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New Cancer Drug Approvals: Less Than Half Of Important Clinical Trial Uncertainties Reported By FDA To Clinicians, 2018–22

Abstract

Uncertainties about the benefits and harms of new drugs are common at the time of approval. It is unclear to what extent the Food and Drug Administration (FDA) communicates these uncertainties in the FDA-approved prescribing information, which is the primary channel of communication between the FDA and physicians. Although physicians might not regularly consult the drug label for prescribing decisions, other information sources used by physicians either index or incorporate information from the label. We searched FDA review documents for uncertainties identified by FDA reviewers with new cancer drugs. We considered the subset of uncertainties highlighted in the FDA's Benefit-Risk Framework as important to the FDA's approval decision. From 2019 to 2022, the FDA approved fifty-two new cancer drugs. In review documents, FDA reviewers identified a total of 213 clinical trial uncertainties with new cancer drugs, 50 percent of which were considered to be important uncertainties to the FDA's approval decision. Labels for physicians reported information on 26 percent of all uncertainties and 48 percent of uncertainties that were important to the FDA's approval decision.

Communicating uncertainties about the evidence of drugs in the label is essential for informing physicians about their safe and effective use.

Food and Drug Administration (FDA) approval signals to physicians that a drug's benefits outweigh its risks of harms. Yet even approved drugs have uncertainties regarding the clinical trial evidence that limit the FDA's ability to fully evaluate the associated benefits and risks. Uncertainties may arise because of limitations in the trial design and conduct (such as the use of single-arm trials or unvalidated surrogate endpoints)[1] or trial findings (such as the risk for long-term harms to patients),[2] both of which are common for many newer drugs approved through expedited programs.[3]

The FDA is uniquely positioned to identify and communicate uncertainties about the benefits and risks of drugs.[4] FDA reviewers conduct detailed assessments of participant-level data underpinning every new drug submission, which are unavailable to other sources. However, the length and technical detail of review documents make them impractical for communicating prescribing information. Instead, the primary channel of communication between the FDA and physicians is FDA-approved drug labeling (prescribing information). The label is proposed by pharmaceutical companies and approved by the FDA. The label is the official summary of the FDA's assessment and guidance on approved information about new drugs, including any limitations with this evidence.[5]

Although physicians might not regularly consult the label for prescribing decisions, the core prescribing information approved by the FDA is communicated through other sources. Point-of-care web-based compendia (including Epocrates,

UpToDate, and the Physicians' Desk Reference) directly index information from the label. Similarly, systematic reviews that form the basis of clinical practice guidelines integrate information from drug labels in evidence synthesis.[6] Physicians are also more likely to consult the label when prescribing a drug for the first time.[7] Although clinical practice guidelines may be a more common source of prescribing information, discrepancies between the label and other sources are not uncommon, as the label only includes information vetted by the FDA.[8,9] Clinical trial publications also have important limitations,[10,11] such as selective reporting and spin, making FDA-regulated information essential for evidence-based prescribing.

To make informed prescribing decisions, physicians need accurate information about the evidence supporting drug approvals, including uncertainties related to this evidence. This includes information about uncertainties associated with trial designs,[12] the generalizability of findings,[13] and the strength of association between surrogate endpoints used for approval and clinically meaningful outcomes for patients.[14] The importance of communicating uncertainty is supported by studies that show that physicians frequently underestimate the harms and overestimate the benefits of drugs.[15–17]

It is unclear to what extent the FDA communicates uncertainties about the evidence of drugs in FDA-approved drug labeling, the official resource for informing physicians about the safe and effective use of prescription drugs. Communicating uncertainties is especially important for new cancer drugs, most of which are approved through expedited programs on the basis of limited evidence.[18] In this study, we evaluated whether information about uncertainties associated with the clinical evidence

for new cancer drugs identified by FDA reviewers was reported in the FDA-approved prescribing information.

