV and could not be established so far.

However, the law stipulates that reimbursement negotiations and the arbitration procedure including discussion documents and transcripts are „confidential“ (Section 130b Para. 1 S. 7 and Para. 4 S. 7 SGB V). This provision that had become part of this law by means of the Structure of Health Care Act of the Statutory Health Insurance (GKV-VStG) – mainly to protect the trade secrets of pharmaceutical companies – was now mobilised, especially by health insurances, in order to restrict third party access to the arbitration awards.

Due to the fact that inspection of arbitration awards had always been possible – though complicated – at the office of the arbitration board according to Section 23, with the GSchO update an opportunity should be provided to send arbitration awards as files or even publish them on the new dashboard of the arbitration institutions at federal level (<https://www.schiedsstelle.de/>).

But this change was not approved by the BMG with reference to the confidentiality clause so that personal inspection still remains the only option. There were even discussions on whether the requirement of confidentiality does not preclude third party inspections. However, this might have created a problematic imbalance: For while the GKV Spitzenverband is involved in every arbitration procedure and is thus aware of all arbitration awards, it would have become rather difficult for pharmaceutical companies to inform themselves accordingly. Moreover, judicial control of a potential self-commitment of the arbitration board would also have been impaired.

II. Current arbitration proceedings

At present (as of 14 March 2020), the arbitration board has four ongoing requests. One request to the „old“ arbitration board regarding Alofisel®/darvadstrocel was processed without negotiation of the arbitration board; it related to the rather marginal question as to whether and to what extent the company is obliged to report its product including all necessary information to the relevant price and product directory according to Section 131 Para. 4 SGB V and framework agreement. The other four ongoing requests were only received by the arbitration board in the course of 2020 and will be outlined below.

1. Kigabeq®/Vigabatrin

This arbitration procedure is about a so-called PUMA pharmaceutical for children for the treatment of infantile spasms (West's syndrome) and refractory partial epilepsy. The company's request for exemption from early benefit assessment due to insignificance was unsuccessful (cf. Section 35a Para. 1a SGB V). The subsequent benefit assessment revealed that the product does not provide any additional benefit; the company didn't even submit a dossier.

Price negotiations between the company and the GKV Spitzenverband did not take place, because the company thinks that the whole benefit assessment process was not suitable for paediatric pharmaceuticals, if the PUMA-approval only relates to the child-friendly dosage form of an already approved active ingredient.

Against this background, the company contacted the arbitration board. In this case, the arbitration board is faced with a particular challenge, as legal provisions are addressed and criticised that are binding for the arbitration board and are not up for negotiation.

2. Rapiscan®/Regadenoson

This arbitration procedure that was initiated by request of the GKV-Spitzenverband involves a rather specific constellation. The product is a diagnostic agent, i.e. a pharmacological stress agent for myocardial perfusion imaging and measurement of fractional flow reserve. The company did not submit a dossier, because the product is not subject to the AMNOG procedure according to their opinion, as – although it received the new indication „measurement of fractional flow reserve“ – it had previously undergone method evaluation according to Section 135 SGB V. Thus, this case is about the relationship between the method evaluation and AMNOG procedure.

3. Tecfidera®/Dimethyl fumarate

This arbitration procedure is the result of a decision of the LSG Berlin-Brandenburg which will be discussed below. The pharmaceutical company submitted the request for the current procedure after the case before the LSG against the benefit assessment decision of the G-BA and the subsequent decision of the arbitration board had failed; the pharmaceutical which is approved for the treatment of relapsing-remitting multiple sclerosis had not

been granted an additional benefit by the G-BA. The court gave special consideration to the time of the assessment of the legitimacy of the arbitration board's decision.

