510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number

K200913

B Applicant

SPD Swiss Precision Diagnostics GmbH

C Proprietary and Established Names

Clearblue® Early Digital Pregnancy Test

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LCX	Class II	21 CFR 862.1155 - Human Chorionic Gonadotropin (HCG) Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New Device

B Measurand:

Human Chorionic Gonadotropin (hCG)

C Type of Test:

Qualitative chromatographic immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Clearblue® Early Digital Pregnancy Test is an over-the-counter chromatographic immunoassay for the qualitative detection of human chorionic gonadotropin (hCG) in urine. This digital test is intended for use as an aid in early detection of pregnancy, in some cases as early as six (6) days before the day of the missed period, i.e. as early as five (5) days before the day of the expected period. The test is intended for home use.

C Special Conditions for Use Statement(s):

OTC - Over The Counter
Clearblue® Early Digital Pregnancy Test is intended for over-the-counter (OTC) use.

D Special Instrument Requirements:

None.

IV Device/System Characteristics:

A Device Description:

The Clearblue® Early Digital Pregnancy Test is a qualitative lateral flow immunoassay for the detection of hCG. Each device is provided in a sealed pouch with instructions for use and a desiccant package to control moisture during storage. The device consists of a plastic-housed test stick containing an immunochromatographic strip and electronic and optical components along with a microprocessor and specific algorithms to digitally display test results.

B Principle of Operation:

The Clearblue® Early Digital Pregnancy test is a lateral flow sandwich immunoassay employing monoclonal antibodies that are specifically directed against the alpha and beta sub-units of hCG. To use the test, the user either urinates directly onto the absorbent wick or collects a sample in a clean, dry container and dips the absorbent wick into the collected sample until the Stop Light begins to flash (which usually takes five seconds for both sampling methods). After the urine specimen is applied to the device, the hCG present in the specimen will react with a mouse anti-hCG monoclonal antibody conjugate. The conjugate complex migrates along the membrane towards the test and control zones. A digital component integral with the chromatographic strip reads and displays the result of the immunochemical reaction on an LCD screen of the device. Once the device self-calibration process is completed, a progress bar symbol appears on the display, indicating that test is working and counting down the time to result. The test is complete after a result (“Pregnant” for a positive result, “Not Pregnant” for a negative result) or an error/invalid result (book symbol) is displayed on the LCD. This occurs within one to five minutes of sample detection.

V Substantial Equivalence Information:

A Predicate Device Name(s):

First Response™ Gold Digital Pregnancy Test

B Predicate 510(k) Number(s):

K123567

C Comparison with Predicate(s):

Device & Predicate Device(s):	K200913	K123567
Device Trade Name	Clearblue® Early Digital Pregnancy Test	FIRST RESPONSE™ Gold Digital Pregnancy Test
General Device Characteristic Similarities		
Intended Use/Indications For Use	Qualitative detection of hCG as an aid in early detection of pregnancy	Same
Early Detection Claim	Pregnancy can be detected as early as six days before the day of the missed period (five days before the day of the expected period)	Same
Intended use environment	Over the counter use	Same
Test Principle	Lateral flow qualitative chromatographic immunoassay with digital result display	Same
Sample Matrix	Urine	Same
Traceability	World Health Organization (WHO) 4th International Standard (IS) for hCG	Same
hCG Sensitivity	10 mIU/mL	Same
General Device Characteristic Differences		
hCG isoforms detected	Intact hCG	Intact hCG Hyperglycosylated hCG hCG β-subunit hCG β-core fragment
Time to result	1-5 minutes	3 minutes

Device & Predicate Device(s):	K200913	K123567
Test result display	Pregnant/ Not Pregnant displayed in words (LCD)	YES+ (for Pregnant results) NO- (for Not Pregnant result)

VI Standards/Guidance Documents Referenced:

None referenced.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
A precision study was performed using a pooled female human negative urine sample spiked with hCG (traceable to the 4th WHO IS) to obtain samples with hCG concentrations of 0, 3, 4.5, 6, 7.5, 9, 10, 12.5 and 25 mIU/mL. Each sample was tested using three lots of Clearblue® Early Digital Pregnancy Test devices in both simulated midstream and dip sampling methods. The tests were performed over the course of 3 non-consecutive days by 3 different operators. A total of 162 replicates were performed per sampling method per hCG concentration. The device cutoff is 10 mIU/mL hCG.

