Can Health Technology Assessment be Used to Demonstrate Significant Benefit for an Orphan Medicinal Product in the EU?

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This article discusses how the conceptual grounds for significant benefit are addressed in the context of the orphan medicinal product regulations in the EU and how techniques used in Health Technology Assessment (HTA) may support the justification for the claim of significant benefit.

Significant benefit for an Orphan Medicinal Product (OMP) has to be assessed at two time points: at Orphan Designation (OD) and at Marketing Authorization (MA). At OD, the criteria are: rare disease or insufficient return on investment, unmet medical need and a sound pharmacological concept in relevant animal models. At the time of the MA, the criteria are: demonstration of significant benefit over already-authorized products in terms of clinically relevant advantage and a major contribution to patient care.[1]

The techniques used in Health Technology Assessment (HTA) have been proposed to support the justification for the claim of significant benefit. Between 2000 and 2016, 72 percent of applications for OD to the EMA were successful (27 percent withdrawn; one percent received a negative opinion), indicating that most applications are viewed favorably.[2]

A HTA review consolidates all the available data on a treatment. This review is useful in the decision process for the reimbursement of the medicinal product. However, for the purpose of assessing significant benefit for an OMP, it may not be appropriate as one of the principle purposes of HTA is to provide evidence of the economic value.

The Quality-Adjusted Life Year (QALY) is a commonly-used unit of measurement for health state. Once all the relevant costs of one therapy are estimated, the cost/QALY as compared to other treatments can be calculated to provide an Incremental Cost Effectiveness Ratio (ICER). In the case of OMPs, ICERs can easily become enormous for two reasons: the incremental benefit in terms of the number of QALYs may be small and the cost of newer products can be high.

Because different countries have different criteria for assessing whether drugs should be reimbursed it is important that sponsors seek protocol assistance for their clinical development program. It also is worth considering seeking advice from the local reimbursement authority.

Introduction

Orphan Designation (OD) can be granted early in the development of an Orphan Medicinal Product (OMP) when only preliminary data are available. However, the sponsor is required to submit a report to maintain the OD at the time of the Marketing Authorisation (MA).

The Committee for Orphan Medicinal Products (COMP) re-evaluates the fulfilment of the criteria in parallel to the MA assessment and its opinion determines if the product should remain on the community register of designated orphan medicinal products.

Sponsors are facing increasing challenges to demonstrate significant benefit at the time of applying for MA, with only a small proportion of OMPs maintaining OD.

In order to maintain OD at the time of the MA, the sponsor has to demonstrate the medicinal product provides significant benefit for those patients affected by that condition. In addition, significant benefit has to be shown to be superior over existing treatments for the condition.[3]

Unlike in the US, where the prevalence of the disease, the disease condition and rationale for the promise of the therapy are required, the EU[4] has in place requirements to provide justifications to support claims of significant benefit at Marketing Authorisation Approval (MAA).[5]

Regulatory Aspects of Significant Benefit

A review of the COMP decisions between 2000 and 2016[6] shows that 72% of applications for OD were successful (27 percent withdrawn; one percent received a negative opinion) and 114 authorized OMPs met the grounds for Significant Benefit at MA.

Commission Regulation (EC) No 141/2000 Article 3 criteria for designation states that if a satisfactory method of diagnosis, prevention or treatment of the condition in question exists, the medicinal product will have to be of significant benefit to those affected by that condition.[7]

Commission Regulation (EC) No 847/2000 defines significant benefit as "a clinically relevant advantage or a major contribution to patient care."[8]

A "clinically relevant advantage" can include improved efficacy or improved safety. Improved efficacy can relate to use in combination and/or efficacy in sub-populations, which allows the product to be used in a wider patient population or previously excluded sub-groups.

A "major contribution" to patient care can relate to availability (e.g., shortage of supply) or ease of use (e.g., formulation/administration route, dosing schedule).

