510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k093420

B. Purpose for Submission:

New device

C. Measurand:

Genotype of Cytochrome P450 2D6 (CYP2D6)

D. Type of Test:

Multiplex PCR followed by multiplex allele specific primer extension for genotyping, hybridized to multiplexed fluorescing microparticles, detected by flow cytometry

E. Applicant:

Luminex Molecular Diagnostics, Inc.

F. Proprietary and Established Names:

xTAG® CYP2D6 Kit

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NTI	II	21 CFR §862.3360 - Drug Metabolizing Enzyme Genotyping System	Toxicology

H. Intended Use:

1. Intended use(s):

   The xTAG® CYP2D6 Kit v3 is a device used to simultaneously detect and identify a panel of nucleotide variants found within the highly polymorphic CYP2D6 gene located on chromosome 22 from genomic DNA extracted from an EDTA or citrate anticoagulated whole blood sample. This kit can also identify gene rearrangements associated with the deletion (*5) and duplication genotypes. The xTAG® CYP2D6 Kit v3 is a qualitative genotyping assay which can be used as an aid to clinicians in determining therapeutic strategy for therapeutics that are metabolized by the CYP2D6 gene product. This kit is not indicated for stand-alone diagnostic purposes. This test is not intended to be used to predict drug response or non-response.

2. Indication(s) for use:

   See Intended use above.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Luminex 100 or 200 IS instruments

I. Device Description:

The xTAG® CYP2D6 Kit v3 includes the following components:

- PCR Mix A (includes dNTPs)
- PCR Mix B (includes dNTPs)
- ASPE Mix (includes dNTPs)
- Bead Mix
- 10x Buffer
- Shrimp Alkaline Phosphatase
- Exonuclease I
- Streptavidin, R-Phycoerythrin conjugate
- Platinum TFI Exo(-) DNA Polymerase and associated $MgCl_2$ and PCR buffer
- xTAG® Data Analysis Software (TDAS) CYP2D6
- LA Taq DNA Polymerase

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Amplichip CYP450 Test

2. Predicate K number(s):

   k042259

3. Comparison with predicate:

Similarities		
Item	Predicate device (k042259)	Proposed device
Indications for use	Intended to identify a patient's CYP2D6 genotype from genomic DNA extracted from a whole blood sample.	Same
Limitation	This test is not intended to be used to predict drug response or non-response.	Same
CYP450 gene genotyped by the test	2D6	Same

Differences		
Item	Predicate device (k042259)	Proposed device
Number of 2D6 star genotypes detected by the device	20	16
CYP450 2D6 star genotypes detected by the test	*1, *2, *3, *4, *5 ,*6, *7, *8, *9, *10, *11, *15, *17, *19, *20, *29, *35, *36, *40, *41	*1, *2, *3, *4, *5 ,*6, *7, *8, *9, *10, *11, *15, *17, *29, *35, *41
Sample types	EDTA anticoagulated whole blood	EDTA and citrate anticoagulated whole blood
Instrument	Affymetrix GeneChip Microarray Instrumentation System	Luminex 100 and 200 IS Instrument
Test principle	PCR amplification of purified DNA, fragmentation and labeling of amplified products, hybridization of amplified products to a microarray and staining of the bound products, and scanning of the microarray	Multiplex PCR followed by multiplex allele specific primer extension for genotyping, hybridized to multiplexed fluorescing microparticles, detected by flow cytometry

K. Standard/Guidance Document Referenced (if applicable):

- Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems - Guidance for Industry and FDA Staff
- Guidance for Industry and FDA Staff: Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
- Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers
- Guidance for Industry and FDA Staff: Content of Pre-Market Submission for Software Contained in Medical Devices
- CLSI Guideline MM01-A2: *Molecular Diagnostic Methods for Genetic Diseases*
- CLSI Guideline MM13-PE: *Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods*
- CLSI Guideline EP05-A2: *Evaluation of Precision Performance of Clinical Chemistry Devices*
- CLSI Guideline EP07-A2E: *Interference Testing in Clinical Chemistry*
- CLSI Guideline EP12-A: *User Protocol for Evaluation of Qualitative Test Performance*
- CLSI Guideline EP17-A: *Protocols for Determining Limits of Detection and Limits of Quantitation*