The company considered the arbitration board's decision to be a continuous administrative act, so that changes should have been taken into account and proceedings referred to the time of the last oral hearing according to Section 48 of the Administrative Procedure Act (VwVfG). However – according to the general principles – the LSG considered the date of the authority's decision to be relevant for the rescissory action. However, the question then arises as to whether and to what extent changes of the factual or legal situation after the arbitration award can be implemented. The LSG's decision indicates that the AMNOG specific regulations on the potential termination of the reimbursement agreement might have superseded the general provisions of SGB X on the withdrawal and revocation of administrative acts. But then the question is what applies here. Meanwhile, the pharmaceutical used as appropriate comparative treatment had to be taken from the market due to a patent dispute. The „succeeding“ pharmaceutical is more expensive, so that the pharmaceutical company would naturally prefer to re-negotiate the reimbursement amount on the basis of the changed situation and has thus terminated the reimbursement negotiations extraordinarily. But was the company entitled to terminate? And if yes, according to which legal provision? Does the provision of unreasonableness of adherence to agreements (Section 59 SGB X) apply here? And if so, is adherence to the contract unreasonable? Does this depend on the regular term of the contract or the economic losses?

This presents an important preliminary question for the arbitration board: Does it consider the request inappropriate due to ineffective termination or do the parties have to enter into new price negotiations?

4. Erleada®/Apalutamide

This procedure is about a pharmaceutical indicated for the treatment of adult patients with non-metastatic castration-resistant prostate cancer who are at a high risk for the development of metastases; the product was granted a low additional benefit by the G-BA. In this case, besides the reimbursement amount, the relationship of the AMNOG procedure to the stipulation of reference prices is controversial.

III. Proceedings and decisions

According to Section 29 Para. 4 No. 3 SGG, the LSG Berlin-Brandenburg is responsible for lawsuits of the first instance against the arbitration board. In many cases, the legal issues are often only clarified by the Federal Social Court (BSG), especially as in case of the LSG two senates are responsible for proceedings against the arbitration board.

In the following section major judicial proceedings and decisions are outlined:

1. BSG of 4 July 2018 (B 3 KR 20/17 R – Eperzan®/Albiglutide)

With this decision, the BSG quite correctly rejected the concerns of the LSG Berlin-Brandenburg against the agreement or stipulation, respectively, of so called mixed prices and acknowledged that a mixed price is unavoidable, if a common price must be stipulated on the one hand, but the G-BA differentiates between patient groups with different additional benefit on the other hand. If the BSG had shared the scepticism of the LSG, the legislator would have been obliged to rectify, as the present price determination process is difficult to imagine without the instrument of the mixed price.

Such rectification would have been possible, and respective proposals were already available. This would have

been more complex in case of the second problem that was solved by the BSG. The LSG had annulled the arbitration board's decision, as it considered the justification for the monetisation of the additional benefit as insufficient. However, high justification requirements raise two problems for the arbitration board.

On the one hand, with the prices of comparable pharmaceuticals and prices in other European countries, the legal system contains certain legal requirements, but it doesn't provide any details on the central criterion, i.e. the extent of the additional benefit against the comparative treatment, and according to which standards this should be monetised. On the other hand, even if the arbitration board had developed a magic formula, there still has to be a majority for a decision, for the chairman or impartial members do not decide alone, but have to motivate one of the stakeholders to „participate“.

As a result, every price determination still has a negotiation momentum; the intention to represent and justify this pricing retrospectively as the one and only adequate price, rather tempts to hypocrisy. In this respect, too, the decision of the BSG will set the course for the future and should be welcomed: It provides a wider scope for the arbitration board and thus the necessary flexibility to reach compromises.

2. BSG of 8 August 2019 (B 3 KR 16/18 R – VAD)

It was referred to the BSG's decision about the German Association of Pharmaceutical Importers (VAD e.V.) as one of the major national associations of pharmaceutical companies at federal level – and thus sponsoring organisations of the arbitration board – that has been established for the representation of the economic interests.

3. BSG of 28 March 2019 (B 3 KR 2/18 R – Constella®/ Linacotide) and LSG proceedings L 1 KR 291/19 KL ZVW

With this decision of the BSG, a case was referred back to the LSG in which the central dispute is about the determination of the appropriate comparative treatment. The LSG objected the G-BA's benefit assessment decision in which no additional benefit had been granted to this pharmaceutical indicated for the treatment of irritable bowel syndrome with constipation (IBS-C), because the G-BA did not substantiate why psychotherapy or the respective costs, respectively, had not been considered within the scope of the comparative treatment. The BSGS took this scenario as an opportunity to point out clearly that neither the G-BA nor the controlling courts had an obligation to examine; with a view to the comparative treatment, only those contents must be considered that the pharmaceutical company outlined in the dossier. After the case was referred back to the LSG, the court requested the pharmaceutical company to put forward which documents he would have provided with the dossier, if he had been advised by the G-BA.

