Common pitfalls in oncology drug applications aiming for conditional marketing authorization.

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Abstract

Early approval mechanisms, such as conditional approval in the EU, have been used extensively to provide timely access to therapeutic innovations to cancer patients with unmet medical needs. While based on promising early evidence, such approvals are challenging from many perspectives due to the lack of comprehensive data. The limitation typically relates to data that demonstrates clinical benefit via particular endpoints and is only acceptable when the early evidence is particularly convincing to assume that the benefits of early access are greater than the potential harms. This paper describes the requirements for conditional approval and reviews common pitfalls in oncology, such as misunderstandings about the strength of evidence from exploratory trials and secondary analyses, lack of planning, and opportunities to improve communication. Thereafter, we present a framework ("EDGE") on how to improve the submission and evaluation of drug applications for conditional approval in the EU.

COMMENTARY

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This paper describes the requirements for conditional approval and reviews common pitfalls in oncology, such as misunderstandings about the strength of evidence from exploratory trials and secondary analyses, lack of planning, and opportunities to improve communication. Thereafter, we present a framework ("EDGE") on how to improve the submission and evaluation of drug applications for conditional approval in the EU.

Introduction

Conditional marketing authorizations (CMA) in the EU and accelerated approvals (AA) in the USA have been set up as regulatory mechanisms to bring promising drugs to patients with unmet medical needs. The mechanisms originated in the 1990s in the USA based on the promise of early endpoints that were likely to predict a clinical outcome, namely viral load for antiretrovirals. These mechanisms have been implemented in different regions over the years with small variations but the emphasis on likely surrogate endpoints for early approval and the need for confirmatory evidence is still considered the cornerstone of these approvals.

To date, in the EU, more than 70 drugs have been approved by the CMA pathway across different therapeutic areas, and of these 24 have been converted to full approval based on the submission of comprehensive data post-approval (1). This pathway allows early approval when the benefit-risk (B/R) balance is deemed positive in situations of unmet medical need, yet the clinical data are not comprehensive. The marketing authorization holder must then comply with conducting studies post-approval to ensure the dossier becomes comprehensive within agreed timelines. CMAs are particularly controversial, as they bring together the potential greatest opportunities for patients with unmet medical needs but also the greatest challenges for other stakeholders in the health system due to the limited evidence. While non-exhaustive evidence may still be compatible with regulatory approval considering the patients' needs, this may be insufficient for other decisions such as pricing and reimbursement.

In this perspective, we briefly introduce the criteria for conditional approval, discuss common pitfalls, and provide suggestions from experience on how to avoid them, drawing from examples of new cancer drug applications submitted to the European Medicines Agency (EMA).

Understanding the requirements for conditional approval

CMAs are intended for treating, preventing, or diagnosing seriously debilitating or life-threatening diseases, including orphan medicines and public health emergency medicines. CMAs may be granted based on less comprehensive clinical data under certain conditions (2, 3), namely, 1) a positive benefit-risk balance; 2) comprehensive data will be provided post-approval; 3) an unmet medical need; and 4) a benefit to public health of the immediate availability.

Concerning the first condition referring to the positive B/R balance, some note an apparent contradiction between a "proven" positive B/R balance on one hand, and the need for confirmation on the other. In practice, this means that for a CMA, "proof" of positive benefit-risk at time of approval can be claimed albeit relying more strongly on assumptions, and that confirmation post-approval refers to the need to verify strong assumptions, so that eventually, in an agreed timeframe, the uncertainty is reduced to the level of a "standard" approval.

"Comprehensive" clinical data is defined as scientific standards of evidence that are necessary for full approval (e.g., control of statistical error concerning endpoints that measure clinical benefit). There is often confusion that a CMA based on a non-randomized controlled trial will systematically require an RCT in the approved indication. Although this may often be the case, the design of studies (prospective, observational, indication, endpoints, etc.) will depend on the objectives, i.e., the evidence required to address the uncertainties

according to conventional scientific standards and will be considered on a case-by-case basis, as occurs with any other standard authorization granted in the EU.

The criterion about unmet medical requires that there are no available treatments or that the drug will bring a major therapeutic advantage over existing therapies. What is often not realized, is that the latter is a bigger hurdle and has been met either when some type of superiority over existing treatments could be shown or, arguably, when it could be justified that the new drug was a significant new addition to a range of available treatments (i.e., adding a non-redundant treatment to the*armamentarium* , typically, a treatment with a new mechanism of action that is not adversely affected by prior existing treatments and does not adversely affect subsequent existing treatments, in situations where patients ultimately run out of treatment options).

