Abstract

IMPORTANCE After US Food and Drug Administration (FDA) approval of a new drug, sponsors can submit additional clinical data to obtain supplemental approval for use for new indications.

OBJECTIVE To characterize pivotal trials supporting recent supplemental new indication approvals of drugs and biologics by the FDA and to compare them with pivotal trials that supported these therapeutics’ original indication approvals.

DESIGN, SETTING, AND PARTICIPANTS This is a cross-sectional study characterizing pivotal trials supporting supplemental indication approvals by the FDA between 2017 and 2019 and pivotal trials that supported these therapeutics’ original indication approvals. Data analysis was performed from August to October 2020.

MAIN OUTCOMES AND MEASURES Number and design of pivotal trials supporting both supplemental and original indication approvals.

RESULTS From 2017 to 2019, the FDA approved 146 supplemental indications for 107 therapeutics on the basis of 181 pivotal efficacy trials. The median (interquartile range) number of trials per supplemental indication was 1 (1-1). Most trials used either placebo (77 trials [42.5%; 95% CI, 35.6%-49.8%]) or active comparators (65 trials [35.9%; 95% CI, 29.3%-43.1%]), and most of these multigroup trials were randomized (141 trials [99.3%; 95% CI, 96.0%-100.0%]) and double-blinded (106 trials [74.5%; 95% CI, 66.6%-81.0%]); 80 trials (44.2%; 95 CI, 37.2%-51.5%) used clinical outcomes as the primary efficacy endpoint. There was no difference between oncology therapies and those approved for other therapeutic areas to have supplemental indication approvals be based on at least 2 pivotal trials (11.5% vs 20.6%; difference, 9.1%; 95% CI, 2.9%-21.0%; P = .10). Similarly, there was no difference in use of randomization (98.3% vs 100.0%; difference, 1.7%; 95% CI, 1.6%-5.0%; P = .43) among multigroup trials, although these trials were less likely to be double-blinded (50.8% vs 92.3%; difference, 41.5%; 95% CI, 27.4%-55.5%; P < .001); overall, these trials were less likely to use either placebo or active comparators (64.9% vs 86.7%; difference, 21.8% 95% CI, 9.8%-33.9%; P < .001) or to use clinical outcomes as their primary efficacy end point (27.5% vs 61.1%; difference, 33.6%; 95% CI, 14.1%-40.9%; P < .001) and were longer (median [interquartile range], 17 [6-48] weeks vs 95 [39-146] weeks). Original approvals were more likely than supplemental indication approvals to be based on at least 2 pivotal trials (44.0% [95% CI, 33.7%-42.6%] vs 15.8% [95% CI, 10.7%-22.5%]; difference, 28.2%; 95% CI, 17.6%-39.6%; P < .001) and less likely to be supported by at least 1 trial of 12 months’ duration (27.6% [95% CI, 17.9%-35.0%] vs 54.8% [95% CI, 46.7%-62.6%]; difference, 27.2%; 95% CI, 14.5%-37.8%; P < .001). Pivotal trial designs were otherwise not significantly different.

CONCLUSIONS AND RELEVANCE These findings suggest that the number and design of the pivotal trials supporting supplemental indication approvals by the FDA varied across therapeutic areas, with

Key Points

Question What is the strength of evidence supporting supplemental new indication approvals for drugs and biologics and how does it compare with the evidence that supported their original approval?

Findings In this cross-sectional study of 107 therapeutics approved for 146 supplemental indications by the US Food and Drug Administration between 2017 and 2019, supplemental approvals for oncology drugs were based on fewer pivotal efficacy trials with less rigorous designs than supplemental approvals for other therapeutic areas. Supplemental approvals were based on fewer pivotal trials than their original indication approvals, but their designs were similar.

Meaning These findings suggest that there was little difference in the evidence supporting supplemental and original indication approvals, but the number and design of pivotal trials supporting supplemental indication approvals varied according to therapeutic area.

Open Access. This is an open access article distributed under the terms of the CC-BY License.
the strength of evidence for cancer indications weaker than that for other indications. There was little
difference in the design characteristics of the pivotal trials supporting supplemental indication and
original approvals.

Introduction

To receive US Food and Drug Administration (FDA) approval for a new small-molecule or biologic
drug, sponsors must submit “adequate and well controlled investigations” to demonstrate the drug’s
efficacy and safety. Although the FDA suggests that sponsors submit at least 2 trials demonstrating
efficacy, also known as pivotal efficacy trials, the number and characteristics of pivotal efficacy trials
supporting new drug and biologic approvals vary widely. For example, approximately one-third of
new approvals are based on a single pivotal trial, whereas nearly one-half are based on trials solely
focused on surrogate markers of disease, as opposed to clinical outcomes. This flexibility highlights
the FDA’s ability to adapt its standards to the clinical context and use of the drug or biologic under
consideration.

Less is known about the clinical trial evidence that supports supplemental indication approvals
by the FDA, which are required when sponsors intend to add use of the originally approved drug for
new clinical indications or in specific subpopulations to the labeling. Supplemental indication
approvals by the FDA for already marketed drugs occur in frequencies similar to those for approvals
for novel therapeutics. For instance, in 2014, the FDA approved 40 new supplemental indications
compared with 44 new drug approvals. Supplemental new indication approvals are particularly
common among oncology therapies, such as the anti-programmed death-1 biologic pembrolizumab
(Keytruda), which was originally approved for the treatment of advanced melanoma in 2014 and has
since been approved for 19 additional clinical indications. Moreover, it is critical that both new and
supplemental indication approvals are based on strong evidence, because certain therapeutics may
be prescribed more often for their supplemental indications than for their initially approved
indication. Supplemental indication approval by the FDA is also critical for ensuring insurance
coverage, especially for more expensive biological therapies and those used for oncology, where
effective treatment options may be more limited.