L. Test Principle:

For each genomic sample being tested, two separate PCR reactions are performed. PCR-A produces an alpha fragment used to detect the mutations in the table below, as well as a duplication amplimer which indicates the presence of the duplication genotype. PCR-B produces a beta fragment used to detect the mutations in the table below, as well as a deletion amplimer indicative of the deletion genotype.

Following PCR amplification, the two reactions (PCR-A and PCR-B) are pooled. To enable efficient incorporation of biotin-dCTP during the ASPE reaction, the pooled PCR product is treated with Shrimp Alkaline Phosphatase to dephosphorylate any remaining nucleotides (particularly dCTP), and with Exonuclease I to degrade any primers left over from the PCR reaction.

ASPE is then carried out using universally-tagged primers supplied in the ASPE primer mix. An aliquot of the ASPE reaction is hybridized with the universal array (Bead Mix) in the presence of the hybridization buffer and incubated with Streptavidin, R-Phycoerythrin conjugate (reporter solution).

Samples are read on the Luminex 100 IS or 200 IS instrument and a signal is generated for each of the loci as well as for the duplication and deletion amplimers, if present. These fluorescence values are then analyzed to determine whether the wild-type/mutant allele for each of the loci has been detected, or whether the samples carry an allele(s) with the deletion or duplication.

Star Genotype	**Mutations and Polymorphisms detected by xTAG® CYP2D6**	
	PCR A	**PCR B**
*1	None	None
*2	**-1584C>G**, 1661G>C,	**2850C>T**, **4180G>C**
*3		**2549A>del**
*4	100C>T, 1661G>C, **1846G>A**,	2850C>T, 4180G>C
*5		**Deletion**
*6	**1707T>del**,	4180G>C
*7		**2935A>C**
*8	1661G>C, **1758G>T**,	2850C>T, 4180G>C
*9		**2613delAGA**
*10	**100C>T**,	1661G>C, 4180G>C
*11	**883G>C**, 1661G>C,	2850C>T, 4180G>C
*15	**138insT**	

Star Genotype	Mutations and Polymorphisms detected by xTAG® CYP2D6	
	PCR A	**PCR B**
*17	**1023C>T**, 1661G>C,	2850C>T, 4180G>C
*29	**1659G>A**, 1661G>C,	2850C>T, **3183G>A**, 4180G>C
*35	-1584C>G, **31G>A**, 1661G>C,	2850C>T, 4180G>C
*41	1661G>C,	2850C>T, **2988G>A**, 4180G>C
DUP	**Duplication**	

Nucleotide changes that define the star genotype (*) are shown in bold font.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Reproducibility of the xTAG® CYP2D6 Kit v3 was assessed using a multiple-center, multiple-operator, multiple-lot, blinded study design. A subset of samples was extracted at each site with a different extraction method, therefore three different DNA extraction methods were included in the study. Reproducibility of the complete assay, including the extraction step, was assessed on 8 EDTA anticoagulated whole blood samples (genotypes provided in table below). Evaluation of the reproducibility of the analytical (post-extraction) steps of the assay was further assessed with testing of 5 purified genomic DNA samples.

   This study was designed to distinguish between Site-to-Site, Lot-to-Lot and Operator-to-Operator reproducibility in the CYP2D6 assay. There were 2 operators per site, each performing one run per day across 3 non-consecutive days (3 runs per operator or 6 runs per site). Thus the number of replicates per sample for this study was:

   (3 sites) x (2 operators/site) x (3 runs/operator) x (2 replicates/run) = 36 replicates.