Two other criteria for CMA are often given less attention, namely that regulators need to conclude that early approval is beneficial from a public health perspective compared to waiting for more comprehensive evidence before approval and that confirmatory studies must be feasible and timely provided by the marketing authorization holder. These are complex criteria to establish, as they need to consider both the consequences of CMA under different scenarios and that aspects of clinical trial conduct are often difficult to predict, e.g., difficulty recruiting due to competing trials or new treatment options.

Lastly, it is important to recall that while there are specific criteria for conditional approvals to be fulfilled, all the remaining requirements still apply. A piece of general advice is that to cope with uncertainty in some parts of the dossier, it is advisable to minimize uncertainties elsewhere to reduce the overall uncertainty (e.g., it is imperative that the data obtained are of the highest quality, particularly concerning the accuracy, lack of bias, precision (4). Moreover, while providing clear information on the conditional nature of the authorizations is a requirement, there is an opportunity to optimize effective communication beyond the standard statements in the summary of product characteristics, to provide exhaustive and continuously up-to-date information about the remaining uncertainties and how they are being addressed to patients and healthcare professionals.

Conditional approval is not a way to rescue "negative" studies.

Developers may consider promising results from *post hoc* analyses of failed confirmatory studies as convincing for a CMA. For example, a drug application was submitted for malignant gastrointestinal stromal tumor (GIST) based on an exploratory analysis of the secondary endpoint overall survival (HR: 0.29; 95% CI: 0.10; 0.85; p-value: 0.016) from a randomized clinical trial (RCT) that observed no difference on the primary endpoint progression-free survival (5). This was considered insufficient for conditional approval due to uncertainties about the efficacy and lack of statistical power to test the hypothesis. A negative result in the overall population may also weigh against the credibility of findings in small subgroups, regardless of the scientific hypotheses. In this respect, a well-planned exploratory study showing a strong signal based on a sound hypothesis may be more convincing than the same signal observed in a subgroup analysis of a negative trial.

More generally, attention to the development plan is needed to ensure generating as strong as possible corroborating evidence to support any assumptions. For instance, there is a need to apply as rigorous "confirmatory" approaches as possible, such as the intention-to-treat principle, and scrutinize the magnitude and quality of effects (e.g., consistency across subgroups and endpoints, analysis sets, dose-response) and outside the study (e.g., pharmacological evidence and rationale, non-clinical evidence, other clinical studies) (4). Careful planning will also allow to optimize the timing and nature of confirmatory studies and may increase the likelihood of meeting the requirements for conditional approval.

While early approval strategies based on outstanding results may work for frequent or rare diseases alike, a common misconception is that for rare diseases it may be acceptable to lower evidentiary standards for approval since adequately sized randomized controlled studies are difficult to conduct. Rather, the emphasis is on using methods to increase the efficiency of the design and analysis of clinical studies (4).

Conditional approval is best when it occurs late in ongoing development.

In oncology, companies typically justify applications for CMA by claiming that frequent and durable objective response from non-randomized controlled trials is a predictor of beneficial effects on clinical endpoints like overall survival and quality of life. Timely confirmation is crucial given the generally poor surrogacy of response rate, unless results are so convincing that surrogacy becomes self-evident. Depending on the uncertainties and how they are communicated, there may be a narrow time window for conducting randomized controlled trials following approval, especially due to the perceived lack of equipoise post-approval. This is an important risk since the failure of timely completion of confirmatory trials may lead to revocation of the authorization. A recommended approach is to time conditional approval to occur after confirmatory studies are well underway (6). For example, for the first CMA granted in the EU, the final analysis of the ongoing confirmatory trial was expected approximately one year after submission, and the recruitment had been completed before approval (7).

When confirmatory trials are ongoing, applicant companies have sometimes offered informal 'previews' of the results to regulators to support early approval. Such practices need to be managed carefully due to several issues, such as the risk of damaging trial integrity, increased type I error, and lack of transparency of the decision. Following standard practices, whenever considering interim data from confirmatory studies during the review, applicant companies or any other evaluator are required to apply formal statistical approaches and beware of undue disclosure that may compromise trial integrity.