There have been few studies characterizing the clinical trial evidence that supported
supplemental indication approvals by the FDA. One study broadly examined nearly 300
supplemental indication approvals between 2005 and 2014 and found that approximately one-third
used active comparator groups and one-third used clinical outcomes as primary end points. Another
study examined new and supplemental indication approvals, as well as off-label indications
included in a Medicare-referenced compendium in oncology, from 2005 to 2012 and found the
number and characteristics of supporting pivotal trials to be similar. However, whether recent
supplemental indication approvals differ from original approvals more broadly and whether the
evidentiary standards required for a supplemental indication approval for oncology therapeutics
differ from those required for other therapeutics remain unknown. This information is particularly
important in the context of ongoing efforts to increasingly leverage observational studies, as
opposed to clinical trials, to support regulatory evaluations and supplemental indication approvals,
including federal legislation like the 21st Century Cures Act.

Accordingly, we reviewed all supplemental new drug applications (sNDAs) and supplemental
biologics license applications (sBLAs) approved by the FDA for new clinical indications from 2017 to
2019 to describe the characteristics of the pivotal efficacy clinical trials supporting their original
indications and supplemental indications. We expect our findings will inform policy makers and
clinician decision-making, particularly our understanding of the clinical evidentiary standards for
supplemental new indication approvals.
Methods

This study was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies. This study did not require institutional review board approval or informed consent because it was based on publicly available information and involved no patient records, in accordance with 45 CFR §46.

Sample Construction

One study author (M.D.) identified all new drugs and biologics approved for supplemental indications between January 2017 and December 2019 using the Drugs@FDA database. We limited our sample to sNDAs and sBLAs approved by the FDA for new clinical indications, identified through full-text review of sNDA and sBLA approval letters; corresponding FDA approval letters and printed labels were obtained as they are hyperlinked in the Drugs@FDA database. Duplicate records were removed, and sNDAs and sBLAs for contrast agents, nontherapeutic agents, and generics and biosimilars were excluded. Furthermore, we excluded any sBLAs that were determined to be (original) BLAs and removed from FDA's Orange Book on March 23, 2020, under the Biologics Price Competition and Innovation Act of 2009. Next, for each therapeutic for which an sNDA or sBLA was identified and included in our study, we identified the original indication NDA or BLA approved by the FDA, along with the pivotal trials supporting the FDA's approval for their original indication using previously described methods.2,3

Supplemental Indication and Regulatory Characteristics

New indication approvals and original indication approvals were characterized by agent type, therapeutic area, and special regulatory status. For each approval, we determined whether the approved therapeutic was a small molecule or biologic from the letter and label. Treatments were characterized as short-term if the therapeutics were expected to be used for less than 1 month, as intermediate if they were expected to be used for 1 month to 2 years, and long-term if they were expected to be used for more than 2 years. Therapeutic area was classified for each approval was based on the World Health Organization Anatomical Therapeutic Classification System.11 Using publicly available information on the FDA website, we determined whether each indication in our sample was evaluated under a special regulatory program such as Priority Review,12 Accelerated Approval,13 Fast Track14 for (NDAs and BLAs only), or Breakthrough Therapy.15

Trial Identification

To identify the pivotal clinical trials supporting the sNDAs and sBLAs, we reviewed the drug labels updated by the FDA to correspond to the specific new indication approval, which typically reference the clinical trial using the ClinicalTrials.gov registration number (ie, National Clinical Trials identifier). Generally, those studies considered pivotal are labeled as such in the Clinical Studies section of the printed label. Furthermore, if not directly stated as pivotal, efficacy for an indication is stated to be based on the evidence from a trial or number of trials. If an approval was based on the results of more than 1 trial, all these trials were included in our study. To identify pivotal trials not directly referenced in the label using a National Clinical Trials number, general study information (eg, number of study participants, primary efficacy endpoint, masking, and randomization) was cross-referenced with study information from ClinicalTrials.gov to identify the relevant National Clinical Trials number.

Pivotal Trial Characterization

For all pivotal trials supporting NDA, sNDA, BLA, and sBLA approval by the FDA, 1 study author (M.D.) extracted the following information from ClinicalTrials.gov if not available from or previously collected as part of prior research from FDA action packages, including approval letters and review documents: randomization, double-blinding, comparator, study end point, agent type, total number of participants, and number of patients in intervention group.2,3 For each trial included in our sample,
we determined its use of randomization and double-blinding and characterized the comparator group as active, placebo, or none. Next, the primary trial endpoint was identified and was designated into 1 of 3 categories—clinical outcome, clinical scale, or surrogate marker—by 1 study author (M.D.) and was reviewed by another study author (J.S.R.); any conflicts were resolved by consensus. In brief, surrogate markers (eg, hemoglobin A1c) are metrics expected to be associated with patient outcomes, where clinical outcomes (eg, death) measure patient outcomes. Importantly, if at least 1 primary trial endpoint was categorized as a clinical outcome or clinical scale, the trial would be categorized as such even if another primary trial endpoint was a surrogate marker. The number of participants, intervention model, and number of patients in the intervention group were also extracted. Trial duration was extracted from study descriptions using methods previously described.\(^2\,^3\) For time-associated end points, duration was defined as the date of measurement of the primary end point. For event-associated end points, duration was determined as the median follow-up time for participants or the weighted average of the median follow-up time in cases in which it differed between study groups.

**Statistical Analysis**

We used descriptive statistics to examine differences in trial characteristics and indication characteristics. Frequencies of use of randomization and double-blinding among the trials in our sample were calculated excluding single-group studies. We next used \(\chi^2\) and Wilcoxon tests where appropriate to examine differences between supplemental indication approvals for therapeutics in our sample at multiple levels, including agent type, special regulatory pathway, and therapeutic area, all of which were defined before data collection. Analyses were performed using R statistical software version 3.4.3 (R Project for Statistical Computing), JMP statistical software version 15.0.0 (SAS Institute), Python statistical software version 3.8 (Python), and Excel spreadsheet software version 16.16.27 (Microsoft). All statistical tests were 2-tailed and used a type I error rate of .01 to account for multiple comparisons. Data analysis was performed from August to October 2020.