Study Data And Methods

Data

We used Drugs@FDA to identify new cancer drugs approved from 2019 to 2022. We then used the FDA's annual summary of new drug approvals to note the approved indications, first-in-class status, use of expedited programs (accelerated approval, breakthrough therapy, fast track, and priority review), and orphan designation. For each drug, we recorded the study characteristics and outcomes of the pivotal trials used for FDA approval from FDA review documents.

Identification Of Clinical Trial Uncertainties

We first conducted a content analysis of FDA review documents, including summary, medical, and statical assessments prepared by FDA reviewers, to identify a comprehensive list of uncertainties related to clinical trial evidence. We focused on uncertainties with the primary outcome of clinical trials considered by the FDA as the basis for approval (pivotal trials), irrespective of the final approved indication.[19] Whenever uncertainties were mentioned by FDA reviewers, one researcher extracted relevant fragments of text (ranging from a sentence to several paragraphs) and compiled these into a data set.

Second, we searched for uncertainties that were discussed at the FDA's Oncology Drugs Advisory Committee meeting, which are summarized in review documents. The FDA convenes an advisory committee to obtain independent advice about the scientific or technical aspects of a drug application. At times this may be due

to uncertainties about the safety or efficacy of a drug that FDA reviewers may be unable to resolve. Because of the importance of advisory committee meetings to FDA decisions,[20] we analyzed this subgroup of uncertainties separately.

Uncertainties Important To The FDA's Decision Making

Third, we searched the FDA's Benefit-Risk Framework to identify the subset of uncertainties that were considered important to informing the FDA's benefit-risk assessment and approval decision. Within review documents, the FDA uses the Benefit-Risk Framework to communicate the key issues, evidence, and uncertainties relevant to each drug. Therefore, in accordance with published guidance from the FDA, uncertainties highlighted in the FDA's Benefit-Risk Framework were defined as uncertainties important to the FDA's decision making.[21–23]

Categorization Of Uncertainties

Next, we deductively coded the uncertainties.[24–29] The initial predefined categories of uncertainties were informed by published research summarizing uncertainties with the evidence of new cancer drug approvals.[30] We then adapted the categories used in previous research to include additional uncertainties that have been identified by the FDA in other research. These included issues with statistical analysis, problems with data integrity, and judgements of benefit and risk.[23–27] Uncertainties were ultimately categorized into one of thirteen mutually exclusive categories (exhibit 1). Online appendix table 1 provides further information about each uncertainty category.[31]

Uncertainties were independently categorized by two researchers (reaching agreement on 74 percent). Disagreements were resolved through discussion by a third

researcher, who also reviewed the categorization of uncertainties for 50 percent of the sample.

Reporting In FDA-Approved Drug Labeling

We next evaluated the reporting of clinical trial uncertainties in FDA-approved drug labeling issued at the time of approval. We systematically screened the entirety of prescribing information in the label, which is intended to convey information about safe and effective use of drugs for health care professionals, and the underlying evidence.

We considered that uncertainties were reported in the label when there was a mention of FDA reviewers' concerns with clinical trial evidence. In some cases, uncertainties were related to how information was reported in the manufacturer's initial evidence submission to the FDA (such as inferences from exploratory analyses or promotional statements not supported by the evidence). If these uncertainties were subsequently resolved during the review process, we considered these to be reported.

Postmarketing Study Commitments And Requirements

We then evaluated whether the label provided information on how uncertainties identified by FDA reviewers would be addressed during the postmarketing period. We reviewed the FDA's approval letter to identify the postmarketing requirements and commitments that were issued for each drug at the time of approval. These included accelerated approval confirmatory trial requirements (subpart H or E regulations), pediatric study requirements (505B(a)), postmarketing safety requirements (section 505(o)(3) regulations), and postmarketing commitments (506B regulations). We reviewed the label to determine whether it included details about postmarketing studies, and how these studies would address the uncertainties identified by FDA reviewers.

