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August 11, 2023

Re: Docket No. FDA-2017-P-6918

Dear Dr. Caudle:

This letter responds to your citizen petition, docket no. FDA-2017-P-6918 (Petition),[1] in which you request that the Food and Drug Administration (FDA or Agency) amend the current contraindication in codeine-containing analgesics[2,3] to read:

> Codeine should not be used to treat pain or cough in children younger than 12 years with the following exception: Outside the setting of post-tonsillectomy or adenoidectomy, codeine may be prescribed for pain management in children younger than 12 years old who are **known CYP2D6 normal metabolizers (NMs) or CYP2D6 intermediate metabolizers (IMs)** based on pharmacogenetic testing that includes *CYP2D6* copy number or gene duplication detection.

(Petition at 1, emphasis in original). For the reasons that follow, your Petition is denied.

I. Background

A. Codeine and CYP2D6

Codeine-containing analgesic products, which contain the opioid codeine, are generally indicated

[1] In preparing the response to this citizen petition, FDA also considered comments received in response to a *Federal Register* notice pertaining to the issues raised in your petition; see 85 FR 38901-38905 (June 29, 2020).

[2] Given the contents of your petition, particularly your emphasis on sickle cell disease patients in need of analgesia for intermittent pain crises, FDA understands your request to be limited to changing the indication of codeine-containing analgesics, rather than all codeine-containing products, regardless of indication.

[3] For example, in the Boxed Warning, the current contraindication reads as follows (see, e.g., https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022402s014lbl.pdf):

> Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children
> Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a *CYP2D6* polymorphism [see Warnings and Precautions (5.4)]. Codeine Sulfate Tablets are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Contraindications (4)]. Avoid the use of Codeine Sulfate Tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.

for the relief of mild to moderate pain where the use of an opioid analgesic is appropriate and for which alternative treatments are inadequate. These products are marketed either as single-ingredient codeine (a Controlled Substances Act (CSA) Schedule II drug) products or in combination with other non-opioid active ingredients, such as acetaminophen (the combination being CSA Schedule III or V drugs, depending on the amount of codeine the product contains); most of the use is in the form of combination products.[4]

Codeine is partially metabolized to morphine, its most potent analgesic metabolite, through the CYP2D6 pathway. CYP2D6 is a polymorphic enzyme (i.e., the enzyme exists in different forms that are determined genetically). There is a high degree of variability in the rate and extent to which codeine is metabolized because of underlying genetic differences in CYP2D6 activity. Because of this variability, depending on CYP2D6 activity, patients may be at risk for therapeutic failure (i.e., failure to achieve sufficient analgesia in "poor metabolizers") or at risk for opioid-related toxicity, including respiratory depression and death (because "ultra-rapid metabolizers" metabolize standard doses of codeine into high circulating levels of morphine). Although there are multiple genetic tests for *CYP2D6* polymorphisms, these tests vary in sensitivity and identification of allele variants, and labs do not necessarily follow a standardized approach to determining, for example, the genetic threshold at which a patient may be classified as a poor, normal/intermediate, or ultra-rapid metabolizer. To date, there is no FDA-cleared, approved or authorized genetic test for *CYP2D6* polymorphisms that is intended for use in making treatment decisions regarding codeine prescribing.

Given the variability in patient metabolism of codeine, the safety of codeine use in children – particularly the risk of life-threatening or fatal respiratory depression in ultra-rapid metabolizers – has been a long-standing concern. Over the past several years, FDA has updated the labeling for codeine-containing prescription drug products multiple times regarding the risk of respiratory depression as a result of *CYP2D6* polymorphism.[5] Consequently, codeine-containing analgesic products approved by FDA are currently contraindicated in children under 12 years of age. This is consistent with decisions made by other regulatory authorities, such as the European Medicines Agency and Health Canada.[6]

B. Regulatory Framework: Contraindications

The "Contraindications" section of drug labeling "must describe any situations in which the drug

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[4] There are also codeine-containing products indicated for the relief of cough, which contain a combination of codeine with other active ingredients in prescription products for cough and symptoms associated with upper respiratory allergies or common cold; however, FDA required removal of the pediatric cough/cold indications from the approved labeling of prescription codeine cough/cold products in January 2018. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-labeling-changes-prescription-opioid-cough-and-cold

[5] The use of codeine in children, and the labeling of codeine-containing analgesics for pediatric use, have a long and complex history. FDA has provided a thorough synopsis of that history in its *Federal Register* notice of June 29, 2020 (see 85 FR 38901-38905 (June 29, 2020)), the contents of which are incorporated by reference herein.

