

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

A. 510(k) Number:

k073014

B. Purpose for Submission:

New device

C. Measurand:

Genotype of Cytochrome P450 2C9 (CYP450 2C9) and Vitamin K epoxide reductase complex subunit 1 (VKORC1)

D. Type of Test:

Genotyping microarray

E. Applicant:

Autogenomics, Inc.

F. Proprietary and Established Names:

INFINITI 2C9-VKORC1 Multiplex Assay for Warfarin

G. Regulatory Information:

1. Regulation section:

21 CFR §862.3360 Drug Metabolizing Enzyme Genotyping Systems

21 CFR §864.7750 Prothrombin time test

21 CFR §862.2570 Instrumentation for Clinical Multiplex Test Systems

2. Classification:

Class II

3. Product code:

ODW Cytochrome P450 2C9 (CYP450 2C9) Drug Metabolizing Enzyme Genotyping System

ODV Vitamin K epoxide reductase complex subunit 1 (VKORC1) Genotyping System

NSU Instrumentation for Clinical Multiplex Test Systems

4. Panel:

Toxicology (91), Hematology (81), Chemistry (75)

H. Intended Use:

1. Intended use(s):

See Indications for use below.

2. Indication(s) for use:

The INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin is an *in vitro* diagnostic test for the detection and genotyping of the *2 and *3 CYP2C9 genetic variants and the VKORC1 3673 (-1639) intronic variant in genomic deoxyribonucleic acid (DNA) obtained from EDTA-anticoagulated whole blood samples. The INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin is a qualitative assay for use in clinical laboratories upon prescription by the attending physician.

The INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin is indicated for use to identify individuals at risk for sensitivity to warfarin.

3. Special conditions for use statement(s):
For prescription use only.

The information provided from this test may supplement therapeutic decision-making and should only be used in conjunction with routine monitoring by a physician. Clinicians should use professional judgment in the interpretation of results from this type of test.

4. Special instrument requirements:
Autogenomics INFINITI Analyzer

I. Device Description:

The INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin is an in vitro diagnostic device which utilizes proprietary film-based microarray technology combined with process automation, reagent management, and software technology for the detection and genotyping of the 2C9*2, 2C9*3, and VKORC1 3673 (-1639) mutations from human whole peripheral blood samples.

The INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin is comprised of the BioFilmChip™ Microarray, the Intellipac Reagent Module and the PCR Amplification Mix. The INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin should be run using the AutoGenomics INFINITI Analyzer.

The BioFilmChip Microarray consists of a polyester film coated with proprietary multi-layer components designed for DNA analysis. There can be up to 240 spots per microarray with each spot representing a different allele. The microarrays are designed to be assay specific.

The Intellipac Reagent Module, which acts as a communication link, contains up to eight reservoirs that house the test reagents and has an integrated memory chip. The assay protocol resides in this memory chip, and upon request is loaded to the INFINITI Analyzer. Information such as expiration date of reagents, volume usage, time of use, and operation parameters are archived in the memory chip and appear on the worklist (run report). The PCR Amplification Mix consists of the reagents needed for the PCR amplification step of the assay.

The INFINITI Analyzer is an instrument used for clinical multiplex systems intended to measure and sort multiple signals from a clinical sample. The INFINITI Analyzer is designed to measure fluorescence signals of labeled DNA target hybridized to BioFilmChip microarrays. The INFINITI Analyzer automates the 2C9 and VKORC1 assays and integrates all the discrete processes of sample (PCR amplicon) handling, reagent management, hybridization, detection, and results analysis. The assays are processed automatically and read by the built-in confocal microscope. Results are analyzed and presented as genotype calls.

