EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
The 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

DECISION SUMMARY
This Decision Summary contains corrections to the [December 2018] Decision Summary.

A. DEN Number:

DEN180028

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

C. Measurand:

Genotype of select alleles in Cytochrome P450 2C19 (CYP2C19), 2C9 (CYP2C9), 2D6 (CYP2D6), 3A5 (CYP3A5), thiopurine methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPYD), UDP glucoronosyltransferase family 1 member A1 (UGT1A1), and solute carrier organic anion transporter family member 1B1 (SLCO1B1)

D. Type of Test:

Qualitative genotyping microarray

E. Applicant:

23andMe, Inc.

F. Proprietary and Established Names:

23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

G. Regulatory Information:

Regulation	Name	Product Code	Panel
21 CFR 862.3364	Pharmacogenetic assessment system	QDJ	Chemistry (75)

H. Indications for Use:

1. Indications for Use:

The 23andMe Personal Genome Service (PGS) is a qualitative genotyping assessment

system applied to genomic DNA isolated from human saliva collected using the Oragene Dx OGD-500.001 to simultaneously detect, report, and interpret genetic variants in a broad multigene test. The assessment system is intended to enable users to access information about their genetics that could aid discussions with a healthcare professional. The 23andMe Personal Genome Service Pharmacogenetic Reports are indicated for reporting of the following variants:

Gene	Variant(s)
CYP2C19	*2, *3, *17
CYP2C9	*2, *3, *5, *6, rs7089580
CYP3A5	*3
UGT1A1	*6, *28
DPYD	*2A, rs67376798
TPMT	*2, *3C
SLCO1B1	*5
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41

This report is for over-the-counter use by adults over the age of 18 and provides genetic information to inform discussions with a healthcare professional about metabolism of therapeutics. This report describes if a person has variants associated with metabolism of some therapeutics, but 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 healthcare professional. The information provided by this report should not be used to start, stop, or change any course of treatment.

2. Special conditions for use statement(s)

- For over-the-counter (OTC) use.
- Results from this test should not be used to make medical decisions. Results should be confirmed in a clinical setting with independent genetic testing before taking any medical action.
- The user should not use results to start, stop, or change any course of treatment. Medications should always be taken as directed. Making changes can lead to harmful side effects or reduce intended benefits of the medication.
- This test does not diagnose any health conditions, predict drug response, provide medical advice, or determine whether a medication is indicated for the user.
- This test does not provide information on associations between specific DNA variants and any specific therapeutic.
- This test does not account for lifestyle or other health factors that may affect individual metabolism of medications.
- This test does not test for DNA variants in other genes that may affect other enzymes involved in the metabolism of medications.
- This test does not test for all possible DNA variants that may affect enzyme or protein function.

- This test is not a substitute for visits to a healthcare professional. The user should consult with a healthcare professional if the user has any questions or concerns about the results.

3. Special instrument requirements:

   Same as referenced in DEN140044.

I. Device Description:

The 23andMe PGS is a non-invasive DNA testing service that uses qualitative genotyping. It is a direct-to-consumer, over-the-counter, DNA genetic test. A user's saliva is self-collected using the Oragene·Dx device manufactured by DNA Genotek, Inc. (previously cleared under K141410), which consists of a sealable collection tube containing a stabilizing buffer solution. Once the sample is collected, it is shipped to one of two Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories for testing.

DNA is isolated from the saliva and tested in a multiplex assay using a customized genotyping beadchip, reagents, and instrumentation. The multiplex assay simultaneously tests for more than 500,000 variants, including those for the previously authorized indications, as well as for the indication proposed herein.

The raw data is generated by the scanning instrument's software, and then sent to 23andMe (the Manufacturer). The data are analyzed using the Manufacturer's proprietary software, and a genotype is determined for each tested variant. The results for certain of these variants, as noted in the indications for use, are used to generate personalized reports for users that provide information about the predicted metabolic function of the tested variants.