[6] See, e.g., https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php; https://www.ema.europa.eu/en/documents/referral/codeine-article-31-referral-codeine-not-be-used-children-below-12-years-cough-cold_en.pdf; https://www.ema.europa.eu/en/medicines/human/referrals/codeine-containing-medicines#:~:text=Codeine%2Dcontaining%20medicines%20should%20only,depression%20associated%20with%20codeine%20use.

should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit."[7] This includes:

> use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable.[8]

FDA's Guidance for Industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011) further specifies that a contraindication would be appropriate where "[t]he risk of the adverse reaction[, …] based on both [its] likelihood and severity […], outweighs any potential benefit to any patient" and "[t]he causal relationship between exposure to the drug and the adverse reaction is well established."[9] This applies to circumstances in which the patient is hypersensitive to the drug,[10] or where the adverse event occurs when the drug is used "in the presence of a comorbid condition or coexistent physiological state" – of which CYP2D6 poor metabolizer status is given as an example.[11]

II. Discussion

The Petition sets forth the following arguments in support of its request (1) "Pharmacogenetic testing can identify which patients may safely receive and benefit from codeine"; (2) "Alternative opioid analgesics also present risks to pediatric patients"; (3) "*CYP2D6* testing is available by Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratories"; (4) "Pre-emptive *CYP2D6* testing has already been shown to inform the safe and effective use of codeine to treat pediatric pain, including in children under the age of 12"; (5) "Codeine in combination with acetaminophen is currently the only Drug Enforcement Administration (DEA) Schedule III opioid analgesic, which allows refills and verbal prescriptions"; and (6) "Codeine is an important analgesic for pediatric patients with acute and chronic pain, including those with sickle cell disease." As explained below, FDA does not find these arguments persuasive.

FDA approves new drugs for prescription use with labeling that, consistent with our regulations, contains information necessary for the safe and effective use of the drug,[12] and includes contraindications when the risks of use in a particular population, or in particular circumstances,

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[7] 21 CFR 201.57(c)(5).

[8] Id.

[9] Guidance for Industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011), https://www.fda.gov/files/drugs/published/Warnings-and-Precautions--Contraindications--and-Boxed-Warning-Sections-of-Labeling-for-Human-Prescription-Drug-and-Biological-Products-%E2%80%94-Content-and-Format.pdf p. 8.

[10] Id. at p. 10.

[11] Id. at p. 9. The guidance further notes that contraindicating a drug in CYP2D6 poor metabolizers should be used only when the dose of the drug could not be appropriately adjusted. See id., fn. 6. The guidance does not recommend any such considerations for CYP2D6 ultra-rapid metabolizers.

[12] See 21 CFR 201.56(a)(1).

clearly outweigh the benefits.[13] Based on review of the scientific literature, adverse events, and other relevant information, in FDA's view, the Petition's proposed change to codeine labeling would still leave children under the age of 12 who meet the *CYP2D6* genotype criteria at substantial risk of respiratory depression. It also may increase codeine adverse events caused by medication errors and off-label use by prescribers. As discussed below, for codeine analgesic use in children under age 12, the Agency is concerned about the sensitivity of, and consistency among, available *CYP2D6* tests (none of which are approved for the contemplated use) and whether the wide range of clinicians caring for these children can reliably and accurately predict patient outcomes based on those tests. Particularly given the serious consequences of error in this vulnerable population, FDA denies your request to change the pediatric contraindication for codeine-containing analgesics.

A. Substantial Risks to Patients Under Age 12 Remain, Even with *CYP2D6* Testing

Fundamental to your request, is your assertion that "[p]harmacogenetic testing can identify which patients may safely receive and benefit from codeine" (Petition at 3). The Agency acknowledges that pharmacogenetic testing is valuable in certain circumstances, particularly when the tests are interpreted by experts, and can be a useful tool in tailoring prescribing decisions to patients. However, the limitations and variability of available *CYP2D6* tests, none of which FDA has approved for the contemplated use, is such that safe use of codeine in patients under age 12 cannot be assured simply because they have been categorized as "normal" or "intermediate" metabolizers.

