



Publication series

INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT

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European Benefit Assessment – Opportunities and Risks

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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

Daring more Europe – Also a motto for the benefit assessment?

By Professor Jörg Ruof

On 15 January 1996, the European Medicines Agency (EMA) – which had been founded in the previous year – published its first General Report. In his foreword, the then chairman Strachan Heppell describes the two central characteristics of the newly established institution:

- i) „The protection of public (...) health and the strengthening of the European single market;
- ii) It is co-ordinated and managed at the centre by the Agency. But the assessment work is carried out by European experts designated by Member States drawing on the experience and expertise of national regulatory agencies.“

The consequence was the standardisation and streamlining of the heterogeneous national approval procedures that partly took up to six years; a success which is widely accepted today.

Parallels to the European Commission's current proposal for a stronger networking and bundling of European competences in Health Technology Assessment (HTA) are obvious. Essentially, the objective is to strengthen the Single European Market in the global competition while ensuring a consistent and appropriate HTA assessment. The current 51 HTA bodies across Europe present significant methodical and procedural heterogeneities.

The present publication series of the Interdisciplinary Platform on Benefit Assessment deals with the current European legislative process on this topic from different perspectives. The thematic spectrum ranges from presenting the European Commission's proposal and the position of the various national stakeholder groups that are involved in the process (G-BA, GKV-SV, KBV, IQWiG, vfa) to summarising the position from the perspective of German politics. One guest paper illustrates the French perspective and ex-

periences and rounds off the national articles:

- In the first article, Anna-Eva Ampelas and Julia Schmitz provide a comprehensive overview of the European Commission's proposal, contentual working priorities as well as the organisational framework.
- The article of Mondher Toumi, Tina Röhricht and Bruno Falissard addresses both strengths and optimisation potential of the French HTA-assessment. The overall picture is that of a functional and robust national HTA system, although a duplication of assessments with the resulting inefficiencies can also be observed in various processes within the Haute Autorité des Santé.
- Antje Haas and Michael Ermisch illustrate the perspective of the National Association of Statutory Health Insurance Fund (GKV-SV) on the European benefit assessment. The emphasis is placed on a constructive participation in the ongoing process. The question is not as to whether European benefit assessment will be introduced, but rather how it will be introduced, from the GKV-SV's perspective with a strong subsidiary focus.
- From the G-BA's perspective, the European Commission's proposal must be looked at critically. Assessment and appraisal should be clearly differentiated and the significance of separate assessments based on the national care landscape needs to be clarified. Moreover, according to Antje Behring, the collaboration within the Coordination Group should be optimised.
- Wiebke Löbker and Karl Broich then provide an overview of the development and operating principle of the European Medicines Agency EMA. They will illustrate some of the many challenges that come along with this European process of harmonisation as well as potential learning effects that could also be useful for the harmonisation of HTA procedures.
- The two final articles cover the industry's perspective

and national political perspective. Han Steutel makes clear that the research-based pharmaceutical companies support the European Commission's proposal emphasising the creation of synergy effects and patient benefit. Time synchronisation of benefit assessments also in other countries could make innovative products available to patients at an early stage.

- From a policy perspective, the commission's proposal came like a thunderbolt they had not really expected and now have to face constructively. From Michael Hennrich's point of view, scientific independence, highest evidence criteria and national autonomy in the determination of prices are the framework conditions for a successful European Health Technology Assessment.

The present publication series and the summary of the discussion at the platform meeting provide a comprehensive overview of the challenges and chances, if we want to – like the current coalition agreement of SPD and CDU/CSU at federal level calls it – „dare more Europe“ in Health Technology Assessment.

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Strengthening EU cooperation on Health Technology Assessment

Anna-Eva Ampelas and Julia Schmitz, European Commission

The European Commission has put forward a proposal for a regulation to strengthen EU cooperation on health technology assessment (HTA). The proposed regulation provides a legal and organisational framework for structured and sustainable HTA cooperation. It aims to ensure the production of high quality and timely outputs that are used in national HTA systems. Joint work will be driven by member state HTA bodies and focus on common scientific, clinical aspects of HTA. Specific areas of cooperation include joint clinical assessments of medicines and medical devices, and joint scientific consultations to advise technology developers on evidence requirements for HTA. Strengthened EU cooperation on HTA is expected to benefit member state HTA bodies and decision-makers, patients across the EU and the health technology industries. The proposed regulation is currently in the legislative process involving the European Parliament and the Council.

Current project-based EU cooperation on health technology assessment (HTA) at scientific-technical level has been ongoing for more than 20 years, in the form of EU-funded projects such as the Joint Action EUnetHTA¹. Such project-based cooperation has facilitated networking among HTA bodies across the EU. It has also enabled the piloting of joint work, e.g. on methodological guidelines², early dialogues with technology developers³, and joint clinical assessments (so-called relative effectiveness assessments⁴). In addition, since 2013, the HTA Network established under the Cross-border Healthcare Directive (Directive 2011/24/EU) has provided a forum for policy-strategic discussions on HTA, which have resulted in strategy and reflection papers⁵.

However, the current project-based cooperation model has faced a number of limitations, in particular limited use of joint work in national HTA processes. Low uptake of joint work in national HTA systems is due to several factors, including legal/administrative hurdles and concerns around quality assurance, timeliness and sustainability of work produced in a project setting⁶.

European Commission proposal for a Regulation on HTA

In January 2018, the European Commission put forward a proposal for an EU regulation on HTA⁷. The proposed regulation provides a legal framework for strengthened and sustainable EU cooperation on HTA and aims to address the shortcomings of the current project-based cooperation. In this regard, a number of key principles for strengthening EU HTA cooperation have been identified⁶, which are summarised in Figure 1 and further elaborated in subsequent sections of this article.

The proposed Regulation focuses on joint work on com-

mon scientific, clinical aspects of HTA. Joint work will be driven by member states HTA bodies, in an organisational framework which includes an over-arching member state coordination group and several subgroups for different technical areas of work (Figure 2). Member states will designate their authorities/bodies responsible for HTA as members of the coordination group and its subgroups. Subgroups will prepare the technical work in the different areas, and all outputs will be approved by the coordination group. A stakeholder network will enable stakeholder associations with an interest in HTA (e.g. healthcare providers, payers, patient organisations, industry associations, scientific societies) to exchange views with the coordination group on cooperation activities. The European Commission will provide the secretariat to the EU cooperation.

Leitprinzipien verstärkter Zusammenarbeit auf EU-Ebene im Bereich HTA

- Gemeinsame Arbeit an wissenschaftlichen, klinischen Aspekten der HTA
- Gemeinsame Arbeit der HTA-Institutionen der Mitgliedstaaten
- Hohe Qualität, Aktualität und Transparenz sicherstellen
- Verwendung der gemeinsamen Arbeit bei nationalen HTA-Prozessen sicherstellen
- Mitgliedsstaaten bleiben verantwortlich für:
 - Schlussfolgerungen zum Zusatznutzen für ihr Gesundheitssystem
 - Entscheidungen zur Preisgestaltung & Erstattung
- Schrittweise Umsetzung

Quelle: Europäische Kommission

Figure 1: The planned HTA regulation shall make European cooperation more sustainable.



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Dr Julia Schmitz is a Policy Officer in the Unit „Medical Products: quality, safety, innovation“ in the Directorate-General for Health and Food Safety of the European Commission. Her work focuses on the development and implementation of EU policies related to Health Technology Assessment (HTA). Her background is in biomedical science, public health and health policy.

Joint clinical assessments

Joint clinical assessments will be conducted for centrally authorised new medicines (new active substances and new therapeutic indications thereof) and for certain high-risk medical devices. Progressive build-up of the system will be facilitated by a transition period of three years, during which the number of assessments is expected to gradually increase.

Joint clinical assessments will be prepared by Member State HTA bodies, which will have technical staff representing them in the respective subgroup (see Figure 1). The scope of the assessment in terms of the patient population (including patient subgroups), the health outcomes and the comparators that are relevant for the different member states will be jointly agreed before the start of the assessment. For each assessment, the drafting will be led by two HTA bodies, which will be selected based on appropriate expertise and capacity. All other HTA bodies will be able to contribute their input and comments during the preparation of the joint clinical assessment report. In addition, external clinical experts and patient experts will be able to provide specialist input, e.g. on the particular therapeutic area concerned. Detailed procedural rules for the conduct of joint clinical assessments will ensure that joint clinical assessments are prepared in a consistent, quality-assured and timely manner.

Joint clinical assessment reports will provide a scientific analysis of the clinical effects observed (e.g. on mortality, specific disease symptoms, adverse events and health-related quality of life). The report will also discuss the strengths and weaknesses of the underlying evidence and any scientific uncertainties.

Member States shall use joint clinical assessment reports in their national HTA processes. They may complement the joint clinical assessment with more context-specific analy-

ses conducted at national level, e.g. related to the specific epidemiological and healthcare context, economic aspects such as costs and budget impact, or social and ethical issues. Depending on the national HTA framework, member states may consider criteria such as the severity of the disease, the rarity of the disease, or the lack of alternative interventions when drawing conclusions on the added value of a health technology for their healthcare system. Member states shall remain responsible for drawing their own conclusions on the added value of a health technology in the context of their healthcare system. They also remain responsible for any subsequent decision-making related to pricing and reimbursement.

Other areas of joint work

Another important area of joint work provided for by the proposed regulation are joint scientific consultations, which enable technology developers to seek advice from HTA bodies on evidence requirements already during the development stage of products. Joint scientific consultations are expected to provide advice on the design of clinical studies (e.g. in terms of comparators, endpoints and health outcomes), in order to facilitate the generation of appropriate evidence for HTA purposes. Joint work in this area will build on the experience gained with so-called „early dialogues“ under EUnetHTA³. For medicines, developers will be able to seek advice in parallel from HTA bodies and the European Medicines Agency (EMA), building on ongoing collaborative work by EUnetHTA and EMA⁸.

Moreover, the proposed Regulation will enable joint work on the identification of emerging health technologies. Such „horizon scanning“ activities (e.g. reviews of the product development pipeline in particular therapeutic areas) can help HTA bodies to be better aware of new technologies which may in the future reach the market and

have a significant impact on healthcare systems.

Joint work will also include the development of common guidance and working documents (e.g. on methodological issues), as well as cross-cutting activities such as the preparation of annual reports and work programmes.

Member States may choose to cooperate on other HTA-related areas, depending on priorities and interests. This could include assessments of technologies other than medicines and medical devices, or joint work on non-clinical aspects of HTA (e.g. methods for economic evaluation). Involvement in such activities would be on a purely voluntary basis.

Expected benefits of strengthened EU cooperation

The proposed Regulation is expected to bring benefits for all EU member states, for patients across the EU and for the health technology industries.⁶

HTA bodies across the EU will be able to pool their resources and expertise, resulting in quality and efficiency gains in the preparation of work on clinical aspects of HTA. Joint scientific consultations conducted at EU level are expected to give European HTA bodies more influence on the design of (often global) clinical trials, promoting the generation of appropriate evidence for HTA. Moreover, requirements for dossiers to be submitted by industry will ensure that HTA bodies have access to the relevant clinical evidence when conducting joint clinical assessments. Joint clinical assessments will result in high quality, timely scientific reports, which will be used in national HTA processes and support evidence-based decision-making at national level.

Patients across the EU will benefit from increased transparency, as joint clinical assessment reports and other joint outputs of EU HTA cooperation will be publicly available. Patients will also benefit from involvement in the HTA pro-

cess, for example by providing input on their experience of a particular disease (e.g. disease symptoms and related quality of life) as part of the joint clinical assessment process.

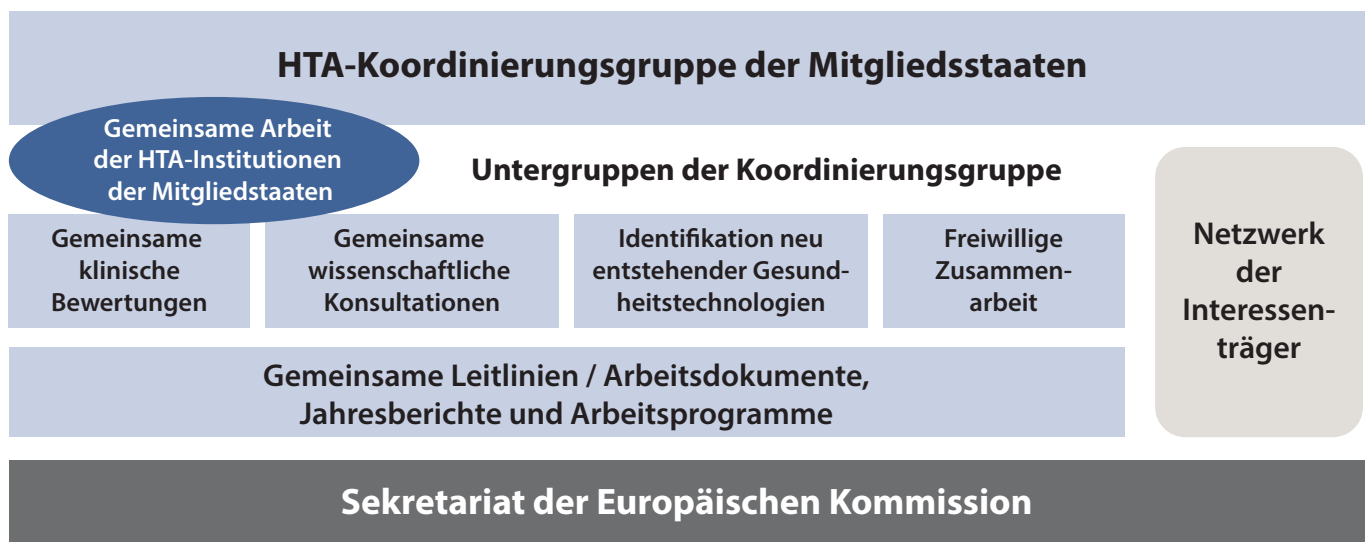
Patient access to health technologies depends on many factors and related decision-making (e.g. on reimbursement) remains the responsibility of member states. The proposed regulation will support timely, evidence-based decision-making at member state level, and is thereby expected to contribute to the objective of improving patient access to truly innovative health technologies across the EU.

Health technology industries will benefit from more clarity on evidence requirements for HTA across the EU, as a result of the joint scientific consultations with HTA bodies. Industry is also expected to benefit from efficiency gains in the preparation of HTA dossiers, as only one single dossier will be required for the joint clinical assessment conducted at EU level.

High scientific quality of joint work is a key aspect of EU HTA cooperation. Factors that contribute to high quality have been considered in the proposed Regulation, including the following:

- Availability of appropriate evidence for HTA (dossier requirements for joint clinical assessments; joint scientific consultations on clinical study design);
- Pooling of expertise across HTA bodies;
- Selection of HTA bodies with appropriate expertise/capacity as lead assessors;
- Specialist input by external experts (e.g. therapeutic area expertise of specialised clinicians and patients);
- Rules to avoid conflicts of interest and ensure scientific independence;
- Transparency (publication of joint outputs, procedural rules, annual reports etc).

Organisatorischer Rahmen



Quelle: Europäische Kommission

Figure 2: Overview of the planned organisational framework for the strengthened HTA cooperation at EU level.

It should be noted that some Member States have established national HTA systems with significant expertise and capacity and high standards of quality, scientific independence and transparency, while other Member States currently have more limited resources and capacities for HTA⁶. EU HTA cooperation aims for „upwards convergence“, i.e. highest standards of scientific quality, independence and transparency across the EU, building on current best practices among Member States. The legal framework, organisational structure and financial support provided for by the proposed Regulation will all contribute to this objective. It is also expected that Member States with advanced HTA systems will play a leading role in the joint scientific work (e.g. as lead assessors for joint clinical assessments), particularly in the beginning of the cooperation,

while Member States with currently less advanced HTA systems will be able to build up their HTA capacity over time.

Legislative process and next steps

In order to enter into force, the Regulation will have to be adopted by both the European Parliament and the Council of the EU. The European Parliament, in October 2018, adopted amendments to the Commission proposal and indicated its readiness to start inter-institutional negotiations with the Council⁹.

In the Council, initial discussions started under the Bulgarian Presidency (January-June 2018), but a full reading of the Commission proposal was only conducted under the Austrian Presidency (July-December 2018). The Austrian Presidency also proposed a compromise text with

amendments to Articles 1-8 of the Commission proposal and concluded with a progress report¹⁰. Discussions are continuing under the Romanian Presidency (since January 2019).

Once the Regulation is adopted by European Parliament and the Council and enters into force, it will apply only three years later. Following the date of application, a transition period of a further three years will enable a gradual build-up of the volume of joint work (e.g. a gradual increase in the number of joint clinical assessments). This timeline for progressive implementation was proposed by the European Commission to give both Member States and industry sufficient time to prepare for and adapt to the new system of EU cooperation.

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Strengths and weaknesses of HTA at the Haute Autorité de Santé

Professor Mondher Toumi, Tina Röhrich, Professor Bruno Falissard

In recent years, the Haute Autorité de Santé (HAS) has established a stable and well recognised system for Health Technology Assessment (HTA). Although the decision framework is outlined in guidelines by the agency, the system is continuously evolving. As a result, new processes are not disclosed sufficiently and thus pricing and reimbursement decisions within the HAS are not transparent for the manufacturers of pharmaceutical products. Analysing previous HAS pricing and reimbursement decisions facilitates the understanding about the underlying factors that play a role in the final decisions. This article provides an overview of the complex decision framework within the HAS, discusses its strengths and weaknesses as well as potential future challenges.

Introduction

The Haute Autorité de Santé (HAS) is a French governmental agency created in 2004¹, which hosts the French Health Technology Assessment (HTA) system for pharmaceuticals through two committees, the Commission de Transparence (TC) and the Commission d'Evaluation Economique et de Santé Publique (CEESP).

While TC is a historical committee existing in the drug medical agency (ANSM), the CEESP is more recent. The TC assesses the clinical evidence² while the CEESP assesses the economic evidence³.