Superior response is not necessarily a "major" advantage.

Establishing that an increase in response rate is a "major" therapeutic advantage compared to available treatments is challenging, even in randomized controlled trials, due to poor surrogacy for time-to-event endpoints, e.g., overall survival. This highlights the fact that conditional approval is more challenging if there are available treatments with proven effects in terms of meaningful clinical outcomes.

For example, a higher complete response rate was observed for a drug submitted for conditional approval in acute leukemia compared to the historical control (18.3%; 95% CI: 11.6, 26.9 v. 7.0%; 95% CI: 1.5, 11.9). However, in the context of the study employing indirect comparisons and a non-validated surrogate endpoint, the results were not considered convincing enough to establish a therapeutic advantage (8).

One successful example, although with diverging views, is based on much higher activity in terms of complete response when used in combination compared to the historical control (40% v. 11%), and a different safety profile and clinical use in the treatment of lymphoma (9).

An additional aspect often overlooked, albeit referring to the framework of EU orphan medicinal product designation and not of marketing authorization, is that meeting the criterion of "major" therapeutic advantage does not automatically constitute a "significant benefit" from the point of view of the criteria for maintenance of orphan designation. "Significant benefit" may have more stringent and specific data requirements for demonstrating improved, broader, or otherwise different beneficial effects compared to the authorized products (10). For example, in the case of teclistamab, a "major therapeutic advantage" was accepted for the CMA based on the product offering an alternative therapeutic option whereas for maintenance of orphan designation, it was highlighted that a demonstration of the product's equivalence in terms of efficacy, safety and benefit/risk balance would likely be needed to confirm "significant benefit" (11, 12).

Non-randomized is not necessarily non-comprehensive (and *vice versa*)

There is often a misunderstanding that if the submission is based on single-arm trials then the outcome, if favorable, must be a CMA. Or that a CMA requires an RCT to be converted to standard approval. This misunderstanding is based on the wrong focus given to the study design rather than the uncertainty and objectives of different studies.

While a commitment to conduct an RCT is practically always necessary when there is a need to confirm an effect on time-related endpoints like overall survival, if the approval was based on single-arm trials, it is possible that on occasion, for example, RCTs conducted in other populations or with slightly different treatment characteristics (e.g., different dose or combination), coupled with reasonable assumptions and extrapolations, still provide sufficient confirmatory evidence. Sometimes uncertainties about reliability or generalizability may be addressed without RCTs, for example through external comparisons using observational studies, or larger non-randomized cohorts to replicate results (e.g., a condition for larotrectinib, approved in a histology-independent indication, was to further confirm the histology-independent effect of larotrectinib in a pooled analysis of a non-randomized "basket" trial with increased sample size) (13).

Ultimately, to design post-marketing studies, the real question is not if the drug developer completed an RCT or not pre-approval but how the existing uncertainties (regardless of the design of submitted studies) can be addressed and minimized to an acceptable level, using any suitable design and taking into account available data, reasonable assumptions and extrapolations.

Communicate, inform, describe.

Conditional authorizations are arguably one of the most important decisions to communicate effectively to patients and doctors, not only for reasons of transparency and accountability but also to better inform clinical decisions. The main tool to inform healthcare professionals is the summary of product characteristics, which is a short document that follows a rigid format. Currently, CMAs are flagged in a short paragraph in the product information, alerting to the fact that confirmatory data is expected.

More extensive educational material for both health professionals and patients could be developed in the form of educational material. This would help manage any risks that doctors and patients may not be well-informed about the uncertainties associated with CMAs. Educational material can be fine-tuned to the relevant population and uncertainties and provide useful information to support clinical decision aids. Patient preference data and quantitative benefit-risk assessment may also highlight situations of heterogeneous preferences where careful clinical decisions are needed based on individual preferences (14). Lastly, up-to-date information can be provided on an ongoing basis about remaining uncertainties and the available data to address them, as they emerge.

Early approval as part of a comprehensive development strategy

For products falling within the scope of CMA, advocating the pursuit of early approval within a comprehensive developmental framework is pivotal. This is in line with the principles of "adaptive licensing", seeking to maximize the positive impact of new drugs on public health by combining timely access for patients with prospectively planned iterative phases of evidence gathering to reduce uncertainties (15).

