



**ASSOCIATION FOR MOLECULAR PATHOLOGY**

*Providing global expertise in molecular testing that drives patient care*

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August 28, 2020

Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Submitted electronically via <https://www.regulations.gov/>

RE: Docket No. FDA– 2020–N–1046 for Use of Codeine Containing Analgesics in Children Under 12 Years of Age Subsequent to CYP2D6 Genetic Testing

To Whom It May Concern:

Thank you for the opportunity to submit these comments in response to your request for information on the “Use of Codeine Containing Analgesics in Children Under 12 Years of Age Subsequent to CYP2D6 Genetic Testing.” The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,500 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

AMP believes that pharmacogenomic information may play a critical role in prescribing decisions and that all patients, regardless of age, should have access to appropriate pharmacogenomic testing to inform treatment and other healthcare decisions. AMP is pleased that FDA recognizes the importance of pharmacogenomic variation, specifically *CYP2D6* in codeine response. Pharmacogenetic testing of *CYP2D6* informs a physician in such a way to enable them to use codeine in children with difficult-to-treat pain, the majority of whom (80%) will not have *CYP2D6* functional variation. In some children with intractable pain, such as those with sickle cell anemia, there are not many pain management options.

In the request for information, the FDA describes its rationale for considering this policy change as being based on a 2017 Citizen’s Petition calling on the Agency to revisit the labeling for codeine and its reference to *CYP2D6* testing for pediatric patients. FDA states,

“In FDA’s view, if Petitioners’ proposed labeling were adopted, a *CYP2D6* genotype/phenotype determination would be essential for the safe and effective use of codeine drug products. Thus, under the Agency’s authorities governing prescription drug labeling, the approved labeling of codeine-containing analgesics would also need to specify that, with respect to use in children under 12 years of age, the products are intended for use only subsequent to the necessary genotype/ phenotype determination using an appropriate, FDA-authorized companion diagnostic device.”

AMP is very concerned about the FDA’s statement indicating that if the Agency updated the label as proposed by the Citizen’s Petition, the Agency would add language requiring the use of an FDA-authorized companion diagnostic device. Currently there are no FDA-authorized *CYP2D6* companion diagnostic tests for codeine, although there is one *CYP2D6* test that has FDA-clearance (but not as a companion diagnostic) for this specific intended use. However, there are currently more than 100 accredited laboratories that offer accurate, validated *CYP2D6* tests, with some of them offering tests with better allele coverage than the FDA-cleared test. Narrowing a drug label to one authorized device would have detrimental consequences in patients’ access to *CYP2D6* testing. Not only could it potentially result in lack of access to the test outright due to factors such as insurance coverage, but it could potentially lead to patient harm by restricting their access to needed analgesic medications.

Further, we strongly encourage the Agency to also consider the Citizen’s Petition submitted in 2020<sup>1</sup> on behalf of the Coalition to Preserve Access to Pharmacogenomics that questioned FDA’s procedures used to set existing regulatory policy for pharmacogenomics and appropriateness of enforcement action taken in the preceding year. AMP submitted a statement in support of this petition<sup>2</sup> and believes that this narrow labeling as proposed by the FDA runs afoul of the same concerns named in the Coalition’s Citizen Petition. We request that the Agency reach a decision on both petitions, and comply with requests made by AMP in its comments, as they both have significant implications for patient access to pharmacogenomic tests and information. Moreover, labels should not be narrowed to only FDA-authorized companion diagnostic tests, especially given the recent statement by Health and Human Services (HHS)<sup>3</sup>, which states that FDA will not require premarket review of laboratory developed testing procedures absent notice-and-comment rulemaking.

As an organization comprised of leaders in the field of molecular pathology, AMP is also pleased to offer its technical expertise to answer these specific questions posted under *Topic 2: CYP2D6 Genotyping Tests*. AMP engaged its expert members and partnered with pharmacogenomics thought leaders to develop practice guidelines that assist molecular pathology professionals in incorporating innovation appropriately into practice based on scientific evidence. Specifically, AMP’s subject matter expert Pharmacogenomics Working Group is in the process of developing consensus, evidence-based recommendations to aid in the design, validation and interpretation of clinical *CYP2D6* genotyping tests. The new guideline will be the fourth in a series of reports intended to facilitate testing and promote standardization for frequently used pharmacogenetic genotyping assays, establishing a two-

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<sup>1</sup> FDA-2020-P-0152-0001

<sup>2</sup> [https://www.amp.org/AMP/assets/File/advocacy/AMP\\_Response\\_to\\_PGx\\_Citizen\\_Petition\\_5-4-2020.pdf?pass=97](https://www.amp.org/AMP/assets/File/advocacy/AMP_Response_to_PGx_Citizen_Petition_5-4-2020.pdf?pass=97)

<sup>3</sup> <https://www.hhs.gov/coronavirus/testing/recission-guidances-informal-issuances-premarket-review-lab-tests/index.html>

tier categorization of alleles that are recommended for inclusion in these clinical assays. Using criteria such as allele frequencies in different populations and ethnicities, the availability of reference materials and functional impact, the Working Group will provide a recommended minimum set of alleles and their defining variants that should be included in all clinical *CYP2D6* genotyping tests (Tier 1), along with a list of optional alleles (Tier 2) that do not currently meet one or more of the criteria for inclusion in Tier 1. Tier recommendations are meant to be a reference guide and not to be interpreted as a restrictive list. These new *CYP2D6* recommendations should be implemented together with other clinical guidelines such as those issued by the Clinical Pharmacogenetics Implementation Consortium, which focus primarily on the interpretation of pharmacogenetic test results and therapeutic recommendations for specific drug-gene pairs.

