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Characteristics of efficacy evidence supporting approval of supplemental indications for prescription drugs in United States, 2005-14: systematic review

BMJ 2015 ; 351 doi: http://dx.doi.org/10.1136/bmj.h4679 (Published 23 September 2015)
Cite this as: *BMJ* 2015;351:h4679

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Accepted 17 August 2015

Abstract

Objective To characterize the types of comparators and endpoints used in efficacy trials for approvals of supplemental indications, compared with the data supporting these drugs' originally approved indications.

Design Systematic review.

Setting Publicly accessible data on supplemental indications approved by the US Food and Drug Administration from 2005 to 2014.

Main outcome measures Types of comparators (active, placebo, historical, none) and endpoints (clinical outcomes, clinical scales, surrogate) in the efficacy trials for these drugs' supplemental and original indication approvals.

Results The cohort included 295 supplemental indications. Thirty per cent (41/136) of supplemental approvals for new indications were supported by efficacy trials with active comparators, compared with 51% (47/93) of modified use approvals and 11% (7/65) of approvals expanding the patient population (P<0.001), almost all of which related to pediatric patients (61/65; 94%). Trials using clinical outcome endpoints led to approval for 32% (44/137) of supplemental approvals for new indications, 30% (28/93) of modified indication approvals, and 22% (14/65) of expanded population approvals (P=0.29). Orphan drugs had supplemental approvals for 40 non-orphan indications, which were supported by similar proportions of trials using active comparators (28% (11/40) for non-orphan supplemental indications versus 24% (10/42) for original orphan indications; P=0.70) and clinical outcome endpoints (25% (10/40) versus 31% (13/42); P=0.55).

Conclusions Wide variations were seen in the evidence supporting approval of supplemental indications, with the fewest active comparators and clinical outcome endpoints used in trials leading to supplemental approvals that expanded the patient population.

Introduction

Before a new prescription drug can be made widely available to patients in the United States, the Food and Drug Administration (FDA) must review a vast array of data relating to its use submitted as part of a

new drug application or biologic licensing application, including clinical trials testing the drug in the population for which it is intended to be marketed. By law, such trials must show both the drug's safety and substantial evidence of its efficacy. Recent studies of the pivotal clinical trials used to meet this standard indicate that approximately half of new drugs are approved after being tested against placebos or in uncontrolled trials.[1] Other reviews have found that a similar number of drugs are approved on the basis of trials using surrogate outcomes, including biomarkers such as low density lipoprotein cholesterol or glycated hemoglobin, rather than actual clinical outcomes such as mortality or clinical cure.[2] The clinical trial evidence supporting approval of new drugs also varies by disease type, with cancer agents and drugs for rare diseases more commonly tested in less robust non-randomized or unblinded studies or studies using surrogate endpoints compared with other therapeutic areas.[3 4]

After their initial approval, many new drugs are approved for additional clinical indications. Such approvals can occur if the manufacturer submits new data via a so called supplemental new drug application or supplemental biologic licensing application. For example, imatinib (Gleevec or Glivec) was initially approved in 2001 for the treatment of chronic myeloid leukemia and was subsequently approved for nine additional indications, including gastrointestinal stromal tumor and pediatric Philadelphia chromosome positive acute lymphoblastic leukemia.[5 6] In 2014 the FDA approved 40 new supplemental indications for already marketed drugs, compared with original approvals of 44 novel small molecule and biologic agents during the same period.[7 8] In some cases, the rate of prescribing for drugs' supplemental indications can exceed that for their original indications.[9]

The legal standard underlying FDA approval remains consistent for original and supplemental indications. Previous research on supplemental indication approvals has found that the average regulatory review times are shorter than for their original indications.[10 11 12] However, the characteristics of trials that support drugs' supplemental indications have not been analyzed. We sought to determine whether the characteristics of studies supporting drugs' supplemental indications differ substantially from those underlying the indications for which the drugs were originally approved. We characterized the quality of clinical trial evidence supporting the supplemental indications of novel agents, focusing on study comparators and trial endpoints. We then compared the evidence supporting the new uses with that providing the basis of approval for these agents' original indications.

