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Attachment B

**Revised Summary of Information
Respecting Safety and Effectiveness**

**Biocircuits IOS™ Quantitative hCG Test Cartridges
and IOS™ Immunoassay Controls**

510(k) Summary of Information Respecting Safety and Effectiveness

A. Submitter:
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Date Prepared: November 1, 1996

B. Device Names:
Proprietary Name: Biocircuits IOS™ Quantitative hCG Test Cartridges
Biocircuits IOS™ Immunoassay Controls
(formerly IOS™ Thyroid Controls)

Common Names: Reagents for hCG (human chorionic gonadotropin)
Quality control materials (assayed and unassayed)

Classification Name: human chorionic gonadotropin (hCG) test system
Quality control materials (assayed and unassayed)

C. Legally Marketed Device:

The IOS Quantitative hCG Test Cartridges are substantially equivalent to the Dade Stratus Fluorometric Enzyme hCG Immunoassay currently manufactured and distributed by Dade International.

D. Device Description:

Quantitative hCG Test Cartridges: Human chorionic gonadotropin is a glycoprotein that is synthesized by the placenta during pregnancy and appears in both serum and urine relatively soon after implantation of the developing embryo. The presence of hCG, and its rapid rise following conception, is thus the basis of pregnancy testing. (1) Quantitation of hCG can aid in the determination of ectopic pregnancy and spontaneous abortion (2, 3). hCG is also secreted by a wide variety of tumors: gestational trophoblastic tumors, testicular and prostatic tumors, and some breast cancers. (4,5).

Human chorionic gonadotropin is composed of two noncovalently linked polypeptides: the alpha and beta subunits. The individual subunits lack biological activity, but become active when combined to form the intact hormone. The alpha subunit of hCG is structurally homologous to the alpha subunits of LH (luteinizing hormone), FSH (follicle stimulating hormone), and TSH (thyroid stimulating hormone). The beta subunit of each of the hormones is structurally unique and confers the biologic and immunologic specificity to each hormone. The beta subunit of hCG contains a unique chain of 30 carboxy-terminal amino acids that confers its specificity (1). Monoclonal antibodies directed against this portion of the beta subunit permit differentiation between hCG and the other pituitary glycoprotein hormones.

Principle of the Test

Quantitative hCG Test Cartridges: The IOS™ Quantitative hCG test is a two-site sandwich immunoassay which utilizes two antibodies directed against hCG: a polyclonal antibody immobilized on the plastic cartridge surface (capture antibody) and a monoclonal antibody labeled with alkaline phosphatase (detection antibody, 'conjugate'). hCG in the patient sample binds to conjugate in the test cartridge, and this hCG-conjugate complex then binds to the immobilized capture antibody. After a short incubation period, unbound hCG-conjugate complex is washed away. Substrate is added, which reacts with the alkaline phosphatase conjugate-hCG-capture antibody 'sandwich' and produces a fluorescent signal. The level of fluorescence is directly proportional to the amount of bound hCG-conjugate, which is directly proportional to the amount of hCG present in the patient sample. All reagents necessary to perform the test are dried in the IOS™ cartridge, and are rehydrated by the addition of patient sample by the operator, or by the addition of buffer by the instrument.

To perform a test, the operator inserts an IOS™ Quantitative hCG cartridge in the IOS™ instrument. When prompted, the operator adds sample to one sample well. A second portion of patient sample is diluted off-line, using the dilution vial supplied with the kit, and pipetted into the second well of the test cartridge. The operator starts the test sequence when sample addition is complete. Patient sample rehydrates conjugate dried in the sample well; the conjugate binds to hCG present in the patient serum sample. This hCG-conjugate complex then flows into the incubation/reaction chamber where it binds to the immobilized capture antibody. At the end of the incubation time, unbound sample-conjugate is washed away by buffer. Buffer is used to rehydrate the dried substrate necessary for signal generation and quantitation of hCG, and the rehydrated substrate is then delivered to the incubation/reaction chamber. The fluorescent signal produced is read as a rate by front-surface fluorometry, compared to the rates produced by a series of calibrators stored in the instrument memory, and the amount of hCG present in the patient sample is calculated from the stored calibration curve. If the signal from the first track (undiluted patient serum) is higher than that of the highest calibrator, the instrument will take a reading from the second track (user-diluted sample) to obtain a quantitative value for the patient sample. This increases the assay range 2500 mIU/mL (undiluted track) to 250,000 mIU/mL (diluted track).

Immunoassay Controls: The use of materials derived from human blood to monitor quality control of clinical chemistry testing in the clinical laboratory has been widely established over the past several years. The Biocircuits IOS™ Immunoassay Controls are two levels of blood-based material for use with Biocircuits IOS™ Test Cartridges.

To run a control, the operator inserts the Control Cartridge (packaged with the controls) into the IOS™ instrument. The instrument reads the lot number and ranges of acceptable values for the control solutions from the Control Cartridge barcode, and then ejects the Control Cartridge. The operator then inserts a test cartridge and follows the instrument prompts to identify the control level, apply control solutions, and begin the test sequence. The IOS™ instrument performs the required buffer additions to rehydrate assay reagents and perform wash steps as necessary, reads the fluorescence signal generated, and calculates and prints the control result just as it would if the cartridge were used to test a patient sample.