Reproducibility of the xTAG® CYP2D6 Kit v3 was demonstrated with a panel of 13 samples representing the following star (*) alleles (also termed 'star genotypes'):

Sample ID	Star Alleles Present	Sample Type
1	*1/*5	genomic DNA
2	*1/*41	genomic DNA
3	*4/*35	genomic DNA
4	*2/*4, DUP	genomic DNA
5	*35/*41	genomic DNA
6	*1/*10	whole blood
7	*10/*17	whole blood
8	*1/*2	whole blood
9	*1/*1	whole blood
10	*2/*10	whole blood
11	*2/*17	whole blood
12	*1/*5	whole blood
13	*2/*2	whole blood

Sample	Geno-type	Repli-cates per site	# Total repli-cates	# correct calls (Site 1)	# correct calls (Site 2)	# correct calls (Site 3)	Total correct calls[1]	# No calls[1]	# Incorrect calls[1]	95% LCB	% Agree-ment
1	*1/*5	12	36	12	12	12	36	0	0	90.25	100.00
2	*1/*41	12	36	12	12	12	36	0	0	90.25	100.00
3	*4/*35	12	36	11	12	12	35	1	0	85.47	97.22
4	*2/*4, DUP	12	36	10	12	12	34	2	0	81.34	94.44
5	*35/*41	12	36	12	12	11	35	1	0	85.47	97.22
6	*1/*10	12	36	12	12	12	36	0	0	90.26	100.00
7	*10/*17	12	36	11	12	7	30	6	0	67.19	83.33
8	*1/*2	12	36	12	12	12	36	0	0	90.26	100.00
9	*1/*1	12	36	9	12	11	32	4	0	73.94	88.89
10	*2/*10	12	36	10	12	10	32	4	0	73.94	88.89
11	*2/*17	12	36	10	12	11	33	3	0	77.53	91.26
12	*1/*5	12	36	8	12	12	32	4	0	73.94	88.89
13	*2/*2	12	36	11	12	12	35	1	0	85.47	97.22

[1] across all three sites

Overall percent agreement after the first test was 94.44% with a 95% lower bound confidence interval of 91.97%.

At Site 1, one replicate of one sample required two re-tests to resolve the No Call. The root cause was identified to be extraction failure. All other No Calls were resolved after one re-test. All Site 3 No Calls were resolved after one re-test.

Reproducibility results presented (# of correct calls per 12 replicates) by site, operator and lot:

Sample	Genotype	Site 1					
		Operator 1			Operator 2		
		Day A Lot 1	Day B Lot 2	Day C Lot 3	Day A Lot 1	Day B Lot 2	Day C Lot 3
1	*1/*5	12	12	12	12	12	12
2	*1/*41	12	12	12	12	12	12
3	*4/*35	12	11	12	12	12	12
4	*2/*4, DUP	11	12	12	12	11	12
5	*35/*41	12	12	12	12	12	12
6	*1/*10	12	12	12	12	12	12
7	*10/*17	12	12	12	12	12	11
8	*1/*2	12	12	12	12	12	12
9	*1/*1	11	10	12	12	12	12
10	*2/*10	12	12	10	12	12	12
11	*2/*17	11	11	12	12	12	12
12	*1/*5	12	12	12	11	11	10
13	*2/*2	11	12	12	12	12	12
Sample	**Genotype**	**Site 2**					
1	*1/*5	12	12	12	12	12	12
2	*1/*41	12	12	12	12	12	12
3	*4/*35	12	12	12	12	12	12
4	*2/*4, DUP	12	12	12	12	12	12
5	*35/*41	12	12	12	12	12	12
6	*1/*10	12	12	12	12	12	12
7	*10/*17	12	12	12	12	12	12
8	*1/*2	12	12	12	12	12	12
9	*1/*1	12	12	12	12	12	12
10	*2/*10	12	12	12	12	12	12
11	*2/*17	12	12	12	12	12	12
12	*1/*5	12	12	12	12	12	12
13	*2/*2	12	12	12	12	12	12

