Impact of EMA clinical trial transparency policies on HTA decisions in Germany

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Background

The European Medicines Agency (EMA) has two policies that govern access to clinical trial data.

Policy 070

- Requires trial overviews, summaries, and clinical study reports (CSRs) from centrally authorized market authorization applications to be published on the EMA's clinical data website.[1]
- Stipulates that trial data should be published 60 days after the European Commission decision and publication of the European Public Assessment Report (EPAR).
- Came into effect in January 2015 for license extensions and in July 2015 for new indications.

Policy 043

- Allows anyone to request CSRs.[2]
- Applies to applications and data submitted before Policy 070 came into effect, and to non-centrally authorized products.

Implications and potential use of data available under these policies

- Manufacturers already provide health technology assessment (HTA) agencies with additional, unpublished data, and authorities can request additional analyses for appraisals.
- However, HTA agencies could use data published under Policy 070 to gain a more complete view of the evidence and competitor landscape, rather than published trials and summaries of product characteristics (SmPCs).

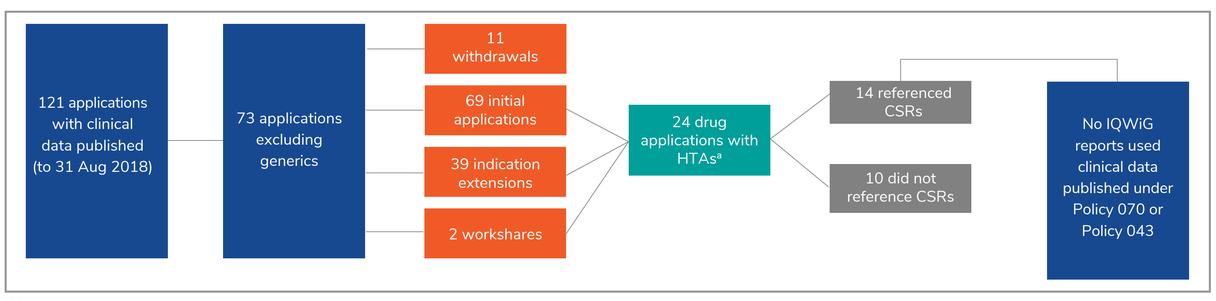
Objective

- Even though these policies have been in place for a number of years, it is not clear if or how the data are being used to support market access.
- The German Institute for Quality and Efficiency in Healthcare (IQWiG) has expressed an interest in the publication of these data; therefore, the objective of this study was to analyze the use of these data in HTAs in Germany.

Methods

- The EMA clinical data publication website was searched for medicines with published clinical data (cut-off 31 August 2018) and for the EPAR publication date/launch date.
- The IQWiG website was searched for assessments of these drugs. The reference lists were then checked to determine whether data published under these policies had been referenced in the assessment process.

Figure 1: Flow diagram of drugs with clinical data published to 31 August 2018



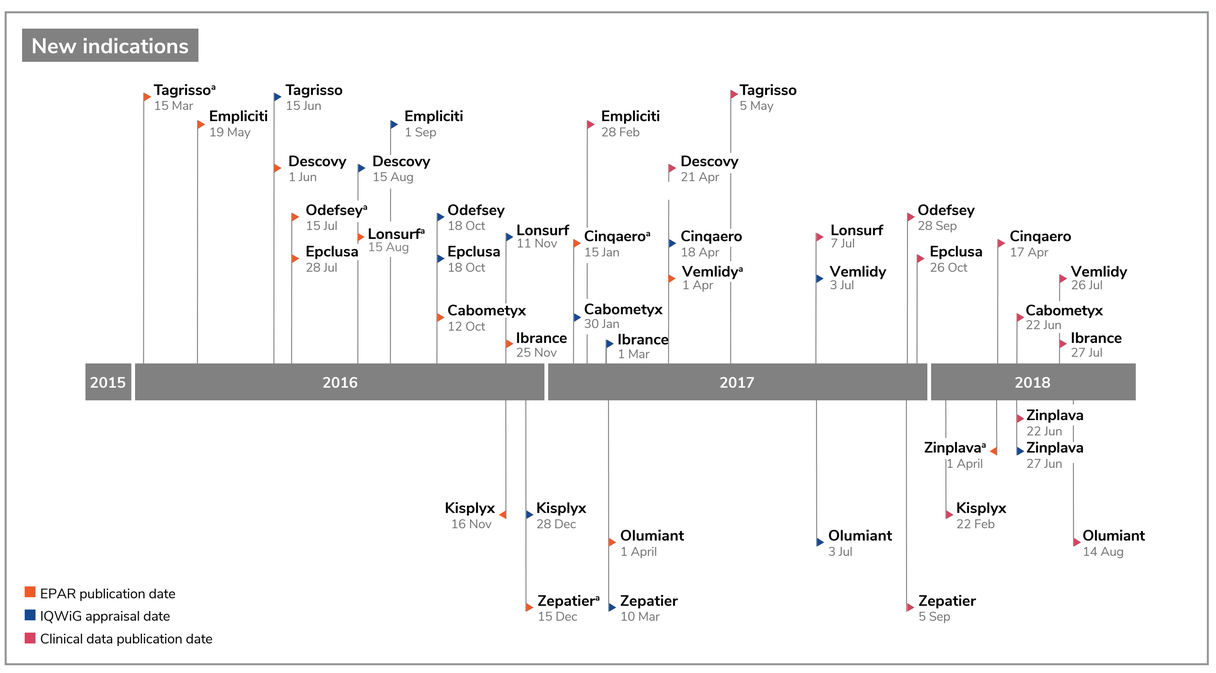
[a]Excluding orphan drugs

HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Healthcare.

