September 30, 2020

Immunodiagnostic Systems Ltd.
Mick Henderson
RA Manager
10 Didcot Way, Boldon Business Park
Boldon, Tyne and Wear NE35 9PD
United Kingdom

Re: K200475
Trade/Device Name: IDS-iSYS Ostase® BAP
Regulation Number: 21 CFR 862.1050
Regulation Name: Alkaline phosphatase or isoenzymes test system
Regulatory Class: Class II
Product Code: CIN
Dated: August 27, 2020
Received: August 31, 2020

Dear Mick Henderson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal

statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Marianela Perez- Torres, Ph.D.
Acting Deputy Director
Division of Chemistry and Toxicology Devices
OHT7: Office of In Vitro Diagnostics and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
k200475

Device Name
IDS-iSYS Ostase® BAP

Indications for Use *(Describe)*
The IDS-iSYS Ostase® BAP assay is an in vitro diagnostic device intended for the quantitative determination of bone-specific alkaline phosphatase (BAP), an indicator of osteoblastic activity, in human serum on the IDS system. Results are to be used in conjunction with other clinical and laboratory data to aid the clinician in the management of postmenopausal osteoporosis and Paget's disease.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) SUMMARY

510k Number k200475

Introduction According to the requirements of 21CFR807.92, the following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

Submitter

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Date prepared: 28 September 2020

Device Name

Proprietary names:	IDS-iSYS Ostase® BAP
Common names:	As above
Classification:	21CFR862.1050 Alkaline phosphatase or isoenzymes test system.
	Class II
Product Code:	CIN

Predicate Device

The IDS-iSYS Ostase® BAP is substantially equivalent to other products in commercial distribution intended for similar use. We claim equivalency to the currently marketed Tandem-MP Ostase Immunoenzymetric Assay (k972666), commercially known as Ostase® BAP EIA.

Device Description

The IDS-iSYS Ostase® BAP assay consists of one reagent cartridge and one set of calibrators (CAL A & CAL B).

The reagent cartridge contains multiple reagents:

- MPM1 (Magnetic particles coated with streptavidin in a phosphate buffer with sodium azide as preservative);
- Ab-BIOT Monoclonal anti-BAP labelled with biotin, in buffer containing horse serum with bovine and mouse proteins and sodium azide as a preservative (<0.1 %)
- SUBS (p-nitrophenyl phosphate in a stabilising buffer containing preservatives).

Calibrators A and B are buffered bovine protein matrix containing human BAP with sodium azide as preservative (<0.1 %).

Indications for Use

The IDS-iSYS Ostase® BAP assay is an *in vitro* diagnostic device intended for the quantitative determination of bone-specific alkaline phosphatase (BAP), an indicator of osteoblastic activity, in human serum on the IDS system. Results are to be used in conjunction with other clinical and laboratory data to aid the clinician in the management of postmenopausal osteoporosis and Paget's disease.

Conditions for use:

For in vitro diagnostic use only.
Rx Only

Special instrument Requirements:

IDS System (k091849)

Comparison Tables

Similarities compared to the chosen (FDA cleared; marketed) predicate device (k972666)

Assay

Assay Performance	**Predicate Device Tandem-MP Ostase Immunoenzymetric Assay (k972666), commercially known as Ostase® BAP EIA**	**Candidate Device IDS-iSYS Ostase® BAP (k200475)**
Intended Use	For quantitative determination of Bone Alkaline Phosphatase concentration	For quantitative determination of Bone Alkaline Phosphatase concentration
Analyte	Bone Alkaline Phosphatase	Bone Alkaline Phosphatase
Sample Volume	50 µL	50 µL
Sample Type	Human Serum	Human Serum
Specificity, Interfering substances & Cross Reactivity	<u>Interfering Substances</u> Acetaminophen 20 mg/dL Alendronate 5 mg/dL Asprin 50 mg/dL Bilirubin – unconjugated 40 mg/dL Calcitonin – salmon 112 IU/dL Calcium 20 mg/dL Ibuprofen 40 mg/dL Pamidronate 18 mg/dL Progesterone 25 mg/dL	<u>Interfering Substances</u> Acetaminophen Same Alendronate Same Asprin Same Bilirubin – unconjugated Same Calcitonin – salmon Same Calcium Same Ibuprofen Same Pamidronate Same Progesterone Same