J. Substantial Equivalence Information:

1. Predicate device name(s):
AmpliChip CYP450 Test for CYP2C19; INFINITI System Assay for Factor II & Factor V
2. Predicate 510(k) number(s):
k043576; k060564
3. Comparison with predicate:

Differences		
Characteristic	Predicate device (k043576)	Proposed device
Number of genes	2	2
Genes	CYP2D6 and CYP2C19	CYP2C9 and VKORC1
Microarray substrate	Reactions occur on a single glass slide	Reactions occur on a single biofilm microarray chip

Similarities		
Characteristic	Predicate device (k043576)	Proposed device
Test principle	Microarray-based genotyping test for simultaneous detection (multiplex system) of DNA sequences	Same
Specimen Type	Purified DNA from whole blood samples	Same
Reaction Conditions	Utilizes thermal cycling and target DNA amplification	Same

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

Drug Metabolizing Enzyme Genotyping System – Class II Special Controls Guidance Document

L. Test Principle:

The INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin is designed to simultaneously detect the *2 and *3 CYP4502C9 genetic variants and the VKORC1 3673 (-1639) intronic variant. The assay protocol is based on five major processes:

- (a) DNA extraction
- (b) PCR amplification of purified DNA from human genomic DNA
- (c) Labeling of the amplified product (allele specific primer extension)
- (d) Hybridization of the labeled amplified product to a microarray by signature Tag/Capture probe hybridization under isothermal conditions.
- (e) Scanning of the microarray
- (f) Signal detection and analysis: determination of the 2C9*2, 2C9*3 and VKORC1 3673 (-1639) genotypes

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Site-to-site: To assess site-to-site reproducibility, three clinical sites (one internal, two external) performed testing using three independent analyzers and three different operators. Three lots of 2C9-VKORC1 assay reagents were used. All three sites tested the same panel of samples, which included 7 genomic DNA samples and 5 clinical samples. Each site used a different DNA extraction method for the clinical samples. The study gave a 99.0% call rate based on 1283 correct calls out of a total of 1296 genotype calls. There were 13 “no calls” in the study, but no incorrect calls were observed.

Sample type, ID number and respective genotypes:

Sample type	ID	Genotype	
		CYP2C9	VKORC1 3673 ¹
Genomic 1	1	*2/*3	AA
Genomic 2	2	*1/*1	GG
Genomic 3	3	*2/*2	GA
Genomic 4	4	*3/*3	GA
Genomic 5	5	*1/*2	GG
Genomic 6	6	*1/*1	GG
Genomic 7	7	*1/*1	GG
Patient 1	8	*1/*1	GA
Patient 2	9	*1/*1	GG
Patient 3	10	*3/*3	GA
Patient 4	11	*1/*2	GA
Patient 5	12	*1/*1	AA

¹G=wild-type; A=mutant

Inter-Laboratory Reproducibility study results (data sorted by sample)

ID	Genotype			Total # Tested	First Time Run					Final Result ^c				
	2C9		VKORC 1 3673 (-1639)		# Genotype Calls made by INFINITI ^a	# Correct Calls ^b	# No Calls	# In-correct Calls	Correct Call Rate ^d (%)	# Genotype Calls made by INFINITI ^a	# Correct Calls ^b	# No Calls	# In-correct Calls	Correct Call Rate ^d (%)
	*2	*3												
1	*1/*2	*1/*3	AA	36	34	34	2	0	94.4	36	36	0	0	100
2	*1/*1	*1/*1	GG	36	36	36	0	0	100	36	36	0	0	100
3	*2/*2	*1/*1	GA	36	35	35	1	0	97.2	36	36	0	0	100
4	*1/*1	*3/*3	GA	36	35	35	1	0	97.2	36	36	0	0	100
5	*1/*2	*1/*1	GG	36	36	36	0	0	100	36	36	0	0	100
6	*1/*1	*1/*1	GG	36	36	36	0	0	100	36	36	0	0	100
7	*1/*1	*1/*1	GG	36	36	36	0	0	100	36	36	0	0	100
8	*1/*1	*1/*3	GA	36	36	36	0	0	100	36	36	0	0	100
9	*1/*1	*1/*1	GG	36	35	35	1	0	97.2	36	36	0	0	100
10	*1/*1	*3/*3	GA	36	36	36	0	0	100	36	36	0	0	100
11	*1/*2	*1/*1	GA	36	36	36	0	0	100	36	36	0	0	100
12	*1/*1	*1/*1	AA	36	36	36	0	0	100	36	36	0	0	100
Total				432	427	427	5	0	98.8	432	432	0	0	100

