U.S. FOOD & DRUG ADMINISTRATION

Kenneth E. Surprenant
[redacted]

December 14, 2022

Re: Docket No. FDA-2020-P-2213

Dear Mr. Surprenant:

This letter responds to your citizen petition, which was received on November 17, 2020 (Petition). In your Petition, you request that the Food and Drug Administration (FDA, Agency, or we) revise the professional labeling[1] for fluorouracil injection and Xeloda (capecitabine) tablets to recommend pre-treatment testing to identify patients with dihydropyrimidine dehydrogenase (DPD) deficiency and to provide additional risk information and recommendations for management of their drug treatment.

The Petition requests that FDA revise the labeling for fluorouracil injection and Xeloda by:

1) Recommending pre-treatment testing to identify patients with [DPD] deficiency and include the recommendation in the content of the drug labels dealing with:
    a. Patient Counseling
    b. Dosage and Administration
    c. Box[ed] Warning
2) Revising the Patient Counseling Information content to: shift responsibility for identifying DPD deficiency from the patient to the prescribing physicians who should also discuss with patients the risk associated with DPD deficiency before the start of treatment.
3) Revising the Dosage and Administration content to: recommend treating physicians pre-screen patients for DPD deficiency and adapt the treatment plan if partial or complete DPD deficiency is identified.
4) Adding a Box[ed] Warning that:
    a. Highlights the risk of severe toxicity when treating patients with DPD deficiency, and
    b. Recommends screening for DPD deficiency prior to the start of treatment and prior to resuming treatment after an adverse event that necessitated treatment modification.

(Petition at 1).

[1] *Professional labeling* (also referred to as the *prescribing information*, *package insert*, or *physician labeling*) is a component of prescription drug labeling that is intended for use by health care professionals and contains the information necessary for the safe and effective use of the product. This labeling is subject to the format and content requirements in 21 CFR 201.56, 201.57, or 201.80. For ease of reading, we use the term *labeling* when referring to the professional labeling in this Petition response.

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We have carefully considered your Petition, comments submitted to the docket, and other relevant data available to the Agency. Based on our review of these materials, and for the reasons stated below, your Petition is granted in part and denied in part. As described more fully below, FDA is approving today certain labeling changes to further clarify information on the risks related to DPD deficiency.

On July 29, 2016, FDA issued a consolidated response to your two previous citizen petitions (2016 Response) that discussed issues related to those in the current Petition.[2] Today's response, at times, refers to the Agency's 2016 Response, which granted in part and denied in part the requests in your previous petitions.

I. BACKGROUND

A. Prescription Drug Labeling

1. Overview of Relevant Statutory and Regulatory Requirements

FDA-approved drug product labeling summarizes the essential information needed for the safe and effective use of the drug and reflects FDA's finding on the safety and effectiveness of the drug under the labeled conditions of use (see 21 CFR 201.56(a)). The primary purpose of FDA-approved labeling for prescription drugs is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby enhancing the safe and effective use of prescription drug products and reducing the likelihood of medication errors. Prescription drug labeling is directed to health care practitioners but may also include additional FDA-approved labeling directed at the patient or caregiver (commonly referred to as *patient labeling*).

2. Certain Labeling Content Requirements and Related Agency Guidance

FDA regulations govern the content and format of prescription drug labeling (see, e.g., 21 CFR 201.56 and 201.57; see also 21 CFR 201.100(c)). The regulations are intended to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[3]

Labeling regulations are further discussed in FDA guidances about specific topics related to the content and format of prescription drug labeling. When finalized, guidances describe the

[2] The 2016 Response is available at www.regulations.gov under Docket Nos. FDA-2014-P-0405 and FDA-2014-P-0497.

[3] Preamble to final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922 at 3928, January 24, 2006) (also known as the Physician Labeling Rule). For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in 21 CFR 201.56 and 201.57, see 201.80. The specific labeling requirements for older drug products differ in certain respects, and generally are not referenced in this response.

Agency's current thinking on a topic.[4] Currently available labeling-related guidances may address a single section of labeling, multiple sections, or a discrete topic on prescription drug labeling.

The three sections of labeling for which revisions are requested in the Petition are discussed below. They are discussed in the order in which they are required to appear in labeling per § 201.56(d)(1).

A BOXED WARNING may be required in labeling for certain contraindications or serious warnings, particularly those that may lead to death or serious injury, because this information is especially important for a health care practitioner to consider in assessing the risks and benefits of a drug (see § 201.57(c)(1)). The BOXED WARNING must briefly explain the risk and then refer to the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section of labeling, where the risk is explained in more detail (see § 201.57(c)(1)).

As stated in FDA guidance[5], a BOXED WARNING is ordinarily used when:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug; or
- There is a serious adverse reaction[6] that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or

[4] Labeling guidances are available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. FDA 's guidance documents generally do not establish legally enforceable responsibilities. Instead, guidances describe the Agency' s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[5] See FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format* (October 2011), at page 11, available at https://www fda.gov/media/71866/download (Warnings Guidance). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] FDA applies the definition of "serious" in 21 CFR 314.80(a). A serious adverse drug experience is defined as:

> [a]ny adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.