Simulated midstream method

hCG concentration (mIU/mL)	Lot 1		Lot 2		Lot 3	
	# Positive / Total #	% Positive	# Positive / Total #	% Positive	# Positive / Total #	% Positive
0	0/54	0.0%	0/54	0.0%	0/54	0.0%
3	0/54	0.0%	0/54	0.0%	0/54	0.0%
4.5	2/54	3.7%	3/54	5.6%	2/54	3.7%
6	7/54	13.0%	8/54	14.8%	6/54	11.1%
7.5	30/54	55.6%	22/54	40.7%	22/54	40.7%
9	50/54	92.6%	50/54	92.6%	47/54	87.0%
10	54/54	100.0%	54/54	100.0%	54/54	100.0%
12.5	54/54	100.0%	54/54	100.0%	54/54	100.0%
25	54/54	100.0%	54/54	100.0%	54/54	100.0%

Dip method

hCG concentration (mIU/mL)	Lot 1		Lot 2		Lot 3	
	# Positive / Total #	% Positive	# Positive / Total #	% Positive	# Positive / Total #	% Positive
0	0/54	0.0%	0/54	0.0%	0/54	0.0%
3	0/54	0.0%	0/54	0.0%	0/54	0.0%
4.5	1/54	1.9%	2/54	3.7%	0/54	0.0%
6	8/54	14.8%	3/54	5.6%	4/54	7.4%
7.5	23/54	42.6%	16/54	29.6%	17/54	31.5%
9	47/54	87.0%	48/54	88.9%	46/54	85.2%
10	54/54	100.0%	54/54	100.0%	54/54	100.0%
12.5	54/54	100.0%	54/54	100.0%	54/54	100.0%
25	54/54	100.0%	54/54	100.0%	54/54	100.0%

2. Linearity:

Linearity is not applicable since this is a qualitative test.

3. Analytical Specificity/Interference:

Interference from exogenous and endogenous substances

A negative pooled human urine sample and a positive pooled human urine sample containing 10 mIU/mL hCG were spiked with potentially interfering exogenous and endogenous substances (test samples). Control samples containing no test substance were also tested and compared to test samples. Test and control samples were tested using five devices from each of three lots of the candidate device. The results demonstrated no interference from substances at the concentrations shown in the table below.

Substance tested	Highest concentration tested that demonstrated no interference (mg/dL)
Acetaminophen	60
Acetone	100
Acetylsalicylic acid	100
Albumin	500
Ampicillin	20
Ascorbic acid	15
Atropine	20
Bilirubin	20
Caffeine	120
Clomiphene citrate	2.4
Cotinine	4
Ethanol	1% v/v
Gentisic acid	20
Glucose	2000

Substance tested	Highest concentration tested that demonstrated no interference (mg/dL)
Hemoglobin	10
Hydrochloric acid	1.25mM
Ibuprofen	10
Oxytetracycline	30
Phenylpropanolamine	20
Sodium hydroxide	1.25 mM
Tetracycline	30
Urea	3000
Uric acid	75
Urobilinogen	10
E3G	620 ng/ml
P3G	4
Leukocytes	$1x10^6$ cells/ml
Blood	0.3% v/v
Semen	5% v/v

Cross-reactivity of structurally-related compounds

Clearblue® Early Digital Pregnancy Test devices were tested with three potential cross-reactants: follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH). Each potential cross-reactant was spiked into a negative pooled human urine sample and a positive pooled human urine sample containing 10 mIU/mL hCG. Control samples containing no test substance were also tested and compared to test samples. Test and control samples were tested in replicates of five with each of three lots of candidate device. The results demonstrated no cross-reactivity from potential cross-reactants up to 500 mIU/mL LH, 1000 mIU/mL FSH, and 1 mIU/mL TSH in either negative or positive urine samples.

Effect of urine pH and Specific Gravity

Negative human urine samples and positive human urine samples containing 10 mIU/mL hCG were adjusted to pH values from 4.0 to 9.0 and tested using the candidate device. The results demonstrated that samples within the pH range of 4.0 to 9.0 do not interfere with either positive or negative results from the device.