^a Excludes samples with indeterminate calls

^b A sample with correct call indicates a correct call at all three loci. One incorrect or no call at one out of the three loci for the sample is considered an incorrect or indeterminate call for the whole sample

^c Final results reflect one time repeat of samples with indeterminate (no) calls

^d Correct call rate = # samples with correct calls/# samples tested

Inter-Laboratory Reproducibility study results (data sorted by each genotype)

Genotype	Samples Tested	Tests Per Site ^a	Site	Geno- type Calls	First run				After second run			
					Corr- ect Calls	In- correct Calls	No Calls	% Corr- ect Calls	Corr- ect Calls	In- correct Calls	No Calls	% Corr- ect Calls
2C9*2 *1/*2	3	36	1	36	36	0	0	100	36	0	0	100
			2	33	36	0	2 ^b	94.4	36	0	0	100
			3	36	36	0	0	100.0	36	0	0	100
2C9*2 *2/*2	1	12	1	12	12	0	0	100.0	12	0	0	100
			2	12	11	0	1 ^b	91.7	12	0	0	100
			3	12	12	0	0	100.0	12	0	0	100
2C9*2 *1/*1	8	96	1	96	95	0	1 ^a	99.0	96	0	0	100
			2	96	96	0	0	100	96	0	0	100
			3	96	96	0	0	100.0	96	0	0	100
2C9*3 *1/*3	2	24	1	24	24	0	0	100.0	24	0	0	100
			2	24	22	0	2 ^b	91.7	24	0	0	100
			3	24	24	0	0	100.0	24	0	0	100
2C9*3 *3/*3	2	24	1	24	24	0	0	100	24	0	0	100
			2	24	24	0	0	100.0	24	0	0	100
			3	24	23	0	1 ^c	95.8	24	0	0	100
2C9*3 *1/*1	8	96	1	96	95	0	1 ^a	99.0	96	0	0	100
			2	96	95	0	1 ^b	99.0	96	0	0	100
			3	96	96	0	1	100.0	96	0	0	100
VKORC1 3673 GA	5	60	1	60	60	0	0	100	60	0	0	100
			2	60	59	0	1 ^b	98.3	60	0	0	100
			3	60	60	0	0	100.0	60	0	0	100
VKORC1 3673 AA	2	24	1	24	24	0	0	100.0	24	0	0	100
			2	24	22	0	2 ^b	91.7	24	0	0	100
			3	24	24	0	0	100.0	24	0	0	100
VKORC1 3673 GG (WT)	5	60	1	60	59	0	1 ^a	98.3	60	0	0	100
			2	60	60	0	0	100	60	0	0	100
			3	60	60	0	0	100.0	60	0	0	100
Total per Site			1	432	429	0	3	99.3	432	0	0	100
			2	432	423	0	9	97.9	432	0	0	100
			3	432	431	0	1	99.8	432	0	0	100
Total				1296	1283	0	13	99.0	1296	0	0	100

^a Site 1: no call given; the error log documented “#41 THS Error Tip not sensed.” The instrument tip height sensor did not detect a pipette tip for that sample and therefore no results were provided for the sample.

^b Site 2: no call given for one of these samples due to tip sensor not sensing liquid due to low volume of wash buffer in one sample; two other samples also gave no calls due to not enough sample added

^c Site 3: one sample had no call; not enough sample added

Chip-to-chip: Using the same genomic DNA sample and the same instrument, the assay was run using five microarray chips from one lot of R-Chip, with each microarray chip run five times. This was repeated with two other instruments. Two-way ANOVA of the mean RFU readings, p-values for chip-to-chip reproducibility were significant (p > 0.001).