The guideline on the *Format and Content ENTR/6283/00 Revision 4, 2014*[9] specifies the claims the sponsor should fulfil as follows:

At the time of orphan medicinal product designation "…the sponsor should provide justification for the assumption of significant benefit where there already existing (EU) authorized (= satisfactory) medicinal products." Recommended elements to support plausibility include compelling evidence of sound pharmacological concept in relevant animal models and preliminary clinical data.[10]

models and preliminary clinical data.[10]

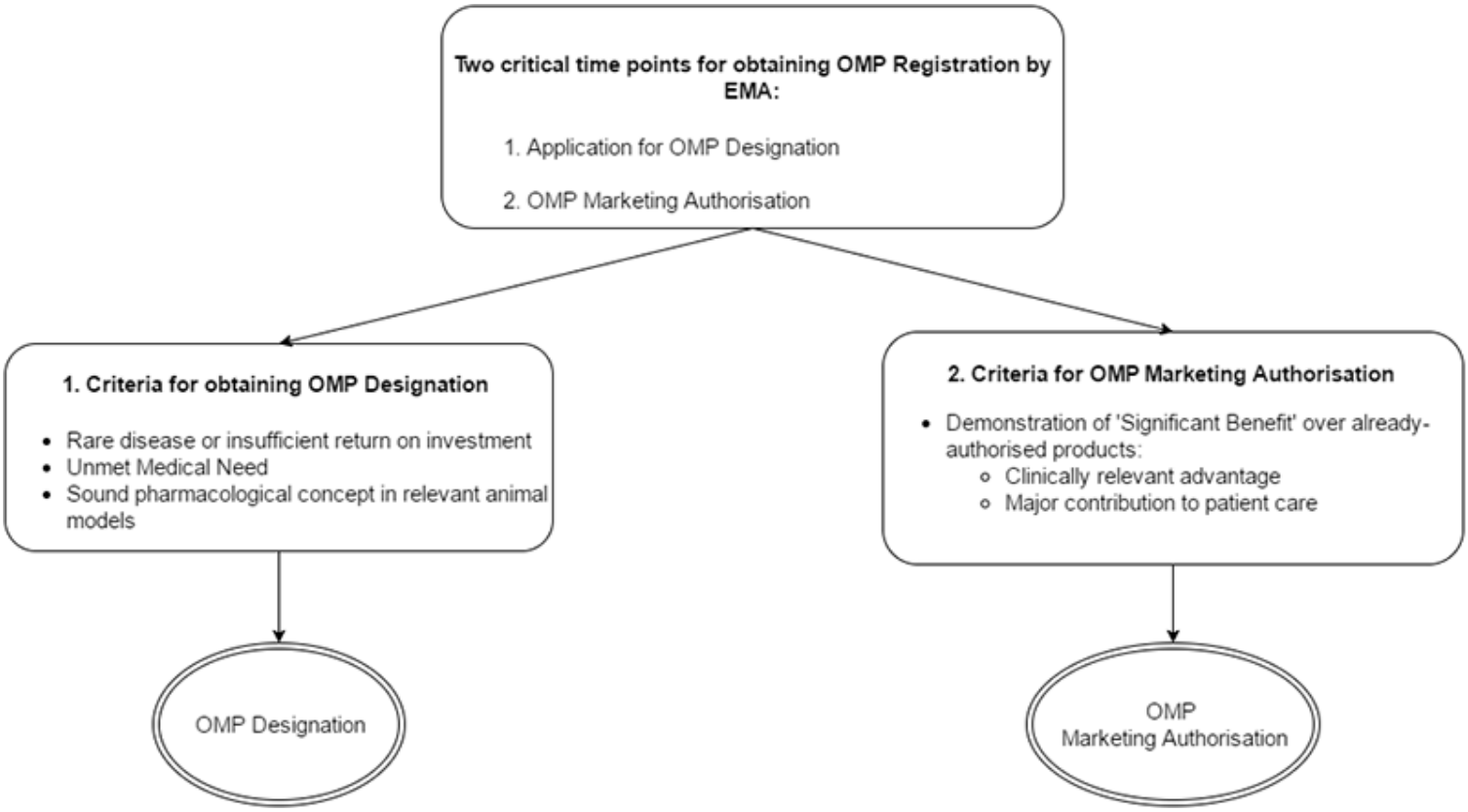
EU regulations offer assistance through its incentives mechanisms.[11] It is recommended that protocol assistance is obtained to ensure an appropriate clinical development and guidance to the sponsor on establishing significant benefit.[12]

At the Time of Marketing Authorisation (MA)

The applicant should "demonstrate significant benefit over currently authorized medicinal products in order to maintain orphan status." The COMP requires a higher level of data/evidence for the maintenance of orphan status than at the time of OD. In case authorized medicinal products are available, the criteria for showing meaningful advantages for the patients become stricter than at the time OD was granted. In addition, there may be rarely used authorized products where an indirect comparison might be appropriate.

