NON-QUANTIFIABLE BENEFIT WITHIN THE GERMAN AMNOG SYSTEM: FACTORS CONTRIBUTING TO TIME LIMITS SET FOR BENEFIT RESOLUTIONS AND POTENTIAL IMPLICATIONS ON PRICE DISCOUNTS

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BACKGROUND

- Since 2011, pharmaceutical companies have been obliged by German law to submit a benefit dossier for a new product when it is launched on the German market or authorized for new indications [Reform of the Market for Medicinal Products (AMNOG)].
- The assessment itself, conducted by the German heath technology assessment (HTA) body Gemeinsamer Bundesausschuss [Federal Joint Committee (FJC)], is evidence-based and can result in "major", "considerable", "minor", "non-quantifiable", "no", or even "less" added benefits.
- Additionally, the FJC can set a time limit for its resolutions, requesting that the pharmaceutical company submit new evidence for a *de novo* assessment.

OBJECTIVE

- This study explored the number of assessments (including all [sub]-labels) with non-quantifiable benefit resolutions, both in the orphan drug (OD) and non-OD setting, in order to investigate the set time limits relative to the clinical evidence and their implications on price discounts negotiated with the National Association of Statutory Health Insurance Funds.
- In addition, information about European Medicines Agency (EMA) market authorization details and their possible impact on the decisions made by the FJC were analyzed.

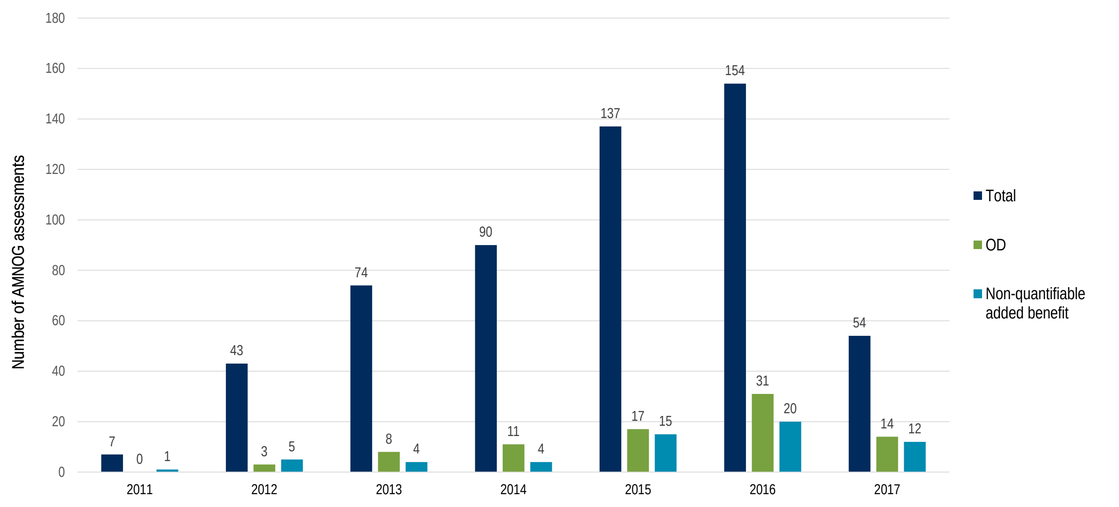
METHODS

- Information on FJC resolutions with the outcome "non-quantifiable" were retrieved from a database containing all AMNOG dossiers that were published on the FJC website. The data cut-off was 16 August 2017.
- The results identified as "non-quantifiable" were subsequently classified in OD or non-OD assessments. Among all findings, information on time limits and clinical evidence was extracted.
- Information regarding market authorization details of the analyzed drugs was obtained from the EMA website.
- Price discounts were analyzed using the LAUER-FISCHER WEBAPO® InfoSystem.