The DOSAGE AND ADMINISTRATION section of labeling must include the recommended dose and, as appropriate, other information related to dosage and administration (see § 201.57(c)(3)(i)). This information may include, but is not limited to, the dosage range, the intervals recommended between doses, and the usual duration of treatment when treatment duration should be limited (see § 201.57(c)(3)(i)(A), (D), and (F), respectively).

The regulations further state that the DOSAGE AND ADMINISTATION section must include, if applicable, any modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease) (see § 201.57(c)(3)(i)(H)). If there are recommendations on dosage modifications (e.g., dosage reduction, dosage interruption, or permanent discontinuation), this information must be stated, as appropriate, in the DOSAGE AND ADMINISTRATION section, and should cross-reference to a more detailed discussion of the information elsewhere in the labeling (e.g., in the WARNINGS AND PRECAUTIONS section).[7]

The DOSAGE AND ADMINISTRATION section should also identify any specific safety monitoring procedures that should be implemented before initiating therapy or during therapy to determine whether to stop a drug, withhold or decrease the dose of a drug given repeatedly, delay an additional course of a drug given cyclically, or otherwise adjust the dosage or regimen.[8]

By regulation, the PATIENT COUNSELING INFORMATION section of labeling must meet the following requirements for content (see § 201.57(c)(18)):

- This section must contain information necessary for patients to use the drug safely and effectively (e.g., precautions concerning driving or the concomitant use of other substances that may have harmful additive effects).
- Any FDA-approved patient labeling must be referenced in this section and the full text of such patient labeling must be reprinted immediately following this section or, alternatively, accompany the prescription drug labeling.

The PATIENT COUNSELING INFORMATION section summarizes the information that a health care provider should convey to a patient (or caregiver when applicable) when a counseling discussion is taking place (e.g., a physician prescribing a drug during an office visit, a nurse

[7] See FDA guidance for industry *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010), at page 3, available at https://www fda.gov/media/72142/download.

[8] Id. at page 3.

providing discharge instructions at a hospital, or a pharmacist conveying information at a pharmacy).[9] Information in the PATIENT COUNSELING INFORMATION section and any FDA-approved patient labeling, along with the provider-patient conversation, are essential and complementary components for the safe and effective use of prescription drugs.[10]

B. Fluoropyrimidine Drugs

Fluorouracil injection and Xeloda (capecitabine) tablets belong to a group of drugs known as fluoropyrimidines and are widely used for the treatment of cancer. In the body, enzymes convert fluorouracil (5-FU) to active metabolites that inhibit the growth of tumor cells. Capecitabine, the active ingredient in Xeloda, is a pro-drug of 5-FU, meaning it is first converted in the body to 5-FU, from where it subsequently undergoes the same metabolic conversions and exhibits the same actions as administered 5-FU. Up to 40 percent of patients receiving fluoropyrimidine drugs experience severe, including sometimes fatal, toxicities.[11,12] One of the causes of such toxicities is a deficiency in the DPD enzyme, which is discussed in section I.C.

1. Fluorouracil Injection

Fluorouracil injection was approved by FDA on April 25, 1962, under NDA 012209, and is currently marketed under multiple abbreviated new drug applications (ANDAs) (i.e., as generic drug products). It is indicated for the treatment of patients with adenocarcinoma of the colon and rectum, adenocarcinoma of the breast, gastric adenocarcinoma, and pancreatic adenocarcinoma.[13]

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[9] See FDA guidance for industry *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014), at page 2, available at https://www fda.gov/media/86734/download.

[10] Id. at page 3.

[11] Amstutz U, Froehlich TK, Largiadèr CR. Dihydropyrimidine dehydrogenase gene as a major predictor of severe 5-fluorouracil toxicity. Pharmacogenomics. 2011 Sep;12(9):1321-1336. doi: 10.2217/pgs.11.72. PMID: 21919607.

[12] Articles from the medical literature cited in this Petition response to provide attribution for specific scientific information may include opinions, recommendations, or conclusions that differ from those articulated here by FDA. Inclusion of a reference in this Petition response does not constitute the Agency's agreement with or endorsement of all information contained in an article.

[13] Injectable formulations of fluorouracil are approved for these cancer indications, and FDA has interpreted the Petition requests as pertaining specifically to these products. Fluorouracil is also available in topical cream and topical solution formulations indicated for certain dermatological conditions, and FDA has interpreted the Petition requests as not pertaining to the topical formulations. Any reference to the labeling of fluorouracil (or 5-FU) in this Petition response is directed at the labeling for the injectable products only.

At present (and when the Petition was received), the approved labeling for fluorouracil injection[14] includes the following information in the WARNINGS AND PRECAUTIONS section:

> **5.1 Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity**
>
> Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil.
>
> Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

In addition, the labeling includes the following information in the PATIENT COUNSELING INFORMATION section:

> [Advise] patients to notify their healthcare provider if they have a known DPD deficiency. Advise patients if they have complete or near complete absence of DPD activity, they are at an increased risk of severe and life-threatening mucositis, diarrhea, neutropenia and neurotoxicity *[see Warnings and Precautions (5.1)]*.