When a product is recommended for approval by the European Medical Agency⁴, the EU commission issues a marketing authorization (MA). The MA will be transposed at the national level by the ANSM^{5,6}.

Then, in order to obtain reimbursement, the manufacturer files a technical dossier to the TC, and eventually to the



Prof. Mondher Toumi is physician, MSc of Biostatistics, MSc of Biological Sciences (option Pharmacology), and PhD of Economic Sciences. He teaches as a professor for Public Health at the Aix-Marseille University and is guest professor at the University of Beijing. After many years of work in the Department of Pharmacology at the University of Marseille, he worked in the pharmaceutical industry from 1995 to 2008. In 2008 he founded the consulting company Creativ-Ceutical.

CEESP, if the product qualifies for the economic assessment. The pricing dossier should be filed in parallel to the French pricing committee (CEPS). (Figure 1)

The TC assesses the evidence and, within a deliberative process, concludes the assessment with 3 main statements/scoring: The actual benefit (AB) in French known as SMR (Service Medical Rendu), the improvement in actual benefit (IAB) in French known as the ASMR (Amélioration du service medical rendu) and the size of the target population for reimbursement^{7,8}.

The AB score drives the reimbursement, the IAB drives the price and the target population drives the price volume agreement. The first is set by the union of national French insurances and the two last by the CEPS. A decree from the Minister of Health will be issued including the price and reimbursement level and will be published in the French official gazette.



Tina Röhricht obtained her Master of Science in Health Economy, Politics and Law at the Erasmus University in Rotterdam, Netherlands. She works with Professor Mondher Toumi in the Price and Market Access team of Creativ-Ceutral. She focusses on primary research with payers for various indications and advises international pharmaceutical companies regarding the peculiarities of the German pricing and reimbursement landscape.



Professor Bruno Falissard studied medicine and specialised in Child and Adolescent Psychiatry. His doctorate in Biostatistics was followed by a post-doctorate in Psychometrics and Multidimensional Screening Procedures. In 1996/97, he was Assistant Professor for Child and Adolescent Psychiatry, from 2002 to 2002 Associate Professor and from 2002 Full Professor for Public Health. He heads the Master's Course in Public Health at the University of Paris and the Centre for Epidemiology and Public Health.

2. The Transparency Commission

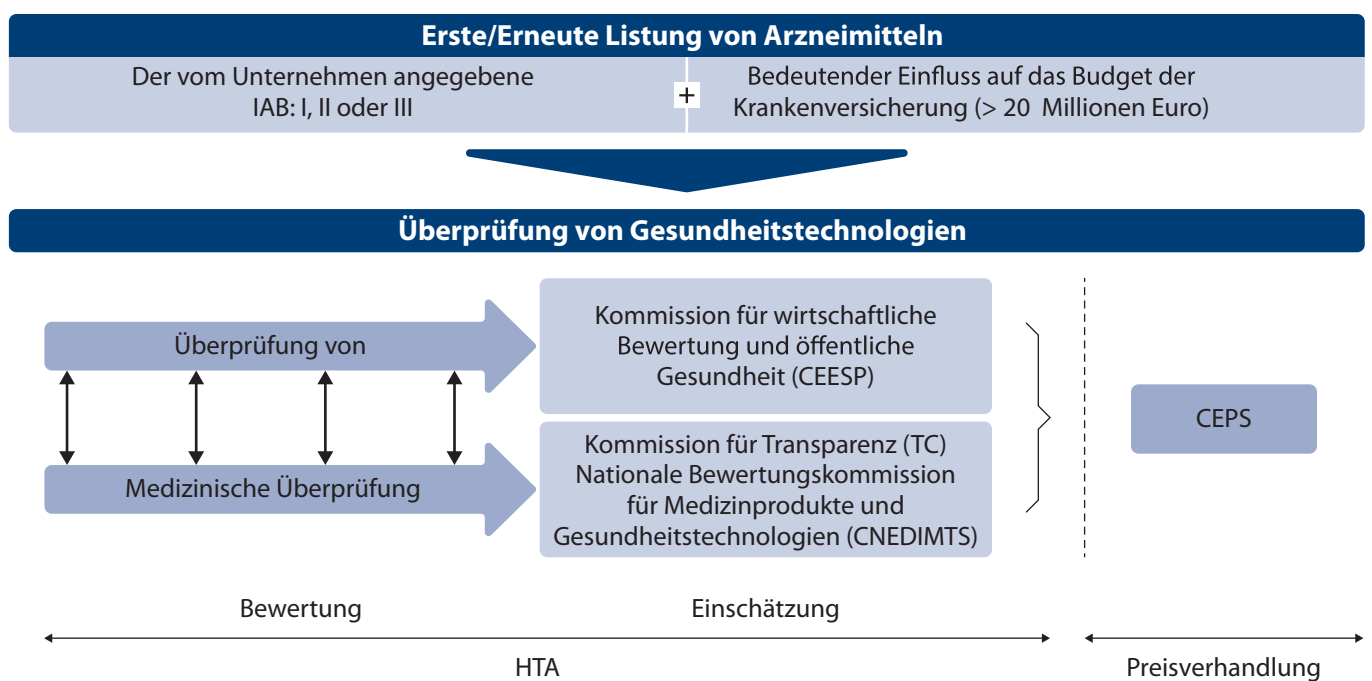
The TC reviews the clinical evidence in parallel of the CEESP when the product is eligible for an economic evaluation. A broad range of case law has overtime created a basis for interpretation of specific situations and provides the TC room to maneuver. The HAS philosophy is to decide on reimbursement based on the intrinsic value of the product outside of any comparison while the price is driven by the additional benefit over the next best alternative.

2.1 The Actual Benefit

The AB is the scoring aggregation of 5 dimensions: the severity of the condition, the efficacy effect size, the position in the treatment strategy/algorithm, the public health impact, and the type of therapy (preventive, curative or symptomatic)². More and more efficacy is driving the AB.

The severity of the condition used to be the main driver,

HTA-Prozess in Frankreich



Quelle: Produkt und Eigentum des Autors

Figure 1: The Transparency Commission and national Medical Devices Committee assess the clinical evidence, while the Economic and Public Health Evaluation Committee (CEESP) evaluates the economic impact.

but overtime it has lost impact and now the efficacy effect size happens to be the key driver⁹.

The public health impact is considered to be very important, but products rarely get recognition of a public health benefit. This concept remains unclear, but potentially impactful in price negotiations. On the opposite, it has little impact on the AB, mainly because almost all products do not qualify for a positive public health impact. So it does not discriminate among products. In theory, it is supposed to be driven by 4 main topics:

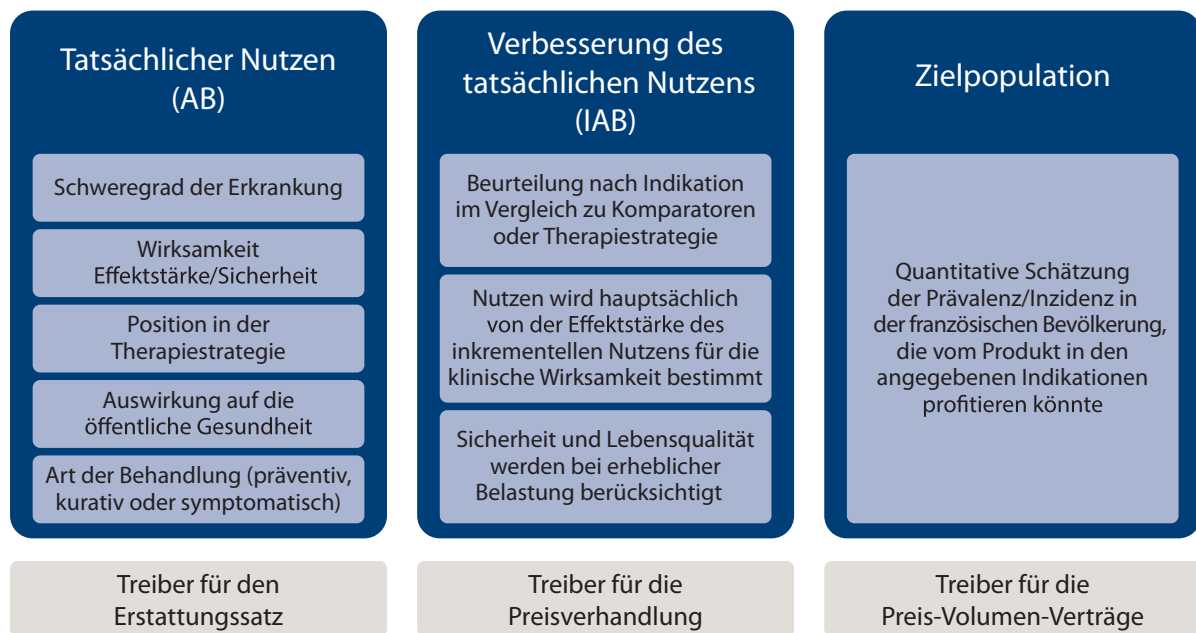
- The disease burden of which the prevalence is a key dri-

ver. Therefore, by definition no orphan drug may have a public health impact.

- The transferability and generalizability of the evidence from the clinical trials, which is often difficult to assess
- The impact on morbidity/mortality
- The impact on health care organizations.

The IAB score is concluded on a 5 level scale: insufficiently weak, moderate, important and major, qualifying respectively to the following reimbursement level: 0%, 15%, 30%, 65%, 65 or 100%^{5,10}. In reality, in France most people benefit from a private insurance (mandatory by law for all

Beurteilung der Kommission für Transparenz



Quelle: Produkt und Eigentum des Autors

Figure 2: The actual benefit (AB) is determined on the basis of a score comprising five factors. The additional benefit and the target population are very important for price negotiations and price volume agreements.

employees) that cover the complementary costs not covered by the national health insurance¹¹. Therefore, the reimbursement level has no impact on the demand. It is just a cost containment tool to lower the national health insurance contribution to the health care cost. Statistics suggest a trend for more products getting denied reimbursement over the last 10 years (Table 1).

2.1 Improvement of additional benefit

The IAB is often perceived as the most important outcome of the TC assessment, because it drives the achievable

price. Most applicants put a lot of emphasis on that score. However, it was shown to be not a good predictor of the later price, except for orphan drugs¹².

IAB is scored from I to V with V being no improvement, IV minor, III modest, II important and I breakthrough. This scale suffers from a floor effect as the large majority of products receive an IAB V or IV. (Table 2) Unlike AB, no clear criteria are set in the law for assessing the IAB. This is more driven by accumulated experience within the TC.

With an IAB of V, the price should be discounted over the comparator¹⁰. With an IAB of IV the drug entry should have

IAB-Verteilung von 2008 bis 2018

CAV	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018 (Jan.– Aug.)
I	2	5	2	1	0	1	2	0	0	0	0
II	5	5	2	0	5	2	8	2	2	0	1
III	3	8	8	2	10	12	11	6	7	8	8
IV	17	20	20	20	19	18	18	34	26	23	22
V	48	65	46	29	46	47	58	57	56	50	31

IAB: Verbesserung des Zusatznutzens (engl. Improvement in Actual Benefit) CAV: Klinischer Mehrwert (engl. Clinical Added Value)
nach: Anne d'Andon and HAS Annual Activity Report 2017

Table 1: The improvement of additional benefit is rated on a scale from I to V. In recent years, the majority of pharmaceuticals received an IAB score of IV or V.

no impact on the drug budget. This means that the drug price should be the weighted average price of the products from which it takes market share¹⁰. This is very complex to measure objectively as it is extremely difficult to identify what would be the dynamic of the market without the entry of the new product. With an IAB of I to III, free pricing applies. Yet, the price has to be in the range of the EU big 4 price (UK, Germany, Italy and Spain)¹³. In reality, this means free pricing only for the list price. Significant negotiations exist for the net price and may substantially reduce the list price. The net price is reached through a combination of rebates and price volume agreements¹⁴. Other tools are used and often make the price negotiation complex so that it may be delayed dramatically.

The IAB assesses an improvement over a comparator. There should be three comparators according to the French regulation: the cheapest, the most used and the most recently assessed product. In reality, this very high requirement happens to be impractical and no applicant

proposed these 3 comparisons in the dossiers submitted unless one single product qualifies for the three attributes.

The comparator remains a critical question and may not necessarily be resolved at the time of development. Unlike Germany, the early scientific advice may not address this question unequivocally, and off-label products may be used as a comparator in France.

The IAB may be granted in isolation with no explicit statement of the comparator, it may be granted vs. the therapeutic class or the most frequent vs. a given product. The trend is that new products should be compared to the next best alternative available¹⁵.

The identification of the right comparator is a challenge for drug developers, especially as HAS requires direct head to head comparative evidence^{16,17}. Although indirect comparisons are acceptable, they are viewed as additional evidence to head to head comparisons and not a replacement. Despite guidelines defining the methodology to be used for such comparisons¹⁸, they are unlikely to weight in

Nicht hinreichender AB für alle Indikationen: negative Empfehlung zur Aufnahme in die Positivliste

Jahre	Anzahl der negativen Stellungnahmen	Anzahl der abgegebenen Stellungnahmen pro Jahr	Prozentsatz der negativen Stellungnahmen
2009	1	68	1,5 %
2010	9	61	14,8 %
2011	7	41	17,1 %
2012	6	60	10,0 %
2013	4	49	8,2 %
2014	6	64	9,4 %
2015	9	63	14,3 %
2016	7	68	10,3 %
2017	8	53	15,0 %
2018 (Jan. – Aug.)	7	40	17,5 %

AB: Tatsächlicher Nutzen (engl. actual benefit)

nach: Anne d'Andon and HAS Annual Activity Report 2017

Table 2: Since 2012, the share of pharmaceuticals without a recommendation of inclusion in the positive list has increased by some 9 percent to 17.5 percent.

the TC opinion. Moreover, an additional benefit cannot be granted without a head to head comparison, unless exceptional circumstances. Figure 3 shows the TC algorithm to grant an IAB, IB depending on the comparative trial design being used.

In France, double blind randomized clinical trials are the gold standard to assess the potential additional benefit.

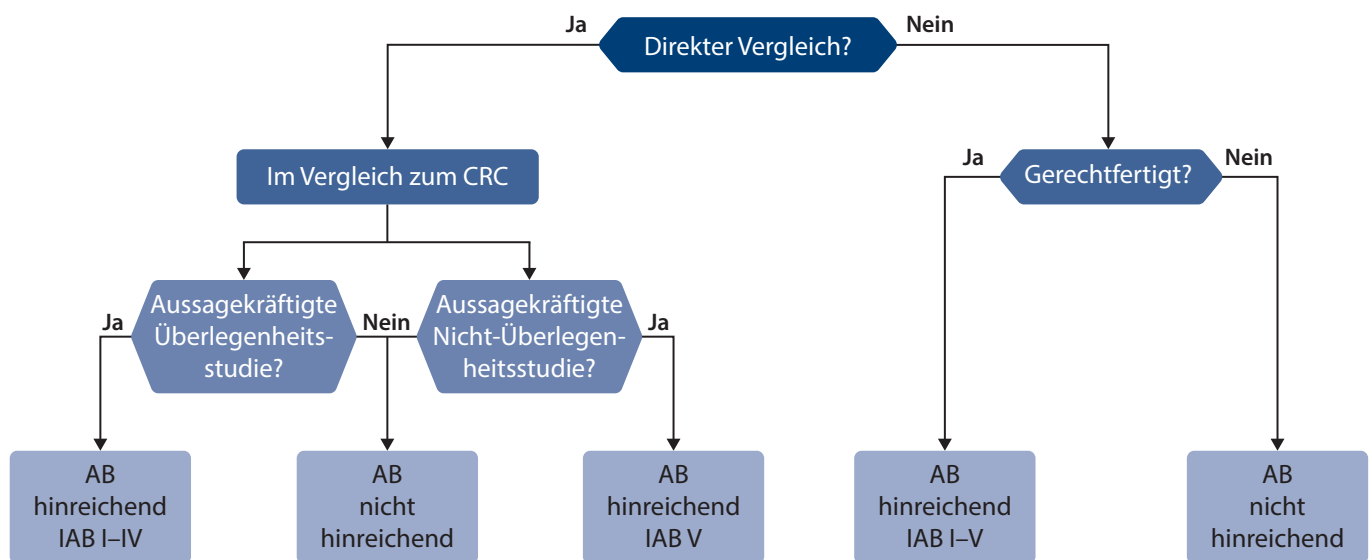
The IAB is driven by the effect size of the benefit over the comparator⁶. The effect size is not the one as calculated by a formula such as the Cohen one for example¹⁹; it is more an appraisal of the benefit, the unmet need, the relative benefit, the quality of the evidence etc. There is a weak correlation between the effect size and the IAB within the same disease area using the same outcome. For example, for oncology products, 3 months additional survival may

eventually be considered as an IAB of III for one product or IV even V for another one²⁰. In the same way, a similar improvement on a PANSS scale may lead to different IAB for two antipsychotics. Ultimately, the so called effect size is put in context in a deliberative process to decide on the IAB⁶. The deliberative process will consider the strength/quality of the evidence, the clinical relevance and the unmet need. These attribute are not quantified according to a specific algorithm but analyzed qualitatively.

Two other impact factors of IAB beyond the pricing negotiation should be considered.

- When a hospital organizes its procurement ,they will consider all products with an ASMR V as similar and make them compete on price to select one. This may be very confusing when a product has an ASMR vs. the

Vergleich der TC-Bewertung



CRC: klinisch relevanter Komparator (engl. clinically relevant comparator), AB: tatsächlicher Nutzen (engl. actual benefit), IAB: Verbesserung des tatsächlichen Nutzens (engl. improvement of the actual benefit)

Nach: HAS, évaluation des médicaments, doctrine de la commission de transparence, September 2018

Figure 3: In the algorithm for the determination of the actual benefit by the pricing committee, double-blind randomised clinical studies are considered the gold standard.

therapeutic class as it suggests that all the product of the class are similar by transitivity reasoning. It may be even more confusing when a product gets an IAB score in isolation, with no reference to any comparator, even not the standard of care.