Methods

Study sample

The FDA lists all supplemental new drug applications and supplemental biologic licensing applications on its Drugs@FDA database.[7] One author (BW) manually extracted all supplemental application approvals that occurred between 2005 and 2014 from this database, excluding supplements categorized by the FDA as relating to "labeling revisions" and "manufacturing change or addition," which focus mainly on administrative or logistical modifications and range from minor wording changes in the label to addition of new dosage strengths and adverse events (see table 1 for definitions of key terminology used in the analysis). We then examined the FDA's letters accompanying the remaining

supplemental application approvals to exclude those unrelated to supplemental indications, such as inclusion in the drug label of additional clinical data supporting an already approved indication (fig 1).

Table 1 Key terminology used in systematic review

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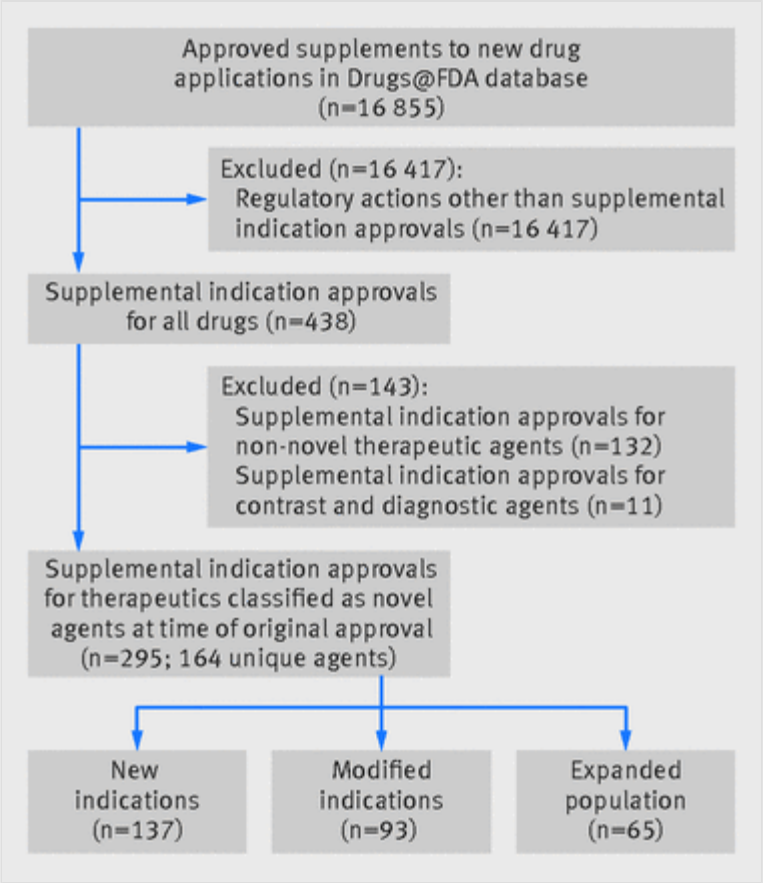

Fig 1 Construction of study sample

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We excluded duplicates, counting only once an approval of the same supplemental indication relating to multiple formulations of the same active ingredient. We also excluded 132 prescription drugs and biologics that were not originally approved as novel therapeutic agents (that is, new molecular entities and original therapeutic biologics), as well as all contrast and diagnostic products (n=11). We were left with 295 supplemental indication approvals relating to 164 unique drugs.

Characteristics of supplemental indications

For each supplemental indication approval, we determined its primary therapeutic area by consensus.

We also classified each supplemental indication into one of three mutually exclusive categories: new indication, meaning that no similar use was ever previously approved for the agent; modification of an already approved indication (for example, a drug initially approved for adjunctive therapy in treatment of partial onset seizures, now also indicated for use as monotherapy in this condition); and expansion in patient population (for example, a drug previously indicated for treatment of Crohn's disease in adults, now also approved for use in all patients aged 6 years and older).

We then used the Drugs@FDA database to gather information on each supplemental indication approval's date and chemical type (small molecule or biologic). We used both the Drugs@FDA database and the FDA's Orphan Drug Product database to determine whether the FDA granted orphan drug designation for each supplemental application as well as for each study drug at the time of original approval.[7] [13] Orphan drug designation has been granted by the FDA's Office of Orphan Product Development to drugs that treat diseases affecting fewer than 200 000 people in the United States each year.[14] This designation is indication specific, so granting such a designation for a drug's original approval should not carry over to all its supplemental indications. For example, onabotulinumtoxinA (Botox, Allergan, Coolock, Dublin, Ireland), which received orphan drug designation for its initially approved indications, was approved in 2013 for treatment of overactive bladder, a far more prevalent condition.[15] [16]