Differences compared to the chosen (FDA cleared; marketed) predicate device (k972666)

Assay

Performance	**Predicate Device Tandem-MP Ostase Immunoenzymetric Assay (k972666), commercially known as Ostase® BAP EIA**	**Candidate Device IDS-iSYS Ostase® BAP (k200475)**
Indications for Use	The Ostase® BAP EIA Assay is an in vitro device indicated for the quantitative measurement of bone-specific alkaline phosphatase (BAP), an indicator of osteoblastic activity, in human serum. This device is intended to be used as an aid in the management of postmenopausal osteoporosis and Paget's disease.	The IDS-iSYS Ostase® BAP assay is an *in vitro* diagnostic device intended for the quantitative determination of bone-specific alkaline phosphatase (BAP), an indicator of osteoblastic activity, in human serum on the IDS system. Results are to be used in conjunction with other clinical and laboratory data to aid the clinician in the management of postmenopausal osteoporosis and Paget's disease
Method of detection (Test methodology)	Manual	Automated
Kit reagent components	**Conjugate** (1 x 14 mL) anti-BAP(mouse monoclonal IgG) with biotin in a bovine/horse protein matrix with 0.09% sodium azide **Microplates** (1 x 96 wells) Streptavidin coated plastic well strips **Zero Calibrator** (1 x 14 mL) A bovine protein matrix containing no detectable concentration of BAP and 0.09% sodium azide **Calibrators** (1-5) (5 x 1 mL) A bovine protein matrix containing approximately 7, 15, 30, 60 and 90 ug human BAP/L and 0.09% sodium azide	**Reagent Cartridge** **MPM1** (1 x 2.6 mL) Magnetic particles coated with streptavidin in a Phosphate buffer with sodium azide as preservative (<0.09%) **Ab-BIOT** (1 x 10.5 mL) Monoclonal anti-BAP labelled with biotin, in buffer containing horse serum with bovine and mouse proteins and sodium azide as a preservative (<0.09%)

	Low Control (1 x 1 mL) A bovine protein matrix containing approximately 11 ug human BAP/L and 0.09% sodium azide **High Control** (1 x 1 mL) A bovine protein matrix containing approximately 45 ug human BAP/L and 0.09% sodium azide **Wash Concentrate** (1 x 50 mL) Phosphate buffered saline containing Tween **Substrate** (1 x 20 mL) p-nitrophenyl phosphate in a stabilizing buffer containing preservatives **Quench Reagent** (1 x 14ml) 1 N Sodium hydroxide	**SUBS** (1 x 40 mL) p-nitrophenyl phosphate in a stabilizing buffer containing preservatives **Calibrators** (1 each of 2 concentrations levels – 2.5ml per bottle). A buffered bovine protein matrix containing human BAP with sodium azide as preservative (<0.09%)
Range of assay	0.7 – 90 µg/L	3 – 70 µg/L
Sensitivity	LoB N/A LoD 0.7 µg/L LoQ N/A	LoB 0.3 µg/L LoD 0.4 µg/L LoQ 0.5 µg/L
Expected values	**Males** Mean 12.3 µg/L Median 11.6 µg/L 95th percentile 20.1 µg/L **Pre-Menopausal** Mean 8.7 µg/L Median 8.5 µg/L 95th percentile 14.3 µg/L **Post-Menopausal** Mean 13.2 µg/L Median 12.5 µg/L 95th percentile 22.4 µg/L	**Males** Mean 13.7 µg/L Median 13 µg/L Range 7.9 to 23.5 µg/L **Pre-Menopausal** Mean 11.5 µg/L Median 11.1 µg/L Range 5.9 to 20.5 µg/L **Post-Menopausal** Mean 15.7 µg/L Median 14.3 µg/L Range 7.9 to 34.2 µg/L

