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

## I Background Information:

### A 510(k) Number

K213379

### B Applicant

SPD Swiss Precision Diagnostics GmbH

### C Proprietary and Established Names

Clearblue ® Early 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 Pregnancy Test is an over-the-counter chromatographic immunoassay for the qualitative detection of human chorionic gonadotropin (hCG) in urine. This 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

### D Special Instrument Requirements:

None

## IV Device/System Characteristics:

### A Device Description:

The Clearblue® Early Pregnancy Test employs an immunochromatographic sandwich assay to detect hCG on a lateral flow test strip. The result is displayed to the user in the test window as two lines for a 'Pregnant' result and one line for a 'Not Pregnant' result. The lateral flow test strip is housed in a cassette.

### B Principle of Operation:

The Clearblue® Early Pregnancy test is a lateral flow sandwich immunoassay employing monoclonal antibodies that are specifically directed against the alpha and beta sub-units of hCG. After the application of urine, the test result is shown in the result window and is read visually after 5 minutes. If hCG is present in the urine sample, it is bound by a conjugated monoclonal anti beta-hCG antibody forming a visible red line indicating a Pregnant result (two lines must appear within five minutes). A 'Not Pregnant' result will have a red line in the control window and no line in the results window. The device also includes a follicle stimulating hormone (FSH)-mediated scavenger zone. This may reduce the risk of false positive results in a small number of women who have low levels of hCG in urine but are not pregnant.

## V Substantial Equivalence Information:

### A Predicate Device Name(s):

First Response Early Result Pregnancy Test

### B Predicate 510(k) Number(s):

K123436

### C Comparison with Predicate(s):

| **Device & Predicate Device(s):** | K213379 | K123436 |
|---|---|---|
| Device Trade Name | Clearblue® Early Pregnancy Test | FIRST RESPONSE Early Result Pregnancy Test |
| **General Device Characteristic Similarities** | | |
| Intended Use/Indications For Use | Qualitative detection of hCG to aid in the early detection of pregnancy | Same |
| Early Detection Claim | Six days before the day of the missed period (five days before the day of the expected period) | Same |
| Test Principle | Lateral flow qualitative chromatographic immunoassay | Same |
| Sample Matrix | Urine | Same |
| Traceability | World Health Organization (WHO) 4$^{th}$ International Standard (IS) for hCG | Same |
| hCG Sensitivity | 10mIU/mL | Same |
| **General Device Characteristic Differences** | | |
| Antibody Recognition | Detects intact hCG.<br>Includes an FSH-mediated hCG scavenger system | Recognizes: intact hCG<br>hyperglycosylated hCG<br>hCG β-subunit<br>hCG β-core fragment |

| Device & Predicate Device(s): | K213379 | K123436 |
|---|---|---|
| Time to Result | 5 minutes | 3 minutes |

## VI Standards/Guidance Documents Referenced:

None referenced.

## VII Performance Characteristics (if/when applicable):

### A Analytical Performance:

1. Precision/Reproducibility:
A pooled negative female urine sample was spiked with hCG (traceable to the 4th WHO International Standard (IS) for hCG) to obtain eight urine samples with hCG concentrations of <1, 2, 3, 5, 7, 10, 15 and 20 mIU/mL. One hundred and thirty-five (135) devices were tested per hCG concentration by three technicians, on five non-consecutive days (spread over 11 days), using the two methods of sampling (dip and simulated in-stream) and 3 lots of the device. On each test day, 3 technicians tested 3 devices each per lot, per hCG concentration, per sampling method. A total of 2160 Clearblue® Early Pregnancy Test devices were tested (3 technicians x 3 replicates x 3 lots x 5 days x 8 hCG concentrations x 2 sampling methods). The results are summarized in the tables below.

Overall Precision Results Dip Sampling Method

| hCG Concentration (mIU/mL) | Positive (n) | Negative (n) | Total (n) | % Positive |
|---|---|---|---|---|
| <1 | 0 | 135 | 135 | 0 |
| 2 | 0 | 135 | 135 | 0 |
| 3 | 33 | 102 | 135 | 24.4 |
| 5 | 92 | 43 | 135 | 68.1 |
| 7 | 119 | 16 | 135 | 88.1 |
| 10 | 135 | 0 | 135 | 100 |
| 15 | 135 | 0 | 135 | 100 |
| 20 | 135 | 0 | 135 | 100 |
| Total | 649 | 431 | 1080 | N/A |

Overall Precision Results Simulated In-Stream Sampling Method

| hCG Concentration (mIU/mL) | Positive (n) | Negative (n) | Samples (n) | % Positive |
|---|---|---|---|---|
| <1 | 0 | 135 | 135 | 0 |
| 2 | 0 | 135 | 135 | 0 |
| 3 | 35 | 100 | 135 | 25.9 |

| hCG Concentration (mIU/mL) | Positive (n) | Negative (n) | Samples (n) | % Positive |
|---|---|---|---|---|
| 5 | 93 | 42 | 135 | 68.9 |
| 7 | 117 | 18 | 135 | 86.7 |
| 10 | 135 | 0 | 135 | 100 |
| 15 | 135 | 0 | 135 | 100 |
| 20 | 135 | 0 | 135 | 100 |
| Total | 650 | 430 | 1080 | N/A |

The sponsor also provided information to show no significant differences in performance between device lots.

