Original Article

DIA

Therapeutic Innovation
& Regulatory Science
1-7

DOI: 10.1177/2168479018759662
tirs.sagepub.com

Outdated Prescription Drug Labeling: How FDA-Approved Prescribing Information Lags Behind Real-World Clinical Practice

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Abstract

Background: Prescription drug labeling is an authoritative source of information that guides the safe and effective use of approved medications. In many instances, however, labeling may fail to be updated as new information about drug efficacy emerges in the postmarket setting. When labeling becomes outdated, it loses its value for prescribers and undermines a core part of the FDA's mission to communicate accurate and reliable information to patients and physicians. *Methods:* We compared the number of drug uses indicated on product labels to the number of uses contained in a leading drug compendium for 43 cancer drugs approved between 1999 and 2011. We defined a "well-accepted off-label use" of a drug as one that was not approved by the FDA and received a category 1 or 2A evidence grade. *Results:* Of the 43 drugs reviewed in this study, 34 (79%) had at least one well-accepted off-label use. In total, 253 off-label uses were identified; 91% were well accepted, and 65% were in cancer types not previously represented on labeling. Off-patent drugs had more well-accepted off-label uses than brand-name drugs, on average (mean 13.7 vs 3.8, $P = .018$). *Conclusions:* The labeling for many cancer drugs, particularly for older drugs, is outdated. Although FDA-approved labeling can never be fully aligned with real-world clinical practice, steps should be taken to better align the two when high-quality data exist. Such steps, if taken, will assist patients and prescribers in discerning which uses of drugs are supported by the highest quality evidence.

Keywords

FDA, labeling, off-label use, compendia, postmarket evidence

Introduction

Each time a new drug is approved for marketing in the United States, an accompanying collection of drug-related information, called "labeling," is made available to health care practitioners to inform safe and effective prescribing. Federal regulations state that labeling must contain a summary of the essential scientific information about a drug, and that the information contained therein must be informative and accurate.[1] The content of labeling is written by drug manufacturers, but must be approved by the Food and Drug Administration (FDA) to ensure that it meets standards laid out in regulations.[2]

Labeling is a crucial source of trusted information about prescription drugs, but it can easily become outdated if new evidence of drug effectiveness is not submitted to the FDA in a timely manner. Most often, labeling becomes outdated when high-quality scientific evidence is generated that supports a new use of a drug, but the drug's manufacturer does not file a supplemental application requesting the new use be added to the drug's labeling. This may occur because the manufacturer did not sponsor the research investigating the new use, or because the manufacturer lacked sufficient incentives to pursue a labeling expansion. Drug manufacturers are not required by law to update their products' labeling with new uses, though they may choose to do so voluntarily when they wish to market their products in new settings.[3]

Uses of drugs in patient populations or for indications that differ from those prescribed on labeling are referred to as "off-label" uses. Off-label use in oncology is common: it has been estimated that more than half of all uses of cancer drugs are beyond the scope of approved labeling.[4,5] The fact that a particular use is off-label does not preclude it from being incorporated into routine practice and covered by insurers. A policy dating back to 1993 requires Medicare to cover off-label cancer drug uses that have been deemed medically accepted by at least

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Submitted 19-Sep-2017; accepted 12-Jan-2018

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one federally designated drug compendium.[6] The National Comprehensive Cancer Network Drugs & Biologics Compendium (NCCN Compendium) is the most widely used compendium of oncology drugs and is used not just by Medicare but by most private insurers to guide coverage decisions.[7] The NCCN Compendium contains a collection of drug uses that have been identified based on an evaluation of the scientific literature and expert judgment and includes both on- and off-label uses.[8]

In this study, we investigate the extent to which the recommendations of medical experts who crafted the NCCN Compendium align with approved uses of drugs on FDA labeling. Although a wide disparity between labeling and the Compendium is to be expected, given the high rate of off-label use in oncology, comparing the 2 sources allows us to quantify the extent to which the labeling of individual drug products diverges from high-quality clinical practice. Furthermore, because NCCN assigns an evidence grade to each off-label use it recommends, it allows us to analyze the quality of evidence supporting off-label indications, and the diversity of the indications themselves.