Results

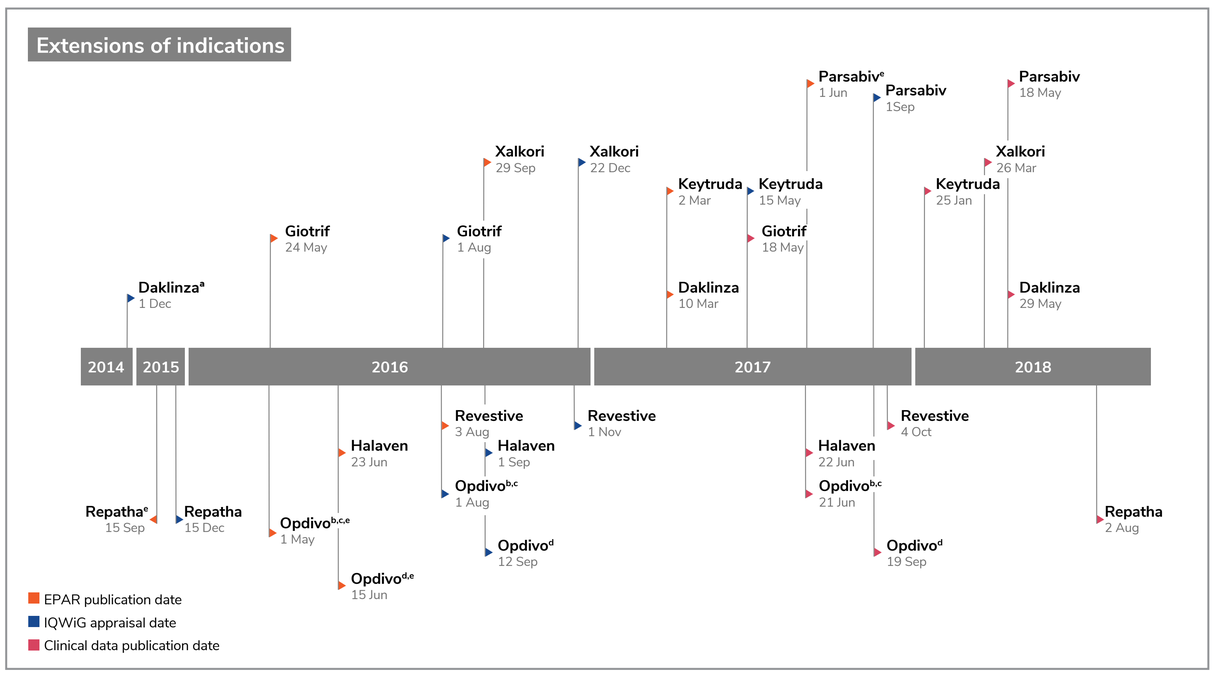
- A total of 121 applications had clinical data published up to the cut-off date; the documents identified included 69 initial applications, 39 indication extensions, and 11 applications that were subsequently withdrawn (see Figure 1).
- When generics were excluded, there were 73 initial applications or extensions and two workshare applications (not included in the analysis), of which 24 had been assessed by IQWiG (see Figure 1).
- IQWiG reports (for drugs without orphan status) were published between 42 and 110 days after publication of the EPAR (see Figures 2 and 3).
- Fourteen of these assessments used CSRs as part of their evidence base; however, these were all for the product under review, rather than for comparators (see Figure 1).
- IQWiG assessment reports were published before the publication of clinical data for all of the drugs, these were published an average of 372 days (range: 249–513 days) before the data were available.
- We found no evidence that IQWiG considered the data published under Policies 070 or 043 (see figure 1); rather, it used data from the submitting companies' CSRs or internal data, or from EPARs, SmPCs, trials published in journals, or HTAs of competitor products.

Figure 2: Timeline of EPAR, HTA, and clinical data publication for drugs submitted to the EMA for approval of a new indication



[a]Drugs did not launch in Germany until later than the approval date; therefore, the launch date was used, not the EPAR date.
EMA, European Medicines Agency; EPAR, European Public Assessment Report, HTA, health technology assessment.

Figure 3: Timeline of EPAR, HTA, and clinical data publication for drugs submitted to the EMA for approval of an indication extension



[a]EPAR updated for new 90 mg tablet; HTA not reassessed; [b]Advanced renal cell carcinoma; [c]Non-squamous non-small cell lung cancer; [d]Unresectable metastatic melanoma; [e]Drugs did not launch in Germany until later than the approval date; therefore, the launch date was used, not the EPAR date.

EMA, European Medicines Agency; EPAR, European Public Assessment Report, HTA, health technology assessment.

