Analysis of the Implementation of Additive PICOs in a European Joint Health Technology Assessment – Implications of EU-HTA for Pharma: A Qualitative Exploration

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Objectives

Since 1995, the European Medicines Agency (EMA) has played an essential role in harmonising regulatory frameworks for medicinal products and devices within the European Union (EU). The publication of the first Europe-wide marketing authorization procedure marked a significant milestone in this process [1]. Until recently, however, Health Technology Assessments (HTA) were conducted exclusively at the national level, leading to fragmentation [2]. These discrepancies affected the selection of patient groups, comparators, and relevant outcomes for national decision-making [3]. As a result, health technology developers (HTD) were required to submit multiple dossiers in different formats to comply with diverse national regulations [4]. The recently implemented EU HTA Regulation (Regulation (EU) 2021/2282) introduced Joint Clinical Assessments (JCAs) using the PICO framework to harmonise the HTA landscape. While these measures aim to reduce duplication and improve efficiency [5], the actual impact on pharmaceutical companies (pU) remains unclear. Moreover, criticism has emerged that instead of reducing complexity, national requirements may simply be transferred to the European level [6]. The presented study aimed to investigate the impact of the EU HTA Regulation on pharmaceutical companies. The objective was to gain deeper insight into the practical implications and to identify the key challenges associated with the new regulatory requirements from the perspective of the pharmaceutical industry by conducting expert interviews with representatives from the pharmaceutical industry and consultancy.

Methods

In consideration of the exploratory character of the research question, a qualitative design was selected. Guided semi-structured expert interviews were conducted to investigate company perspectives on the implication and implementation of the new regulation. This method enabled a balance between structured comparability and the flexibility to capture unique insights. The interviews took place between October and December 2024.

Selection of experts: Experts were defined as individuals with role-based knowledge derived from professional experience, consulting practice, or participation in scientific associations. Potential participants were identified via direct email requests, consulting agency websites, contact portals, or academic and professional publications. After a screening of responses, eight experts from the pharmaceutical and consultancy sectors consented to participate.

Interview guide: The interview guideline was derived from the research question, the existing literature, and was structured into eight thematic categories: (1) General questions on EU HTA; (2) Challenges; (3) Participation in EU HTA; (4) Scoping; (5) Number of analyses; (6) Scaling of PICOs; (7) Business perspective; (8) Future prospects. It was established that each primary category would contain both principal and supplementary questions, with the objective of ensuring comprehensive coverage. The design of the study enabled both the comparison of results across interviews and the inclusion of open-ended responses.

Conducting and transcription: The interviews were carried out via videoconference in preferred language (German or English). All participants received prior information about the purpose, objectives, and anonymization of the study and signed informed consent forms. For confidentiality, participants were labelled Expert-1 to Expert-8. The conversations were recorded and subsequently transcribed according to Kuckartz's guidelines [7], which ensured standardized treatment of word variations, dialects, and pauses. Non-essential sections were excluded, while core content relevant to the research question was retained.

Data analysis: Content analysis is a methodical approach that aims to systematically identify and evaluate relevant information from empirical data [8]. In the context of expert interviews, category-based approaches to qualitative content analysis, when conducted with the assistance of a guideline, have demonstrated particular efficacy.

The transcripts were analysed using qualitative content analysis [9]. Following a deductive-inductive approach [10], initial categories were derived from the interview guide and then refined or expanded by themes emerging directly from the extracted data. This process ensured both theoretical grounding and openness to unexpected insights.

Conclusions

The EU HTA introduces substantial methodological and financial burdens. Tight timelines and uncertain PICO requirements force companies to anticipate evidence needs early, while limited resources create particular challenges, especially for smaller entities. Despite these hurdles, experts emphasized that harmonisation may yield long-term benefits.
The requirement to prepare the dossier within 100 days [5] forces companies to manage an enormous number of PICOs and analyses, raising concerns about feasibility and quality. By comparison, a German AMNOG dossier requires 12 months and costs around €800,000 [11]. The reliance on indirect comparisons and network meta-analyses further increases uncertainty about acceptance by HTA bodies [12]. Companies face a dilemma: address all PICOs at the risk of compromising quality [12], or prioritise selected ones, which may affect reimbursement decisions in key markets, with one-third of the European market (€143 billion) [13]. In previous systems, revenues from early launches could be reinvested to refinance later assessments [3], but this is no longer possible under EU HTA, raising financial risks. Parallel EMA/EU HTA dossiers increase upfront costs before market entry, entailing billions in sunk R&D costs [3] and up to $250 million in launch expenses [14] if approval fails. For smaller companies, the cost–benefit ratio may therefore be less favourable than in the U.S. market, which accounts for 53% of global sales [15] and has fewer regulatory hurdles [16]. Smaller and less experienced companies are particularly constrained by limited resources [17].
Pharmaceutical companies thus face a significant challenge that, if met, will allow them to maintain market presence. Yet experts highlighted potential long-term benefits: harmonised assessments could streamline market access, accelerate reimbursement in smaller markets, and increase consistency across Europe. High positive assessment rates in Germany and France [18] suggest that, with careful prioritisation and strategic planning, participation in EU HTA can remain economically viable. Nevertheless, the true impact remains uncertain. A learning process across stakeholders and closer collaboration between industry and HTA bodies will be crucial to overcoming methodological challenges, reducing inefficiencies, and realizing the benefits of a harmonised system. The EU HTA Regulation must be seen both as a risk and as an opportunity, requiring proactive adaptation by the industry.