Personalized reports are generated for each user to provide results of the testing performed. These reports tell the user which variant(s) has/have been detected in their sample and provide information on the predicted metabolic function of the specific genetic variants. The genetic variants detected by the test are associated with the metabolism of some therapeutics. If no variant is detected, that information is also provided. If the association between the predicted metabolic function and the combination of detected variants has not been established, the report indicates that the results cannot be determined. The personalized reports are intended to present scientific concepts to users in an easy-to-understand format. The reports provide information about the association between the detected variant and the predicted metabolic function that has been associated with the metabolism of some drugs, further described below. The reports are designed to help users understand the meaning of their results and inform conversations with their doctor or other healthcare professional. The test reports do not provide any information on associations between the detected variants and any specific therapeutic and therefore, the test does not describe if a person will or will not respond to any specific therapeutic.

The 23andMe PGS Pharmacogenetic Reports detect 33 variants in 8 genes: CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP2D6, DPYD, TPMT, and UGT1A1. The 23andMe PGS

Pharmacogenetic Reports provide information on the associated enzyme or protein function and the predicted metabolizer phenotype for variants in drug metabolizing enzymes: CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP2D6, DPYD, TPMT, and UGT1A1. The predicted metabolizer phenotype is identified according to the number and consequence of each allele where two no-function alleles are associated with being poor metabolizers, one no-function allele is associated with being an intermediate metabolizer, two functional alleles are associated with being normal metabolizers, one gain-of-function allele is associated with being a rapid metabolizer, and two gain-of-function alleles are associated with being an ultrarapid metabolizer. The predicted metabolizer phenotype or protein function is then used to provide information on the potential consequence on metabolism of some medications. For example, poor metabolizers may process some medications slower, intermediate metabolizers may process some medications slightly slower than normal, normal metabolizers may process some medication at a normal rate, rapid metabolizers may process some medications slightly faster than normal, and ultrarapid metabolizers may process some medications faster than normal.

The 23andMe PGS Pharmacogenetic Report for SLCO1B1 will indicate that the detected variant is associated with a loss-of-function and slightly decreased transport of some medications.

J. Standard/Guidance Documents Referenced:

None.

K. Test Principle:

The PGS is indicated to be performed using a genotyping BeadChip assay, which covers more than 500,000 genetic markers. The BeadChip consists of silicon wafers etched to form wells loaded with silica beads, on which oligonucleotide capture probes are immobilized. DNA from saliva is fragmented and captured on a bead array by hybridization to immobilized SNP-specific primers, followed by extension with hapten-labeled nucleotides. The primers hybridize adjacent to the SNPs and are extended with a single nucleotide corresponding to the variant allele. The incorporated hapten-modified nucleotides are detected by adding fluorescently labeled antibodies in several steps to amplify the signals. Instrumentation is used for extraction and processing of the DNA, and the BeadChip is used for scanning and quantification of the results. The genotype content is separated, analyzed, and then integrated into pre-defined report templates specific for each condition associated with each genotype. Genotypes are determined using[(b) (4)] software packages. For the 23andMe PGS Pharmacogenetic Reports, the variants detected are:

Gene	Variants
CYP2C19	*2, *3, *17
CYP2C9	*2, *3, *5, *6, rs7089580
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, and *41
CYP3A5	*3
TPMT	*2, *3C

Gene	Variants
DPYD	*2A, rs67376798
UGT1A1	*6, *28
SLCO1B1	*5

L. Performance Characteristics:

1. Analytical performance:

Data to demonstrate analytical performance for the three detected alleles for CYP2C19 were provided and are described herein. Protocols and acceptance criteria to establish the analytical performance of each detected allele for CYP2C9, CYP2D6, CYP3A5, DPYD, TPMT, UGT1A1, and SLCO1B1 were reviewed and found to be acceptable. The sponsor will perform testing of the additional genes/variants according to the specified protocols, and if the validation data meet the specified acceptance criteria, they may add those genes/variants to the Pharmacogenetic Reports.

a. Reproducibility/Precision:

Reproducibility studies were conducted for the three CYP2C19 alleles reported by the PGS Pharmacogenetic report. The reproducibility studies were designed to determine the imprecision due to assay run, lot, instrument, operator, day, and site. DNA samples were obtained from an external vendor and genotyped in blinded fashion. Genotypes of the DNA samples were confirmed using bidirectional Sanger sequencing.