4. LSG Berlin-Brandenburg of 27 January 2020 (L 9 KR 82/19 KL – Tecfidera®/Dimethyl fumarate)

This decision of the LSG that was already mentioned above was mainly about the stipulation of the appropriate comparative treatment. In the benefit assessment decision, the G-BA juxtaposed three alternatives; it was argued whether these are interchangeable or are all necessary for different patient groups and treatment situations, so that a „small mixed price“ should have been stipulated for the determination of the costs of the comparative treatment.

The arbitration board did not accept this reference to an explanatory information by the G-BA. The LSG confirmed this opinion, as no clear stepped treatment regimen was

apparent here and thus dismissed the appeal of the pharmaceutical company. Moreover, the decision contains interesting statements on other specific questions of the AM-NOG procedure, i.e. on the time of the assessment of the legitimacy of the arbitration board's decision, the limits of the binding / binding obligation to the benefit assessment decision by the arbitration board and a potential forfeiture of the pharmaceutical company's right of action, if the agreed price had been agreed for a long time. The decision is not final, as the pharmaceutical company filed an appeal with the BSG (Ref. B 3 KR 3/20 R). Parallel proceedings with almost identical legal issues are still ongoing before the other senate of the LSG.

5. LSG Berlin-Brandenburg of 27 January 2020 (L 9 KR 5614/15 KL – Betmiga®/Mirabegron)

With this decision that was taken on the same day by the same senate as the decision mentioned above, another case of a pharmaceutical company against an arbitration award was rejected. It was about a pharmaceutical without any proven additional benefit indicated for the treatment of urinary urgency and urinary incontinence. The reasoning is not yet available.

IV. Conclusion: Arbitration board and Europeanisation of HTA

Considering the arbitration board's activity against the background of the discussion about a potential Europeanisation of HTA, it becomes clear that a governance problem of the AMNOG procedure could be solved with Europeanisation: It is certainly not an optimal decision design, if the GKV-Spitzenverband is involved in the decision about a potential additional benefit in the G-BA for pharmaceuticals for which it later negotiates the price and pays for. Even if the final assessment remains with the authorities of

the member states in case of a Europeanisation of HTA, a potential conflict of interest (or the mere appearance of such a conflict) could be avoided by concentrating powers of HTA at a higher level (also known as Hochzonung).

On the other hand, another central problem of the arbitration board's work wouldn't be solved by HTA Europeanisation, i.e. frictions at the interface between benefit assessment and pricing. It remains one of the constant challenges of the arbitration board to adopt a position on benefit assessment decisions, especially on the determination of an appropriate comparative treatment including costs, as the overview of current procedures has shown. It may well be doubtful whether Europeanisation – which means moving even further away from the circumstances of the respective national healthcare system – will simplify the arbitration board's work. Consequently, Europeanisation remains an ambivalent process from the arbitration board's point of view.

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¹ LSG Berlin-Brandenburg, decision of 24 May 2018, L 9 KR 303/15 KL

² see III. 2.

³ cf. Huster S/Kalenborn T (2012): „Transparenz und Selbstverwaltung: Wie diskret können die Arzneimittelpreise in der GKV behandelt werden?“ (Transparency and self-administration How discrete can pharmaceutical prices be handled in GKV?). Neue Zeitschrift für Sozialrecht: 881-884.

⁴ Justification cf. BT-Drks. 17/6906, p. 86.

⁵ cf. below under III. 4.

⁶ LSG Berl-Brdbg, decision of 27 January 2020, L 9 KR 82/19 KL, p. 36 f.

⁷ As previously Huster S (2017): „Mischpreis und Nutzenmonetarisierung. Die neuere Rechtsprechung zum AMNOG-Verfahren“ (Mixed price and benefit monetisation. Recent legislation on the AMNOG procedure). Neue Zeitschrift für Sozialrecht: 681-686.

⁸ cf. above under I.2.

⁹ LSG Berl-Brdbg, decision of 25 January 2018, L 1 KR 295/14 KL.

¹⁰ cf. as above under II.3.

¹¹ Proceeding L 1 KR 218/18 KL (Aubagio®/Teriflunomide).