2. Xeloda (capecitabine) Tablets

Xeloda (capecitabine) tablets were approved by FDA on April 30, 1998, under NDA 020896, and are currently marketed as the brand name drug and under multiple ANDAs (i.e., as generic drug products). At the time the Petition was received, Xeloda was indicated for certain cases of adjuvant colon cancer, metastatic colorectal cancer, and metastatic breast cancer.

At present (and when the Petition was received), the approved labeling for Xeloda[15] includes the following information in the WARNINGS AND PRECAUTIONS section (which is identical to the wording in the fluorouracil injection labeling, except for the subsection number and title):

[14] Currently approved labeling (revised July 29, 2016) for fluorouracil injection (NDA 012209), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/012209s040lbl.pdf.

[15] Currently approved labeling (revised May 19, 2021) for Xeloda, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020896s043lbl.pdf.

> **5.4 Dihydropyrimidine Dehydrogenase Deficiency**
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> Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by XELODA.
>
> Withhold or permanently discontinue XELODA based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No XELODA dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

The Xeloda labeling also includes the following information in the PATIENT COUNSELING INFORMATION section (which differs somewhat from that in the fluorouracil labeling):

> Dihydropyrimidine Dehydrogenase Deficiency
> Advise patients to notify their healthcare provider if they have a known DPD deficiency. Advise patients if they have complete or near complete absence of DPD activity they are at an increased risk of acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity) *[see Warnings and Precautions (5.4)]*.

C. Testing for DPD Deficiency

As noted above, both 5-FU and Xeloda belong to the fluoropyrimidine class of drugs. DPD is the primary enzyme in the fluoropyrimidine metabolic pathway and plays a key role in eliminating fluoropyrimidines from the body by breaking down the active drug metabolites into inactive metabolites. The DPD enzyme is encoded by the *DPYD* gene.

Individuals with certain genetic variants in the *DPYD* gene (i.e., certain genotypes) may have complete DPD deficiency (from complete absence or near complete absence of DPD activity) or partial DPD deficiency (from partial DPD activity), and thus cannot degrade fluoropyrimidines to the same extent as patients with normal DPD activity. This decrease in DPD activity increases the risk of severe adverse reactions because of higher systemic exposure to fluoropyrimidine active metabolites.

DPD deficiency results in wide variability in how it manifests in patients receiving fluoropyrimidine drug treatment (i.e., variable phenotypes), ranging from mild adverse reactions to life-threatening toxicities. As described in the labeling for fluorouracil and Xeloda, the most frequently observed serious adverse reactions from fluoropyrimidine use in patients with DPD deficiency include, but are not limited to, potentially life-threatening cases of mucositis, diarrhea, neutropenia, and neurotoxicity.

It is estimated that approximately 3 to 5 percent of White populations have a partial absence, and 0.2 percent of White populations have a complete or near complete absence of DPD activity due to certain genetic variants in *DPYD*.[16] In Black or African American populations, the prevalence of DPD deficiency is estimated to be higher than in White populations.[17,18] Currently available data are insufficient to allow an estimation of the prevalence of partial or absent DPD activity in other racial and ethnic populations.

Among the hundreds of variants identified in the *DPYD* gene, only a small number have been associated with deficient DPD activity that could, in part, explain some cases of fluoropyrimidine toxicity. Four specific *DPYD* variants (c.1905+1G>A (*DPYD* *2A), c.1679T>G (*DPYD* *13), c.2846A>T, and c.1129-5923C>G (Haplotype B3)) have been identified that increase a patient's risk of severe or life-threatening adverse reactions from fluoropyrimidine-based treatment.[19] Among the many variants identified in *DPYD* that may potentially reduce DPD activity, these four are the most well characterized and thus currently are considered the most clinically relevant. As reported in the literature, most *DPYD* genetic tests available at present focus on these four variants or a subset thereof.[20]

A variety of genetic and phenotype-based testing approaches are available to detect DPD deficiency to predict risk of fluoropyrimidine toxicity, including *DPYD* genotyping and sequencing, assessing enzymatic activity with DPD phenotyping, and combined genotyping/phenotyping. Some genotyping approaches are targeted to detect specific *DPYD* gene variants, whereas genetic sequencing is a variant-agnostic approach consisting of sequencing *DPYD* (or other genes, the entire exome, or even the whole genome) to identify any gene variants. Phenotype-based approaches consist of either direct or indirect measurements of DPD enzymatic activity, and tests that combine genetic and phenotype-based methods are also available. The different testing approaches may select different patients and perform differently with respect to identifying patients at risk for serious fluoropyrimidine-related toxicity.

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[16] Morel A, Boisdron-Celle M, Fey L, Soulie P, Craipeau MC, Traore S, Gamelin E. Clinical Relevance of Different Dihydropyrimidine Dehydrogenase Gene Single Nucleotide Polymorphisms on 5-Fluorouracil Tolerance. Mol Cancer Ther. 2006 Nov;5(11):2895-2904. doi: 10.1158/1535-7163.MCT-06-0327. PMID: 17121937.

[17] Mattison LK, Fourie J, Desmond RA, Modak A, Saif MW, Diasio RB. Increased Prevalence of Dihydropyrimidine Dehydrogenase Deficiency in African-Americans Compared With Caucasians. Clin Cancer Res. 2006 Sep 15;12(18):5491-5495. doi: 10.1158/1078-0432.CCR-06-0747. PMID: 17000684.

