Improving Safety and Transparency in America's Food and Drugs

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MODERN Labeling Act

Testimony of Jeff Allen, PhD, President and CEO, Friends of Cancer Research

Good morning, Chairman Pallone, Chairwoman Eshoo, Ranking Members Walden and Burgess, and Members of the committee. I am Dr. Jeff Allen, President and CEO of Friends of Cancer Research, a cancer research advocacy organization dedicated to accelerating science & technology from bench to bedside. I would like to thank all Members and the staff of this committee for putting together this important hearing. It is an honor to testify before you today and provide our perspective regarding outdated prescription drug labels and the proposal to help the FDA ensure that all drug labels contain the most accurate and up-to-date information possible.

Each time a new drug is approved for marketing in the United States, an accompanying collection of drug-related information, called "labeling" (also known as the "professional labeling" or "package insert"), is made available to health care practitioners to inform safe and effective prescribing.[1] Federal regulations state that labeling must contain "a summary of the essential scientific information needed for the safe and effective use of the drug," and that it must be "informative and accurate."[2] 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.[3] Labeling is a crucial source of trusted information about prescription drugs. The package insert is the FDA's primary means of communicating information about approved drugs, which confers to it a special status: labeling is meant to contain the "essential" information about a drug.

When it is kept up to date, labeling represents the most authoritative drug-related information that is available to prescribers. However, labeling can become outdated when high-quality scientific evidence is generated in the post-market setting, but the drug's manufacturer does not file a supplemental application requesting a modified 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.[4]

Uses of drugs in patient populations or for indications that differ from those prescribed in accordance with the product label 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

[1] Federal Register Notice. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices71 F.R. 3922, 2006.
[2] US Department of Health and Human Services. Requirements on content and format of labeling for human prescription drug and biological products. 21 CFR §201.56. https://www.gpo.gov/fdsys/ granule/CFR-2012-title21-vol4/CFR-2012-title21-vol4-sec20156. Effective April 1, 2012. Accessed February 20, 2018.
[3] Lindstrom J. Sources of drug information: FDA-approved labeling and other official FDA sources. Dermatol Ther. 2009;22: 246-256.
[4] Greene SM, Noah L. Debate: Off-label drug promotion and the first amendment. Univ PA Law Rev. 2015;62:239-267.

labeling.[5,6] 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 one federally designated drug compendium.[7] 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[8]. 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.[9] We believe that actively managed guidelines, like NCCN and those of other expert organizations, are a valuable tool for healthcare practitioners and should remain the basis of evidence used by insurers for coverage decisions given their robust and rapidly iterative processes that actively involve the advice of leading experts in specific fields. However, this does not mean that they should serve as a replacement for maintaining accuracy of individual drug labels following the initial approval of a drug. As previously noted, drug labels serve as an unbiased and factual basis from which the communications about a drug's use is derived.

In a recent study my organization published in the peer-reviewed journal Therapeutic Innovation and Regulatory Science, we investigated the extent to which the recommendations of medical experts who crafted the NCCN Compendium align with approved uses of drugs on FDA labeling.[10] The complete findings of our study are included as Appendix 1. To summarize, our analysis of the NCCN Compendium and FDA drug labels included the 43 cancer drugs approved between 1999 and 2011 and identified hundreds of off-label uses, most of which were strongly supported by NCCN expert panels. More specifically:

- In almost every case (34 of 43; 79%), the NCCN compendium had more recommended uses than those described in the FDA label for the drugs analyzed in this study,

- Of the 450 NCCN-recommended uses associated with all drugs included in the study, 253 (56.3%) were outside the scope of the FDA label,

- 65% of the off-label uses in the NCCN Compendium represented new disease indications, meaning these uses were in disease settings not currently represented on FDA-approved labels, and

[5] Pfister DG. Off-label use of oncology drugs: the need for more data and then some. J Clin Oncol. 2012;30:584-586.
[6] Soares M. "Off-label" indications for oncology drug use and drug compendia: history and current status. J Oncol Pract. 2005;1: 102-105.
[7] Abernethy AP, Raman G, Balk EM, et al. Systematic review: reliability of compendia methods for off-label oncology indications. Ann Intern Med. 2009;150:336-343.
[8] Abernethy AP, Raman G, Balk EM, et al. Systematic review: reliability of compendia methods for off-label oncology indications. Ann Intern Med. 2009;150:336-343.
[9] National Comprehensive Cancer Network. About the NCCN Drugs & Biologics Compendium (NCCN Compendium®). Accessed December 5, 2017.
[10] Shea MB, Stewart M, Van Dyke H, et al. Outdated Prescription Drug Labeling: How FDA-Approved Prescribing Information Lags Behind Real-World Clinical Practice. Therapeutic Innovation and Regulatory Science. 2018;52(6):771-777.

