

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

A. 510(k) Number: k042479

B. Purpose for Submission: New assay and calibrators. Changes to calibrator verifiers.

C. Measurand: Gentamicin

D. Type of Test: Quantitative homogeneous enzyme immunoassay

E. Applicant: Ortho-Clinical Diagnostics Inc.

F. Proprietary and Established Names: VITROS Chemistry Products Gentamicin Reagent, Calibrator Kit 13, TDM Performance Verifier I, II and III.

G. Regulatory Information:

1. Regulation section: Gentamicin Test System (21CFR862.3450)
Assayed controls (21 CFR 862.3280)
Calibrators (21 CFR 862.3200)
2. Classification: Class II
3. Product code: 91LCD, 91DLJ, 91DIF
4. Panel: 91, Toxicology

H. Intended Use:

1. Intended use(s):
VITROS Chemistry Products GENT Reagent is used to quantitatively measure gentamicin (GENT) concentration in human serum and plasma.

VITROS Chemistry Products Calibrator Kit 13 is used to calibrate VITROS 5,1 FS Chemistry Systems for the quantitative measurement of gentamicin.

VITROS TDM Performance Verifier is an assayed control used to monitor performance of ACET, CRBM, DGXN, PHBR, PHYT, and GENT on VITROS Chemistry Systems.
2. Indication(s) for use:
For *in vitro* diagnostic use only. Serum or plasma gentamicin measurements are used in the diagnosis and treatment of gentamicin overdose and in monitoring levels of gentamicin to ensure appropriate therapy.

3. Special conditions for use statement(s): For prescription use
4. Special instrument requirements: For use on the VITROS 5,1 FS

I. Device Description:

Reagent 1 contains murine monoclonal antibodies to gentamicin, glucose-6-phosphate, NAD and other unreactive components. Reagent 2 contains Gentamicin labeled with glucose-6-phosphate dehydrogenase and other unreactive components.

Calibrator Kit 13 is an aqueous solution containing gentamicin, buffer, BSA, salts, proteins, surfactants and preservatives. Nominal values of gentamicin (ug/mL): 0, 0.6, 2, 4, 6, 10.

The performance verifiers are assayed controls prepared from bovine serum to which therapeutic drugs, salts and preservatives are added. Range of means for controls are provided on performance verifier assay sheets.

J. Substantial Equivalence Information:

1. Predicate device name(s): Syva[®] EMIT[®] 2000 Gentamicin Plus Assay and calibrators. VITROS Chemistry Products Performance Verifiers.
2. Predicate 510(k) number(s): k962519, k953197
3. Comparison with predicate: The devices are similar in intended use and methodology. Both devices are homogeneous enzyme immunoassays. The predicate device is for use on Syva Analyzer Systems; the new device is for use on the VITROS 5,1 FS Chemistry System.

The VITROS Chemistry Products TDM Performance Verifiers are substantially equivalent to VITROS Chemistry Products TDM Performance Verifiers, currently in commercial distribution (K953197). The difference is the addition of gentamicin (and other therapeutic drugs, for other TDM assays).

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

L. Test Principle:

Patient sample is added to reagent 1, which contains gentamicin antibody, glucose-6-phosphate and NAD, followed by reagent 2, which contains gentamicin conjugated with glucose-6-phosphate dehydrogenase. The activity of the gentamicin-enzyme conjugate, which competes with gentamicin in the sample, decreases upon binding with the antibody. Therefore, gentamicin in the sample is inversely related to enzyme activity and

can be monitored spectrophotometrically at 340 nm. Unknown sample concentrations are determined using the (stored) calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Within-day and within laboratory precision was determined using bovine serum-based QC materials, i.e. the VITROS Chemistry Products TDM Performance Verifiers, levels 1,2, and 3. The evaluation followed NCCLS EP-5A, with 2 replicates per run, two runs per day for 22 days, n=88 observations. Within-day runs were separated by at least 2 hours. Calibration was performed once each week. The sample order was randomized. Results for within-day and within-lab are shown. Testing of multiple lots and instruments yielded similar results.

Sample	Mean (ug/mL)	N	Within- day SD	Within- lab
Control level 1	1.38	88	0.027	0.073
Control level 2	4.36	88	0.095	0.191
Control level 3	7.86	88	0.146	0.363

Within-run precision was also estimated for patient serum pools at concentrations near the low end of the reportable range. Precision estimates were based on standard deviations, calculated for 5 replicates, for each of 3 reagent lots, at each gentamicin levels (i.e. total of 15 observations at each level). The within-run standard deviation limits are approximately 0.11 ug/mL for gentamicin concentrations ranging from 0.3-1.2 ug/mL gentamicin.

b. Linearity/assay reportable range:

Serum pools with gentamicin concentrations at 10 levels spanning the reportable range were evaluated. Each level was tested in replicates of 5 and average values of observed/expected concentrations were determined. The assay reportable range is 0.6-10 ug/mL. In this range deviations from linearity ranged from -0.39 to +0.31 ug/mL, for the samples tested.

Recovery after sample dilution with the recommended diluent was also evaluated. Serum samples with gentamicin concentrations in the range of approximately 7-10 ug/mL were diluted 2x and 4x. Average recoveries (from triplicates) ranged from 105-111%.

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
VITROS Chemistry Products Calibrator Kit 13, and performance verifiers I, II and III are for use with this device.