- When products are too expensive to fit into the disease related group (DRG) tariff, it is charged through an additional national budget on the top of the DRG (List en sus²¹). To qualify for funding on top of the DRG, products need to have an IAB I to III. If the product does not qualify because of a low IAB score, hospitals will not be

able to fund the therapy as it is too expensive. This happens regularly, and prevents access unless an exceptional funding is allocated by the Ministry of Health and Finance jointly.

IAB may not discriminate enough as it will not differentiate a product with clear evidence of no benefit, from a product with a potential additional benefit but for which evidence is not compelling (immature data for example), and a product with obvious benefit but impossible to quantify. In France those products are expected to all receive an IAB of V while being fundamentally different. In that case, the

wording of the TC opinion will use specific terminology agreed with the CEPS to convey discretely the message.

2.2 Target population

The size of the target population for reimbursement or of the target population subgroup, for which the benefit may be differentiated according to the population, is an important information for the CEPS but not for the TC for its decision framework. The CEPS will use this information to determine the price volume agreement and to set a penalty in case sales go beyond the size of the target population²².

The calculation of the size of the target population is done for the reimbursed population which may not necessarily match the marketing authorization. In case of subgroup analysis with different IAB score, the TC will have to estimate the size of each subgroup also. This will help the CEPS to calculate the weighted average price.

This has become a complex exercise as increasingly populations are sliced based on clinical features, genetic markers, molecular biomarkers that may be combined. Because these markers for population segmentations are very new, little information is available and often the available data are for the US market only available.

In some circumstances, modelling may be required to assess the size of the target population especially when a product may affect the prevalence or the incidence of the disease to an extent the target population may evolve. This may be the case in hepatitis C as the potential for cure would inevitably impact the prevalence. This may be the case in SMA type I as the new treatment may impact survival of the larger proportion of patients who used to die within a couple of year and now survive. SMA type I patients represent 80% of the yearly incidence, but have a very low prevalence. Now the dynamic is changing.

3. Health Economics Committee (CEESP)

In 2008, the Social Security Funding Law (LFSS) requested HAS to initiate health economic assessments. In response to this requirement, HAS created CEESP for this purpose⁶. Until 2012, this committee operated as an internal group within HAS but did not have a legal existence as it was not mentioned nor listed in the social Security Code.^{23,24} The opinions and recommendations issued by the CEESP had a relatively low impact and mainly targeted old products with no actual question mark on price or value.

- In an effort to enhance the financial sustainability of the healthcare system, the LFSS for 2012 introduced the CEESP as a specialized committee under Article 47 of the Social Security Code, in charge of providing recommendations and health economic opinions. Concurrently, the board and structure of this committee were revised to match these new objectives and responsibilities²⁵.

The CEESP will review pharmaceuticals that meet the two following criteria:

- IAB claimed by the company is major, important, or moderate (I, II, or III);
- The health product is susceptible to having a significant impact on the health insurance, professional practices, or patient care and, when applicable, its price.

Later HAS interpreted the second criteria as a yearly budget impact of €20 million²⁶. This allowed standardizing a difficult concept.

Health economic evaluations of the applicant dossier are conducted by the CEESP, in parallel and independently of the TC. The initial role of the CEESP was to conclude if the applicant deviates from the HAS guidelines for health economic evaluation. But overtime, the CEESP was requested to define the condition of efficiency for the use of the drug.²²

The CEESP opinion is critical for the applicant. If a product gets an IAB of I to III, it is eligible for free pricing. But if the CEESP concludes that the applicant did not follow the HAS health economic guidelines, the new product and therefore the manufacturer will lose the opportunity of free pricing. So it is an imperative for the applicant to ensure no major deviations from the HAS guidelines.

Following the launch of new hepatitis C products, payers experienced that cost effective products can threaten the sustainability of the health insurance system because of the high prevalence of the condition. A new regulation made it mandatory to file a budget impact analysis on the top of the cost effectiveness analysis for products that are expected to reach 50million € yearly sales volume.²⁶

The use of health economic analysis by payers remains unclear. The following process has been reported: payers use cost effectiveness analysis to obtain a cost effective net price. In the absence of an incremental cost effectiveness (ICER) threshold, it has been identified that the French ICER is 50K€ and like in Sweden it is variable and may be as high as 300K€ for orphan drugs.²⁶

The opinions of CEESP are only released after the price negotiation are finalized which leads to unacceptable long delays in access according to public information²². The CEESP dossier follows a very detailed template as does the CEESP opinion which makes it very transparent and easy to read and understand. Opinions of CEESP are straightforward.

4. Strength and weaknesses of the French HTA system

The French HTA system has shown to be very robust and stable. At the same time it evolved slowly but significantly to adapt to a novel environment.

Often accused of being intransparent and unpredictable, the French HTA system is well predictable and transpa-

rent for the experts who know the system. It is a system that does not communicate enough and has developed a strong analytical capability that has served to structure the decision framework but may have published the full decision framework. A lot of expertise and know-how remains in the committee and the assessor's hands/brains, but not fully spread out. This is why insiders have a very good understanding of a system which they consider to be reasonably understandable while others may perceive it as being in-transparent.

The assessors are talented, very well trained and have a high expertise in the critical review of clinical evidence. They are obviously public health driven. The TC has shown a high focus and attention on women's health, children and other highly vulnerable populations.

The system remains complex, especially with two indexes IAB and AB that are increasingly overlapping because efficacy is dominating the AB scoring. The decision process needs to be updated as it is not enforced entirely and by some may be seen as obsolete. There are inefficiencies in duplication of work by two committees operating in parallel the TC and CEESP. They should be merged²².

Real world evidence studies are widely requested or filed by applicant but rarely used for decision making. The system remains almost exclusively driven by randomized double blind trials and clinical end points. However, there is a slight trend to better consider quality of life, and an opening for accepting network meta-analysis.

The requirement for hard evidence and the difficulties to cope with uncertainty will make the HAS decision framework obsolete if it does not develop further. The ecosystem is tight by the impact of its decisions on prices by CEPS and the way industry systematically leverages the HAS opinions. HAS, as a public agency, is put in the position of arbitrator between CEPS and Industry. Therefore,

HAS may become rigid in managing uncertainty, while all potential breakthrough products reach the market with high uncertainties and immature data.

5. Future trends

It has been a long lasting discussion on the issue of replacing IAB and AB by a single score called Therapeutic Index²⁷. This seems to be progressing and it is on the agenda of HAS. The decision framework is under assessment and will likely be described in a more accurate way with a strong will to make it transparent, reproducible and reliable for applicants.

The development of time limited resolutions is also on the table. It is a sensitive political topic as it may have a significant impact on the drug budget. However, applicants will be required to file real world evidence to increase the chance to reach the market with immature data. Multiple technology assessments are expected to become more frequent and to gather all technologies for a given indication. However, it is unclear if this would happen within the current budget, so more resources should be allocated.

Big data is also on the agenda and synergies between multiple stakeholders are being explored. They may eventually be used more systematically by HAS in the future. The level of evidence to qualify for a given IAB level will increase as well as the effect size. Blind electronic vote may be introduced to avoid distortion from the most vocal members and protect voting members from position leaks.

6. Conclusion

Although not perfect, the French HTA system hosted within HAS remains a robust, reliable and effective one. It should gain more transparency and simplification for non-experts. However, it remains unlikely that the duplication of work between TC and CEESP will be addressed soon.

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Common European benefit assessment – Ways and aberrations

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On 31 January 2018, the European Commission published a draft regulation for a European benefit assessment. Joint clinical assessments must meet the highest quality standards, they must not restrict the member states' freedom of choice in shaping their health systems. The first draft did not fulfil these requirements. Feasible amendments proposed by the European Parliament point the way towards a potential compromise, but are still not well-balanced. Therefore, much will now depend on the ongoing consultations of the Health Ministers.

G **enesis of the draft regulation**
The term Health Technology Assessment (HTA) was introduced by the US Office of Technology Assessment (OTA) in 1975 and defines the process of systematic assessment of medical procedures and technologies of health care provided to the population. Therefore, HTA should not only be considered as a mere scientific method, but as the objective of taking evidence-based decisions on a potential benefit of therapies thus contributing to cost-effective medical care¹. Health Technology Assessments have been used for decades in the member states of the European Union. In 2004, the European Commission Expert Group concluded that a European network is urgently required in order to allow for an efficient exchange of information between national HTA agencies and Health Ministries and support member states in establishing their own national HTA agencies².

Based on this report, the EUnetHTA project was established between 2006 and 2008. This project was aimed at reducing overlapping and double work strengthening the significance of HTA in the EU and the connection between HTA and health policy and support member states with little experience in HTA. In 2009, the EUnetHTA Collaboration was established; since then three so-called Joint-Actions were financed from EU funds addressing different focuses, i. e. from the development of common methods through the preparation of joint HTA reports to the description of possibilities to allow for joint assessments in the member states³. Coordination of the cooperation was further intensified on the basis of Article 15 of the Directive on the Application of Patients' Rights in Cross-Border Healthcare (2011/24/EU) about the HTA network of the European Commission and the member states since 2013⁴.

However, the goal of sustained cooperation cannot be

achieved by EUnetHTA alone. European law implications prohibit further financing on a project basis after completion of the third Joint Action. For this reason, the Council of the European Union⁵ and the European Parliament⁶ requested the European Commission to reflect on the future of HTA cooperation.

The European Commission responded to these demands and published their first impact analysis (Inception Impact Assessment on Strengthening of the EU Cooperation on Health Technology Assessment) on 14 September 2016 and conducted a public consultation. It includes five possible scenarios for shaping the future cooperation of HTA bodies and their impact. Based on these findings, it presented the Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU (Procedure 2018/0018/COD – COM (2018) 51) on 31 January 2018. With this regulation, a long-term cooperation of national

HTA agencies under the supervision of the European Commission shall be established to ensure enhanced functioning of the Single European Market and contribute to a high level of health protection. Upon presentation of the draft regulation, an ordinary legislative procedure by the European Union was initiated⁷.

Evaluation of the draft regulation

The draft regulation includes five chapters and 36 articles with comprehensive provisions for a binding cooperation of HTA bodies in the member states for the joint preparation of HTA reports, joint consultations of developers on clinical studies, conduction of a horizon scanning as well as development of methodological principles of HTA. Moreover, a support frame is established for the further voluntary cooperation of HTA authorities. Clinical assessments for all new pharmaceuticals that are subject to the central approval procedure by the European Medicines Agency (EMA)

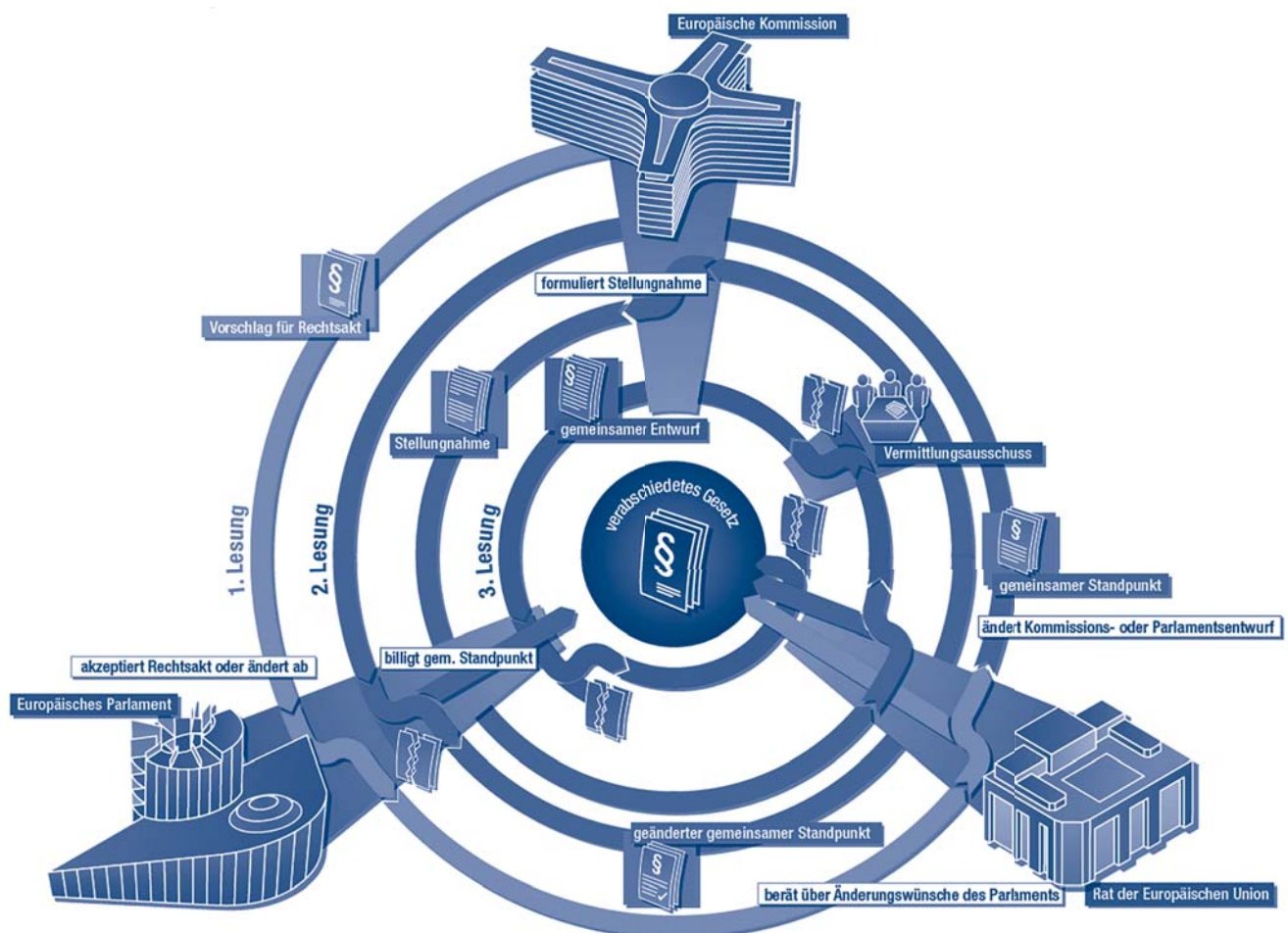


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Ablauf eines ordentlichen Gesetzgebungsverfahrens der Europäischen Union



Quelle: Bundeszentrale für politische Bildung, 2010, www.bpb.de

Figure 1: With the draft regulation presented end of January 2018 a complex legislative procedure was initiated.

would be centralised. In addition, certain medical devices and in vitro diagnostics shall be selected for assessment according to specified criteria. HTA reports that have been prepared within the scope of the compulsory cooperation

shall then be used as a basis for national decisions on pricing and reimbursement, while individual clinical assessments will be prohibited. Moreover, joint procedural rules and assessment instruments shall also apply for local (i. e.

decentralised) health technology assessments in the member states.

Thus, the European Commission's proposal intervenes into the existing national systems without ensuring high-quality central assessments and efficient implementation of findings in the member states in consideration of specific national treatment contexts. It ignores that there are sometimes considerable differences in the member states with regard to laws and methods on the assessment of health technologies.

This is all the more interesting, as a study commissioned by the European Commission revealed heterogeneous assessment methods across the member states with little consistency of the assessment results, even if a trend towards more homogeneity can be observed⁸. The European Commission mentions these differences in its recitals to the proposed regulation, but suggests, however, that these are not justified. The truth is that these differences can be attributed to different assessment objectives and set up of the health systems: Value judgements in the individual countries specify in what way cost-benefit-aspects, e. g. in form of QUALYs, will be considered in the assessment or whether and to what extent macro-social aspects should also be considered besides the individual benefit a certain treatment has for the patient⁹.

Moreover, treatment standards that are used as a basis for the assessment of the additional benefit of a new pharmaceutical may vary significantly between member states. This can have medical and financial reasons: The results of the QUEST-RA study revealed significant regional differences of the treating physicians in the selection of the second cDMARD following methotrexate¹⁰. For some pharmaceuticals that are already accepted standard of care in some countries in the treatment of hepatitis B and C infections, the European Association of Liver Patients reported hete-

rogeneous availability within Europe in 2017 which can probably mainly be attributed to different financial potentials of the healthcare systems and strategical market decisions of the pharmaceutical companies¹¹.

An alignment without considering these differences constitutes an intervention in the member states' responsibility for the organisation of their healthcare system and medical care. This is another reason why the draft of 31 January 2018 should be rejected. Moreover, from the viewpoint of the National Association of Statutory Health Insurance Funds there's currently no sufficient evidence for the necessity of an "elimination of obstacles in the Single European Market" as a legal basis.

And yet: The plan to continue the existing cooperation reasonably and extend it towards a joint assessment process step-by-step is to be welcomed. Because by means of a continuous cooperation of HTA agencies at EU level, a better and more extensive use of high-quality HTA can be achieved and further developed in the decision-making of national health care systems. For this reason, the National Association of Statutory Health Insurance Funds proposed comprehensive enhancements in its opinion of 8 May 2018¹² and will continue monitoring and supporting the legislative procedure.

Joint clinical assessments

The objective of HTA cooperation across Europe is not to establish a regulatory body, but to further develop cooperation of the organisations responsible for HTA in the member states. All decisions of these HTA organisations shall be taken by consensus whenever possible.

Thus, the planned „decision by simple majority“ proposed in the draft regulation is just as hardly reasonable as the intended central role of the European Commission in the Coordination Group of HTA organisations. The propo-

sed leading role of the Co-chair and the competence to adopt specific provisions relating to procedures and methods would contradict the nature of an independent body.

HTA organisations of the member states should take the lead with administrative support by the European Commission. All decisions should be taken by consensus whenever possible. However, in disputable cases, decisions should be taken by qualified majority (55 percent of the member states representing 65 percent of the EU population) in order to strengthen confidence in the results.

The draft regulation proposes to define methods and processes for clinical assessments by delegated legal acts and implementing acts. This way, they would be excluded from the EU legislative process and remain the exclusive responsibility of the EU Commission. This does not take adequate account of the importance for the quality of clinical assessments. Procedures and methods for joint clinical assessments must be developed and jointly decided upon by all involved HTA organisations. It must also be kept in mind that the significance of individual clinical criteria also depends on their further use: It is important whether only the additional benefit of a certain technology is assessed – like in Germany – or whether the results of the assessment will be used for cost-benefit analyses.