**Results**

Between January 2017 and December 2019, the FDA approved 3721 new sNDA and sBLAs (3200 sNDAs and 521 sBLAs), among which were 146 supplemental indication approvals for a new clinical indication, for a total of 107 therapeutics. Among the 146 supplemental indication approvals, 99 (68%) were for pharmacologics and 47 (32%) were for biologics; 74 (51%) were approved using at least 1 special regulatory program, including 20 using the Accelerated Approval pathway and 61 designated for Priority Review (Table 1). Most commonly, the supplemental indication approvals were for the treatment of cancer (78 approvals [53%]) or autoimmune and musculoskeletal (24 approvals [16%]) disease.

**Pivotal Trials Supporting Supplemental Indication Approvals**

The FDA approved these 146 supplemental indications on the basis of 181 pivotal trials, with a median (interquartile range [IQR]) of 1 (1-1) trial per approval; 23 (15.8%) supplemental indication approvals were approved on the basis of at least 2 pivotal trials. Most pivotal trials supporting these indications used either an active (65 trials [35.9%; 95% CI, 29.3%-43.1%]) or placebo (77 trials [42.5%; 95% CI, 35.6%-49.8%]) comparator, and the majority of these multigroup trials were randomized (141 trials [99.3%; 95% CI, 96.0%-100.0%]) and double-blinded (106 trials [74.5%; 95% CI, 66.6%-81.0%]); 80 trials (44.2%; 95 CI, 37.2%-51.5%) used clinical outcomes as the primary efficacy end point (Table 2). The median (IQR) trial duration was 46.3 (16-117) weeks. The median (IQR) number of patients in the pivotal trials was 460 (226-734), and the median (IQR) number of patients in the intervention groups was 267 (149-473).
Supplemental Indication Approvals, Comparing Product Types

The 99 pharmacologic supplemental indication approvals were supported by 125 pivotal trials, whereas the 47 biologic approvals were supported by 56 trials (Table 2). The median (IQR) number of trials per approval was 1 (1-1) for pharmacologic approvals and 1 (1-1) for biologic approvals; 18 pharmacologic indications (18.2%) and 5 biologic indications (10.6%) were approved on the basis of at least 2 pivotal trials. Likewise, the trials supporting supplemental indication approvals were broadly similar in design between pharmacologics and biologics. Trials supporting pharmacologic approvals were as likely as trials supporting biologic approvals to be randomized (100.0% [95% CI, 96.4%-100.0%] vs 97.2% [95% CI, 85.5%-99.5%]; \( P = .26 \)) and double-blind (77.5% [95% CI, 68.4%-84.5%] vs 65.7% [95% CI, 49.2%-79.2%]; \( P = .18 \)) when multigrouped (106 trials for pharmacologic approvals and 36 trials for biologic approvals), and to use a clinical outcome as their primary efficacy end point (48.8% [95% CI, 42.5%-59.8%] vs 33.9% [95% CI, 22.9%-47.0%]; \( P = .08 \)), but were more likely to have either an active or placebo comparator group (84.8% [95% CI, 77.5%-90.9%] vs 64.3% [95% CI, 51.2%-75.5%]; \( P = .002 \)). The duration of trials supporting pharmacologic approvals did not differ from the duration of trials supporting biologic approvals (median [IQR], 40.7 [12.2-121.3] vs 47.1 [24-101.7] weeks). The number of overall patients in the pivotal trials (median [IQR] 518 [276-797.5] vs 305.5 [163.8-559] patients) and in the intervention groups (median [IQR], 304 [158-480] vs 223.5 [125-338] patients) did not differ between pharmacologic and biologic approvals.

When aggregating all the pivotal trials that supported the indication approval, the number of patients overall (median [IQR], 514 [269-834] vs 306 [157-713] patients) and in the intervention groups overall (median [IQR], 281.5 [155-451] vs 222 [105-340] patients) did not differ between pharmacologic and biologic approvals (Table 3). Pharmacologic and biologic approvals did not differ in there being at least 1 pivotal trial that was randomized (81.8% [95% CI, 73.1%-88.2%] vs 63.8% [95% CI, 49.5%-76.0%]; \( P = .02 \)), double-blinded (65.7% [95% CI, 55.9%-74.3%] vs 44.7% [95% CI,

### Table 1. Characteristics of Supplemental New Indication Drugs and Biologics Approved by the US FDA for New Indications from 2017 to 2019, and the New Drugs and Biologics Approved by the FDA for the Corresponding Original Indications

| Characteristic | Approvals, No. (%) |
|---------------|--------------------|
|               | Supplemental new indication (n = 146)* | Original (n = 109) |
| Approval year |
| Before 2010   | NA                 | 23 (21) |
| 2010-2014     | NA                 | 45 (41) |
| 2015-2019     | 146 (100)          | 41 (38) |
| Agent type    |
| Pharmacologics| 99 (68)            | 69 (63) |
| Biologics     | 47 (32)            | 40 (37) |
| Special regulatory program |
| Any           | 74 (51)            | 57 (52) |
| Accelerated approval | 20 (14)       | 25 (23) |
| Priority review | 61 (42)          | 55 (50) |
| Fast track    | NA                 | 10 (9)  |
| Breakthrough  | 35 (24)            | 17 (16) |
| Therapeutic area |
| Autoimmune or musculoskeletal | 24 (16) | 5 (5) |
| Infectious diseases | 5 (3) | 6 (6) |
| Neurology     | 8 (5)              | NAa |
| Dermatology   | NAa                | 7 (6)  |
| Cardiovascular, diabetes, and lipids | 9 (6) | 13 (12) |
| Cancer        | 78 (53)            | 46 (42) |
| Other         | 22 (15)            | 7 (6)  |

Abbreviations: FDA, US Food and Drug Administration; NA, not applicable.