Abbreviation	Meaning	Abbreviation	Meaning
AMNOG	Pharmaceuticals Market Reorganization Act	JCA	Joint Clinical Assessment
EMA	European Medicines Agency	JSC	Joint Scientific Consultation
EU	European Union	MAA	Market authorisation application
EU HTA	Europen Health Technology Assessment	MS	Member State
EU HTAR	Europen Regulation on Health Technology Assessment	pU	Pharmaceutical Company
HTA	Health Technology Assessment	R&D	Research and Development
HTD	Health Technplogy Developers		

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Results

Challenges for pharmaceutical companies
The analysis revealed that pharmaceutical companies anticipate a wide range of challenges in adapting to the EU HTA framework. A major concern relates to procedural and time related excessive requirements (n=8), which complicate adherence to tight regulatory deadlines. Closely linked are the demands of requiring extensive data at an early stage (n=5). Experts further emphasized resource constraints, including shortages of human resources (n=5) and the need to restructure internal processes (n=5) to handle the potential additional workload. The complexity of parallel processes, particularly the alignment of EU HTA and national procedures (e.g., AMNOG in Germany), was highlighted as a potential bottleneck (n=5). Half of the interviewed experts (n=4) highlighted methodological concerns, including data gaps, process and outcome uncertainties, and the difficulty of predicting additive PICO requirements as well as the data gap (see Figure 1).

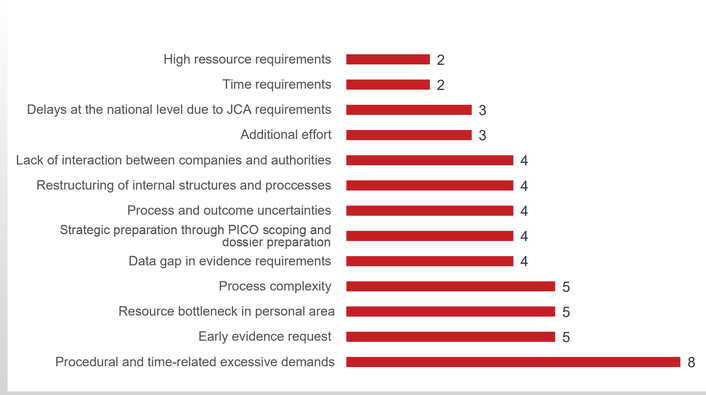

Figure 1: Challenges for pharmaceutical companies: Areas of concern arising from the new regulation (own illustration)

Methodology
The expert interviews revealed several methodological challenges associated with the EU HTA Regulation. It was evident that the most substantial of the challenges were associated with the methodology of preparing the dossier (see Figure 2). All experts (n=8) emphasized the tight timelines, which make it difficult to prepare dossiers within the required deadlines. Experts further highlighted the lack of data availability (n=7), PICO prioritisation (n= 3), and the high volume of required analyses (n=5), which increase the need for indirect comparisons, network meta-analyses, and real-world evidence.

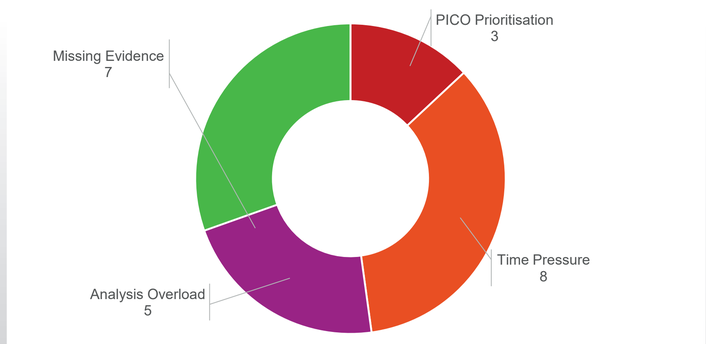

Figure 2: Methodological challenges in EU HTA dossier preparation through the company (own illustration)

In addition, experts pointed to a range of broader methodological challenges that go beyond dossier preparation and affect the overall feasibility of the EU HTA process (see Figure 3). Moreover, more than half of the experts (n=5) agreed that additional national requirements will constitute a methodological challenge and that differences in PICO frameworks between member states (MS) will further complicate the EU procedure for pharmaceutical companies. The parallel application of approval for market authorisation application (MAA) and national HTA procedures, combined with the absence of established precedents, amplifies complexity (n=4). The uncertainties associated with PICO scoping, including late changes to comparators and difficulties in predicting requirements, were identified as a bottleneck by four experts (n=4).