The key elements of a comprehensive evidence-generation plan consist of timing of studies and assessments; diagnosing gaps and uncertainties; guidance about decision rules and adaptations; and engagement with stakeholders and decision makers ("EDGE", see Figure 1).

Initiating this process should be the careful design of an, focusing on generating and assessing available evidence at submission and subsequent milestones, as well as acquiring knowledge on drug utilization, and monitoring. The primary objective of the plan is to describe expected evidence and uncertainties at each time point, which is crucial for benefit and risk assessment, and managing uncertainties. Special attention should be devoted to the timing of conditional approval and the design, conduct, and feasibility of the confirmatory trial(s).

At each milestone, the plan should describe the expected evidence gaps, strength of evidence, and uncertainties, such as internal and external validity, heterogeneity in response, and selection bias. When expected gaps are identified, it is important to assess the impact on the B/R balance and propose strategies to ad-

dress uncertainties (e.g., further analyses of data; further studies; communication; other risk minimization measures).

The plan should describe prospectively defined decision rules about key aspects of development (e.g., use of external comparator studies, evidence thresholds for early submission) should be pre-specified as much as possible, to allow assessment and advice about chosen strategies including study adaptations or submission timelines. The plan should include analyses addressing scenarios when some of the planned studies do not deliver expected evidence or if the studies are delayed.

Engaging stakeholders throughout the design of studies and relevant stages of development should be standard practice and is particularly important for early approval. Scientific and regulatory advice should be sought about the adequacy of the evidence-generation plan, aiming to address expected uncertainties in a timely way. Advice should be sought in parallel with other stakeholders and decision-makers (e.g., regulators from different regions, patients, health professionals, and health technology assessors), striving for efficiency of evidence generation whenever possible. Communication should be an integral part of the overall planning, making use of all available tools, including educational material to ensure informed clinical decisions, informing patients and doctors about uncertainties and how they are being addressed.

The plan, gap analysis, and advice should be regularly updated during the development.

Figure 1. Key elements of a comprehensive evidence-generation plan to describe iterative phases of evidence gathering and regulatory assessment ("EDGE").

Summary

Common pitfalls in CMA submissions highlight the need for a switch from a framework where unexpected findings from exploratory data are rushed for a regulatory decision to a planned strategy for the early generation of convincing evidence within a comprehensive confirmatory strategy and transparent communication.

Extensive consultation of different decision-makers in the system, along the lines of EMA-FDA parallel scientific advice and Joint Parallel EMA/HTA (Health Technology Assessment) scientific advice procedures, provide a great opportunity for ensuring that the evidence generation fulfills the needs of different stakeholders as efficiently as possible.

A thorough discussion on what uncertainties need to be addressed and what can be accepted will play a vital role in the final decision on whether a drug should be approved or not. Understanding the limitations of a given dossier, such as validity, reliability, internal and external consistency, missing data, precision, etc., and assessing what is acceptable and what is not, will greatly reduce the unpredictability of such submissions.

It is imperative to understand that the required evidence can vary over time for a given indication, as more and more knowledge and data accumulate. With this, it is important to emphasize that drug developers must understand the changing regulatory landscape, recent trends, and approvals. Repeated advice may be needed to address the evolving scenarios and requirements.

Companies and regulators need to make an extra effort to justify and communicate what is expected in terms of clinical benefit, the data and assumptions that form the basis of their deliberations, and any remaining uncertainties and coping mechanisms making use of the vast toolbox of communication means at their disposal. This will inform clinical and other decisions.

What uncertainties concerning CMA can or cannot be accepted from different perspectives? This is what matters in the end. By avoiding common pitfalls and by careful planning, developers can support timely and comprehensive evidence generation to address unmet medical needs and inform decisions.

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FIGURE LEGENDS

Figure 1, Key elements of a comprehensive evidence-generation plan to describe iterative phases of evidence gathering and regulatory assessment ("EDGE")

SUPPLEMENTARY MATERIALS

None

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CONFLICT OF INTEREST

SBS, PK, AM, and SS have no conflict-of-interest statement other than working in a consulting firm. JC has no conflict-of-interest statement other than working in a pharmaceutical company. SBS, PK, SS, and JC are all former (alternate-) members of the Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA). AM is the former Deputy Director, Oncology Center of Excellence, Food & Drug Administration (FDA). The views and opinions expressed in this paper, are those of the authors and should not be attributed to Parexel or MSD.

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