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

A. 510(k) Number:

k063605

B. Purpose for Submission:

New Device

C. Measurand:

Parathyroid Hormone

D. Type of Test:

Quantitative, Immunoenzymatic assay

E. Applicant:

Tosoh Bioscience Inc.

F. Proprietary and Established Names:

ST AIA-PACK Intact PTH Assay
ST AIA-PACK Intact PTH Calibrator Set
ST AIA-PACK Intact PTH Control Set

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
Parathyroid Hormone (CEW)	Class II	21 CFR 862.1545 Parathyroid hormone test system	75 Clinical Chemistry(CH)
Product Code	**Classification**	**Regulation Section**	**Panel**
Calibrator (JIT)	Class II	21 CFR 862.1150 Secondary calibrator	75 Clinical Chemistry(CH)
Product Code	**Classification**	**Regulation Section**	**Panel**
Control (JJX)	Class I reserved	21 CFR§ 862.1660 Quality control material (assayed and unassayed)	75 Clinical Chemistry(CH)

H. Intended Use:

1. Intended use(s):

    Refer to Indications for use below.

2. Indication(s) for use:

    ST AIA-PACK Intact PTH is designed for IN VITRO DIAGNOSTIC USE ONLY for the quantitative measurement of the levels of parathyroid hormone in human serum and EDTA plasma on specific TOSOH AIA System analyzers. Measurements of parathyroid hormone levels are used in the differential diagnosis of hypercalcemia (abnormally high levels of calcium in the blood) and

hypocalcemia (abnormally low levels of calcium in the blood) resulting from disorders of calcium metabolism.

The ST AIA-PACK Intact PTH CALIBRATOR SET is intended for IN VITRO DIAGNOSTIC USE ONLY for the calibration of the ST AIA-PACK Intact PTH Assay.

The ST AIA-PACK Intact PTH CONTROL SET is intended for IN VITRO DIAGNOSTIC USE ONLY for performing quality control procedures with the ST AIA-PACK Intact PTH Assay.

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

4. Special instrument requirements:
For use with the specific TOSOH AIA System analyzers. Performance characteristics were established using TOSOH AIA-1800 System. The TOSOH AIA-600 or AIA-1200 Series Analyzers cannot be used to perform the ST AIA-PACK Intact PTH assay.

I. Device Description:

The ST AIA-PACK Intact PTH Assay is supplied as plastic test cups (5 trays x 20 test cups) containing twelve lyophilized magnetic beads coated with anti-PTH goat polyclonal antibody and anti-PTH goat polyclonal antibodies conjugated to bovine alkaline phosphatase with 0.1% sodium azide as a preservative.

The ST AIA-PACK Intact PTH CALIBRATOR SET contains a bovine protein matrix with assigned levels of Intact Parathyroid Hormone (0 – 2400 mg/dL). The Calibrator set has been prepared using synthesized Intact PTH.

The AIA-PACK Intact PTH CONTROL SET contains buffered bovine serum albumin with the assigned levels of Intact PTH. The Control set has been prepared using synthesized Intact PTH.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Roche Elecsys Parathyroid Hormone Test System

2. Predicate 510(k) number(s):
k992680

3. Comparison with predicate:

Assay / Feature	ST AIA-PACK Intact PTH	Roche Elecsys PTH assay (k992680)
Analyte	Human Parathyroid Hormone	Human Parathyroid Hormone
Intended Use	The Tosoh Bioscience, Inc. ST AIA-PACK Intact PTH is designed for IN VITRO DIAGNOSTIC USE ONLY for the quantitative measurement of Intact Parathyroid Hormone (Intact PTH) in human serum and EDTA plasma on specific TOSOH AIA System analyzers.	For the quantitative determination of intact parathyroid hormone and for differential diagnosis of hypercalcemia and hypocalcemia.