Methods

Sample Construction and Data Collection

We identified all new molecular entities and new biological products approved by the FDA between January 1, 1999, and December 31, 2011, for anticancer indications. For each drug in our sample, we recorded the approved uses that were listed on labeling, which are contained in the "Indications and Usage" portion of the physician package insert and are marked with a unique numerical listing or a separate bulleted entry. We then accessed entries for the sampled drugs in the NCCN Compendium and recorded the description, disease setting, ICD-10 code, and NCCN evidence category for each recommended use.

Uses in the NCCN Compendium were divided into 2 groups based on NCCN-designated evidence categories. Uses graded category 1 or 2A were deemed to be "well-accepted" because of NCCN's assertion that these uses are supported by "uniform" consensus, meaning a majority panel vote of at least 85% is required.[9] Uses graded category 2B or 3 were not deemed to be well accepted because they lack uniform consensus from NCCN committees. Uses in the Compendium that were both well accepted and not FDA approved were assigned the category of "well-accepted off-label use."

Comparison of FDA-Approved Labels and the NCCN Compendium

We conducted a comparison of uses listed in the NCCN Compendium with uses listed on approved labeling. An NCCN-recommended use was classified as "on-label" if the following criteria were met: (1) the use was indicated for a cancer type listed on approved labeling or a subtype of a broader cancer type listed on approved labeling; *and* (2) all conditions of use mentioned on the label (eg, line of therapy, drug combinations, prior treatments, biomarker selection criteria) did not differ between NCCN's description of the recommended use and the description of the use on labeling. We then identified which products had outdated labels, defining the term "outdated label" to mean a label that was missing at least one well-accepted off-label use (ie, one use that NCCN graded as category 1 or 2A).

Classification of NCCN-Recommended Off-Label Uses

We grouped the off-label uses in the Compendium into 3 mutually exclusive categories adapted from an existing classification system.[10] The categories were (1) new disease indication; (2) modified disease indication; and (3) expanded patient population. New indications were uses in separate disease settings than those listed on the FDA label; modified indications were uses that represented a new line of therapy, a new drug combination, or a new purpose (eg, adjuvant therapy vs symptom palliation); expanded patient populations were new uses that represented closely related subtypes to already-approved indications, new age groups, and new biomarker selection criteria. Disease subtypes were clarified and terminological differences reconciled using the World Health Organization's (WHO's) ICD-10 online browser.

Statistical Analysis

We ran a series of paired and 2-sample t tests as well as a Mann-Whitney U test to evaluate differences between the number of FDA-labeled uses and NCCN-recommended uses, as well as differences between NCCN-recommended uses of different categories. For additional detail on our methods and statistical analysis, see Supplemental Information.[i] This article does not contain any studies with human or animal subjects performed by any of the authors.

Results

We identified 43 anticancer agents approved by the FDA between 1999 and 2011 (Figure 1). A total of 99 FDA-labeled uses were identified, compared to 451 NCCN-recommended uses. The average difference between the number of NCCN-recommended and FDA-labeled uses for each drug was 8.16 ($P < .001$). All FDA-labeled uses were also recommended in the Compendium, with the exception of 2 non-oncology indications for imatinib. Among the 451 NCCN-recommended uses, 198 (43.9%) were classified as on-label uses and 253 (56.1%) were classified as off-label uses. Of the 253 off-label uses in the NCCN Compendium, 26 (10.3%) were graded category 1, and 205 (81%) were graded category 2A (Table 1). Thus, 231 (91%) of uses were deemed a "well-accepted off-label use" according to our definition of the term.[ii] There was evidence that the proportion of drugs with well-accepted off-label uses is greater than the proportion of drugs with no well-accepted off-label uses ($P < .001$). Additionally, of the 253 off-label uses, 165 (65.2%) were

