

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k050613

B. Purpose for Submission:

New Device

C. Measurand:

Beta-2 microglobulin

D. Type of Test:

Quantitative, latex particle- enhanced immunoturbidimetry.

E. Applicant:

Biokit S.A.

F. Proprietary and Established Names:

Quantia Beta-2 Microglobulin

G. Regulatory Information:

1. Regulation section:

21 CFR §866.5630, Beta-2-microglobulin Immunological Test System
21CFR§ 862.1660, Quality Control Material (Assayed and Unassayed)
21CFR§ 862.1150, Calibrator

2. Classification:

Device and calibrator - Class II
Quality control material - Class I

3. Product code:

JZG, System, test, beta-2-microglobulin immunological
JJX, Single (Specified) Analyte Controls (Assayed and Unassayed)
JJS, Calibrator, Primary

4. Panel:

Immunology 82

H. Intended Use:

1. Intended use(s):

The Quantia Beta-2 Microglobulin is intended as a latex particle enhanced immunoturbidimetric assay for the *in vitro* quantitative determination of beta-2-microglobulin concentration in human serum or plasma (EDTA) on the AEROSET® instrument as an aid in the diagnosis of active rheumatoid arthritis and kidney disease.

Quantia Proteins Control is intended for use in monitoring the quality control of results obtained with the Quantia Beta-2 Microglobulin and Quantia A1-AT reagents by turbidimetry. (NOTE: This control has been also 510(k) FDA submitted for use with A1-AT). For *in vitro* diagnostic use.

Quantia Beta-2 Microglobulin Standard is intended for use in establishing the calibration curve for the Quantia Beta-2 Microglobulin reagents by turbidimetry. For *in vitro* diagnostic use.

2. Indication(s) for use:
Same as Intended use.
3. Special conditions for use statement(s):
The device is for prescription use only.
4. Special instrument requirements:
Abbott AEROSET® instrument (k980367)

I. Device Description:

The device is an automated latex enhanced immunoassay for the quantitative in vitro diagnostic determination of beta-2-microglobulin (β_2 -M). The determination is based upon particle enhanced immunoturbidimetry using serum or plasma (EDTA) samples. The reagent kit contains 2 reagents, reagent 1 (4x6 mL) and reagent 2 (4x3 mL). Reagent 1 is a buffer and reagent 2 is latex particles coated with rabbit IgG anti-human β_2 -M.

Quantia Beta-2-microglobulin standard (for calibration): The calibrator is prepared from purified β_2 -M in a buffer with a concentration of 4 mg/L \pm 5%.

Quantia Proteins Control I/II: Controls are supplied in two levels. Control I is a low normal control with 0.7-1.3 mg/L of β_2 -M and Control II is a high control with 5.0-7.0 mg/L of β_2 -M. (NOTE: This control has been also 510(k) FDA submitted for use with A1-AT).

J. Substantial Equivalence Information:

1. Predicate device name(s):
IL Test Beta-2-Microglobulin (Instrumentation Laboratory Co.)
2. Predicate 510(k) number(s):
k943686
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Manufacturer	Biokit SA in Barcelona, Spain	Same
Intended Use	Quantitative in vitro diagnostic determination of β_2 -M	Same
Methodology	Particle Enhanced Immunoturbidimetry	Same
Test Principle	Two point kinetic assay	Same
Reagents	Reaction buffer and Latex Reagent	Same

Differences		
Item	Device	Predicate
Sample type	Serum, and Plasma (EDTA)	Serum, Plasma (EDTA, sodium heparin) and urine

Differences		
Item	Device	Predicate
Instrument	AEROSET® system	Monarch Instrument and ILab Chemistry Systems
Automatic rerun capability for samples below 0.25 mg/L and for samples above 16 mg/L	Yes	No
Calibration	System uses a multipoint calibration curve. The analyzer automatically prepares the 5 different concentrations of calibrator from the single level calibrator provided at 4 mg/L.	System uses a one-point calibration curve (4 mg/L).
Control	Quantia Proteins Controls sold separately by Biokit. Two level controls are lyophilized human sera with different concentrations of human β_2 -M.	Either Bio-Rad Lyophochek Tumor Marker Control, or the Pharmacia β_2 -M Control

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

CLSI/NCCLS EP5-A, EP6-A, EP7-A and EP9-A2.

L. Test Principle:

The Quantia Beta-2-microglobulin reagent is a suspension of polystyrene latex particles of uniform size coated with the IgG fraction of an anti-human β_2 -M specific serum. When a sample containing β_2 -M is mixed with the reagent, a clear agglutination occurs which can be measured by turbidimetry. Absorbance readings are taken at wavelengths of 572 nm. β_2 -M results are reported in mg/L.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

i. Precision:

Precision was performed on an AEROSET® system using three samples. The samples were Quantia Proteins Control I (low control, 0.7 – 1.3 mg/L), Control II (high control, 5.0 – 7.0 mg/L) and a negative serum sample spiked with pure β_2 -M at 10-15 mg/L. The samples were run in duplicate twice a day over twenty days (n=80) following the NCCLS EP5-A guidelines. The precision study met the acceptance criteria for all three samples which were < 5% for “Within Run CV” and < 6% for “Total CV”.

	β_2 -M Mean (mg/L)	Within run		Total	
		SD	CV (%)	SD	CV (%)
Low control	1.00	0.011	1.1	0.019	1.9
High control	5.46	0.049	0.9	0.071	1.3
Spiked serum	13.61	0.13	0.9	0.15	1.1

ii. Lot to lot reproducibility:

Lot to lot reproducibility was performed using three different lots of reagents and by comparing 7 different levels of calibrators.