- 91% of off-label uses were graded as NCCN Category 1 or 2A, indicating they are based on strong existing evidence and backed by uniform consensus from NCCN advisory committees

From these findings, we can conclude 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.

When sections of FDA-approved labeling become outdated they may lose value for prescribers and fail to communicate essential information about drugs to patients and healthcare providers. In such cases, and even if labeling is kept up to date, prescribers routinely use other information such as peer-reviewed treatment guidelines in making decisions for patients. In the past, physicians have been found to have limited knowledge of FDA-approved indications of drugs vs. unapproved uses, suggesting low levels of use of labeling.[11] A Friends of Cancer Research online questionnaire, developed in collaboration with the Deerfield Institute, to survey physician use and perceptions of drug labeling, indicated that oncologists use multiple sources, in addition to FDA product labeling, when making decisions including clinical practice guidelines, drug compendia, and UpToDate.[12] However, while physicians report generally favorable perceptions of the major prescribing resources in their field, "timeliness" of the source information was a particularly important consideration for prescribers.

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.[13] 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.[14] Therefore, unforeseen consequences for patients may arise from both the disregard of labeling and the overreliance on other sources, such as compendia alone. 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. In the case of the drug oxaliplatin, the disparity between the uses recommended by NCCN and those approved by the FDA is especially stark (Appendix 2).

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[11] Chen DT, Wynia MK, Moloney RM, et al. U.S. physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. Pharmacoepidemiol Drug Saf. 2009;18:1094-1100.

[12] Stewart M, Shea M, Audibert C. Data Driven: How oncologists perceive FDA-approved drug labeling compared to major prescribing resources. 2019. Friends of Cancer Research. Available at https://www.focr.org/blog/engaging-innovation/data-driven-how-oncologists-perceive-drug-labeling. Accessed January 22, 2020.

[13] Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of Cisapride: impact of food and drug administration regulatory action. JAMA. 2000;284:3036-3039.

[14] Green AK, Wood WA, Basch EM. Time to reassess the cancer compendia for off-label drug coverage in oncology. JAMA. 2016; 316:1541-1542.

Oxaliplatin 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, as of 2017, 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 approved between 1999 and 2011 had well-accepted off-label uses in disease settings not currently represented on labeling.

Older drugs may be particularly susceptible to outdated product labeling, especially regarding the "effectiveness" portions of labeling, including information relating to dosage and clinical studies. In the case of oncology, the ongoing evolution of information may be particularly important for identifying appropriate uses in different populations, such as pediatrics, or for use of drugs in combination, which is the case for numerous of these older drugs.

Both brand name and generic drug companies have an ongoing responsibility to report safety information to FDA, and the Agency has the authority to order changes relating to new safety information for both brand name and generic drugs.[15] However, as is the case for new uses of a drug, manufacturers of products that will soon lose or have already lost marketing exclusivity or patent protection often lack an incentive to actively maintain up-to-date labeling, aside from signals of serious adverse events. In some cases, brand name manufacturers of older drugs will voluntarily withdraw their products from the market for reasons other than safety or efficacy, leaving only generic manufactured products on the market (if generic versions of the drug exist). This situation is often referred to as a withdrawn reference listed drug or Withdrawn RLD. In these cases, patient access to the drug typically is not a concern due to the availability of multiple generics. However, access to accurate information about the drug can essentially become frozen in time.

Under the 1984 Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA), generic drug labeling necessarily relies on the brand name drug labeling as a matter of product approval. The Hatch-Waxman Amendments established the modern generic drug industry and required "sameness" for generics with the brand-name drug counterpart in all material respects. The statute mandates that generic drug products have the same active ingredients, strength, dosage, indications, and safety labeling as the reference drug. In fact, the Hatch-Waxman statute's whole premise is that generic drugs are materially indistinguishable from their brand-name counterparts, and so naturally must bear labeling that "is the same as the labeling approved for the [brand-name] drug" on which the generic product's approval is based.[16] In enacting the Hatch-Waxman Amendments, Congress provided that FDA cannot approve an abbreviated new drug application (ANDA) if, with certain exceptions (e.g., patent carve-outs), the labeling proposed for the generic drug is not the same as the labeling approved for the listed drug.[17] Those requirements subsequently were incorporated into FDA's regulations.[18]

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[15] See, e.g., U.S. FDA, FDA announces enhanced warnings for immediate-release opioid pain medications related to risks of misuse, abuse, addiction, overdose and death available at https://www.fda.gov/newsevents/newsroom/pressannouncements/ ucm491739.htm.

[16] 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added).

[17] See 21 U.S.C. §355(j)(4)(G); see also 21 U.S.C. §355(j)(2)(A)(v) (requiring that ANDAs include information to show the labeling proposed for the generic drug is the same as the labeling approved for the listed drug).