1. Testing Variability

As noted previously, to date, there is no FDA-cleared, approved or authorized genetic test for *CYP2D6* polymorphisms that is intended for use in making treatment decisions regarding codeine prescribing. FDA is aware nevertheless of several available CYP2D6 tests. Significant variability exists in laboratory testing for *CYP2D6* alleles, particularly in terms of assigning phenotype based on allele variations.[14] Some tests do not test for some *CYP2D6* rare variants or allele duplications.[15] *CYP2D6* tests are not standardized and it is possible that a rare variant or gene duplication may not be detected; thus, a patient with such a genotype may be characterized

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[13] See 21 CFR 201.57(c)(5).

[14] See Pratt, Victoria M., et al., "Characterization of 137 Genomic DNA Reference Materials for 28 Pharmacogenetic Genes: A GeT-RM Collaborative Project," J Mol Diagn. 2016 Jan;18(1):109-23.

[15] According to the Genetic Testing Registry (GTR) (see https://www.ncbi.nlm.nih.gov/gtr/), as of October 24, 2022, 65 *CYP2D6* tests are available in the United States that are performed in CLIA-accredited laboratories (note that information submitted to GTR is not independently verified and may have been updated). These tests have varying intended uses (e.g., some of the tests listed are intended for therapeutic management of specific diseases, rather than general screening), and varying sensitivities – e.g., at least 22 of these tests appear to be able to be used to perform a CYP2D6 gene deletion/duplication analysis, which may improve the likelihood of identifying CYP2D6 ultra-rapid metabolizers. Tests that may be used for *CYP2D6* genotyping have been cleared by FDA (i.e., xTAG CYP 2D6 Kit v3, Roche AmpliChip CYP450 microarray, 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports); however, these tests are not intended for use in identifying patients who may safely be treated with codeine (https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm330711.htm).

as a normal metabolizer by default.[16] Some tests also may report the *CYP2D6* genotype (e.g., *CYP2D6*4/*10*) without a corresponding phenotypic classification (e.g., CYP2D6 intermediate metabolizer), further diminishing the utility of such tests where no experts are available to interpret the results. The proportion of patients who are ultra-rapid metabolizers varies among ethnic groups – ranging from 1% to 7% of patients,[17] but noted to be up to 29 percent in one studied group of Ethiopian patients[18] – and the consequences of testing errors may be significant, not only on a per-patient basis, but also on a population basis.

2. Imprecise Genotype-Phenotype Correlation

In addition to concerns about the sensitivity of a given test, predicting a patient's phenotype based on genotype, particularly when that genotype is uncommon, can be challenging. There is wide variability in CYP2D6 activity, and it is not clear that patient classification based on *CYP2D6* genotype – even assuming the genotype is accurately identified, which, as discussed above, may not always occur – reflects that patient's precise capacity for CYP2D6 activity. For example, the range of CYP2D6 activity in normal/intermediate metabolizers has been noted to overlap with the range of CYP2D6 activity in ultra-rapid metabolizers. Therefore, as FDA explained in its February 20, 2013 Drug Safety Communication, the CYP2D6 activity of a patient classified as a normal/intermediate metabolizer may, in fact, be similar to that of an ultra-rapid metabolizer.[19] If prescribing decisions are made based solely on that patient's reported metabolizer status, the result could be a substantial risk of respiratory depression and toxicity.

In your Petition, you discuss a study from Gammal, et al. (Gammal study), regarding use of pre-prescribing *CYP2D6* testing in pediatric patients at St. Jude Children's Research Hospital. In the system described in the Gammal study, the hospital established a step-by-step process integrated into a patient's electronic health record, intended to guide the action of clinicians who prescribe codeine. The process involved:

1. A pre-test alert to prescribers of codeine, indicating that a patient does not have *CYP2D6* genotype information on file;
2. Patient classification as one of several phenotypes (extensive (normal) metabolizer, intermediate metabolizer (i.e., less than normal metabolism), poor metabolizer (i.e., little or no metabolism), ultra-rapid metabolizer (i.e., more than normal metabolism), possible ultra-rapid metabolizer, or possible intermediate metabolizer, or — in patients with a complex *CYP2D6* hybrid structure with indeterminate allele function — an unassigned

[16] See Pratt, Victoria M., et al., "Characterization of 137 Genomic DNA Reference Materials for 28 Pharmacogenetic Genes: A GeT-RM Collaborative Project," J Mol Diagn. 2016 Jan;18(1):109-23.