β_2 -M mg/L	16	8	4	2	1	0.5	0.25
Mean Abs	580	296	133	59	27	13	5
SD	30.7	9.5	4.6	2.6	2.1	0.6	1.5
CV (%)	5.3	3.2	3.5	4.5	7.6	4.6	32.7

The mean values given above are absorbance values. A high SD was seen for the highest level of calibrator (16 mg/L) and high CV was seen for the lowest level of calibrator (0.25 mg/L). The sponsor pointed out that the quadruplicate runs performed for the linearity study gave a standard deviation of 0.017 for the 16 mg/L sample; and a CV of 2% for the 0.25 mg/L sample.

b. *Linearity/assay reportable range:*

Linearity testing was performed on an AEROSET® system using a serum sample containing around 20 mg/L of β_2 -M diluted in physiologic saline at different % dilutions (80%, 50%, 30%, 15%, 8% and 4%). Each dilution was analyzed in quadruplicate. The AEROSET® automatically reruns samples above 16 mg/L using a 1:6 dilution of the sample volume and for samples below 0.25 mg/L by adding 10 times more sample than the regular test.

Without rerun, the linearity studies together with the limit of quantification test demonstrated acceptable CVs and inaccuracies within the interval concentrations 0.25 – 22.2 mg/L. In order to prevent prozone problems, the claim for the upper limit of the test range has been decreased to 16 mg/L.

Within this range, 0.25-16.0 mg/L, the test has a slope of 1.00, an intercept of 0.0 mg/L and a correlation coefficient (r^2) 0.9995. With the automatic re-run, the linearity claims were extended from 0.02 – 100 mg/L.

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

Stability: The reference standard for β_2 -M is the WHO international standard for β_2 -M (1st international standard preparation).

Controls: The bulk product for the Control material is manufactured by BioRad and the product has been 510(K) cleared (k851202/A1) under the name LYPHOCHEK IMMUNOLOGY PLUS CONTROL. The lyophilized vials are purchased unlabeled from BioRad. The vials are labeled and packaged at Biokit. The target values and acceptance ranges to each level of controls are assigned at the Quality Control Department of Biokit with an AEROSET

Instrument using one lot of calibrator and two different lots of reagents.

Calibrator: The calibrator is manufactured from commercially purified and concentrated β_2 -M using the Quantia Beta-2 Reagents on an ILab 600 System (k980757). The purified and concentrated β_2 -M is diluted in a buffer to a concentration of 4 mg/L \pm 5% by comparison with a house standard. The house standard is traceable to the reference standard, the 1st WHO international standard preparation. Value assignment procedure was provided. System uses a five-point calibration curve. The analyzer automatically prepares the 5 different concentrations of calibrator from the single calibrator level vial provided at 4 mg/L.

Stability: On-board instrument stability was performed on reagents which showed 5 weeks stability for both reagents (R1 and R2). The reagent shelf-life stability at 2-8° C was also performed and the reagents were found to be stable for 19 months at 2-8° C. The calibration was shown to be stable for 30 days. The reconstituted controls were shown to be stable for 15 days at 2-8°.

d. *Detection limit:*

The detection limit was determined by running 30 replicates of physiological saline on an AEROSET® system. The detection limit is defined as the mean reported value for the physiologic saline plus 2 standard deviations. The detection limit is claimed as 0.046 mg/L.

e. *Analytical specificity:*

Interference testing was performed by spiking a serum sample containing β_2 -M with the various interfering substances and assayed on an AEROSET® system. The acceptance criteria for the percent of recovery β_2 -M in the spiked sample are within 95-105% of the unspiked sample. Based on the acceptance criteria, no significant interference was found with hemoglobin up to 482 mg/dL, bilirubin up to 20.8 mg/dL, triglycerides up to 1327 mg/dL and turbidity of the sample up to 2.18 AU/cm at 660 nm. Interference by rheumatoid factor (RF) is below 10% for RF concentration up to 288 IU/ml.

No cross-reactivity studies were performed with heterophile antibodies and have updated the package insert with the disclaimer statement “no cross-reactivity studies have been conducted with heterophile antibodies”.

f. *Assay cut-off:*

No assay cut off was provided.

2. Comparison studies:

a. *Method comparison with predicate device:*

The Method Comparison study was performed with 105 patient serum samples covering all the clinical range (1.01 to 101.1 mg/L of β_2 -M) on the new device and the predicate device, IL Test Beta-2 Microglobulin, (k943686) on an ILab 900 instrument which was cleared in k932467. The samples were obtained from two hospitals in Spain. The required specifications were: slope 1.0 ± 0.20 ; r (correlation coefficient) ≥ 0.950 . Linear regression analysis

showed a slope of 0.876 (95% CI: 0.868 to 0.886) and an intercept of 0.59 (95%CI: 0.385 to 0.772). The correlation coefficient was 0.9986.

b. Matrix comparison:

The plasma to serum correlation data was generated with 30 paired samples on an AEROSET® system. The recovery met the acceptance criteria which is $\pm 15\%$ of the serum sample result. The correlation coefficient was 0.996, the intercept was -0.091 (95%CI: -0.154 to -0.029) and the slope was 0.977 (95%CI: 0.942 to 1.012).

3. Clinical studies:

a. Clinical Sensitivity:

Not provided

b. Clinical specificity:

Not provided

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not provided

5. Expected values/Reference range:

The package insert provides literature reference for expected values for normal population. In the serum or plasma of apparently healthy persons, the normal range is approximately 0.97 to 2.64 mg/L. Due to the many variables which may affect results, each laboratory is expected to establish their own normal range.

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.