At the MA, the COMP evaluates whether there is a high probability for the patients to experience a clinically relevant benefit in comparison with authorized products during the time period between OD and MA. This determination should be based on data in the MA application and arguments presented by the sponsor.[13]

Figure 1. Critical Time Points for Obtaining OMP Registration[14]



If there is no plausible medical evidence for significant benefit at the time of MA, the product will lose its orphan designation. However, a marketing authorisation as a non-orphan product is still possible and there is no obligation to repay incentives obtained.

Role of HTA

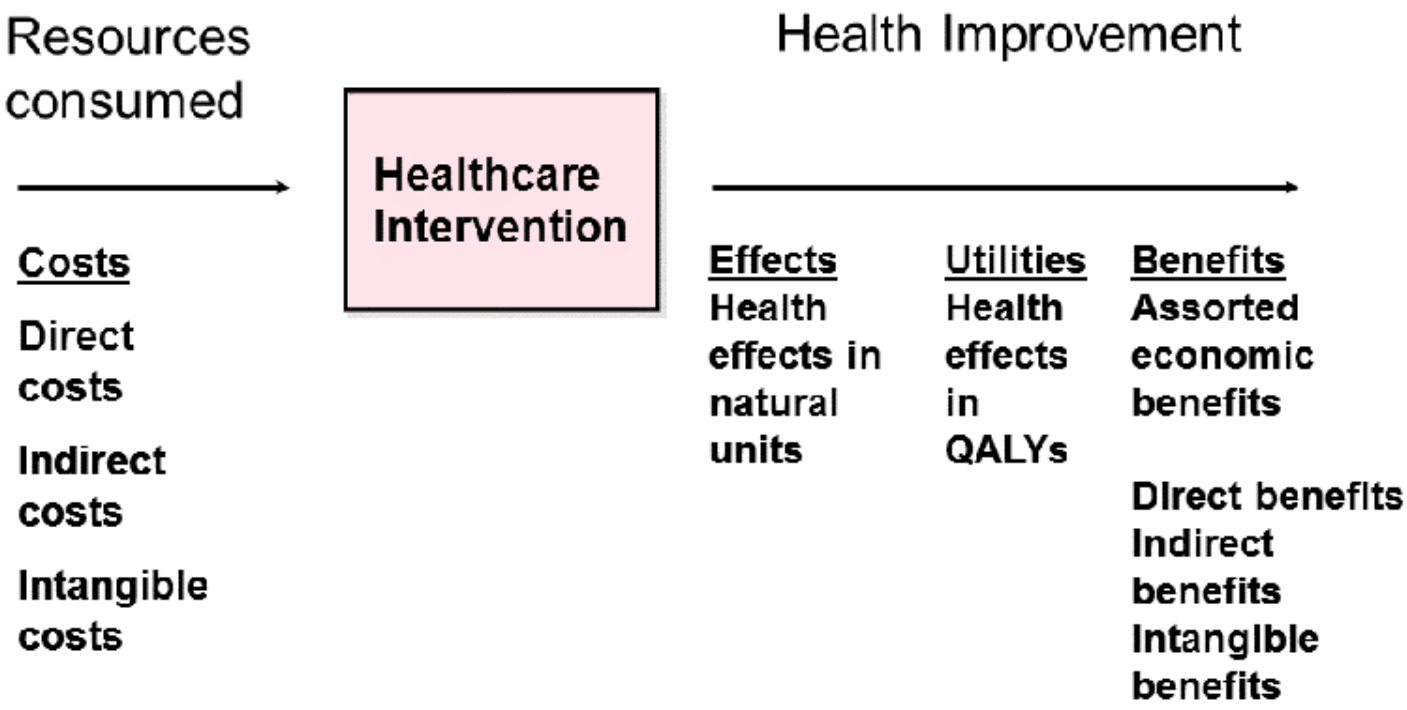
As mentioned, the *Commission Regulation (EC) No 847/2000*[15] defines significant benefit as "A clinically relevant advantage or a major contribution to patient care." The definition of 'clinically relevant advantage' is unclear and the definition for 'a major contribution to patient care' is even less-well defined. To address this problem, techniques used

in HTA have been suggested as potentially useful in the context of OD.

A HTA review is a synthesis of all the available data on an intervention, including the incidence, prevalence and current management of the condition. The HTA review also consolidates the efficacy and safety of the medicinal product under question and its place in the range of options for managing the condition in terms of its economic value. The HTA review is not designed for making a decision, but serves as an aid in the decision process, particularly with respect to whether or not to allow the medicinal product to be reimbursed.

The assessment of efficacy and safety compared to other therapies for a condition is well understood, but the estimation of the relative value of a therapy, particularly in monetary terms, may be less so.