[17] See "FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death" (August 15, 2012) (available at http://wayback.archive-it.org/7993/20170112031654/http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm#table).

[18] See Aklillu E, Persson I, Bertilsson L, Johansson I, Rodrigues F, Ingelman-Sundberg M. Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. J Pharmacol Exp Ther 1996; 278:441-6.

[19] See "FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy – Additional Information for Healthcare Professionals" (Feb. 20, 2013) (available at http://wayback.archive-it.org/7993/20170112031640/http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm).

phenotype) for those patients who agreed to *CYP2D6* genotyping;
3. A post-test alert to those who had prescribed codeine, telling them when a given patient's genetic test results suggested they were ultra-rapid metabolizers or possible ultra-rapid metabolizers; and
4. A suggestion of alternative analgesics to prescribe.

Gammal and colleagues reported that, after implementation of this genetic testing and prescription alert system, codeine prescriptions went down, and no severe adverse events because of codeine toxicity were reported. You cite this study as evidence that "using CYP2D6 to guide codeine prescribing for pediatric pain outside the setting of post-AT (e.g., sickle cell disease) is feasible and enables the safe and effective use of codeine in patients who are most likely to benefit and least likely to experience toxicity (i.e., CYP2D6 NMs and IMs)."[20]

As an initial matter, we note that the study does not include a comparator arm, which would have strengthened its conclusions; for example, without having comparator data, it is possible to interpret that the reduction in codeine prescribing could be due in part to the general trend away from prescribing codeine in pediatric patients over the course of the study (2013-2015). Perhaps even more significantly, however, the experiences detailed in the Gammal study cannot be generalized to other centers in which the majority of pediatric pain patients – particularly patients who live in areas far from major medical institutions – will be treated. First, the level of assay sensitivity of the tests in the Gammal study does not necessarily reflect the level of assay sensitivity of available tests (see discussion above). Second, although the records integration and prescriber guidance processes available at St. Jude Children's Hospital may exist in other specialty care centers, many other clinical points of care do not use similarly sophisticated systems. Without the easy access to patient information and specialized systemic guardrails for prescribing decisions, the risks of adverse events are likely to increase. And third, the patients at care centers such as St. Jude Children's Hospital (e.g., children with more complex medical needs, receiving longer-term care) are not likely to reflect the broader population of patients for whom codeine-containing analgesics may be prescribed (e.g., patients with acute pain from injury, when pre-emptive genotyping is extremely unlikely to have been conducted).[21] Therefore, this study has limitations and its results cannot be applied to the general clinical practice where codeine-containing analgesics may be prescribed.

3. Inconsistent Test Access and Clinician Experience

For all treatment decisions, a patient's clinician must have the knowledge and the resources not only to order the necessary tests before initiating treatment, but also to review the results and correctly predict the patient's needs and the likely outcome of the treatment in question. Responses to FDA's *Federal Register* notice of June 29, 2020, however, suggest that many clinicians do not enjoy the same level of access to, or experience with, the type of genetic testing

[20] Petition at 4.

[21] For those patients experiencing acute pain because of injury or other short-lived diseases or conditions, it may not be feasible to order a genetic test, await results, and then consult a clinician or genetic counselor with the experience necessary to make a prescribing recommendation. In an emergency room setting, for example, there may rarely be time to undertake such a complex process when clinical priorities are patient triage, stabilization, and symptom relief.

described in the Gammal study for purposes of prescribing medications.[22] This is a particularly noteworthy limitation when such testing is proposed to be used "off-label," as there is no FDA-cleared, approved or authorized genetic test for CYP2D6 polymorphisms that is intended for use in making treatment decisions regarding codeine prescribing. Against a backdrop of inconsistent testing and variable prescriber experience, changing the contraindication as Petitioners suggest may ultimately result in more patients put at risk than would benefit.

