November 27, 2023

Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
Docket No. FDA–2019–N–5959
5360 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA–2019–N–5959: Medication Guides: Patient Medication Information Proposed Rule

Dear Commissioner Califf:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on the Medication Guides: Patient Medication Information Proposed Rule (Proposed Rule). ACS CAN advocates for evidence-based public policies to reduce the cancer burden for everyone. As the American Cancer Society's nonprofit, nonpartisan advocacy affiliate, ACS CAN is making cancer a top priority for public officials and candidates at the federal, state, and local levels. By engaging advocates across the country to make their voices heard, ACS CAN influences legislative and regulatory solutions that will end cancer as we know it, for everyone. We are providing comments on the proposed rule through the lens of cancer patients.

ACS CAN applauds the U.S. Food and Drug Administration's (FDA) long-standing commitment to ensuring patients can use their prescription drugs safely and effectively. The proposed rule seeks to improve the current system in which patients receive prescription drug information by requiring the creation and distribution of a new type of Medication Guide referred to as Patient Medication Information (PMI) for prescription drugs used, dispensed, or administered on an outpatient basis.

Improving Written Patient Prescription Drug Information

People taking prescription drugs need clear, concise, and easily understood information about the drugs including how to take them and their possible adverse effects. Currently, the information patients receive about their prescription drugs comes from several different sources, the information is presented in different formats, and it is not always consumer friendly. In certain circumstances, for specific drugs or drug classes, FDA requires sponsors to develop FDA-approved information to assist patients in the safe and effective use of their drugs such as through Patient Package Inserts, Medication Guides, and Instructions for Use. According to the FDA, research has shown that under this current system, frequently the information that patients receive is "*duplicative, incomplete, conflicting, or difficult to read and understand and such information is not sufficient to meet the needs of patients.*[1]"

ACS CAN supports FDA's efforts to improve the current system to provide patients with clear, concise, accessible, and useful written prescription drug product information delivered in a consistent and easily understood format. We agree that prescription drug product information may help patients reduce preventable adverse drug events and improve health outcomes. It is important that PMI includes clinically relevant pharmacogenomic (PGx) prescription drug product information. **ACS CAN urges FDA to encourage**

the inclusion of PGx information in FDA-approved PMI under the heading "Important Safety Information" in final guidance for all new and approved new drug applications (NDAs) and biologics license applications (BLAs) when such information can help patients avoid, detect, or quickly address severe adverse effects from known gene-drug interactions.

Written Pharmacogenomic Information

PGx information and testing can help to maximize therapeutic benefits and minimize adverse effects of drugs used for cancer treatment and supportive care. However, the adoption of PGx testing in clinical practice is currently limited by several factors including inconsistencies in drug labeling and patient awareness and education. We have previously commented on FDA draft guidance for industry and the oncology community has developed consensus recommendations to improve the consistency, completeness, and location of PGx information in drug labels (i.e., Prescribing Information).[2,3,4] PGx information can often be found in several of the 17 sections typically found in a drug's FDA-approved Prescribing Information (PI); however, its location and language can vary significantly between products. This information is a vital resource for communicating PGx concerns related to a specific drug. However, FDA-approved PI is written specifically for health care professionals; therefore, the language related to PGx included within PI may not be readily accessible to patients. The proposal for PMI represents an opportunity to provide written PGx information in a format that best meets patients' needs.

The proposed rule would withdraw the current regulations governing Medication Guides described in 21 CFR § 208 after all prescription drug products that had Medication Guides have FDA-approved PMI. However, for many oncology drugs, information about the potential for severe adverse effects from gene-drug interactions for patients with specific gene variations is not currently included in existing FDA-approved patient specific labeling resources like Medication Guides, although this information could help prevent serious adverse effects and meet the scope and purpose described in 21 CFR § 208.1. In one example, the drug fluorouracil can result in increased risk of serious or fatal adverse reactions in patients with low or absent dipyrimidine dehydrogenase (DPD) activity. This warning is reflected in the PI and in FDA's table of Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations,[5,6] yet there is no fluorouracil Medication Guide. If patients are aware that they have deficiencies in an enzyme crucial to a drug's metabolism (such as DPD), they could notify their health care provider who could make adjustments to treatment (e.g., lower dose, switch to a different drug).

A recent survey of 1,155 cancer patients and survivors suggests that there is a low general awareness of PGx testing and current drug information is ineffective in communicating PGx information to patients, yet there is a high expectation of determining treatment based on PGx information.[7] The survey found that 42% of respondents were aware of PGx testing before taking the survey. Most of those (45%) learned about PGx testing from a provider, while just 4% of those aware of PGx testing learned about it in written information about drugs they took. Once aware of PGx testing and its potential to identify risk of a severe reaction in advance of treatment, 70% of respondents would be concerned about being prescribed a drug associated with severe reactions without receiving prior PGx testing. **ACS CAN supports the inclusion of clinically relevant PGx information in the proposed PMI because it would empower patients with information currently missing from Medication Guides and other patient drug labeling resources, which in turn could help prevent serious side effects caused by specific gene-drug interactions.**