Negative human urine samples and positive human urine samples containing 10 mIU/mL hCG were adjusted to specific gravity values from 1.000 to 1.035 and tested using the candidate device. The results demonstrated that samples within the specific gravity range of 1.000 to 1.035 do not interfere with either positive or negative results from the device.

Effect of hCG β-core fragment

To evaluate potential interference from hCG β core fragment (hCGβcf), worst-case, physiologically-relevant combinations of intact hCG and hCGβcf (as supported by published literature and internal testing) were assessed with the candidate device. Testing was conducted using multiple devices from 3 lots of devices. No hCGβcf interference was observed for the following test conditions:

- Pooled negative urine spiked with 10 mIU/mL hCG and 150 pmol/L hCGβcf (a level far above expected physiologic hCGβcf levels for this level of hCG).
- Pooled negative urine spiked with 1,000,000 pmol/L hCGβcf and 25,362 mIU/mL hCG (representative of mean levels of hCG at 6-7 weeks of pregnancy when hCGβcf is reliably detectable in urine).
- Pooled urine from women 6-7 weeks pregnant spiked with 1,000,000 pmol/L hCGβcf.
- Pooled negative urine spiked with 1,000,000 pmol/L hCGβcf and 46,920 mIU/mL hCG (representative of mean levels of hCG at 9-12 weeks of pregnancy when hCGβcf reaches peak levels).
- Pooled urine from women 9-12 weeks pregnant spiked with 1,000,000 pmol/L hCGβcf.
- 30 individual clinical samples from women weeks 9-12 weeks of pregnancy with hCG levels ranging from 19,454 to 226,980 mIU/mL and hCGβcf levels ranging from 276,000 to 1,086,000.

High dose hook effect study
Negative pooled human urine and negative pooled human urine spiked up to 1,000,000 mIU/mL hCG were tested in replicates of five with each of three lots of candidate device. No hook effect was observed at concentrations of up to 1,000,000 mIU/mL hCG.

4. Assay Reportable Range:

   Not applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   The Clearblue® Early Digital Pregnancy Test is calibrated against the World Health Organization (WHO) 4th International Standard (IS) for hCG (NIBSC code 75/589).

6. Detection Limit:
   An analytical sensitivity/cutoff study was performed using a pooled negative female human urine sample spiked with 0, 3, 6, 7.5, 8.5, 10, and 12.5 mIU/mL hCG (traceable to the 4th WHO International Standard). Samples were tested by dip sampling method in replicates of thirty-four for each of three lots of devices. The results of the study are shown below. The device cutoff is 10 mIU/mL hCG.

hCG concentration (mIU/mL)	Lot 1		Lot 2		Lot 3	
	# Positive / Total #	% Positive	# Positive / Total #	% Positive	# Positive / Total #	% Positive
0	0/34	0.0%	0/34	0.0%	0/34	0.0%
3	0/34	0.0%	0/34	0.0%	0/34	0.0%
6	11/34	32.4%	8/34	23.5%	5/34	14.7%
7.5	28/34	82.4%	25/34	73.5%	24/34	70.6%
8.5	33/34	97.1%	31/34	91.2%	31/34	91.2%
10	34/34	100.0%	34/34	100.0%	34/34	100.0%
12.5	34/34	100.0%	34/34	100.0%	34/34	100.0%

See also Section VII.A.1. above for additional precision/reproducibility information for midstream and dip sampling methods.

7. Assay Cut-Off:
The device cutoff is 10 mIU/mL hCG. See Detection Limit (Section VII.A.6.) and Precision/Reproducibility (Section VII.A.1.) sections above.

8. Accuracy (Instrument):
Not applicable.

9. Carry-Over:
Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:
Urine samples from 204 women aged 18 to 50 years were masked and randomized prior to testing by professionals using the candidate device (Clearblue® Early Digital Pregnancy Test; in simulated midstream mode and in dip mode) and the predicate device (First Response™ Gold Digital Pregnancy Test; in dip mode). The results are summarized below.

