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Confirmatory versus explorative endpoint analysis: Decision-making on the basis of evidence available from market authorization and early benefit assessment for oncology drugs

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ABSTRACT

The early benefit assessment of pharmaceuticals in Germany and their preceding market authorization pursue different objectives. This is reflected by the inclusion of varying confirmatory endpoints within the evaluation of oncology drugs in early benefit assessment versus market authorization, with both relying on the same evidence. Data from assessments up to July 2015 are used to estimate the impact of explorative in comparison to confirmatory endpoints on market authorization and early benefit assessment by contrasting the benefit-risk ratio of EMA and the benefit-harm balance of the HTA jurisdiction. Agreement between market authorization and early benefit assessment is examined by Cohen's kappa (k). 21 of 41 assessments were considered in the analysis. Market authorization is more confirmatory than early benefit assessment because it includes a higher proportion of primary endpoints. The latter implies a primary endpoint to be relevant for the benefit-harm balance in only 67% of cases (0.078). Explorative mortality endpoints reached the highest agreement regarding the mutual consideration for the risk-benefit ratio and the benefit-harm balance (0.000). For explorative morbidity endpoints (−0.600), quality of life (−0.600) and side effects (−0.949) no agreement is ascertainable. To warrant a broader confirmatory basis for decisions supported by HTA, closer inter-institutional cooperation of approval authorities and HTA jurisdictions by means of reliable joint advice for manufacturers regarding endpoint definition would be favorable.

1. Introduction

The efficacy, safety and quality of a new drug are considered to have been proven upon market authorization. According to the 'Act to Reorganize the Pharmaceuticals Market in the SHI System' (AMNOG), which came into effect on 1 January 2011, an additional benefit of new drugs based on patient-relevant outcomes has to be demonstrated for time-shifted reimbursement negotiations by means of an early benefit assessment.

Given this fact, pharmaceutical manufacturers now face the challenge of fulfilling the discrepant requirements of market authorization and early benefit assessment with regard to the conception of pivotal clinical trials [1]. This is not always possible and can lead to disadvantageous evaluations within the early benefit assessment with a potential subsequent negative impact on national reimbursement and international reference pricing [1,2]. The differences between the two evaluation processes, which rely on the same evidence, become obvious when analyzing how they deal with confirmatory and explorative endpoints.

As a working definition for confirmatory endpoints in this paper we refer to every primary or co-primary endpoint, for which the clinical trials of the included cases are powered for to establish effectiveness. All the other endpoints are summarized as explorative endpoints including secondary endpoints, since their purpose according to the rationale of ICH Guidelines (ICH-E9) and EMA's CHMP "Points to consider" is only supportive resp. explorative and the clinical trials are not powered for them.

Due to the equalization of both endpoint types for the purpose of the early benefit assessment according to the applied methods [3], oftentimes confirmatory endpoints are not considered even though they are relevant for the market authorization [4]. This results in a loss of information for the added benefit assessment

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because, due to their pre-specification, confirmatory endpoints (i.e. primary endpoints) provide decisive hypothesis-testing results regarding the primary study objective [5]. To derive a benefit-risk ratio within market authorization, a confirmatory evaluation based on the inclusion of primary endpoints is however a prerequisite for subsequently proving safety using explorative endpoints. This problem has been extensively discussed in recent literature [4,6], especially with regard to oncological products. However, as yet no closer investigation has been carried out regarding the balance of the use of explorative versus confirmatory endpoints within early benefit assessment and market authorization. Nevertheless, this is essential to identify the consequences of the problem in order to then be able to develop and implement possible solutions across the institutions involved.

Hence, the following two hypotheses were tested:

(i) The early benefit assessment process as defined by the German Social Code is less confirmatory than the market authorization process.
(ii) Neither evaluation process is confirmatory from a procedural point of view.

2. Methods

To allow for a comparison between market authorization and early benefit assessment, the benefit-risk ratio was compiled using the assessment reports of the European Medicines Agency (EMA) and the respective benefit-harm balance from the dossier evaluations of the Institute for Quality and Efficiency in Health Care (IQWiG), the German HTA body, for all completed early benefit assessments of oncological products up to mid July 2015.