	Measurements of parathyroid hormone levels are used in the differential diagnosis of hypercalcemia (abnormally high levels of calcium in the blood) and hypocalcemia (abnormally low levels of calcium in the blood) resulting from disorders of calcium metabolism.	
Specimen	Serum and Plasma	Serum and Plasma
Assay Format	The ST AIA-PACK Intact PTH assay is a two-site immunoenzymatic ("sandwich") assay (IEMA)	Electrochemiluminescence immunoassay employing the sandwich principle (ICMA)
Result Read Time	Approximately 20 Minutes	9 – 18 minutes
Reportable range	1.2-2200 pg/mL	1.2-5000 pg/mL
Analytical Sensitivity	≈1.0 pg/ml	≈ 1.20 pg/ml
Normal Range	8.2 – 83.5 pg/ml	15 – 65 pg/ml

K. Standard/Guidance Document Referenced (if applicable):
  None referenced

L. Test Principle:
  The ST AIA-PACK Intact PTH is a two-site immunoenzymatic assay which is performed entirely in the AIA-PACK. Intact PTH present in the test sample is bound with polyclonal antibody immobilized on magnetic beads and enzyme-labeled polyclonal antibody in the AIA- PACK. The magnetic beads are washed to remove unbound enzyme-labeled polyclonal antibody and are then incubated with the fluorogenic substrate 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled polyclonal antibody that binds to the beads is directly proportional to Intact PTH concentration in the test sample. A standard curve is constructed using known levels of calibrators, and unknown sample concentrations are calculated using this curve. The sponsor claims that calibration curve for the ST AIA-PACK Intact PTH is stable for up to 90 days. Calibration stability is monitored by quality control performance and is dependent on proper reagent handling and AIA System maintenance according to the manufacturer's instructions.

M. Performance Characteristics:

  1. Analytical performance:

    a. Precision/Reproducibility:
      The sponsor determined the within run precision using three controls each of serum and plasma samples in a total of 20 runs. Within each run, one set of duplicates per control was assayed. The mean of each duplicate was used to obtain the pooled standard deviation (SD), which was then used to calculate

the coefficient of variation (CV). Total precision was determined by the duplicate assay of three controls each of serum and plasma samples in 20 separate runs. The means of each run were used to calculate the standard deviation (SD) and coefficient of variation (CV).

Within-run Precision

Sample	Mean (pg/mL)	Pooled SD (pg/mL)	Coefficient of Variation (%)
Serum A3	27.7	0.89	3.2
Serum B3	243.6	8.68	3.6
Serum C3	1123.5	45.49	4.0
Plasma A3	27.1	1.07	3.9
Plasma B3	247.1	9.52	3.9
Plasma C3	1217.2	40.13	3.3

Day-to-day Precision

Sample	Mean (pg/mL)	Standard Deviation (pg/mL)	Coefficient of Variation (%)
Serum A3	27.7	1.00	3.6
Serum B3	243.6	8.94	3.7
Serum C3	1123.5	44.54	4.0
Plasma A3	27.1	1.32	4.9
Plasma B3	247.1	11.50	4.7
Plasma C3	1217.2	44.16	3.6

b. Linearity/assay reportable range:

Linearity studies were performed on the TOSOH AIA-1800 System. The Intact PTH Calibrators diluted to 12 equally spaced concentration levels (7.9 – 2370 pg/ml) were used for linearity analysis. Each test level was run in triplicate on the above analyzer. The sponsor established the acceptance criteria of measured values being within 90-110% of the assigned value. Based on the summarized results below and the results obtained from Limit of Detection studies (see Limit of Detection below), the sponsor has claimed the assay reportable range of 1.2 – 2200 pg/ml.

Concentration (pg/ml)	AVG	SD	CV	Ratio of Values Assigned/Obtained
0	0.43			0.00
7.9	8.28	0.10	1.2	0.95
15.8	15.89	0.53	3.3	0.99
33.9	33.23	0.90	2.7	1.02
52.0	52.73	1.15	2.2	0.99
129	122.99	0.58	0.5	1.04
205	214.39	4.21	2.0	0.96

512	497.08	13.01	2.6	1.03
819	792.96	4.00	0.5	1.03
1207	1113.99	31.86	2.9	1.08
1595	1458.46	43.43	3.0	1.09
1983	1847.06	29.71	1.6	1.07
2370	2222.38	143.38	6.5	1.07

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

The sponsor's protocols indicate that each calibrator/control lot is traceable to the manufacturer's primary reference material. The primary reference material was prepared by diluting commercially available synthesized Intact PTH with Intact PTH Negative buffer solution. The value was originally assigned by comparing measured results with those obtained with another commercially available Intact PTH assay for patient samples.

