Data Sources Used to Determine the Target Population Size for Orphan Drugs – A Review of German AMNOG Benefit Assessments

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BACKGROUND

- In 2011, the Act on the Reform of the Market for Medicinal Products (AMNOG) introduced Health Technology Assessment standards in Germany. It requires pharmaceutical companies to submit a value dossier (VD) to the Federal Joint Committee (G-BA) at market launch to prove an added benefit of the respective pharmaceutical product.[1]
- The target population (TP) benefiting from the new pharmaceutical product is described in Module 3 of the VD. A key requirement is the specification of the TP size from the perspective of the German statutory health insurance (SHI). Amongst others, the German Institute for Quality and Efficiency in Healthcare (IQWiG) assesses the provided information regarding transparency and plausibility before the G-BA decides on the level of added benefit.
- For rare diseases, the availability of prevalence and incidence can be limited. Therefore, gathering relevant information and determining the TP size can be challenging for orphan drugs.

OBJECTIVE

- Aim of this study was to explore the data sources used in Module 3 to determine the TP size indicated for the respective orphan drugs and to analyze the corresponding IQWiG assessments concerning transparency and plausibility of the determined TP sizes.

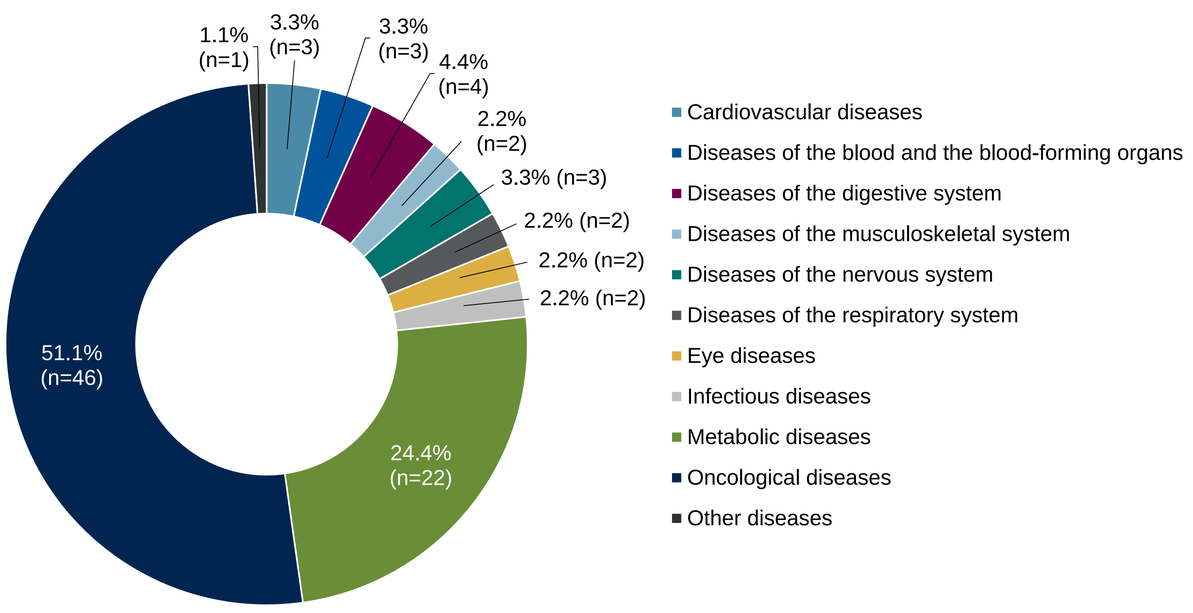
METHODS

- All available Modules 3 and the respective IQWiG assessments for orphan drugs published until May 14th, 2019 were included in this study. Each module was downloaded from the G-BA's website and screened by two independent reviewers.
- In a first step, each VD Module 3 was investigated in terms of data sources used to determine the size of the TP. In this context, number, classification and combinations of data sources were identified for each Module 3.
- In a second step, corresponding IQWiG assessments were screened. Statements on transparency and plausibility of the reported TP sizes were categorized and frequencies of defined categories were investigated. Transparency statements were either categorized as transparent, not transparent, or no information on transparency. Plausibility statements were categorized as plausible, overestimation, underestimation, uncertain, no final evaluation of plausibility, and no information on plausibility.