The question of whether access to a certain technology will be granted prior or after an assessment, whether there is a fourth hurdle for pharmaceuticals affects dealing with and requirements for clinical assessments and must thus be considered. Only on the basis of a joint regulation of methodological principles taking the member states' different healthcare systems into account and assuring consistently high quality of assessments, harmonisation of HTA can be further promoted.

It also seems odd to impose a binding obligation for member states to use joint clinical assessments at national

level while prohibiting individual clinical or equivalent assessments of the same healthcare technologies as proposed in the draft regulation. Provided that joint clinical assessments meet the required methodological quality standards and adequately take the different healthcare systems into account, repeating a European assessment at national level that is already available and ready-to-use would be uneconomical. The proposed unconditional obligation for the incorporation of the results bears the risk that assessments must be performed on the basis of a HTA report that is not transferable to the national treatment context and is thus useless.

Comparing current EUnetHTA reports and German HTA reports from the AMNOG procedure, significant differences can be observed in key areas that are decision-relevant for Germany, such as the selection of comparators and assessment of patient relevance of endpoints. Individual evaluations seem incomplete and do not address methodological and substantive deficits of the underlying studies that have been identified by the IQWiG. As the dossier used for the assessment is not publicly available, the causes of these weaknesses cannot be identified. However, these differences undermine the confidence in the current structures of joint clinical assessments and have a direct influence on the reliability and relevance of conclusions in the results and thus its usability at national level.

The question, then, is whether the adoption of assessments results shall and must be optional for the member states. At national level, amendments and modifications of the joint assessments may also become necessary. Own assessments should also be possible, e. g. if further clinical data and their re-evaluation must be submitted for reimbursement in individual states¹³.

As long as it is ensured that joint HTA reports can be used as a sound basis for decision-making, member states

will adopt the results of joint assessments without any compulsion.

Another prerequisite is that assessment procedures fulfil the highest transparency requirements: HTA supports decisions about the benefit of healthcare technologies and ultimately has an impact on the claims of the insured against their health insurance. Thus, patients have a right to verifiable assessments. The resulting claim of transparency is not fulfilled with the proposed procedure (see Figure 2): According to the draft regulation, the assessor must implement any comments or remarks by the manufacturer, stakeholders and the European Commission even before submission of a preliminary assessment report to the subgroup.

After approval of the assessment report by the Coordination Group of the HTA organisations, the assessor has to make sure that all data considered as trade and business secrets are removed from the approved report of the joint clinical assessment and the approved summarised report. The Coordination Group will forward these summarised reports to the Commission that will in turn publish them on the respective internet platform that will be set up. Member states, stakeholders and the general public shall have „reasonable“ access to this platform. The European Commission shall define the term „reasonable access“ in this context.

It is neither intended to publish the complete basis of the assessment nor to ensure that the assessment is only based on publicly accessible data. This approach is not in accordance with the claim of healthcare systems and its involved patients of being fully informed. The German AMNOG-procedure furnishes proof that comprehensive transparency is possible. Confidential information from the manufacturer's dossier will only be used for plausibility verification of other data. If this information is essential for an assessment, the manufacturer will be asked to disclose it. If the manufacturer refuses this for confidentiality reasons, the provided data will

be classified as incomplete¹⁴. The dossier of the manufacturer, the assessment by the IQWiG and the decision of the G-BA including justification as well as the documents of the hearing procedure will be published on the website of the G-BA and publicly accessible. A European assessment procedure must not fall behind this standard.

Scientific advice

Besides conducting joint clinical assessments, the proposal also proposes a procedure for joint scientific consultations that is very similar to the joint clinical assessment.

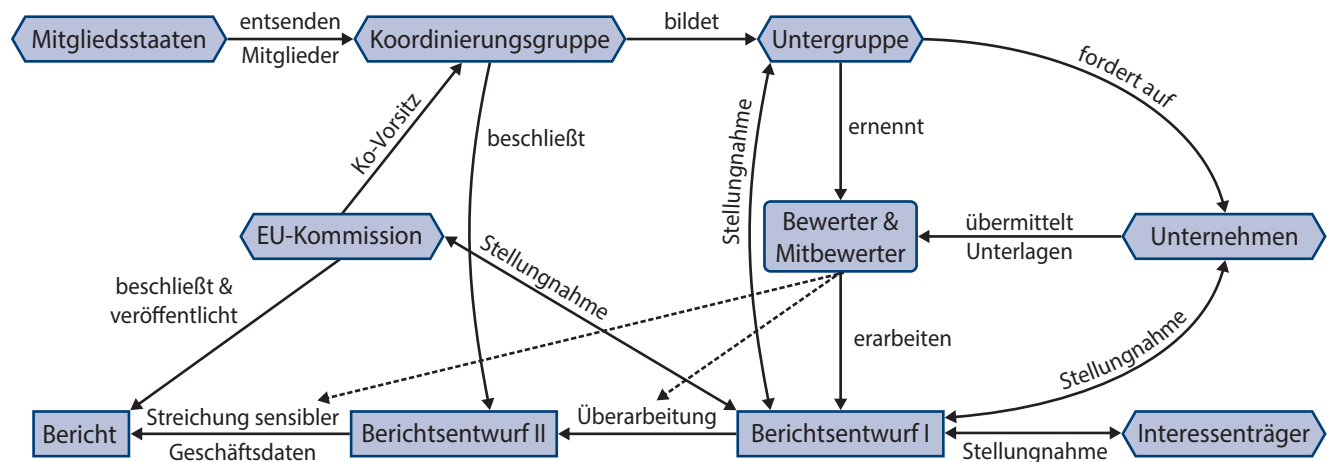
Manufacturers should be informed how to generate and process evidence that is required for the assessment of their technology. Within the scope of Joint Actions, EU-netHTA and EMA have developed a system for joint consultations that delivers satisfactory results for all stakeholders and should be continued based on current estimates. The only point that should be considered is in which cases publicly accessible information should be provided instead of conducting individual and confidential consultations. Experiences show that the majority of the recommendations made during consultations are issued several times.

However, different healthcare and assessment systems in the member states should be considered in the consultations. Consensus of the involved HTA organisations cannot be achieved on every question and approval authorities and HTA organisations do not always obtain the same results^{15,16}. Consultation will then also be held based on these various estimates. This level of flexibility should be retained. Moreover, adequate arrangements should be made to avoid influence being exerted over the involved persons and institutions.

Horizon scanning

According to the draft regulation, the Coordination Group

Ablauf und Teilnehmer gemeinsamer klinischer Bewertungen nach den Vorschlägen der Europäischen Kommission



Quelle: Eigene Darstellung

Figure 2: So far, the procedure proposed by the EU Commission for the process of joint clinical assessments does not meet the requirements of full independence and transparency.

shall prepare a study about new healthcare technologies on an annual basis (Horizon Scanning) to allow for selection of assessment items and provide indications on budgetary impacts. Further cooperation also makes sense here, but should not only have a direct added value for European procedures, but also for the healthcare systems of the member states. Thus, from the National Association of Statutory Health Insurance Funds' perspective, a central database should be established that could also be used e. g. for the budget planning of the national payers.

Political responses to the draft regulation

In March 2018, the German Bundestag reprimanded that the European Commission's proposal infringes on the prin-

ciples of subsidiarity and proportionality. According to its opinion, the principle of subsidiarity was not complied with, as the proposal includes binding regulations that have an impact on the design of national healthcare systems. The Members point out that preparation of HTA reports and subsequent assessment decisions have a great impact on both reimbursability and pricing of pharmaceuticals. Since apart from Germany only France and the Czech Republic filed a formal subsidiarity objection, the required quorum for a rejection of the proposal was not reached. However, the parliaments of Lithuania, Poland, Sweden, Slovakia, and Spain also criticised the legal basis of the proposal¹⁷.

Consultations in the Council of the European Union

During the discussion of the 28 EU Health Ministers in June 2018 it became apparent that despite the common will to further develop the draft law, there are different opinions mainly regarding the binding use of clinical assessments and that the European Commission's proposal did not receive the required majority in the member states. Particularly larger member states rejected the legal obligation, whereas predominantly small countries generally supported the European Commission's proposal. This includes states that have not yet established a national HTA system. The Bulgarian Presidency summarised that the European Commission's proposal does not reach a qualified majority in the Council and that the text proposal would thus have to be modified significantly¹⁸.

The Austrian Presidency that was in office during the second half of the year intensified consultations on the draft regulation. At the time of publication of this article it is not clear whether it will be able to reach the interim objective of a partial general direction on Articles 1-8 or whether it will only submit a progress report at the end of the year. It is known that Germany, France, and Austria have prepared proposals for a possible modification of the draft regulation.

Consultations of the European Parliament

On 4 May 2018, correspondent Soledad Cabezón Ruiz had already – and thus surprisingly quick – submitted a draft report to the European Parliament of the committee responsible for health (ENVI committee). The draft reflected the Parliament's request for a substantially more binding European HTA cooperation and at the same time stronger consideration of the healthcare systems' individual needs. During summer, the Members of Parliament responded to the draft report with numerous modification proposals. On this basis, a final draft report was accepted on 3 October

2018 by the European Parliament (P8_TA-PROV (2018) 0369) – at the time of publication of this article, the formal first hearing was still due and is expected for March 2019 – subject to the results of the discussion in the Council of the European Union¹⁹.

In this final report, the European Parliament apparently attempts to mediate between the European Commission and the Council of the European Union. The opinion of the National Association of Statutory Health Insurance Funds on the draft regulation also seems to have been taken into consideration. There are concerns both about the actions proposed in the report on the containment of the Commission's role and the voting changes in the event of disputes. In the report, the European Parliament clearly commits itself to evidence-based medicine and separation between clinical assessment and its appraisal. The latter shall and must remain a member state competence.

However, particularly the possibility of deviating assessments at national level, the role of HTA organisations as well as methodological clarity and transparency of the procedure are still insufficient. Besides, the European Parliament's proposal to further reduce the number of medical devices eligible for assessment as compared to the European Commission's proposal would fail to take account of the products and their significance for healthcare. The European Parliament's requests to develop a different methodology for the assessment of pharmaceuticals for rare diseases should be clearly declined. Even if specific incentives are provided for developers for the approval of pharmaceutical products under pharmaceutical law, ranging from exemption from charges for consultations by the approval authorities to specific protection mechanisms after approval, a special status in HTA is not appropriate.

HTA aims at providing comprehensive information to users and patients about the benefit of pharmaceuticals

against the current treatment standard. In this context, patients suffering from rare diseases have the same right to valid information as all other patients. The European Parliament's proposal brings one issue to the fore which has not yet been addressed due to the general conflicts: Practicability of the time schedule for a joint clinical assessment (see Figure 3).

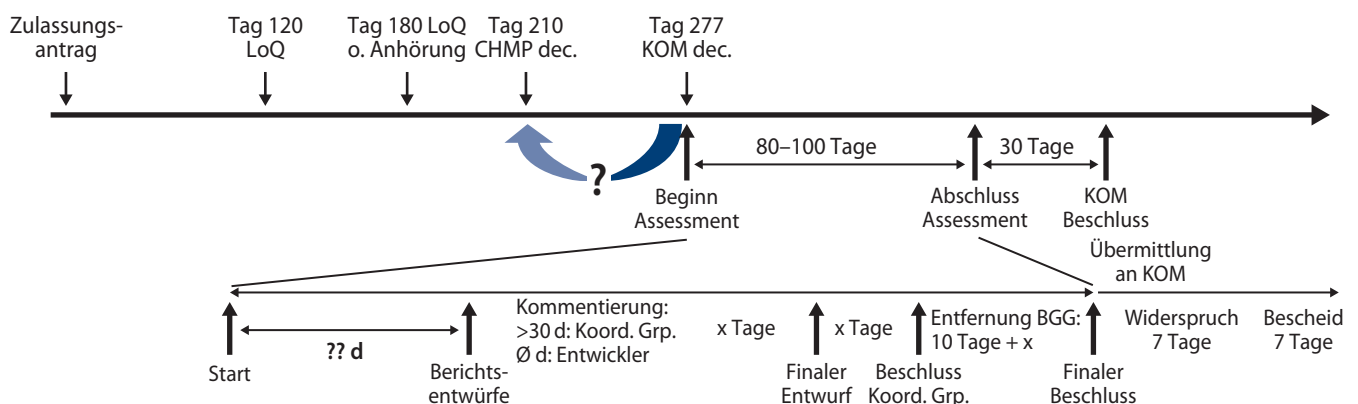
The German procedure of early benefit assessment according to Section 35a SGB V provides a period of three months for the preparation of a HTA report. This rather tight deadline can only be kept, as the available evidence is limited, is provided by the manufacturer in his dossier in a well-structured manner, and the leading question is very focussed. Moreover, large investments in personnel and resources were made upon the introduction of the early benefit assessment. Normally, the duration of the procedure

for benefit assessments of the IQWiG ranges from six months (rapid report) to two years (report).

Only in case of a full assessment within the scope of a report, a hearing procedure is part of the assessment. Thus it appears unrealistic, if the European Parliament's proposal stipulates a period of 100 days for the assessment, if during that period consultations with various stakeholders and several internal discussions about the report must also take place. This shortens the actual time period for the preparation and jeopardises the goal to provide a high-quality report. For this reason, an extension of the period for the assessors should be discussed in the further course.

Impact of common clinical assessments for Germany
From the perspective of the German healthcare system, a

Zeitlicher Ablauf gemeinsamer klinischer Bewertungen nach den Vorschlägen des Europäischen Parlaments

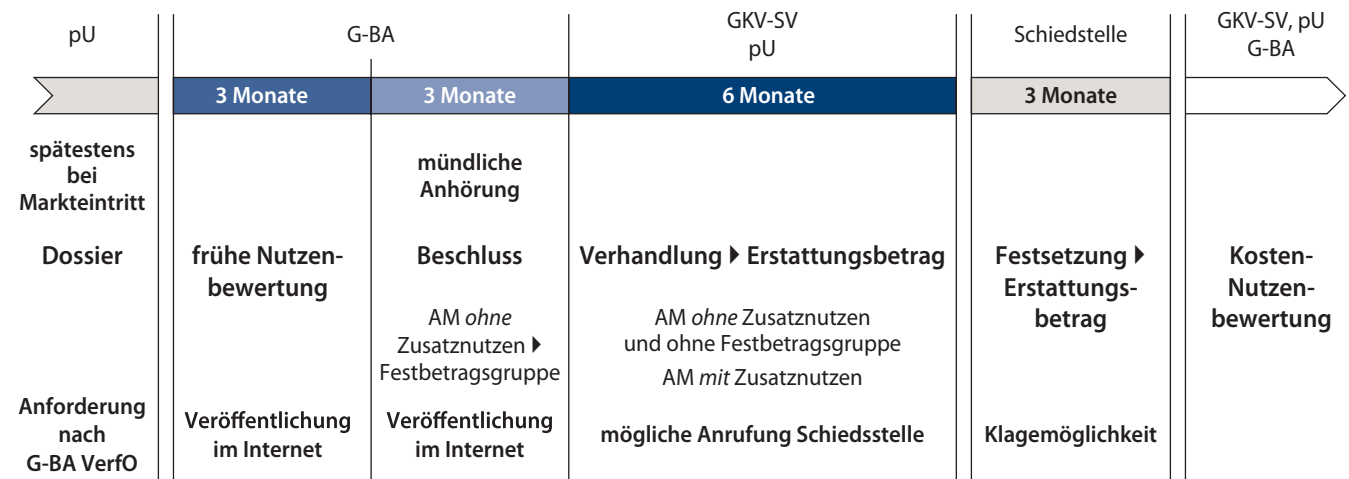


BGG – Betriebs- und Geschäftsgeheimnisse; CHMP - EMA Ausschuss für Humanarzneimittel; KOM – EU Kommission; Koord. Grp. – Koordinierungsgruppe; LoQ – List of Questions

Quelle: Eigene Darstellung

Figure 3: The EU Commission's proposed procedure only provides a period of 100 days for the actual assessment. This appears unrealistic, as comprehensive consultations shall also be conducted during that period.

Zeitlicher Ablauf und Fristen im AMNOG-Verfahren



Quelle: Eigene Darstellung

Figure 4: In principle, the AMNOG procedure allows for the use of high-quality European HTA reports, if these are available 3 months after market entry at the latest and do not anticipate the G-BA decision on the additional benefit.

stronger European cooperation during benefit assessment of healthcare technologies would be desirable under certain conditions. The integration of joint clinical assessments into German benefit assessment procedures is generally possible. It is of decisive importance that joint HTA reports fulfil the high methodological requirements, provide in-depth analyses, and allow for national adjustments. Falling back behind standards already achieved is not acceptable and must be avoided at all costs.

It is advantageous that the assessment and appraisal are already separated in the process of early benefit assessment: The report of the IQWiG primarily provides a qualified overview of effect estimates for the evaluated patient-relevant endpoints as assessment; the final decision as to whether these differences have a low, significant or no additional benefit is, however, taken by the G-BA in the ap-

praisal in consideration of the report and other aspects. Subsequent proven price negotiations by the National Association of Statutory Health Insurance Funds with the manufacturer could be preserved (see Figure 4).

It is incomprehensible why medical devices and other high-risk products shall not be assessed independently of the scrutiny procedure and in vitro diagnostics. From the National Association of Statutory Health Insurance Funds' perspective this is indispensable to ensure that the development of new disruptive technologies can be evaluated at EU level. This way, the German HTA procedure for medical devices could also benefit significantly from joint assessments.

Conclusion

It is of common European interest to strengthen the co-

operation on HTA within the EU and extend it step-by-step. Member states that were not yet able to establish their own HTA system or are faced with insoluble problems at national level should be supported with a high-quality HTA system that is open for national adaptations. All patients in the European Union shall benefit from scientifically substantiated and independent information about the benefit of pharmaceuticals and medical devices and rely upon a safe and economic supply with these products.