[18] See 21 C.F.R. §314.94(a)(8) (providing that ANDAs must include labeling that is the same as labeling approved for listed drug and must include [a] statement that the applicant's proposed labeling ... is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section).

The result is that most older drugs have aspects of FDA-approved labeling that need to be modernized to prevent the dissemination of incorrect information and to enable the communication of information pertinent to safe and effective prescribing. 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.[19] Then in 2006, the FDA altered the structure of labeling to make it more user-friendly.[20] 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."[21] Most recently, the FDA Oncology Center of Excellence has launch an initiative called Project Renewal[22] designed to update oncology drug labels that have fallen out of date. Thus far, the oncology experts at FDA have identified 44 candidates of older drugs that would benefit from a labeling review. However, for over a quarter of the drugs identified, the RLD has been withdrawn which prevents label updates from taking place.

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. 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]

In collaboration with numerous stakeholders, Members of this Committee developed a legislative proposal to address the prevalence of outdated labels in cases where the brand name reference listed drug that a generic product relies upon has been withdrawn from the market. In such circumstances, it is essential that FDA manage the review of new clinical data and maintain the sameness requirement, whereby all generic labeling changes at once after an FDA order. The legislation would address this problem by giving the FDA the authority to require updating of labels to reflect new information relevant to the drug and its use. The legislation also determines a process through which the FDA can identify labels to be updated, notice label holders, and allows for a process for label holders to submit modifications to the notice.

Specifically, under the proposed legislation, the FDA may:

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[19] Dissemination of information on unapproved/new uses for marketed drugs, biologics, and devices. Fed Regist. 1998;63:31143.

[20] United States Food and Drug Administration. Guidance for industry: labeling for human prescription drug and biological products—implementing the PLR content and format requirements. Rockville, MD: FDA, 2013.

[21] Prescription drug labeling improvement and enhancement initiative; request for comments and information. Fed Regist. 2013;78:8446.

[22] FDA Oncology Center of Excellence Annual Report. https://www.fda.gov/media/122837/download

[23] US Department of Health and Human Services. Food and Drug Administration Amendments Act of 2007. Public Law 110–85. Effective September 27, 2007. https://www.gpo.gov/fdsys/pkg/ PLAW-110publ85/pdf/PLAW-110publ85.pdf. Accessed February 20, 2018.