RESULTS

- As of May 14th, 2019, N=90 VDs including N=103 Modules 3 (some VDs included more than one TP) for N=67 active ingredients were included in the study.
- An active orphan drug status was present in 77 (85.6%) VDs, while the orphan status was removed in 13 (14.4%).
- Furthermore, the most common therapeutic areas among these orphan drug VDs were oncological and metabolic diseases (**Figure 1**).

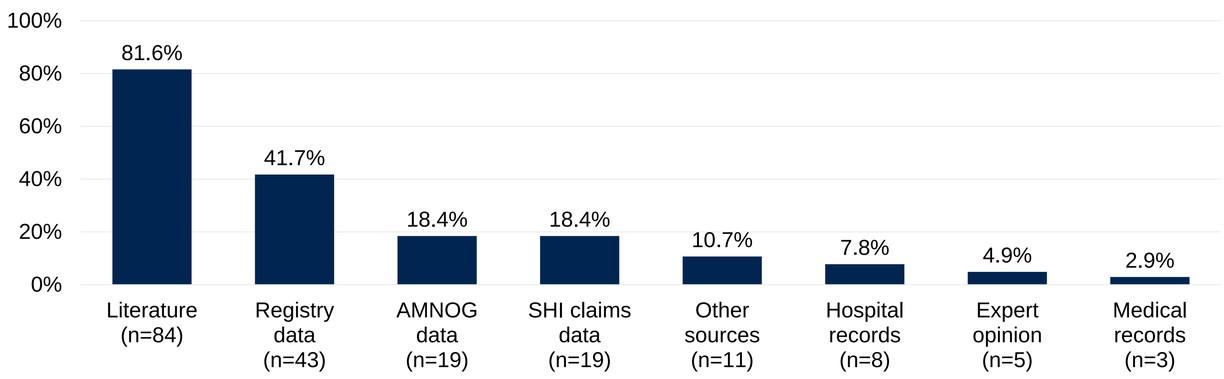
Figure 1. Therapeutic Areas Among the Identified Value Dossiers (N=90)



Data Sources

- Based on all of the identified data sources used for determining the TP size, the following categories were established: literature, AMNOG data (information gathered in the process of prior AMNOG assessments), medical records, hospital records, SHI claims data, registry data, expert opinion, and other sources (residual category for other data sources such as official mortality tables, documented patient case numbers, models by the pharmaceutical company and information from pharmacy data processing centers).
- Literature was identified in 84 (81.6%) and registry data in 43 (41.7%) Modules 3 resulting in the most frequently used data sources. Expert opinions as well as medical records were the two least used data sources (**Figure 2**).
- Only 19 (18.4%) Modules 3 waived the use of literature. In these, registry and SHI claims data, used in nine (47.4%) of these modules, were the most frequently utilized data sources. AMNOG data was used in six (31.6%) of the aforesaid modules, while medical records, hospital records and other sources were each employed in one (5.3%) Module 3 to determine the TP size.