European Commission, European Parliament and member states have indicated their willingness to further work towards a compromise solution. It is important that this compromise is elaborated thoroughly and without excessive haste, even if European Parliament elections will be held in May 2019. The procedure for a joint European HTA must combine the best of all national systems and any loss of confidence as a consequence of a minimal consensus may be avoided.

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National versus European benefit assessment: Pros & cons from the G-BA's perspective

Dr Antje Behring | Acting Head of the Department Pharmaceuticals at the Federal Joint Committee (G-BA)

With the draft regulation published on 31 January 2018, the European Commission made a proposal for a uniform European assessment of health technologies. Although it is understandable that a legal foundation shall be created for HTA cooperation after years of project-related funding, the regulation will clearly interfere with national healthcare systems of the member states. Especially, the intended binding adoption of European benefit assessments for national assessment processes is quite difficult before framework conditions, content and scope of the assessments as well as uniform methodological principles have been established. With the early benefit assessment, high quality standards concerning methodology, transparency and process flow have been established in Germany. The same quality standards shall apply for a joint European HTA-assessment. However, the draft regulation remains unclear in several fundamental aspects and requires further clarification and specification.

Introduction

With the introduction of the German Pharmaceutical Market Reorganisation Act (AMNOG) in 2010, the legislator initiated a paradigm shift with far-reaching consequences for the pharmaceutical market in Germany and literally „reorganised“ it. Mandatory proof of an additional benefit on the basis of patient-relevant endpoints against a standard therapy (appropriate comparative treatment, ACT) for all new active substances upon market launch was controversial and widely discussed in Germany, especially regarding a potential „added value“ against the decisions of the approval authorities.

Eight years later, elements of the AMNOG process resurface in a proposal by the European Commission (EC) for a regulation on the assessment of health technologies (Health Technology Assessment, HTA). However, a critical look should be taken at the implementation of this proposal and its impact on the pharmaceutical supply in Germany, especially against the background that major issues have only been addressed vaguely and remain open in the proposed provisions, but at the same time adoption of the results of the European benefit assessment shall be mandatory.

Expectations regarding European benefit assessment

With the regulation, expectations of various stakeholders regarding a European benefit assessment shall be fulfilled. Policy-makers expect that the Single European Market and patient rights will be harmonised across Europe and consistency established among HTA assessments. Smaller countries without or only insufficient HTA assessment shall benefit from the experience of other countries with appropriate expertise. Moreover, more HTA assessments could be performed and thus capacities and resources used efficiently as a consequence of potential synergy effects.

From the patients' perspective, they are expected to have a faster access to new health technologies across the EU while high safety standards for these products will be ensured. The pharmaceutical industry expects in particular a faster market access, reduced effort in the preparation of the benefit dossier, and an enhanced planning reliability for Europe (see Figure 1).

According to the explanatory memorandum of the proposal, the European Commission sees three major reasons that a European benefit assessment is required:

1. Limited and distorted market access in Europe for health technologies,
2. Duplication of work for national HTA bodies, and
3. Unsustained cooperation on HTA.

From a perspective of the German healthcare system, it should be questioned whether these objectives can be achieved with the regulation. If a European benefit assess-

ment shall contribute to eliminating bias and restrictions of market access, this is in fact not an obstacle in Germany. This is neither delayed nor accelerated by the AMNOG benefit assessment due to the fact that the process of benefit assessment will be initiated at the same time as the market launch. The companies choose the date of market access for their pharmaceuticals. There is no so-called „fourth hurdle“ for the listing of a pharmaceutical in the statutory health insurances' catalogue of services only after completion of the benefit assessment and reimbursement negotiations.

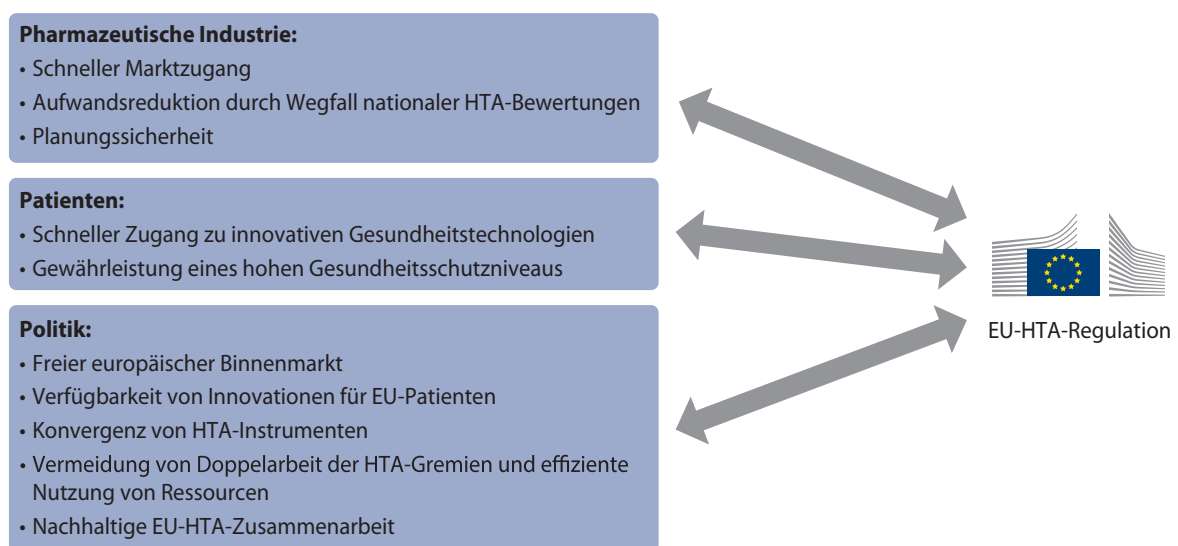
Furthermore, duplication of work by HTA institutions shall be reduced. Therefore the question arises as to whether – upon closer examination – the assessment really contains redundancies. In the individual countries, HTA constitutes the context-specific addressing of national questions as a basis for reimbursement and price decisions. These decisions must remain the responsibility of the member states requiring independent evaluation of clinical data against the existing treatment standard. Thus, duplication of work can only be avoided, if a uniform common standard has been established and accepted for comparative assessments.

This does not only apply to the evidence-based determination of one or more comparative treatments, but also to the specification of patient-relevant endpoints that have to be considered for the assessment. Harmonisation of health technology assessments at European level will not reduce national HTA assessments before such a standard has been established. Although it is a step into the right direction to create a legal basis for a stronger European cooperation on HTA after several years of project-based funding during EUnetHTA, a binding adoption of central benefit assessments is only acceptable after adequate standards, preparatory procedures and methodological principles have been agreed upon.



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EU-HTA-Regulation: Ziele und Erwartungen der unterschiedlichen Interessenvertreter



Quelle: Dr. Antje Behring/G-BA

Figure 1: Stakeholders' expectations towards a European benefit assessment are manifold and differ, particularly regarding a rapid availability of new health technologies.

Critical views on the draft regulation

From the G-BA's perspective, the following aspects of the European Commission's draft regulation of 31 January 2018 should undergo critical evaluation:

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

Ad 1. Legal basis Article 114 TFEU

In Germany, prescription pharmaceuticals are prescribable at the expense of the statutory health insurance, if they have been approved by the competent authorities. This principle applies for both domestic and foreign pharmaceuticals and was not changed with the introduction of the benefit assessment by AMNOG.

All new active pharmaceuticals that come onto the market and their new therapeutic indications must undergo an early benefit assessment. Consequently, the free movement of goods within the single market is not restricted in Germany by the binding stipulation of a central European benefit assessment according to Article 114 TFEU and thus

there is no need for remedial action. The main focus of the regulation is to establish a central procedure for comparative benefit assessment of new pharmaceuticals and medical devices in order to promote availability of these health technologies for national health insurance systems.

This affects the member states' responsibility according to Article 168 Paragraph 7 TFEU that needs to be taken into account through the inclusion of the legal basis into the introduction text of the regulation. All measures set out in the regulation must ensure limitation of the exercise of competences of Article 168 Paragraph 7 TFEU. This underlines the member states' responsibility and right to structure their health legislation and organise their healthcare system and medical care.

Ad 2. Binding adoption of the European benefit assessment (Joint Clinical Assessments, JCA)

Article 8 No. 1b of the draft regulation stipulates the binding application of the European benefit assessment at member state level: The phrase „Member States shall apply joint clinical assessment reports...“ could be interpreted as if the result of the European benefit assessment is decisive for the determination of the additional benefit in the member states.

In Germany, the result of the additional benefit assessment becomes part of the German Pharmaceutical Directive (AM-RL) with the G-BA decision thus having an influence on prescribers within the scope of the 5th German Social Codebook (Sozialgesetzbuch V, SGB V) on the one hand and the reimbursement amount on the other hand. Consequently, the pharmaceutical supply of the population is significantly influenced by the decisions on the additional benefit. The decision about the additional benefit of a given pharmaceutical is taken in consideration of the national treatment landscape: the previously defined appropria-

te comparative treatment and the assessment of the therapeutic additional benefit by means of patient-relevant endpoints against the appropriate comparative treatment based on the dossier assessment by the IQWiG and in consideration of the opinions.

In a uniform European benefit assessment, different national assessment procedures cannot be considered sufficiently and adopted on a compulsory basis, as long as no uniform European standard basis of assessment has been established e. g. for the determination of the comparative treatment or patient-relevant endpoints. At present, the standard treatment used for the comparison during HTA assessment is defined according to different standards in countries in which a national benefit assessment is performed for pharmaceuticals. It must therefore be possible to deviate from the European result and perform additional or individual assessments. Nevertheless, member states can voluntarily integrate the European benefit assessment into their own decisions and adopt the results, but would, however, not be obliged to adopt content in the event it is not appropriate for the national treatment context. Under these circumstances, a mandatory adoption instead of voluntary incorporation of the results would be premature.

It should be made clear that the actual content of the European benefit assessment is not clear so far. It is questionable whether it will include a purely scientifically descriptive processing and analysis of scientific evidence or whether it will comprise value judgements with e. g. consideration of the prolongation of life with side-effects, including general conclusions on the clinical additional benefit.

The latter, i. e. classification of the therapeutic added value, including determination of the extent of the additional benefit, remains the responsibility of the member states. Within the course of the benefit assessment, this step will be taken into account during the „appraisal“ and directly

linked to allocation, price and reimbursement decisions. The different steps, i. e. processing and analysing scientific data and available evidence („assessment“) must be differentiated from their evaluation, including contextualisation to the national treatment landscape („appraisal“). This distinction is not made in the present draft regulation.

Especially because the content-related design of the European benefit assessment is still not clear, value judgments will probably pre-empt the national assessment processes. Therefore, individual or complementary HTAs must be possible in addition to the European benefit assessment to account for potential differences regarding comparators, patient populations, endpoints due to the specific national treatment landscapes.

For example, if a different comparator is determined in the planning phase, it should be possible to initiate an individual assessment before the European benefit assessment and refrain from a binding adoption of the JCA (opt-out). The same applies, if not all relevant patient groups or other major aspects of an indication that are relevant for the national treatment context, e. g. regarding patient-relevant endpoints, are addressed.

Ad 3. Competences of the European Commission (EC)

In the draft regulation, the European Commission provides for codetermination rights at various steps in the process. This is also reflected by the fact that the EC shall get a chairing function as co-chair within the Coordination Group. From the G-BA's perspective and according to the European Parliament's proposal, more responsibilities regarding the content- and organisation-related design of HTA cooperation shall be shifted to the Coordination Group and the EC shall only have administrative tasks without any context-related codetermination right in the Coordination Group. Any substantive evaluation and control by the EC of

the methodological principles and strategical decisions that will be developed by the Coordination Group is not feasible against the background of the sufficient scientific and practical expertise of the Coordination Group.

Especially the possibility of a „harmonising exertion of influence“, e. g. by means of „approvals“ and acceptance of reports after substantive evaluation put a question mark on the independence of the scientific work and shall be excluded by means of clear competence provisions.

In this context, it is criticised that according to the draft regulation a dissent draft benefit assessment would be adopted in the Coordination Group by a simple majority of the member states. The introduction of a qualified majority (55 percent of the member states and 65 percent of the overall population) – as the European Parliament also suggested – is therefore required.

It should be clearly declined that additional or superseding benefit assessments at national level must be authorised by the European Commission (Article 34 of the draft regulation, safe-guard-clause). An unconditional opt-out (no use of European benefit assessment and individual national benefit assessment) directly after determination of the comparative treatment or interrogation for the European benefit assessment must also be possible for member states outside the stipulated scope without the EC's permission. This shall also apply for additional analyses that are relevant for the specific national context and required for national assessment procedures (appraisal). Moreover, this shall also apply for the use of further clinical data that are not part of the European benefit assessment.

Ad 4. Process flow and requirements with respect to quality and transparency

Various aspects relating the process flow, documents to be submitted and the content of the benefit assessment

remain abstract and must be further defined by delegated legal acts. However, these details are decisive for the acceptance or rejection of the European benefit assessment. In the formulation of these specifications it must be avoided that the procedure mainly serves the interests of the pharmaceutical companies that manufacture health technologies. Therefore, it is important that certain experiences and practices from the early benefit assessment will be considered in the processes.

Time frame

The schedule for the European benefit assessment is still unclear both in terms of the processing time granted, but mainly regarding the start time of the procedure itself. Discussions about a rapid procedure indicate that it is intended that the assessment shall be completed at the same time as the approval process. However, knowledge of the wording of the indication as well as other application-related specifications by the approval authorities, like dosage and contraindications are important to be able to carry out an appropriate assessment for the German treatment context. Carrying out a benefit assessment before this information and conclusions from the approval process are available might result in an assessment that is not transferable to future prescription landscape and might thus be useless.

Documents to be submitted and content of a European benefit assessment

For the benefit assessment, it is important that the study reports including all appendices/amendments are submitted by the pharmaceutical company. Only if all documents are available, the assessors can carry out an adequate assessment within the time given. An assessment on the basis of preselected data provided by the pharmaceutical

company only or on the basis of scientific publications or study register entries does not provide enough information and does not allow for an in-depth analysis that would, however, be required to create a sound basis for decision-making for the subsequent procedures in the individual member states. In particular, measures should be defined if pharmaceutical companies fail to provide comprehensive information that is considered essential for the assessment.

Benefit assessments should process and present available study results and evidence base according to generally accepted standards of evidence-based medicine; any conclusions and valuations should, however, not be included. Although the decision-making mechanisms for the determination of the assessment contents are open, it is considered important that besides the presentation of the results against certain comparators that have been defined as relevant by the member states, sufficient information is provided about included patients, potential uncertainties regarding the study population, study design as well as operationalisation of endpoints and – in the event that no information is available – these evidence gaps should be disclosed. Patient-relevant endpoint categories, mortality, morbidity, quality of life and side-effects should be addressed on a regular basis, irrespective of whether endpoints were actually collected in these categories or not.

It should go without saying that benefit assessments should not contain any speculations and statements on possible trends. In any case, clear criteria should be documented in writing and the assessment scope defined transparently by the assessors in consideration of the member states' feedback.

Consequently, for the development of a joint methodology by the Coordination Group, sufficient time should be provided before the first European benefit assessment can be carried out to ensure a constantly high level of quality.

This applies particularly in view of the fact that so far assessments that have been carried out on the basis of the EUnetHTA core model did not fulfil the high quality standards of the German benefit assessment in several aspects. As also requested by the European Parliament, the regulation must not lower the standards that have been established in individual member states.

Transparency of the procedure

The documents to be published also need be defined. Publication of the whole dossier by the pharmaceutical company, including all clinical results and information about the methodology used, has already proved successful in the early benefit assessment. Confidential documents could be filed in a separate appendix and should not be published.

However, it should be defined which information will be „confidential data for commercial reasons“ within the scope of the HTA assessment, because for an informed hearing procedure it is not acceptable that only selected fragmentary results and data are available.

In the German process, a hearing procedure has been established. After completion of an independent benefit assessment, the professional public, patient representatives are involved and statements of the pharmaceutical industry integrated into the discussion about the additional benefit. In contrast, the European benefit assessment procedure intends to conduct a separate annotation phase by the pharmaceutical company already during European benefit assessment.

This approach corresponds to the so-called „fact check“ that is currently part of the EUnetHTA Joint Action 3-Joint Assessments. On the basis of the experience gained to date, this step should be evaluated critically, as it was used as an opportunity by the pharmaceutical companies to

exert influence. An added value of a separate annotation phase by the pharmaceutical company as compared to a joint commenting of the draft benefit assessment by all stakeholders is not obvious and is contradictory to an independent evaluation of the evidence.

Inconsistency with the flow of the AMNOG-process

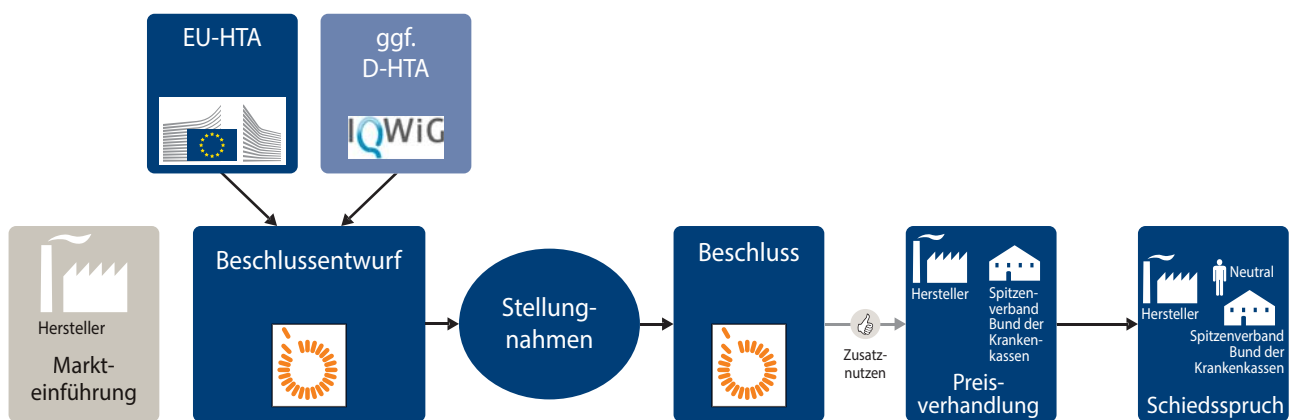
For an incorporation of a European benefit assessment into the current procedure it is necessary that the G-BA still has a certain scope for assessment and adoption of any potential value judgement to the benefit assessment is not mandatory. Moreover, evidence must be processed in a qualitative, transparent and complete manner to provide a sound basis for national decisions.