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Analysis

We first recorded the number and categories of uncertainties identified by FDA reviewers related to new cancer drugs, including the uncertainties that were important to the FDA's decision (that is, included in the FDA's Benefit-Risk Framework). Second, we examined the association between uncertainties and drugs approved through various regulatory pathways, as well as drugs that were discussed at the FDA's Oncology Drugs Advisory Committee. Third, we calculated the proportion of uncertainties that were reported in the label, according to their importance to the FDA, the category of uncertainty, and approval through various regulatory pathways. Fourth, we evaluated whether the label provided details on how these studies would address uncertainties identified by FDA reviewers.

Limitations

This study has limitations. First, our qualitative analysis required some degree of subjective interpretation, although agreement between the three researchers involved in data analysis was high. Second, we did not independently appraise the evidence for these trials or determine whether FDA reviewer judgements were made consistently (although FDA reviewers were consistent in some ways, explicitly identifying uncertainties relating to the choice of a single-arm trial design for thirty-eight of thirty-nine single-arm trials). Third, our study provides a conservative estimate, as additional uncertainties may be reported in the scientific literature that were not mentioned in FDA assessments.[18,32]

Fourth, we were unable to analyze the content of postmarketing requirements and commitments, given the limited information provided in FDA approval letters.[33] Fifth,

as we focused on cancer drugs, our findings might not be generalizable to drugs in other therapeutic areas, which are less likely to be reviewed through expedited programs or receive orphan drug designation.[3] However, cancer drugs represent the largest share of new drug approvals. Finally, we did not examine the extent to which other commonly used sources of clinical information used by oncologists, such as clinical practice guidelines, communicated uncertainties about new cancer drugs.

Study Results

From 2019 to 2022, the FDA approved fifty-two new cancer drugs. Clinical evidence for approval was based on fifty-six clinical trials (see appendix tables 2 and 3 for additional information about the sample characteristics).[31]

Uncertainties With Clinical Trial Evidence

FDA reviewers identified 213 uncertainties with the clinical trial evidence supporting these new cancer drugs at the time of approval. This corresponded to uncertainties with each of the fifty-six clinical trials supporting the approval of these drugs.

Exhibit 2 summarizes the categories of clinical trial uncertainties with new cancer drugs identified by FDA reviewers. The appendix presents these results for drugs approved through the various regulatory pathways (appendix figure 1).[31] From the fifty-six clinical trials reviewed by the FDA, generalizability of clinical evidence (forty-one of fifty-six trials, 73 percent), such as low enrolment of Black patients and patients of other racial and ethnic minority groups, was the most common uncertainty raised by FDA reviewers. The next most common uncertainties related to the use of single-arm trial designs (thirty-eight of fifty-six trials, 68 percent), long-term benefits and harms (thirty-

seven of fifty-six trials, 66 percent), the benefit-risk balance of the drug (twenty-six of fifty-six trials, 46 percent), and the measurement of the outcome (including concerns about bias due to open-label trial designs and compromised blinding; twelve of fifty-six trials, 21 percent).

Four (7 percent) of fifty-six clinical trials (for four cancer drugs) were referred to the FDA's Oncology Drugs Advisory Committee because of uncertainties with the clinical trial evidence. For all four trials, FDA reviewers identified uncertainties with the benefit-risk balance of the drug. Three of the four trials also had additional uncertainties that were discussed at advisory committee meetings, relating to the use of a single-arm trial design, generalizability of clinical trial results, and the magnitude of therapeutic benefit.

Uncertainties Important To The FDA's Decision Making

Of the 213 clinical trial uncertainties identified by FDA reviewers in their assessment of new cancer drugs, 50 percent (107 of 213 uncertainties) were highlighted in the FDA's Benefit-Risk Framework and were considered important to the FDA's decision. These uncertainties pertained to forty-four of fifty-six clinical trials (79 percent), which supported new cancer drug approvals.