RESULTS

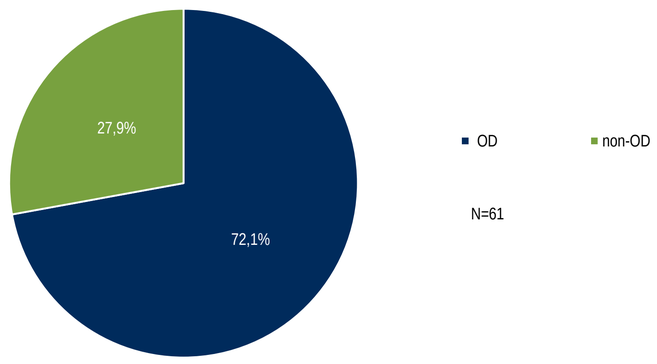
- Since the enactment of AMNOG in 2011, 559 (sub)-labels have been assessed by the FJC until 16 August 2016; of which, 84 assessments were OD (Figure 1A).

Figure 1A. Number of AMNOG assessments, including all (sub)-labels from 2011 up to 2017



Key: AMNOG – Arzneimittelmarkt-Neuordnungsgesetz; N – number of assessments up to 2017; OD – orphan drug.
Note: First assessment was August 2011 and data cut-off was 16 August 2017.

Figure 1B. Distribution of OD vs. non-OD status of all assessments with a non-quantifiable added benefit

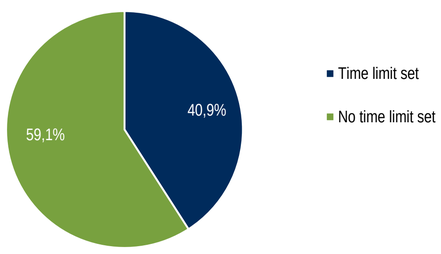


Key: N – number of assessments up to 2017; OD – orphan drug.
Note: First assessment was August 2011 and data cut-off was 16 August 2017.

- 61 relevant resolutions with a non-quantifiable added benefit were identified (10.9 % of all assessments), including 44 OD (72.1 %) and 17 non-OD (27.9 %) assessments (Figure 1B).
- The majority of non-quantifiable added benefits were granted after 2014 (73.8 %), with an increase in proportions of the total published resolutions starting in 2015 (Figure 1A).

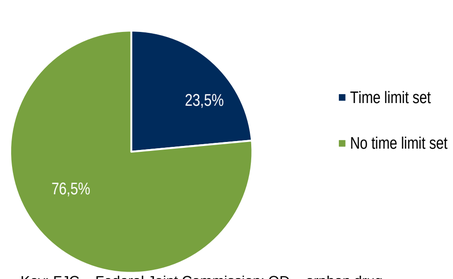
Figure 2A and Figure 2B. Distribution of time limits set by the FJC:

2A. OD resolutions with a non-quantifiable added benefit



Key: FJC – Federal Joint Commission; OD – orphan drug.

2B. Non-OD resolutions with a non-quantifiable added benefit

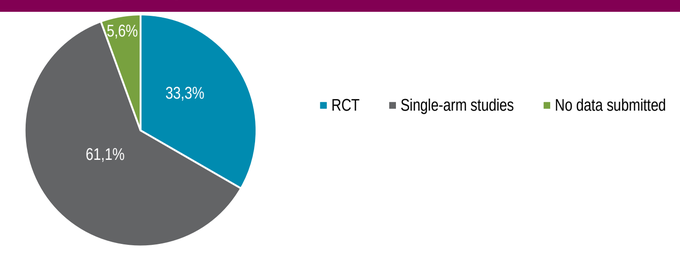


Key: FJC – Federal Joint Commission; OD – orphan drug.

- Overall, FJC set a time limit for 22 resolutions, from which the majority were for OD (N=18; 81.8 %).
- From all the OD assessments with a non-quantifiable added benefit, 40.9 % got a time limit; whereas for the non-OD assessments, only 23.5 % were timely limited (Figure 2A and Figure 2B).

