

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

A. 510(k) Number:

k110874

B. Purpose for Submission:

New device

C. Measurand:

β 2-Microglobulin

D. Type of Test:

Quantitative, latex-enhanced immunoturbidimetric

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

ADVIA® Chemistry β 2-Microglobulin reagent

ADVIA® Chemistry β 2-Microglobulin calibrator

G. Regulatory Information:

1. Regulation section:

21 CFR §866.5630 Beta-2-Microglobulin Immunological Test System

21 CFR §862.1150 Calibrator

2. Classification:

Class II

3. Product code:

JZG, Beta-2 Microglobulin Immunological Test System

JIT, Calibrator, Secondary

4. Panel:

Immunology (82)

Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

Reagent: For *in vitro* diagnostic use in the quantitative determination of β 2-microglobulin in human serum and plasma (lithium heparin and potassium EDTA) on ADVIA® 1650 Chemistry systems. The ADVIA® 1650 Chemistry β 2-Microglobulin (B2M) assay aids in the diagnosis of active rheumatoid arthritis and kidney disease.

Calibrators: For *in vitro* diagnostic use in the calibration of ADVIA® 1650 Chemistry systems for the ADVIA® Chemistry β 2-Microglobulin method.

2. Indication(s) for use:

Same as above

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

ADVIA® 1650 Chemistry Systems

I. Device Description:

The ADVIA® 1650 Chemistry β 2-Microglobulin reagent consists of the following:
Reagent 1 in a 20-mL container, consisting of 0.5% bovine serum albumin, Tris buffer

(pH 8.2) and sodium azide; Reagent 2 in a 20-mL container, consisting of latex-particles coated with antihuman β 2-microglobulin antibodies (goat), Tris buffer (pH 8.0) and sodium azide. The components of the package are available as a kit only. The ADVIA® 1650 Chemistry β 2-Microglobulin calibrator is a lyophilized, buffer-based product containing bovine serum and human β 2-microglobulin. The kit consists of 3 vials of a single level calibrator. The calibrator requires reconstitution with 1 mL of distilled water prior to use.

J. Substantial Equivalence Information:

1. Predicate device name (s) and 510(k) numbers:

N Latex β 2-Microglobulin, k002731

N/T Protein Standard SL, k052788

2. Comparison with predicate:

Assay Similarities		
Item	Device	Predicate
Intended Use/Indication for Use	For <i>in vitro</i> diagnostic use in the quantitative determination of β 2-microglobulin in human serum or plasma as an aid in the diagnosis of active rheumatoid arthritis and kidney disease.	Same
Measurement	Quantitative	Same
Storage Temperature	2-8°C	Same
Format	Liquid	Same
Use of Calibrators	Yes	Same

Assay Differences		
Item	Device	Predicate
Platform	ADVIA® 1650 Chemistry System	BN system
Assay Principle	Turbidimetric	Nephelometric
On Board Stability	21 days	Minimum 5 days
Sample Type	Serum, plasma	Serum, plasma, urine
Antibody Source	Goat polyclonal antibody	Mouse polyclonal antibody
Assay Range	0.25 – 18.0 mg/L	0.7 – 23.0 mg/L (serum/plasma)
Reference Range (Expected Values)	1.0 to 2.4 mg/L	1.09 to 2.53 mg/L

Calibrator Similarities		
Item	Device	Predicate
Number of Calibrators	1	Same
Storage temperature	2-8°C	Same

Calibrator Differences		
Item	Device	Predicate
Number of Analytes	One	Multiple
Format	Lyophilized – buffer based	Liquid – serum based
Stability	30 days after reconstitution	14 days after opening
Instrument	ADVIA® 1650 Chemistry System	BN Systems

K. Standard/Guidance Document Referenced:

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Clinical and Laboratory Standards Institute; 2004.

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Clinical and Laboratory Standards Institute; 2004.