¹² cf. above under II. and III.

Arbitration board and Europeanisation of HTA

I. Governance problem:

National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) participates in the decision about the additional benefit **and** negotiates dependent price

→ European Health Technology Assessment principally a reasonable solution

II. but: key problems of the AMNOG procedure are:

- Determination of the appropriate comparative treatment
- Extent of binding of pricing to the G-BA decision

→ especially these aspects are not solved by a Europeanisation process, but might even be aggravated by it

The technical obstacles have been determined – EU states must show political colours

By Dr Florian Staeck

Even more than two years after the publication of the draft regulation by the EU Commission in January 2018, the prospects of a joint European benefit assessment are still hardly identifiable, as the impacts and implications of a European harmonisation on the member states are not predictable, as long as no consensus has been reached on the central political course – first in the European Council – and then between the 27 governments.

In a second step, the partly different conceptions would have to be harmonised within a so-called triad between the Council, European Parliament and EU Commission. In particular, in view of Germany's EU Council Presidency which begins on 1 July 2020, an agreement should have been reached by the end of 2020. But the Corona pandemic has led to a drastic shift in political priorities both nationally and across the EU, so that currently – in spring 2020 – a successful negotiation outcome is not yet foreseeable.

Against this background, participants of the 11th meeting of the „Interdisciplinary Platform on Benefit Assessment“ on 13/14 March 2020 discussed about the prospects of a European benefit assessment under the title „European HTA: Advances and Pitfalls“. This year's event in Fulda addressed the meaningful topic of a planned European benefit assessment which had already been a topic in Volume 8 of this series in autumn 2018.

Participants reported that extensive negotiations on EU level since the presentation of the draft regulation brought about fundamental differences regarding the scope and design of a EU-Health Technology Assessments (HTA) and the legal validity and binding force, so that hardly any negotiation progress was recognisable at present. In February 2018, when four member states imposed a subsidiarity objection, it became apparent how controversial the Com-

mission's proposal was received. As a result of its consultations, the EU Parliament returned behind the EU Commission's proposal currently taking a moderating role between the Commission and the Council of Heads of State and Government.

Highly significant legal basis

The question as to which legal basis will be chosen for the regulation is of central importance for the negotiations. If it was based on Article 114 AEUV only, this would imply imposing legal obligations for the member states. If it was, however, based on Article 168 AEUV, this would provide a more cautious competency framework. A paper that was agreed by and brought into the negotiations by Germany and France chooses a middle way citing both legal bases – a procedure which had also been used in the Patient Mobility Directive (DIR 2011/24/EU).

Participants reported that a compromise seemed to be emerging in the negotiations about the scope of the regulation, while a political agreement on this key question was still pending. In its proposal of January 2018, the Commission wanted to include all newly approved pharmaceuticals and certain high-risk medical devices. Germany and France were now promoting a selection of approximately ten pharmaceuticals per year that might be subject to the regulatory regime of EU-HTA. They reported that there seemed to be a focus on individual indications, especially cancer. Another controversial question in the negotiations was how the assessment at the end of the EU-HTA shall be designed – as a decision-preparing step or as a decision. Participants pointed out that this was associated with legal issues, e.g. the binding force of decisions taken at EU level.

While the Commission initially only wanted to allow minor and clearly defined national deviations within the scope of a safeguard clause procedure, „weaker“ formulations

were now taken into consideration increasing the scope of action of the member states.

This caused major concern, mainly on the part of the pharmaceutical industry, as they fear that deviations from the EU-HTA might become the rule rather than the exception. Participants warned that this would inevitably lead to a significant duplication of work, as in addition to the European assessment the previous dossier would still be required for the national HTA procedure. In the course of the discussion it became apparent that the initial positive assessment of the Commission's first proposal by pharmaceutical companies had now turned into increasing scepticism.

There were extensive discussions about the prevailing uncertainty with regard to the legal character of the EU-HTA. A report as a merely technical assessment could only replace the IQWiG report for the Federal Joint Committee (G-BA) in Germany, while national appraisal procedures would remain unaffected. Participants who are familiar with EU law referred to the procedure of economic policy coordination – the Lisbon process – as a possible variant. Although these country-specific recommendations had no legal binding force for the member states, they provided a useful orientation. This could be a compromise to solve opposing positions between countries pleading for legally binding EU-HTA procedures and those requesting consideration of national particularities.

