EVALUATING THE HTA IMPACT OF REAL-WORLD EVIDENCE FROM FORMAL ORPHAN DRUG REGISTRIES

Bustamante M[1]; Yang E[2]; Anderson K[1]

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[1]CBPartners, New York, NY, USA, [2]CBPartners, San Francisco, CA, USA

INTRODUCTION

In mid-2019, the G-BA (Federal Joint Committee) obtained the authority to implement registries for any orphan drug with a conditional approval through the GSAV ("Law for More Security in the Supply of Medicines"); the collected data would then be used for a re-assessment of that drug's added benefit rating.

Following the enactment of the GSAV, the G-BA commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to outline best practices and guidelines for the collection and use of this registry data, a document which was published in January 2020.

On the other side of the world, Brazil's National Committee for Health Technology Incorporation (CONITEC) has recently increased the pace of granting public funding to orphan drugs, though several of these approvals have been conditional on the implementation of patient registries. Data from an orphan drug's registry would be reviewed in 3 years' time and may affect its future funding status.

OBJECTIVE

To perform a comparative assessment of the formal registry requirements in Germany and Brazil for orphan therapies with limited clinical evidence in order to pinpoint the future role of real-world evidence (RWE) in health technology assessments (HTAs).

METHODS

This study conducted a targeted policy and literature review of the orphan drug registry requirements of the G-BA / IQWiG in Germany and CONITEC in Brazil, two markets with very different priorities for market access decision-making.

To understand the impact of these real-world evidence requirements to-date, CBPartners performed an analogue assessment of recent orphan therapies that went through each country's orphan drug approval process.

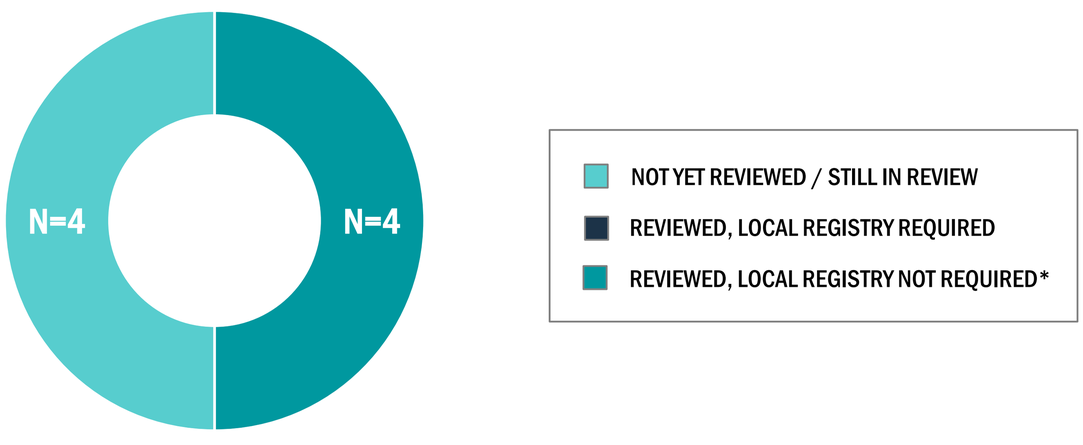
RESULTS

GERMANY

At this point in time, no drugs have been required by the G-BA to provide additional registry data directly under the GSAV policy (see Figure 1).

Of the 41 orphan drugs approved by EMA between 2017-2020, 10 drugs were asked by EMA to provide additional data through registries to better evaluate safety and efficacy; all of these products either completed their G-BA review before GSAV was passed or had not yet completed their G-BA review at the time of this research.

FIGURE 1: G-BA REVIEW OF ORPHAN DRUGS APPROVED BY THE EMA SINCE ENACTMENT OF GSAV (N=8)



**Includes 2 orphan drugs that were exempt from benefit assessment but were approved*

One of these drugs, KYMRIAH for ALL / DLBCL, stood out as having the most follow-up requirements from the EMA – 3 registry-based studies and 2 additional clinical data report-outs.

In this instance, the G-BA recognized the need for further data on effectiveness and safety, echoing the opinion of EMA of potential selection bias due to the high failure rate of patients with poor prognosis.

However, since this review occurred right before GSAV took effect, the G-BA only requested submission of an additional cut of updated trial data and set a shorter window to trigger re-evaluation (i.e., 1 year for KYMRIAH, whereas YESCARTA, a fellow CAR T therapy, received a window of 3 years).

Results of the KYMRIAH re-evaluation are not expected until September 2020, and it remains to be seen if GSAV will have any influence on this review.

The original GSAV legislation did not specify any standardized requirements for registry impact but put the onus on IQWiG to provide an assessment on how to use these additional data to quantify the added benefit of a new pharmaceutical product.

IQWiG came to a final determination in early 2020, which outlined best practices and guidelines for these real-world data (see Table 1).