* Supplemental approvals are not eligible for Fast Track designation.

a Therapeutic areas with fewer than 5 new indications or original indication approvals, respectively, are consolidated into the other category.
Table 2. Characteristics of Trials Supporting Supplemental New Indication Approvals by the US Food and Drug Administration Between 2017 and 2019

| Characteristic | Trials, No. | Randomized* | Double-blind* | Comparator Placebo | Active | Single group | Clinical end point | Trial duration, median (IQR), wk | Overall Patients, median (IQR), No. | Intervention group Patients, median (IQR), No. |
|---------------|-------------|-------------|---------------|-------------------|-------|-------------|-------------------|----------------------------------|----------------------------------|------------------------------------|
| Overall       | 181         | 99.3 (96.0-100.0) | 74.6 (66.6-81.0) | 42.5 (35.6-49.8) | 35.9 (29.3-43.1) | 21.6 (16.2-28.1) | 44.2 (37.2-51.5) | 46.3 (16-117) | 460 (226-734) | 267 (148.5-473) |
| Agent type    |             |             |               |                   |       |             |                   |                                 |                                  |                                    |
| Pharmacologic sNDAs | 125       | 100.0 (96.4-100.0) | 77.5 (68.4-84.5) | 46.4 (37.9-55.1) | 38.4 (30.3-47.2) | 15.2 (9.9-22.5) | 48.8 (42.5-59.8) | 40.7 (12.2-121.3) | 518 (276-797.5) | 304 (158-480) |
| Biologic sBLAs | 56          | 97.2 (85.5-99.5) | 65.7 (49.2-79.2) | 33.9 (22.9-47.0) | 30.4 (19.9-43.3) | 35.7 (24.5-48.8) | 33.9 (22.9-47.0) | 47.1 (24-101.7) | 305.5 (163.8-559) | 223.5 (126-338) |
| Pvalue        | .26         | .18         | .002          | .002              | .002  | .08         | .71               | .92                | .10                             |                                    |
| Special regulatory pathway |     |             |               |                   |       |             |                   |                                 |                                  |                                    |
| Any           | 87          | 98.2 (90.2-99.7) | 59.4 (46.0-71.3) | 28.7 (20.3-39.0) | 37.9 (28.5-48.4) | 33.3 (24.3-43.8) | 32.2 (23.3-42.6) | 62.1 (30-128.6) | 450 (207-726) | 271 (149-444) |
| Accelerated approval | 25      | 87.5 (52.9-97.8) | 37.5 (13.7-69.4) | 12.0 (4.2-30.0) | 24.0 (11.5-43.4) | 64.0 (44.5-79.8) | 24.0 (11.5-43.4) | 52.7 (34.1-107.4) | 340 (177.5-743) | 270 (152-424) |
| Priority review | 74      | 97.9 (89.1-99.6) | 64.6 (50.4-76.6) | 33.8 (24-45.1) | 36.5 (26.4-47.9) | 29.7 (20.5-40.9) | 32.4 (22.5-43.7) | 56.4 (30-129) | 449 (207.8-706.25) | 256 (149.8-439.5) |
| Breakthrough  | 44          | 100 (85.1-100) | 45.5 (26.9-65.3) | 13.6 (6.4-26.7) | 40.9 (27.7-55.6) | 45.5 (31.7-59.9) | 18.2 (9.5-31.9) | 100.5 (42.1-128.9) | 448.5 (206.2-710.8) | 319.5 (159.5-319.5) |
| Pvalue (any special regulatory program vs none) | .39        | .<001       | .<001         | .<001             | .<001 | .02        | .001              | .004              | .07                             |                                    |
| Therapeutic area |         |             |               |                   |       |             |                   |                                 |                                  |                                    |
| Autoimmune or musculoskeletal | 36      | 100 (89.3-100) | 96.9 (84.3-99.4) | 69.44 (53.1-82.0) | 22.2 (11.7-38.1) | 8.3 (2.9-21.8) | 66.7 (50.3-79.8) | 24 (14.5-25.7) | 329 (188-546) | 212.5 (104.3-344) |
| Cancer         | 91          | 98.3 (91.0-99.7) | 50.8 (38.4-63.2) | 23.1 (15.6-32.7) | 41.8 (32.2-52.0) | 35.2 (26.1-45.4) | 27.5 (19.4-37.4) | 94.9 (38.6-145.7) | 501 (292-737) | 297 (136-476) |
| Cardiovascular, diabetes, or lipids | 11     | 100 (74.1-100) | 100 (74.1-100) | 54.6 (28.0-78.7) | 45.5 (21.3-72.7) | 0 | 81.8 (52.3-94.9) | 100.3 (51.1-134.3) | 4541 (2531-9941) | 2266 (1252-4668) |
| Infectious diseases | 6       | 100 (61.0-100) | 66.7 (30.0-93.0) | 16.7 (3.0-56.4) | 83.3 (43.6-97.0) | 0 | 66.7 (30.0-90.3) | 1.8 (1.48) | 621.5 (448-887.3) | 311.5 (213.8-414.5) |
| Neurology      | 9           | 100 (67.6-100) | 100 (67.5-100) | 77.8 (45.3-93.7) | 11.1 (2.0-43.5) | 11.1 (2.0-43.5) | 66.7 (35.4-48.9) | 4 (4.4) | 212 (146.5-375) | 155 (89.5-251.5) |
| Other          | 28          | 100 (84.5-100) | 85.7 (65.4-95.0) | 57.1 (39.1-73.5) | 21.4 (10.2-39.5) | 21.4 (10.2-39.5) | 42.9 (26.5-60.9) | 18.5 (6.52) | 291 (106.8-699.8) | 199 (99-433.3) |
| Pvalue (oncology v nononcology) | .43        | .<001       | .<001         | .<001             | .<001 | .<001      | .<001             | .62               | .88                             |                                    |

Abbreviations: IQR, interquartile range; sBLA, supplemental biologics license application; sNDA, supplemental new drug application.  
* Excludes single-group studies.
used a clinical outcome as the primary efficacy end point (51.5% [95% CI, 41.8%-61.1%] vs 31.9% [95% CI, 20.4%-46.2%]; \( P = .02 \)), and had a duration of at least 6 months (66.7% [95% CI, 56.9%-75.2%] vs 72.3% [95% CI, 58.2%-83.1%]; \( P = .49 \)) or 12 months (54.6% [95% CI, 44.8%-64.0%] vs 55.3% [95% CI, 41.2%-68.6%]; \( P = .93 \)), but pharmacologic approvals were more likely to have at least 1 pivotal trial that used either an active or placebo comparator (84.8% [95% CI, 76.5%-90.6%] vs 66.0% [95% CI, 51.7%-77.8%]; \( P = .009 \)) (Table 4).