Notably, a change in contraindication to permit "normal" or "intermediate" metabolizers under the age of 12 to be prescribed codeine may also increase adverse events because of increased prescribing in the absence of genetic testing. A labeling change permitting "normal" metabolizers to safely take codeine may create a false sense of security in clinicians who have no reason to suspect that their patients – even untested ones – are anything but "normal." Particularly where barriers to testing are high, and there is pressure to alleviate patient pain quickly and conveniently, clinicians may make prescribing decisions based on statistical likelihood of a "normal" genetic status, to the detriment of patient safety. For example, comments on FDA's June 29, 2020 Federal Register notice from the Society for Pediatric Pain Medicine and the Society for Pediatric Anesthesia jointly noted similar concerns, stating that adding exceptions to the contraindication may lead to wider use of codeine in pediatric patients than the limited circumstances proposed by the Petitioner, even potentially without the needed genotype testing.[23]

4. Safety Concerns Beyond CYP2D6 Phenotype

The Agency acknowledges that a patient's CYP2D6 phenotype can help predict therapeutic failure and toxicity from the use of codeine. Nevertheless, as discussed above, *CYP2D6* testing, particularly in the absence of expert interpretation, is not always an adequate identifier of CYP2D6 phenotype – and CYP2D6 phenotype is not the only patient characteristic that may influence the risk of respiratory depression. Although *CYP2D6* is the most-studied gene involved in codeine metabolism, functionally important variants of other genes such as UGT2B7 have also been shown to influence this metabolic pathway,[24] though their effects on codeine toxicity and therapeutic failure have not been conclusively demonstrated in humans.[25]

In addition, while you do not propose to alter the contraindication for patients undergoing

[22] See, e.g., comments at FDA-2020-N-1046-0004 ("Very few pediatricians have experience interpreting CYP2D6 genotyping test results."); -0005/-0006 ("Few pediatric pain physicians or anesthesiologists report using genotype testing routinely."); -0010.

[23] See FDA-2020-N-1064-0005 and -0006 ("We fear that the recommendation for testing will be ignored by prescribers, leading to widespread use of codeine again.").

[24] See generally, e.g., Sawyer, Michael B., et al., "A pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine" *Clin Pharmacol Ther*. 2003 Jun;73(6):566-74; Darbari, DS, *et al.*, "UGT2B7 promoter variant -840G>A contributes to the variability in hepatic clearance of morphine in patients with sickle cell disease," *American Journal of Hematology*, 01 Mar 2008, 83(3):200-202; Innocenti, F., et al., "Single nucleotide polymorphism discovery and functional assessment of variation in the UDP-glucuronosyltransferase 2B7 gene," *Pharmacogenetics and Genomics*, 01 Aug 2008, 18(8):683-697; Lötsch, Jörn, et al., "Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives," *Clin Pharmacokinet*. 2004;43(14):983-1013.

[25] Lötsch, Jörn, et al., "Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives," *Clin Pharmacokinet*. 2004;43(14):983-1013.

tonsillectomy/adenoidectomy, FDA has noted that obstructive sleep apnea, obesity, concomitant use of other medications that cause respiratory depression, and severe pulmonary disease have all been identified as increasing a patient's likelihood of experiencing respiratory depression with codeine.[26] For example, in a study by Kelly et al., pediatric tonsillectomy patients with obstructive sleep apnea were shown to be more sensitive to the *respiratory* depressant effects of morphine, codeine's main active metabolite, than were pediatric patients without obstructive sleep apnea.[27] For a young patient cohort, then, physiological conditions other than CYP2D6 activity may be important sources of risk – and focusing on *CYP2D6* test classification may give clinicians a false sense of security in prescribing codeine to patients.

B. Codeine's Role in the Treatment of Pediatric Pain

Although Petitioners contend that "codeine is an important analgesic for pediatric patients with acute and chronic pain, including those with sickle cell disease,"[28] FDA is not aware of, and the Petition does not cite to, evidence in support of this statement, or evidence that "national guidelines recommend codeine as a front-line drug for the management of pain in individuals with [sickle cell disease], and this practice has been adopted at many institutions nationwide."[29] As far back as 2015, pediatric pain specialists at the December 10, 2015 joint Drug Safety and Risk Management/Pulmonary-Allergy Drugs Advisory Committee meeting stated that codeine/acetaminophen combination products were not appropriate for the treatment of painful sickle cell crises because the acetaminophen limits the dose of codeine that can be administered to patients.[30]

In response to FDA's June 29, 2020 *Federal Register* notice seeking input on these issues, FDA received input from stakeholders in pediatrics, pain management, genetic testing, and other relevant areas. A small number of commenters were in agreement that codeine has been helpful in pediatric patients with acute pain;[31] others indicated that changing the contraindication may facilitate more use of codeine in appropriately genotyped patients.[32] However, the American Academy of Pediatrics, the Nemours Children Health System, the Society for Pediatric Pain Medicine, and the Society for Pediatric Anesthesia all provided responses suggesting that

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[26] See "FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women" (Apr. 20, 2017) (available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and).

