Therapeutic value of first versus supplemental indications of drugs in US and Europe (2011-20): retrospective cohort study

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ABSTRACT

OBJECTIVE

To analyze the therapeutic value of supplemental indications compared with first indications for drugs approved in the US and Europe.

DESIGN

Retrospective cohort study.

SETTING

New and supplemental indications approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) between 2011 and 2020.

MAIN OUTCOME MEASURES

Proportion of first and supplemental indications rated as having high therapeutic value using ratings from the French and German national, independent health authorities.

RESULTS

The cohort study included 124 first and 335 supplemental indications approved by the FDA and 88 first and 215 supplemental indications approved by the EMA between 2011 and 2020; the largest subset was for cancer disorders. Therapeutic ratings were available for 107 (86%) first and 179 (53%) supplemental indications in the US and for 87 (99%) first and 184 (86%) supplemental indications in Europe. Among FDA approved indications with available ratings, 41% (44/107) had high therapeutic value ratings for first indications compared with 34% (61/179) for supplemental indications. In Europe, 47% (41/87) of first and 36% (67/184) of supplemental indications had high therapeutic value ratings. Among FDA approvals, when the sample was restricted to the first three approved indications, second indication approvals were 36% less likely to have a high value rating (relative ratio 0.64, 95% confidence interval 0.43 to 0.96) and third indication approvals were 45% less likely (0.55, 0.29 to 1.01) compared with the first indication approval. Similar findings were observed for Europe and when weighting by the inverse number of indications for each drug.

CONCLUSIONS

The proportion of supplemental indications rated as having high therapeutic value was substantially lower than for first indications. When first or supplemental indications do not offer added therapeutic value over other available treatments, that information should be clearly communicated to patients and physicians and reflected in the price of the drugs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

After initial regulatory approval, a new drug may subsequently be approved for supplemental indications

Health technology assessment organizations in different countries assess the therapeutic benefit of new medicines

Approximately one third of new drugs (first indications) have a high therapeutic value

WHAT THIS STUDY ADDS

An increasing number of supplemental indications have been approved over the past decade in the US and Europe, with more than half indicated for treatment of cancer

The proportion of supplemental indications rated as having high therapeutic value was substantially lower than for first indications

Introduction

After initial regulatory approval, a new prescription drug may subsequently be approved for additional indications.[1] Supplemental approvals are particularly common among drugs for cancer.[2-5] For example, pembrolizumab was originally approved in the US and Europe for the treatment of advanced melanoma and subsequently approved for treatment of non-small cell lung cancer, head and neck squamous cell cancer, and renal cell carcinoma, among other conditions.[6 7] In some cases, the volume of use for a drug's supplemental indications can exceed that of its first indication.[8] Drug approval standards are consistent across drugs' first and supplemental indications.[2 3] One important feature of drug approval in the US and Europe is that neither the US Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) requires data on the magnitude of a drug's effectiveness compared with other treatments for the same condition. Consequently, several countries, such as France or Germany, evaluate the comparative therapeutic benefit of new drugs via a health technology assessment organization. Ratings from health technology assessment bodies can help to identify drugs providing high added therapeutic value that should be made rapidly available, provide guidance to clinicians and patients on treatment selection, and serve as a basis for price negotiations.[9] These ratings also inform government level reimbursement decisions and negotiation of prices in these settings.[10 11]

In previous research, approximately one third of drug approvals by the FDA or EMA for initial indications were rated as having high added therapeutic value in health technology assessments.[11 12] When limited to a cohort of cancer drugs, gains in quality adjusted life years were higher for first indication approvals than for the conditions targeted in second or subsequent approvals in the US.[4] How added therapeutic value compares across first and supplemental indications in the US and Europe for all therapeutic areas has not been reported,

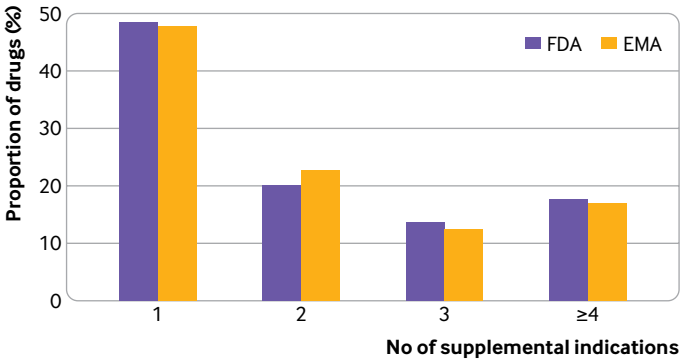

Fig 1 | Proportion of drugs with one or more supplemental indications approved in US and EU, 2010-21. EMA=European Medicines Agency; FDA=US Food and Drug Administration

however. This information is particularly important in the context of the increasing number of drugs approved for multiple indications,[8 13 14] and it may have policy implications—for example, for the FDA's Split Real Time Application Review (STAR) pilot program launched in October 2022, which aims to shorten the time from the date of submission to the action date for supplemental indications.[15] In this study, we aimed to analyze the therapeutic value of drugs approved for more than one indication and assess the therapeutic value of supplemental indications compared with first indications for drugs approved in the US and Europe.