Values assigned to calibrators are traceable to the USP gentamicin reference standard. Expanded uncertainties (defined as 2x the total uncertainty in the calibrator assigned value) are calculated as 0.11 for 0.6 ug/mL and 0.48 for 10 ug/mL.

Calibrator long-term stability: Calibrators tested were stored at 9 degrees C and evaluated using the EMIT[®] Assay with calibrators stored at – 20 degrees C. Results support calibrator expiration dating. Bias limits for long term stability are shown:

Value (ug/mL)	Bias limits (+/-)
0	<0.3 ug/ml
0.6	34.8 %
2	11.6%
4	7.0%
6	6.9%
10	7.5%

Calibrator opened-bottle stability: Opened bottle stability is evaluated by at intervals and restored at 2-8 degrees C. Bias is determined relative to previously unopened calibrators. Acceptance limits range from approximately +/-3% for higher concentrations and +/- 11% for low concentrations.

Value assignment for calibrator verifiers: Performance verifier lots are tested with each reagent to establish target values. Testing is conducted with at least 2 instruments, 2 calibrations and a total of 32 replicates for each performance verifier. The range of means is calculated from precision data from multiple systems placed within different laboratories. A pooled SD is determined based on total SD's from each site and the range is calculated based on 3x pooled SD.

Verifier stability: Long-term stability for controls is evaluated using vials stored at -18 degrees C until testing. Analyte concentrations are compared to those at "time 0". Opened stability is evaluated using vials opened and stored at 2-8 degrees C between test dates. Acceptance criteria in terms of bias limits are shown below:

Control Level	Gentamicin Concentration (ug/mL)	Bias Limit (ug/mL) (+/-)	
		Long-term	Opened
I	1	0.258	0.171
II	4	0.684	0.435
III	7	1.209	0.775

d. **Detection limit:**

The lower limit of the reportable range listed in the package insert is 0.6 ug/mL. Data in the 510(k) support this value.

The limit of detection was determined based on gentamicin-negative serum samples from 10 human donors not taking gentamicin, as well as from low level calibrator material. Three lots and 2 calibrator kits were used in testing. The sampling plan is similar to EP-17A, but based on blank samples only. Calculations of the detection limit incorporate error contributed by calibration.

The acceptance criteria for within-run precision (total n=15, over 3 lots) is SD +/-0.108 ug/ml for concentrations < 1ug/mL.

The limit for deviation from linearity at samples near the low end of the reportable range is 0.325 ug/mL.

e. *Analytical specificity:*

Two human serum pools with gentamicin concentrations approximately 3 and 9 ug/mL were spiked with bilirubin (60 mg/dL), hemoglobin (1000 mg/dL) and intralipid (500 mg/dL). A serum pool with 5 ug/mL gentamicin was spiked with other drugs to evaluate interference: amikacin, 500 ug/mL; carbenicillin, 500 ug/mL; cefalotxin, 2500 ug/mL; cephalothin, 500 ug/mL; chloramphenicol, 500 ug/mL; clindamycin, 500 ug/mL; erythromycin, 500 ug/mL; penicillin G, 500 ug/mL; sulfamethoxazole, 600 ug/mL; tetracycline, 200 ug/mL; tobramycin, 50 ug/mL. Testing followed EP-7A for the paired-difference method.

The endogenous substances and the drugs listed above were found not to interfere within acceptance criteria for bias (< 0.4 for 3 ug/mL, <1.2 for 10 ug/mL, and < 0.52 for 5 ug/mL).

Cross-reactivities of approximately 6% and 7% were observed for netilmicin and sisomicin. Trimethoprim at a concentration of 25 ug/mL resulted in a positive bias of 0.57 ug/mL.

f. *Assay cut-off:*

NA. This is a quantitative assay.

2. Comparison studies:

a. *Method comparison with predicate device:*

One hundred and eight human serum samples were evaluated with the VITROS Chemistry Products Gentamicin Reagent and the Syva EMIT[®] Gentamicin Plus. Samples were selected to be patient serum samples of 2 mL or more that contained gentamicin across the reportable range of

the assay. Each sample was measured in triplicate. The analysis was also performed using singlicates, and showed no difference to the results listed below. Similar results were obtained for 3 lots tested. Results of regression analysis is shown: Slope = 1.00, intercept = 0.0, $r = 0.99$, $sy/x = 0.31$.

b. Matrix comparison:

Serum and plasma (EDTA and lithium heparin) samples were evaluated by paired difference testing of samples ranging from approximately 1-9 ug/mL. The bias between the mean values (n=3) was defined as: bias = test sample-serum sample.

Biases observed ranged from approximately -5% to 4% for lithium heparin plasma tubes and -4 to 6% for full EDTA plasma tubes. Results support use of the assay with serum and plasma (EDTA and lithium heparin) samples. The device is not for use with other anticoagulants.

3. Clinical studies:

a. Clinical Sensitivity:

N/A. (Not typically reviewed for this type of test)

b. Clinical specificity:

N/A. (Not typically reviewed for this type of test)

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

4. Clinical cut-off:

N/A. See expected values

5. Expected values/Reference range:

Reference ranges from the literature¹ are provided in the labeling.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

¹ National Academy of Clinical Biochemistry Symposium. Laboratory guidelines for monitoring of antimicrobial drugs. Catherine A. Hammett-Stabler and Thomas Johns. Clinical Chemistry 44:5 1129-1140 (1998).

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.