Instrument #1012: $p = 1.77904E-43$ (F-test)
 Instrument #1020: $p = 3.73325E-71$ (F-test)
 Instrument #1022: $p = 1.31994E-29$ (F-test)
 All genotype calls were 100% correct.

Lot-to-lot: Three lots of each of the BioFilmChip Microarray, Intellipac Reagent and Amplification Mix were tested in duplicate using three different genomic DNA samples.

Lot	# samples tested	Correct call rate (1 st run) (%)	Correct call rate (2 nd run) (%)
A	144	99.3*	100
B	144	100	100
C	144	97.2*	100

* 5 tests gave no call. Tests were repeated and gave correct calls on second run.

Within chip: Five chips from one lot of biofilm microarray were used for this study. Mean is the average RFU reading of the three spots for the analyte/probe. All genotype calls were 100% correct. The following table provides average % CV within a chip and average % CV for each analyte/probe:

Chips	R10D31		R10D32		R10D33		R10D34		R10D35	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
2C9*2WT	793.7	1.2	583.1	1.7	909.6	4.2	732.6	3.3	927.0	4.8
2C9*2M	1.0	11.2	5.4	6.3	5.4	10.9	13.5	16.7	3.5	1.3
2C9*3WT	1389.7	10.3	1220.1	7.3	1755.4	3.7	1616.7	4.2	1614.0	1.1
2C9*3M	15.5	0.8	8.2	0.5	16.3	12.7	11.7	5.5	5.8	2.3
VKR3673G	1354.1	4.2	1276.9	7.0	1661.6	1.0	1456.9	6.1	1384.2	4.2
VKR3673A	1048.1	6.3	905.1	2.5	190.9	2.9	117.3	6.6	1191.1	4.1

Run-to-run (intra-instrument) reproducibility: Run-to-run assay reproducibility was evaluated using one microarray chip (R-Chip) scanned five times on each of three different instruments. All genotype calls were 100% correct.

Inter-instrument reproducibility: Five microarray chips were scanned five times on three different instruments to determine inter-instrument assay reproducibility. Using two-way ANOVA, there was no significant difference detected in the five runs ($p > 0.01$). All genotype calls were 100% correct.

b. *Linearity/assay reportable range:*
 Not applicable.

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

Controls: Positive or negative controls are not included with this assay. The manufacturer has recommended that a positive (heterozygous and/or homozygous for the three genotypes) sample for each mutation, a negative control (a sample that does not contain the mutation of interest, i.e., a wild type sample); and a “Non-Template Control” be included with each test run. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations.

Pre-immobilized negative and positive controls: These controls are related to the hybridization process, and indicate that the hybridization has taken place. There are five (5) negative control spots and three (3) positive control spots. The negative control is a 3'biotinylated 24mer to which nothing should bind. The positive control is a 3'biotinylated 24mer that hybridizes the complementary Cy5 labeled oligonucleotide.

Stability: BioFilmChip Microarray is stable for 180 days at 15-30°C, the Intellipac Reagent for 180 days when stored at 2-8°C, and the Amplification Mix is stable for 180 days when stored at -10°C. Stability testing protocols, acceptance criteria for stability testing and release criteria have been reviewed and found to be acceptable.

d. Detection limit:

In order to determine the lowest concentration of DNA at which this assay is accurate, serial dilutions (200, 100, 50, 25, 10, 1, 0.1 ng) of a genomic sample were assayed multiple times using the 2C9-VKORC1 assay. Low detection limit was determined as 1 ng of purified DNA per reaction, which is the lowest DNA amount that gave the correct genotyping call for all test runs. The 0.1 ng DNA sample did not always provide a test result. The recommended DNA concentration for the INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin is 25ng/μl. The assay requires 2μl of DNA sample or the equivalent of 50ng per test.