Methods

Study cohort

We used data publicly available on the FDA and EMA websites to identify new drugs approved between January 2011 and December 2020.[6 16] We then identified approvals for supplemental indications for these drugs in both the US and the EU through December 2021. Among this initial list, we excluded supplemental approvals that only expanded the age range in the original indication. We included all supplements covering indications in different disease entities compared with the original approved indication(s) of the same drug or treating the same disease entity but encompassing new combination therapy or targeting a separate mutation. We excluded generic, biosimilar, and diagnostic (for example, contrast and imaging) agents. For each indication approval, we extracted the date, indication, and therapeutic area based on the World Health Organization's Anatomic Therapeutic Classification system.

Ratings of therapeutic value

Some well established health technology assessment agencies publish only a decision on coverage, without providing a rating of the level of added therapeutic value (for example, the National Institute for Health and Care Excellence) or provide a rating only for the first indication but not for supplemental indications of a drug (for example, the Canadian Human Drug Advisory Panel). We therefore excluded these.

We identified two health technology assessment bodies that publish therapeutic value ratings for first and supplemental indications in France (Ministry of Health) and Germany (Federal Joint Committee).[17 18] We included value ratings based on evaluations and re-evaluations of drugs conducted and published as of December 2022.

The German and French agencies assess the added benefits of a drug's approved indication compared with existing therapies. Germany differentiates between ratings of major, considerable, minor, or no or not quantifiable benefit. Criteria for the therapeutic value assessment are improvement in health, reduction in the disease duration, increase in survival, reduction in side effects, and improvement in quality of life.[19] In France, ratings of major, considerable, moderate, or minor added benefit or insufficient benefit are distinguished. The therapeutic value assessment is based on the severity of the treated disease, the efficacy of the drug, the drug's adverse effects, and its priority in France's therapeutic strategy.[20] We defined ratings of moderate or greater added value over available options by at least one agency as "high."[9 11 12] We only included those indications that had an assessment score in our analysis. Neither agency considers cost or cost effectiveness in its ratings, and both are independent from the pharmaceutical industry.

Statistical analysis

We used descriptive statistics to analyze the unadjusted proportion of first and supplemental indications rated highly by the French or German health authorities. To obtain adjusted estimates of the probability for supplemental indications to be rated highly, we used Poisson regression analyses, with the following algebraic representation: $\log[E(Y_{i,j})]=\beta_j x_{i,j}+\alpha_i+\alpha_t$. The

Table 1 | Characteristics of first and supplemental indications approved by FDA and EMA. Values are numbers (percentages)

	FDA		EMA	
Therapeutic area	First indications (n=124)	Supplemental indications (n=335)	First indications (n=88)	Supplemental indications (n=215)
Alimentary and metabolism	9 (7)	13 (4)	6 (7)	11 (5)
Anti-infective	19 (15)	34 (10)	7 (8)	11 (5)
Blood and cardiovascular	7 (6)	18 (5)	4 (5)	6 (3)
Cancer	53 (43)	209 (62)	43 (49)	134 (62)
Immunomodulation	12 (10)	25 (7)	15 (17)	28 (13)
Nervous system	10 (8)	13 (4)	3 (3)	3 (1)
Others	14 (11)	23 (7)	10 (11)	22 (10)

EMA=European Medicines Agency; FDA=US Food and Drug Administration.