Characteristics of efficacy studies

We first sought to assess the characteristics of the clinical evidence underlying supplemental indication approvals in the same way that other investigators have studied such data in original drug approvals: using publicly available FDA medical reviews, which are documents that explore in detail the efficacy and safety of the novel agent demonstrated in clinical trials. However, we found medical reviews for only 20% of all supplemental indication approvals during our study time period, with such information available for one of 26 supplemental indication approvals from 2013 and for none of 40 from 2014. Instead, we assessed the supporting clinical evidence for all supplemental indications at the time of approval by accessing the earliest FDA drug label in the Drugs@FDA database that mentioned the newly approved use. In contrast to most medical reviews, FDA drug labels do not contain a description of all preclinical studies and clinical trials supporting an approved indication. However, drug labels do describe the study design and results of the so called pivotal trials that most clearly establish a drug's efficacy for that use.

We determined the study comparator used in the major studies that were conducted to establish the evidence of the drug's efficacy, as designated in the drug labels. We first classified the comparators as active, placebo, historical, or none. Drugs included active comparator data if at least one major efficacy trial compared the drug (drug A) versus an alternative therapeutic option (for example, drug A versus drug B or drug A versus standard of care).[2] We classified drugs as being supported by placebo comparator trials if no major efficacy studies relating to the supplemental indication approval included active comparators and at least one study included a placebo comparator (drug A versus placebo). Historical controlled trials compared patients treated with the drug of interest with those in earlier

cohorts, either treated or untreated. Drugs tested in single arm trials or drugs with multiple doses evaluated without separate comparators were classified as having no comparators.

We then determined the main endpoints in these efficacy trials and classified the endpoints as clinical outcomes, clinical scales, or surrogate outcomes.[2] Clinical outcomes measure mortality or patients' function and include endpoints such as death or incidence of disease. Clinical scales serve as quantitative gradations for patients' symptoms, such as the American College of Rheumatology criteria to measure response to rheumatoid arthritis.[17] Surrogate endpoints are intermediate outcomes intended to predict clinical benefit or harm and include laboratory values and other measures such as tumor size. In cases where multiple types of endpoints were used in the efficacy trials, we classified the endpoint under the more robust outcome.

Finally, for each supplemental indication approval, we used the same classification frameworks to evaluate the characteristics of the major efficacy trials supporting the drugs' originally approved indications. We used the Drugs@FDA database and Physicians' Desk Reference to gather the initial or earliest accessible drug labels for each drug.

We were unable to assess additional characteristics of efficacy trials, including blinding, trial size, and study duration, because such information was not included or inconsistently described in a substantial number of the drug labels we evaluated.

Statistical analysis

We did pre-specified χ^2 tests of the study comparators and endpoints based on the supplement category, chemical type, therapeutic area, and orphan drug status. We also used χ^2 tests to compare efficacy trials for supplemental indication approvals with analogous data from the original indications. Each drug's originally approved indication(s) was counted only once for each comparison, even if the drug featured approvals of multiple supplemental indications.

Patient involvement

No patients were involved in setting the research question or the outcome measures; nor were they involved in the design and implementation of the study. We have no plans to involve patients in dissemination.

Results

The FDA approved 295 supplemental indications (see web appendix) between 2005 and 2014, representing 164 unique drugs and ranging from 20 approvals in 2012 to 48 in 2006 (fig 2). Fifty eight (35%) drugs had two or more approved new uses during our study period. New indications constituted almost half (n=137; 46%) of supplemental indication approvals, and nearly all supplemental indications that specifically expanded the patient population of a previously approved use (n=65) related to pediatric patients (61/65; 94%). The top therapeutic area was oncology (80; 27%), followed by infectious disease (44; 15%); orphan drug designation was granted to 60 (20%) of supplemental indication

approvals (table 2).