Exhibit 2 shows the categories of uncertainties important to FDA decision making that were highlighted in the FDA's Benefit-Risk Framework. Uncertainties associated with the use of single-arm trial designs, long-term benefits and harms, and benefit-risk balance were most frequently highlighted in the FDA's Benefit-Risk Framework. Although generalizability was the uncertainty most often mentioned by FDA reviewers in

their assessment, this was far less cited as an uncertainty important to the FDA's approval decision.

Clinical trials for cancer drugs approved through the FDA's priority review program had the highest number of uncertainties highlighted in the FDA's Benefit-Risk Framework, followed by drugs that received orphan designation and drugs that were marketed via the accelerated approval program (for the number of uncertainties corresponding to each expedited program, see appendix figure 1).[31]

Uncertainties that were discussed at FDA advisory committee meetings were not always noted in the FDA's Benefit-Risk Framework. Of the seven clinical trial uncertainties discussed at an advisory committee meeting, three were highlighted in the FDA's decision for approval in the FDA's Benefit-Risk Framework: one related to the magnitude of therapeutic benefit and two related to the benefit-risk balance of the drug (for example, safety concerns).

Reporting Of Uncertainties In The Label

FDA-approved drug labeling reported information on 26 percent (fifty-six of 213) of clinical trial uncertainties that FDA reviewers identified with new cancer drugs at the time of approval. Among uncertainties that were highlighted in the FDA's Benefit-Risk Framework and considered important to the FDA's decision, 48 percent (fifty-one of 107 uncertainties) were reported in the label. Uncertainties from FDA reviewers not included in the FDA's Benefit-Risk Framework were rarely reported in the label (five of 106 uncertainties, 5 percent) (data not shown).

Exhibit 3 shows the extent to which each category of uncertainty was reported in the label. Despite FDA reviewers identifying uncertainties with unvalidated surrogate

endpoints, biases with randomization, deviation from intended interventions, missing outcome data, the magnitude of therapeutic benefit, and other uncertainties for several trials, none of these were reported in the label.

Exhibit 4 summarizes how frequently uncertainties with clinical trial evidence were reported in the label based on drug characteristics. Cancer drugs with first-in-class status were the most likely to have these uncertainties reported in the label (33 percent of any uncertainties and 68 percent of uncertainties important to FDA decisions), followed by cancer drugs with priority review (27 percent and 52 percent, respectively) and those with accelerated approval (26 percent and 49 percent, respectively). Cancer drugs that received fast-track review were the least likely to have uncertainties reported in the label (21 percent and 39 percent, respectively).

Although uncertainties with evidence from four clinical trials were discussed at the FDA's Oncology Drugs Advisory Committee, the label did not report that these drugs were reviewed at an advisory committee meeting or mention the associated uncertainties discussed for any of these drugs (for further information about the uncertainties mentioned in advisory committee meetings, see appendix table 4).[31]

Postmarketing Study Commitments And Requirements

Fifty of fifty-two new cancer drugs were approved with postmarketing requirements or commitments for new clinical studies. Information about postmarketing studies and how these would address uncertainties with clinical trial evidence was infrequently reported in the label, making up 6 percent (twelve of 213 uncertainties) of all uncertainties and 9 percent (ten of 107 uncertainties) of those highlighted in the FDA's Benefit-Risk Framework. Postmarketing requirements reported in the label were

exclusively for accelerated approval confirmatory trials. These studies were intended to address uncertainties identified by FDA reviewers with the long-term benefits and harms (ten of thirty-five uncertainties, 29 percent), benefit-risk balance (one of twenty-nine uncertainties, 3 percent), and single-arm trial design of cancer drugs (one of thirty-seven uncertainties, 3 percent). Although the accelerated approval statement in labels always referred to uncertainty, these labels were not always sufficient at conveying the extent of the uncertainties identified by FDA reviewers (data not shown).