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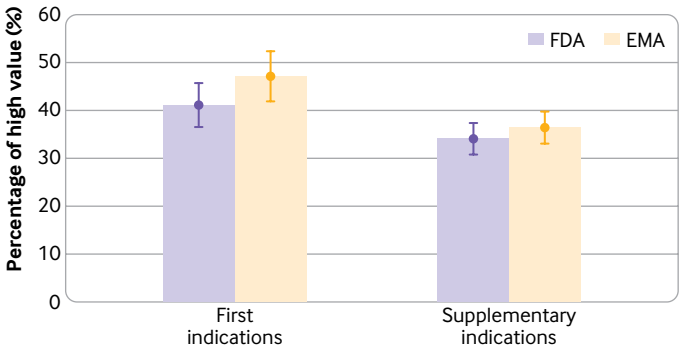

Fig 2 | Unadjusted percentage of high added therapeutic value ratings among first and supplemental indications of drugs approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Bars represent unadjusted proportions of indications with high therapeutic value designation. Whiskers represent 95% confidence interval

outcome was the high (1) or low (0) value rating Y, of drug *i*, for indication *j*. The coefficient of interest was β_j, the difference in expected value of the second *j=2* and the third or more *j≥3* indications with respect to the first *j=1*. We accounted for active ingredient specific fixed effects α_i, which controlled for differences in ratings across drugs, and year fixed effects α_t, which controlled for time trends.

We applied two analytical approaches to assess the sensitivity of the results. In the first analysis, we restricted our study cohort to first, second, and third indications. In the second analysis, we classified indications as first, second, and third or more (that is, we considered third or subsequent indications as one category). We applied weighting by the inverse number of drug specific indications to enable the unit of constant observation at the drug level. Without such an adjustment, a drug with, for example, 12 indications would have three times more weight in the analysis than a drug with four indications. Our analysis assumed that missing values in ratings were randomly distributed. In case the lack of rating information was more prevalent in low therapeutic value drugs and supplemental indications, our estimates would be biased toward the null.

We used R (version 4.1.2) for all statistical analyses and considered P values <0.05 to be statistically significant. This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures. Nor were they involved in developing plans for design or implementation of the study. Patient and public involvement was not commonly used in our discipline in this region when we started the study.

Results

Our study cohort included 124 first indications and 335 supplemental indications approved by the FDA and 88 first indications and 215 supplemental indications approved by the EMA. Of these drugs, 63 first and 164 supplemental indications were approved by both agencies.

In the US, 48% (60/124) of drugs had one supplemental indication, 20% (25/124) had two supplemental indications, 14% (17/124) had three supplemental indications, and 18% (22/124) had four or more supplemental indications. In Europe, 48% (42/88) of drugs had one supplemental indication, 23% (20/88) had two supplemental indications, 13% (11/88) had three supplemental indications, and 17% (15/88) had four or more supplemental indications (fig 1). Most indications approved by the FDA and EMA were indicated to treat oncologic (58%), infectious disease (9%), or immunomodulating disorders (10%) (table 1).

Therapeutic ratings were available for 107 (86%) first indications and 179 (53%) supplemental indications in the US and for 87 (99%) first indications and 184 (86%) supplemental indications in Europe. The κ statistic between the French and German value scores was 0.3907. The results held when we conducted the analysis with the ratings of each health technology assessment organization separately.

Indications with high therapeutic value

Among FDA approved indications with at least one available rating, 41% (44/107) had high added therapeutic value ratings for first indications, compared with 34% (61/179) for supplemental indications (P=0.29). In Europe, 47% (41/87) of first indications and 36% (67/184) of supplemental indications had high added therapeutic value ratings (P=0.12) (fig 2).

Therapeutic value of supplemental indications compared with first indications

Among FDA approvals, when we restricted the sample to the first three approved indications, second indication approvals were 36% less likely to have a high value rating (relative ratio 0.64, 95% confidence interval 0.43 to 0.96; P=0.04) and third indication approvals were 45% less likely (0.55, 0.29 to 1.01; P=0.08) compared with the first indication approval. We observed similar findings among European approvals, as second indication approvals were 37% less likely to have a high value rating (relative ratio 0.63, 0.43 to 0.92; P=0.02) and third indication approvals were 52% less likely (0.48, 0.29 to 0.78; P=0.004) compared with the first indication approval (fig 3).

We obtained similar results when weighting by the inverse number of indications for each drug (fig 3). Among FDA approvals, when we restricted the sample to the first three approved indications, second indication approvals were 35% less likely to have a high value rating (relative ratio 0.65, 0.43 to 0.98; P=0.05) and third indication approvals were 47% less likely (0.53, 0.31 to 0.93; P=0.03) compared with the first indication approval. Among European approvals, second indication approvals were 35% less likely to have a high value rating (relative ratio 0.65,