A European benefit assessment would have to be classified and evaluated together with complementary national HTA assessments (where applicable) by the G-BA before a decision about the extent of the additional benefit is taken. One possibility could be – deviating from the current procedure – to provide the opportunity to not only comment on the published documents, but also on the results of the consultations about the classification of this evidence and its valuation as well as the statement on the extent of the additional benefit in consideration of the national treatment landscape (see Figure 2).

Thus, in combination with the European benefit assessment or complementary evidence processing and national statements (where applicable), a decision could be taken that is comparable to the previous additional benefit decisions.

It remains to be seen to what extent additional assessment and preparation by the pharmaceutical company are required, how documents that have been prepared and published in English will be dealt with so that patient representatives can be involved. For the time being, a noti-

Möglicher Ablauf des EU-HTA /AMNOG-Verfahrens



Quelle: modifiziert nach BMG: Faire Preise für Arzneimittel

Figure 2: A European benefit assessment should be performed – together with complementary national HTA assessments – prior to a G-BA decision on the extent of the additional benefit.

ceable reduction of effort cannot be expected for the pharmaceutical companies.

Conclusion

Due to the numerous unclear and controversial proposed provisions, the European Commission's proposal for a European health technology assessment of 31 January 2018 must be looked at critically from the G-BA's perspective. Especially the binding adoption of the European benefit assessment as a basis for national reimbursement and price decisions is not acceptable.

To avoid restricting the member states' competence to exert an influence on reimbursement and price decisions by determining the extent of the additional benefit, individual or complementary assessments must be possible without any restrictions or authorisation requirements. Besi-

des the need for adaptation of the legal basis (amendment of Article 168 Paragraph 7 TFEU), further specifications are required regarding the process flow, decision-making mechanisms, content of the benefit assessment, and transparency. Without knowing the specific design of the benefit assessment, the European approach cannot be supported unconditionally.

Therefore, efforts should now be made to agree on uniform standards and methods and promote cooperation, e. g. with regard to joint consultations about clinical studies of pharmaceutical companies prior to joint benefit assessments.

Harmonised HTA assessment: Experiences on the way to centralised approval

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

With the draft EU regulation „on the assessment of health technologies“ the European Commission pursues the objective of a uniform Health Technology (HTA) assessment of pharmaceuticals and selected medical devices in Europe. This initiative has given rise to controversial discussions in many countries in which HTA procedures have already been established. There are concerns that these harmonisation efforts could result in a degradation of already established standards and thus lower quality and treatment standards¹. Assessment processes and criteria for clinical evidence in benefit risk assessment of pharmaceuticals have been gradually harmonised in Europe in many intermediate steps. This article investigates the experiences national approval authorities made on the way to a common European view to clinical evidence and what HTA organisations can learn from the establishment of this regulatory network.

From individual national assessment towards central approval: Experiences from the development of harmonised standards and uniform assessment of clinical evidence.

Before the first harmonisation steps were made, the legal framework and thus requirements for the traffic of pharmaceuticals was very heterogeneous in Europe. Since the beginning of the 1960s, the pharmaceutical sector has also experienced a step-wise harmonisation and enhancement of the legal framework and (assessment)processes for the production and marketing authorisation of pharmaceuticals in the development of a uniform European legal framework for the reduction or elimination of obstacles within the single market – with the objective to achieve a consistently high level of protection of public health, especially by means of a faster access to innovative and safe pharmaceuticals and a more stringent control of pharmaceutical safety².

One of the central starting points for the pharmaceutical sector was the Treaty of Rome on the harmonisation of European legislation requesting e. g. a national pharmaceutical law. Unlike the other member states of the European Economic Community, Germany did not have a national medicinal products act at that time. In November 1961, the then Federal Government complied with its obligation and established a Ministry of Health; in the same year, the first Medicinal Products Act entered into force in Germany (see Figure 1).

While this first version of the medicinal products law did not impose an obligation for the assessment of both efficacy and safety of pharmaceuticals, but requested a registration only, in the subsequent years several amendments and guidelines came into force mainly for the adaptation to European legislation³.

A further cornerstone for the harmonisation of legislation in the EU that was significant for the pharmaceutical sector was laid with Directive 65/65/EEC. For the first time, this directive defined key terms like „pharmaceutical“ and provided specifications or requirements for the marketing approval of pharmaceuticals: the proof of therapeutic efficacy, safety and quality². With Directive 75/318/EEC and especially 75/319/EEC, the provisions for pharmaceutical control were gradually aligned and not only minimum requirements regarding the production and assessment and details for production and import authorisations defined, but also a committee established for pharmaceutical specialities – composed of representatives of the member states and the Commission – to facilitate granting of authorisations for the marketing of one pharmaceutical speciality in several member states, i. e. to avoid assessment of a pharmaceutical that has already been approved in one member state and consequently additional work in another

member state (Mutual Recognition Procedure, MRP).

In Germany, these directives were implemented with the amendment of the Medicinal Products Act of 1976, especially with the introduction of a compulsory approval procedure including the obligation to furnish proof of quality, efficacy and safety.

The introduction of the central approval procedure provided for by Regulation (EEC) No. 2309/93 of 22 July 1993 presented another major milestone. These provisions for a centralised approval process were initially intended for high-technology pharmaceuticals (in the biotechnology sector) to ensure a joint assessment of these complex products across Europe on the basis of the best available expertise from the EU member states – and thereby prevent that these innovative products cannot or only insufficiently be assessed in one or more member states and thus not be launched on the market.

With the possibility of submitting one single approval



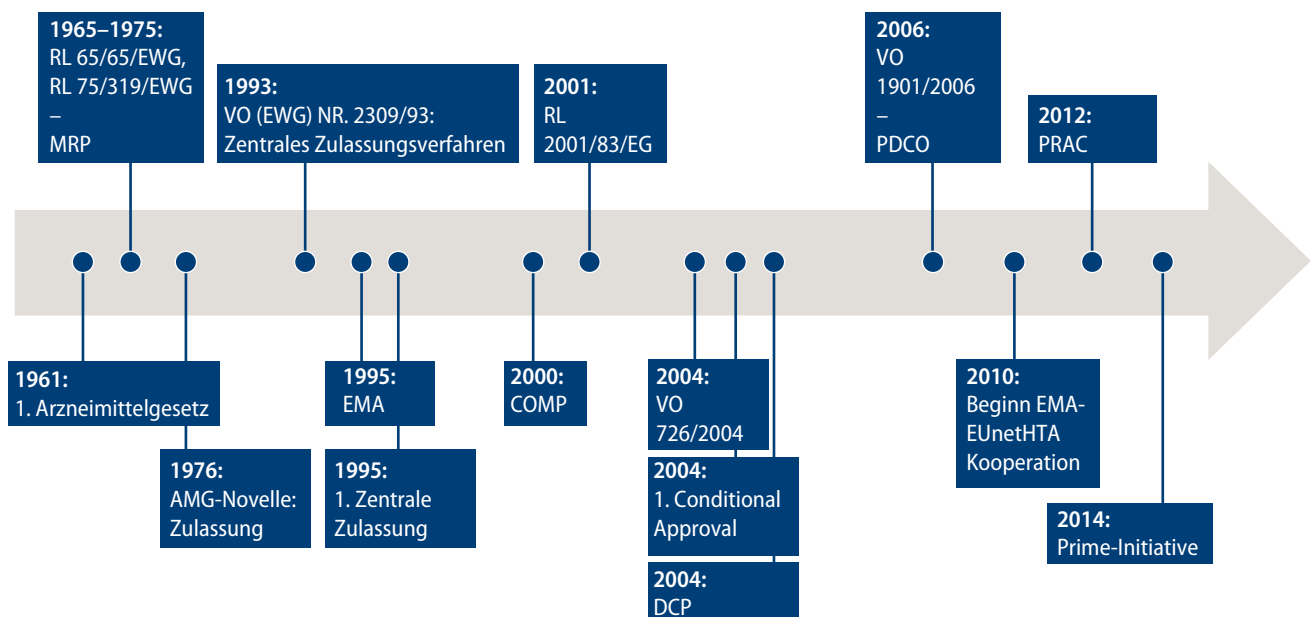
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Meilensteine der Harmonisierung von Rechtsvorschriften und Bewertungsverfahren

Meilensteine und Weiterentwicklungen auf dem Weg von heterogenen nationalen Vorgaben über Harmonisierungen der Rechtsvorschriften und Bewertungsverfahren für Arzneimittel in der EU.



Quelle: Dr. Wiebke Löbker

Figure 1: On the basis of the first Medicinal Products Act in 1961, assessment criteria and processes of clinical evidence have been harmonised in many intermediate steps during approval.

application and pooling of the best available scientific expertise in the EU member states for benefit risk assessment based on continuously harmonised standards, the objective was not only to ensure uniform patient protection across Europe, but also to further reduce administrative work in order to be able to focus on the key scientific issues on the therapeutic benefit, quality and safety of a pharmaceutical.

As a consequence of this directive, the European Medicines Agency (EMA) – formerly called European Agency for

the Evaluation of Medicinal Products (EMA) – was established in 1995 simultaneously to the central approval procedure. With its Secretariat, the scientific committees consisting of representatives of the member states, it has a key coordinating function in the approval and control of pharmaceuticals across Europe.

In the same year, the first authorisation was granted for the marketing of a pharmaceutical (Gonal-F (follitropin-alpha)) within the scope of the central approval procedure⁴.

With Directive 2001/83/EU and especially Regulation

(EU) No. 726/2004, further fundamental adjustments of the legal framework and benefit risk assessment procedure were made based on a report by the Commission. With Directive 2001/83/EU all directives relating to the pharmaceuticals sector (for human use) valid at the time were summarised in one directive.

This Directive codifies the principles for the production, marketing and control of pharmaceuticals and has been modified continuously. With the adoption of this directive and introduction of the decentralised procedure (DCP), another opportunity was created to obtain national marketing authorisations for pharmaceuticals in several member states of the EU at the same time. Ultimately, Regulation (EU) No. 726/2004 replaced Regulation (EEC) 2309/93 promoting the further expansion of pharmaceuticals for which the centralised authorisation procedure is compulsory.

Moreover, the regulation provided the opportunity of „conditional“ approval, i. e. a preliminary approval is granted subject to defined conditions. This form of authorisation is used for pharmaceuticals for the treatment of severe or life-threatening diseases for which other effective treatment options are not yet available, for which available data show a positive benefit risk ratio, and a significant patient benefit has been come apparent. These conditional approvals will be reviewed on a yearly basis with other reliable evidence (from recent or ongoing clinical studies). In order to increase transparency, it was agreed to publish European Public Assessment Reports (EPAR)⁵.

On the basis of further legal acts, new committees were established in the EMA – e. g. Committee for Orphan Medicinal Products (COMP) in 2000 on the basis of Regulation (EC) No. 141/2000 and six years later the Paediatric Committee (PDCO) on the basis of Regulation (EC) 1901/2006 – to increase pharmaceutical supply for these specific pati-

ent groups. With the foundation of the PRAC (Pharmacovigilance Risk Assessment Committee, PRAC) in 2012, monitoring of pharmaceutical safety was intensified across Europe.

Besides these legal framework conditions, support options provided by the EMA and European network, respectively, for the development of innovative pharmaceuticals were extended: In 2010, cooperation between EMA and the HTA institutions of the European network EUnetHTA⁶ – previously on a voluntary basis – was further intensified, which, among other things, resulted in a better understanding and establishment of a permanent platform for joint consultations on regulatory and HTA aspects (parallel consultation)⁷.

With the PRIME (PRiority Medicines) initiative that was introduced in 2014, the EMA and European network support the development of pharmaceuticals with high medical needs; this voluntary initiative is based on a stronger interaction and early dialogue with developers of promising innovative pharmaceuticals in order to optimise development plans and accelerate assessment to ensure that these products will be developed in accordance with the current status and applicable guidelines from the very beginning and reach patients without undue delay⁸. Innovation offices that have been established by numerous national approval authorities point in the same direction⁹.

The European network: Collaboration between EMA and national approval authorities

Through the comprehensive harmonisation of the requirements in the pharmaceutical sector in the European Union (EU), the division of labour in the approval or risk assessment procedure, but above all through the simultaneous introduction of a central approval procedure and establishment of the EMA, a strong European regulatory network

has developed gradually in recent years sharing the best available expertise from the individual European member states and thus employs an efficient approach.

The EMA constitutes the central administrative coordination unit. Experts of the more than 50 national approval authorities across the EU or the European Economic Community (EEC), respectively, work in seven committees and (temporary) working groups in the EMA and are responsible for the scientific assessment. The Committee for Human Medicinal Products (CHMP) and Committee for Veterinary Medicinal Products (CVMP), respectively, take a central role; both work closely with the other committees (PRAC, COMP, PDCO; Committee on Herbal Medicinal Products (HMPC), Committee for Advanced Therapies (CAT)) and the subordinated working groups.

Such a constellation does not only allow for pooling of the best available expertise from the European member states for the specific field and a high procedural efficiency, but also obviates the current criticism that the member states' national sovereignty would be sacrificed by a central European HTA assessment.

The EMA's committees in which (at least) one expert from every member state is represented and that are supported by the EMA Secretariat, do not only carry out the professional assessment of the centrally submitted applications and EU risk assessment procedures, but also take care of the development and updating of scientific guidelines. These guidelines reflect a harmonised interpretation and uniform assessment standards, of the EU member states and the EMA for the comprehension and application, respectively, of the requirements specified in the community directives for the proof of quality, safety and efficacy and thus support developers during the implementation of their projects. Additional questions will be discussed during consultation procedures at national level or the

EMA (Scientific Advice; Protocol Assistance) by the responsible working group of the CHMP, e. g. the Scientific Advice Working Party.

For every scientific assessment of a procedure, one of the Committee members is appointed as rapporteur or co-rapporteur, respectively. Selection of the (co-)rapporteur is performed on the basis of objective criteria – such as professional expertise, experience in the assessment of similar procedures/products etc. – to guarantee the best available expertise at all times. Rapporteur and co-rapporteur, respectively, are responsible for the scientific assessment and preparation of the assessment report (EPAR).

All committed decisions shall be taken by consensus whenever possible. In the event of unanimity not being achieved, the scientific expert assessment will be accepted, if the majority of committee members (absolute majority) votes for it; deviating positions and representatives of this opinion will be mentioned in the EPAR¹⁰.

The scientific assessment report that has been prepared by the rapporteur and co-rapporteur and accepted by the CHMP forms the basis for the decision about the approval that will finally be taken by the European Commission.

Common activities – Approval authorities and HTA-bodies

While requirements of approval authorities have been harmonised to a great extent in the last decades in Europe and thus also in Germany, this does not yet apply to the specifications of social legislation across Europe. At present, HTA assessments and reimbursement decisions are only taken at national level; the systems in the member states are quite heterogeneous regarding methodology and time/time frame. With the German Pharmaceutical Market Reorganisation Act (AMNOG) an early benefit assessment was introduced in Germany according to Section

35a of the 5th German Social Codebook (Sozialgesetzbuch V, SGB V) for new pharmaceuticals that provide the basis for decisions about the reimbursement amount between manufacturer and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband). While the focus of the assessment during the approval of pharmaceuticals is on sufficient quality, efficacy and safety, during the early benefit assessment it is examined which therapeutic added value („additional benefit“) a new pharmaceutical has against the treatment standard that has been established in Germany justifying – where applicable – a higher price as compared to the treatment standard.

Even if different questions are addressed during the approval of pharmaceuticals and early benefit assessment according to Section 35a SGB V and different assessment criteria used, the assessment is mainly performed on the basis of the same evidence. Therefore, the challenge for pharmaceutical companies is to design clinical studies that meet both the approval authorities' requirements for global multinational clinical assessments and the requirements for the additional benefit assessment in Germany.

As other countries have also implemented partly rather complex HTA procedures, these studies – most of which are multinational – must also comply with these requirements that complicate the conduction of the respective studies. For the predominantly internationally operating companies this means that the national marketing and market access departments that are responsible for reimbursement negotiations in the member states must be involved in global development programmes much earlier than before in order to cover most of the requirements. Scientific consultations by the involved institutions are becoming more important in the planning of pivotal studies. At national level, reciprocal participation in consultations at the approval authorities (Federal Institute for Drugs and

Medical Devices (BfArM) and the Paul Ehrlich Institute, PEI) or Federal Joint Committee (G-BA), respectively, and above all participation of higher federal authorities in consultations according to Section 35a SGB V by the G-BA have been established¹¹. Pharmaceutical companies make increasing use of these common consultations. However, they should use this offer even more, in order to make themselves familiar in a timely and efficient manner with both the requirements for additional benefit assessment according to Section 35a SGB V and approval requirements (see Figure 2).

Additional challenges arise from the approval and with regard to the additional benefit assessment as a consequence of the increasingly complex study design (e. g. so-called basket/bucket, umbrella or platform design studies). Accelerated approval procedures for active substances for the treatment of rare diseases with high medical needs are also caught between approval and additional benefit assessment; critics of these procedures – where authorisation is e. g. granted for a limited period and subject to certain predefined conditions – often say that at the time of approval and thus due to the close temporal relationship to the time the additional benefit assessment is performed, the available evidence is often not sufficient to finally assess the efficacy and safety of these pharmaceuticals¹².

Moreover, digitisation in the healthcare sector, strong stakeholder network and ever-increasing amount of data from various sources (big data) leading to a change of the pharmaceutical market¹³ will have an impact on assessment processes during approval and HTA assessment.