2. Linearity:

Linearity is not applicable since this is a qualitative test.

3. Analytical Specificity/Interference:

Urine specimens from non-pregnant females were pooled and used to prepare samples with hCG levels <1 mIU/mL and 10 mIU/mL that were then spiked with the potentially interfering exogenous and endogenous substances. Control samples containing no test substance were also tested to compare to the test samples. Each condition was tested in five replicates on three lots (for a total n of 15) for each of the two hCG concentrations using the dip method. No interference effect was observed at the tested concentrations shown in the table below.

List of Potentially Interfering Substances and Concentrations Tested

| Interfering Substance | Concentration |
|---|---|
| Acetylsalicylic acid | 1.0 mg/mL |
| Acetone | 1.0 mg/mL |
| Albumin | 5 mg/mL |
| Ampicillin | 200 ug/mL |
| Ascorbic acid | 150 µg/mL |
| Atropine | 200 µg/mL |
| Bilirubin | 200 ug/mL |
| Blood | 0.3 % v/v |
| Caffeine | 1.2 mg/mL |
| Cannabinol | 100 ug/mL |
| Clomiphene citrate | 24 µg/mL |
| Cotinine | 40 µg/mL |
| Ethanol | 1% v/v |

| Interfering Substance | Concentration |
|---|---|
| E3G | 620 ng/mL |
| Gentisic acid | 200 ug/mL |
| Glucose | 20 mg/mL |
| Hemoglobin | 100 µg/mL |
| Hydrochloric acid | 1.25 mM |
| Ibuprofen | 100 µg/mL |
| Leukocytes | $1x10^6$ cells/mL |
| Oxytetracycline | 300 µg/mL |
| Acetaminophen | 600 µg/mL |
| Phenylpropanolamine | 200 ug/mL |
| P3G | 40 µg/mL |
| Semen | 5% v/v |
| Sodium hydroxide | 1.25 mM |
| Tetracycline | 300 µg/mL |
| Urea | 30 mg/mL |
| Uric acid | 750 µg/mL |
| Urobilinogen | 100 µg/mL |

Cross-reactivity of structurally related compounds:

The candidate device was evaluated for potential cross-reactivity from FSH, luteinizing hormone (LH), and thyroid stimulating hormone (TSH). Urine pools negative for hCG were used to prepare samples with hCG concentrations <1 mIU/mL, 4 mIU/mL and 10 mIU/mL. These samples were spiked with the potential cross reactants at the concentrations described in the table below and tested using 5 devices from each of 3 lots per testing condition (n of 15 per test condition). The results show that all the devices tested returned the expected result.

Results of Cross-Reactivity Study

| Concentrations tested (mIU/mL) | Positive result | Negative result |
|---|---|---|
| <1 hCG | 0 | 15 |
| 10 hCG | 15 | 0 |
| <1 hCG, 500 LH | 0 | 15 |
| 10 hCG, 500 LH | 15 | 0 |
| <1 hCG, 1 TSH | 0 | 15 |
| 10 hCG, 1 TSH | 15 | 0 |
| <1 hCG, 1000 FSH | 0 | 15 |

| Concentrations tested (mIU/mL) | Positive result | Negative result |
|---|---|---|
| 10 hCG, 15 FSH | 15 | 0 |
| 4 hCG, 100 FSH | 0 | 30 |
| 4 hCG, 1000 FSH | 0 | 30 |
| 4 hCG, 100 FSH, 1 TSH | 0 | 30 |
| 4 hCG, 100 FSH, 500 LH | 0 | 30 |

Effect of hCG β-core fragment:

Urine samples (<1 and 10 mIU/mL hCG) were spiked with hCG β-core fragment up to 1 µmol/L and were tested. The results support that the performance of the candidate device is not affected by concentrations of hCG beta-core fragment up to 1 µmol/L.

Effect of urine pH and specific gravity:

The sponsor conducted studies to show that the device test result is not impacted by pH conditions ranging from 4.0 to 9.0 and specific gravity conditions ranging from 1.000 to 1.035.

Hook effect:

The sponsor conducted a hook effect study and showed that no hook effect was observed at concentrations of 1,000,000 mIU/mL hCG.

4. Assay Reportable Range:

Not applicable.

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

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

6. Detection Limit:

The detection limit was determined in the precision study (see Section VII.A.1. above).

7. Assay Cut-Off:

The device cutoff is 10 mIU/mL hCG. See Precision/Reproducibility (Section VII.A.1. above).