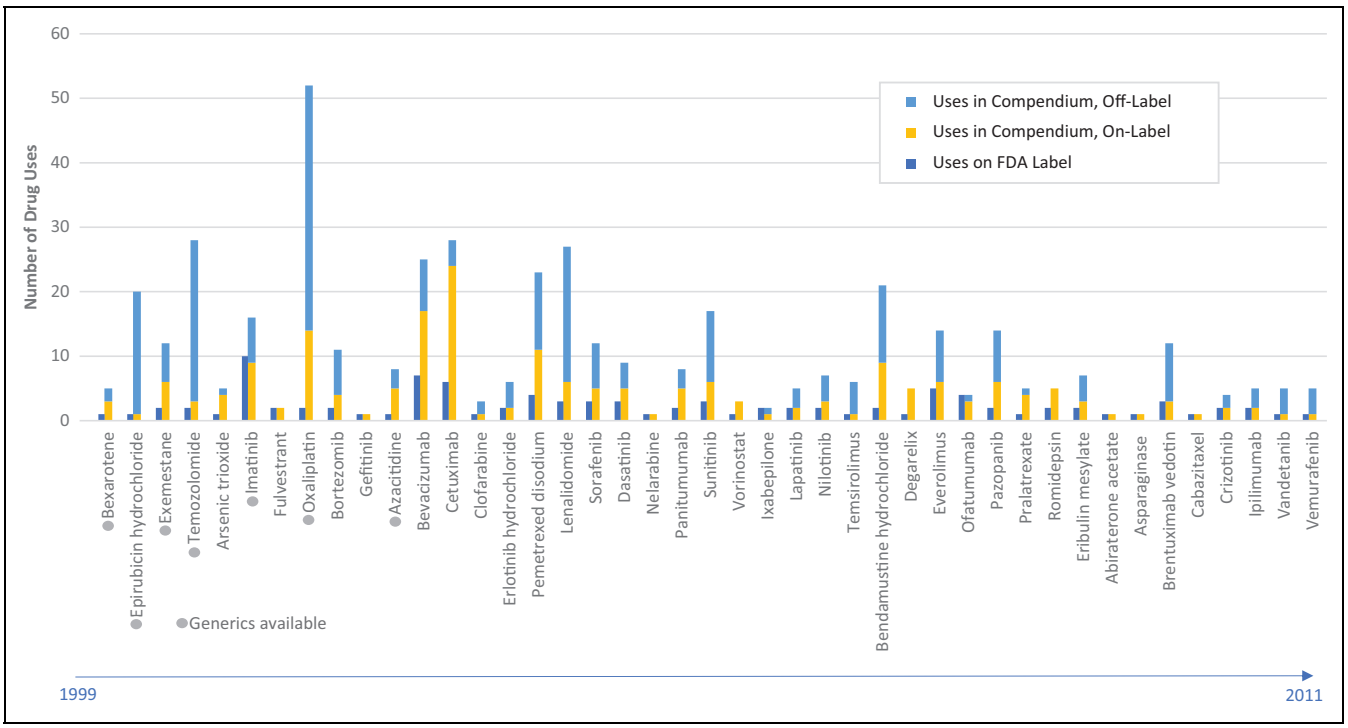

Figure 1. Oncology drug uses listed on FDA-approved labeling vs the NCCN Compendium, 1999-2011. The figure shows a comparison of FDA-approved labeling and the NCCN Compendium for 43 cancer drugs approved between 1999 and 2011. Drug uses listed in approved labeling were counted from the Indications and Usage section of physician package inserts. Drug uses listed in the NCCN Compendium were categorized as either within or outside the scope of labeling (ie, "on-label" or "off-label") through a direct comparison with uses listed on labeling. The average difference between the number of NCCN-recommended and FDA-labeled uses for each drug was 8.16 ($P < .001$). The total number of uses supported by the NCCN Compendium also differed for drugs with and without generic competition ($P = .018$).

Table 1. Characteristics of Drug Uses Included in the NCCN Compendium.[a]

	Total Uses (n = 451)		On-Label Uses (n = 198)		Off-Label Uses (n = 253)	
Characteristic	Number	Percent	Number	Percent	Number	Percent
Use category						
On-label	198	43.90	198	100	0	0
Off-label: New indication	165	36.59	0	0	165	65.22
Off-label: Modified indication	32	7.10	0	0	32	12.65
Off-label: Expanded population	56	12.42	0	0	56	22.13
NCCN evidence grade						
Category 1	81	17.96	55	27.78	26	10.28
Category 2A	339	75.17	134	67.68	205	81.03
Category 2B	25	5.54	8	4.04	17	6.72
Category 3	6	1.33	1	0.51	5	1.98

[a]The table shows the breakdown of uses recommended on the NCCN Compendium for 43 cancer drugs approved between 1999 and 2011, stratified by use category and evidence grade. Use categories were assigned to each NCCN-recommended use by the authors using a process described in the article. Evidence grades are assigned to each recommended use in the Compendium by NCCN panels. Evidence grades are defined by NCCN as follows: category 1—based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; category 2A—based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate; category 2B—based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate; category 3—based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

categorized as "new indications," meaning they were in disease settings not represented on labels (Table 1).