### **3. Describe your experience with interpreting CYP2D6 genotyping test results and using those results to make drug prescribing decisions.**

In AMP's 2019 position statement titled, "Best Practices for Clinical Pharmacogenomic Testing,"<sup>4</sup> AMP states that a pharmacogenomic test report should be comprehensible by healthcare providers without medical genetics or pharmacogenomics training and include the interpretation of the findings, the significance of the results, as well as the limitations of the test. AMP believes that pharmacogenomic testing provides the greatest clinical benefit to patients when the healthcare provider is able to easily determine when an actionable prescribing change and/or treatment decision is indicated by a patient's genotype. Therefore, AMP strongly supports the practice of including the following information in the test report within the interpretation of the findings and the significance of the pharmacogenomic test results:

- A statement of the metabolizer status determined by the genotype for the genes that affect drug metabolism;
- A list of the drugs for which responsiveness may be affected by the genotype;
- A generalized statement to alert healthcare providers when alternate dosage or drug treatment may be considered based on the results;
- A list of resources and references that the healthcare provider can utilize to learn more about the genotyping result, the drug-gene association, and how to incorporate the result into actionable decisions.

AMP believes this information will enable treating physicians to easily and accurately integrate pharmacogenomic information into medication prescribing decisions and hence, should be included in every test report.

### **4. For a CYP2D6 genotyping test to appropriately identify patients who can safely receive a codeine-containing drug product, what is the minimum genotyping accuracy and minimum acceptable coverage of the currently known genotypes that typically result in a poor metabolizer or ultra-rapid metabolizer phenotype?**

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<sup>4</sup> [https://www.amp.org/AMP/assets/File/position-statements/2019/Best\\_Practices\\_for\\_PGx\\_9\\_4\\_2019.pdf?pass=29](https://www.amp.org/AMP/assets/File/position-statements/2019/Best_Practices_for_PGx_9_4_2019.pdf?pass=29)

First, evidence for clinical validity should be demonstrated before a pharmacogenomic test is offered to patients to inform treatment decisions, which is the same standard as any laboratory test used in clinical care. Such evidence may be established and/or demonstrated through peer-reviewed literature, clinical practice guidelines, and/or FDA drug labels.

Additionally, best laboratory practices to establish test accuracy should be utilized and all test validation reports should provide information on the assay's analytical sensitivity and specificity. Genotyping accuracy and the characteristics of the test should fit the clinical situation as well. Furthermore, the pharmacogenomic testing provider must comply with the CLIA statute and regulations, as is required for all other clinical laboratory tests, including by having documented analytical validity, a robust quality management system, and employing appropriately licensed or credentialed laboratory personnel. Test results must be verified under the supervision of, and interpreted and reported by, board-certified molecular laboratory professionals. Additionally, as required by CLIA, details regarding analytical methodology, validity, and quality should be readily available to the healthcare providers upon request.

With regard to minimum acceptable coverage, as stated above, AMP's subject matter expert Pharmacogenomics Working Group is currently developing consensus, evidence-based recommendations that include a two-tier categorization of alleles that are recommended for inclusion in these clinical assays. Using criteria such as allele frequencies in different populations and ethnicities, the availability of reference materials and functional impact, the Working Group will provide a recommended minimum set of alleles and their defining variants that should be included in all clinical *CYP2D6* genotyping tests (Tier 1), along with a list of optional alleles (Tier 2) that do not currently meet one or more of the criteria for inclusion in Tier 1. The Tier 1 alleles encompass AMP's recommended minimum acceptable coverage of the currently known genotypes and include detection of the most common *CYP2D6* alleles that are associated with safety and efficacy of codeine.

**5. Regarding detection of ultra-rapid metabolizers, what is the type of test output that would be needed for copy number? Is a result of "duplication present" (i.e., more than one copy) sufficient, or is specific quantitation of the number of copies needed?**

AMP believes that detection of "duplication present", in the absence of genetic variants that are associated with no or reduced function, is sufficient in the test report, keeping in mind that the evidence of the clinical impact of multiple duplication events is still evolving and the consensus on the interpretation of the evidence may also change over time. Detection of gene duplication is essential for determining ultra-rapid metabolizer status; whereas quantitation of the number of gene duplications (i.e., more than one copy) would not result in different treatment recommendations at the present time.

We hope that this information and expertise is helpful to your work in enabling safe and appropriate pediatric access to codeine containing analgesics. Thank you for your consideration and please do not hesitate to contact Tara Burke at [tburke@amp.org](mailto:tburke@amp.org) if AMP may be of further assistance.

Sincerely,

Karen E. Weck, MD, FCAP  
President, Association for Molecular Pathology