The study was performed at two sites across three days using three operator teams. Samples were genotyped in replicates of three using three lots of reagents, and three instrument sets.

Results obtained are summarized below stratified by genotype and site:

CYP2C19*2

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs* and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
	Site 1					
Homozygous Common (GG)	1	81	81	0	0	0
Heterozygous (AG)	2	162	162	0	0	0

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs* and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
Homozygous Rare (AA)	1	81	81	0	0	0
	Site 2					
Homozygous Common (GG)	1	81	81	0	0	0
Heterozygous (AG)	2	162	157	0	5	0
Homozygous Rare (AA)	1	81	81	0	0	0

*FQC = Failed quality controls

CYP2C19*3

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
	Site 1					
Homozygous Common (GG)	2	162	162	0	0	0
Heterozygous (AG)	1	81	81	0	0	0
Homozygous Rare (AA)	1	81	81	0	0	0
	Site 2					
Homozygous Common (GG)	2	162	157	0	5	0
Heterozygous (AG)	1	81	79	0	2	0
Homozygous Rare (AA)	1	81	81	0	0	0

*FQC = Failed quality controls

CYP2C19*17

Genotype	Number of samples (81 replicates per sample)	Number of total replicates (including FQCs and no calls)	Number of Correct Calls	Number of Incorrect Calls	Number of FQCs (first run)	Number of No Calls
	Site 1					
Homozygous Common (CC)	2	162	162	0	0	0
Heterozygous (CT)	1	81	81	0	0	0
Homozygous Rare (TT)	2	162	162	0	0	0
	Site 2					
Homozygous Common (CC)	2	162	158	0	4	0
Heterozygous (CT)	1	81	80	0	1	0
Homozygous Rare (TT)	2	162	160	0	2	0

*FQC = Failed quality controls

A second precision study was conducted at two sites on one day. At each site, one sample of each genotype for each allele was genotyped in replicates of three using two lots of reagents and three operator teams. Among samples with valid calls, the precision study yielded 100% correct genotype calls with a valid call across multiple days, operator teams, instruments, and reagent lots at both laboratory sites. There were zero 'no calls' in this study. The percentage of failed quality controls (FQCs) ranged from zero to 22.2% per sample.

b. *Linearity/assay reportable range:*

Not applicable.

c. *Traceability, Stability, Expected values:*

The PGS requires (b) (4)

[redacted]

DNA is extracted and genotyped on the 23andMe BeadChip

according to routine laboratory SOPs. Each new lot of the reproducibility control is tested by comparison with reference BeadChip genotype results.

The sample processing control is run on every sample genotyping plate and the reproducibility control is run approximately once per week. Historical data from all such runs were analyzed for one lot of the sample processing control spanning three months and one lot of the reproducibility control spanning one year.

Stability protocols and acceptance criteria were reviewed and acceptable. The information provided demonstrates that the sample processing control is stable for up to three months and the reproducibility control is stable for up to 12 months.

d. Detection limit:

The Limit of Detection (LoD) study was performed to determine the lowest concentration of DNA that is necessary for successful assignment of the correct CYP2C19*2, *3, and *17 variants using the 23andMe PGS test. Study samples were obtained from an external vendor based on their listed genotypes and included homozygous common, heterozygous common, and homozygous rare genotypes for each allele.

Three replicates of each sample were diluted to three different DNA concentrations (5, 15, and 50 ng/µl) and genotyped by the PGS test in a blinded fashion using 3 lots of reagents. To confirm the genotype call, each sample was sequenced by bidirectional Sanger sequencing. Genotype calls from the PGS test were compared with genotypes from Sanger sequencing to determine the rates of correct genotype calls at each DNA concentration.

