Added therapeutic benefit and drug licensing

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One aspect of the ongoing debate about drug pricing is the added therapeutic benefit of new drugs compared with existing — and potentially cheaper — therapies. Here, we discuss the merits and pitfalls of proposals that are being discussed with regard to the role of regulatory agencies in establishing added therapeutic benefit.

Some new drugs are game-changers but others show no or only modest benefits over existing treatment options, even though their benefit–risk profile is positive. Nevertheless, nearly all new drugs come with a price tag higher than already available therapies, leading health-care payers and other stakeholders to emphasize that 'innovation' is not synonymous with 'added therapeutic benefit' and to increasingly resist paying breakthrough prices for absent or small added benefit.

At the European Medicines Agency (EMA), we hear various proposals to ensure, or at least make transparent, the added therapeutic benefit of novel treatments. The aim of these proposals is to contain the rising cost of what is often perceived as the nebulous concept of 'innovation'. In this article, we discuss the potential benefits and risks of some of these proposals.

Potential regulatory policy developments

Based on the current debate, we identify at least four levels where added benefit could be inserted into drug regulation.

Requiring added therapeutic benefit. The most fundamental proposal is to only authorize new drugs that have demonstrated added therapeutic benefit (see Related links). This would be a departure from the current statutory requirement that the benefits of a new drug outweigh its risks, which does not require superiority to other products. The idea is well intentioned, but there would probably be unintended consequences.

First, introducing an added-benefit criterion may not be in patients' best interests. Several clusters of so-called 'me-too' drugs appeared to be almost interchangeable at the time of launch. Yet, as more treatment experience accumulated during routine use, they proved to have different safety profiles (for example, antidiabetic agents), different drug–drug interactions (for example, antifungal agents) or different efficacy profiles or effect sizes (for example, quinolones for treating bacterial infections)[1,2].

Second, even when average or median effect sizes of products appear similar, treatment responses in individual patients may differ from one drug in a class to the next, owing to known or unknown individual patient characteristics. For example, this has been observed with tumour necrosis factor inhibitors[3] and may become more important in the future. High hopes are riding on the ability of 'omics' research to prospectively identify high responders to individual drugs. If the potential of precision medicine is to be realized, more than one class of drugs is likely to be required to serve more than one subgroup of patients.

Third, patients express different preferences; some are focused on maximising efficacy while others wish to minimize adverse effects[4]. Having only one product in a class or indication would deny patients and physicians this choice.

Last, the added-benefit proposal may even counteract the intention to control costs. Many 'me-too' products are the result of simultaneous drug development by different companies for the same drug target. Having similar products on the market can bring down prices by preventing or breaking monopolies.

Requiring head-to-head comparisons. A second proposal is that all new drug products be authorized only on the basis of head-to-head comparison with other treatments. This does not necessarily require demonstration of added benefit, but would mandate active-controlled randomized controlled trials (RCTs) in all cases.

Comparison with the best available treatment is indispensable in many clinical scenarios, but active controls are not always feasible or useful. The best available therapy is a moving target; by the time the results of long-running RCTs become available, a new standard of care or different use of the active comparator may have emerged. In fast-moving fields, and where ethically acceptable, placebo controls may provide a more durable 'anchoring' of the efficacy information about a new treatment. Also, there is often no agreement on the best available comparator. Conducting randomized comparisons against multiple existing treatments is not practical and, in such cases, added benefit will have to be estimated by indirect comparisons.

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Active comparator trials, including platform trials, should be encouraged where useful, but flexibility in the choice of direct or indirect comparators, including placebo, is needed to account for a range of different clinical scenarios.

Planning for indirect comparisons. Third is a proposal to simply recognize that assessment of added therapeutic benefit will often need to be based on indirect comparisons and to plan for it. Mixed treatment comparisons (MTCs) are a family of study designs indirectly comparing two treatments by using existing data from two or more RCTs that have compared each of the treatments with a common comparator (for example, placebo). A key requirement for successful MTCs is common end point definitions across RCTs. However, clinical trial sponsors often select what they measure in isolation from other trials, making it impossible to directly compare their results.

For several years, the EMA has been hosting multi-stakeholder consultations with post-licensing decision-makers at the beginning of clinical development of a product and, more recently, also around the time of authorization. These meetings allow regulators as well as health technology assessment (HTA) bodies and payers to advise developers on what they consider appropriate clinical trial designs. Hoped-for results of these multi-stakeholder consultations are to enable more meaningful MTCs at the time of product launch as well as pre-planned description and continued monitoring of added benefits for relevant patient subgroups once the product is on the market. Experience shows that in the majority of cases a workable understanding can be reached between developers, regulators and HTA bodies[5].

Focusing on comparative efficacy. At the fourth level, a proposal to address added benefit calls for a more explicit focus on regulatory assessments and communications on the comparative efficacy part of benefit–risk assessments. We note that any good or bad effects of a treatment must necessarily be described by comparing it with a counterfactual scenario; the concept of 'absolute' benefits or harms is a commonly held misconception. The counterfactual may be treatment with another drug or no treatment (or placebo treatment), the latter corresponding to the natural history of the disease. Regulators could perhaps be more explicit about this fact and in quantifying comparative effects.

Moreover, benefit–risk is not assessed in a therapeutic vacuum. Even with placebo-controlled trials, benefits and risks are necessarily contextualized. For example, in therapeutic indications where treatment with a medicine of inferior efficacy would risk increasing mortality or may delay more effective treatment, leading to irreversible harm, the benefit–risk balance may be deemed negative even when the comparison with placebo seems favourable. We have heard from external stakeholders that more emphasis should be placed on contextualizing the effect of new medicines and to be more explicit about negative, neutral or positive added benefit where possible in relevant patient subgroups. The EMA is now engaged in dialogues with HTA bodies and payers to explore how best to serve these information needs (see Related links).

Conclusion

Eliminating scientifically justified flexibility in drug development and authorization, although well intentioned, may not produce good results for patients and health-care systems. A better approach is 'evidence by design', that is, to plan upfront for quantification of added therapeutic benefit. This can be achieved by mutual understanding among all relevant decision-makers on clinical trial designs, with a view to using the entire spectrum of methodologies, including MTCs, not only head-to-head comparisons.

Coupling this collaborative approach with more explicit reasoning on added benefit by regulators at the time of authorization is probably the best available option to reduce uncertainty about added benefit in the decisions of HTA bodies, payers, clinicians and patients by separating the merely 'new' from the truly 'better'.

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Competing interests
The authors declare no competing interests.

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