In addition, analytical studies demonstrated that DNA concentrations of 100ng and 200ng which were in excess of the recommended sample (50ng) did not interfere with the INFINITI 2C9 & VKORC1 Multiplex Assay.

e. Analytical specificity:

Evaluation of potential interference from bilirubin, cholesterol, and heparin demonstrated that presence of these compounds in concentrations of 8mg/dl bilirubin, 70mg/dl cholesterol and 133v/dl heparin does not interfere with the INFINITI 2C9 & VKORC1 Multiplex Assay. Three whole blood samples were split and spiked with various concentrations of cholesterol, bilirubin and heparin, the DNA was extracted and run on the INFINITI 2C9 & VKORC1 Multiplex Assay. The correct genotype calls for these three samples were obtained at all compound concentrations.

Sample carry-over:

Two genomic DNA samples with different genotypes and water were used in this study. Four ‘samples’ were tested in this order: a high DNA concentration sample (300ng), a low DNA concentration sample (10ng) of a different genotype, followed by the high DNA concentration sample again, then a water blank. This protocol was run multiple times, and in all cases, the correct call (or an indeterminate call for the water ‘sample’) was obtained, illustrating no sample carry-over between samples.

Assay carry-over:

Assay interference study was conducted to demonstrate that running the Assay for Factor II & Factor V (k060564) and the 2C9 & VKORC1 Multiplex assay on the same instrument does not affect the results of each assay. These assays utilize different chips and reagents, but use the same wash buffer stored on the instrument. Two genomic DNA samples were used for the 2C9-VKORC1 assays with distinct genotypes at all loci, and two other genomic samples were used for the Factor II-Factor V assay (also with distinct genotypes at the two loci). On the first day, using one INFINITI analyzer, one run of 2C9-VKORC1 assays (consisting of 4 assays) was followed by one run of Factor II-Factor V assays (consisting of 4 assays). Simultaneously, on another INFINITI analyzer, the testing was repeated with samples tested in reverse order. These studies were repeated on a second day. All genotype calls made by the 8 runs were correct. Assay interference was not detected.

Day	Analyzer	Run	Assays	Correct call rate (%)
1	1025	1	2C9-VKORC1	100
		2	FII-FV	100
	1028	3	FII-FV	100
		4	2C9-VKORC1	100
2	1025	5	FII-FV	100
		6	2C9-VKORC1	100
	1028	7	2C9-VKORC1	100
		8	FII-FV	100

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

The method comparison study was completed at three external sites. All three sites compared the results of samples run on the INFINITI 2C9-VKORC1 Multiplex Assay to bi-directional sequencing results (sequencing was completed at one site). Each site provided their own clinical samples.

Agreement between INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin and Bi-directional DNA Sequencing (by loci)

Genotype ^a	Number Tested	Replicates per Sample	Number of Correct Genotype Calls ^b	Number of Incorrect Calls	No Calls	Agreement	95% One-Sided Confidence Lower Limit
2C9*2 *1/*2	35	1	34	0	1	97.1%	88.2%
2C9*2 *2/*2	2	1	2	0	0	100.0%	50% ^d
2C9*2 *1/*1	113	1	111	0	2	98.2%	94.91%
Total for 2C9*2	150	1	147	0	3	98.0%	95.09%
2C9*3 *1/*3	20	1	19	1 ^c	0	95.0%	80.45%
2C9*3 *3/*3	1	1	1	0	0	100.0%	0% ^e
2C9*3 *1/*1	129	1	126	0	3	97.7%	94.30%
Total for 2C9*3	150	1	146	1	3	97.3%	94.09%
VKORC1 3673 (-1639) GA	63	1	62	0	1	98.4%	93.74%
VKORC1 3673(-1639) AA	27	1	25	0	2	92.6%	79.01%
VKORC1 3673 (-1639) GG	60	1	60	0	0	100.0%	98.33%
Total for VKORC1 3673 (-1639)	150	1	147	0	3	98.0%	95.09%
Total for Assay	450	1	440	1	9	97.8%	96.86%

^a Genotype determined through bi-directional DNA sequencing

^b Calls produced on first run

^c Initial INFINITI results (*1/*1 for 2C9*2, *1/*3 for 2C9*3 and GG for VKORC1 3673) did not match bi-directional sequence results (*1/*1 for 2C9*2, *1/*1 for 2C9*3 and GG for VKORC1 3673). The same INFINITI results were obtained on repeat run. Reason unknown.