[18] Saif MW, Lee AM, Offer SM, McConnell K, Relias V, Diasio RB. A DPYD Variant (Y186C) Specific to Individuals of African Descent in a Patient With Life-Threatening 5-FU Toxic Effects: Potential for an Individualized Medicine Approach. Mayo Clin Proc. 2014 Jan;89(1):131-136. doi: 10.1016/j.mayocp.2013.09.008. PMID: 24388031; PMCID: PMC4071869.

[19] See footnote 11.

[20] Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, Klein TE, McLeod HL, Caudle KE, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018 Feb;103(2):210-216. doi: 10.1002/cpt.911. Epub 2017 Nov 20. PMID: 29152729; PMCID: PMC5760397.

FDA has not cleared, authorized, or approved any in vitro diagnostic device[21] intended to identify DPD deficiency or identify patients at risk for fluoropyrimidine-related toxicity.[22,23]

II. DISCUSSION

In the Petition, you requested that FDA make certain revisions to the labeling for fluorouracil injection and Xeloda (capecitabine) tablets. These requests are discussed in turn below.

A. Recommendation to Screen All Patients

You argue that information regarding screening for DPD deficiency should be added to the labeling of fluorouracil and Xeloda in part because the practice of screening for DPD deficiency would enable treating physicians to identify at-risk patients, and pre-treatment diagnosis of DPD deficiency is the only way to pre-emptively identify patients at risk for these severe toxicities (Petition at 4).

As noted above, none of the currently available tests used to identify patients at risk of serious adverse reactions to fluorouracil or Xeloda have received FDA marketing authorization, and the accuracy of available tests may vary. In addition, testing to identify DPD deficiency has limitations, including those discussed below.

For currently available laboratory developed tests, the rates of false positive results (incorrectly identifying a patient with normal DPD activity as having complete absence of, near complete

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[21] See 21 CFR 809.3. In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.

[22] Tests to detect DPD deficiency may be available as laboratory developed tests (LDTs) that are offered without FDA approval, clearance, or authorization. An LDT is an in vitro diagnostic device that is intended for clinical use and designed, manufactured, and used within a single laboratory that is certified under the Clinical Laboratory Improvement Amendments (CLIA) (42 U.S.C. 263a) and that meets the requirements to perform tests of high complexity, as described in 42 CFR 493.17(c)(4) and 493.25, and is a location that has its own CLIA certificate as described in 42 CFR 493.43(a). The FDA has generally exercised enforcement discretion with respect to LDTs, meaning that, except in certain circumstances, the FDA generally does not exercise its authority to enforce the regulatory requirements for these devices, although it maintains that authority.

[23] In 2018, FDA authorized the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports, a qualitative genotyping assessment system indicated for reporting certain gene variants, including two *DPYD* variants (*2A and rs67376798, respectively). However, this test is not intended to identify patients with DPD deficiency. Furthermore, the test is not intended to be used to provide information on specific therapeutics. Specifically, as described in the test's indications for use:

> . . . the test does not describe if a person will or will not respond to a particular therapeutic and does not describe the association between detected variants and any specific therapeutic. The PGS Pharmacogenetic Reports are not a substitute for visits to a health care professional, and information provided by this test should not be used to start, stop, or change any course of treatment.

As stated in the test's labeling per special controls under 21 CFR 862.3364, any genetic variants detected by the test should be confirmed prior to making any medical decisions.

absence of, or impaired DPD activity) or false negative results (incorrectly identifying a patient with complete absence of, near complete absence of, or impaired DPD activity as having normal DPD activity) are not known. False results may occur, in part, because of technical problems with the test or, for genetic tests, because of the existence of rare or previously unidentified *DPYD* variants that contribute to toxicities from DPD deficiency. Inaccurate results have implications for patient care. They may inappropriately provide reassurance about the expected tolerability of these drugs in an individual patient. Furthermore, use of an unreliable test could result in a decision not to administer a drug to a patient who could, in fact, tolerate and benefit from it, or to administer an inadequate dose.

Literature suggests that available genetic tests have low sensitivity to detect DPD deficiency and the risk of severe fluoropyrimidine toxicity, though this finding may depend on which *DPYD* variant(s) a test identifies, as well as the ancestry of the patient tested.[24] Moreover, there is not always a clear association between *DPYD* genotype and DPD deficiency phenotype.[25] Some genotypic results (e.g., certain variants) may not correlate with phenotypic response (e.g., decreased DPD activity and adverse clinical manifestations) because there is high interindividual variability in DPD enzyme activity, even within specific *DPYD* genotypes.[26] DPD deficiency is a potential, but not the sole, prerequisite for the development of serious adverse reactions during fluoropyrimidine therapy. In addition, because there is not always a clear association between genotype and phenotype, a positive genetic test result for *DPYD* variants does not guarantee that a patient will experience major toxicities at standard doses.

Most known *DPYD* variants associated with decreased DPD activity are reported to be of low frequency. Even in a situation where a theoretical perfect test existed, in some situations, given the low prevalence of *DPYD* variants, it may be in a patient's best interest to receive fluoropyrimidine treatment without testing (e.g., a patient with metastatic disease who needs immediate treatment to relieve a gastrointestinal obstruction or other organ compromise).