Figure 2. Costs and Outcomes in Healthcare Interventions[16]



Any intervention consumes monetary resources measurable in human resources, cost of a hospital stay or the cost of drugs. Hopefully, there will be some measurable health improvement, such as cancer survival, numbers of patients achieving glycemic stability, as a result of the intervention. When two interventions for the same condition are compared and inputs and outputs converted to monetary units, this would be considered a Cost-Effectiveness Analysis (CEA).

CEA can be useful when assessing a drug's benefits from the point of view of the payer. However, CEA provides no information on how to compare the management of a range of conditions or how to best manage their overall budget.

For this purpose, a Cost Utility Analysis (CUA) is employed where a common measure across therapies is used. This is most usually the Quality Adjusted Life Year (QALY), which is the length-of-life after an intervention adjusted by indices of functionality or health.

The basic premise of the QALY is that a year of life lived in perfect health is worth one QALY (one Year of Life × one

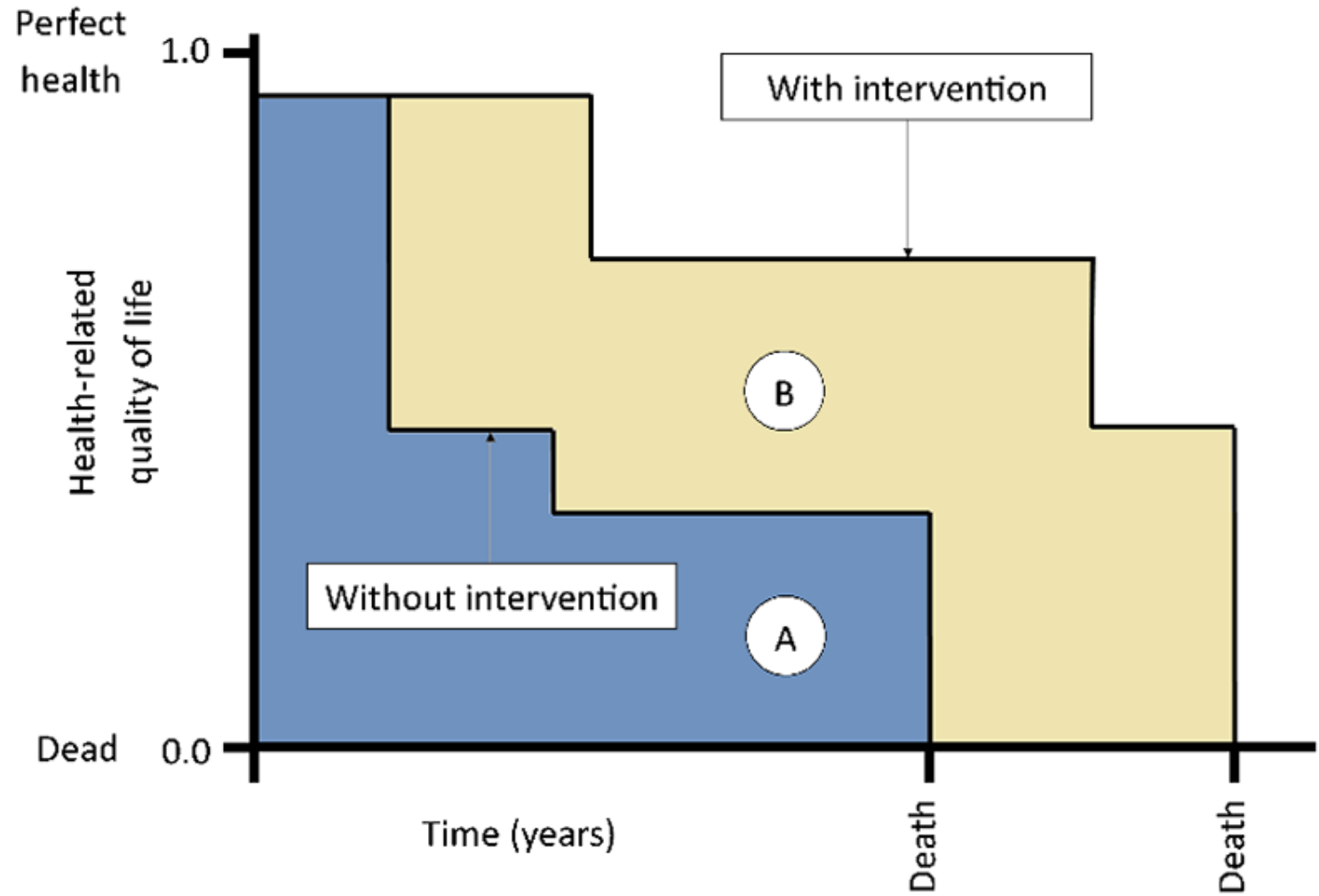
Utility value = one QALY) and that a year of life lived in a state of less than this perfect health is worth less than one. If the cost of being in one or other health state is calculated, the cost/QALY can be estimated. This kind of analysis is referred to as a CUA.