Precision	<u>Within Run Precision n =20</u> 2.6% to 6.5% in the concentration range 7.4 to 79.5 µg/L <u>Between Run Precision n = 20</u> 2% to 6.4% in the concentration range 8.4 to 81.1 µg/L	<u>Repeatability n =80</u> 1.7% to 2.8% in the concentration range 6.2 to 59.8 µg/L <u>Within Laboratory n = 80</u> 3.0% to 7.6% in the concentration range 6.2 to 59.8 µg/L
Specificity, Interfering substances And Cross Reactivity	<u>Interfering Substances</u> Bilirubin – conjugated: 20 mg/dL Biotin: No Claim Cholesterol: 400 ng/dL Estradiol: 105 mg/dL Etidronate: 500 mg/dL Haemoglobin: No Claim HAMA: No Claim PTH 1-34: No Claim PTH 1-84: No Claim Raloxifene: No Claim Red Blood Cells: No Claim Rheumatoid Factor (Rf): No Claim Risedronate: No Claim Total Protein: 14 g/dL Triglycerides: 2000 mg/dL 25-hydroxyvitamin D: 80,500 IU/dL <u>Cross Reactivity</u> Intestinal ALP 100U/L yields a result of 1.0 µg/L Liver ALP 100 U/L yields a result of 6.2µg/L Placental ALP Non detectable	<u>Interfering Substances</u> Bilirubin – conjugated: 40 mg/dL Biotin: 400 ng/mL Cholesterol: 340 mg/dL Estradiol: 400 µg/mL Etidronate: 90 mg/dL Haemoglobin: 300 mg/dL HAMA: 4000 ng/mL PTH 1-34: 20 µg/dL PTH 1-84: 11.8 µg/dL Raloxifene: 20 µg/mL Red Blood Cells: 0.3% Rheumatoid Factor (Rf): 1200 IU/mL Risedronate: 50 µg/dL Total Protein: 12 g/dL Triglycerides: 667 mg/dL 25-hydroxyvitamin D: 125 ng/mL <u>Cross Reactivity</u> Intestinal ALP Spiked 745 µg/L yields 0.1% Liver ALP Spiked 90 U/L yields 0.5% Placental ALP Non detectable
Method comparison	Against Tandem-R Ostase (k961573) n = 136 Ostase® BAP EIA = 1.02 x (Tandem-R Ostase) + 0.28 µg/L Correlation coefficient (r) = 0.97	Against Ostase® BAP EIA: n = 150 IDS-iSYS Ostase® BAP = 0.99 x (Ostase® BAP EIA) + 0.17µg/L Correlation coefficient (r) = 0.99

Linearity	No Claim	Observed = 0.98 x (Expected) -0.9 µg/L Regression coefficient R^2: 1.00

Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:
Precision was evaluated in accordance with a modified protocol based on CLSI EP-5A3, "Evaluation of Precision Performance of Quantitative Measurement Methods". Ten (10) native serum samples were assayed using three reagent lots in duplicate, twice per day for 20 days (n= 80 replicates per sample) on three systems.

Results from one representative reagent lot (Lot #3):

Sample	N	Mean Conc. (µg/L)	Repeatability		Within Laboratory	
			SD (µg/L)	%CV	SD (µg/L)	%CV
Sample 1	80	6.1	0.2	2.5%	0.2	2.8%
Sample 2	80	8.4	0.1	1.6%	0.2	2.8%
Sample 3	80	11.4	0.2	2.0%	0.4	3.9%
Sample 4	80	12.1	0.3	2.2%	0.5	4.5%
Sample 5	80	18.0	0.4	2.4%	0.8	4.5%
Sample 6	80	19.8	0.5	2.5%	0.9	4.6%
Sample 7	80	45.1	1.2	2.7%	1.6	3.5%
Sample 8	80	52.4	1.0	1.9%	1.9	3.5%
Sample 9	80	54.3	0.9	1.7%	1.6	2.9%
Sample 10	80	58.6	1.1	1.8%	1.5	2.5%

Results for the combined 3 lots:

Sample	N	Mean Conc. (µg/L)	Repeatability		Within Laboratory	
			SD (µg/L)	%CV	SD (µg/L)	%CV
Sample 1	240	6.2	0.2	2.8%	0.4	5.9%
Sample 2	240	8.7	0.1	1.7%	0.5	6.2%
Sample 3	240	11.7	0.3	2.5%	0.8	6.6%
Sample 4	240	12.5	0.3	2.4%	0.9	7.1%
Sample 5	240	18.4	0.4	2.4%	1.3	6.8%
Sample 6	240	20.6	0.5	2.5%	1.5	7.2%
Sample 7	240	45.5	1.0	2.3%	1.4	3.0%
Sample 8	240	53.2	1.1	2.1%	1.8	3.4%
Sample 9	240	54.7	0.9	1.7%	2.1	3.9%
Sample 10	240	59.8	1.1	1.9%	2.3	3.8%

b. Linearity/assay reportable range:

A linearity study was conducted based on CLSI EP6-A for the candidate device. A high human serum sample and a low human serum sample were used to create 11 evenly spaced dilutions by mixing the high and low sample to cover the assay measuring range as indicated below:

Sample	Dilution	Dilution Factor (%)
1:	Low (L)	0
2:	0.90L + 0.10H	10
3:	0.80L + 0.20H	20
4:	0.70L + 0.30H	30
5:	0.60L + 0.40H	40
6:	0.50L + 0.50H	50
7:	0.40L + 0.60H	60
8:	0.30L + 0.70H	70
9:	0.20L + 0.80H	80
10:	0.10L + 0.90H	90
11:	High (H)	100

Results:

Observed = 0.98 x (Expected) -0.9 ng/mL

Regression coefficient R^2: 1.00

The IDS-iSYS Ostase® BAP assay linear range was determined as 0.9 to 78.5 µg/L, with a measuring (reportable) range of 3 to 70 µg/L.

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

Calibrator traceability and value assignment

The IDS-iSYS Ostase® BAP kit calibrators are value assigned against in house secondary standard (IRs) using an internal QC procedure. The IR's are value assigned against the predicate device (Ostase® BAP EIA assay) using the predicate assay procedure. Therefore, the kit calibrators are traceable to the predicate device via the secondary standards.

Calibrator Value Assignment and Verification Method

For kit calibrator value assignment, the kit calibrators are tested as unknowns in a minimum of 20 assay runs on one IDS-iSYS system. The secondary standards (IRs) are assayed in each of the runs, and the values of the Kit Calibrators are assigned with direct reference to the secondary standards (IRs). The assigned kit calibrator values are then verified following the IDS QC procedure; by running the assay on three different IDS systems and analyzing IQCs of known values across the range of the assay.

Stability

Full kit stability was performed in which the kit calibrators were tested in combination with all kit combination reagents.

The stability based on real time studies determined a shelf life of 12 months.

d. Detection limit:

The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) were determined with guidance from CLSI EP17-A, "Protocols for Determination of Limits of Detection and Limits of Quantitation" in three (3) kit lots.

Each LoB sample was measured in duplicate, for a total of five assays in a five-day period, generating a total of 60 replicates per kit lot. Each kit lot was tested on a different instrument. Analyse-It software was used to calculate the LoB.

The LoD was determined using ten (10) samples with very low BAP concentrations. Each LoD sample was measured in duplicate, for a total of five assays in a five-day period per kit lot. Each kit lot was tested on a different instrument. Analyse-It software was used to calculate the LoD.

The LoQ was calculated using ten (10) samples with low BAP concentration. Each LoQ sample was measured in duplicate, for a total of five assays in a five-day period. Each kit lot was tested on a different instrument. Analyse-It software was used to calculate the predicted LoQ. The claim limit for each kit lot is the actual closest value to the Analyse-It's precited value.

The limit of blank (LoB), limit of detection (LoD) and limit of quantitation (LoQ) were determined with guidance from CLSI EP17-A, "Protocols for Determination of Limits of Detection and Limits of Quantitation" using 60 replicates of blank and 10 low level samples.

Sensitivity	**BAP Concentration (µg/L)**
LoB (Limit of Blank)	0.3
LoD (Limit of Detection)	0.4
LoQ (Limit of Quantitation)	0.5

e. Analytical specificity:

Interference and cross-reactivity studies were performed in accordance with the CLSI EP07-A3 Interference.

To determine potential interference, two serum samples at two different concentrations of BAP were spiked with the potential interferent. Control samples (blank) were spiked with a volume of Phosphate Buffer saline (PBS) (0 ng/mL) or relevant diluent equal to that of the spiked interferent. The mean of 26 replicate assays, for both spiked and control samples,

were then compared. The differences observed between the mean spiked and control sample values were examined and assessed according to acceptance criteria.