The current scientific knowledge about *DPYD* variants may not be generalizable to the U.S. population as a whole. The prevalence of the alterations in the *DPYD* gene has been established primarily in populations of European ancestry and may have limited generalizability to other racial or ethnic groups.[27] In African American populations, for example, a different variant,

[24] Diasio RB, Offer SM. Testing for Dihydropyrimidine Dehydrogenase Deficiency to Individualize 5-Fluorouracil Therapy. Cancers (Basel). 2022 Jun 30;14(13):3207. doi: 10.3390/cancers14133207. PMID: 35804978; PMCID: PMC9264755.

[25] Coenen MJH, Paulussen ADC, Breuer M, Lindhout M, Tserpelis DCJ, Steyls A, Bierau J, van den Bosch BJC. Evolution of Dihydropyrimidine Dehydrogenase Diagnostic Testing in a Single Center During an 8-Year Period of Time. Curr Ther Res Clin Exp. 2018 Oct 31;90:1-7. doi: 10.1016/j.curtheres.2018.10.001. PMID: 30510603; PMCID: PMC6258870.

[26] Id.

[27] See footnote 20.

c.557A>G (p.Y186C), was found to lead to reduced DPD activity.[28,29] These population differences raise concerns about the accuracy of available tests for the general U.S. population, given the variability of population-based frequencies of genetic alterations and the diversity of the population from a wide spectrum of racial, ethnic, and ancestral backgrounds. Poor characterization of genetic variants for certain groups of patients can lead to inconsistencies in the ability to provide accurate information for DPD deficiency for certain ancestral groups compared with those of European ancestry. Targeted genetic tests can be biased based on the population in which they were developed and diversity therein. We concur with your statement in the Petition that false negative results may occur in non-White patients if genotype panels do not test for variants that are more prevalent in a range of racial or ethnic groups (Petition at 5) and are concerned that available panels may fail to include the most common and relevant variants for different racial and ethnic groups. Although the lack of available information in such groups would not necessarily preclude a testing directive in labeling, additional research is needed to ensure that testing all patients for *DPYD* variants can benefit the diverse U.S. population.

Phenotypic tests (and, hence, combined genotypic/phenotypic tests) also have limitations and are not well standardized in terms of their methodology or interpretation.[30] Our review has shown that such tests have not been widely incorporated into clinical practice, in part because of the need for specialized equipment and reagents, as well as the high degree of technological expertise required for their use.

Lastly, you state in the Petition that the National Comprehensive Cancer Network (NCCN) acknowledges the potential and feasibility of pre-treatment testing to identify and manage patients at risk for severe toxicity in its clinical practice guideline for colon cancer, and you include an excerpt of the guideline (Petition at 4). This portion of the NCCN guideline, however, concludes with the following statement, which was not included in the Petition and does not support screening for DPD deficiency:

> However, because fluoropyrimidines are a pillar of therapy in [colorectal cancer] and it is not known with certainty that given *DPYD* variants are necessarily associated with this risk, universal pretreatment *DPYD* genotyping remains controversial and the NCCN Panel does not support it at this time.[31]

In sum, insufficient evidence exists regarding the relative benefits and risks of existing testing approaches to support a recommendation in labeling to screen all patients for DPD deficiency before initiating, adapting, or restarting fluoropyrimidine therapy after a treatment interruption,

[28] See footnote 17.

[29] See footnote 18.

[30] See footnote 25.

[31] See NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, Version 1.2022, February 25, 2022, at page MS-41, available at https://www nccn.org/guidelines/guidelines-detail?category=1&id=1428.

especially when the risks of inaccurate testing include withholding or reducing the dose of an effective life-prolonging or curative chemotherapy treatment.

However, given the negative benefit-risk profile in patients with complete or partial DPD deficiency, especially those with homozygous or compound heterozygous variants in the *DPYD* gene, FDA is today revising certain sections of the labeling for Xeloda to add information about DPD deficiency and testing. The revisions to the Xeloda labeling are being made as part of "Project Renewal," a voluntary public health initiative from FDA's Oncology Center of Excellence to update the labeling for certain older oncology drugs.[32,33] To the extent that your Petition is requesting certain changes to the labeling for Xeloda, those requests are granted in part and denied in part as described below. The labeling for fluorouracil injection is also slated for revision under Project Renewal[34], and we anticipate that relevant labeling revisions for Xeloda described in this Petition response will be considered for the labeling for fluorouracil injection, as appropriate, under that initiative (if not otherwise addressed sooner). Because the labeling for fluorouracil remains under review as part of Project Renewal, this response does not address the Petition requests for labeling changes for that drug, and, therefore, the requests for revisions to the fluorouracil labeling are denied.

B. Specific Labeling Requests

1. BOXED WARNING

The Petition requests that a new BOXED WARNING be added to the labeling for fluorouracil injection and Xeloda that: (1) highlights the risk of severe toxicity when patients with DPD deficiency receive treatment with fluorouracil or Xeloda, and (2) recommends screening for DPD deficiency prior to the start of treatment with fluorouracil or Xeloda and prior to resuming treatment after a modification resulting from an adverse reaction (Petition at 1).