L. Test Principle:

In the ADVIA® 1650 Chemistry β 2-Microglobulin assay, a sample is diluted and reacted with a buffer that contains latex particles coated with antibody specific for β 2-microglobulin. The formation of the antibody-antigen complex during the reaction results in an increase in turbidity, the extent of which is measured as the amount of light adsorbed at 545nm. The β 2-microglobulin concentration in a sample is determined by constructing a standard curve from the absorbance of a reagent blank and a single-level calibrator.

M. Performance Characteristics:

1. Analytical performance:

a. *Precision/Reproducibility:*

A precision study was conducted in accordance with CLSI document EP5-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods*; Approved Guideline. Five samples were used for the study including two β 2-microglobulin-spiked serum pools (i.e., Pool 1 and Pool 2) and three serum-based liquid controls (i.e., Control 1, Control 2, Control 3) that were prepared by spiking a pool of serum samples with β 2-microglobulin. All samples were analyzed in duplicate per run with 2 runs per day for 20 days using two reagent lots and two systems with one operator. The results are summarized below:

Serum Sample	No. of Rep	Mean Spiked B2M (mg/L)	Within Run		Between Run		Between Day		Total	
			SD mg/L	CV %	SD mg/L	CV %	SD mg/L	CV %	SD mg/L	CV %
Control 1	80	0.74	0.01	1.8	0.02	2.3	0.01	1.4	0.02	3.3
Control 2	80	1.77	0.02	1.0	0.01	0.4	0.04	2.4	0.05	2.6
Control 3	80	3.68	0.04	1.1	0.03	0.9	0.07	1.9	0.09	2.4
Pool 1	78 ^[1]	12.52	0.06	0.5	0.11	0.9	0.22	1.8	0.26	2.1
Pool 2	80	17.43	0.20	1.1	0.10	0.6	0.27	1.6	0.35	2.0

Note: ^[1]2 replicates were mislabeled and thus excluded from the analysis.

b. *Linearity/assay reportable range:*

Serum linearity across the assay range (0.25 to 18.00 mg/L) was evaluated by

testing nine serum samples with concentrations of β 2-microglobulin evenly distributed throughout the assay range. The series of nine serum samples were prepared by dilution of a sample with high concentration of β 2-microglobulin (approximately 18.88 mg/L) with a fresh normal human serum sample with an undetectable level of β 2-microglobulin. Each sample was tested in three replicates. The % recovery was calculated as the difference of the expected values and the observed values. The % recovery ranged from 93.6% to 104.0%, which met the established acceptance criteria. In addition, linear regression of observed values versus expected values showed that the slope, intercept and r^2 were 0.9963, -0.0989 (mg/L) and 0.9987, respectively.

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

Traceability:

The ADVIA® 1650 Chemistry β 2-Microglobulin assay is calibrated using the ADVIA® Chemistry β 2-Microglobulin Calibrator. The calibrator is traceable to WHO 1st International Preparation for β 2-microglobulin (NIBSC Code# B2M).

Value Assignment of Calibrators:

The values of the Master Lot of Calibrators were initially assigned based on Siemens N-latex β 2-Microglobulin method and then confirmed by acceptable recovery of the WHO first International Standard for β 2-microglobulin (NIBSC Code# B2M). The values of the ADVIA® Chemistry β 2-Microglobulin Calibrators in each production lot are assigned based on recovery of the Master Lot Calibrator and confirmed by testing of controls and Master Lot Calibrators as samples in triplicate using the β -2 Microglobulin method calibrated with the new production lot of calibrators with the newly assigned values.

Stability:

Real time stability studies were performed to support the following stability claims of the ADVIA® Chemistry β 2-Microglobulin reagents and ADVIA® β 2-Microglobulin Calibrator:

- Onboard stability is 21 days with a calibration frequency of 21 days.
- Shelf-life stability of the unopened ADVIA® Chemistry β 2-Microglobulin reagent stored at 2-8°C is 18 months.
- Shelf-life stability of the unopened ADVIA® Chemistry β 2-Microglobulin calibrators stored at 2-8°C is 24 months.
- Shelf-life stability of the opened (recapped) vial ADVIA® Chemistry β 2 Microglobulin calibrators stored at 2-8°C is 30 days.