This study yielded 100% correct calls per genotype for all samples across all reagent lots, at all sample concentrations tested. Therefore, the LoD is set at the lowest concentration tested (5 ng/µL). The performance requirement for the PGS test, specified in the laboratory SOPs, is set at a minimum of 15 ng/µL DNA and maximum of 50 ng/µL DNA.

e. Analytical specificity:

Endogenous and Exogenous Substances
A series of studies were conducted to assess the effects of endogenous substances, exogenous substances, microbial substances, and smoking on the 23andMe PGS Test. The results of the Endogenous and Exogenous Interference studies can be found in the Decision Summary for DEN140044.

Interfering Mutations
Analyses were performed to identify potentially interfering variants within the 50-nucleotide probe-binding regions of the three CYP2C19 variants detected by this test. Two potentially interfering mutations near *2, four potentially interfering mutations

near *3, and eight near *17 that are within the binding region for the variant being tested have been identified (see list below). The labeling specifies that the following mutations may potentially interfere with the CYP2C19 test.

CYP2C19 Variant	Potentially Interfering Mutation
(b) (4)	(b) (4)
(b) (4)	
(b) (4)	

f. Assay Cut-off:

Not applicable.

g. Specimen Stability at 2–8°C

Saliva samples for testing are collected with the Oragene·Dx OGD-500.001 collection device. See K141410 for sample stability information.

h. Shipping Stability

Saliva samples are shipped for testing in the Oragene·Dx OGD-500.001 collection device. See K141410 for sample shipping stability information.

2. Comparison studies:

a. Comparison with Sanger bidirectional Sequencing:

Accuracy was evaluated through calculation of agreement of the genetic variant determinations between the 23andMe PGS test results and Sanger bidirectional sequencing (comparator) results. Saliva samples were selected from the 23andMe customer biobank based on predetermined genotypes and the minimum volume required for testing. All chosen samples were then genotyped using Sanger bidirectional sequencing. Genotyping results were compared between the PGS test and bidirectional sequencing to calculate percent agreements with the sequencing

results used as the reference. The comparison study results for each allele detected for the CYP2C19 study report are shown below.

CYP2C19*2

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls (FQCs)	%PPA	%NPA	95% CI
Homozygous Common (GG)	47	0	0	3	100	100	92.5-100
Heterozygous (AG)	49	0	0	0	100	100	92.7-100
Homozygous Rare (AA)	48	0	0	3	100	100	92.6-100

*FQC = Failed quality controls

CYP2C19*3

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls (FQCs)	%PPA	%NPA	95% CI
Homozygous Common (GG)	48	0	0	2	100	100	92.6-100
Heterozygous (AG)	45	0	0	3	100	100	92.1-100
Homozygous Rare (AA)	39	0	0	1	100	100	91.0-100

*FQC = Failed quality controls

Genotype	Correct Calls	Incorrect Calls	No Calls	Failed Quality Controls (FQCs)	%PPA	%NPA	95% CI
Homozygous Common (CC)	49	0	0	1	100	100	92.7-100
Heterozygous (CT)	45	0	0	4	100	100	92.1-100
Homozygous Rare (TT)	47	0	0	0	100	100	92.5-100

*FQC = Failed quality controls

Due to the large margin of error (i.e., wide confidence intervals), and selection bias

(i.e., samples were chosen from a biobank based on the variants already detected by the candidate assay), there is residual uncertainty about the analytical results of this test. This uncertainty is mitigated because this device is indicated as providing only a preliminary test result that must be confirmed using an independent pharmacogenetic test. Results from this device should not be used for clinical decision making.

The labeling for the device indicates the following: "Results from this test should not be used to make medical decisions. Results should be confirmed in a clinical setting with independent genetic testing before taking any medical action."

b. Matrix Comparison

Not applicable.