Of the 43 drugs in the analysis, 34 (79.1%) had at least one well-accepted off-label use; 34.8% had at least 5 well-accepted off-label uses; and the mean number of well-accepted off-label uses was 5.4. The mean number of well-accepted off-label uses in the NCCN Compendium also differed for drugs with and without generic competition (mean 13.7 vs 3.8, $P = .018$). The difference between FDA labeling and the NCCN Compendium is further illustrated by a case

Table 2. Diversity of Disease Settings Represented in FDA Labeling and the NCCN Compendium: 3 Case Studies.[a]

	✓ = At least 1 use in disease setting					
	Eloxatin (oxaliplatin)		Avastin (bevacizumab)		Erbitux (cetuximab)	
Disease setting[b]	FDA	NCCN	FDA	NCCN	FDA	NCCN
Breast cancer				✓		
Central nervous system cancers			✓	✓		
Cervical cancer			✓	✓		
Chronic lymphocytic leukemia		✓				
Colorectal cancer	✓	✓	✓	✓	✓	✓
Esophageal cancer		✓				
Gastric cancer		✓				
Head and neck cancers					✓	✓
Hepatobiliary cancers		✓				
Kidney cancer			✓	✓		
Malignant pleural mesothelioma				✓		
Neuroendocrine tumors		✓				
Non-Hodgkin lymphoma		✓				
Non-melanoma skin cancers						✓
Non–small cell lung cancer			✓	✓		✓
Occult primary		✓				
Ovarian cancer		✓	✓	✓		
Pancreatic cancer		✓				
Penile cancer						✓
Soft tissue sarcoma				✓		
Testicular cancer		✓				
Uterine neoplasms				✓		

[a]The 3 drugs listed were initially approved by the FDA for colorectal cancer indications. Two of 3 (bevacizumab and cetuximab) were subsequently approved in additional disease settings, but for all 3 drugs, the number of disease settings represented in the NCCN Compendium is greater than what is represented on approved labeling. This chart illustrates the variety of supplemental uses that are recommended by NCCN but are not contained on approved labeling.
[b]Disease categories listed reflect NCCN's grouping of cancer types.

study of 3 drugs initially approved for colorectal cancer indications (Table 2).

A review of 5 of the largest private payers' coverage policies identified 80% (4 of 5) with policies that explicitly use the NCCN Compendium to support coverage decisions at the time of this writing. Medical and pharmacy coverage policies containing explicit reference to NCCN evidence categories accepted for coverage were obtained for all but Humana. Aetna, Cigna and United Healthcare policies accepted categories 1, 2A, and 2B; and Anthem's accepted categories 1 and 2A.[11-14] The percentage of off-label uses in the Compendium that were category 1, 2A, or 2B, and thus accepted by 3 of the 5 largest payers, was 98% (248 of 253) (Supplemental Table 1).

Discussion

Our analysis of the NCCN Compendium and FDA drug labels for 43 cancer drugs approved between 1999 and 2011 identified hundreds of off-label uses, most of which were strongly supported by NCCN expert panels. Ninety-one percent of off-label uses were "well accepted" (defined in this study as receiving a category 1 or 2A evidence grade), and 65% were for cancers not currently represented in labeling. Drugs that had gone off patent had the most well-accepted off-label uses associated with them. From these findings, we infer that the labeling of many cancer drugs is out of date, and this is especially true for older, generic products.