### Supplemental Indication Approvals, Comparing Therapeutic Areas

The 78 oncology supplemental indication approvals were supported by 91 pivotal trials, whereas the 68 nononcology approvals were supported by 90 pivotal trials (Table 2). The median (IQR) number of trials per approval was 1 (1-1) and 1 (1-1), respectively, and 9 oncology indications (11.5%) and 14 nononcology indications (20.6%) were approved on the basis of at least 2 pivotal trials (difference, Table 4).

**Table 3. Number and Characteristics of Aggregated Pivotal Efficacy Trials Providing the Basis for Original and Supplemental Indication Approvals by the US Food and Drug Administration Between 2017 and 2019, Stratified by Supplemental or Original Indication, Therapeutic Agent, and Indication Characteristics**

| Variable                      | Trials, No. | Pivotal efficacy trials, median (IQR), No. | Patients in aggregated pivotal efficacy trials, median (IQR), No. | Overall | Intervention group |
|-------------------------------|-------------|------------------------------------------|---------------------------------------------------------------|---------|-------------------|
| Supplemental or original indication |             |                                          |                                                                |         |                   |
| Original                      | 109         | 1 (1-2)                                  | 326 (161.5-676)                                               | 256.3   | (120.1-375.4)     |
| Supplemental                  | 146         | 1 (1-1)                                  | 445 (211.8-799.3)                                             | 256.5   | (144.8-447.3)     |
| \( P \) value                 | \(<.001\)   | .05                                      | .12                                                           |         |                   |
| Therapeutic agent             |             |                                          |                                                                |         |                   |
| Pharmacologic sNDA            | 99          | 1 (1-1)                                  | 514 (269-834)                                                | 281.5   | (155-451)         |
| Biologic sBLA                 | 47          | 1 (1-1)                                  | 306 (157-713)                                                | 222     | (105-340)         |
| \( P \) value                 | \(.26\)     | .05                                      | .16                                                           |         |                   |
| Therapeutic area              |             |                                          |                                                                |         |                   |
| Oncology sNDA or sBLA         | 78          | 1 (1-1)                                  | 505 (300.8-873)                                              | 286     | (200-471.5)       |
| Nononcology sNDA or sBLA      | 68          | 1 (1-1)                                  | 334.3 (153.3-749.8)                                          | 215.5   | (99-421)          |
| \( P \) value                 | \(.13\)     | .06                                      | .04                                                           |         |                   |

Abbreviations: IQR, interquartile range; sBLA, supplemental biologics license applications; sNDA, supplemental new drug application.

**Table 4. Proportion of Indication-Level Approvals of Novel Therapeutic Agents by the US Food and Drug Administration on the Basis of at Least 1 Trial That Met the Criteria Below, Stratified by Supplemental or Original Indication, Therapeutic Agent, and Indication Characteristics**

| Variable                      | Trials, No. | \( \geq 2 \) Pivotal trials | \( \geq 1 \) Randomized trial | \( \geq 1 \) Double-blind trial | \( \geq 6 \) mo | \( \geq 12 \) mo | With active or placebo comparator | With clinical outcome as primary efficacy end point |
|-------------------------------|-------------|-------------------------------|-------------------------------|-------------------------------|----------------|----------------|----------------------------------|--------------------------------------------------|
| Supplemental or original indication |             |                               |                               |                               |                |                |                                  |                                                  |
| Original                      | 109         | 44.0 (33.7-42.6)              | 80.0 (71.4-86.5)              | 63.8 (54.3-72.4)              | 51.5 (43.3-62.6) | 27.6 (17.9-35.0) | 78.8 (70.0-85.6) | 53.9 (46.2-65.0) |
| Supplemental                  | 146         | 15.8 (10.7-22.5)              | 76.0 (68.5-82.2)              | 58.9 (50.8-66.6)              | 68.5 (60.6-75.5) | 54.8 (46.7-62.6) | 78.9 (71.4-84.6) | 45.2 (37.4-53.3) |
| \( P \) value                 | \(<.001\)   | .54                           | .51                           | .01                           | \(<.001\)      | .87            | .18                              |                                                  |
| Therapeutic area              |             |                               |                               |                               |                |                |                                  |                                                  |
| Pharmacologic sNDA            | 99          | 18.2 (11.8-26.9)              | 81.8 (73.1-88.2)              | 65.7 (55.9-74.3)              | 66.7 (56.9-75.2) | 54.6 (44.8-64.0) | 84.8 (76.5-90.6) | 51.5 (41.8-61.1) |
| Biologic sBLA                 | 47          | 10.6 (4.6-22.6)               | 63.8 (49.5-76.0)              | 44.7 (31.4-58.8)              | 72.3 (58.2-83.1) | 55.3 (41.2-68.6) | 66.0 (51.7-77.8) | 31.9 (20.4-46.2) |
| \( P \) value                 | \(.24\)     | .02                           | .02                           | .49                           | .93            | \(.009\)       | \(.03\)                          |                                                  |
| Therapeutic area              |             |                               |                               |                               |                |                |                                  |                                                  |
| Oncology sNDA or sBLA         | 78          | 11.5 (6.2-20.5)               | 68.8 (57.9-77.8)              | 35.7 (27.7-48.5)              | 93.6 (85.9-97.2) | 76.9 (66.4-84.9) | 71.9 (61-80.6) | 32.1 (22.7-43.0) |
| Nononcology sNDA or sBLA      | 68          | 20.6 (12.7-31.6)              | 84.8 (74.3-91.6)              | 84.8 (74.3-91.6)              | 39.7 (28.9-51.6) | 29.4 (19.9-41.1) | 86.8 (76.7-92.9) | 60.3 (48.4-71.1) |
| \( P \) value                 | \(.10\)     | .04                           | \(<.001\)                     | \(<.001\)                     | \(<.001\)      | \(.03\)        | \(<.001\)                      |                                                  |

Abbreviations: sBLA, supplemental biologics license application; sNDA, supplemental new drug application.
The trials supporting therapeutics used for oncology indications did not differ significantly from the trials supporting indications used for all other therapeutic areas with respect to use of randomization (98.3% vs 100.0%; difference, 1.7%; 95% CI, 1.6%-5.0%; \( P = .43 \)), but were significantly less likely to be double-blinded (50.8% vs 92.3%; difference, 41.5%; 95% CI, 27.4%-55.5%; \( P < .001 \)) when multigrouped (59 oncology trials and 78 nononcology trials); overall, these trials were less likely to use either a placebo or active comparator group (64.9% vs 86.7%; difference, 21.8%; 95% CI, 9.8%-33.9%; \( P < .001 \)) and to use clinical outcomes as their primary efficacy endpoint (27.5% vs 61.1%; difference, 33.6%; 95% CI, 14.1%-40.9%; \( P < .001 \)).