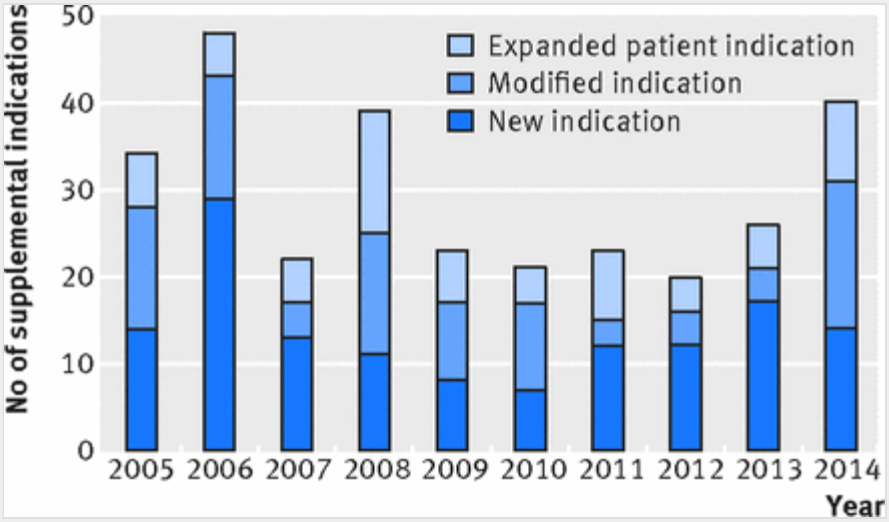

Fig 2 Supplemental indications approved by the FDA for novel therapeutic agents, 2005-14. Types of supplemental indications: new indication denotes no similar use was ever previously approved for agent (for example, drug initially approved for schizophrenia, now approved for bipolar mania); modified indication denotes agent previously approved for different aspect of same indication (for example, drug initially approved for adjunctive therapy in treatment of partial onset seizures, now indicated for use as monotherapy in this condition); expanded patient population denotes agent previously approved for same indication in different group of patients (for example, drug previously indicated for treatment of Crohn's disease in adults, now approved for use in all patients aged 6 years and older).

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Table 2 Characteristics of supplemental indications for novel therapeutic agents approved by US Food and Drug Administration, 2005-14

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Clinical evidence supporting supplemental indication approvals

We found significant differences in study comparators among the different supplement categories, with more than half of modified indications (47/93; 51%) being supported by at least one trial using an active comparator compared with 30% (41/136) of new indications and just 11% (7/65) of indications expanding the patient population (P<0.001) (a study comparator was not identifiable in one case among new indication supplemental approvals). Uncontrolled trials formed the basis of approval for 34% (22/65) of expanded population supplements, and nine (14%) of these supplemental approvals had no clinical efficacy trials.

Clinical trial endpoints were similar among the supplemental categories, with 32% (44/137) of new

indication supplemental approvals using clinical outcome endpoints compared with 30% (28/93) of modified indications and 22% (14/65) of expanded population supplements (P=0.29)

We also found significant differences in study comparators among different therapeutic areas; the number of active comparator studies ranged from 0/34 supplemental indication approvals for psychiatric drugs to 55% (44/80) among drugs targeting cancer (P<0.001) (table 3). Clinical outcomes were most often used in trials supporting supplemental indication approvals of neurologic (11/23; 48%) and infectious disease drugs (20/44; 45%); by contrast, 70% (56/80) of oncology supplemental indications were supported exclusively by trials using surrogate outcomes (table 4).

Table 3 Supplemental indication approvals for novel therapeutic agents approved by US Food and Drug Administration between 2005 and 2014 supported by at ≥1 trial with active comparator or exclusively by trials using placebo comparators. Values are numbers (percentages) unless stated otherwise

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Table 4 Supplemental indication approvals for novel therapeutic agents approved by US Food and Drug Administration between 2005 and 2014 that were supported by ≥1 trial that used clinical outcome as study endpoint, and proportion supported exclusively by trials using clinical scale or surrogate outcome as study endpoint. Values are numbers (percentages) unless stated otherwise

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Among orphan designated supplemental indications, more than a third (35%; 21/60) were supported exclusively by uncontrolled or historical controlled trials. In addition, orphan drug supplemental indications were supported by a lower proportion of trials using clinical outcome endpoints than were non-orphan approvals (18% (11/60) for orphan approvals versus 32% (75/235) for non-orphan approvals; P=0.04) and a higher proportion of studies using surrogate outcomes (57% (34/60) versus 35% (82/235); P=0.002).

Comparing supplemental and original indication approvals

The 164 drugs in the cohort were originally approved for 202 indications. Fewer supplemental approvals for new indications than originally approved indications were supported by trials using active comparators (30% (41/136) for supplemental indications versus 45% (90/201) for original indications; P=0.007), and more were supported by placebo controlled studies (57% (77/136) versus 42% (85/201); P=0.01) (table 3). By contrast, similar rates of clinical outcome endpoints were used by efficacy trials forming the basis of approval for new indication supplements and those supporting originally approved indications (32% (44/137) versus 39% (78/202); P=0.22) (table 4).