[27] Kelly LE, Sommer DD, Ramakrishna J, et al. Morphine or Ibuprofen for Post-tonsillectomy Analgesia: A Randomized Trial. *Pediatrics* 2015; 135(2): 307-13. In this study, children with sleep-disordered breathing were monitored with pulse oximetry for oxygen saturation and apnea events the night before and the night after tonsillectomy (with or without adenoidectomy). Only 13% of children receiving morphine for analgesia showed improvement in oxygen desaturations, compared with 65% of children who received ibuprofen.

[28] Petition at 5.

[29] Id.

[30] Meeting materials are available at https://wayback.archive-it.org/7993/20170403223846/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm433818.htm.

[31] See comments at FDA-2020-N-1046-0002 and FDA-2017-P-6918-0018.

[32] See comment at FDA-2020-N-1046-008.

codeine has little to no role in the treatment of pediatric patients under age 12.[33]

Even before FDA's 2013 boxed warning and contraindication in the post-tonsillectomy and/or post-adenoidectomy setting, a study by Livingstone, et al., concluded that, based on data from 154,362 children ages 0-17, the estimated number of pediatric patients who were dispensed codeine in the outpatient setting fell from 1.08 million in 1996 to 1.03 million in 2013.[34] The trend has continued since then: According to drug utilization data, the estimated number of pediatric patients under 12 years of age who were dispensed prescriptions for any codeine-containing products declined from 907,508 (49 percent of patients dispensed any codeine prescriptions in the age group 0 to 18) in 2014 to 114,443 (20 percent of patients dispensed any codeine prescriptions in the age group 0 to 18) in 2018.[35] Specifically, the estimated number of pediatric patients under 12 years of age who were dispensed prescriptions for codeine-containing analgesic products decreased by 86 percent from 586,464 patients in 2014 to 83,641 patients in 2018.[36]

In support of your views regarding the importance of being able to prescribe codeine in young pain patients, you assert that "other opioid analgesics also carry risks of adverse effects in pediatric patients and are more potent than codeine," stating: "[i]t is plausible that the adverse effects of these alternative opioids might result in more adverse effects in children compared to genotype-directed use of codeine."[37] Although we agree with your assertion that all opioid analgesics carry risk, and that opioid analgesics have some inherent variability in potency (whether across the class of opioids or from patient to patient for the same opioid) we are not aware of any reliable studies that attempt to establish the safety of codeine alongside other opioid analgesics in pediatric patients, particularly in patients who have received *CYP2D6* genotyping. In the absence of supporting data, your assertion that other opioids used in this population may pose greater risks does not warrant a conclusion that use of codeine in patients under age 12 has sufficient benefits to outweigh the serious risks – even with genetic testing (which, as explained above, has not been approved for this use) – that gave rise to the existing contraindication.

C. Prescriber Convenience and Patient Access

One concern underlying Petitioner's request to change the pediatric contraindication is patient access: a desire to be able to call in and refill a prescription for a pediatric patient in need of pain

[33] See comments at FDA-2020N-1046-0004, -0005, -0006, -0010. Notably, there were differences of opinion regarding the potential for future use of codeine for different provider departments within the Nemours system (*see* FDA-2020-N-1046-0010).

[34] Livingstone, M. J., Groenewald, C. B., Rabbitts, J. A., & Palermo, T. M. (2017). Codeine use among children in the United States: a nationally representative study from 1996 to 2013. Paediatr Anaesth, 27(1), 19-27. The study also noted that pain associated with trauma was the most common reason for receiving codeine (32% of patients). Id.

[35] Notably, the boxed warning and contraindication regarding the use of codeine in children post-tonsillectomy and/or adenoidectomy was added to labeling in 2013. Tonsillectomies and/or adenoidectomies are most commonly performed in children under age 11.

[36] Source: IQVIA Total Patient Tracker™. 2014-2018. The estimated number of pediatric patients under 12 years of age who were dispensed prescriptions from 2014 to 2018 also decreased for hydrocodone-containing, tramadol-containing, and morphine-containing analgesic products, but increased for oxycodone-containing products.