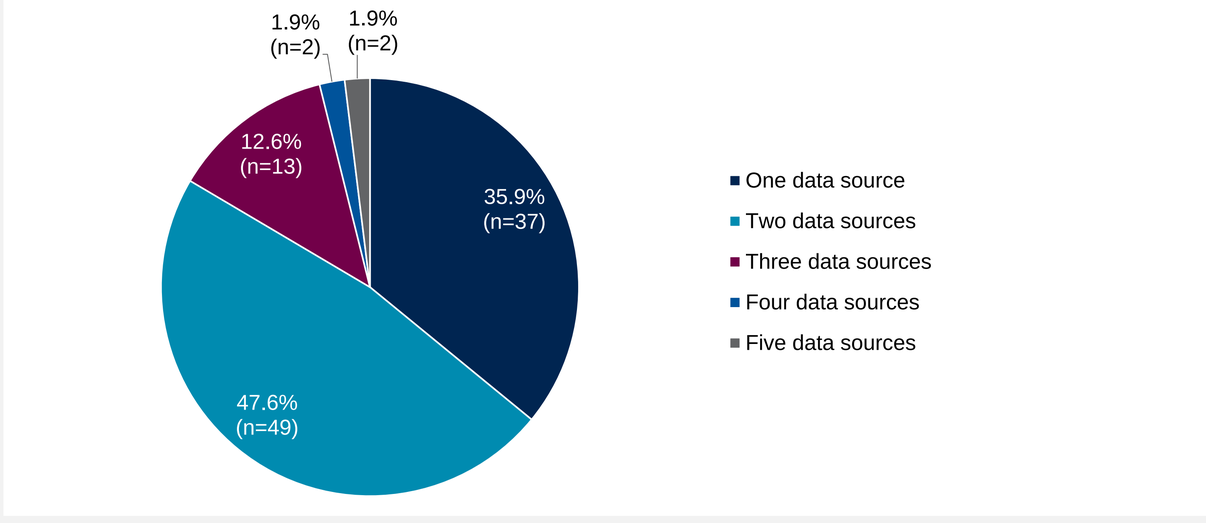
Figure 2. Data Sources Used in Modules 3 (N=103)



RESULTS (CONTINUED)

- In 66 (64.0%) Modules 3, more than one data source was used with most modules relying on two sources (**Figure 3**).

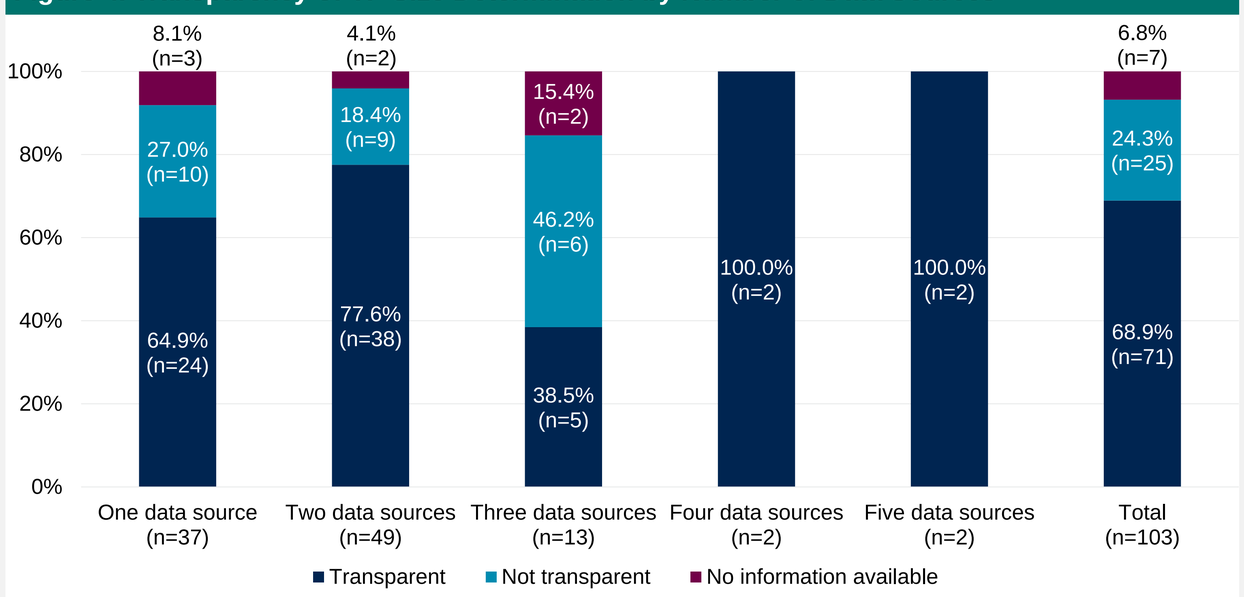
Figure 3. Modules 3 Stratified by Number of Used Data Sources (N=103)