A review of commercial payer coverage policies further illustrates the divergence between labeling and high-quality clinical practice. We found that 4 of the 5 largest private payers, as well as Medicare, cover over 90% of uses listed on the NCCN Compendium (uses graded 1 and 2A), suggesting widespread acceptance of these uses by diverse stakeholders . While standards for FDA approval differ from standards for coverage determinations, these findings indicate that the gulf between labeled uses and covered uses may be needlessly wide.

The absence from approved labeling of many well-accepted drug uses presents a significant public health concern. Labeling is the FDA's primary means of communicating information about drugs, and as such it contains a rich supply of information about drug safety and effectiveness. But as labels fall out of date, their status as useful resources may decline, causing prescribers to rely instead on other sources of information. Labeling has already been shown to be of limited interest to many physicians, many of whom cannot accurately identify labeled indications of the medications they commonly prescribe.[15] Inattention to labeling can cause patient harm, as was seen in

the case of cisapride, when a revised label warning of life-threatening adverse events did not change prescribing behavior.[16] By the same token, overreliance on sources other than labeling, such as compendia, may result in misplaced confidence in some off-label uses. While compendia recommend many strongly supported uses of drugs, they have also been shown to recommend uses that are supported by far less rigorous evidence.[17] Therefore, unforeseen consequences for patients may arise from both the disregard of labeling and the overreliance on other sources, such as compendia.

Given that the prevalence of off-label use in oncology is well known, the existence of outdated labeling will likely not come as a surprise to many observers. However, these findings demonstrate the extent to which individual drugs are strongly recommended for many (sometimes dozens) off-label uses, and that the diversity of these uses themselves is often striking. The case studies presented in Table 2 further illustrate this point. In the case of the drug Eloxatin (oxaliplatin), the disparity between the uses recommended by NCCN and those approved by the FDA is especially stark. Eloxatin was initially approved in 2002 for relapsed metastatic colorectal cancer, and an additional use was added in 2004 for adjuvant treatment of stage III colon cancer. Since then, no new indications were added to the drug's labeling. In contrast, at the time of this analysis, the NCCN Compendium included 38 off-label uses of the drug, representing 10 additional disease settings beyond those that are approved by the FDA. This is not just true of oxaliplatin: over half of the drugs in our sample had well-accepted off-label uses in disease settings not currently represented on labeling.

Restoring the relevance of approved labeling is an important public health goal. While other high-quality sources of clinical prescribing information exist, labeling is the sole source of information that reflects the scientific and methodological rigor of the FDA approval process. Patients and prescribers can have the assurance that the use of medicines in conformity with drug labeling is supported by a positive benefit-risk assessment. The inclusion of new uses in product labeling, as appropriate, will provide patients and prescribers with these assurances of safety and effectiveness on a more frequent basis.

However, it is equally important to consider the critical role of off-label use to safe and effective prescribing. As a former editor of the *Journal of the American Medical Association* put it, "There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician's ability to [prescribe off-label] . . . when it is medically appropriate."[18] Thus, while restoring the relevance of approved labeling would foster greater trust in medical products, it should not come at the expense of lowering access to important off-label uses.

Congress recognized the importance of off-label prescribing in 1997 with the passage of the Food and Drug Administration Modernization Act (FDAMA), which described ways in which manufacturers could disseminate medical and scientific information about unapproved uses without violating the legal prohibition against off-label promotion. These "safe harbors" have been reinforced in subsequent FDA guidance documents.[19] However, the FDA has noted in these guidance documents that allowing the dissemination of information about unapproved uses is predicated on the assumption that a manufacturer would soon seek FDA approval for such unapproved uses. As such, permitting the dissemination of information about off-label uses is not intended to be a substitute to the eventual inclusion of such uses onto approved labeling.

Owing to its desire to communicate effectively with prescribers through labeling, the FDA has attempted at several points in the past 20 years to maximize labels' accessibility and usability. In 1998, the FDA issued proposed regulations aimed at helping speed the incorporation of "new uses" of approved products onto labeling.[20] Then in 2006, the FDA altered the structure of labeling to make it more user-friendly.[21] Most recently, in 2013, FDA launched the Prescription Drug Labeling Improvement and Enhancement Initiative to "enhance the safe and effective use of prescription drugs by facilitating optimal communication through labeling."[22] In total, these actions represent a concerted effort on the part of FDA to make labeling a more valuable source of prescribing information, but they have not had their desired effect.