A close cooperation with early exchange between approval authorities and HTA institutions is essential – despite the various tasks and resulting requirements – in order to design clinical trials as efficiently as possible in terms of the data base required for approval and benefit assessment.

In view of a potential introduction of a uniform HTA assessment procedure in Europe that shall be performed after the benefit risk assessment, follow-up opportunities will arise that will require a close dialogue and exchange between the institutions that are responsible for the approval of pharmaceuticals and control on the one side and institutions for HTA assessment on the other side.

Summary

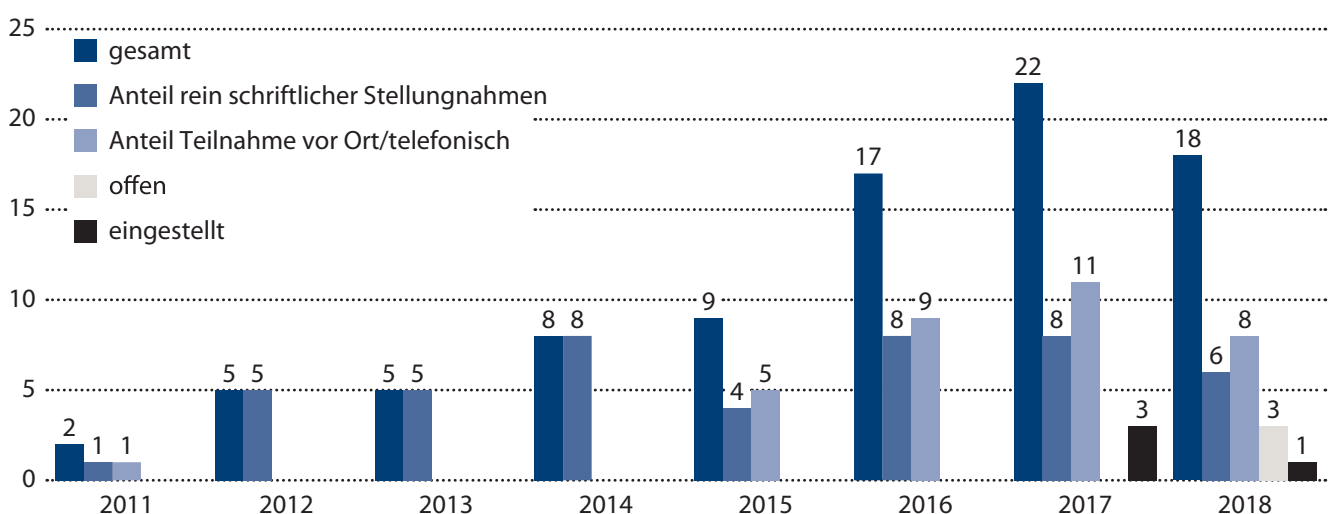
The process of harmonisation of European pharmaceutical legislation and the resulting assessment processes were time-consuming and – starting from heterogeneous assess-

ment criteria in the individual member states and after numerous amendments, specifications and continuous optimisations – the current European network was established consisting of the EMA at the centre as coordinating unit and the national approval authorities.

The structure of scientific committees at the EMA with experts of the national approval authorities and the European member states or the EEC, respectively, has proven especially valuable ensuring that the best possible scientific expertise is available for benefit risk assessments. In these committees, a common understanding of regulatory and procedural requirements has been developed on a

Entwicklung der Zahl der Beratungsgespräche unter Beteiligung des BfArM

Beratung nach § 35a SGB V durch den G-BA unter Beteiligung des BfArM 2011 bis 2018



Aufgeschlüsselt nach Art der Teilnahme (schriftlich, telefonisch bzw. vor Ort/offen/eingestellt; Gründe für die Einstellung: Rücknahme des Beratungsantrages durch den Antragsteller, parallel laufender Scientific Advice bei der EMA oder keine Fragen zu geplanten klinischen Studien in der Anfrage enthalten).

Quelle: BfArM

Figure 2: Pharmaceutical companies make increasing use of the offer of joint consultations by the G-BA and higher federal authorities.

continuous basis and a common set of standards established as scientific guidelines; this does not only allow for uniform assessment and efficient division of labour, but also ensures that national conditions are considered. It provides an important support tool for developers in the preparation of applications for approval.

Moreover, increasing transparency, e. g. through the publication of assessment reports (including presentation of differing positions and discussions in the committees) and guidelines – that generally undergo public consultation – plays an important role and should be considered in the development of a uniform HTA assessment process and the required structures from the beginning.

Taking into account the very heterogeneous HTA processes and healthcare systems in the individual European countries, the proposal of a uniform HTA assessment will only be the first step on a long road towards the ultimate objective, i. e. a uniform access to efficient and safe pharmaceuticals across Europe. Continuation of the dialogue between the institutions that are responsible for the approval and for HTA assessment can certainly contribute to a successful establishment of a European HTA process. As mentioned above, extensive experiences gained on the way towards a common European look at clinical evidence during the approval of pharmaceuticals can be very valuable and useful.

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European benefit assessment as a chance for Germany and Europe

Han Steutel | Association of Research-Based Pharmaceutical Companies (vfa)

With a draft law on the simplification and harmonisation of national assessments of health technologies, the EU commission presented a proposal for a uniform European benefit assessment (EU-HTA) in January 2018. It is the logical continuation of the voluntary cooperation of national HTA authorities within the scope of EUnetHTA while ensuring conformity with the German AMNOG system. Research-based Pharmaceutical companies support this proposal, as EU-HTA promises a substantial benefit primarily for patients and creates synergy effects for the assessment of pharmaceuticals.

While the marketing authorisation of pharmaceuticals has been further standardised and centralised across Europe since the establishment of the European Medicines Agency (EMA) in 1995, there are still major discrepancies in the subsequent national processes for the consideration of evidence within the scope of so-called Health Technology Assessment (HTA). The resulting efforts to intensify collaboration between HTA authorities and systems were substantiated with the establishment of EUnetHTA in 2006. Various so-called Joint Actions were conducted to strengthen and operationalise the cooperation of national HTA authorities.

With the first Joint Action from 2010 to 2012 HTA methods were developed that were subsequently applied as pilot projects to already approved pharmaceuticals during Joint Action 2 until 2016 to gain first practical experiences. The current Joint Action 3 which will run until 2020 focuses on a joint benefit assessment (joint clinical assessment) simultaneously to the process of marketing authorisation of pharmaceuticals. In mid November, a list of products was published for which EUnetHTA and the respective national HTA authorities have a particular interest that a benefit assessment is conducted.

For the further development of this previously voluntary, project-based cooperation beyond 2020 and the application of the evidence generated, the EU commission presented a draft law on 31 January 2018. Essentially, this „Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU“ requires a European clinical benefit assessment instead of national solo efforts. The ultimate goal is to improve the evidence base at European level following the EMA’s model. Besides the identification of emerging health technologies (horizon scanning) and

voluntary cooperation in other HTA-related areas, the two fundamental pillars are joint scientific consultation and joint clinical assessment.

The primary objective is to establish a high-quality and efficient system of joint clinical benefit assessment with a process supported by the member states after joint consultation and coordination of the necessary requirements for evidence generation. The decision about the specific additional benefit and the resulting context-specific and national pricing would thus remain within the individual national HTA systems – e. g. for Germany the key stakeholders are the Federal Joint Committee (G-BA) and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) (see Figure 1).

Research-based pharmaceutical companies support this draft law and the resulting objectives. Major obstacles and bias in the transfer to national health systems resulting from the voluntary approach could thus be avoided. This applies particularly to the lack of sustainability of the cur-

rent cooperation resulting from unclear responsibilities and evidence requirements and duplication of work for companies and national HTA bodies due to country-specific enquiries.

High patient benefit

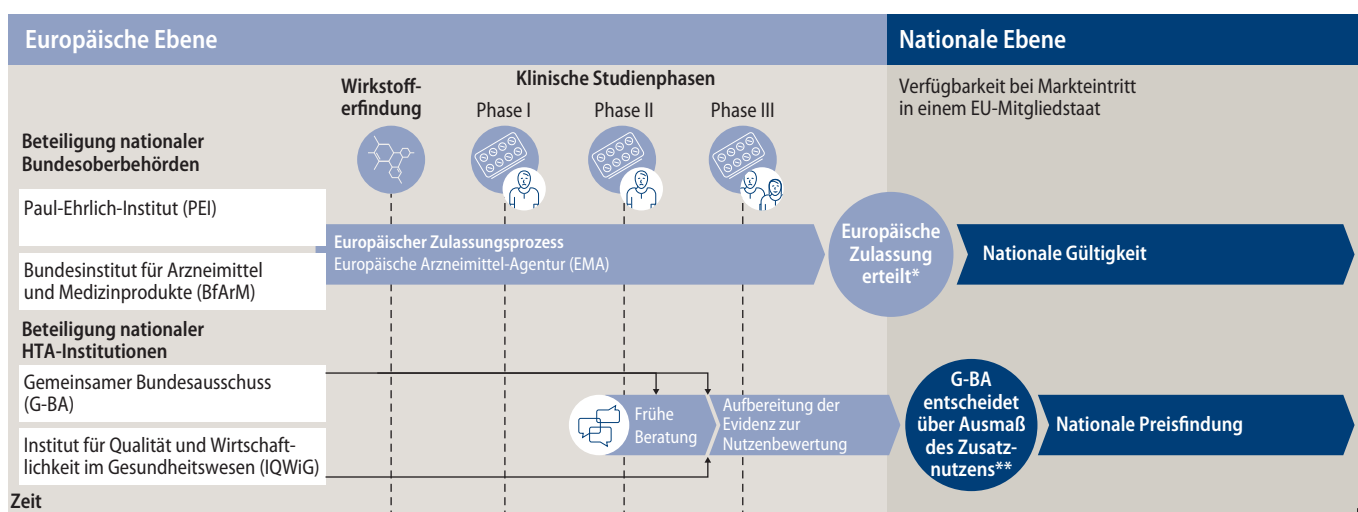
The previous mode of early dialogue for a non-binding exchange about evidence requirements would be put on a solid and legally-binding foundation through joint scientific consultation. Joint scientific consultations would facilitate coordination of the required data with the EMA and HTA bodies. Consequently, these findings could be considered for study planning so that the required evidence is generated in a feasible and efficient way for both areas, i. e. approval and benefit assessment. In fact, this improved coordination between approval authorities and HTA bodies would reduce unnecessary conflicts and discrepancies regarding the consideration of study data. And patients would benefit from high-quality and more precisely customised clinical studies. At the same time, the determination of procedural rules and methods for clinical assessment by primary legislation would also provide a reliable organisational framework for the preparation of the joint HTA report.

At present, the highly valued German system, immediate availability of pharmaceuticals for patients directly after their approval with simultaneous benefit assessment cannot be taken for granted in other countries. By means of temporal synchronisation between the centralised approval procedure and the proposed coordination mechanism, the results of a joint clinical benefit assessment would be available to all member states at the time of market authorisation or immediately afterwards. This would ensure faster access to new pharmaceuticals for EU patients without jeopardising the existing timely patient access to innovati-



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Der Kommissionsvorschlag sieht eine europäische Lösung statt nationaler Alleingänge vor



*Voraussetzung: Positives Nutzen-Risiko-Verhältnis; **Zusatznutzen gegenüber einer Vergleichstherapie Quelle: vfa

Figure 1: Following a common scientific consultation about the definition of evidence requirements, the process in the member states shall create an efficient system for clinical benefit assessment.

ve therapies in Germany. For this purpose, clear milestones and deadlines are required.

In order to ensure a high relevance of the assessment for both clinical practice and patients, it is also vital that all relevant stakeholders are involved in the process. For this reason, patients, clinical experts and other stakeholders should be given the opportunity to issue their opinion and make comments during the preparation of the HTA report.

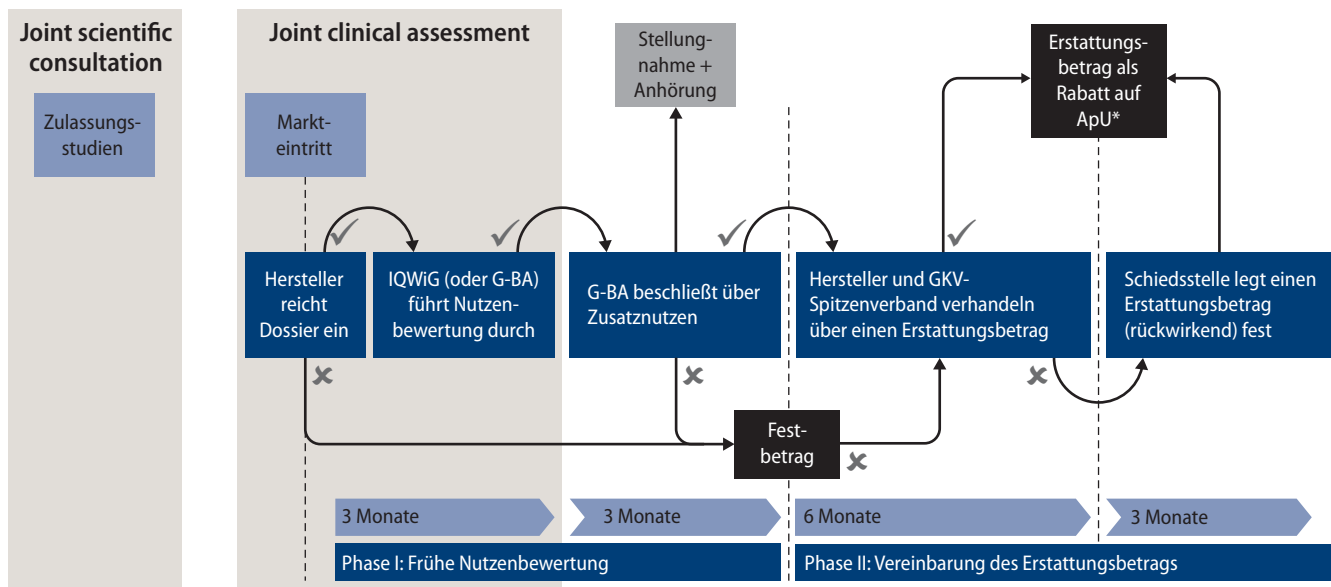
Compatibility with the German AMNOG system

Despite this process of clinical benefit assessment at EU level, all reimbursement decisions would remain the responsibility of the German healthcare system and would still be subject to the principle of self-administration. Thus, the G-BA would still be responsible for the whole procedure. Mo-

reover, the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) would be responsible for subsequent price negotiations to set the reimbursement amount. Specific arrangements, e. g. for orphan drugs, would remain unchanged (see Figure 2).

Only the „technical“ assessment of the additional benefit which is currently performed by the Institute for Quality and Efficiency in Healthcare (IQWiG) would be shifted to the European level – with the participation of the IQWiG. National framework conditions, e. g. appropriate comparative treatment in the AMNOG process as determined by the G-BA, do not present an obstacle. Within the scope of joint scientific consultations, key parameters such as comparators and endpoints could be discussed and considered at an early stage. Especially different reference therapies

Wie passt EU-HTA zum AMNOG?



*ApU: Abgabepreis pharmazeutischer Unternehmer

Quelle: vfa

Figure 2: Only the „technical“ assessment of the additional benefit which is currently performed by the IQWiG would be shifted to the European level. All reimbursement decisions would remain in the national context.

could easily be included, if the specific needs of a certain member state require it. Nevertheless, it is of fundamental importance that the parameters thus determined will in fact be taken into consideration by HTA bodies. This is the only way that more clarity regarding the required generation of evidence already during the clinical development would also enhance planning and customised adaptation of clinical studies on the basis of the requirements of benefit assessment. In addition, the G-BA and particularly the IQWiG would not at all lose its importance during benefit assessment: Within the scope of the voluntary European cooperation under EUnetHTA, both institutions already play a major role in the development of methodology,

quality assurance and generation of evidence. As part of the future Coordination Group they would also be substantially involved in decision-making processes. It is worth taking a clear look at the success of the Europeanised approval process of the EMA: Despite harmonised and centralised approval at European level, the institutes that are relevant for Germany, i. e. the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute, have not lost but rather gained in importance.

Obligation creates synergy

Though the cooperation of national bodies at EU level in a well-structured procedure, all skills and experiences can be

used as needed and can be consolidated. The G-BA could actively participate in the specification of an appropriate and relevant comparative treatment and thus apply the high national quality and assessment standard to the EU level. This pooling of competences of the member states with active participation of German institutions would certainly contribute to an improved HTA quality at EU level.

Furthermore, the resulting elimination of inefficient parallel structures would allow for an efficient allocation of human and financial resources – both by companies and the competent authorities. The gain in efficient evidence is of great importance, as HTA bodies will define their requirements at an early stage within the scope of parallel advice so that this information can be considered in the planning phase of international studies.

From the industry's perspective, it is crucial that the European cooperation is not repeated at national level to avoid duplication of work. This could be achieved with binding provisions and feasible application of the results from the joint clinical benefit assessment. Moreover, the (sub)populations and comparative treatments that have been defined by the Coordination Group during the scientific consultation should be binding. For this is the only way that an enhanced planning capability and predictability achieved by the joint scientific consultation would also have a consolidated and consistent effect on the result of the joint benefit assessment.

Irrespective of all harmonisation efforts – also based on the EMA's model – approval and HTA should interlock as much as possible, but still remain two separate processes. Despite specified milestones and deadlines, potential deviations in the completion of one procedure would thus have no impact on the successful conduction of another.

As of 2020 – after a three-year period of tertiary implementation – the Commission provides for a three-year in-

troductory phase. During this phase, participation is optional, but the specified standards are binding. As of 2026, consideration of the joint HTA report would then be binding for all member states. For Europe and Germany this offers the opportunity to align and harmonise any differences in the subsequent benefit assessment and integration of innovative therapies into the national healthcare systems after successful Europeanisation of marketing authorisation of pharmaceuticals.