The European Centre for Disease Prevention and Control, ECDC) was one example how these assessments could in future impact national procedures. Recommendations by this European epidemic authority were formative and would be adopted by the majority of the member states.

Potentials of voluntary cooperation exploited

Participants of the meeting agreed that the potentials of the experimental voluntary cooperation within the scope

of EUnetHTA since 2006 have now reached their limits. Against this background, a legislative process with a stronger legal binding force of the current process was considered inevitable. In many areas, EUnetHTA's work was determined by resource shortages.

This was for example the case for the process of early dialogues with pharmaceutical companies submitting applications – at present, EUnetHTA's capacity limit was reached at 1.5 dialogues on average per month and they could not keep up with demand at present. Further bottlenecks would arise as a result of the lack of precise predictions as to when the vote of Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) would be given. For during this period, EUnetHTA would have to hold already scarce human resources ready to be able to start working on the assessment. They considered it a structural deficit of EUnetHTA's previous work that applying pharmaceutical companies could not be forced to disclose data they don't want to become public.

Thus, the current approach could not ensure data completeness, a fact that was unacceptable e.g. for the German system. Typically, only 50 percent of the data required for benefit assessment were publicly accessible. By contrast, the AMNOG procedure created transparency. Participants were also critical of the fact that the EU-Parliament – in contrast to the Commission's proposal – wanted to allow the applying company to remove „commercially sensitive“ information from the data body prior to the assessment process.

Previous experiences with EUnetHTA procedures had shown that the pharmaceutical company had not deleted or redacted data on production processes, but clinically relevant data. Participants pointed out that this information was in fact relevant for the treatment of patients. They war-

ned that – extrapolated to the future – this would drastically limit the usability of European assessment reports in the German treatment context.

It was of vital importance for the implication of future EUnetHTA reports that these take a European perspective and do not primarily reflect country-specific needs of the rapporteurs. This applied centrally to the selected comparator in the assessment report.

Moreover, treatment situations were partly extremely heterogeneous among the member states – for example regarding the application of CAR-T cells in oncology. Moreover, participants reported that availability of other oncology products that have been newly approved by the EMA in 2018 and 2019 varied drastically between the member states. They warned that this fact would have to be taken into account, because otherwise the joint assessment report of the EUnetHTA would not sufficiently address questions asked in the national context of individual member states.

Much improvement would still be needed here – e.g. a timely PICO process before the development of the approval study was still in its very early stages reflecting the diverse treatment situations in the EU-27. They suggested that it might be useful if the early advice focussed on EUnetHTA's level while the member states stepped back in this process. Regarding the comparator to be selected, they argued that clusters should be formed reflecting two or three variants of the heterogeneous treatment situation rather than performing a PICO process with 27 modifications.

Reports only completely adopted by four countries

It will be a tightrope walk to find the right balance between European streamlining in the preparation of the assessment reports and individual national requirements.

Participants reported that HTA reports by the EUnetHTA had only been adopted one-to-one by four member states. In case of doubt, national HTA bodies could request an additional dossier – a process that might take the pharmaceutical company up to one year. Companies would require long lead times to anticipate which resources they will have to provide in future in order to support both the German and European HTA procedure in parallel.

Other participants pledged for a „less autonomous“ design of the EU-HTA process to avoid running the risk to lose contact to professional associations as well as orientation on guidelines and the state of knowledge. As a consequence, the assessment might result in decisions that are too far away from the patient. Other participants replied that the Commission's proposal stipulated the hearing of experts. They reported that the final design of this process as an explicit consulting right would, however, be discussed controversially in the working groups. Clinical representatives emphasised that e.g. for the determination of comparative treatments, professional associations needed to be more involved beyond a mere hearing.

The major task of the whole EUnetHTA process should be to prepare the system in the best possible way for the „new world“ of EU-HTA as of January 2024. Against this background, they perceived with great interest that a fourth project-based funding of EUnetHTA beyond 2021 was in fact within the range of the possible. Financial resources of the Commission had already been budgeted for this purpose. In general, joint action programs were only prolonged three times, but in the present case, the cooperation within the scope of EUnetHTA was considered that positive that a continuation of the program beyond 2021 was anticipated.

