SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k110137

B. Purpose for Submission:

New device

C. Measurand:

Creatinine

D. Type of Test:

Enzymatic colorimetric, quantitative

E. Applicant:

Horiba ABX SAS

F. Proprietary and Established Names:

1. ABX PENTRA Enzymatic Creatinine CP
2. ABX PENTRA Multical
3. ABX PENTRA N Control
4. ABX PENTRA P Control
5. ABX PENTRA Urine Control L/H

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
JFY	Class II	21 CFR 862.1225 Creatinine Test System	Clinical Chemistry (75)
JIX	Class II	21 CFR 862.1150 Calibrator	Clinical Chemistry (75)
JJY	Class I, reserved	21 CFR 862.1660 Quality Control Material	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

Refer to indication for use below

2. Indication(s) for use:

   ABX PENTRA Enzymatic Creatinine CP reagent, with associated calibrator and controls, is a diagnostic reagent for quantitative in vitro determination of Creatinine in human serum, plasma and urine based on an enzymatic method using a multi-step approach ending with a photometric end-point reaction. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.

   The ABX PENTRA Multical is a calibrator for use in the calibration of quantitative Horiba Medical methods on Horiba Medical clinical chemistry analyzers.

   The ABX PENTRA N Control is for use in quality control by monitoring accuracy and precision.

   The ABX PENTRA P Control is for use in quality control by monitoring accuracy and precision.

   The ABX PENTRA Urine Control L/H is for use in quality control by monitoring accuracy and precision.

3. Special conditions for use statement(s):

   For *in vitro* diagnostic use only

4. Special instrument requirements:

   ABX PENTRA 400 Clinical Chemistry Analyzer

I. Device Description:

The ABX PENTRA Enzymatic Creatinine CP is an in vitro diagnostic assay for the quantitative in vitro determination of creatinine in human serum, plasma and urine based on an enzymatic method using a multi-step approach ending with a photometric end-point reaction. It is composed of a bi-reagent cassette (R1= 22 mL;R2= 8 mL). Reagent is a chemical solution with additives.

The ABX PENTRA Multical is a lyophilized human serum calibrator with chemical additives and materials of biological origin. The assigned values of the calibrator's components are given in the labeling, ensuring optimal calibration of the appropriate HORIBA ABX SAS methods on the ABX PENTRA 400 analyzer. This calibrator is provided in ten vials of 3 ml.

The ABX PENTRA N Control and ABX PENTRA P Control are quality control

products consisting of lyophilized human serum with chemical additives and materials of biological origin added as required to obtain given component levels. The assigned values of the control components are given in the labeling, ensuring control of the appropriate HORIBA ABX SAS methods on the ABX PENTRA 400 analyzer. Each control is provided in ten vials of 5 ml.

The sponsor stated in the labeling that all donor units of serum used in the preparation of Calibrators and Controls were tested by FDA-approved method and found negative for HIV (HIV I/II antibody), HBV (HBsAg) and HCV (antibody).

The ABX PENTRA Urine Control L/H is a two-level (Low and High) quality control consisting of liquid solutions prepared from human urine with chemical additives and materials of biological origin added as required to obtain given component levels. The assigned values of the control components are given in the labeling, ensuring control of the appropriate HORIBA ABX SAS methods on the ABX PENTRA 400 analyzer. Each control level is provided in one vial of 10 ml.

The sponsor stated in the labeling that the serum from each donor contributing urine for this product was tested by FDA accepted methods and found non-reactive for Hepatitis B Surface Antigen (HBsAg), antibody to Hepatitis C (HCV) and antibody to HIV-1/HIV-2.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Diagnostic Chemicals Limited Enzymatic Creatinine Assay

   ABX PENTRA Multical; ABX PENTRA Control N and P; ABX PENTRA Urine Control L/H (k072115)

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

   k070383, k072115

3. Comparison with predicate:

Items	ABX PENTRA Enzymatic Creatinine CP (Candidate Device)	Diagnostic Chemicals Limited Enzymatic Creatinine Assay (Predicate Device)
Similarity		
Intended use/Indication for use	Same	Intended for the quantitative determination of creatinine in serum, plasma and urine. Creatinine measurements are used in the diagnosis and treatment of renal diseases, in monitoring renal dialysis, and as a calculation basis for measuring other urine analytes.
Test method	Same	Enzymatic colorimetric, quantitative
Sample type	Same	Serum, plasma, urine
Difference		
Measuring range	Serum/plasma 0.11– 16.95 mg/dL Urine 3.56– 175 mg/dL	Serum/plasma 0.04-30 mg/dL Urine 0.03-175 mg/dL

Items	ABX PENTRA Multical (Candidate Device)	ABX PENTRA Multical (k072115)
Intended use/Indication for use	Same	For use in the calibration of quantitative Horiba Medical methods on Horiba Medical clinical chemistry analyzers.
Matrix	Same	Lyophilized human serum with chemical additives
Number of Analyte	26 (addition of Creatinine)	25