For Rheumatoid factor (Rf) or total cholesterol, the interference was tested by recovery of BAP from a high serum pool spiked into a serum sample with known Rf levels or cholesterol levels. % Interference was calculated using below formula:

$$\% \text{ Interference} = \frac{(\text{mean spiked concentration} - \text{mean un-spiked concentration})}{\text{mean un-spiked concentration}} \times 100$$

% Recovery was calculated using the formula below:

Recovery value = Observed mean spiked value – Observed mean unspiked value

% Recovery = (Recovery value / Expected Recovery value (Analyte added)) x 100

The following compounds were tested and found not to interfere significantly with the test, based on the predefined acceptance criteria of non-significant interference of <10% bias between the test and control samples:

Potential Interfering Substance	**Highest concentration tested that demonstrated no significant interference**
Acetaminophen	20 mg/dL
Alendronate	5 mg/dL
Bilirubin (Conjugated)	40 mg/dL
Bilirubin (Unconjugated)	40 mg/dL
Biotin	400 ng/mL
Calcium Chloride	20 mg/dL
Cholesterol	325 mg/dL
Estradiol	400 µg/mL
Etidronate	90 mg/dL
Haemoglobin	300 mg/dL
HAMA	4000 ng/mL
Ibuprofen	40 mg/dL
Pamidronate	18 mg/dL
Progesterone	25 mg/dL
PTH 1-34	20 µg/dL
PTH 1-84	11.8 µg/dL
Raloxifene	20 µg/mL
Red Blood Cells	0.3%
Rheumatoid Factor (RF)	1200 IU/mL
Risedronate	50 µg/mL
Salicylic Acid (Asprin)	50 mg/dL
Salmon Calcitonin	112 IU/dL
Total Protein	12 g/dL
Triglycerides	667 mg/dL
25-hydroxyvitamin D	125 ng/mL

Cross-reactivity testing was performed on Liver, Placental and Intestinal derived ALP.

the indicated substances were spiked into serum samples and measured with the IDS-iSYS Ostase® BAP, following the CLSI EP7-A2. The percent cross-reactivity was calculated using below formula:

$$\% \text{ cross reactivity} = \frac{(\text{Mean concentration of spiked sample} - \text{mean concentration of un-spiked sample})}{\text{Spike concentration}} \times 100\%$$

The substances with structures similar to bone alkaline phosphatase (BAP) were spiked into serum samples and measured with the IDS Ostase® BAP, following the CLSI EP7-A2. The exogenous substances were tested at the concentration listed below and determined to have the following percent cross-reactivity:

Cross-Reactant	Spiked Concentration	% Cross Reactivity
Liver ALP	745 µg/L	0.1%
Placental ALP	90 U/L	0.5%
Intestinal ALP	500 µg/L	Undetectable

f. Assay cut-off:
Not applicable

2. Comparison studies:

The IDS-iSYS Ostase® BAP assay was compared against the IDS Ostase® BAP EIA assay, following CLSI EP-9A2 "Method Comparison and Bias Estimation Using Patient Samples". A total of 150 samples, selected to represent a wide range of BAP concentrations [3.0 to 67.6 µg/L], was assayed by each method. Passing-Bablok regression analysis was performed on the comparative data:

N	Slope	95% CI	Intercept (µg/L)	95% CI	Corr. Coefficient (r)
150	0.99	0.97 to 1.02	0.17	-0.1 to 0.5	0.99

3. Expected values/Reference range:

The BAP concentration was measured in serum samples collected from 419 apparently healthy donors from the United States using the IDS Ostase® BAP assay. The study population included 140 males (35 to 75 years of age), 140 pre-menopausal women (35 to 45 years of age) and 139 post-menopausal women (55 to 75 years of age). The observed ranges (2.5th to 97.5th percentile) were established, according to CLSI guideline C28-A3c, "How to Define and Determine Reference Intervals in the Clinical Laboratory" are summarized in the below table:

Population	N	Age (years)	BAP Concentration (µg/L)

		Median	Min.-Max	Mean	Median	SD	Observed Range
Males	140	49	35 to 75	13.7	13.0	4.1	7.9 to 23.5
Pre-menopausal	140	39	35 to 45	11.5	11.1	3.9	5.9 to 20.5
Post-menopausal	139	58	55 to 75	15.7	14.3	6.7	7.9 to 34.2

The above ranges should be considered as guidelines only; it is recommended that each laboratory establish its own expected range based upon its own patient population.

Conclusion:

The IDS-iSYS Ostase® BAP assay data presented and provided are complete and supports the basis for substantial equivalence to the predicate device.