d. *Detection limit:*

Testing for limit of detection (LoD) and limit of blank (LoB) was conducted in accordance with CLSI guideline EP-17A. Sixty replicates of a blank sample were used along with 60 replicates of a low serum sample (serum sample with an approximate concentration of 0.74 mg/L). The following results were obtained:

$$\text{LoB} = 0.20 \text{ mg/L}$$

$$\text{LoD} = 0.25 \text{ mg/L}$$

e. *Analytical specificity:*

Interference by endogenous and other substances was evaluated by testing β 2-microglobulin at concentrations of approximately 1, 3 and 11 mg/L within the assay range. Aliquots of each serum pool were spiked with 5 equally diluted concentrations of the interferent. The five concentrations were prepared by diluting the pool with the highest concentration of interferent with the control pool without interferent. All samples were run in duplicate using one reagent lot on one system. The following is a list of the interferents and the respective highest concentrations that were tested: bilirubin (conjugated and unconjugated, 60 mg/dL); hemolysis (hemoglobin, 1000 mg/dL); lipemia (from intralipid, 1000 mg/dL); rheumatoid factor (RF, 2500 IU/mL) and ascorbic acid (50 mg/dL, 100 mg/dL, 150 mg/dL and 200 mg/dL); acetone (1000mg/dL); cholesterol (500 mg/dL); creatinine (500 mg/dL); ethanol (1000 mg/dL); glucose (2000 mg/dL); immunoglobulin G (5000 mg/dL); immunoglobulin M (1600 mg/dL); riboflavin (15 mg/dL); total protein (12 g/dL); urea (60 mg/dL) and uric acid (16 mg/dL). No significant interference (i.e., sample recovers $\pm 10\%$) was observed with the interferents tested with the exception of the following: ascorbic acid spiked at 100 mg/dL to samples containing 1.21 mg/L β 2-microglobulin (-15.3%) and at 200 mg/dL to samples containing 10.73 mg/L β 2-microglobulin (-13.4%).

f. *Assay cut-off:*

Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

Performance of the ADVIA® 1650 Chemistry β 2-Microglobulin assay was evaluated against the predicate, Siemens N Latex β 2-Microglobulin (N B2M). The study included a total of 88 remnant serum specimens. Samples were analyzed on the ADVIA® 1650 Chemistry system using β 2-Microglobulin reagent and on the predicate device in parallel on the same day. Samples were tested in duplicate on each system (ADVIA® Chemistry and predicate) using one lot of reagents for each system. Results from least squares linear regression of the data from the first replicates are summarized below.

N	Range (mg/L)	Slope (95% Confidence Intervals)	Intercept (95% Confidence Intervals)	R	Syx (mg/L)
88	0.65 – 16.00	1.03 (1.017 – 1.052)	-0.38 (-0.53 – -0.24)	0.996	0.408

b. *Matrix comparison:*

Serum/Plasma equivalency studies were performed to support the use of lithium heparin and potassium EDTA tubes for the collection of serum and plasma samples. Fifty-seven matched sets of serum and plasma (lithium heparin and potassium EDTA) were used. Ten paired serum and plasma pairs (from the same donors) were spiked with β 2-microglobulin to achieve concentrations of β 2-microglobulin across the assay range. The samples were analyzed using the ADVIA® 1650 Chemistry β 2-Microglobulin method using one lot of reagent, in duplicate. Results from linear regression on the data from the first replicates are summarized below.

Linear Regression	N	Range (mg/L)	Slope	Intercept	R	Syx (mg/L)
Serum vs Lithium Heparin	57	0.97 – 17.75	1.01	0.01	0.99	0.21
Serum vs Potassium EDTA	57	0.97 – 17.75	1.00	-0.04	0.99	0.19

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):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The reference range was determined by calculating the 2.5th and the 97.5th percentile generated from sera from 120 apparently healthy adults. Samples were analyzed in singlet using the ADVIA® 1650 Chemistry β 2-Microglobulin assay.

The range was determined to be 1.0 to 2.4 mg/L.

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.