3. Clinical studies:

a. Clinical Sensitivity

Not applicable.

b. Clinical Specificity

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable)

i. Predicted Pharmacogenetic Associations: The impact of protein or enzyme function for each allele and the predicted metabolizer phenotypes were identified from data in the literature for each allele for each gene.

ii. User Comprehension Study: A user comprehension study was conducted to assess comprehension of the proposed labeling of the pharmacogenetic test reports in a demographically diverse (e.g., age, education) set of users naïve to the study subject. A total of 602 participants completed the study; the completion rate was 100%. Participants were assigned to one of five different types of pharmacogenetic reports (e.g., variant(s) detected, results cannot be determined, cannot interpret results). Eight participants (1.3%) were excluded from the analysis because they were determined to be a careless responder who got a pre-defined "red-herring" question wrong (6), determined to have previously received a 23andMe report (1), or a technical issue occurred during testing (1). Therefore, 594 subjects were included in the primary endpoint analysis. A second analysis was performed excluding participants that did not scroll/read through the test reports as identified by the moderators of the test (63 participants). It may not be appropriate to exclude participants that did not scroll/read the test reports, since users may not read or scroll through the test report when receiving and interpreting results from this device.

The results of the overall comprehension rate for each identified comprehension concept are summarized below for each analysis provided by the sponsor:

Comprehension Concept	All participants (n=594)	Participants that scrolled/read the test reports (n=531)
Purpose of the test	89.9%	90.8%
Result and meaning	89.9%	90.2%
Limitations and variant coverage	93.1%	94.2%
Limitations of medication coverage	94.8%	95.1%
Appropriate actions	92.3%	92.8%
Treatment adherence	97.0%	97.2%
Other risk factors	95.0%	95.5%

iii. Frequently Asked Questions: The labeling for each pharmacogenetic report includes a Frequently Asked Questions (FAQ) section. The FAQ section was created to provide users information to adequately understand the purpose, limitations, and the meaning of the results of the test. The concepts covered in the FAQ section include: the test results, the purpose of the test, limitations of the test, the meaning of the result, other risks factors that contribute to drug metabolism, and appropriate follow-up actions (e.g., user should not stop or change any medication they may be taking, results should be confirmed in a clinical setting with additional testing prior before taking any medication action).

4. Expected Values

The package insert and user test reports include allele frequencies from 23andMe customers. The package insert for each test report indicates that the allele frequencies provided are from the 23andMe customer database and may not be representative of the actual allele frequencies in the presented populations. The following allele frequencies will be provided in the CYP2C19 package insert and user test report:

Ethnicity	*2	*3	*17
European	(b) (4)		
African American			
Ashkenazi Jewish			
East Asian			
Hispanic/Latino			
South Asian			

c. Instrument Name:

Same as referenced in DEN140044.

d. System Description:

1. Modes of Operation:

   Same as referenced in DEN140044.

2. Software:
   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes___X___or No _____

   Level of Concern

   Moderate

   Software Description:

   Same as referenced in DEN140044.

   Revision Level History:

   Changes since DEN140044 and DEN170046 were reviewed and found acceptable.

   Unresolved Anomalies:

   Sponsor states that there are no known unresolved anomalies associated with the system software.

   EMC Testing:

   Not applicable.

3. Specimen Identification:
   Same as referenced in DEN140044.

4. Specimen Sampling and Handling:

   Same as referenced in DEN140044.

5. Calibration:

   Same as referenced in DEN140044.

6. Quality Control:

   Same as referenced in DEN140044.

M. Other Supportive Instrument Performance Characteristics Data Not Covered In the "Performance Characteristics" Section above:

Not applicable.

N. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

O. Patient Perspectives:

This submission did not include specific information on patient perspectives for this device. However, in making our decision, we considered that patients want easy access to information about their genetics, and they want this information in a manner they can easily understand and appropriately apply.