Sample	Genotype	Site 3					
		Operator 1			Operator 2		
		Day A Lot 1	Day B Lot 2	Day C Lot 3	Day A Lot 1	Day B Lot 2	Day C Lot 3
1	*1/*5	12	12	12	12	12	12
2	*1/*41	12	12	12	12	12	12
3	*4/*35	12	12	12	12	12	12
4	*2/*4, DUP	12	12	12	12	12	12
5	*35/*41	12	12	12	11	12	12
6	*1/*10	12	12	12	12	12	12
7	*10/*17	12	10	10	12	12	11
8	*1/*2	12	12	12	12	12	12
9	*1/*1	12	12	12	12	11	12
10	*2/*10	12	12	11	11	12	12
11	*2/*17	12	12	12	12	12	11
12	*1/*5	12	12	12	12	12	12
13	*2/*2	12	12	12	12	12	12

b. *Linearity/assay reportable range:*

Not applicable.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Quality control materials are not provided with the kit. The package insert states that previously characterized clinical samples or commercially available 2D6 controls are recommended for quality control testing. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or requirements.

Stability: The stability performance of the xTAG® CYP2D6 Kit v3 was evaluated using three kit lots. The stability protocol includes testing under real-time and accelerated conditions. Real-time data is based on kit components stored at the recommended temperature of -20˚C. Accelerated data is based on stressed conditions where components are stored at 25˚C. The current claimed shelf-life for the xTAG® CYP2D6 Kit v3 is 12 months. Real-time stability testing is on-going. In addition, repeated freeze-thaw cycles (up to 6) of the xTAG CYP2D6 Kit v3 are acceptable; stability testing protocols, acceptance criteria and summary of the data was reviewed and found to be acceptable.

d. Detection limit:

The limit of detection (LoD) and range of the xTAG® CYP2D6 Kit v3 was assessed by analyzing serial dilutions of genomic DNA samples from cell lines and whole blood samples containing one or more mutations or polymorphisms analyzed by the assay. DNA concentrations tested ranged

from 0.1 – 300 ng/uL. Determination of the DNA range of the assay was performed at 1 site, with 3 operators running a total of five samples across three consecutive days, 2 lots of reagents, and 3 different sets of equipment. Genotypes for all samples were established by bi-directional DNA sequencing.

Five samples used in the study had the following genotypes: *1/*41, *1/*5, *35/*41, *17/*29, and *2/*4 DUP.

Results for the Limit of Detection study:

Input DNA (ng/µL)	Number of Samples	# Correct Calls	# Incorrect Calls	# No calls	% Agreement	Lower Bound of 95% Confidence Interval	Upper Bound of 95% Confidence Interval
100	160	160	0	0	100.00	97.72	100.00
82.5[1]	40	40	0	0	100.00	91.19	100.00
50	200	199	0	1	99.50	97.25	99.99
10	200	200	0	0	100.00	98.17	100.00
5	200	196	0	4	98.00	94.96	99.45
2	200	200	0	0	100.00	98.17	100.00
1	200	200	0	0	100.00	98.17	100.00
0.1	200	105	1[2]	94	52.50	45.34	59.59

[1]The highest DNA concentration extracted from the whole blood sample was 82.5 ng/µL.
[2]For one replicate, the *1/*5 sample was incorrectly called as *1/*1.

The recommended DNA concentration for this assay is 10 ng/µL and the lowest level of DNA that should be used is 2 ng/µL.

e. Analytical specificity:

Six patient blood samples were tested in this study. The genotypes of the samples were: *1/*1, *1/*5, *2/*2, *1/*10, *2/*17 and *10/*17. A given blood sample was split into 6 equivalent parts. One part was bi-directionally sequenced. One part was left as a control. The other parts of the blood sample were mixed, respectively, with hemoglobin, albumin, bilirubin, or triglycerides. Each was then split into three, and underwent DNA extraction by one of three different DNA extraction methods. The following potential interferents and the levels tested were: 500 mg/dL hemoglobin, 20 mg/dL bilirubin, 3000 mg/dL albumin and 2000 mg/dL triglycerides. Genotypes for all samples were established by bi-directional DNA sequencing.