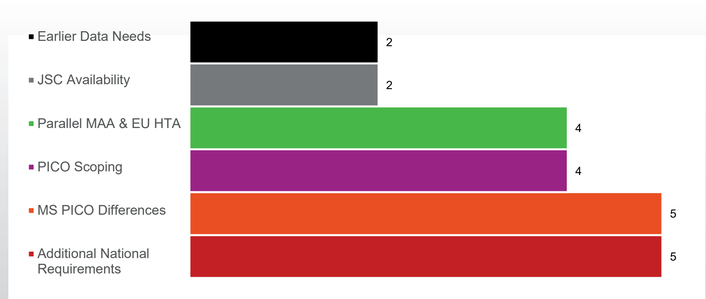

Figure 3: Methodological challenges that companies must face as a result of the new legislative act (own illustration) (JSC = Joint Scientific Consultation; MS = Member State; MAA = Market Authorization Application)

Company comparison
The consensus among experts in the field was that a company's capacity to meet the demands of the new EU HTA is significantly influenced by its size (n=8). The expert interviews revealed that financial and resource-related factors strongly influence companies ability to adapt to the EU HTA process (n=8). Company size was seen as a key predictor: large firms benefit from extensive resources (n=8), established European networks (n=4), and financial strength (n=8), while smaller companies face limitations in staffing and funding (n=8). However, experts also noted that smaller firms may benefit from greater flexibility (n=3) and from the facilitation of market access in smaller markets through EU-level harmonisation.
Prior experience with HTA processes was identified as being of equal importance to company size (n=3). In order to address the issue of limited resources, the utilisation of external entities, either through the process of outsourcing (n=5) or the establishment of partnerships (n=1) with larger firms was deliberated as a viable strategy. Moreover, the potential for technological solutions, such as the utilisation of artificial intelligence in the domain of data processing, was identified to manage the augmented workload (n=1). Table 1 illustrates the dynamics between smaller and larger pUs in terms of their respective advantages in navigating the EU HTA.

Smaller	Larger
Flexibility	HTA experience
Fast internal processes	Extensive resources
	Established EU networks
	Financial strength

Table 1: Comparative advantages of smaller vs. larger pharmaceutical companies in navigating the EU HTA (own illustration)

Strategy
The expert interviews indicated varying perspectives on the potential adjustments companies may make to their strategies in response to the EU HTA Regulation. While some experts argued that fundamental strategies would remain unchanged (n=4), one agreed that the timing of strategic decisions and market launch planning could shift. It has been proposed by several experts that the JCA may encourage companies to expand beyond the traditional Five Wave Countries by providing a uniform data foundation for additional markets (n=5). Concurrently, the increased complexity and costs associated with EU HTA could lead some firms, particularly those based in the United States, to reevaluate the significance of the European market (n=4). The strategic responses that were discussed included the greater use of national consultations to clarify PICO requirements and broader evidence generation through indirect comparisons and meta-analyses (n=1).

Financial Implications
The expert interviews revealed substantial financial implications of the EU HTA Regulation. Most experts agreed that the procedure would have no impact on pricing in Germany (n=6), but some anticipated indirect effects (n=1), particularly in countries without established comparative HTA, and speculated that a new pricing structure might develop as a result. Furthermore, the potential consequences for international reference prices were emphasized, as harmonised EU procedures have the capacity to accelerate reimbursement decisions (n=2) while also affecting pricing strategies beyond Germany (n=1). Moreover, it was anticipated that companies would encounter considerable additional expenses, primarily due to the necessity of establishing new teams (n=3), allocating resources in advance (n=5), and preparing multiple PICOs (n=2).

Summary
The analysis revealed challenges in terms of strategic planning, operational challenges, and resource allocation, which were grouped into six key topics: methodological challenges, resource burden, strategic uncertainty, company-specific adaptability, financial implications, and long-term benefits. The collective opinion of the experts was that the implementation of EU HTAR would result in favourable outcomes in the long term (see Table 2). Due to the extensive number of identified subcategories, Table 2 presents a reduced set of examples (3 – 4 per main category) to illustrate the findings and maintain readability. The complete analysis provides a comprehensive categorisation of the subject.