Items	ABX PENTRA Control N and P (Candidate Device)	ABX PENTRA Control N and P (k072115)
Intended use/Indication for use	Same	For use in quality control by monitoring accuracy and precision.
Matrix	Same	Lyophilized human serum with chemical additives
Number of Analytes	26 (addition of Creatinine)	25

Items	ABX PENTRA Urine Control L/H (Candidate Device)	ABX PENTRA Urine Control L/H (k072115)
Intended use/Indication for use	Same	For use in quality control by monitoring accuracy and precision.
Matrix	Same	Human urine with chemical additives
Number of analytes	10 (addition of Creatinine)	9

K. Standard/Guidance Document Referenced (if applicable):

- CLSI Guideline EP5-A2
- CLSI Guideline EP6-A
- CLSI Guideline EP9-A2
- CLSI Guideline EP17-A

L. Test Principle:

This enzymatic method for creatinine utilizes a multi-step approach ending with a photometric end-point reaction. The enzyme creatinine amidohydrolase is used to convert creatinine to creatine. Creatine is broken down to sarcosine and urea by creatine amidinohydrolase. Further enzyme linked steps with sarcosine oxidase and peroxidase yield a colored chromogen read at 545nm.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Study Protocol:
Within run precision was established by assaying two levels of control and patient samples 20 times in a single run. Total precision was established by assaying the same set of samples in duplicate twice a day for 20 days. The results are summarized below.

Result Summary:

Within-run precision

Matrix	Sample	N	Mean (mg/dL)	CV%
Serum	Control 1	20	0.90	2.18
	Control 2	20	4.05	0.54
	Patient 1	20	0.56	2.86
	Patient 2	20	1.52	1.08
	Patient 3	20	6.46	0.29
Urine	Control 1	20	66.52	0.83
	Control 2	20	148.78	0.87
	Patient 1	20	10.91	2.21
	Patient 2	20	89.26	0.83

Total precision

Matrix	Sample	N	Mean (mg/dL)	CV%
Serum	Control 1	80	1.29	2.23
	Control 2	80	5.20	2.24
	Patient 1	80	0.57	4.12
	Patient 2	80	1.51	2.07

	Patient 3	80	6.32	2.82
Urine	Control 1	80	70.5	3.06
	Control 2	80	157.0	3.08
	Patient 1	80	11.2	4.84
	Patient 2	80	92.2	2.55

b. Linearity/assay reportable range:

Study Protocol:
Linearity was evaluated following CLSI guideline EP6-A. For serum linearity, a spiked serum sample was used as the high sample and a diluted serum sample (2x in 0.9% NaCl) was used as the low sample. The intermediate concentrations in creatinine were prepared by serial dilution of the highest sample using the low sample as the diluents. For urine linearity, a spiked urine sample was used as the high sample and 0.9% NaCl was used as the low sample. For both studies, the mean of 4 replicate measurements were used in the regression analysis.

Summary:
Based on results of the linearity study and the limit of detection study (see below in *d*), the sponsor claimed that the reportable range for the serum assay is 0.11-16.95 mg/dL, the reportable range for urine assay is 3.55-175 mg/dL. The sponsor has also provided data to support that automatic dilution can go up to 50.85 mg/dL for serum and 846.9 mg/dL for urine.

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

Traceability:

The ABX PENTRA enzymatic creatinine assay, calibrators, and controls are traceable to NIST reference material SRM909b.

Stability:

Real-time testing was conducted. The stability study protocol and the acceptance criteria have been reviewed and found to be acceptable. The study results support the following stability claims in the labeling:

Closed-Vial and Open-Vial Stability

Item	Storage Conditions		Claimed Stability
Reagent Packs	Close-Vial	2-8°C	18 months
	Open-Vial	On system, 2-8°C	30 days
Calibrators	Close-Vial	2-8°C	24 months
	Open-Vial	-25 °C to -15°C	2 weeks
		2-8°C	2 days
		15°C to 25°C	8 hours
Serum controls	Close-Vial	2-8°C	30 months
	Open-Vial	-25 °C to -15°C	1 month
		2-8°C	5 days
		15°C to 25°C	12 hours

Urine Controls	Close-Vial	2-8°C	2 years
	Open-Vial	2-8°C	30 days

Calibration Interval:
Stability across a 14 day calibration interval was assessed by calculating the percentage bias of 2 control specimens on each day from the result obtained on day 0. The results support the product claim of a 14-day calibration interval. The sponsor also noted in the labeling that a recalibration is recommended when reagent lots change, and when quality control results fall outside the range established.