Information on the risks related to DPD deficiency is included in the current labeling for fluorouracil and Xeloda in the WARNINGS AND PRECAUTIONS section, which, by regulation:

> . . . must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions),

[32] For more information on Project Renewal, see https://www.fda.gov/about-fda/oncology-center-excellence/project-renewal.

[33] Kluetz PG, Keegan P, Demetri GD, Thornton, K, Sul J, Kim J, Katzen H, Burke LB, Harvey RD, Alebachew E, Agrawal S, Nair A, Donoghue M, Pierce WF, Shord SS, Gao JJ, and Pazdur R. FDA Oncology Center of Excellence Project Renewal: Engaging the Oncology Community to Update Product Labeling for Older Oncology Drugs. Clin Cancer Res. 2021 Feb 15;27(4):916-921. doi: 10.1158/1078-0432.CCR-20-3213. Epub 2020 Nov 30. PMID: 33257426.

[34] Id. at page 919.

> limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification).

(See § 201.57(c)(6)(i)).

Information about an adverse reaction or other risk that is described in the WARNINGS AND PRECAUTIONS section may also be described in a BOXED WARNING, the most prominent warning available in labeling.

As noted above, a BOXED WARNING is ordinarily used, among other reasons, to highlight certain situations for prescribers, including when there is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug; or when there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug.[35] For oncology drugs like fluorouracil and Xeloda, complex safety profiles accompany their ability to extend or preserve lives. FDA's decision to emphasize certain risks in a BOXED WARNING in labeling are based, in part, on the seriousness of the condition being treated relative to those risks. Additionally, ongoing concerns about limitations of available tests weigh against adding a recommendation in a BOXED WARNING to screen all patients for DPD deficiency. For these reasons, FDA has determined that the WARNINGS AND PRECAUTIONS section remains the appropriate location in labeling for information on the risks related to DPD deficiency and that a BOXED WARNING is not warranted at this time.

We have determined, however, with today's approval of revised labeling for Xeloda, that certain modifications to the existing warning about DPD deficiency are warranted based on our review of currently available scientific information. The warning about DPD deficiency now describes clinical circumstances for consideration by prescribers when making decisions regarding testing for *DPYD* variants, with accompanying information that failure of a test to identify *DPYD* variants does not rule out the risk of serious adverse reactions; there is no FDA-authorized test currently available intended to identify patients at risk of serious adverse reactions; and currently available tests used to identify *DPYD* variants may vary in accuracy and design, including which *DPYD* variant(s) they identify.

Accordingly, in the WARNINGS AND PRECAUTIONS section of the labeling for Xeloda, in addition to some minor editorial revisions to the existing text, we are adding two new final paragraphs to the warning, which now reads in full:

> **5.2 Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency**
>
> Patients with certain homozygous or compound heterozygous variants in the *DPYD* gene known to result in complete or near complete absence of DPD activity (complete DPD deficiency) are at increased risk for acute early-onset toxicity and serious, including fatal, adverse reactions due to XELODA (e.g., mucositis, diarrhea, neutropenia, and

[35] See Warnings Guidance at page 11.

> neurotoxicity). Patients with partial DPD activity (partial DPD deficiency) may also have increased risk of serious, including fatal, adverse reactions.
>
> XELODA is not recommended for use in patients known to have certain homozygous or compound heterozygous *DPYD* variants that result in complete DPD deficiency.
>
> Withhold or permanently discontinue XELODA based on clinical assessment of the onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe reactions, which may indicate complete DPD deficiency. No XELODA dose has been proven safe for patients with complete DPD deficiency. There are insufficient data to recommend a specific dose in patients with partial DPD deficiency.
>
> Consider testing for genetic variants of *DPYD* prior to initiating XELODA to reduce the risk of serious adverse reactions if the patient's clinical status permits and based on clinical judgement *[see Clinical Pharmacology (12.5)]*. Serious adverse reactions may still occur even if no *DPYD* variants are identified.
>
> An FDA-authorized test for the detection of genetic variants of *DPYD* to identify patients at risk of serious adverse reactions due to increased systemic exposure to XELODA is not currently available. Currently available tests used to identify *DPYD* variants may vary in accuracy and design (e.g., which *DPYD* variant(s) they identify).

Along with these revisions, the warning about DPD deficiency in the Xeloda labeling is being elevated within the WARNINGS AND PRECAUTIONS section to increase its prominence. The order in which adverse reactions are presented in the WARNINGS AND PRECAUTIONS section should reflect the relative clinical significance of the adverse reactions,[36] i.e., topics in this section of labeling should be ordered by decreasing importance. Accordingly, the warning about DPD deficiency in the Xeloda labeling is being moved from 5.4 to 5.2. (Subsection 5.1 is a warning about an important drug interaction risk that is the subject of a BOXED WARNING, making it appropriately the first topic presented in the WARNINGS AND PRECAUTIONS section.)[37]

We also note your contention that FDA has "established a logical precedent for using Box[ed] Warnings to include genetic screening recommendations prior to treatment to prevent severe adverse reactions in patients who are known to have unacceptable risk of treatment-related fatality" (Petition at 7).[38] The determination to include a BOXED WARNING is made on a case-by-case basis, and we do not agree that the labeling for fluoropyrimidine drugs should

[36] Id. at page 7.