Categories	Subcategories	Definition	Example
Challenges for Companies	Data gap in evidence requirements	Statements about insufficient data availability.	"Und es ist eben sehr wahrscheinlich, dass sie dazu nicht überall Studien haben werden und sich dann immer die Frage was wird denn dann eigentlich aus diesen Fragestellungen? Also in der Regel wird man sie dann vielleicht gar nicht beantworten können." (Expert 7)
	Process and Outcome Uncertainties	Statements about uncertainties associated with both the process and the expected output.	"Jetzt ist es noch die Unsicherheit, weil es natürlich keine Verfahren gibt bisher." (Expert 4)
	Restructuring of internal structures and processes	Statements about adjustment and optimization of internal processes and team structures.	"Alle Firmen müssen sich umstrukturieren." (Expert 1)
	Process complexity	Statements about the process complexity and coordination.	"Das heißt, diese Komplexität ist sicherlich eine große Herausforderung und da eben den Blick für das Wesentliche nicht zu verlieren." (Expert 4)
Company Comparison	Success factors for handling EU HTA	Statements about the characteristics and organizational features a company must have in order to successfully meet the requirements of EU HTA	"Aber ich glaube, man kann das gar nicht so unterscheiden zwischen große Firmen und kleinere Unternehmen, sondern muss eher unterscheiden in erfahrenen Firmen." (Expert 6)
	Small business	Statements about possible advantages and disadvantages of small companies in dealing with the new regulation.	"Man hat einen kleinen, ich sag mal, einen kleinen Vorteil vielleicht im Sinne der Priorisierung." (Expert 4)
	Large business	Statements about possible advantages and disadvantages of large companies in dealing with the new regulation.	"Je größer ich bin, desto mehr Personal habe ich, desto einfacher ist das." (Expert 7)
Methodological Challenges	Time-related challenges	Statements about the time challenges in managing the process.	"(..) dass sie bei dieser vielen, weil wenn sie, je mehr PICOs sie angeben, desto schlechter wird das sein, was sie da sozusagen für die entsprechenden PICOs an Daten bekommen, weil das einfach in der Zeit nicht geleistet werden kann." (Expert 7)
	Methodological requirements and uncertainties	Statements about the requirements and possible uncertainties regarding the requirements.	"(..) Und also ich glaube, hier muss das System und alle Beteiligten müssen halt lernen, mit diesen Unsicherheiten, wenn es also Unsicherheiten, sprich, wenn Studien halt nicht ganz ähnlich sind, aber trotzdem da etwas rausziehen zu wollen." (Expert 6)
	Strategic and national requirements	Statements about the strategic direction and objectives in implementing regulatory requirements,	"(..) dann werden die Unternehmen vermutlich die Entscheidung treffen müssen, aus Zeitnot heraus im Schwerpunkt kümmern und was sie eben vielleicht dann eben nicht mehr in der Tiefe betrachten können." (Expert 7)
Financial Implication	Financial burdens	Statements about the financial impact associated with the fulfillment of requirements and the management of processes	"Denn das ist natürlich jetzt auch, sagen wir mal, finanziell auch ein Punkt, den man muss man erstmal stemmen, ob man es jetzt selber macht oder ob man es outsourced, kostet beides Geld und Ressourcen." (Expert 4)
	impact on pricing	Statements about the possible impact on the German reimbursement price	"(..) Also garantiert 100 % gehe ich davon aus, dass sich Indirekteffekte auch auf die Erstattungs- und Preisfragen ergeben werden." (Expert 5)
	price strategy optimization	Statements about possible pricing strategies and optimization	" (..) Ansonsten, wenn ich aus pU Perspektive denke, was meine Preisstrategie angeht, dann würde ich auch sagen, oder würde ich auch empfehlen, dass man den Zeitpunkt der Strategieentwicklung nach vorne verlagert, dass man sich sehr früh schon Gedanken darüber macht, welche Komparatoren sind denn für mich gut, was möchte ich denn haben." (Expert 2)
Strategy	Adjustment of processes and time management	Statements about changes in time management and process management	"Ich glaube, der Zeitpunkt, zu dem man sich für eine Strategie entscheidet, der wird sich ändern." (Expert 2)
	Strategic market evaluation	Statements about the evaluation and prioritization of markets	"Das kann sein, dass das alles viel zu kompliziert ist, dass die einfach sagen, mir reicht auch der amerikanische Markt ist." (Expert 7)
	Alternative approaches and prioritisation	Statements about the development of new strategic approaches and priorities	"Denn wir würden schon davon ausgehen, wenn man kurz vorher ein Beratungsgespräch hat und nach dem PICO fragt, dass dann das auch das PICO ist, was der G-BA im Scoping an die EU übermittelt. Ja, also wenn das zeitlich kurz vorher ist, würden wir nicht davon ausgehen, dass sich das irgendwie unterscheidet zwischen Beratung und was an das Scoping übermittelt wird." (Expert 2)

Table 2: Category system for qualitative content analysis of expert interviews: Definitions and examples of application of categories and subcategories (own illustration)

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