TABLE 1: IQWIG'S STANCE ON G-BA REQUEST OF REGISTRY DATA COMPARED TO HISTORICAL OUTCOMES IN GER AND BRA

PROCESS STEP	IQWiG COMMENT
Identification of an evidence gap in the G-BA decision on a benefit assessment according to 35a SGB V	• Evidence gap: relevant data gap for the comparison of the new drug with the (appropriate) comparator therapy with regard to patient-relevant outcomes (especially if the evidence gap does not allow quantification of the added benefit)
Description of the G-BA specifications for routine practice data collection according to GSAV and transmission to the pharmaceutical company	• Description of the research question • Duration, type, and scope of data collection (duration of data collection per patient, sample size based on a sample size estimation) • Type and scope of the analysis (depending on the study type used) • Specification of the time points for the evaluation of the data obtained (at least every 18 months) • Specification of the requirements, taking into account ongoing and planned data collection, especially those resulting from requirements of the regulatory authorities (e.g., EMA)
Evaluation of the data collected and the obligation to collect data	• At the time of the first evaluation, the G-BA will check whether a (publicly available) study protocol including an analysis plan is available that reflects the routine practice data collection according to GSAV as requested • At the first and each subsequent evaluation time point, the G-BA will evaluate the available data and decide whether the data collection can be stopped or should be continued

IQWiG identified reasons why the effective implementation of registry requirements could drive an overall improvement in data quality.

Between 2014 and 2018, the largest evidence gaps in manufacturers' submissions that led to lack of quantifiability were related to mortality, morbidity, health-related quality of life, and adverse events.

The guidelines indicate that the G-BA will take into account existing EMA registry requirements but may go even further with its local data requirements in order to answer targeted questions around the benefit provided by the orphan drug

Nevertheless, IQWiG cautioned that critical information for benefit assessments, like late-onset adverse events, may not necessarily be best-suited for tracking within targeted GSAV registries and would need to be considered in each individual case.

BRAZIL

In contrast, Brazil has not developed any national guidance or protocols around orphan drug registries but already has several drugs that have been approved for public funding conditional to a re-evaluation of registry data in 3 years' time.

Of the 13 most recent CONITEC approvals (see Figure 2), 3 were rejected for public funding, 6 were given a positive recommendation, and 4 received a conditional positive recommendation contingent upon the following:

- Additional negotiations to lower the price (or implement a risk-sharing agreement in the case of SPINRAZA)
- The manufacturer creating and maintaining a patient registry for SUS
- CONITEC re-assessment being scheduled in 3 years' time

These conditional approvals were given to:
- SOLIRIS for PNH
- VIMIZIM for MPS IVa
- NAGLAZYME for MPS IV
- SPINRAZA for 5Q-SMA

In all four cases, CONITEC's initial recommendation was negative due to poor quality data and insufficient evidence of cost-effectiveness, but following a public consultation period, the HTA body was convinced to provide conditional funding.

There is no mention of specific data requirements that would need to be prepared during the registry period.

The re-evaluation of all of these products will occur in 2021, so there is not yet any example of how the registry data will be reviewed. However, given criticisms of Brazil's limited amount of information on local rare disease epidemiology and patient outcomes, these registries will likely have an impact on how formal clinical protocols area developed in the future within these disease areas.

FIGURE 2: OUTCOMES OF THE MOST RECENT CONITEC ORPHAN DRUG REVIEWS BETWEEN 2017-2020 (N=13)

**Includes 1 case, PROMACTA, where the manufacturer chose to restrict the targeted patient population to overcome an initial negative recommendation*

CONCLUSION

To-date, no changes to the initial G-BA benefit assessment outcomes have occurred. That said, given the G-BA's direct role in designing these registries, all data produced are likely to be considered in the re-assessment.

IQWiG has indicated that the implementation of GSAV will have a greater impact on routine data collection in Germany rather than on the process of orphan drug benefit assessments. Greater confidence in the utility of RWE by the G-BA may prompt higher expectations for manufacturers to provide high-quality, comprehensive data in the future. Our analysis and IQWIG's report suggest that the requirement of G-BA registry use will be rarely used, possibly only in cases where significant data uncertainty exists and the EMA has not already issued a request for RWE / registry creation.

While CONITEC is further along in requiring registry creation, because CONITEC generally has less structured data requirements than the G-BA (and has still not fully aligned on a formal cost-effectiveness threshold for orphan drug funding), there may be more heterogeneity of impact for data that is ultimately produced by these registries.

Ultimately, RWE from formal registries is unlikely to have a significant positive impact on future HTA decisions but may contribute to worsened outcomes if efficacy or safety perform worse than expected. Manufacturers will need to be more cautious about producing RWE outside of formal registries, as HTA bodies with more experience may be highly selective on what data they accept.

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