As previously, participants discussed controversially other elements of a future EU-HTA regulation (see summary

of the discussions in Volume 8 of this series):

- **Confidentiality:** Participants referred to the possibility for manufacturers to submit data confidentially to the EMA and individual national HTA bodies so that these would not be included in the joint assessment report. So far, EUnetHTA had not been able to agree on framework specifications on confidentiality with its members. However, other participants emphasised the importance of comprehensive data sets. It should not be permissible that study results that were relevant for both patient and physician are confidential. An assessment report without disclosing its data sources would not allow for a comprehensible assessment.
- **Surrogate endpoints:** Participants critically reflected on several procedures for early benefit assessments in Germany during which the primary surrogate endpoint of the studies was considered not sufficiently relevant. Even after several years of discussion, the disagreement over the status of surrogate endpoints had been reduced, it remained basically unsolved. This dispute was sparked by the fact that different standards were used for approval and HTA procedures. Participants emphasised that a positive benefit risk balance was one basic prerequisite: no approval without evidence for a patient-relevant benefit. However, others were convinced that a consistent view on surrogate parameters during approval and HTA could only be achieved during a joint „learning curve“.
- **Patient relevance:** The significance of patient-relevance in the separate processes of approval and HTA was similarly controversial. Given the very tight time frame allowed for assessment reports, it was mandatory to focus on data that are relevant for the national healthcare systems. The codification of patient relevance in the SGB V was not helpful – it would still be a normatively

loaded statement that couldn't be derived from the exegesis of the German Social Codebook.

- **Comparative treatment:** There was also a clear disagreement about the determination of the appropriate comparative treatment. Participants said, that from a clinical viewpoint, both the recommendations in the clinical guidelines and respective treatment realities should be given major consideration.

Individual participants urgently called for an alignment of the assessment criteria during approval and HTA procedures and avoidance of duplication of work in both steps to achieve a consistent EUnetHTA process. In case of similar questions, HTA bodies could build on what approval authorities had already submitted, e.g. in referencing preclinical data. It was important to assess available data using consistent criteria to establish standards on the appropriate handling of evidence.

FDA promotes rapid availability by means of cooperation

Participants stated that there was no time for national navel gazing referring to the „Orbis“ project initiated by the US Food and Drug Administration (FDA). This cooperation of several national authorities comprises a parallel assessment of first approvals or indication extensions for oncology products in order to make these pharmaceuticals available more quickly. Besides the FDA, approval authorities from Australia, Canada and Singapore participate in this project, and in March 2020 Swiss Medic joined the project. Participants assumed that sooner or later – in the course of leaving the EU – Great Britain would probably also participate in „Orbis“.

Together with its partners, the FDA is committed to promoting a rapid decision-making practice for new pharmaceuticals. Against this background, the EU-27 with their

rather cautious-reluctant HTA practice would have to face a growing global trend. The intended regulation for EU-HTA would thus also reflect the attempt to set common standards for the assessment of evidence. Participants outlined that this could, however, only be successful if the member states that together represent the globally second largest market also acted homogeneously. A rapid market access would not be consistent with HTA principles without sufficient evidence of a patient benefit.

In March 2020, a failure of the HTA proposal in the European Council still seems possible irrespective of these global influences. Similarly, the Commission might veto against a significantly changed proposal of the Council. But participants were still convinced that this would be a severe setback for the dynamics of European integration in the area of pharmaceuticals and medical devices.

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IMPRINT**PUBLISHER**

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Springer Medizin Verlag GmbH
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MORISSE / Stock.Adobe.com
Blister: seen / Stock.Adobe.com
Stars: sba

LAYOUT/GRAPHICS

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PRINT

F&W Druck- und Mediencenter GmbH
Holzhauser Feld 2, 83361 Kienberg

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Berlin, September 2020

 Springer Medizin

In cooperation with and with the
kind support of AbbVie Deutschland
GmbH & Co. KG, DAK Gesundheit,
MSD Sharp & Dohme GmbH,
Novo Nordisk Pharma GmbH, Roche
Pharma AG, Verband Forschender
Arzneimittelhersteller e.V.,
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INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

European HTA Procedure: Advances and Pitfalls

Volume 11
September
2020