To ensure adequate quality control, the sponsor recommends assaying two quality controls having approximate values 50 and 800 pg/mL, once each day on which Intact PTH assays are scheduled.

The sponsor claims that all unopened materials are stable until the expiration date on the label when stored at the specified temperature. ST AIA-PACK Intact PTH test cups may be stored for up to 1 day at 18-25°C. When stored unopened and refrigerated at 2–8°C, calibrators are stable until the expiration date on the label. After opening, the calibrators should be used within 24 hours. When stored unopened and refrigerated at 2–8°C, the AIA-PACK Intact PTH Control Set is stable until the expiration date on the label. Control materials should be used within 7 days of opening or reconstituting provided that the vials are kept sealed and refrigerated at 2-8°C.

d. Detection limit:

The sponsor determined the lower Limit of Detection (LOD) based on the algorithm in EP Evaluator software program version 4.0. This was defined as that concentration of Intact PTH, which corresponds to the rate of fluorescence that is two standard deviations from the mean rate of fluorescence of 5 replicate determinations of a zero calibrator.

$$\text{Sensitivity} = \frac{\text{(Assigned value of non-zero calibrator) X 2 SD}}{\text{(Mean rate of non-zero calibrator – mean rate of zero calibrator)}}$$

Using different lots of Intact PTH calibrator 1 with zero concentration and a non-zero calibrator (52.0 pg/ml), the sponsor determined the value to be 0.96, hence the claimed LOD is 1.0 pg/mL.

e. Analytical specificity:

The sponsor evaluated the effect of the interfering substances listed below for the recovery of PTH. Serum and plasma samples each with 3 levels of PTH (low, medium and high) were spiked with the interferents, and then compared with unspiked control. Based on the sponsor-defined interference limit of ± 10% from each sample containing no interferents, following interference limit claims were set by the sponsor.

Substance	Interference		
	Interferent Concentration	Limit for Serum	Limit for Plasma
Hemoglobin (mg/dL)	0-440	440	440
Lipemia (mg/dL)	0-1666.7	1600	1600
Unconjugated bilirubin (mg/dL)	0 – 17.4	17	17
Conjugated Bilirubin (mg/dL)	0-17.8	17	17
Albumin (mg/dL)	0-5000	5000	5000
Trisodium Citrate (mg/mL)	0-20	20	20
Sodium-heparin (U/mL)	0-100	100	100
Potassium-EDTA (mg/mL)	0-10	10	10
Ascorbic acid (mg/dL)	0-20	20	20
Rheumatoid factor (IU/mL)	500	500	500

The following PTH fragments were tested for cross-reactivity. The cross-reactivity (%) is the percent of the PTH fragments which will be identified as Intact PTH. If these PTH fragments are present in the specimen at the same concentration as Intact PTH, the final result will be increased by these percentages.

PTH fragment	Cross-reactivity (%)
1-84	100
7-84	107.4
1-34	< 0.02
13-34	< 0.02
39-84	< 0.02
53-84	< 0.02

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:
Performance of the ST AIA-PACK Intact PTH assay on AIA-1800 instrument was compared with performance of the predicate device, Roche Elecsys PTH assay using 153 patient serum samples with PTH values ranging 8 – 1537.0 pg/ml. A linear regression analysis conducted to determine the correlation between the device and the predicate resulted in the equation, $y = 1.013x - 10.457$ and correlation value of 0.997.

b. Matrix comparison:
To demonstrate comparable performance between serum and EDTA-plasma, the sponsor compared 134 paired serum and plasma samples on AIA-1800

analyzer using ST AIA-PACK Intact PTH assay. The values for sera ranged 13.3 – 1931.7 pg/mL, and the linear regression analysis resulted in the equation, $y = 0.9921x+7.8816$ and R=0.9957.

The sponsor indicated in the labeling that heparinized or citrated plasma should not be used for specimen collection and handling.

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 sponsor established the expected reference range based on 144 samples from apparently healthy individuals. Sample values ranged 9.5 – 98 pg/ml indicated a slightly skewed pattern from Gaussian distribution. Reference range was established at 8.2 – 83.5 pg/mL based on the mean (45.9 pg/ml) ± two standard deviations (SD=18.8 pg/mL).

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.