None of the substances tested interfered with the assay, since test results of all samples that had added compounds were 100% in agreement with the expected genotype determined by sequencing.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Four hundred and fifty-nine clinical samples were analyzed in the method comparison study. Samples were either EDTA or citrate whole blood samples. Results using the xTAG® CYP2D6 Kit v3 was compared to bidirectional dideoxy sequencing. The percent agreement for genotype detection of the xTAG® CYP2D6 Kit v3 was calculated by determining the percentage of tested samples with the correct genotype assigned, compared to the total number of samples tested of that genotype.

CYP2D6 Allele Star (*) Genotype	Number of Alleles Sequenced	xTAG® CYP2D6 Kit v3 First Run Results			
		# Correct Calls	# Incorrect Calls	# No Calls	% Agreement
***1**	199	198	0	1	99.45
***2**	143	139	1[1]	3	97.20
***3**	15	15	0	0	100.00
***4**	124	123	0	1	99.14
***5**	59	57	0	2	96.61
***6**	16	16	0	0	100.00
***7**	2	2	0	0	100.00
***9**	28	28	0	0	100.00
***10**	82	79	0	3	95.12
***11**	2	2	0	0	100.00
***15**	1	1	0	0	100.00
***17**	73	72	0	1	98.61
***29**	23	22	0	1	95.64
***35**	45	45	0	0	100.00
***41**	106	106	0	0	100.00
Total	**918**	**905**	**1**	**12**	**98.4**

[1] Incorrect call for *2/*10; result given by xTAG® CYP2D6 Kit v3 was *10/*35 because of a HET call at the 31 G>A loci

Results by sample genotype:

CYP2D6 Genotype	Total Unique Samples	xTAG® CYP2D6 Kit v3 First Run Results			
		# Correct Calls	# No Calls	# Incorrect Calls	% Agreement
*1 / *1	17	17	0	0	100
*1 / *1, DUP	1	1	0	0	100
*1 / *10	16	16	0	0	100
*1 / *17	21	21	0	0	100
*1 / *2	29	28	1	0	96.55
*1 / *2, DUP	5	5	0	0	100
*1 / *29	6	6	0	0	100
*1 / *29, DUP	1	1	0	0	100
*1 / *3	6	6	0	0	100
*1 / *3, DUP	1	1	0	0	100
*1 / *35	12	12	0	0	100
*1 / *4	25	25	0	0	100
*1 / *41	17	17	0	0	100
*1 / *5	13	13	0	0	100
*1 / *5, DUP	1	1	0	0	100
*1 / *6	5	5	0	0	100
*1 / *9	5	5	0	0	100
*10 / *10	18	18	0	0	100
*10 / *17	8	7	1	0	87.50
*10 / *35	1	1	0	0	100
*10 / *41	5	5	0	0	100
*15 / *41	1	1	0	0	100
*17 / *17	4	4	0	0	100
*17 / *29	4	4	0	0	100
*17 / *29, DUP	1	1	0	0	100
*17 / *41	4	4	0	0	100
*2 / *10	6	4	1	1[1]	66.67
*2 / *17	10	10	0	0	100
*2 / *17, DUP	1	1	0	0	100
*2 / *2	7	7	0	0	100
*2 / *2, DUP	3	3	0	0	100
*2 / *29	3	3	0	0	100
*2 / *3	1	1	0	0	100
*2 / *35	6	6	0	0	100
*2 / *11	2	2	0	0	100
*2 / *4	21	21	0	0	100
*2 / *41	14	14	0	0	100