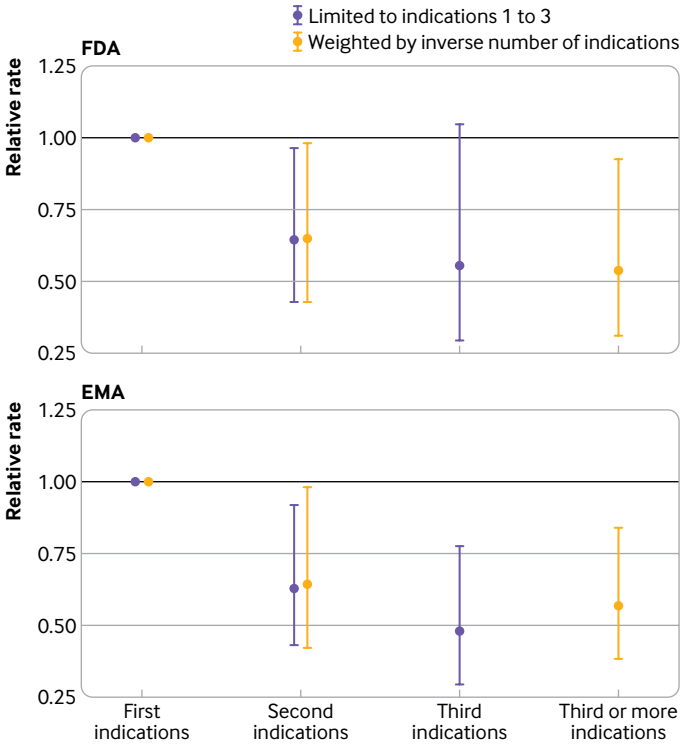

Fig 3 | Relative ratio of drugs approved by US Food and Drug Administration (FDA) (top panel) or European Medicines Agency (EMA) (bottom panel) having high added therapeutic values among first versus supplemental indications. In first analysis (purple), study cohort was restricted to first, second, and third indications. In second analysis (yellow), indications were classified as first, second, and third or more, weighted by inverse number of drug specific indications to enable unit of constant observation at drug level

0.42 to 0.98; P=0.05) and third indication approvals were 44% less likely (0.56, 0.38 to 0.84; P=0.007) compared with the first indication approval

Discussion

We examined all new drugs approved for more than one indication in the US and Europe between January 2011 and December 2020 and assessed the therapeutic value of supplemental indications compared with first indications. Fewer than half of approved first indications in the US and Europe were rated as having high therapeutic value. Over the past decade, a substantial number of drugs have had multiple approved supplemental indications in the US and Europe, particularly among drugs treating cancer. The likelihood that supplemental indications were rated as having high added therapeutic value was substantially lower than for the drugs' initial indications. When indications do not offer added therapeutic benefit over other available treatments, that information should be clearly communicated to patients and reflected in the price of the drugs.

Strengths and limitations of this study

Although some studies have already focused on the therapeutic benefit of first indications,[9 11 12] none has compared the therapeutic value of first and supplemental indications across all therapeutic areas.[4 5] Our findings highlight that the likelihood that supplemental indications would be rated as having high added therapeutic value was substantially lower compared with the drugs' initial indications.

Limitations of the study include the fact that therapeutic value ratings were not available for all indications, particularly indications approved in the US but not in Europe. However, a previous study found that indications approved only in the US and not also in Europe were more likely than indications approved in both jurisdictions to offer low added therapeutic value.[21] Furthermore, the methods and value assessment system can be influenced by country specific factors and assumptions. To be conservative, we focused on the outcome of the highest rating provided by any of the rating systems.[11] Additionally, future re-evaluations by health technology assessment organizations may alter the therapeutic value of an indication. However, few indications substantially change their therapeutic value on re-evaluation.[9] Finally, although the criteria and frameworks for the value assessments were similar for both health technology assessment organizations, the methods and scoring system can also be influenced by country specific factors and assumptions. We focused on the primary outcome of the highest rating provided by one of the two health technology assessment organizations. We also did sensitivity analyses with the value scores of each HTA organization separately, which confirmed the primary results.

Policy implications of findings

Fewer than half of approved first indications in the US and Europe were rated as having high therapeutic value. In previous studies, approximately one third of initial drug approvals were rated as having high added therapeutic value.[11 12] This difference can be explained by the different study cohorts. In this study, we included only drugs for which at least one supplemental indication was approved by 2020, whereas the previous studies included all initial indication drug approvals irrespective whether supplemental indications were later approved. We found that supplemental indications had an even lower probability of high value ratings in both the US and Europe. The therapeutic value of all indications for new drugs should be communicated clearly to patients and physicians to help them make informed and optimal decisions about the treatment, particularly as these drugs are often highly expensive.