Transparency of the TP Size Calculation

- In 71 (68.9%) Modules 3, the approach to determine the TP was deemed transparent according to the IQWiG assessment. In contrast, the determination of the TP was found to be non-transparent in 25 (24.3%) modules. For seven (6.8%) Modules 3, no information on transparency was available in the corresponding IQWiG assessments.
- Of those Modules 3 using only one data source to calculate the TP size, 24 (64.9%) were considered as transparent by the IQWiG. Moreover, 38 (77.6%) of the modules relying on two different data sources and five (38.5%) of the modules using three sources received a transparent assessment by the IQWiG. Beyond that, all identified Modules 3, which utilized more than three different data sources for the TP size determination were deemed transparent by the IQWiG (**Figure 4**).

Figure 4. Transparency of TP Size Determination by Number of Data Sources



Plausibility of the TP Size

- Only in 54 (52.4%) of all modules the IQWiG was able to provide an unambiguous assessment of the TP size. The IQWiG provided two assessments of the TP size in 34 (33.0%) modules and was furthermore not able to provide a final evaluation in 10 (9.7%) modules. In another 5 (4.9%) evaluated modules the IQWiG stated no information regarding the plausibility of the TP size.
- According to the IQWiG, about one quarter of all Modules 3 (n=27, 26.2%) contained TP sizes that were plausible to at least some extent. More than half of all TP calculations (n=55, 53.4%), were evaluated as uncertain, while in nearly one third of the cases (n=31, 30.1%), the TP size was deemed to be underestimated. In comparison, an overestimation of the TP was less common.
- TP sizes relying on registry data (n=12, 27.9%), literature (n=22, 26.2%), and SHI claims data (n=4, 21.1%) were mostly assessed as plausible. In contrast, the highest uncertainty regarding the TP size was seen in the use of expert opinions (n=4; 80.0%) as well as hospital records (n=6, 75.0%) (**Table 1**).

Table 1. Plausibility of TP Size by Type of Data Source

Data Source	N	Plausible		Overestimate		Underestimate		Uncertain	
		n	%	n	%	n	%	n	%
Literature	84	22	26.2	9	10.7	27	32.1	45	53.6
Registry data	43	12	27.9	4	9.3	15	34.9	21	48.8
Medical records	3	0	0.0	1	33.3	1	33.3	1	33.3
Expert opinion	5	0	0.0	1	20.0	3	60.0	4	80.0
AMNOG data	19	3	15.8	1	5.3	4	21.1	9	47.4
SHI claims data	19	4	21.1	2	10.5	3	15.8	11	57.9
Hospital records	8	1	12.5	1	12.5	1	12.5	6	75.0
Other sources	11	2	18.2	1	9.1	4	36.4	3	27.3
Total (distinct)	**103**	**27**	**26.2**	**9**	**8.7**	**31**	**30.1**	**55**	**53.4**

Note: Most of the reviewed modules rely on more than one data source. Accordingly, represented TP size assessments do not necessarily relate directly to the corresponding data source.

CONCLUSIONS

- Most Modules 3 relied on two or more different data sources. For most of the modules, the IQWiG assessed the TP size derivation to be transparent. However, only in 26.0% of all modules the TP size was deemed to be plausible.
- The results show that even if information on prevalence and incidence for rare diseases is available and a transparent approach is used, determining the TP size of a new orphan drug can be challenging.

Reference: 1. Gemeinsamer Bundesausschuss (G-BA). Nutzenbewertung von Arzneimitteln gemäß § 35a SGB V. 2019. https://www.g-ba.de/institution/themenschwerpunkte/arzneimittel/nutzenbewertung35a. Accessed September 09, 2019.