Supplemental indications for drugs treating infectious diseases (48% (21/44) for supplemental indications versus 76% (31/41) for original indications; P=0.008) and psychiatric conditions (0% (0/34)

versus 62% (8/13); P<0.001) were supported by a lower proportion of trials using active comparators than were original indications in these therapeutic areas. The rate of active comparator studies was higher for oncology supplemental indications than for original indications for drugs in this disease category (55% (44/80) versus 32% (13/41); P=0.02) (table 3).

A similar proportion of supplemental and original indications granted orphan drug status were supported by trials using active comparators (28% (17/60) for supplemental indications versus 24% (10/42) for original indications; P=0.61) and clinical outcome endpoints (18% (11/60) versus 31% (13/42); P=0.14). Drugs granted orphan drug designation at the time of original approval were subsequently approved for 77 supplemental indications, 40 (52%) of which were indications not related to rare diseases. Compared with the original orphan indications, these non-orphan supplemental indications were supported by a similar proportion of active comparator trials (28% (11/40) for non-orphan supplemental indications versus 24% (10/42) for original orphan indications; P=0.70) and studies using clinical outcome endpoints (25% (10/40) versus 31% (13/42); P=0.55).

Discussion

Our analysis of clinical trials showing the efficacy of FDA approved supplemental indications between 2005 and 2014 found rates of use of active comparators and clinical outcome endpoints that were low and similar to those seen in other studies evaluating such features for original indication approvals. Supplements that expanded a drug's approved patient population were supported by the fewest active comparator trials and studies using clinical outcome endpoints. Drugs granted orphan drug designations at the time of original approval had the same rates of active comparator and clinical endpoint use in subsequently approved indications, even when such supplemental indications were for non-rare conditions. Almost all of the supplements expanding a drug's approved patient population were for pediatric patients, and nearly half of these supplemental indication approvals were supported by uncontrolled studies or no additional clinical studies, with approval based on extrapolation from adult studies alone.

Policy considerations

Uncontrolled studies or studies testing surrogate endpoints are likely to be completed relatively quickly and inexpensively. Yet in the case of supplemental approvals for pediatric use, such studies will lead to six months of additional market exclusivity under the Best Pharmaceuticals for Children Act, which can be extremely lucrative for the sponsor.[18] [19] Although we do not conclude that any of these approvals were mistaken, pediatric patients have unique physiologies and pharmacokinetic characteristics that may require more rigorous trials to confirm both the efficacy and the safety of drugs previously approved only for use in adults.[20] [21] [22] Policy makers should re-examine the six month exclusivity incentive and perhaps replace it with an incentive that better encourages higher quality trials.

Furthermore, despite the limited data on which many supplemental indication approvals are based, legislation that recently passed the US House of Representatives threatens to further diminish the level

of evidence needed to obtain a supplemental indication for an approved prescription drug. In the 21st Century Cures legislation, the FDA is instructed to develop a process to approve new uses for existing drugs on the basis of lower quality evidence, including “therapeutic use,” “observational studies,” and “registries,” rather than clinical trials.[23] The FDA would also be permitted to approve such indications on the basis of only summaries of data in such circumstances, rather than being required to review the data in detail.

Our results indicate the importance of post-approval surveillance of drugs’ supplemental indications, particularly those that expand the eligible patient population. The FDA’s Sentinel Initiative is a nationwide active surveillance program that draws on multiple sources of healthcare data and has the potential to shorten the time needed to identify safety problems related to drugs and medical products, although major hurdles must still be surmounted before this system can reliably serve as the principal source for risk assessment and decisions about drug safety.[24] [25] [26] In addition to these safety studies using large databases, timely confirmatory prospective post-approval efficacy trials of the supplemental indications are needed. However, other studies have shown that post-approval confirmatory studies required by the FDA are frequently delayed or not completed because the FDA has limited power to enforce these commitments.[27] [28]

