Evidence Transfer in (European) Drug Approval and (German) Early Benefit Assessments – An Empirical Analysis

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Objectives

The development and approval of pediatric drugs have been the subject of intense debate in international health science/policy for several years. For the European area, the European Medicines Agency decides on the approval of a drug [1]. In Germany, these approved drugs must also undergo an early benefit assessment (EBA) following Section 35a SGB V at the Federal Joint Committee (G-BA) to then be appropriately priced. The pharmaceutical company must submit a comprehensive dossier to the G-BA for the EBA of a drug with a new active ingredient. Based on the dossier, the pharmaceutical company should demonstrate the added benefit of a drug compared to an appropriate comparator therapy defined by the G-BA using published and unpublished clinical studies [1-3]. However, studies in which drugs are tested on children are rare for ethical, monetary, and organizational reasons [4], so there is often insufficient clinical data on the use of drugs in children and adolescents [5]. The lack of clinical studies in children and adolescents means that the (added) benefit of drugs can often not be quantified. Due to the lack of evidence, negotiations between the umbrella organisation of statutory health insurance funds (GKV-Spitzenverband) and pharmaceutical companies on the reimbursement amount are problematic, and pediatric drugs cannot be priced correctly on the German market [6].

To simplify the approval and reimbursement process for pharmaceutical companies because of the difficult study situation in children and adolescents, the implementation of evidence transfers was approved [7-9]. Since 2017, pharmaceutical companies have therefore been able to use evidence transfers as part of the EBA. An added benefit can also be recognized if "the transfer of evidence to the benefit assessment is also permissible and justified according to the current state of scientific knowledge" [10 english translation]. Accordingly, pharmaceutical companies no longer have to prove the added benefit of their drug with studies on children and can transfer the evidence from other studies, provided these have already been approved for adults [7,8]. In this context, we aimed to investigate how many evidence transfers have been submitted to G-BA since 2017 and for what reasons they were rejected or accepted. In addition, we aimed to compare decisions by G-BA with EMA decisions.

Methods

We conducted a retrospective quantitative content analysis. EBA from Institute for Quality and Efficiency in Health Care (IQWiG)/G-BA and European Public Assessment Reports (EPAR) from the EMA were used. When searching for EBAs on the G-BA website, only EBAs containing drugs for children and adolescents <18 years of age and evidence transfer were considered. In addition, only EBA that had been completed and for which Module 4 of the dossier was available were included. At the EMA, only those drugs were included that were also identified at the G-BA. As the EMA has several EPARs for one drug, only those EPARs were included for which the indication or indication extension matched the indications of the G-BA. In addition, the EMA's EPARs often contain several indications that were subdivided at the G-BA and processed in individual EBAs. For this reason, fewer documents were included and evaluated for the EMA than for the G-BA. For better comparability of the data, the EPARs were extrapolated to the number of analysis units of the G-BA.

The handling of evidence transfers of both institutions and reasons for rejection/acceptance were extracted starting from 2017 to December 2023. The extracted data was recorded in a Microsoft Excel data extraction sheet. For the descriptive analysis of the extracted data, the reasons for and against evidence transfer, which were extracted in the form of text passages, had to be keyworded and then categorized. In the next step, frequency tables were created for all evaluation categories.

Conclusions

There are considerable differences in the acceptance of evidence transfers between G-BA and EMA. The different assessments of G-BA and EMA are due to the fact that EMA assesses evidence transfers in the context of approval procedures or indication extensions and G-BA assesses evidence transfers in the context of EBA, whereby the pharmaceutical companies are more restricted in the selection of studies when submitting dossiers due to the appropriate comparator therapy specified by G-BA and have to resort to studies with a lower level of evidence.

The differences in the assessments also highlight the need for aligned and transparent criteria for evidence transfer. A continuous exchange between G-BA and EMA as well as the inclusion of explicit regulations on evidence transfer in the G-BA's rules of procedure could help to make decisions regarding the acceptance of evidence transfer transparent and create a uniform basis for decision-making. Without agreed and transparent criteria for evidence transfer, it is currently difficult to predict the success or failure of evidence transfer.

Results

Included documents

A total of 62 documents (35 benefit assessments [11-45] and 27 EPARs [46-73]) were identified and included in the analysis (see Figure 1).

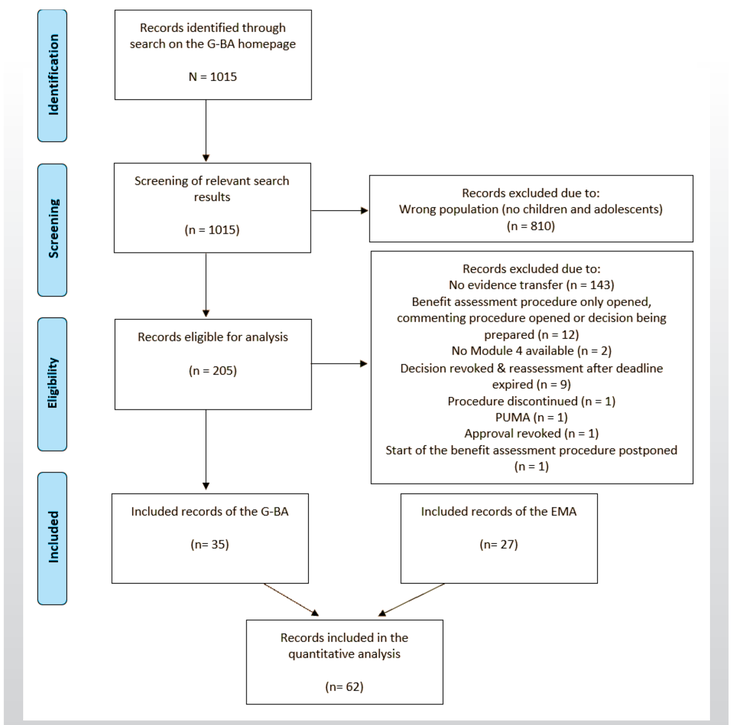

Figure 1: Selection process of the documents included in the analysis (own presentation based on [74])