The most common disease indications in our study cohort were related to anticancer drugs, followed by anti-infective and immunomodulating drugs. Although unmet need exists in these therapeutic areas, that approved cancer and anti-infective drugs (first and supplemental indications) have high therapeutic value for the patients they are intended to benefit is nonetheless crucial.[22-25] Some drugs receive low therapeutic value ratings because the data on their effects on clinical outcomes are insufficient at the time of regulatory approval, whereas others receive low

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ratings because they are not shown to be superior to existing therapies.[26 27] Insufficient data at the time of regulatory approval indicate the importance of post-approval studies. In the past, post-approval studies have frequently been delayed or not completed, and, until recently, drugs given accelerated approval in the US were not expeditiously withdrawn on failure of confirmatory studies.[28] The Food and Drug Omnibus Reform Act of 2022 gave the FDA greater authority to require initiation of confirmatory studies before accelerated approval, setting of enrolment targets, and biannual reporting of the study progress.[29]

Many of the drugs in the study cohort had one or two supplemental indications. For example, ticagrelor was first approved by the FDA and EMA to reduce the risk of thrombotic cardiovascular events in patients with acute coronary syndrome and was later also approved to reduce the risk of myocardial infarct or stroke. However, some drugs have many more supplemental indications, especially among cancer drugs. For example, pembrolizumab was approved by the FDA for more than 30 supplemental indications and by the EMA for more than 15, and nivolumab was approved for more than 20 supplemental indications by the FDA and more than 10 by the EMA. The number of approved supplemental indications has increased over the past years.[23] This trend is likely to continue with the growth of immunotherapies and gene therapies, which may be used to target multiple conditions.

Other reports suggest that less rigorously collected data were being accepted to support FDA approvals over time, particularly for supplemental indications.[30-32] In one recent study, regulatory approvals for first indications were found to be more likely than those for supplemental indications to be based on at least two pivotal trials.[3] An important implication of these trends relates to new regulatory initiatives such as the FDA's STAR pilot program, which aims to shorten the time from the date of submission to the action date for supplemental indications across all therapeutic areas. The goal is to allow earlier access for patients to drugs that tackle an unmet medical need and for which clinical evidence from adequate and well controlled investigations suggests that the supplemental indication may show substantial improvement in a clinically relevant endpoint over available therapies.[15] But our data show a disconnect between these criteria and a drug actually showing added therapeutic value.

The therapeutic value and cost effectiveness of supplemental indications could be more systematically taken into account in discussions about models for assuring fair pricing and reasonable incentives for investment in innovation.[23] To achieve this, weighted pricing across indications or indication based pricing of drugs has been suggested in the literature.[4 13 33 34] Weighted pricing has already been implemented in Germany and England, and Switzerland and France introduced indication based pricing.[13] Weighted pricing means that a drug has one blended price based on the value of the different indications per drug.[13] Indication based pricing is a differential pricing method that prices a drug according to the therapeutic value it delivers for each indication.[13 33 35] One rule in Switzerland is that the first price of a drug is the highest price possible, thereby serving as a ceiling for prices for supplemental indications, which must be the same or lower.[13] A study showed that for other countries, such as Canada and Australia, the use of managed entry agreements increased with the number of supplemental indications of a drug entering the market, likely to help to ensure that the therapeutic value is aligned with the prices paid for subsequent supplemental indications.[4]

Our study cohort included more first and supplemental indications for the US (124 first indications; 335 supplemental indications) than for Europe (88 first indications; 215 supplemental indications). This is likely because most drugs are first approved in the US rather than Europe,[25 36] and the FDA approves more drugs overall compared with Europe.[36 37] Thus, some drugs (including both first and supplemental indications) may have been included in our study cohort for the US but not for Europe.

Conclusions

Over the past decade, regulators have approved an increasing number of supplemental indications for drugs, with more than half indicated for treatment of cancer. Fewer than half of approved first indications in the US and Europe were rated as having high therapeutic value, and the proportion of approved supplemental indications rated as having high therapeutic value was substantially lower than for approved first indications. When first or supplemental indications do not offer added therapeutic value over other available treatments, that information should be clearly communicated to patients and physicians and reflected in the price of the drugs.

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Contributors: All authors contributed to the conception and design of the study. CEGG extracted the data, and MSB did the statistical analysis. KNV wrote the first draft. All authors read and critically revised the manuscript for important intellectual content. All authors approved the final version for publication. The corresponding author

attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. KNV is the guarantor.

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Ethical approval: Not needed, as this was a study of publicly available data.

Data sharing: Data are publicly available.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The authors plan to disseminate the study and study results to research institutions, governmental agencies, medical associations, and patient communities.

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