**B. Comparison Studies:**

1. Method Comparison with Predicate Device:

   See Section VII. C. 3 below.

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):

   Lay user studies:

   The first lay user study was performed with a total of 295 women (pregnant and not pregnant) with diverse educational and professional backgrounds, between the ages of 18 to 55. Each subject performed the testing following the package insert instructions without any assistance. Their results were compared to their clinical pregnancy status and to the results obtained from trained technicians testing the same urine samples and the same sampling method (in-stream or dip).

   Lay User Versus Clinical Status (Simulated In-Stream Method)

| Clinical status | Volunteer results, simulated in-stream method | | |
|---|---|---|---|
| | Pregnant | Not pregnant | Total |
| Pregnant | 59 | 0 | 59 |
| Not pregnant | 0 | 57 | 57 |
| Total | 59 | 57 | 116 |

Lay User Versus Clinical Status (Dip Method)

| Clinical status | Volunteer results, dip method | | |
|---|---|---|---|
| | **Pregnant** | **Not pregnant** | **Total** |
| Pregnant | 93 | 0 | 93 |
| Not pregnant | 0 | 86 | 86 |
| Total | 93 | 86 | 179 |

Lay User Versus Technician Results

| Trained technician test results | Volunteer results | | |
|---|---|---|---|
| | **Pregnant** | **Not pregnant** | **Total** |
| Pregnant | 152 | 0 | 152 |
| Not pregnant | 0 | 143 | 143 |
| Total | 152 | 143 | 295 |

The second lay user study was conducted with a total of 318 women with diverse educational and professional backgrounds between the ages of 18 years to 46. Lay users performed the testing using samples spiked with 0, 2, 3, 5, 10 and 15 mIU/mL hCG using 3 lots of the device evaluating both sampling methods. Results are summarized below.

Lay Users Testing Spiked Samples

| hCG (mIU/mL) | Total (n) | Pregnant (n) | % Pregnant |
|---|---|---|---|
| 0 | 107 | 0 | 0 |
| 2 | 107 | 2 | 1.9 |
| 3 | 103 | 28 | 27.2 |
| 5 | 106 | 74 | 69.8 |
| 10 | 105 | 105 | 100 |
| 15 | 108 | 108 | 100 |

Early pregnancy detection study:

A total of 933 early pregnancy urine samples from day -10 to -1 relative to the day of the missed period were collected from women between the ages of 18 to 55. Each sample was tested using both methods of sampling (dip and in-stream) using three lots of the device. The specific detection rates per day are summarized in the table below.

Early Pregnancy Detection Study

| Days relative to missed period | Dip method | | | Simulated in-stream method | |
|---|---|---|---|---|---|
| | Sample (n) per sampling method | Pregnant (n) | Pregnant (%) | Pregnant (n) | Pregnant (%) |
| -10 | 21 | 0 | 0.0 | 0 | 0.0 |
| -9 | 36 | 0 | 0.0 | 0 | 0.0 |
| -8 | 60 | 3 | 5.0 | 3 | 5.0 |
| -7 | 102 | 30 | 29.4 | 28 | 27.5 |
| -6 | 102 | 78 | 76.5 | 80 | 78.4 |
| -5 | 102 | 96 | 94.1 | 95 | 93.1 |
| -4 | 102 | 100 | 98.0 | 100 | 98.0 |
| -3 | 102 | 102 | 100.0 | 102 | 100.0 |
| -2 | 102 | 102 | 100.0 | 102 | 100.0 |
| -1 | 102 | 102 | 100.0 | 102 | 100.0 |
| 0 | 102 | 102 | 100.0 | 102 | 100.0 |

A study was performed to evaluate the number of false positive test results obtained using the Clearblue® Early Digital Pregnancy Test. Urine samples were collected from 150 women from each of four cohorts: non-pregnant pre-menopausal women between the ages of 18-40, non-pregnant peri-menopausal women between the ages of 41-55, post-menopausal women > 55 years of age, and 51 pregnant women. Urine samples were collected from individual women from each cohort and were tested by technicians with three lots of the candidate device using both sampling methods (dip and simulated in-stream). The results are summarized in the tables below.

Summary of Specificity Testing (Dip Method)

| Cohort | Samples (n) | Specificity (%) |
|---|---|---|
| Non-pregnant, pre-Menopausal | 150 | 100 |
| Non-pregnant, peri-Menopausal | 149 | 100 |
| Non-pregnant, post-Menopausal | 150 | 100 |
| All non-pregnant | 449 | 100 |
| Pregnant | 51 | 100 |

Summary of Specificity Testing (Simulated In- Stream Method)

| Cohort | Samples (n) | Specificity (%) |
|---|---|---|
| Non-pregnant, pre-Menopausal | 150 | 100 |
| Non-pregnant, peri-Menopausal | 150 | 100 |
| Non-pregnant, post-Menopausal | 150 | 100 |
| All non-pregnant | 450 | 100 |
| Pregnant | 51 | 100 |

**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.