*2 / *41, DUP	2	2	0	0	100
*2 / *5	9	8	1	0	88.89
*2 / *6	3	3	0	0	100
*2 / *7	2	2	0	0	100
*2 / *9	9	9	0	0	100
*29 / *41	3	3	0	0	100
*3 / *3	1	1	0	0	100
*3 / *35	2	2	0	0	100
*3 / *4	1	1	0	0	100
*3 / *5	1	1	0	0	100
*3 / *9	1	1	0	0	100
*35 / *35	2	2	0	0	100
*35 / *41	6	6	0	0	100
*4 / *10	6	6	0	0	100
*4 / *17	4	4	0	0	100
*4 / *17, DUP	2	2	0	0	100
*4 / *29	1	1	0	0	100
*4 / *29 DUP	2	1	1	0	50.00
*4 / *35	7	7	0	0	100
*4 / *35, DUP	1	1	0	0	100
*4 / *4	12	12	0	0	100
*4 / *4, DUP	1	1	0	0	100
*4 / *41	20	20	0	0	100
*4 / *5	3	3	0	0	100
*4 / *5, DUP	2	2	0	0	100
*4 / *6	1	1	0	0	100
*4 / *9	2	2	0	0	100
*41 / *41	13	13	0	0	100
*5 / *10	4	3	1	0	75.00
*5 / *17	10	10	0	0	100
*5 / *29	2	2	0	0	100
*5 / *35	3	3	0	0	100
*5 / *41	2	2	0	0	100
*5 / *5	3	3	0	0	100
*5 / *6	3	3	0	0	100
*6 / *35	2	2	0	0	100
*6 / *6	1	1	0	0	100
*9 / *35	1	1	0	0	100
*9 / *41	6	6	0	0	100
*9 / *9	2	2	0	0	100
Total	**459**	**446**	**6**	**1**	**98.4[2]**

[1] Incorrect call for *2/*10; result given by xTAG® CYP2D6 Kit v3 was *10/*35 because of a HET call at the 31 G>A loci
[2] 95% Lower Bound Confidence Interval = 96.89%

For rare alleles, the performance of the xTAG® CYP2D6 Kit v3 was evaluated by blending plasmids with mutations for rare alleles with homozygous genomic DNA. Plasmid clones for the *8 allele were created by blending plasmids harboring mutations for rare alleles with genomic DNA. A total of 5 blends of genomic DNA and plasmid were tested. Four replicates of each blend were amplified (total of 20 samples) and assayed by xTAG® CYP2D6 Kit v3. Genotype results using plasmid clone-genomic DNA blends are shown in the table below. The CYP2D6 genotype call rate was 100% for plasmid clone genomic DNA blends.

Plasmid Genotype	**Genomic DNA Genotype**	**Blended sample Expected genotype**	**Blended samples (n)**	**# Correct Calls**	**# Incorrect calls**	**# No calls**	**% Agreement**
*8	*1/*1	*1/*8	4	4	0	0	100
*8	*35/*2	*35/*8	4	4	0	0	100
*8	*17/*17	*17/*8	4	4	0	0	100
*8	*2/*2	*2/*8	4	4	0	0	100
*8	*4/*4	*4/*8	4	4	0	0	100
Total			**20**	**20**	**0**	**0**	**100**

b. Matrix comparison:

Twenty five specimens were tested that had been collected both in EDTA and citrate, extracted and run on the Luminex 2D6 assay. There were no No Calls or Incorrect calls. In addition, citrate anticoagulated whole blood samples were tested in the method comparison study in 2a above.

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):

Not applicable.

4. Clinical cut-off**:**

Not applicable.