Value Assignment:

- Calibrators: The target value is determined by the median of 150 results from 6 ABX PENTRA 400 analyzers. The median is acceptable when percentage deviation is less than 10%.
- Controls: The target value is determined by the median of 150 results from 6 ABX PENTRA 400 analyzers. The median is acceptable when percentage deviation is less than 10%. The lot specific range was assigned as mean ± 3 SD. If 3 SD > 20% compared to the target value, the acceptable percentage will be of 20%, if 3SD <10% compared to the target values, the acceptable percentage will be 10%.

d. Detection limit:

Study Protocol:

Limit of Blank (LoB) and Limit of Detection (LoD) were determined following CLSI guideline EP17-A. For LoB determination, 0.9% NaCl was used as the Zero sample and assayed 90 times on 3 different Pentra 400 instruments. For LoD determination, 4 altered serum or urine samples with creatinine concentrations between LoB and 4xLoB were assayed 20 times for each sample.

For LoQ determination, a range of low concentration samples were prepared by 10% serial dilution and were assayed 10 times for each sample. The CV% and the bias at each tested concentration were calculated. LoQ is defined as the lowest concentration that meets CV% < 15% and the relative bias is in the +/-10% range.

Summary:
Based on the limit of quantitation determined in this study (see result in the below table) and the result from the linearity study in M1 b, the sponsor claimed a detection limit of 3.56 mg/dL in the labeling.

	LoB	LoD	LoQ
Serum	0.011 mg/dl	0.026 mg/dl	0.11 mg/dl
Urine	0.011 mg/dl	0.66 mg/dl	1.71 mg/dl

e. Analytical specificity:

- Interference

  Study Protocol:
  The sponsor evaluated the effect of the interfering substances following the Valtec guideline (Vassault et al., Ann. Biol. Clin., 1986, (44), 686-745).

  Pooled serum/urine samples with low and high levels of creatinine (approximately 1.5 mg/dL, 6.5 mg/dL in the serum pools, and 11 mg/dL and 88 mg/dL in the urine pools) were used as the base samples. Each interfering substance was added to the base samples and tested at 4 different concentrations.

  Result Summary:
  Based on the sponsor-defined limit of ± 5% bias between sample with and without interfering substances, the following claims were made:

  - Serum assay:

    The below compounds at the indicated concentration do not cause significant interference with the serum assay.

Compound	Concentration up to
Haemoglobin	500 mg/dL
Triglycerides	612.5 mg/dL
Total Bilirubin	27.4 mg/dL
Direct Bilirubin	9.9 mg/dL

  - Urine assay:

    The below compounds at the indicated concentration do not cause significant interference with the serum assay.

Compound	Concentration up to
Haemoglobin	390 mg/dL
Triglycerides	612.5 mg/dL
Direct Bilirubin	13.4 mg/dL
Ascorbic Acid	5.98 mg/dL

  - The sponsor also referenced Young's effect for list of drugs and preanalytical variables known to affect this methodology.

    Young DS. Effects of Drugs on Clinical Laboratory Tests. 4th Edition, Washington, DC, AACC Press (1997) 3: 143-163.

    Young DS. Effects of Preanalytical Variables on Clinical Laboratory Tests. 2nd Edition, Washington, DC, AACC Press (1997) 3: 120-132.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Study Protocol:

Unaltered patient samples (Serum N=153, Urine N=106) were used in the comparison studies. Each sample was assayed in singlet using the proposed assay on ABX PENTRA 400 and the predicate method on Olympus AU400 analyzer.

Result Summary:

The result of Linear Regression analysis is summarized in the below Table.

	N	Claimed measuring range (mg/dL)	Range of samples (mg/dL)	Slope	Intercept	R^2
Serum	153	0.11-16.95	0.35-16.15	1.00	0.02	0.999
Urine	106	3.56-175	6.61-171.28	0.96	0.40	0.997

Conclusion:
Based on the regression analysis result, the sponsor claimed equivalency to the predicate assay.

b. Matrix comparison:

Matched sets of serum, Li-Heparin plasma, and EDTA plasma were obtained from 40 patients. The reported values for each sample and for each matrix were obtained from single measurements (one replicate). Results of linear regression are summarized in the below table.

Matrix Y	Matrix X	Slope	Intercept	R^2	N	Sample Range (mg/dL)
Lithium heparin plasma	Serum	0.9963	0.0515	1.000	40	0.40-15.42
K3-EDTA plasma	Serum	1.0177	0.0427	1.000	40	

Conclusion:
Based on the regression result, the sponsor concluded that there is no significant matrix effect between serum, Li-Heparin plasma, and EDTA plasma specimens.

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):

None

4. Clinical cut-off**:**

Not applicable

5. Expected values/Reference range:

The sponsor stated in the labeling that each laboratory should establish its own reference ranges and the values given in the insert are used as guidelines only.

Serum/Plasma:
Men: 0.62 - 1.10 mg/dL
Women: 0.45 - 0.75 mg/dL

Urine (24 hours):
Men: 14 - 26 mg/kg/day
Women: 11 - 20 mg/kg/day

Reference:
Reference Information for the Clinical Laboratory, TIETZ Textbook of Clinical Chemistry and Molecular Diagnostics. 4th Ed; Burtis CA, Ashwood ER, Bruns DE, (Elsevier Saunders eds. St Louis, USA), (2006):2264.

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.