However, trials supporting oncology indications were longer than trials supporting indications in all other therapeutic areas (median [IQR], 95 [39-146] weeks vs 17 [6-48] weeks). The number of overall patients the pivotal trials (median [IQR], 501 [292-737] vs 393.5 [203-747] patients) and in the intervention groups (median [IQR], 297 [196-476] vs 243 [104.8-449.3] patients) did not differ between trials supporting oncology indications and indications in all other therapeutic areas.

When aggregating all the pivotal trials that supported the indication approval, the number of patients overall (median [IQR], 505 [300.8-873] vs 334.3 [153.3-749.8] patients) and in the intervention groups (median [IQR], 286 [200-471.5] vs 215.5 [99-421] patients) did not differ between oncology and nononcology approvals (Table 3). Oncology approvals were not less likely to be supported by at least 1 pivotal trial that was randomized (68.8% [95% CI, 57.9%-77.8%] vs 84.8% [95% CI, 74.3%-91.6%]; \( P = .04 \)) or used either an active or placebo comparator (71.9% [95% CI, 61.0%-80.6%] vs 86.8% [95% CI, 76.7%-92.9%]; \( P = .03 \)), but were less likely to be supported by at least 1 trial that was double-blinded (37.5% [95% CI, 27.7%-48.5%] vs 84.8% [95% CI, 74.3%-91.6%]; difference, 47.3%; 95% CI, 33.9%-61.3%; \( P < .001 \)) and that used a clinical outcome as the primary efficacy end point (32.1% [95% CI, 22.7%-43.0%] vs 60.3% [95% CI, 48.4%-71.1%]; difference, 28.2%; 95% CI, 12.7%-43.8%; \( P < .001 \)), and were more likely to be supported by at least 1 trial that had a duration of at least 6 months (93.6% [95% CI, 85.9%-97.2%] vs 39.7% [95% CI, 28.9%-51.6%]; difference, 53.9%; 95% CI, 41.0%-66.7%; \( P < .001 \)) or 12 months (76.9% [95% CI, 66.4%-84.9%] vs 29.4% [95% CI, 19.9%-41.1%]; difference, 47.5%; 95% CI, 33.2%-61.8%; \( P < .001 \)) (Table 4).

### Supplemental Indication Approvals Compared With Original Indication Approvals

The 107 therapeutics for which we identified supplemental indication approvals were originally approved by the FDA for 109 clinical indications (Table 1); original indication approvals took place between 1991 and 2018, and 18% (19 of 107 approvals) were approved for a supplemental indication in a different therapeutic area from the original indication approval, the majority of which (11 approvals) were approved for a supplemental indication for use for autoimmune or musculoskeletal disease after an original approval for a different clinical use. The median (IQR) number of trials per approval was 1 (1-2) and 1 (1-1), respectively (Table 3); original indication approvals were significantly more likely to be supported by at least 2 pivotal efficacy trials compared with supplemental indication approvals (44.0% [95% CI, 33.7%-42.6%] vs 15.8% [10.7%-22.5%]; difference, 28.2%; 95% CI, 17.6%-39.6%; \( P < .001 \)). There was no difference between original and supplemental indication approvals with respect to being supported by at least 1 pivotal trial that was randomized (80.0% [95% CI, 71.4%-86.5%] vs 76.0% [95% CI, 68.5%-82.2%]; \( P = .54 \)), double-blinded (63.8% [95% CI, 54.3%-72.4%] vs 58.9% [95% CI, 50.8%-66.6%]; \( P = .51 \)), used either an active or placebo comparator (78.8% [95% CI, 70.0%-85.6%] vs 78.9% [95% CI, 71.4%-84.6%]; \( P = .87 \)), and used a clinical outcome as the primary efficacy end point (53.9% [95% CI, 46.2%-65.0%] vs 45.2% [95% CI, 37.4%-53.3%]; \( P = .18 \)); however, original indication approvals were significantly less likely to be supported by at least 1 trial that had a duration of at least 6 months (51.5% [95% CI, 43.3%-62.6%] vs 68.5% [95% CI, 60.6%-75.5%]; difference, 17.0%; 95% CI, 3.7%-27.8%; \( P = .01 \)) or 12 months (27.6% [95% CI, 17.9%-35.0%] vs 54.8% [95% CI, 46.7%-62.6%]; difference, 27.2%; 95% CI, 14.5%-37.8%; \( P < .001 \)) (Table 4). There was no difference between original and supplemental indication approvals with respect to the number of patients in the aggregated pivotal trials overall (median [IQR], 326
Discussion

Among all supplemental new indications approved by the FDA between 2017 and 2019, we found that the number and design of the pivotal trials supporting supplemental indication approvals varied on the basis of therapeutic area, with the strength of evidence for cancer indications weaker than those for other indications. However, there was little difference in the number and design of the pivotal trials supporting pharmacologic and biologic supplemental indication approvals, or between supplemental and original indication approvals by the FDA. These findings suggest that the evidentiary standards for supplemental new indication approvals varies across therapeutic areas but that the FDA’s standard for approval is consistent between supplemental and original indications for use.

Our study suggests that the trials supporting supplemental indication approvals for oncology therapeutics vary significantly from those trials supporting indications in all other therapeutic areas, with a tendency to be fewer in number and less robust in design compared with trials supporting supplemental approvals for indications in all other therapeutic areas. This variation highlights the flexible approach taken by the FDA, guided by the severity of the disease and availability of treatment alternatives. Flexible standards, with greater laxity for oncology approvals, was previously demonstrated in our study characterizing the pivotal efficacy trials supporting original indication approval of novel therapeutics. In addition, substantial variation has been described with regard to the pivotal efficacy trials supporting the approval of novel oncology therapeutics.