5. Expected values/Reference range:

Final TDAS Output (*genotype or * allele)	SNPs that xTAG® CYP2D6 v3 kit detects	Frequency in the U.S. Caucasian population[1]	Frequency in the African American population[2]	Predicted Enzyme Activity	Reference where the effect of the genotype on drug metabolism is described
*1	None	37 – 40%	29 – 35%	Normal	(Kimura, Umeno et al. 1989; Marez, Legrand et al. 1997; Sachse, Brockmoller et al. 1997)
*2	-1584C>G, 1661G>C, 2850C>T, 4180G>C	26 - 33%	18 - 27%	Normal	(Johansson, Lundqvist et al. 1993; Panserat, Mura et al. 1994; Marez, Legrand et al. 1997; Raimundo, Fischer et al. 2000; Sakuyama, Sasaki et al. 2008)
*3	2549A>del	1%	0.2%-0.6%	None	(Kagimoto, Heim et al. 1990; Marez, Legrand et al. 1997)
*4	100C>T, 1661G>C, 1846G>A, 4180G>C, 2850C>T	18 - 20%	6 - 9%	None	(Gough, Miles et al. 1990; Hanioka, Kimura et al. 1990; Kagimoto, Heim et al. 1990;Sachse et al, 1997; Marez et al, 1997)
*5	deletion	2 - 4%	6 - 7%	None	(Gaedigk, Blum et al. 1991; Steen, Molven et al. 1995)
*6	1707T>del, 4180G>C	1%	0.5%	None	(Evert, Griese et al. 1994; Saxena, Shaw et al. 1994; Daly, Leathart et al. 1995; Marez, Legrand et al. 1997)
*7	2935A>C 1661G>C, 1758G>T, 2850C>T, 4180G>C	Not known	Not known	None	(Evert, Griese et al. 1994)
*8	1661G>C, 1758G>T, 2850C>T, 4180G>C	Not known	Not known	None	(Broly, Marez et al. 1995)

*9	2613delAGA	2 - 3%	0.3%	Reduced	(Tyndale, Aoyama et al. 1991; Broly and Meyer 1993)
*10	100C>T, 1661G>C, 4180G>C	2 - 8%	0.3%-0.4%	Reduced	(Yokota, Tamura et al. 1993; Johansson, Oscarson et al. 1994; Ishiguro, Kubota et al. 2004; Sakuyama, Sasaki et al. 2008)
*11	883G>C, 1661G>C, 2850C>T, 4180G>C	Not known	Not known	None	(Marez, Sabbagh et al. 1995)
*15	138insT	Not known	Not known	None	(Sachse, Brockmoller et al. 1996)
*17	1023C>T, 1661G>C, 2850C>T, 4180G>C	0.2-0.3%	15 - 26%	Reduced	(Masimirembwa, Persson et al. 1996; Oscarson, Hidestrand et al. 1997)
*29	1659G>A, 1661G>C, 2850C>T, 3183G>A, 4180G>C	Not known[3]	Not known[3]	Reduced	(Marez, Legrand et al. 1997; Wennerholm, Johansson et al. 2001; Wennerholm, Dandara et al. 2002)
*35	-1584C>G, 31G>A, 1661G>C, 2850C>T, 4180G>C	7.4%[4]	1%[4]	Normal	(Marez, Legrand et al. 1997; Gaedigk, Ryder et al. 2003)
*41	1661G>C, 2850C>T, 2988G>A, 4180G>C	9%[4]	11%[4]	Reduced	(Raimundo, Fischer et al. 2000; Raimundo, Toscano et al. 2004)

[1] [2], Bradford, L. D. (2002). "CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants." Pharmacogenomics **3**(2): 229-43.

[3] The frequency of the *29 allele in the U.S. population is not known; however, it is very common in Tanzanian Africans, with an allele frequency of 20 percent (Wennerholm, A., I. Johansson, et al. (2001). "Characterization of the CYP2D6*29 allele commonly present in a black Tanzanian population causing reduced catalytic activity." Pharmacogenetics **11** (5): 417-27).

[4] Gaedigk, A., D. L. Ryder, et al. (2003). "CYP2D6 poor metabolizer status can be ruled out by a single genotyping assay for the -1584G promoter polymorphism." Clinical Chemistry **49**(6 Pt 1): 1008-11.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.