Comparison between G-BA and EMA

The handling of evidence transfer of both institutions is shown in Table 1. In 13 of 35 (37.1%) EBAs, the G-BA accepted an added benefit based on evidence transfer. In 21 cases (60%), the acceptance of an added benefit based on evidence transfer was rejected. In one EBA (2.9%), the G-BA made no statement on evidence transfer. The EMA accepted evidence transfer in 18 of 27 (66.7%) approval procedures or indication extensions. In 9 of the 27 approval procedures (33.3%), no evidence transfers were cited, as sufficient pediatric studies were submitted. Taking into account the indications subdivided by the G-BA and extrapolating the data from the EPARs to the 35 analysis units of the G-BA, the EMA accepted the use of evidence transfers in 25 out of 35 cases (71.4%) and rejected them in 10 out of 35 cases (28.6%).

		G-BA		EMA		EMA (extrapolated)	
Category	**Characteristics**	**Frequency**	**%**	**Frequency**	**%**	**Frequency**	**%**
Evidence transfer	Yes	13	37.1	18	66.7	25	71.4
	No	21	60.0	9	33.3	10	28.6
	No statement on evidence transfer	1	2.9	0	0.0	0	0.0
	Total	**35**	**100**	**27**	**100**	**35**	**100**

Table 1: Comparison of the assessment of G-BA and EMA on evidence transfer

When comparing the assessments, it becomes clear that the G-BA and the EMA agree in the assessment of evidence transfer in 18 of the 35 cases (51.4%) and differ in 17 of the 35 cases (48.6%) concerning the assessment of the acceptance of evidence transfer (see Table 2).

Concordance between EMA and G-BA on evidence transfer	Frequency (extrapolated)	%	Frequency	%
Yes	18	51.4	15	55.6
No	17	48.6	12	44.4
Total	**35**	**100**	**27**	**100**

Table 2: Concordance between EMA and G-BA on evidence transfer

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Reasons for rejection/acceptance

The reasons for the rejection/acceptance of evidence transfer by the G-BA are presented in Figure 2.

The G-BA rejected evidence transfers mainly due to the non-fulfillment of the evidence transfer criteria, such as a missing, deviating, or inconsistently implemented appropriate comparator therapy (n= 13), a missing added benefit in the reference population (n= 9) as well as unclear or missing comparability of the mechanism of action (n= 3), the efficacy (n= 4), the clinical pattern (n= 8), or the patient population/ characteristics (n= 13). It also rejected evidence transfers due to missing or unsuitable evidence and methodological inaccuracies. The G-BA justified the acceptance of evidence transfers mainly with the fulfillment of the evidence transfer criteria, such as an added benefit in the reference population (n= 5), an identical appropriate comparator therapy (n= 10), a comparable mechanism of action (n= 6), comparable efficacy and safety (n= 13) and a comparable disease pattern (n= 17). The G-BA also justified the acceptance of evidence transfer with the special features and limitations in the conduct of pediatric clinical trials (n= 9) as well as previous assessments or findings of the EMA on the medical rationale of data transfer (n= 14). The EMA also justifies accepting evidence transfer by fulfilling the evidence transfer criteria. In addition, the EMA cites special features such as a low incidence, making it difficult to conduct studies with sufficient participants (see Figure 3)

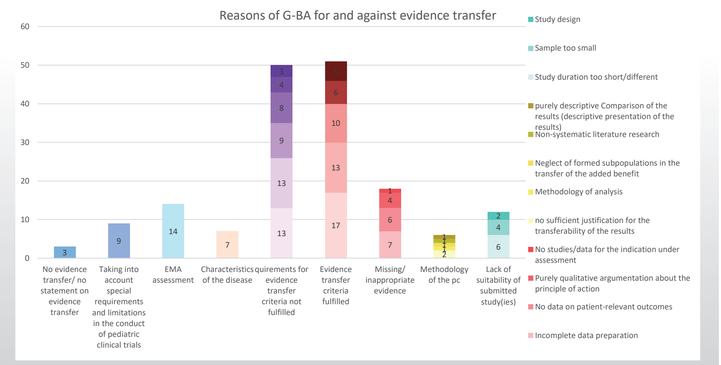

Figure 2: Reasons of G-BA for and against evidence transfer

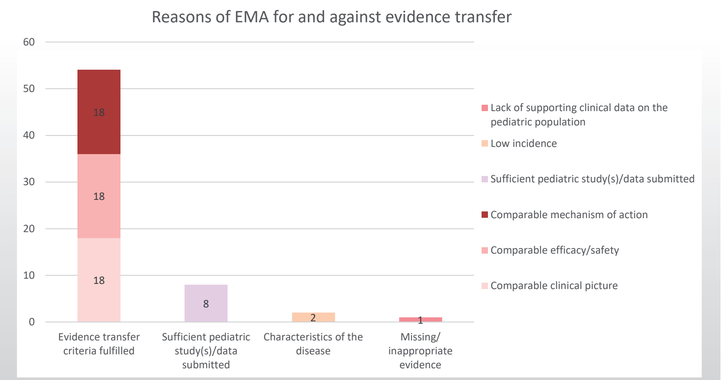

Figure 3: Reasons of EMA for and against evidence transfer [absolute frequencies] (own presentation)

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