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

A. 510(k) Number:
k060853

B. Purpose for Submission:
New device

C. Measurand:
Tobramycin

D. Type of Test:
Quantitative, homogeneous microparticles agglutination immunoassay

E. Applicant:
Roche Diagnostics Corp.

F. Proprietary and Established Names:
ONLINE TDM Tobramycin

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
Radioimmunoassay, Tobramycin (KLB)	Class II	21 CFR 862.3900, Tobramycin test system.	91 CLINICAL TOXICOLOGY (TX)

H. Intended Use:

1. Intended use(s):
   The ONLINE TDM Tobramycin assay is for the quantitative determination of tobramycin in human serum or plasma on Roche automated clinical chemistry analyzers.

2. Indication(s) for use:
   The ONLINE TDM Tobramycin assay is for the quantitative determination of tobramycin in human serum or plasma on Roche automated clinical chemistry analyzers. Measurements obtained by this device are used in the diagnosis and treatment of tobramycin overdose and in monitoring levels of tobramycin to ensure appropriate therapy.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:
   Roche Hitachi 911/912/917 and MODULAR P analyzers

I. Device Description:

The test consists of ready-to-use reagents containing anti-tobramycin antibody (sheep polyclonal), glucose-6-phosphate, nicotinamide adenine dinucleotide, and bovine albumin in serum.

J. Substantial Equivalence Information:

Predicate	**k964457, COBAS INTEGRA Tobramycin**
Describe the item being compared	
The Roche ONLINE TDM Tobramycin assay is substantially equivalent to other products in commercial distribution intended for similar use. Most notably, it is substantially equivalent to the currently marketed Roche COBAS INTEGRA Tobramycin (k964457). The ONLINE TDM Tobramycin assay is for the quantitative determination of tobramycin in human serum or plasma on Roche automated clinical chemistry analyzers. The proposed labeling indicates the Roche Hitachi 911, 912, 917 and Modular P analyzers can be used with the Roche ONLINE TDM Tobramycin reagent kits.	
Similarites	
The new device and the predicate are both indicated for the quantitative determination of Tobramycin In human serum or plasma on Roche automated clinical analyzers.	
Differences	
The ONLINE TDM Tobramycin uses a homogeneous microparticles agglutination immunoassay. In Contrast, the Roche COBAS INTEGRA tobramycin assay utilizes a fluorescence polarization immunoassay (FPIA) system.	

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

CLSI EP5-T2, Evaluation of Precision Performance of Quantitative Measurement Methods

Guidance for Industry and FDA Staff; Replacement Reagent and Instrument Family Policy, December 11, 2003

L. Test Principle:

The assay is based on a homogeneous enzyme immunoassay technique used for the quantitative analysis of tobramycin in human serum or plasma. The assay is based on competition between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for antibody binding sites. Enzyme activity decreases upon binding to the antibody, so the drug concentration in the sample can be measured in terms of enzyme activity. Active enzyme converts oxidized nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that is measured spectrophotometrically. Endogenous serum G6PDH does not

interfere because the coenzyme functions only with the bacterial (Leuconostoc mesenteroids) enzyme employed in the assay.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The precision study was conducted on control material and spiked human serum pools using a modified version of CLSI-EP5-T2. The evaluation included using triplicate samples, 3 runs per day over 21 days (n=63). The results of the study met the sponsor's acceptance criteria for within-run precision (SD no greater than 0.14 up to a concentration of 2 µg/mL or CV ≤ 7% at higher concentrations) and total and between-day precision (SD no greater than 0.18, up to a concentration of 2 µg/mL or CV ≤ 9% at higher concentrations). The results are tabulated below:

Specimen	Low spike	High spike	Control 1	Control 2	Control 3
Total mean (ug/ml)	3.22	8.64	1.31	4.15	7.10
Within-run SD (ug/ml)	0.0255	0.0614	0.0514	0.0374	0.0412
Within-run %CV	0.8	0.7	3.9	0.9	0.6
Total SD (ug/ml)	0.0553	0.1523	0.0685	0.0685	0.0928
Total %CV	1.7	1.8	5.2	1.7	1.8
Between-day SD (ug/ml)	0.0491	0.1393	0.0453	0.0574	0.0832
Between-day %CV	1.5	1.6	3.5	1.4	1.2

b. *Linearity/assay reportable range:*

To assess the linearity of the assay, an 11-level dilution series was prepared using tobramycin spiked human serum pool diluted with a tobramycin negative human serum pool. The percent recoveries within the reportable range (0.33 – 10.0 ug/mL) were 94.2-101.8% and met the sponsor's acceptance criteria of % recovery within ± 10% of the theoretical value up to 10 µg/mL. Results were evaluated by linear regression. The linearity results are tabulated below:

% High Sample	Theoretical Value (µg/mL)	Assayed Value (µg/mL)	% Recovery	Recovery range limit
100	13.3	11.78	88.6	Out of

% High Sample	Theoretical Value (µg/mL)	Assayed Value (µg/mL)	% Recovery	Recovery range limit
				range
90	11.97	11.01	92.0	Out of range
80	10.64	10.02	94.2	In range
70	9.31	9.19	98.7	In range
60	7.98	8.12	101.8	In range
50	6.65	6.65	100.0	In range
40	5.3	5.36	100.8	In range
30	3.99	3.82	95.7	In range
20	2.66	2.66	100.0	In range
10	1.33	1.35	101.5	In range

The sponsor evaluated the performance of the TDM Preciset Multianalyte Calibrator diluent by comparing results of the diluted samples with neat samples (8.6 and 9.3 ug/mL) and the results of the diluted samples with spiked samples (12 and 17 ug/mL). The sponsor's acceptance criteria for these studies: percent (%) difference ±10% of the values of the neat samples and the spiked samples.