Discussion

The label is the primary channel of communication between the FDA and physicians, conveying important prescribing information about the evidence and limitations of drugs. From 2019 to 2022, FDA reviewers identified uncertainties with the clinical trial evidence supporting all new cancer drug approvals. However, few uncertainties were reported in the prescribing information, including less than half of those considered important to the FDA's decisions.

Our findings confirm that many cancer drugs are approved despite uncertainties with the underlying clinical trial evidence. One reason for this is the more frequent use of expedited programs in oncology compared with other therapeutic areas.[3] This limits the evidence that FDA reviewers have to inform their assessments of drug benefits and risks. Reviewers may then rely on other aspects of clinical trial evidence to inform their decisions.[27,34]

A key part of our analysis distinguished between uncertainties identified by the FDA as important for its decision making.[21–23] However, these might not be the most important sources of uncertainty for physicians and patients. One such example is the

use of unvalidated surrogate endpoints. There is growing evidence suggesting that patients might not value improvements in surrogate endpoints in the absence of longer survival.[35,36] However, uncertainties about the validity of surrogate endpoints to predict clinical outcomes was often not included in the FDA's Benefit-Risk Framework, even though the majority of clinical trials were approved on the basis of these endpoints.

Previous research has shown that prescribing information on clinically meaningful outcomes is not consistently reported in the label.[37,38] For example, information on whether a new cancer drug extends overall survival, which is the most definitive and patient-relevant outcome in cancer drug trials, is not routinely communicated in the label.[29] Our study contributes to this literature and is the first to investigate whether uncertainties identified by FDA reviewers about the evidence supporting new drug approvals was reported in the label.

The incomplete reporting of clinical trial uncertainties in the label is concerning. One potential reason for incomplete reporting is that the FDA tries to limit the amount of technical information communicated in the label.[39] A consequence is that important information gets lost. Physicians generally believe that the FDA approves drugs when the benefits outweigh the risks, but physicians' knowledge about uncertainties with the evidence underlying new cancer drug approvals are lesser known.[16,17,40] Without knowledge of these uncertainties, physicians may overestimate the benefits of new cancer drugs, which is often associated with increased prescribing without reducing mortality.[41,42]

There are actions the FDA can take to communicate uncertainties and ensure that they are addressed without delays. The FDA has historically resisted changes to

the label over concerns that adding further information would overwhelm physicians and patients.[39] Yet, studies show that brief explanations about uncertainties are effective at improving understanding and decision making.[16,43,44] The label for drugs with accelerated approval includes a description about uncertainties with clinical outcomes and requirements for a confirmatory study. However, the current description lacks sufficient detail to inform prescribing decisions.[45] The FDA could test more informative statements to effectively communicate uncertainties with clinical evidence.

In addition, uncertainties with clinical trial evidence may be inevitable, given the increasing use of expedited programs and the limited data available to regulators at the point of review.[1] Postmarketing requirements are necessary to ensure that they are addressed without delays. It is critical, then, that uncertainties are communicated at the time of approval in the label so that physicians are aware of these uncertainties, and whether they will be resolved with additional data collection in the future.[46] However, research shows that postmarketing studies are often inadequate at addressing uncertainties with clinical evidence that exist at the time of approval, and are frequently delayed or never completed.[47–49] One strategy would be to require the initiation of confirmatory studies to address uncertainties before approval, similar to proposals for drugs with accelerated approval.[50]

Conclusion

FDA reviewers identified uncertainties with the clinical trial evidence supporting all new cancer drug approvals from 2019 to 2022. However, few uncertainties overall were reported in the prescribing information of the label, including less than half of those the FDA considered to be important to its decisions. Communicating uncertainties about

the evidence of cancer drugs in the label is essential for informing physicians about their safe and effective use.