Among drugs originally approved using orphan drug designations, we expected the trials leading to their non-orphan supplemental indication approvals to be more robust. Trials leading to the original approval of drugs with orphan drug or other special developmental designations infrequently use clinical endpoints or active comparators.[29] Such study designs are ethically and practically justified when no alternative treatments are available in order to facilitate earlier access for patients to potential therapeutic advances, despite the increased likelihood of postmarketing safety problems and unconfirmed efficacy associated with expedited drug approvals.[30] However, we found that many drugs approved via the orphan drug designation were tested in trials not using clinical endpoints or active comparators for supplemental indications, even when those supplemental indications do not qualify for the same designation. For example, eltrombopag (Promacta, GlaxoSmithKline, London, UK), originally approved using orphan drug designation in 2008 for the treatment of thrombocytopenia in patients with immune thrombocytopenic purpura, was later approved for thrombocytopenia in patients with hepatitis C, a non-rare condition. The two efficacy trials in eltrombopag’s supplemental indication approval used placebo comparators and surrogate outcome endpoints.[31]

Communication to providers and patients of the nature of the evidence supporting supplemental indications can help to promote knowledge of drugs’ expected benefits and risks. One step towards such enhanced communication would be greater transparency of the medical reviews relating to supplemental indication approvals, which faithfully summarize the clinical evidence in the application. We found that 80% of FDA medical reviews for supplemental indication approvals were not accessible. Other researchers have suggested the inclusion of a summative statement or grade to indicate the quality of evidence supporting a drug’s initial approval.[2] Such statements are also needed for supplemental indication approvals.

Strengths and limitations of study

Our study has several limitations. Firstly, we included only supplemental indication approvals for drugs originally approved as novel therapeutic agents, so our study findings are not representative of the evidence base supporting all supplemental indication approvals, including for new formulations and other non-novel therapeutics, which may be subject to different requirements for demonstration of clinical evidence, including approval on the basis of bioequivalence studies. Secondly, we assessed the clinical trial evidence supporting supplemental and original indication approvals by using FDA approved drug labels rather than the detailed FDA medical reviews. However, the distribution of study comparators and clinical endpoints for the originally approved indications in our study, including the proportion of supporting trials using active comparators and clinical outcome endpoints, is consistent with previous research.[1 2] In addition, as we assessed the data contained in drug labels for both supplemental and original indication approvals, the results should reflect the degree to which the clinical evidence differs between these two sets of indications. Finally, we assessed only evidence supporting the efficacy of drugs for supplemental and original indications, focusing on the trials' comparators and endpoints. Other important aspects of pre-approval trials, including randomization, blinding, and duration, should be explored in future studies.

Conclusions and policy implications

Nearly 300 supplemental indication applications relating to approved prescription drugs have been approved in the past decade, providing FDA validation for a wide range of uses beyond the drugs' original indications. However, the high degree of heterogeneity of supporting evidence for supplemental indications, in the setting of legislation promoting drug approvals based on decreasing evidentiary standards, underscores the need for a robust system of post-approval drug monitoring for efficacy and safety, timely confirmatory studies, and re-examination of existing legislative incentives to promote the optimal delivery of evidence based medicine.

What is already known on this topic

- New prescription drugs are approved by regulatory agencies such as the US Food and Drug Administration (FDA) on the basis of pivotal clinical trials that vary in some of their essential features, including type of comparator and study endpoint
- Approvals of therapeutics based on single arm trials or that use surrogate endpoints pose risks to patients, as the efficacy and safety profiles may not be fully characterized
- After a prescription drug has been authorized, it may subsequently be approved and prescribed for supplemental indications; the legal evidentiary standard is the same as for original indication approvals

What this study adds

- Prescription drugs approved for supplemental indications by the FDA were supported by low rates of clinical trials using active comparators or study endpoints directly related to patients' function or mortality
- This was especially the case among supplements that expanded the drugs' approved patient populations
- Robust post-approval surveillance and confirmatory studies of a drug's safety and efficacy for its supplemental indications may help to reduce the risk to patients from using prescription drugs for these indications

Notes

Cite this as: *BMJ* 2015;351:h4679

Footnotes

Contributors: Both authors conceived the study. Both authors analyzed and interpreted the data. Both authors drafted and revised the manuscript, and both approved the final version. ASK is the guarantor.

Funding: This investigator initiated study was not funded by industry. ASK's work is supported by the Greenwall faculty scholars program in bioethics and the Harvard program in therapeutic science. The funders had no role in the conception, writing, or review of the manuscript.

Competing interests: Both authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethics approval was not required for this study because it was based on publicly available data and involved no individual patient data collection or analysis.

Transparency: 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.

Data sharing: No additional data available.

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