E. Intended Use:

The IOS™ Quantitative hCG Test Cartridges are to be used for the quantitative determination of human chorionic gonadotropin (hCG) in serum for the early detection of pregnancy. They are intended to be used with the IOS™ instrument in clinical laboratories, physicians' office laboratories, and other alternate sites of use close to the point of patient care.

The IOS™ Immunoassay Controls Kit is to be used to assist in monitoring accuracy and precision in the IOS™ immunoassay test cartridges.

F. Comparison with the Predicate Device:

Table I summarizes the comparative features of the IOS and Stratus assays.

G. Performance Data:

Quantitative hCG Test Cartridges:

Non-clinical testing performed in the manufacturer's laboratories gave the following results:

1. Precision:

Control Level	1	2	3
Mean, overall (mIU/mL)	36.8	169.2	339.3
SD, overall (mIU/mL)	4.26	16.39	34.46
% CV, within-day (n ≥ 19)	8.88	8.35	5.76
% CV, between-day (n ≥ 60)	10.89	9.06	10.75
% CV, total	11.57	9.69	10.16

2. Accuracy: A comparison of methods was performed by testing a total of 165 patient samples in the manufacturer's laboratories using the IOS™ Quantitative hCG cartridges and a commercially available fluorescent enzyme immunoassay. Of the range of hCG concentration from 2 mIU/mL to 2270 mIU/mL (neat sera), 107 samples tested gave a correlation coefficient (r) of 0.981 with the line of regression described by the equation $y = 5.63 + 0.89x$. Diluted samples with hCG concentrations up to 181,000 mIU/mL (n = 58) were also tested in the study, giving a correlation coefficient of 0.986 and a line of regression of $y = 0.002 + 0.955x$ for the entire range of samples tested (2 - 181,000 mIU/mL hCG).

Clinical testing performed in typical physicians' office laboratories gave the following results:

1. Precision:

Control Level	1	2
Number of replicates	39	31
Mean (mIU/mL)	35.34	152.79
SD, overall (mIU/mL)	4.08	13.72
% CV, total	11.54	8.98

2. Accuracy: A comparison of methods was performed by users in three typical physicians' office laboratories. Sites of testing included an OB/GYN practice, an Internal Medicine practice, and a Reproductive Endocrinology/Fertility practice. Users included medical technologists, medical assistants, and front-office personnel. A total of 121 patient samples were tested using the IOS™ Quantitative hCG cartridges in the office laboratories; the samples were split and sent to the manufacturer's laboratory for retesting on the predicate device. These studies gave a correlation coefficient (r) of 0.996 with the line of regression described by the equation $y = 0.002 + 0.880x$. Samples tested ranged from 2.0 mIU/mL to 202,598 mIU/mL, and included diluted samples.

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Immunoassay Controls

The following ranges for the IOS™ Immunoassay Controls were determined in studies in the manufacturer's laboratories. To establish the ranges, the controls were tested in at least 40 cartridges each, over several days, using several IOS™ instruments. These values only apply to this lot of IOS™ Immunoassay Controls. Different lots of Immunoassay Controls will likely have slightly different ranges. Your laboratory should establish its own range for these controls over time.

Analyte	Control Level 1		Control Level 2	
	Mean	Range	Mean	Range
T4 (ug/dL)	8.1	6.48-9.72	12.9	10.32-15.4
T-Uptake (%)	32.4	29.25-35.55	39.7	36.85-42.55
hCG (mIU/mL)				

It is self-evident from the data and information presented here that the Biocircuits IOS™ Quantitative hCG Test Cartridges are as safe, effective, and perform as well as the Dade Stratus hCG Fluorometric Immunoassay manufactured and distributed by Dade International.

Attachment: Table I: Assay Comparison

TABLE 1
Dade STRATUS vs. Biocircuits IOS™
Assay Comparison

ATTRIBUTE	STRATUS hCG	IOS™ hCG
Technology	Fluorometric enzyme immunoassay	Fluorometric Enzyme immunoassay
Assay format	Sandwich (two-site)	Sandwich (two-site)
Enzyme label	Alkaline phosphatase	Alkaline phosphatase
Substrate	Methylumbelliferyl phosphate	Methylumbelliferyl phosphate
Reagents		
Immobilization Medium	Reaction tab	Plastic cartridge
Dry	Monoclonal antibody only	Polyclonal antibody, monoclonal antibody-conjugate, substrate
Wet	2 (assay-specific), loaded by operator at start of each run	1 (used for all assays), continuously on board
Delivery	Fully automated	Fully automated
Calibration	User-generated	Factory-generated
Calibration Stability	14 days (minimum)	90 days (minimum)
Storage	Refrigerated (2-8°C)	Room Temperature (15-30°C)
Sample		
Type	Serum or plasma	Serum
Volume	0.2 ml (minimum)	0.1 mL
Measurement Needed	Non-precision	Non-precision
Dilution	Manual or programmable	Manual, run at same time as undiluted sera
Operating environment	22°-32° C	15°-30° C
Data analysis	Microprocessor-controlled Stored standard curves	Microprocessor-controlled Stored standard curves
Data output	LCD display Printed alphanumeric hard copy	LCD display Printed alphanumeric hard copy

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