[37] In the current fluorouracil injection labeling, the topic of DPD deficiency already appears as 5.1, the most prominent warning in the WARNINGS AND PRECAUTIONS section, obviating the need to relocate the information in the future.

[38] The Petition cites the labeling for Ziagen as an example. The currently approved labeling for Ziagen (abacavir sulfate) tablets (NDA 020977) and oral solution (NDA 020978) includes a BOXED WARNING that recommends screening patients for the presence of a certain genetic variation that increases the risk of serious hypersensitivity reactions.

include a recommendation to screen all patients for DPD deficiency, either in a BOXED WARNING or elsewhere in the labeling.

In summary, FDA has concluded that a new BOXED WARNING that further highlights the risks of DPD deficiency and recommends screening for DPD deficiency is not warranted at this time. The revised labeling content and format in the WARNINGS AND PRECAUTIONS section described above for Xeloda conveys the information on this topic that FDA has determined to be necessary for safe and effective use of the drug. Accordingly, to the extent you are requesting that information be added to the labeling for Xeloda to highlight the risk of severe toxicities when treating patients with DPD deficiency and to recommend testing to screen all patients prior to treatment, we are granting those requests in part with the revisions to the content and format of the labeling for Xeloda described above, which include the newly added information in the WARNINGS AND PRECAUTIONS section that testing can be considered for certain patients. To the extent that you are requesting that the labeling for Xeloda recommend screening prior to treatment in all patients and that such information appear in a BOXED WARNING, those requests are denied.

2. DOSAGE AND ADMINISTRATION

Your Petition requests that the DOSAGE AND ADMINISTRATION section of labeling be revised to include language recommending that treating physicians screen patients for DPD deficiency and adapt the treatment plan if partial or complete DPD deficiency is identified (Petition at 1). We have already stated our position on the first of these requests (screening all patients for DPD deficiency) and will now address the second.

As noted in the Background section of this response, at the time your Petition was submitted, the labeling for fluorouracil and Xeloda each stated in the WARNINGS AND PRECAUTIONS section: "No fluorouracil [or XELODA] dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test."

Whereas the scientific rationale for the recommendation to avoid fluoropyrimidines in patients with complete DPD deficiency is clear, the available data about the use of these drugs in patients with partial DPD deficiency are less definitive. As you note in the Petition, there is information in the published literature about the use of modified initial dosages of fluoropyrimidines in patients with known partial DPD deficiency (Petition at 5), and certain international organizations and health authorities have authored or endorsed guidelines on the subject (Petition at 3-4). In general, the types of evidence used to support recommendations made in journal articles and treatment guidelines are different from, and can be less rigorous than, the evidence used to support regulatory decision-making, including the text of FDA-approved labeling. FDA has not received or reviewed data from well-controlled randomized clinical trials, should they exist, that prospectively evaluate whether the clinical efficacy outcomes of cancer treatment in patients receiving reduced initial fluoropyrimidine doses because of partial DPD activity are no worse than (non-inferior to) outcomes in patients receiving standard doses. Currently available information reviewed by FDA on specific initial dosage regimens claimed to be both safe and effective in patients with partial DPD deficiency are insufficient to support the inclusion of such recommendations in labeling.

All patients undergoing cancer treatment with fluoropyrimidines should be closely monitored for the development of adverse reactions. At the time you submitted your Petition, the labeling for both fluorouracil and Xeloda each included a subsection in the DOSAGE AND ADMINISTRATION section providing instructions for managing certain types and severities of adverse reactions with dosage modifications or drug discontinuation, where clinically appropriate. These recommendations, which include but are not specific to DPD deficiency-related adverse reactions, are being retained.

Accordingly, your request to revise the DOSAGE AND ADMINISTRATION section of the labeling for Xeloda is denied.

3. PATIENT COUNSELING INFORMATION

You have requested that FDA revise the PATIENT COUNSELING INFORMATION section of labeling to recommend pre-treatment testing to identify patients with DPD deficiency and to "shift responsibility for identifying DPD deficiency from the patient to the prescribing physicians who should also discuss with patients the risk associated with DPD deficiency before the start of treatment" (Petition at 1). We have already stated our position on the first of these requests (to recommend screening for all patients), which is reflected in revisions described above to the WARNINGS AND PRECAUTIONS section of labeling for Xeloda stating that prescribers may consider testing for certain patients based on their clinical status.

We agree that the risks of DPD deficiency should be discussed with patients prior to treatment, as part of the regular patient-prescriber conversation; this recommendation is already included in the PATIENT COUNSELING INFORMATION section of the labeling for fluorouracil and Xeloda (as described in section I.B. above). We do not agree with your contention that the current language places the burden of identifying DPD deficiency on patients themselves.