For HTA purposes, it is the Incremental Cost Effectiveness Ratio (ICER) that is important. This can be represented in the following equation:

$$ICER = \frac{Cost_1 - Cost_2}{Efficacy_1 - Efficacy_2}$$

This is shown graphically in **Figure 3**:

Figure 3. Graphical Representation of the ICER[17]



Having estimated all of the relevant costs of one therapy (from whichever perspective is appropriate), the cost/QALY as compared to other treatments can be calculated. To encourage some level of innovation, a positive ICER is allowed. In the UK, the National Institute for Health and Clinical Excellence (NICE) allows around £20,000-30,000/QALY ($30,000-$45,000); above this level, a therapy is more likely to be rejected unless there are mitigating circumstances, such as end-of-life scenarios.

Discussion

Although appropriate clinical studies can help provide evidence to substantiate significant benefit at time of MA, it is very hard to meet the requirements of all future stakeholders—physicians, patients/caregivers and payers.

After obtaining OD, the drug developer faces numerous risks in achieving meaningful data for significant benefit; notably, other competitive products being developed, new endpoints/measures being established.

At OD, the expectation of significant benefit is simply laid out, but its real demonstration has to be given at MA to maintain its OMP status. The difficulty in this is highlighted by the increasing number of OMPs withdrawn after OD.

How significant benefit at the time of MA is assessed has been called into question over the past years. Sponsors and patient organizations have constantly advocated for a fair trade-off between sufficient evidence and too high requirements.

A major issue for the pharmaceutical industry and for patient access is the definition of significant benefit remains unclear. Another issue is that it is not in line with the introduction of adaptive pathways, where the aim is to generate evidence of significant benefit all along the lifecycle of an OMP.

It may be difficult to obtain sufficient data to demonstrate significant benefit at the time of MAA. Some products may receive a Conditional Marketing Authorisation (CMA) where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required.

The requirements for CMA are: the benefit-risk balance of the product is positive; it is likely the applicant will be able to provide comprehensive data; unmet medical needs will be fulfilled and the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to the need for further data.

A CMA means the significant benefit would only have to be shown when the confirmatory studies are completed, at which point the CMA will be converted to a normal marketing authorisation.

In the case of OMPs, the ICERs can easily become enormous because the incremental increase in QALYs may be small, but the cost of newer products can be high.

In many therapeutic areas, such as oncology, improvements are incremental. It is difficult to show demonstrate large differences between authorized treatments and new medicinal products. However, the effectiveness of a new medicinal product for a particular disease can be impressive when compared to older treatments.

For example, in the past two decades, the median survival of patients with advanced colorectal cancer has doubled. These survival improvements have come in small, yet steady increments.[18] In these situations, a new OMP may receive MA from the European Commission. However, in the UK, it might not be made available to the National Health Service (NHS) by the National Institute for Health and Clinical Excellence (NICE) as it would be being compared to the best alternative treatment and the resulting ICER could be too high.

While mechanisms for assessing OMPs can reasonably be centralized, there is no common EU HTA body. Submissions for MA and reimbursement are separate. Each country has different criteria for assessing whether drugs should be reimbursed and implicit in this assessment is the declaration of the cost of the drug. In the UK, a drug will not be reviewed by NICE until it has been launched to the market and the cost revealed. Unless a future EU Directive states that pricing is to become part of a combined regulatory package, it is inappropriate to provide evidence of the economic value for an OMP when applying for MA.

This is not to say that preparation for HTA should not be done early in the clinical development.

Indeed, HTA preparation should be started as early as possible and developed in an iterative process as more data become available.

There are several reasons for this: certain parts of a HTA review also are required for the MAA, such as natural history of the condition, prevalence/incidence; it can help identify data gaps that could be filled during the course of the clinical development program; it can help identify a reasonable and justifiable price; it can contribute to investment decisions.

It would be useful to seek advice on protocol assistance from the EMA and advice on the development of the HTA submission from the local reimbursement authority.

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The rules are spelled out in 21 CFR Part 200 --

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