[37] Petition at 4.

relief. Petitioners are correct that CSA Schedule II opioids are not permitted to be refilled, and that, in general, a written prescription must be provided. It should be noted however, that verbal prescriptions for Schedule II controlled drug substances are permitted in emergency circumstances.[38] Perhaps more importantly, though, over the past few years – and particularly during the COVID-19 public health emergency – electronic prescribing is now permitted for Schedule II drugs, and the use of telemedicine is increasing. Some states have passed laws that require 100 percent electronic prescribing for all prescriptions, including Schedule II drugs. For example, we understand that as of January 1, 2021, the state law of Tennessee, where St. Jude Children's Hospital is located, requires that all controlled substances be electronically prescribed.[39]

Concerns about patient access issues, particularly in children who need intermittent opioid analgesic therapy, are not new. For example, at the 2015 joint advisory committee meeting, a mother of a child with sickle cell disease expressed concerns regarding her daughter's ability to access opioid analgesics generally (not codeine combination products specifically) at home. She noted the difficulty in obtaining opioid medications for control of sickle cell disease-related pain crises if a patient has to go to the emergency department for care and see physicians who are not familiar with the patient or the patient's family. Although FDA understands these concerns, they ultimately do not stem from the pediatric contraindication in the approved labeling for opioid analgesics. Accordingly, revising the contraindication is not the appropriate solution to these patient access issues.

D. The Existing Contraindication Continues to Reflect Agency Views

For the reasons explained above, FDA remains concerned that acute pain patients under the age of 12, even when classified as CYP2D6 normal/intermediate metabolizers, may be at substantial risk of respiratory depression from the use of codeine-containing analgesics.

FDA acknowledges that there are instances in which the inclusion of genetic testing-based prescribing recommendations in drug labeling may be appropriate.[40] These types of decisions are made on a case-by-case basis, involving a careful analysis of relevant facts (e.g., about the drug, the gene(s), the patients, the consequences of drug exposure across genotypes/phenotypes, etc.), including the circumstances in which the testing will be undertaken. For codeine-containing analgesics in children under 12, however, the concerns FDA identified in conjunction with the 2017 labeling change remain. Although FDA, like some commenters to its June 29, 2020 *Federal Register* notice, acknowledges the promise that appropriately-implemented pharmacogenetic testing can hold for individualizing patient care,[41] FDA declines to find that a

[38] See 21 CFR 1306.11(d) (providing that, in the case of an emergency situation, "a pharmacist may dispense a controlled substance listed in Schedule II upon receiving oral authorization of a prescribing individual practitioner"). There are additional requirements applicable in such circumstances.

[39] See section 63-1-160(c) of the Tennessee Code Annotated, as amended by Public Chapter No. 124, section 4.

[40] For example, *CYP2D6* genotype-specific information is included in the Indications and Usage statements and Contraindications for CERDELGA (eliglustat) (see https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf). However, this drug is prescribed for another serious illness (Gaucher's disease), in a non-urgent treatment setting, in patients likely to take concomitant medications and who have more complex pharmacokinetic profiles, and with resultant adverse events that do not include potentially fatal respiratory depression.

[41] See, e.g., comments at FDA-2020-N-1046-0007, -0011.

change to the existing contraindication is appropriate at this time given the risks of use of codeine-containing analgesics in this patient population. This is particularly true given the severity of the adverse outcome (potentially fatal respiratory depression), the context in which codeine is commonly administered (management of acute pain), and the input from stakeholders reflecting the lack of experience with, and access to, the type of genetic testing – none of which is currently FDA-cleared, approved or authorized for CYP2D6 polymorphisms intended for use in making treatment decisions regarding codeine prescribing – that would be required to identify high-risk patients.

FDA is sympathetic to the needs of pediatric patients, such as those with sickle cell disease, who experience painful conditions and need access to safe and effective treatments to manage their symptoms. We also understand the frustrations that prescribers and patients may experience in accessing important therapies. However, after careful consideration of your petition and the available evidence, the Agency declines to amend the pediatric contraindication of codeine-containing analgesics as you have requested at this time.

III. Conclusion

For the foregoing reasons, your petition request is denied.

Sincerely,

Douglas C. Throckmorton -S

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Date: 2023.08.11 10:05:21 -04'00'

Patrizia Cavazzoni, MD
Director
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