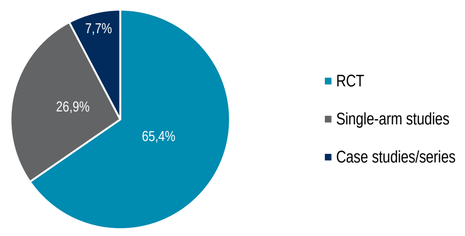
Figure 3A, Figure 3B, and Figure 3C. Clinical evidence levels in AMNOG dossiers, whose assessments resulted in a non-quantifiable added benefit:

3A. OD resolutions with time limits (N=18)



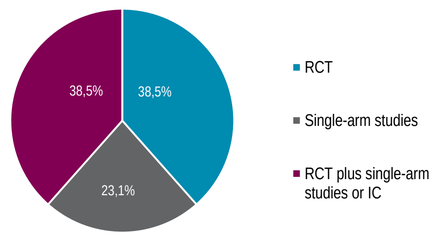
Key: AMNOG – Arzneimittelmarkt-Neuordnungsgesetz; N – total number of assessments in the named setting; OD – orphan drug; RCT – randomized controlled trial.

3B. OD resolutions without time limits (N=26)



Key: AMNOG – Arzneimittelmarkt-Neuordnungsgesetz; N – total number of assessments in the named setting; OD – orphan drug; RCT – randomized controlled trial.

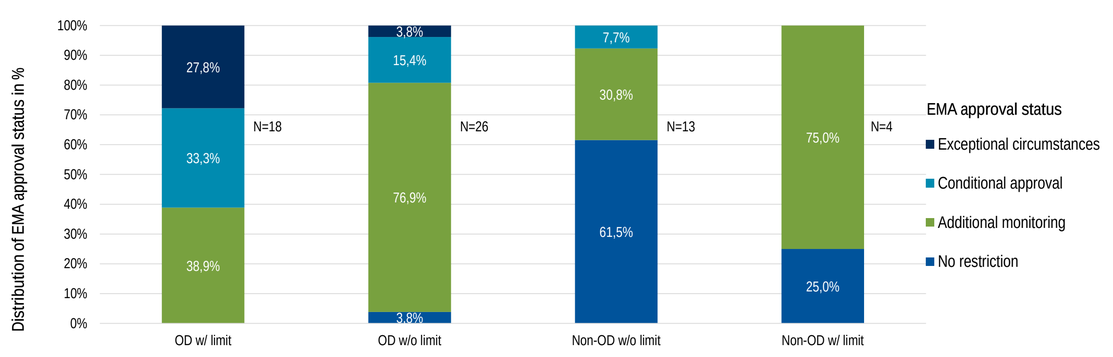
3C. Non-OD resolutions without time limits (N=13)



Key: AMNOG – Arzneimittelmarkt-Neuordnungsgesetz; IC – indirect comparison; OD – orphan drug; RCT – randomized controlled trial.

- Regarding the clinical evidence as a basis for the OD assessments with a time limit set by the FJC, 61.1 % of the assessments were based on single-arm clinical trials and 33.3 % on randomized controlled trials (RCT) (Figure 3A).
- In contrast, OD assessments resulting in a non-quantifiable added benefit but no time limit were mainly based on RCT (65.4 %), followed by single-arm studies (26.9 %), and case studies/series (Figure 3B).
- Among the non-OD AMNOG resolutions without a time limit (13/17), 77.0 % of the decisions were based on RCT, or RCT and additional evidence, and 23.1 % were based on non-randomized clinical trials (Figure 3C).

