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510(k) Summary of Safety and Effectiveness

A. Submitter:

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B. Device Names:

Proprietary Name:	Biocircuits IOS™ TSH Test Cartridges Biocircuits IOS™ Thyroid Controls
Common Name:	Reagents for thyroid stimulating hormone assay Quality control materials (assayed and unassayed)
Classification Name:	Thyroid stimulating hormone test system Quality control materials (assayed and unassayed)

C. Legally Marketed Device:

The IOS™ TSH Test Cartridges are substantially equivalent to the Stratus ultra-sensitive hTSH test currently manufactured and distributed by Dade International (formerly Baxter Dade).

D. Device Description:

Thyroid stimulating hormone (TSH) is a glycoprotein with a molecular weight of about 28,000 daltons that is secreted by the anterior pituitary gland. TSH interacts with a specific receptor on the thyroid gland cell surface, stimulating production and secretion of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Secretion of TSH is regulated by two factors: 1) a hormone secreted by the hypothalamus called thyrotropin releasing hormone (TRH) which stimulates the pituitary to produce and release TSH; and 2) the concentration of unbound thyroid hormones T4 and T3 in the interstitial fluid of the brain. An increase of the concentrations of T4 and T3 inhibits the production and secretion of TSH, while a decrease in T4 and T3 levels stimulates production and secretion of TSH, forming a negative feedback mechanism. Failure at any level of regulation of the hypothalamic-pituitary-thyroid axis will result in either under-production (hypothyroidism) or over-production (hyperthyroidism) of T4 and/or T3.

Primary hypothyroidism is associated with low thyroid hormone levels and elevated TSH levels, while secondary (pituitary) and tertiary (hypothalamic) forms of hypothyroidism are associated with both low levels of T4 and/or T3 and low-to-undetectable levels of TSH. All three forms of hypothyroidism can be differentiated by the patient's TSH response to TRH.

Primary hyperthyroidism is associated with high levels of thyroid hormones and very low or undetectable levels of TSH. The TRH challenge test has been used to confirm primary hyperthyroidism. More recently, sensitive TSH assays have been developed which can differentiate overtly thyrotoxic patients from euthyroid individuals.

TSH is composed of two noncovalently linked subunits, designated "alpha" and "beta". The alpha portion is essentially identical to the alpha subunits of human luteinizing hormone (hLH), human follicle stimulating hormone (hFSH), and human chorionic gonadotropin (hCG), differing only in carbohydrate moieties. The beta subunits of each of these hormones is structurally unique and contains the biologic and immunologic specificity. Both subunits are needed for biological activity.

The Biocircuits IOS™ TSH assay uses a monoclonal antibody against the beta subunit of TSH to specifically capture the patient TSH, and a polyclonal antibody also against the beta subunit for the enzyme conjugate. This allows specific determination of the concentration of TSH without cross-reactivity with other glycoprotein hormones.

Principle of the Test:
TSH: The IOS™ TSH test is a two-site sandwich immunoassay. TSH in the patient sample binds to monoclonal anti-TSH antibody in the test cartridge. After a short incubation time, excess sample is washed away and enzyme-labeled polyclonal anti-TSH antibody (conjugate) is added, which binds to any antibody-bound TSH, forming an antibody-antigen-labeled antibody sandwich. After another short incubation time, excess conjugate is washed away and substrate is added. The rate of the enzyme-substrate reaction is directly proportional to the amount of conjugate bound, which is directly proportional to the amount of TSH 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™ TSH cartridge into the IOS™ instrument. When prompted, the operator adds sample to the sample well and starts the test sequence. The instrument draws the cartridge inside to be incubated. Patient sample flows into the incubation/reaction chamber where patient TSH binds to anti-TSH antibody. At the end of the sample incubation time, excess patient sample is washed away using buffer added by the instrument. Buffer is also added by the instrument to rehydrate dried conjugate in a separate reagent chamber for the next step; the rehydrated conjugate is then allowed to enter the incubation/reaction chamber and bind to antibody-bound TSH. At the end of the conjugate incubation time, excess conjugate is washed away by buffer. Buffer is used to rehydrate the substrate necessary for signal generation and quantitation of TSH in a second reagent chamber; rehydrated substrate is then allowed to enter 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 instrument memory, and the amount of TSH present in the patient sample is calculated from the stored calibration curve.