The evidentiary standard for supplemental new indication approval has important implications for clinical care and regulatory decision-making, offering insight into whether the FDA follows the precedent set by the therapeutic’s original approval or whether a lower, or even a higher, standard is used. There are competing reasons for why the FDA might adopt a different standard for supplemental approvals. On the one hand, if safety was established through the agency’s original approval, some might argue that additional trials are not needed for other clinical uses. Instead, safety may be inferred from prior use. This scenario plays out frequently through off-label prescribing of approved drugs and biologics, as reported by 21% of office-based physicians and as occurs among 80% of inpatient episodes of care among certain subpopulations, such as children. As opposed to physicians prescribing therapies off-label, with little to no evidence, perhaps regulatory standards could be lowered to incentivize any postmarket clinical evidence generation for new clinical uses after original approval.

On the other hand, there is an argument that standards could be strengthened once a therapeutic is available for widespread use. The FDA could require larger and longer duration trials to more fully characterize longer-term risks of approved therapeutics, and this higher standard approach could preclude the use of surrogate markers as primary trial end points. Thus, the FDA could require more robust clinical trial designs to demonstrate drug safety and efficacy that would better inform physician-patient decision-making and coverage decisions. For more expensive therapies, supplemental new indication approval by the FDA generally guarantees insurance coverage for that therapeutic use, as opposed to broad coverage of the therapeutic for any use. For instance, the Centers for Medicare & Medicaid Services provides coverage of oncology drugs for any FDA-approved indication for use, as well as any off-label use listed in certain compendia, facilitating patient access even while supplemental indications are tested by sponsors and evaluated by the FDA.

Our findings suggest that the FDA maintains consistent evidentiary standards for both supplemental new and original indication approvals. However, ongoing efforts to increasingly leverage observational studies to support regulatory evaluations and approvals, as opposed to clinical trials, may affect these standards. The 21st Century Cures Act, which was signed into law on December 13, 2016, contains a provision to promote the use of real-world evidence (RWE)—that is,
studies of drugs and biologics that are derived from data collected in routine medical settings. In response, the FDA launched an initiative to explain the agency’s former use of RWE for safety evaluations and plans for future uses, including for supplemental new indication approvals. Even before this legislation, the FDA had used RWE to inform approvals, such as in 2014, when blinatumomab (Blincyto) received accelerated approval by the FDA for the treatment of relapsed or refractory, Philadelphia chromosome-negative, acute lymphoblastic leukemia on the basis of a single-group, open-label phase 2 study. In this case, RWE came in the form of historical controls who received standard of care, and efficacy was shown according to a weighted analysis of data from medical record reviews.

Generating additional drug safety and effectiveness evidence through observational research may offer advantages with respect to time and resources, compared with clinical trials. However, there are outstanding issues to resolve, including data definitions, establishing which data are fit for purpose, and establishing best practices, such as study registration. Furthermore, our recent study found that few of the recently published, highest-impact trials could be feasibly replicated using RWE because much of the data needed for randomized clinical trials are not captured in electronic health records in a structured format, if at all. Although the strengths and limitations of using RWE for the evaluation of supplemental new indication approvals for therapeutics already available for use are better characterized, there is a clear opportunity to complement randomized clinical trials to offer more information on product safety and efficacy.

Limitations
Our study has some limitations. First, we only assessed a recent, 3-year sample of therapeutics approved by the FDA for supplemental new clinical indications and, therefore, could not capture long-term trends in supplemental indication approvals or supplemental indication approvals by other national regulators. Second, our study did not evaluate whether the FDA considered other data regarding use of these therapeutics in other countries, which may have informed the agency’s efforts to evaluate supplemental new indication approval safety and efficacy.

Conclusions
In this cross-sectional study, we found that there was little difference in the evidence supporting supplemental and original indication approvals by the FDA, but the number and design of pivotal trials supporting supplemental indication approvals varied according to therapeutic area, with the strength of evidence for cancer indications weaker than that for other indications. Overall, our results highlight the need for ongoing postmarket evaluation of supplemental new indications to ensure our understanding of product benefit and safety, as well as to inform both clinicians’ and policy makers’ decisions, including ongoing efforts to leverage observational studies and RWE, as opposed to clinical trials, to support FDA regulatory decisions and evaluations.

ARTICLE INFORMATION
Accepted for Publication: April 14, 2021.
Published: June 10, 2021. doi:10.1001/jamanetworkopen.2021.13224
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2021 Dhodapkar M et al. JAMA Network Open.
Corresponding Author: Joseph S. Ross, MD, MHS, Section of General Medicine and the National Clinical Scholars Program, Department of Internal Medicine, Yale University School of Medicine, PO Box 208093, New Haven, CT 06520-8093 (joseph.ross@yale.edu).
Author Affiliations: Yale School of Medicine, Yale University, New Haven, Connecticut (Dhodapkar, Puthumana); Department of Medicine, Duke University School of Medicine, Durham, North Carolina (Zhang); Bain Capital Life Sciences, Boston, Massachusetts (Downing); Division of Health Care Policy and Research, Robert D. and Patricia E.
Clinical Studies Used for US FDA Supplemental Indication Approvals of Drugs and Biologics, 2017-2019

Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota (Shah); Section of General Medicine and the National Clinical Scholars Program, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut (Ross); Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut (Ross); Center for Outcomes Research and Evaluation, Yale-New Haven Health System, New Haven, Connecticut (Ross).

Author Contributions: Ms Dhodapkar and Dr Ross had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Dhodapkar, Ross.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Dhodapkar, Downing.

Critical revision of the manuscript for important intellectual content: Dhodapkar, Zhang, Puthumana, Shah, Ross.

Statistical analysis: Dhodapkar.

Administrative, technical, or material support: Dhodapkar, Puthumana.

Supervision: Ross.