Consumer Testing for PMI

Rather than require consumer testing of PMI, FDA is considering the establishment of a publicly available database, potentially through a public-private partnership, of consumer-tested phrases and terms that would assist in the development of written patient materials, including PMI. For many patients, PGx and the terms used to describe it will be new. For example, in an ACS CAN survey of cancer patients and cancer survivors, 44% of respondents were not aware of PGx testing to better understand risk for drug reactions.[7] Furthermore, most of the existing FDA-approved drug information on PGx is written for health care professionals; therefore, some applicants may not have experience in communicating PGx information in a patient- or consumer-friendly format. **ACS CAN supports the establishment of a publicly available database of consumer-tested phrases that would assist in the development of written patient materials, including PGx information to be included in PMI.**

Updating Prescription Drug Information

The proposed rule would require that PMI for NDAs and BLAs be updated when new information becomes available that would cause PMI to become inaccurate, false, or misleading. This provision would require that PMI for abbreviated new drug applications (ANDAs) be updated when the PMI for the reference listed drug (RLD) is updated or the FDA-created template is updated (for ANDAs with withdrawn RLDs). The field of PGx has been rapidly advancing and FDA has recently issued new draft guidance for industry on Pharmacogenomic Data Submissions (FDA-2022-D-2856) intended to facilitate progress in the field of pharmacogenomics and the use of pharmacogenomic data in drug development.[8] Once this guidance is finalized and fully implemented by applicants, new, clinically relevant PGx information may become available and may require existing PMI for NDAs or BLAs be updated. **ACS CAN supports the requirement that PMI for NDAs and BLAs be updated when new PGx information becomes available that would cause PMI to become inaccurate, incomplete, or misleading.**

Waivers

The proposed rule would allow for waivers from one or more of the requirements for PMI if FDA determines that any requirement is inapplicable, unnecessary, impracticable, or contrary to patients' best interests for a particular prescription drug product. One example, given in the proposed rule is a waiver or extension if complying with PMI requirements could contribute to a drug shortage or otherwise prevent patient access to the drug product. **ACS CAN supports waivers or extensions to PMI essential to maintain patient access to their prescription drugs. We also would support waivers to exceed the one-page requirement, if needed, for an applicant to include PGx information.**

FDA considers the one-page requirement a key feature of PMI and rarely envisions granting a waiver to this requirement. We agree that conciseness along with consumer-friendly language will be important to improve readability and comprehension. **However, we urge FDA to allow maximum flexibility and applicant discretion for this requirement, permitting in limited cases waivers of the one-page requirement, to ensure a patient's safe and effective use of their prescription drugs.**

Conclusion

Reducing preventable adverse drug events can improve health outcomes for cancer patients, including PGx-

related adverse events which have led to patient harm and even death.[9] Current FDA-approved information to assist patients in the safe and effective use of their prescription drugs does not address patient information needs as it relates PGx. Likewise, FDA-approved PI is written specifically for health care professionals and is often inconsistent and incomplete. The proposal for PMI represents an opportunity to provide written PGx information in a format that best meets patients' needs and can lead to improved health outcomes by preventing adverse drug events.

Thank you for the opportunity to comment on the Medication Guides: Patient Medication Information Proposed Rule. If you have any questions, please feel free to contact me or have your staff contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science.

Sincerely,

Lisa A. Lacasse, MBA
President
American Cancer Society Cancer Action Network

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[1] Office of Information and Regulatory Affairs; Medication Guides; Patient Information. Accessed at: https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201710&RIN=0910-AH68.
[2] ACS CAN Comments on FDA-2022-D-2856: Pharmacogenomic Data Submissions; Draft Guidance for Industry. Accessed at: https://www.fightcancer.org/sites/default/files/acs_can_comments_fda_pgx_guidance_final.pdf.
[3] ACS CAN Comments on FDA-2022-D-2629: Post-marketing Approaches to Obtain Data on Under-Represented Populations in Clinical Trials; Draft Guidance for Industry. Accessed at: https://www.fightcancer.org/policy-resources/acs-can-comments-fda-draft-guidance-postmarketing-studies.
[4] ACS CAN Pharmacogenomic (PGx) Consensus Recommendations. Accessed at: https://www.fightcancer.org/policy-resources/pharmacogenomic-pgx-consensus-recommendations.
[5] Highlights of Prescribing Information Fluorouracil. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/012209s040lbl.pdf.
[6] FDA Table of Pharmacogenetic Associations Accessed at: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations
[7] ACS CAN Survivor Views on Pharmacogenomics August 2023. Accessed at: https://www.fightcancer.org/sites/default/files/national_documents/s10_polling_summary_pgx.pdf.
[8] U.S. Food and Drug Administration. Pharmacogenomic Data Submissions. Accessed at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacogenomic-data-submissions-0.
[9] Ma WW, Saif MW, El-Rayes BF, Fakih MG, Cartwright TH, Posey JA, King TR, von Borstel RW, Bamat MK. Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. Cancer. 2017 Jan 1;123(2):345-356. doi: 10.1002/cncr.30321. Epub 2016 Sep 13. PMID: 27622829; PMCID: PMC5248610