Next steps in the European benefit assessment – From a policy perspective

By Michael Hennrich | Member of the German Bundestag

Does a certain health technology work better, as good as or worse than existing alternatives? Since the introduction of AMNOG, we took the answer to this question as the basis for pricing of prescription pharmaceuticals in Germany, the so-called Health Technology Assessment (HTA). At the same time, an increased (rather than deepened) networking of HTA bodies was observed at EU level. When the European Commission announced its plans in the Commission Work Programme 2017 to intensify the cooperation on EU benefit assessment, this was taken note of. But the proposal for a joint assessment of health technologies at EU level presented on 31 January 2018 came like an unexpected thunderbolt.

B **ackground**
In the 1970s, the first national agency was established with the Swedish SBU followed by an initial wave of agency foundations between the end of the 1980s and end of the 1990s. Normally, there is a central national assessment body. Regional HTA assessments are performed in countries with strong regions, e. g. in Great Britain or Spain, where the healthcare system is managed at regional level and different HTA bodies in the provinces. Meanwhile, national structures have also been established.

Since 2011, the additional benefit assessment of new pharmaceuticals under the German Pharmaceutical Market Reorganisation Act (AMNOG) represents a national HTA. Pricing of pharmaceuticals takes place in cooperation between IQWiG and G-BA on a systematic and feasible basis depending on the patient benefit. It was especially important for us that decisions are taken independent of politics. This procedure was designed as an adaptive system and was continuously evaluated and further developed since then – recently with the German Act on Strengthening Pharmaceutical Supply in Statutory Health Insurance (AM-VSG) in 2017. As a result, it proved to be a sustainable success.

Yet the question of the so-called „fourth hurdle“ is not applicable in Germany. This means that after 1. quality, 2. efficacy, and 3. safety, cost-effectiveness of pharmaceuticals will not be examined in a fourth step. In fact, the decision about costs (reimbursement by statutory health insurances) is the result of the AMNOG procedure. In Germany, we chose this approach deliberately. The alternative option would have been that a certain pharmaceutical is only reimbursable, if it is below a defined (cost-)threshold. This value is measured in quality-adjusted life years (QALY). Even at this stage, significant normative differences can be

observed to other EU countries, such as the Netherlands, Great Britain, or Sweden. From the industry's perspective, criticism of the national responsibility for the benefit assessment is not new. Pharmaceutical manufacturers argue that a uniform benefit assessment across Europe after EU approval by the European Medicines Agency (EMA) would be a consistent approach. From the companies' perspective, this individual character of the member states is associated with an additional expenditure and thus costs. It should also be noted that German politics generally aims at promoting European integration. According to the first chapter of the current coalition agreement of the Great Coalition the objective is to „dare more Europe“.

After the first joint projects have been completed within the scope of the European network for Health Technology Assessment (EUnetHTA) in 2006, the EUnetHTA Collaborati-



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on was established in 2009 ensuring – by means of human and financial resources – that the structures and tasks that have been initiated during the project can be continued. The focus was placed on reducing cultural, linguistic or contextual barriers. Since 2010, this approach has been continued in EUnetHTA Joint Action 1 (2010-2012) and 2 (since 2012). The purpose of the Joint Action was to further develop the work of the Pharmaceutical Forum and contribute to a sustained establishment of a functioning and effective HTA cooperation across Europe. However, participation is on a purely voluntary basis.

The proposal of the European Commission

But what is the currently discussed European Commission's proposal all about? The EMA as approval authority for pharmaceuticals and the Medical Device Regulation served as a model for the European Commission's proposal on the implementation of a benefit assessment of health technologies across Europe. The main focus is on strengthening the Single European Market. Duplication of work by companies and HTA bodies shall be eliminated. Medical devices and pharmaceuticals shall be made available across Europe at a consistently high level of quality. In any case, the European Commission achieved one goal: The focus is now on HTA. Within the scope of the current budget negotiations, the EUnetHTA will certainly not be forgotten.

In practice, HTA procedures shall be performed for all prescription pharmaceuticals, selected medical devices of risk classes IIb and II, and in vitro diagnostics. They shall be evaluated for safety and efficacy from a medical point of view as well as for economic efficiency, ethics and patient-orientation from a non-medical point of view. The Coordination Group composed of representatives of the member states shall be responsible for the procedures. From the beginning, the intended position of the European Commissi-

on in this Coordination Group as Co-chair was criticised. Especially from a German perspective, this strong role of the executive is quite strange. In Germany, IQWiG and G-BA are much more independent. This is all the more important, as the results of the European HTA must be adopted in the harmonised areas on a mandatory basis and any deviation at national level shall not be permitted.

Admittedly, the European Commission's came all of a sudden for federal politics. We did not have the impression that the proposal was signalled in advance by means of consultations. There was a tremendous outcry from the GKV emphasising the legal differences and methodologies of benefit assessment in the EU states. The main concern of the G-BA is that it must be safeguarded that a comparator must still reflect the generally accepted standards of medical knowledge in future.

The proposal was generally welcomed by pharmaceutical manufacturers. Certainly not only because a Europeanisation will create and make use of synergy effects, but also because the intended early involvement of the manufacturers represents a paradigm shift as compared to the German procedure. The results of the first reflections already showed that there are still many obstacles to overcome, before European HTA can be used as a sound basis for national pricing. For us in Germany it is important that the G-BA remains formally responsible for the AMNOG procedure and can still take its own decisions.

Response of the German legislator

In general, Germany is one of the most EU-friendly countries. Against this background, it is no surprise that in particular the Federal Chancellery's initial reaction to the Commission's proposal – in its coordinating role – was positive. However, many questions had to be answered in the German Bundestag (federal parliament). Besides content-rela-

ted aspects, fundamental issues were discussed, such as jurisdictional provisions and legal basis for a European HTA.

For the German Bundestag and Bundesrat (federal council) the only legal instrument to formally interfere in European legislation is a subsidiarity objection. As according Article 5 Paragraph 3 of the Treaty on European Union (EU Treaty, TEU), the Union shall act only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the member states, but can rather be better achieved at Union level. If one third of the national parliaments adopt the objection, the EU proposal must be changed, withdrawn, or reviewed.

In April 2018, German Bundestag and Bundesrat adopted such a decision. France, the Czech Republic, Poland and Portugal acted likewise. But the quorum was missed. Despite the fact that our criticism was perceived, we did not succeed. In retrospect, it would have been sufficient – and easier – to make a motion for a resolution covering all points of criticism.

The legal basis was the major point of criticism in the objection. The Commission used Article 114 TFEU (Treaty on the Functioning of the European Union, TFEU), i. e. to focus on the functioning of the Single European Market. However, Article 168 TFEU stipulates in which cases the EU may become active in health policy issues. There is a catalogue with a list of different case scenarios. Paragraph 7 states, however, that in any case, responsibility for health policy lies within the member states.

In particular, Article 8 of the Commission's proposal could be interpreted as exceeding EU competences, as it proposes the preparation of HTAs and assessment decisions that have a significant influence on reimbursability and pricing. Nevertheless, it would be more feasible to initially promote voluntary cooperation between the member states. Thus, the question is whether a mandatory co-

operation is actually required to achieve the goal of a strengthened European Single Market. A stronger structured cooperation on a voluntary basis would already be a step into the right direction.

Especially from a German perspective we don't want to compromise on the independence of a European HTA body. Therefore, we don't want the body to become politicised through a stronger role of the political opposition, as the scientific character must remain in the centre of attention. Any lowering of benefit assessment standards must be avoided. Another fact is that the manufacturers' role remains unclear, if it is not precisely defined what it means that they shall be provided the opportunity to provide feedback without going into detail.

Perspective

Subsequently to the subsidiarity objection, Germany and France pointed out in a joint paper what is important for us in the discussion about European benefit assessment. Of course, we have to be constructive and participate in the development of content for a European benefit assessment. European HTA can become a success, if scientific independence, highest evidence criteria and national autonomy are guaranteed in the determination of prices.

The European Parliament followed this approach on 3 October 2018 with a clarification of the member states' rights. As compared to the Commission's proposal, parliament voted for a stricter division between the EU's and member states' competences. In particular, additional studies at member state level shall be possible, e. g. if the respective medical standard cannot be sufficiently fulfilled in the respective country by examination of the comparative treatment at European level.

The European Parliament decided about the usual voting procedure for the decision body with a qualified major-

ity. Initially, the Commission proposed that the group (one person for every member state) that decides about the scientific work, takes a unanimous decision whenever possible. However, it left open what happens in the event of unanimity not being achieved. A qualified majority in the Council means that 55 percent of the member states must vote for a proposal, i. e. in practice this means 16 out of 28 member states; and altogether they must represent 65 percent of the overall population of the European Union.

Thus, our national discussion is beginning to bear fruit. Due to the approaching European election, a fast decision-making process cannot be expected. However, we will keep an eye on this topic beyond the European election in summer 2019.

Benefit assessment across the EU: The perspective is right, but that will be a real labour of Hercules

By Dr Florian Staeck

The intended establishment of a benefit assessment of new pharmaceuticals at EU level presents both opportunities and risks. Which perspective will finally prevail, will predominantly depend on the specific design of the future EU regulation. Many of the effects of a European harmonisation of benefit assessment for the national healthcare systems are not yet foreseeable (i. e. in autumn 2018) in view of the ongoing legislative process. However, the majority of the participants of the 8th meeting of the Interdisciplinary Platform on Benefit Assessment in „Early benefit assessment in the European context – Perspectives and positioning“ noted positively that critical remarks will be considered in the further consultation process.

During the meeting on 12th/13th October 2018 in Fulda the European Commission's initiative was honoured as a potential development. However, participants referred to the many questions that have not been answered yet, how a harmonised European benefit assessment will relate to the current AMNOG procedure in Germany and the fundamental principles of evidence-based medicine.

Supporters: Supporters of the EU regulation say that the past project-based EU funding of a voluntary cooperation within the scope of EUnetHTA hardly brought any substantial progress and further specifications relating to the European cooperation is required. Participants noted that limitations of the previous approach were clearly visible. Project funding that had been practised for the last 20 years in some member states was associated with permanently understaffed organisations. In addition, EUnetHTA reports were hardly used at national level, as member states refrain from implementing the results due to national specifics that would make extensive amendments of national legal framework necessary. Moreover, EUnetHTA reports were considered „hardly readable“, because the involved

HTA authorities worked on the basis of different standards.

Supporters of the harmonised EU HTA procedure also refer to the global perspective of approval and assessment of new pharmaceuticals. In contrast to the US, Europe was a subordinated market in global terms. Participants emphasised that it was all the more important for the EU member states to have one „strong voice“ especially for manufacturers. The EMA's development was mentioned as an example for consolidated processes at European level.

Besides, predictability and plannability of the HTA process would be enhanced for manufacturers, if the clinical assessment was carried out in a joint procedure according to predefined rules. Thus, duplication of work could be reduced for both industry and HTA authorities. While the assessment comprises the examination, the appraisal constitutes the final rating of the benefit on the basis of previous evaluation.

Sceptics: Sceptics stressed, however, that details of the EU procedure were hardly foreseeable and could jeopardise the undeniable advantages of the AMNOG system, including reimbursement of the new pharmaceutical from the first day of approval, but also protection against an excessive financial burden for statutory health insurances. They continued that further advantages comprised the short period of time allowed for the decision, commitment to patient-relevance in the HTA process, a high methodological standard, as well as the high-quality comparator used in AMNOG. From the professional associations' perspective, the high level of transparency that had been achieved with AMNOG shouldn't be forgotten.

Altogether, the expected benefits of a European benefit assessment procedure for Germany, for e. g. obstacles regarding market access or availability of new pharmaceuticals, would primarily depend on the economic performance of national healthcare systems, which would, howe-

ver, not be applicable for Germany. By contrast, existing national problems would not be alleviated by joint European assessments. Examples included the privileged status of orphan drugs, lack of recognition of patient-relevance of clinical endpoints and the fact that prescribing physicians did not have economic prescription security in the whole therapeutic area through some AMNOG assessments – especially in the event of inconsistent assessment results in the subgroup area of an active ingredient.

Dispute about the binding force: The question of the binding force of a European assessment that has not been decided politically was controversially discussed. Hence, participants noted that the EU Parliament had somehow put the binding adoption of the European benefit assessment into perspective in its decision of 3 October 2018 as compared to the Commission's draft of 31 January 2018, but the extent to which national assessment standards could be used in future had not yet been finally clarified and depended on further negotiations in „trialogue“ between EU Parliament, European Commission and Council of Ministers. Furthermore, key questions like Rule of Procedures and Methods Paper should not be part of the EU Regulation according to current knowledge, but should be established within the scope of subordinate delegated legal acts. On the other hand, it was not considered appropriate to regulate a Methods Paper by a legal act. There was no reason for concern on that matter, as benefit assessments should remain the member states' responsibilities.

The participants' counter-argument was that both processes could not be separated from each other. If a comparator was used in the assessment that is considered inappropriate in one member state, the subsequent appraisal process would be delayed. They continued that this could cause problems in the tightly scheduled AMNOG process and reduce planning reliability for manufacturers. It would

be unrealistic to expect that all member states always agree on one comparator. A comparator that is considered „right“, was always related to the respective national treatment structures that – in case of Germany – were also influenced by Disease Management Programmes. However, some stakeholders declared they wouldn't mind having two or three comparators that would be projected next to another in the clinical assessment.

Possibility of complementary national assessments: The participants saw several uncertainties regarding the opportunity to carry out additional separate assessments against the background of highly varying treatment contexts in the member states. Pre-treatment of patients as well as the treatment sequence, e. g. in the field of oncology, sometimes vary considerably in the member states. They explained that this would result in heterogeneous treatment standards – in particular because e. g. certain cost-intensive pharmaceuticals would not be used as first-line treatment or would not be available in the individual member states.

Some HTA authorities would still request data from a national patient cohort in addition to EU assessment data. Participants recalled that the survival benefit of a new pharmaceutical might in fact differ from one country to another depending on the individual treatment structure. Thus, the question would arise as to whether national „transfer modules“ could be linked to the European assessment. Putting this topic into perspective, they pointed out that contextuality of treatment was not measured in Germany, as data were normally based on multinational studies. Consequently, the future EU process was considered to have certain deficiencies that could not be remedied by the national procedure.

In this context, participants stressed the need to keep the discourse between regulatory authorities and profes-

sional associations alive at national level. Classification and professional exchange – including hearing procedure – in the Federal Joint Committee would be indispensable elements of the whole procedure. Participants raised some concerns that this discourse might decrease in intensity or even end, if the procedure was shifted to European level without the possibility of a national veto.

Potential procedural problems in the HTA procedure:

Regarding the procedure at the G-BA, the question arises as to how time limitation and handling of new fields of application shall be regulated in a future central HTA process. They then mentioned that during later assessment 45 percent (last update 2017) of the subgroups would be assessed differently as compared to the early assessment. At present, it was not predictable whether and how these later assessments could be integrated into a European HTA system. This would present another challenge independent of the proposed EU regulation. For more and more evidence would be available on new pharmaceuticals that has been generated after their approval. So far, no widely accepted procedures can be discerned for the handling of new data packages, such as „Real World Evidence“ (RWE). Especially as the level of evidence of such data was still considered with a critical eye by the IQWiG.

Early consultation as centrepiece of the central HTA procedure: Participants expressed their hope that the early consultation of pharmaceutical manufacturers could become the centrepiece of the future centralised HTA procedure. At national – German – level, the involved authorities BfArM, PEI and G-BA had already established early consultations as routine procedures. This helps to identify aspects that are important for both approval and HTA at an early stage and pool them accordingly. The participants emphasised that convergence of requirements was not the objective, but rather safeguarding at an early stage that sound

evidence can be generated for both procedures. They reported that many national authorities had not yet conducted these consultations and would thus be quite reluctant to new tasks and the required expertise. Many smaller EU states simply lacked qualified personnel.

However, participants also underlined the improvement potential within the national consultation process. On the one hand, the number of joint consultations was still low. On the other hand, the procedure was still inefficient, as many manufacturers had identical questions, but the answers – e. g. within an indication – had not been published yet. Here, the publication of guideline documents could be useful. Furthermore, the schedule for a centralised HTA at European level had not yet been finally clarified. Depending on the proposed deadlines, conflicts to the previous national appraisal procedures might arise. For example Italy and Spain would start assessing shortly after the approval, but would normally need more than one year until new products are reimbursable after the approval. They explained that an assessment period of 100 days would not interfere with the AMNOG procedure.

Role model of a central approval: During the meeting, participants discussed in detail whether this historic development of a central approval at the EMA could be a role model for the future HTA procedure at EU level. The procedure of mutual recognition had been introduced in several steps and – based on the directive adopted in 1965 – 30 years had passed until the first centrally approved pharmaceutical came onto the market. This had been possible, because the best available expertise from the member states was pooled.

Today, the EMA was a network of national authorities in which particularly highly populated member states have not lost influence. Instead, the large national approval authorities still shaped the core work with their expertise. For

the involvement of „small“ member states, the EU Commission provided the regulation that the responsible rapporteur for the respective pharmaceutical remains responsible, but experts from other countries would also be involved. The former inclusion criteria for the first central approvals should provide information for future procedures in central benefit assessments. At that time, the central approval procedure started with entirely new product groups, e. g. HIV drugs.

Other elements of the European approval process were regarded with scepticism regarding a central HTA procedure. In light of several draft reports incorporated in the present EU Commission proposal, a clock stop procedure was proposed, i. e. the processing time for the authority is suspended and further data can be requested from the manufacturer. Other participants warned that such an instrument would allow member states that were unwilling or unable to provide rapid access to new pharmaceuticals to „play for time“. The European HTA procedure would thus become completely unmanageable for manufacturers and patients.

Political chances and perspectives of EU benefit assessment: Irrespective of the actual progress of the legislative process, participants considered it essential to create joint standards and transparency in order to promote the process of a European benefit assessment. However, the challenge remained to find the right compromise between a voluntary (previous EUnetHTA cooperation) and mandatory adoption of the central HTA assessment. In autumn 2018, many questions remain open regarding the actual integration of the assessment into the rather heterogeneous national healthcare systems.

Until spring 2019, a partial political agreement on key sections of the proposal seemed possible. The participants were convinced that the further the legislative process pro-

ceeded during this legislative period until May 2019, the more likely it was that a future EU Commission would take up the procedure again.

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