Conflict of Interest Disclosures: Ms Dhodapkar reported receiving grants from Yale School of Medicine Medical Student Summer Fellowship outside the submitted work. Dr Zhang reported receiving research support through the Collaboration for Research Integrity and Transparency at Yale University from the Laura and John Arnold Foundation. Dr Shah reported receiving research support through Mayo Clinic from the Food and Drug Administration, the Centers of Medicare & Medicaid Innovation under the Transforming Clinical Practice Initiative, the Agency for Healthcare Research and Quality (grants R01HS025164, R01HS025402, R03HS025517, and K12HS026379), the National Heart, Lung and Blood Institute of the National Institutes of Health (grants R56HL130496, R01HL131353, and R01HL151662), the National Science Foundation, the Medical Device Innovation Consortium as part of the National Evaluation System for Health Technology, and the Patient-Centered Outcomes Research Institute to develop a Clinical Data Research Network. Dr Ross reported receiving grants from Food and Drug Administration, Johnson & Johnson, Medical Devices Innovation Consortium, Agency for Healthcare Research and Quality, National Heart, Lung and Blood Institute of the National Institutes of Health, and the Laura and John Arnold Foundation outside the submitted work. No other disclosures were reported.

Funding/Support: This project was supported by research funds to Ms Dhodapkar, Dr Zhang, and Dr Shah through Yale University from the Yale Medical Student Summer Research program as part of the Yale–Mayo Clinic Center of Excellence in Regulatory Science and Innovation (grant U01FD005938).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. US Government Printing Office. New drugs: grounds for refusing application; approval of application; “substantial evidence” defined, 21 USC §355d. Published 2010. Accessed April 10, 2021. http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355.htm

2. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. JAMA. 2014;311(4):368-377. doi:10.1001/jama.2013.282034

3. Zhang AD, Puthumana J, Downing NS, Shah ND, Krumholz HM, Ross JS. Assessment of clinical trials supporting US Food and Drug Administration approval of novel therapeutic agents, 1995-2017. JAMA Network Open. 2020;3:e203284. doi:10.1001/jamanetworkopen.2020.3284

4. Hamburg MA, Rubin R. Margaret A. Hamburg, MD, reflects on 6 years at FDA. JAMA. 2015;313(23):2309-2310. doi:10.1001/jama.2015.3911

5. Munos B. 2014 New drug approvals hit 18-year high. Forbes. Published January 2, 2015. Accessed April 10, 2021. https://www.forbes.com/sites/bernardmunos/2015/01/02/the-fda-approvals-of-2014/#ad87b731189

6. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. Accessed April 10, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/

7. Berndt ER, Cockburn IM, Grépin KA. The impact of incremental innovation in biopharmaceuticals: drug utilisation in original and supplemental indications. Pharmacoeconomics. 2006;24(2)(suppl):69-86. doi:10.2165/00019053-200624002-00008

8. Abernethy AP, Raman G, Balk EM, et al. Systematic review: reliability of compendia methods for off-label oncology indications. Ann Intern Med. 2009;150(5):336-343. doi:10.7326/0003-4819-150-5-20090303-00107
9. Wang B, Kesselheim AS. Characteristics of efficacy evidence supporting approval of supplemental indications for prescription drugs in United States, 2005-14: systematic review. BMJ. 2015;351:h4679. doi:10.1136/bmj.h4679

10. Su KW, Gross CP, Downing NS, Adelman KB, Ross JS. Cancer therapeutic clinical trials supporting FDA approval and compendia inclusion. Am J Pharm Benefits. 2017;9:84-92. Accessed May 3, 2021. https://www.pharmacytimes.com/view/cancer-therapeutic-clinical-trials-supporting-fda-approval-and-compendia-inclusion

11. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2021. Updated December 17, 2020. Accessed April 10, 2021. https://www.whocc.no/atc_ddd_index/

12. US Food and Drug Administration. Priority NDA and BLA approvals. Updated April 7, 2021. Accessed April 10, 2021. https://www.fda.gov/drugs/nda-and-bla-approvals/priority-nda-and-bla-approvals

13. US Food and Drug Administration. Accelerated approvals. Updated January 14, 2021. Accessed April 10, 2021. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals

14. US Food and Drug Administration. Fast track approvals. Updated January 14, 2021. Accessed April 10, 2021. https://www.fda.gov/drugs/nda-and-bla-approvals/fast-track-approvals

15. US Food and Drug Administration. Breakthrough therapy approvals. Updated April 2, 2021. Accessed April 10, 2021. https://www.fda.gov/drugs/nda-and-bla-approvals/breakthrough-therapy-approvals

16. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA. 2011;305(22):2320-2326. doi:10.1001/jama.2011.769

17. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006;166(9):1021-1026. doi:10.1001/archinte.166.9.1021

18. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med. 2007;161(3):282-290. doi:10.1001/archpedi.161.3.282

19. Wallach JD, Ross JS. Gabapentin approvals, off-label use, and lessons for postmarketing evaluation efforts. JAMA. 2018;319(8):776-778. doi:10.1001/jama.2017.21897

20. US Food and Drug Administration. Real-world evidence. Updated November 30, 2020. Accessed April 10, 2021. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

21. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? N Engl J Med. 2016;375(23):2293-2297. doi:10.1056/NEJMsbl609216

22. Baumfeld Andre E, Reynolds R, Caubel P, Azoulay L, Dreyer NA. Trial designs using real-world data: the changing landscape of the regulatory approval process. Pharmacoepidemiol Drug Saf. 2020;29(10):1201-1212. doi:10.1002/pds.4932

23. Ross JS, Dhruva SS, Shah ND. Commentary on Bertagnolli et al.: leveraging electronic health record data for clinical trials—a brave new world. Clinical Trials. 2020;17:243-246. doi:10.1177/1740774520913850

24. Dhruva SS, Shah ND, Ross JS. Mandatory registration and results reporting of real-world evidence studies of FDA-regulated medical products. Mayo Clin Proc. 2020;95(12):2609-2611. doi:10.1016/j.mayocp.2020.04.013

25. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of using real-world data to replicate clinical trial evidence. JAMA Netw Open. 2019;2(10):e1912869. doi:10.1001/jamanetworkopen.2019.12869