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List of Exhibits

Exhibit 1 (table)

Exhibit 2 (table)

Exhibit 3 (figure)

Caption: Reporting of clinical trial uncertainties by category in Food and Drug Administration (FDA)-approved drug labeling, 2019–22.

Source/Notes: SOURCE Authors' analysis of FDA review documents and FDA-approved drug labeling, 2019–22. NOTES Figure shows the number of uncertainties identified from FDA review documents, the subset of uncertainties considered important to the FDA's decisions (that is, included in the FDA's Benefit-Risk Framework), and the number of uncertainties reported in the label. One uncertainty with "other" was excluded from the figure. Five uncertainties not mentioned in the FDA's Benefit-Risk Framework were reported in the label.

Exhibit 4 (figure)

Caption: Uncertainties reported in the label for drugs approved through various regulatory pathways, 2019–22

Source/Notes: SOURCE Authors' analysis of Food and Drug Administration (FDA) review documents and FDA-approved drug labeling, 2019–22. NOTE Important uncertainties were those identified from the FDA's Benefit-Risk framework.

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EXHIBITS

Exhibit 1: Uncertainties with clinical trial evidence for new cancer drugs identified by FDA reviewers, 2019–22

Uncertainty	Details mentioned in FDA review
Unvalidated surrogate endpoint	Limited information about the validity of a surrogate endpoint to predict clinical outcomes (how patients feel, function, or survive)
Single-arm trial design	Absence of control therapy, randomization, and data on time-to-event endpoints; lack of blinding or open-label treatment allocation
Statistical analysis	Improper statistical analysis procedures (invalid noninferiority and superiority testing)
Data integrity	Completeness, consistency, and accuracy of data; poor data handling practices
Randomization	Imbalanced demographics, disease characteristics, or treatments received between groups
Deviation from the intended intervention	Protocol deviations that could affect the integrity of findings
Missing outcome data	Missing data on safety or efficacy from the intention-to-treat population
Measurement of the outcome	Confounding, informative censoring, concerns about open-label trial designs, unblinding of participants or investigators
Selection of the reported result	Reporting of nonprespecified analyses (exploratory, interim) and selective reporting of analyses with favorable benefits
Long-term benefits and harms	Short duration of follow-up and need for additional data to confirm long-term safety and efficacy
Magnitude of therapeutic benefit	Modest or unclear magnitude of benefit; small or unclear added value relative to the control therapy or other approved drugs
Benefit-risk balance	Uncertainty regarding the balance of benefits and harms (for example, because of uncertainty about optimal dose)
Generalizability	Small study size and trial unrepresentative of the target population (including sex, age, ethnicity, race, disease, geography)

SOURCE Authors' analysis of FDA review documents, 2019–22.

"Cherla_manuscript_RFCE.docx"; 4/27; dl 4/28; lw to ah 5/5; ah to lw 5/13; lw to au 5/13;

Exhibit 2: Percent of uncertainties with clinical trial evidence supporting new cancer drugs identified by Food and Drug Administration (FDA) reviewers, 2019–22

Uncertainty	Clinical trials with uncertainties (*n* = 56 clinical trials), %	Clinical trials with uncertainties included in the FDA's Benefit-Risk Framework (*n* = 44 clinical trials), %
Generalizability	73	21
Single-arm trial	68	57
Long-term benefits and harms	66	57
Benefit-risk balance	46	43
Measurement of the outcome	21	7
Selection of the reported result	20	16
Magnitude of therapeutic benefit	18	14
Randomization	16	2
Data integrity	13	7
Unvalidated surrogate endpoint	11	5
Deviation from intended intervention	11	5
Statistical analysis	9	7
Missing outcome data	7	5
Other	2	0

SOURCE Authors' analysis of FDA review documents, 2019–22. NOTE Uncertainties are not mutually exclusive; therefore, the columns do not sum to 100 percent.

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To access the authors' disclosures, click on the Details tab of the article online.BIOS for

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