Discussion

Pushback from some manufacturers

- Transparency of clinical data can be considered to be vital for clinicians, payers, and the general public to have confidence in the drugs they are prescribing, buying, and taking, respectively.[3, 4]
- Some manufacturers have already taken the initiative to publish all trial data (e.g., GSK, which set up a study register in 2004).
- Conversely, other manufacturers have resisted publication: Amicus Therapeutics has recently taken the EMA to court to prevent the publication of the pivotal CSRs for Galafold (migalastat).
- The General Court of Justice for the European Union has sided with the EMA in cases against three other companies who wanted to prevent trial data being made available under Policy 043.[5]

Issues with implementation

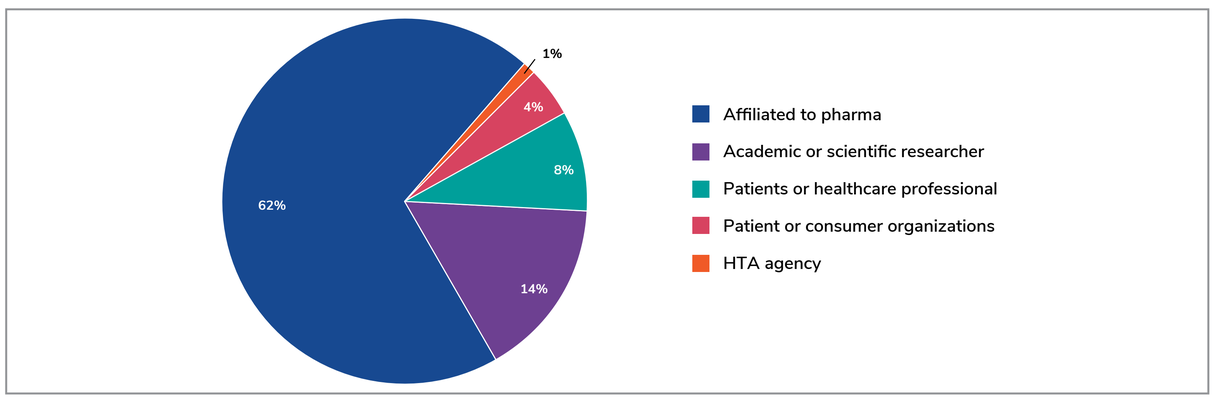
- We were not surprised to find that IQWiG did not appear to have used the data available through Policy 070; this could be due to the following:
  - Data were not available when the assessments were conducted.
  - Implementation of the policy is still in its early stages, and clinical data can be published up to 618 days after publication of the EPAR.
- Publishing the clinical data closer to the target of 60 days after the EPAR could allow these data to be considered in the HTA process, although the time between EPAR publication and IQWiG's decisions was often short, on one occasion only 42 days.

IQWiG's stance

- IQWiG strongly supported Policy 070 in a document summarizing the agency's comments on the draft policy.
- It stated: "There is overwhelming evidence, that so far publicly available trial data are insufficient to provide a complete and unbiased picture of a given healthcare intervention. HTA needs additional independent and high quality data sources."[4]

Utility of the clinical data site

- The EMA conducted an online survey in mid-2017, in part to determine the roles of the people accessing the data.[3]



- Interestingly, HTA agency affiliation was reported by 1% of the respondents,[3] but we do not know which agencies they were affiliated with.

Global trend towards more transparency of data in regulatory decisions

- There appears to be a global trend towards transparency in regulatory decision-making and clinical trials:
  - EMA – hosted delegates and visiting experts from the US Food and Drug Administration (FDA), Health Canada, and the Japanese Ministry of Health, Labour and Welfare to enhance international cooperation on clinical data publication, enabling sharing of best practices and development of standardized processes.[3]
  - Health Canada – the Protecting Canadians from Unsafe Drugs Act (also known as Vanessa's Law) is under development.
  - FDA – a pilot program, known as the Clinical Data Summary Pilot (started in January 2018).

EMA priorities

- As of 1 August 2018 the EMA has suspended all new activities related to clinical data publication under Policy 070.[3]
- Clinical data submitted by the end of July 2018 will still be processed but no new data packages will be processed until further notice.[3]

Conclusions

- The EMA clinical trial data publication site is a key resource that is being underutilized in HTAs; this is likely to be due to delays in the publication of clinical data submitted in 2015 and 2016.
- A potential limitation of the study is that we would not have detected the use of the published clinical data in systematic reviews submitted by manufacturers.
- The introduction of similar schemes by other regulatory agencies suggests a global trend towards increased transparency.

References

1. EMA. European medicines agency policy on publication of clinical data for medicinal products for human use (Policy 070). 2014.
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3. EMA. Clinical data publication (Policy 0070) report Oct 2016-Oct 2017. 2018.
4. IQWiG. Submission of comments on 'Policy 070 on publication and access to clinical-trial data'. 2013.
5. EMA. General Court confirms EMA approach to transparency. *Three rulings clarify the scope of commercial confidentiality with regard to authorised medicines*. London 2018

Acknowledgements

We would like to thank Sarah Corke for production of the poster and design of the figures.