The FDA's past attempts to achieve more up-to-date labels have not succeeded in part because responsibility to update labeling largely falls on drug manufacturers, not the FDA. Under current law, drug manufacturers can request that additional uses of their products be added to labeling by submitting supplemental new drug applications. This is a voluntary process; manufacturers are not required to update labeling with new information about drug effectiveness. Thus, manufacturers typically submit new efficacy data about previously approved drugs only if they wish to market their products for additional uses. In 2007, the Food and Drug Administration Amendments Act added new authority for FDA to require safety-related labeling changes when new safety information becomes available after approval, but no such requirement currently exists for the addition of efficacy-related information.[23]

To ensure that labeling is updated in a timely manner, drug manufacturers should be encouraged to submit more frequent supplemental applications to the FDA. Progress has recently been made on this front: the sixth reauthorization of Prescription Drug User Fee Act, passed in August 2017, eliminated user fees for supplemental applications.[24] However, since there may be scenarios in which manufactures lack any incentive to submit efficacy supplements, such as when a drug has gone off patent, the FDA may need to play a more proactive role in promoting drug labeling that is up-to-date and accurate. One method of accomplishing this would involve a collaboration between the FDA and the developers of clinical guidelines and drug compendia. The latter, who aggregate and synthesize postmarket evidence, could work with the FDA to evaluate existing evidence about approved drugs and suggest updates to labeling. Manufacturers would then be able to reference this material in supplemental applications, thus

lowering the barriers associated with the submission of such applications.

The collaboration envisioned between the FDA and clinical experts would be far less resource-intensive than a program requiring FDA to update labeling on its own. Many professional societies and guideline developers have already spent much time evaluating postmarket evidence supporting off-label drug use. Moreover, such a collaboration would result in labeling that includes new uses of drugs that are supported by strong evidence. Thus, not all the off-label uses currently recommended by NCCN should be incorporated into labeling, but rather only those that are supported by "substantial evidence" of effectiveness, a term that is defined in Section 505 of the Food, Drug and Cosmetic Act and expanded upon in federal regulations.[25,26] It is likely that many of the off-label uses recommended by NCCN would in fact meet existing evidentiary standards, given the widespread acceptance of these uses by physicians and payers, as well as frequent assertions by the FDA and others that many off-label uses have become standard of care.[27-30] The method outlined above, which would seek to encourage more frequent labeling updates by drug sponsors, may not adequately facilitate label extensions when a brand-name product has been withdrawn from the market and generic versions remain available. Existing laws requiring that generic product labels be the "same" as brand-name reference product labels, as well as ongoing concerns over product liability, complicate the initiation of labeling changes by generic firms.[31] Our analysis of NCCN guidelines has some limitations. First, it was limited to oncology drugs, although the issue of outdated labeling extends beyond this disease setting. In fact, outdated labeling may pose an even greater risk in settings where well-curated compendia do not exist, or where reimbursement is tied to the contents of labeling, as sometimes takes place in rheumatology.[32] Additionally, we did not conduct an analysis of changes to labeling or the NCCN Compendium over time. Further research into the evolution of these resources following the approval of a new drug would help illustrate how postmarket evidence is developed and identify additional opportunities to incorporate it into labeling.

Conclusions

This study provides evidence that FDA-approved labeling is missing a large amount of important and clinically relevant information about the effectiveness of cancer drugs. Labeling can be a valuable resource for prescribers, but can easily lose its utility if it becomes outdated. Over time, the presence of outdated labeling erodes the FDA's ability to communicate important prescribing information to physicians, which is a core part of the Agency's mission. Facilitating the timely addition of new drug uses to approved labeling will enable patients and prescribers to discern which uses of drugs are supported by the highest quality evidence.

Declaration of Conflicting Interests

No potential conflicts were declared.

Funding

No financial support of the research, authorship, and/or publication of this article was declared.

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Supplemental Material

Supplementary material for this article is available online.

Notes

i. See Supplemental Information.
ii. See Methods. Uses graded category 1 or 2A were deemed to be "well-accepted" due to NCCN's assertion that these uses are supported by "uniform" consensus, meaning a majority panel vote of at least 85% is required.

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