^d For sample sizes 1 and 2, and 100% agreement, $SE(p2-p1) = 0$. Pure sample size correction for sample size 2 is 50% and for sample size 1 is 100%, therefore the 95% One-Sided Confidence Lower Limits are 50% (n=2) and 0% (n=1).

Agreement between INFINITI 2C9 & VKORC1 Multiplex Assay for Warfarin and Bi-Directional DNA Sequencing (by Sample Type)

Sample Description Genotype ^a			First Time Run					Final Result ^d			
2C9	VKORC1 3673 (-1639)	# Samples Tested	# Correct Calls ^c	# No Calls	# In- correct Calls	Correct Call Rate ^e (%)	# Correct Calls ^c	# No Calls	# In- correct Calls	Correct Call Rate ^e (%)	
*2	*3										
*1/*1	*1/*1	AA	20	18	2	0	90.0	20	0	0	100
*1/*1	*1/*1	GA	34	34	0	0	100	34	0	0	100
*1/*1	*1/*1	GG	43	42	0	1 ^f	97.7	42	0	1	97.7
*1/*2	*1/*1	AA	4	4	0	0	100	4	0	0	100
*1/*2	*1/*1	GA	15	14	1	0	93.3	15	0	0	100
*1/*2	*1/*1	GG	12	12	0	0	100	12	0	0	100
*1/*1	*1/*3	AA	2	2	0	0	100	2	0	0	100
*1/*1	*1/*3	GA	10	10	0	0	100	10	0	0	100
*1/*1	*1/*3	GG	3	3	0	0	100	3	0	0	100
*2/*2	*1/*1	GA	1	1	0	0	100	1	0	0	100
*2/*2	*1/*1	GG	1	1	0	0	100	1	0	0	100
*1/*2	*1/*3	AA	1	1	0	0	100	1	0	0	100
*1/*2	*1/*3	GA	2	2	0	0	100	2	0	0	100
*1/*2	*1/*3	GG	1	1	0	0	100	1	0	0	100
*1/*1	*3/*3	GA	1	1	0	0	100	1	0	0	100
Total			150	146	3	1	97.3	149	0	1	99.3

^a Genotype determined through bi-directional DNA sequencing

^b Excludes samples with indeterminate/no calls

^c A sample with correct call indicates a correct call at all three loci. One incorrect or no call at one out of the three loci for the sample is considered an incorrect or indeterminate call for the whole sample

^d Final results reflect one time repeat of samples with indeterminate calls

^e Correct call rate = # samples with correct calls/# samples tested

^f Initial INFINITI results (*1/*1 for 2C9*2, *1/*3 for 2C9*3 and GG for VKORC1 3673) did not match bi-directional sequence results (*1/*1 for 2C9*2, *1/*1 for 2C9*3 and GG for VKORC1 3673). The same INFINITI results were obtained on repeat run. Reason unknown.

- 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):
 4. Clinical cut-off:
Not applicable.
 5. Expected values/Reference range:
The following provides the allele frequency across ethnic groups for the CYP2C9 and VKORC1 variants which have been shown to affect an individual's sensitivity to warfarin.

Allele	Ethnic Group		
	Caucasian	African	Asian
CYP2C9*2	0.9 - 20% ¹	0.8 - 7% ¹	0% ¹
CYP2C9*3	0 - 14.5% ¹	0.4 - 3% ¹	0 - 8.2% ¹
VKORC1 3673 (-1639)	37% ²	14% ²	89% ²

¹ Lee CR, Goldstein JA, Pieper JA. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics* 2002; 12: 251-263.

² Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, Blough DK, Thummel KE, Veenstra DL, Rettie AE. Effect of *VKORC1* haplotypes on transcriptional regulation and warfarin dose. *NEJM* 2005; 352: 2285-2293.

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.