



June 20, 2023
Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
Docket No. FDA-2022-D-2856
5360 Fishers Lane
Room 1061
Rockville, MD 20852

**Re: FDA-2022-D-2856: Pharmacogenomic Data Submissions; Draft Guidance for Industry;
Availability 88 FR 16640 (March 20, 2023)**

Dear Commissioner Califf:

The American Cancer Society Cancer Action Network (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. ACS CAN appreciates the opportunity to comment on Pharmacogenomic Data Submissions; Draft Guidance for Industry (Draft Guidance).

Pharmacogenomics in Oncology

The field of pharmacogenomics (PGx) has rapidly advanced since the U.S. Food and Drug Administration (FDA) published final guidance on "Pharmacogenomic Data Submissions" in 2005. The advent and utilization of high-throughput sequencing platforms have made it easier to generate and use genomic data during drug development. As defined in the draft guidance, pharmacogenomics, "*the study of variations of DNA and RNA characteristics as related to drug response*" has numerous applications in the field of oncology. In oncology, advancements in PGx have led to testing that can inform personalized treatments to maximize therapeutic benefits and minimize adverse effects of drugs used for cancer treatment and supportive care.

Testing of tumors for somatic (i.e., acquired) variants is now the standard of care for several cancer types and there are several examples illustrating how germline (i.e., inherited) variation can influence the effectiveness and safety of drugs in oncology. Despite the benefits of PGx testing, greater adoption in clinical practice, particularly adoption of PGx testing of germline variants, is limited by several factors including inconsistencies in drug labeling and payor coverage, inadequate evidence synthesis and available guidelines, and insufficient provider and patient awareness and education. FDA plays a pivotal role in facilitating progress in the field of PGx in oncology through guidance on the use PGx data in submissions.

Ambiguity Between Reporting and Conducting Studies

The draft guidance makes clear that when study data related to PGx exists it should be included in either detailed or summary form. It is less clear whether the actual studies are required to be included as well. Clearly when a sponsor intends to use a biomarker on the label, to determine the study population, or in the analysis, the studies and the associated data reporting are required. But in other cases, such as identification of risk or subgroup differences, the guidance indicates that "findings" from studies must be reported, but it is ambiguous whether this means that sponsors are compelled to conduct such studies and submit data, or that

if such studies are conducted then data must be reported. The difference between compelling that studies be conducted and reported versus compelling reporting whenever studies are voluntarily conducted is an important distinction. We believe the intention is to compel studies and reporting but believe the language should be clearer in that regard.

Submission of Pharmacogenomic Data Under IND Regulations

We support the recommendation in the draft guidance that if PGx study findings support the use of a genomic biomarker in the design, conduct, or analysis of planned clinical trials that this be reported to the FDA with detailed information about such findings and that these reports be submitted in the IND under the Previous Human Experience section. A summary of previous human experience should include studies with evidence suggesting potential PGx subgroup differences. Sponsors should ensure that research plans be formulated to explore potential differences, whether through recruiting appropriate trial populations or other definitive methods.

Submission of Pharmacogenomic Reports and Data Under NDA and BLA Regulations

We support the recommendation in the draft guidance that if PGx study data is to be used in drug labeling, data should be reported as subject-level data in a detailed report, including *“data pertaining to pharmacogenomic biomarkers that inform labeling because that data pertain to selecting patients for clinical trials (whether enrollment is limited to or stratified by the biomarkers), determining dosing and administration, or informing drug-drug interactions (or lack thereof).”* We request that FDA recommend sponsors also include data pertaining to pharmacogenomic biomarkers *“informing adverse drug-gene interactions”* established in PGx study data.

Demographic reporting data

The draft guidance suggests reporting the demographics of the overall and genotyped populations. It is important to include more detailed ancestry information where possible. PGx variants differ significantly based on ancestry rather than traditional racial or ethnic categories, which are social constructs. For example, HLA allele frequencies between different groups all identified under the umbrella term of “Asian” may show more variation than between specific Asian subgroups and non-Asian groups. Similarly, PGx alleles may vary significantly between African populations from different parts of the continent. These examples demonstrate the risk of sampling one ancestral subgroup that belongs to a broader racial category and making erroneous assumptions about representativeness of that subgroup to the larger demographic category. Reporting of PGx data, therefore, should be as granular as possible with respect to ancestry, it should acknowledge limitations of representation, and be augmented with externally available information on variant prevalence in different ancestral groups.

Role of Labels

While separate FDA drug labeling guidance exists and is not the focus of this draft guidance, FDA-approved drug labels are an important resource for PGx information that assists health care providers in selecting the right drug at the right dose for the right patient. PGx information on drug labels originating from pharmacogenomic data submissions can be found throughout the 17 sections typically found in an FDA-approved drug label. Despite FDA guidance recommending placement of PGx information, the location where it appears and format in which it is presented in a label can be inconsistent, even between drugs with identical active ingredients or drugs with the same drug-gene interactions. We urge FDA to update labeling

guidance, to encourage greater consistency related to location and format of PGx information in FDA-approved drug labels.

Thank you again for the opportunity to provide comments, and we look forward to working with you to facilitate the generation and use of PGx data during drug development. If you have any questions, please do not hesitate to contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science.

Sincerely,

A handwritten signature in black ink, appearing to read "Lisa A. Lacasse". The signature is fluid and cursive, with a long horizontal stroke at the end.

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