We have determined, however, that the discussion of the topic of DPD deficiency in this section of labeling would benefit from revisions providing additional clarity. We are approving, with the revised labeling for Xeloda, updated language in the PATIENT COUNSELING INFORMATION section. The revisions in this section more explicitly recommend that prescribers discuss the potential risks of treatment related to DPD deficiency with their patients and add a recommendation to discuss whether DPD testing is appropriate. The following text replaces the existing text about DPD deficiency in the PATIENT COUNSELING INFORMATION section in the labeling for Xeloda and will now appear as the second (instead of third) topic in the section:

> Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency
> Inform patients of the potential for serious and life-threatening adverse reactions due to DPD deficiency and discuss with your patient whether they should be tested for genetic variants of *DPYD* that are associated with an increased risk of serious adverse reactions from the use of XELODA. Advise patients to immediately contact their healthcare provider if symptoms of severe mucositis, diarrhea, neutropenia, and neurotoxicity occur *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.5)]*.

Accordingly, your request to revise the PATIENT COUNSELING INFORMATION section of labeling for Xeloda is granted in part and denied in part. To the extent that you are requesting that this section of labeling include information that prescribers should discuss the risks associated with DPD deficiency with patients before the start of treatment, that request is granted in part with the revisions in content and format being made to the Xeloda labeling described above. To the extent that you are requesting that this section of labeling for Xeloda recommend pre-treatment testing of all patients, that request is denied.

C. Additional Labeling Revisions Regarding *DPYD* Variants and DPD Deficiency

Although not requested in the Petition, FDA is also making a change to the Xeloda labeling with the addition of a new subsection entitled *Pharmacogenomics* in the CLINICAL PHARMACOLOGY section.[39] Per FDA's guidance[40] on the CLINICAL PHARMACOLOGY section of labeling, this subsection, if included, "should include clinically relevant data or information on the effect of genetic variations affecting drug therapy."

The Xeloda labeling approved today includes the following text in the new subsection entitled *12.5 Pharmacogenomics:*

> The *DPYD* gene encodes the enzyme DPD, which is responsible for the catabolism of >80% of fluorouracil. Approximately 3-5% of White populations have partial DPD deficiency and 0.2% of White populations have complete DPD deficiency, which may be due to certain genetic no function or decreased function variants in *DPYD* resulting in partial to complete or near complete absence of enzyme activity. DPD deficiency is estimated to be more prevalent in Black or African American populations compared to White populations. Insufficient information is available to estimate the prevalence of DPD deficiency in other populations.
>
> Patients who are homozygous or compound heterozygous for no function *DPYD* variants (i.e., carry two no function *DPYD* variants) or are compound heterozygous for a no function *DPYD* variant plus a decreased function *DPYD* variant have complete DPD deficiency and are at increased risk for acute early-onset of toxicity and serious life-threatening, or fatal adverse reactions due to increased systemic exposure to XELODA. Partial DPD deficiency can result from the presence of either two decreased function *DPYD* variants or one normal function plus either a decreased function or a no function *DPYD* variant. Patients with partial DPD deficiency may also be at an increased risk for toxicity from XELODA.
>
> Four *DPYD* variants have been associated with impaired DPD activity in White populations, especially when present as homozygous or compound heterozygous variants: c.1905+1G>A (*DPYD* *2A), c.1679T>G (*DPYD* *13), c.2846A>T, and c.1129-5923C>G (Haplotype B3). *DPYD**2A and *DPYD**13 are no function variants, and c.2846A>T and

[39] 21 CFR 201.57(c)(13)

[40] See FDA guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016), at page 14, available at https://www fda.gov/media/74346/download.

c.1129-5923C>G are decreased function variants. The decreased function *DPYD* variant c.557A>G is observed in individuals of African ancestry. This is not a complete listing of all *DPYD* variants that may result in DPD deficiency *[see Warnings and Precautions (5.2)]*.

Lastly, revisions are being made to the patient labeling for Xeloda related to DPD deficiency. Existing text in the "Patient Information" labeling document about DPD deficiency will be replaced with, under the heading "**XELODA can cause serious side effects including:**":

- **Serious side effects in people with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency**. People with certain changes in a gene called "DPYD" may have a deficiency of the DPD enzyme. Some of these people may not produce enough DPD enzyme, and some of these people may not produce the DPD enzyme at all.
  - People who do not produce any DPD enzyme are at increased risk of sudden side effects that come on early during treatment with XELODA and can be serious, and sometimes lead to death. **Call your healthcare provider right away if you develop any of the following symptoms and they are severe**, including:
    - sores of the mouth, tongue, throat, and esophagus (mucositis)
    - diarrhea
    - low white blood cell counts
    - nervous system problems.
  - People with some DPD enzyme may have an increased risk of serious side effects with XELODA treatment that can sometimes lead to death.

  Your healthcare provider should talk with you about DPYD testing to look for DPD deficiency.

III. CONCLUSION

For the reasons set forth above, your requests for labeling changes for Xeloda are granted in part and denied in part. Because the labeling for fluorouracil injection remains under review, this response does not address the Petition's requested labeling changes for that drug, and therefore, those requests are denied. As with all FDA-approved products, we will continue to monitor and review available safety information related to fluoropyrimidine drug products throughout the product life cycles and will take further action if we determine it is appropriate to do so.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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Patrizia Cavazzoni, MD
Director
Center for Drug Evaluation and Research