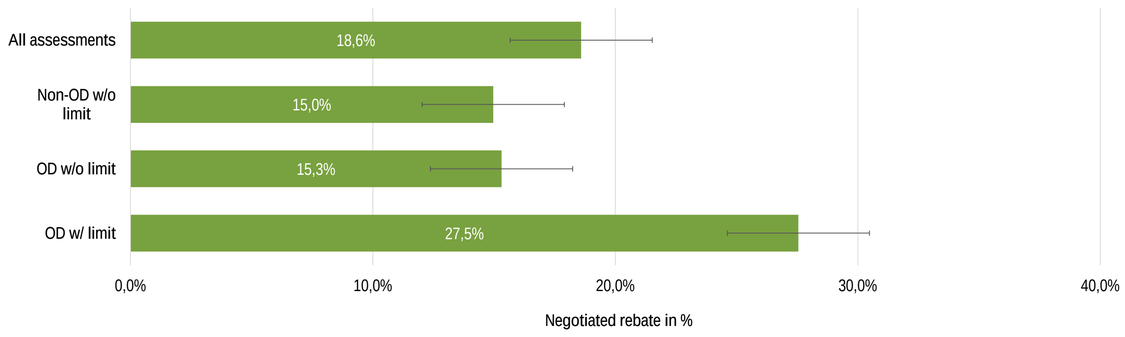
Figure 4. Distribution of EMA approval status for drugs assessed by FJC with a non-quantifiable added benefit listed, according to OD status and time limit set by the FJC



Key: EMA – European Medicines Agency; N – total number of assessments in the named setting; OD – orphan drug; w/ – with; w/o – without.

- Regarding the market authorization decisions made by EMA, it is evident that more OD assessments with a time limit were approved under exceptional circumstances than those without one (27.8 % vs. 3.8 %) or non-OD assessments (27.8 % vs. 0 %) (Figure 4).
- Additionally, the rate of conditional approvals, which indicates less comprehensive data than is normally required for market authorization, decreases from OD status with a time limit (33.3 %) over OD status without a time limit (15.4 %) to non-OD status without a time limit (7.7 %) (Figure 4).
- Every OD approval with a time limit set by FJC had a different kind of restriction compared to the other settings, which were, to some extent, approved without any restriction (Figure 4).
- In contrast to OD approvals, 61.5 % of the non-ODs that got resolutions without a time limit set by FJC were approved without any restrictions (Figure 4).

Figure 5. Discounts negotiated with the National Association of Statutory Health Insurance Funds for drugs with a non-quantifiable added benefit, according to OD status and time limit set by the FJC



Key: FJC – Federal Joint Committee; OD – orphan drug; w/ – with; w/o – without; SE – standard error. Note: The percentages are means +/- SE.

- The analysis of price discounts negotiated with the National Association of Statutory Health Insurance Funds shows that the average discount for OD resolutions, which got a time limit set by FJC, is higher (27.5 %; range from 9% to 47.5 %) than for those that got no time limit (15.0 %; range from 10.3 % to 27.3 %) (Figure 5).
- In case of discounts negotiated for ODs with no time limited resolutions, 5 list prices were adjusted (lowered) before the negotiations were finalized, resulting in a lower public discount.
- Overall, for 2 drugs, the manufacturer chose the possibility of opting out, and 12 rebates could not be calculated due to ongoing price negotiations or an unclear process status.

CONCLUSIONS

- The likelihood of a time limit set by the FJC in terms of a non-quantifiable added benefit increases with the decrease in the evidence level of data presented in the dossier.
- Since the clinical trials for OD approval are often single-armed, due to the rarity and severity of the disease and are often combined with immature data, it is more likely to get a time limit set for OD than for non-OD dossiers, which generally contain data based on RCT.
- It seems to be that market authorization decisions made by EMA might influence a time limit for the benefit resolutions made by the FJC. This is possibly triggered by the common ground of less comprehensive data or immature data submitted for both assessments (often due to the OD status of the drug).
- Furthermore, it seems plausible that a time-limited resolution negatively influences the extent of the price discount negotiated with the Association of Statutory Health Insurance Funds in the OD setting.

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