Thyroid 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. (1) The Biocircuits IOS™ Thyroid Controls are two levels of blood-based material for use with Biocircuits IOS™ thyroid assays test cartridges (T4/TU, T4, or TSH).

To run a control, the operator inserts the Thyroid 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:

TSH: The IOS™ TSH Test Cartridge is to be used for the quantitative determination of thyroid stimulating hormone (TSH, thyrotropin) levels in serum using the Biocircuits IOS™ system.

Thyroid Controls: The IOS™ Thyroid Controls Kit is to be used to assist in monitoring accuracy and precision in the IOS™ thyroid assays.

F. Comparison with the Predicate Device:

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

G. Performance Data:

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

1. Precision
A laboratory study performed at the manufacturer for within-day and between-day precision in the IOS™ TSH assay used three levels of control material. The following data were obtained:

Control Level	**1**	**2**	**3**
Mean (uIU/mL)	0.78	12.02	23.60
SD, overall (uIU/mL)	0.11	1.18	2.67
% CV, within-day (n=10)	6.4%	9.9%	11.3%
% CV, between-day (n=40)	13.6%	9.2%	11.3%
% CV, overall	13.5%	9.8%	11.3%

2. Accuracy
A comparison of methods obtained by testing 206 patient samples in the manufacturer's laboratories using the IOS™ TSH assay and a commercially available fluorescent enzyme immunoassay gave a correlation coefficient ('r') of 0.98, with the line of regression described by the equation $y = 0.141 + 1.07x$. Samples tested ranged from ≤ 0.173 uIU/mL to 26.30 uIU/mL.

Clinical testing performed at a typical physician's office laboratory gave the following results:

1. Precision
A study was performed in a typical physicians' office laboratory for total precision in the IOS™ TSH assay. Data were collected over twelve working days. The following data were obtained:

Control Level	**1**	**2**
Number of replicates	23	18
Mean (uIU/mL)	0.773	12.93
SD, overall (uIU/mL)	0.071	1.78
% CV, overall	9.2%	13.8%

2. Accuracy

A comparison of methods was also performed by users in a typical physicians' office laboratory. A total of 43 patient samples were tested using the IOS™ TSH assay in the office laboratory; the samples were split and sent to the manufacturer's laboratory for testing by the predicate method. These studies gave a correlation coefficient ('r') of 0.978, with the line of regression described by the equation $y = 0.255 + 0.922x$. Samples tested ranged from ≤ 0.173 uIU/mL to 23.06uIU/mL.

Thyroid Controls:

The following ranges for the IOS™ Thyroid Controls were determined in studies in the manufacturer's laboratories. To establish the ranges, the controls were tested in a total of 40 cartridges each, over at least 10 days, using several IOS™ instruments. These values only apply to this lot of IOS™ Thyroid Controls. Different lots of Thyroid 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
TSH (uIU/mL)	0.78	0.45 - 1.11	12.02	8.48 - 15.56

It is self-evident from the data and information presented here that the Biocircuits IOS™ TSH Test Cartridges as as safe, effective, and perform as well as the Stratus ultra-sensitive hTSH assay in commercial distribution by Dade International.

Attachment: Table I: Assay Comparison

TABLE 1
Baxter STRATUS vs. Biocircuits IOS™
Assay Comparison

ATTRIBUTE	STRATUS hTSH	IOS™ TSH
Technology	Fluorometric enzyme immunoassay	Fluorometric enzyme immunoassay
Assay format	Sandwich	Sandwich
Enzyme label	Alkaline phosphatase	Alkaline phosphatase
Substrate	Methylumbelliferyl phosphate	Methylumbelliferyl phosphate
Reagents		
Immobilization Medium	Reaction tab	Plastic cartridge
Dry	Monoclonal antibody only	Monoclonal antibody, polyclonal 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)	0.15 mL
Measurement Needed	Non-precision	Non-precision
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