P. Identified Risks to Health and Identified Mitigations:

Identified Risks to Health	Identified Mitigations
Incorrect test results (false positive or false negative results)	Special controls (1), (2), (3), (4), and (5)
Incorrect interpretation of test results	Special controls (1)(ii), (2), (3), (4), (5) and (6)
Incorrect action based on test results	Special controls (1)(ii), (2), (3), (4), and (6)

Q. Benefit/Risk Analysis

Summary of the Assessment of Benefit
For the Proposed Indications for Use

The PGS test pharmacogenetic reports provide users with easier access to their own health data compared to traditional genetic tests. This test does not require a prescription from a healthcare professional and the sample collection kits are mailed directly to the users. Adults may potentially benefit from the use of this test to inform conversations with their healthcare professionals regarding DNA variants that may impact metabolism of some therapeutics. These conversations may then prompt clinicians to perform confirmatory pharmacogenetic tests which may have an impact on personalizing medical management.

Summary of the Assessment of Risk
For the Proposed Indications for Use

Risks associated with this device include erroneous test results (false positive or false negative results), incorrect interpretation of the test report by the user or healthcare provider, incorrect user action based on the test result (e.g., self-directing a change in drug dosage or stopping of a medication that has been prescribed by a healthcare provider), and incorrect action by the healthcare provider (e.g., use of the results by the healthcare provider prior to confirming the test result). Incorrect interpretation and action by the user may lead to user harm. Incorrect interpretation and action by the healthcare provider may lead to inappropriate clinical decision making and user harm.

Summary of the Assessment of Benefit-Risk
For the Proposed Indications for Use

Given that there are possible risks associated with an incorrect test result, incorrect interpretation of test results, and incorrect action based on the test result, the benefit-risk balance of this device is undetermined and requires additional mitigations in the form of limitations and special controls, beyond general controls.

Summary of the Assessment of Benefit-Risk, considering risk mitigation strategies
For the Proposed Indications for Use

The risks of incorrect user interpretation and self-directing a change in drug dosage or stopping of a medication (i.e., an incorrect action based on test results) is mitigated by results from a user comprehension study that demonstrated overall comprehension of the critical concepts for the device including medication adherence. This risk is further mitigated by labeling which includes user reports that specify that users should not use the results to stop or change any medication. The user test report also indicates that the test does not provide any information on any specific medication.

The risk of erroneous interpretation and incorrect action by the healthcare provider is mitigated by adequate labeling including user test reports that specify that results should not be used for clinical decision making and that results should be confirmed in a clinical setting with additional testing before making any medical decisions.

Risks associated with erroneous test results are mitigated by limited analytical performance studies, supportive clinical information for each allele, and adequate labeling. The user test report indicates that results should not be used for clinical decision making and that results should be confirmed by an independent pharmacogenetic test before making any medical decisions since there is residual uncertainty associated with the analytical validation data.

Overall, the likelihood of benefit of the pharmacogenetic reports to describe variants associated with the metabolism of some drugs in user reports and inform conversations with healthcare providers that may prompt confirmatory pharmacogenetic testing outweighs the likelihood of erroneous interpretation and incorrect action by the user or healthcare provider,

when considering the mitigations provided by the limitations and special controls, beyond general controls.

R. Conclusion:

The information provided in this de novo submission is sufficient to classify this device into class II under regulation 21 CFR 862.3364. FDA believes that the special controls, in combination with the general controls, provide a reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: QDJ
Device Type: Pharmacogenetic assessment system
Class: II (special controls)
Regulation: 21 CFR 862.3364

a.) Identification: A pharmacogenetic assessment system is a qualitative in vitro molecular diagnostic system intended to detect nucleic acid variants isolated from human specimens for the purpose of assessing the presence of genetic variants that impact the metabolism, exposure, response, risk of adverse events, dosing, or mechanisms of prescription or over-the-counter medications. The intended use of the device must not include an indication for use in supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or presenting a potential, unreasonable risk of illness or injury.

b.) Classification: Class II (special controls). A pharmacogenetic assessment system must comply with the following special controls:

(1) Design verification and validation must include:
  (i) Data appropriate, as determined by FDA, to demonstrate the analytical accuracy and reliability of the device in intended use specimens, including but not limited to precision, reproducibility, accuracy, limits of detection, and interferences. This information must include:
    (A) Data demonstrating appropriate, as determined by FDA, reproducibility for each genotype using each claimed sample type. Reproducibility data shall be evaluated using specimens collected and processed in a manner consistent with the device's instructions for use, or, as determined by FDA, an appropriate alternative sample panel.
    (B) Analytical data demonstrating the limits of detection, including the minimum amount of input DNA that will consistently produce accurate results.
    (C) Data demonstrating no clinically significant effects from endogenous and exogenous interferents relevant to each intended use specimen type. Interference data must also include an

assessment of potentially interfering genetic sequences (e.g., variants proximal to the variant of interest, pseudogenes).

(D) Validation data appropriate, as determined by FDA, to support specimen collection and handling claims.

(E) Clinical data generated in intended use patient populations demonstrating the pharmacogenetic association between the genetic variant tested and any clinical claims or therapy-related recommendations associated with that genotype.

(ii) Results from an appropriate, as determined by FDA, user comprehension study that demonstrate the intended user can use the device safely. The user comprehension study must be designed to include the following:

(A) Study participants from a statistically sufficient sample size and a demographically diverse (e.g., age, education level) population that is representative of the intended use population and naïve to use of the device, and

(B) An evaluation of all result comprehension concepts that are critical for safe use of the device.

(2) The 21 CFR 809.10 labeling must include:

(i) Clear information, written in language appropriate for the intended user, that describes instructions for how test results should be interpreted. These instructions must be supported by valid scientific evidence and include:

(A) Appropriate explanation of the claimed pharmacogenetic associations for all variants included in the test, any relevant variants not included in the test (e.g., that may contribute to false negative results), and specific considerations by ethnicity, and

(B) Appropriate explanation of non-genetic and non-tested genetic factors that may impact interpretation of the test results;

(ii) Detailed descriptions of analytical performance including, as applicable, precision, reproducibility, accuracy, limits of detection, and interferences as specified in paragraph (b)(1)(i) of this section, in language appropriate for the intended user;

(iii) A warning statement that the patient should not use the test results to stop or change any medication, and that medications should always be taken as prescribed by a healthcare professional;

(iv) A limiting statement explaining that this test is not intended to inform the patient about their current state of health, including whether or not the patient should or should not take a medication, or how much of a medication the patient should take, as appropriate;

(v) A warning statement that the test does not diagnose any health conditions and is not a substitute for visits to a doctor or other healthcare professional; and

(vi) A prominent and conspicuous limiting statement that the test provides only a preliminary test result that needs to be confirmed using an independent pharmacogenetic test without such a limitation prior to making any medical decisions. Alternatively, appropriate design

verification and validation activities, including the generation of robust analytical data demonstrating appropriate analytical accuracy and reliability of test results for each genetic variant included in the test report, must be performed that demonstrate that the test can be used to make well-informed clinical decisions.

(3) The test report must include an appropriate description of how the test results should be used by healthcare providers who may receive the test results from their patients, as applicable.

(4) Publicly available pre-purchase labeling with unrestricted access that contains the following information must be provided:
   (i) A clear description of the test and its technology, the genotypes detected, and relevant clinical claims associated with each genotype;
   (ii) A clear description of what information the test will provide. This includes, but is not limited to, variant information, the limitations associated with the test, and any precautionary information about the test the user should be aware of before purchase; and
   (iii) A discussion of answers to frequently asked questions that is sufficient to provide intended users with an appropriate understanding of information specific to each pharmacogenetic association that is claimed.

(5) The genetic test must use a sample collection device that is FDA-cleared, -approved, or classified as 510(k) exempt, with an indication for *in vitro* diagnostic use in DNA testing.

(6) The intended use of the device must not include an indication for use in supporting or sustaining human life, being of substantial importance in preventing impairment of human health, or presenting a potential, unreasonable risk of illness or injury.