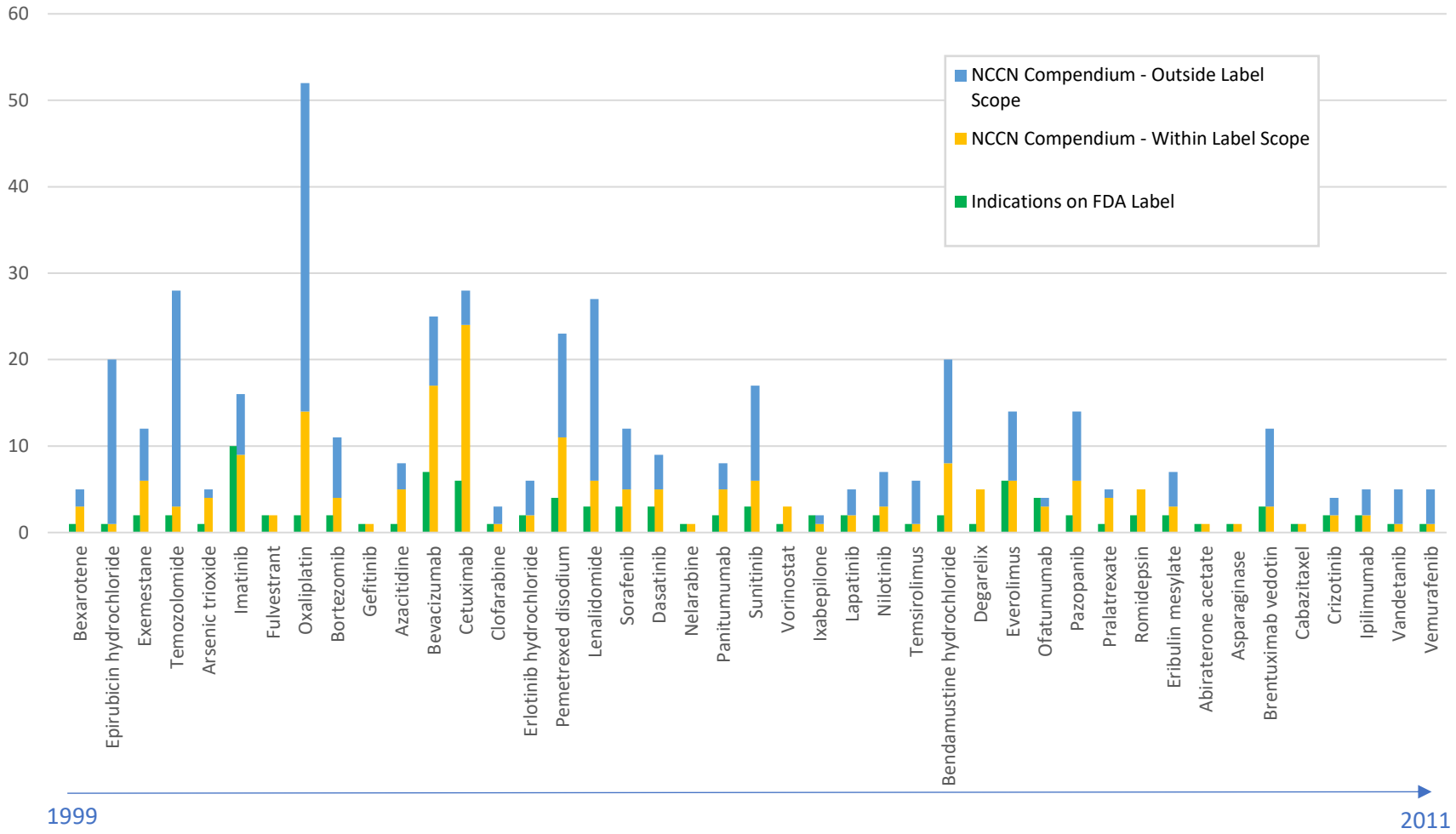
1. Identify one or more drug products for which labeling is missing critical information about drug safety or effectiveness or includes outmoded prescribing instructions and has a withdrawn RLD.
2. Notify the sponsor(s) of drugs identified and proceed if agreement to pursue revised labeling is obtained.
3. Enter into cooperative agreements or contracts with private entities to review the available evidence concerning drugs identified.
4. Seek public input concerning such evidence (including, as determined appropriate by the Secretary, holding public meetings or seeking public comments).
5. Determine, with respect to a drug identified, whether the evidence reviewed is sufficient to meet existing regulatory standards for revising the labeling of the drug.
6. Provide notice to holders of approved applications for a generic version of the drug that:
    a. Summarizes the findings supporting the determination of the Agency that the available evidence is sufficient to meet the standards under section 505 of the FDCA for amending the labeling of the drug as an additional indication for the drug
    b. Describes the determined modifications for the labeling
7. Allow the sponsor of a selected drug to respond to a notice; including any request for further discussion with FDA in order to modify the labeling of the drug in accordance with the statement of the FDA in the relevant notice.

It is important to note that the procedures for making the finalized updates to the generic drug label proposed in the MODERN Labeling Act would be no different than those that generic drug manufacturers use for updating their labels when an active RLD holder submits a supplement or change to their label. This process is familiar, routine, and presents little added burden to generic manufacturers at the value of having more accurate information available about the drug.

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. Not only does labeling contain the most trusted information about drugs, it reflects the basis for each approval decision. 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. For this reason, preserving the accuracy and reliability of labeling may be viewed as tantamount to preserving trust in and the relevance of the entire drug approval system. The MODERN Labeling Act would aid in maintaining up-to-date drug labels for certain generic drugs and restore the relevance of approved labeling to foster greater trust in medical products for physicians and patients.

I, again, thank you for the opportunity to testify on this important topic and look forward to answering your questions.

Appendix 1: Oncology Indications Approved by FDA vs. those Supported by NCCN Compendium, 1999-2011



Oncology Indications Approved by FDA vs. those Supported by NCCN Compendium, 1999-2011

The number of indications listed on FDA-approved labeling was compared to uses supported on the NCCN Drug and Biologics Compendium. The NCCN Compendium is often much more specific than FDA labeling, leading to many uses being listed without necessarily going outside the scope of the label. Drug uses listed on the NCCN Compendium were categorized as either within the scope of FDA labeling or outside the scope. Drug uses categorized outside the scope of the label were considered to be off-label uses.

Appendix 2: Uses of Oxaliplatin Described in FDA Labeling and NCCN Compendia

	FDA	NCCN
	Disease Indications Contained on Label	Disease Indications contained on Compendium
Chronic Lymphocytic Leukemia		✓
Colon Cancer	✓	✓
Esophageal Cancer		✓
Gastric Cancer		✓
Hepatobiliary Cancers		✓
Neuroendocrine Tumors		✓
Non-Hodgkin Lymphoma		✓
Occult Primary		✓
Ovarian Cancer		✓
Pancreatic Cancer		✓
Rectal Cancer[24]	✓	✓
Testicular Cancer		✓

[24] Oxaliplatin is indicated for two colorectal cancer uses on the FDA-approved label.