Dip method

Candidate device (Dip)	Predicate device (Dip)		
	Negative	Positive	Total
Negative	101	1*	102
Positive	0	102	102
Total	101	103	204

Simulated midstream method

Candidate device (Simulated midstream)	Predicate device (Dip)		
	Negative	Positive	Total
Negative	101	1*	102
Positive	0	102	102
Total	101	103	204

*The predicate device returned a positive result and the candidate device returned a negative result for a sample from a woman clinically confirmed to be not pregnant.

There was 100% agreement between Clearblue® Early Digital Pregnancy Test results and each woman's clinical status.

2. Matrix Comparison:

Not Applicable. The device is intended for urine samples only.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Detection of hCG in Early Pregnancy Clinical Samples
   A total of 831 urine samples from days 0 to -9 relative to the day of the expected menstrual period (EMP) were collected from women aged 18 to 50 years from the intended use population. Each sample was tested using both dip and simulated midstream methods of sampling across three lots of devices. The early pregnancy detection results are summarized in table below.

Days Relative to EMP	% Positive		
	Dip method	Simulated midstream method	Overall
-9	0.0	0.0	0.0
-8	0.0	0.0	0.0
-7	5.0	5.0	5.0
-6	34.3	39.2	36.8
-5	75.5	81.4	78.4
-4	93.1	93.1	93.1
-3	99.0	99.0	99.0
-2	100.0	100.0	100.0
-1	100.0	100.0	100.0
0	100.0	100.0	100.0

   Lay user study
   A lay user study was performed with a total of 203 lay users from the intended use population. The lay users were 18 to 45 years old and had diverse educational and professional backgrounds. A valid midstream result was obtained from 195 of the lay users and a valid dip result was obtained from 199 of the lay users. Lay user results compared to clinical pregnancy status and professional user results are shown below. Ease of use of the candidate device was assessed through a questionnaire that was completed at the end of the study. The questionnaire results indicated that lay users found the test easy to use, the results clear and easy to read and the instructions for use easy to understand.

   Lay user versus Clinical status

Lay user (Midstream)	Clinical status		
	Pregnant	Not Pregnant	Total
Positive	94	0	94
Negative	0	101	101
Total	94	101	195

Lay user (Dip)	Clinical status		
	Pregnant	Not Pregnant	Total
Positive	95	0	95
Negative	0	104	104
Total	95	104	199

Lay user versus Professional user

Lay user (Midstream)	Professional user (Dip)		
	Positive	Negative	Total
Positive	94	0	94
Negative	0	101	101
Total	94	101	195

Lay user (Dip)	Professional user (Dip)		
	Positive	Negative	Total
Positive	95	0	95
Negative	0	104	104
Total	95	104	199

Lay user spiked sample study

In a separate study, a total of 200 lay users (100 lay users using dip method and 100 lay users using simulated midstream method) each tested four urine samples spiked with 3, 7.5, 8.5, or 10 mIU/mL hCG. Standards were blinded and the order of testing was randomized. Professionals also conducted testing with the spiked urine samples. A comparison of lay user and professional results for each urine sample and sampling method is shown below.

	Simulated midstream		Dip	
hCG level (mIU/mL)	Lay user % Positive	Professional % Positive	Lay user % Positive	Professional % Positive
3	0%	0%	0%	0%
7.5	47%	58%	53%	47%
8.5	69%	63%	79%	70%
10	100%	100%	100%	100%

Specificity Study to Determine False Positive Result Rate

A study was performed to determine the incidence of false positive test results from Clearblue® Early Digital Pregnancy Test. Urine samples were collected from 150 women from each of four cohorts: non-pregnant pre-menopausal women aged 18-40 years, non-pregnant peri-menopausal women aged 41-55 years, non-pregnant post-menopausal women > 55 years of age, and pregnant women. Samples were tested by trained technicians with three device lots. Results of the study are shown in the table below.

Cohort	# Positive / Total #	% Positive
Non-pregnant, Pre-menopausal	0 / 150	0.0%
Non-pregnant, Peri-menopausal	0 / 150	0.0%
Non-pregnant, Post-menopausal	1 / 150	0.7%
All non-pregnant women	1 / 450	0.2%
Pregnant	150 / 150	100.0%

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

Not applicable.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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