The rationale of our dichotomous definition confirmatory versus explorative endpoints is based on the different statistical view between the approval authorities and the (German) HTA. The first one is based on the 'Neyman-Pearson' approach; where the p-value is driving dichotomous decisions with a focus on a formal confirmatory prove of effectiveness on the basis of primary endpoints where secondary and explorative endpoints are only supportive for the decision and not decisive. This approach controls therefore for alpha and beta error. We used the statistical view of the approval authorities as our reference. The second one follows the "Fisher" approach, where the p-value is reflecting the grade of evidence against the Null-Hypothesis and confirmatory prove is not an issue. This leads to no differentiation between primary and other endpoints, and finally alpha and beta error are not controlled.

2.1. Primary data source selection and further containment of early benefit assessments

The endpoint analysis focused on early benefit assessments of oncological products which were completed and therefore respective relevant information sources (i.e. submitted value dossiers, evaluations of the dossiers and where applicable addenda and the assessment report) for data selection were available [7,8].

Based on accessible primary data sources, suitable cases from those considered to be included for the endpoint analysis were selected. Suitable cases can be regular or special with respect to the approach of endpoint capturing. For regular cases, the regular methodology of endpoint capturing was applicable.

For special cases a deviating methodical approach was applied for the collection of endpoints by using additional data (i.e. addenda) or unique procedural incidents (e.g. more relevant trials). Orphan drugs for the treatment of rare diseases are excluded from the analysis, because no cross-procedural endpoint capture is possible in accordance with the basic method applied.

The following restricting criteria were applied for the endpoint analysis with regard to the respective (sub-)populations of the included cases: (i) at least one relevant study has to be available; (ii) the relevant definition of study population and the appropriate comparative therapy are consistent between the Federal Joint Committee (FJC) and IQWiG; and (iii) as far as possible, the study results of the submitted dossier are applicable to the results used by FJC/IQWiG.

2.2. Focus of analysis

The analysis of the proportion of primary endpoint use focuses on two key figures reflecting the impact of primary endpoints on a cross-procedural and case-specific level for the benefit-risk ratio and benefit-harm balance. The higher the respective primary endpoint proportion, the stronger the impact of a primary endpoint is on a case-specific and a cross-procedural level.

$$\textit{Total primary endpoint proportion} = \frac{\textit{Cases with an included primary endpoint}}{\textit{All included cases}}$$

$$\textit{Procedural primary endpoint proportion} = \frac{\textit{Number of included primary endpoints}}{\textit{Number of all included endpoints}}$$

The total primary endpoint proportion is a cross-procedural key figure which gives a first impression of the confirmatory approach. With this figure it should be taken into consideration that once a case has been assigned to the numerator, that does not inevitably mean that all actual primary endpoints within the case have been included (for example co-primary endpoints). The procedural primary endpoint proportion intends to reflect a case-specific view and is calculated for every included case separately.

A cross-procedural analysis with cross tables is conducted to compare the utilization rate of confirmatory and explorative endpoints within the benefit-risk ratio and the benefit-harm balance. To do so, all cross-procedurally included endpoints are categorized according to their relevance for both the early benefit assessment and the market authorization. We used next to proportion of agreement between Market Authorization and Early Benefit as an established agreement measure also Cohen's kappa (k) [9], interpreting the results according to the values proposed by Altmann [10].

2.3. Endpoint capture for benefit-harm-balance

Regarding benefit-harm balance data selection, reference is made to the positive and negative effects in the dossier evaluation, which are presented in tabular form in the "Overall conclusion on the added benefit" chapter. Endpoints are partially presented in a combined form comprising several individual endpoints. In this case it is not necessary to capture the combined endpoints but rather the corresponding individual endpoints to consolidate the precision of the analysis. A first classification is carried out for all included endpoints based on the tabular results in the "Study characteristics" chapter of the dossier evaluation. The final endpoint categories for the included endpoints are those presented in the "Evaluation of the added benefit on an endpoint level" chapter.

If several studies are pooled in a meta-analysis to derive a conclusion on the added benefit within the early benefit assessment, the pooled endpoints are considered separately and not as a combined endpoint. As a result of the inclusion of several relevant studies within one early benefit assessment, when contrasting

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