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

The 18 month shelf life claim for the Online TDM Tobramycin reagent was initially assessed by accelerated stability experiments and followed up with real time stability experiments. The 60 days on board instrument stability claim was assessed with real time studies. The sponsor's acceptance criteria was reviewed and found to be acceptable.

Calibrators and controls were previously cleared (k060429 and k031856) and are sold separately.

d. *Detection limit:*

The lower detection limit claim of 0.33 ug/ml is based on the mean and two standard deviations of 21 determinations of zero calibrator material. A linear interpolation model, based on these determinations of the zero calibrator material well as five replicate determinations of Calibrator B (1.0 ug/mL), was used to calculate the concentration equivalent to the mean plus two standard deviations.

e. *Analytical specificity:*

To evaluate potential interference from drugs and metabolites, serum pools were spiked with potential interferents and approximately 3 ug/ml tobramycin. Drugs found to cross-react at high concentrations were run in a series of dilutions. Percent cross reactivity for drugs and metabolites were defined as: [(Da-Dt)/C] x100, where Dt = the measured concentration of the control analyte, Da = measured concentration of the control analyte + cross-reactant and C= known concentration of cross-reactant. Calculated cross-reactivities are based on the median of triplicate determinations Observed cross-reactivities with the compounds tested are tabulated below:

Compound	Concentration (ug/ml)	% cross-reactivity
Amikacin	100	1.55
Kanamycin	100	5.32

No cross-reactivity was detected for the following drugs (concentrations in ug/ml): chloramphenicol (1000), erythromycin (1000), tetracycline (1000), sulphamethoxazole (600), trimethoprin (25), carbenicillin (1000), cephalothin (1000), clindamycin (1000), gentamicin (25), gentamicin (100), neomycin (100), netilmicin (100), penicillin G (1000), sisomycin (100), streptomycin (100) and vancomycin (200).

Sixteen common drugs were tested for interference on the Hitachi 917 in normal human serum pools spiked with tobramycin at 2.5 µg/mL. Sponsor's acceptance criteria: recovery +/- 10% of the control value. No significant interference was observed for the following drugs at the concentrations tested (concentrations in ug/ml):

acetylcysteine (150) , ampicillin (1000), ascorbic acid (300) , K-Dobesilate (200), methyldopa (20), Doxycycline (50), cyclosporine (5), levodopa (20), metronidazole (200), phenylbutazone (400) , acetylsalicylic acid (1000) , rifampicin (60), acetaminophen (200), ibuprofen (500), cefoxitin (2500), and theophylline (100).

To evaluate interference from endogenous compounds, a series of dilutions containing varying levels of the endogenous compounds was prepared from spiked pooled serum. Testing was in the presence of 3 ug/ml tobramycin (except for intralipid, conjugated and unconjugated bilirubin in which samples contained 7 ug/ml tobramycin.) Percent recovery was calculated relative to control samples containing tobramycin without spiked endogenous

compounds. The median of triplicate determinations was used in calculations of recovery. Concentrations ranges of endogenous compound in which assay recovery ≥ 90% is observed are tabulated below:

Compound/sample condition tested	Concentration range within recovery criteria (+/- 10% bias)
Bilirubin (conjugated and unconjugated)	I index up to 30 (approximately equivalent to 30 mg/dL)
Hemoglobin	H index up to 800 (approximately equivalent to 800 mg/dL)
Lipemia	L index up to 750 (no significant interference from triglycerides up to 750 mg/dL intralipid)
Rheumatoid factor	Up to 100 IU/ml
Samples containing HAMA 1/HAMA 2	100.2 %/100.8 %
Total protein	Range: 2-12 g/dL

f. *Assay cut-off:*
Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*
Fifty five clinical samples with concentrations below, within and above the medical decision points were analyzed in singlicate using the new device and a commercially available tobramycin assay. Sample values ranged from 0.2 – 9.0 ug/ml as measured by the predicate device. Results of the sponsor's analysis based on the Passing-Bablok model are shown below:

	Lower CI	Upper CI
Slope	1.006	1.060
Intercept	0.1572	0.2436

Fifty two clinical samples with concentrations below, within and above the medical decision points were analyzed in singlicate using the new device and a commercially available tobramycin assay. Sample values ranged from 0.3 – 9.3 ug/ml. Results of the sponsor's analysis based on the Passing-Bablok model are shown below:

$y = 0.92x + 0.01$, $r = 0.983$, SD (md 95) = 0.680.

	Lower CI	Upper CI
Slope	0.851	0.999
Intercept	-0.1284	0.1156

b. *Matrix comparison:*

To evaluate the effect of plasma anticoagulants, comparisons of serum samples versus samples containing EDTA, sodium heparin, sodium fluoride/potassium oxalate, citrate, and lithium heparin were conducted. Thirty samples were included for fluoride/potassium oxalate and citrate anticoagulants; fifteen samples were included for EDTA, sodium heparin, and lithium heparin. No significant bias due to these anticoagulants was observed.

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 therapeutic range for this specific assay was not determined. The sponsor stated that similar diagnostic technologies have shown that in most adults, a peak therapeutic response is achieved with tobramycin concentration ranges of 6-10 µg/mL and trough concentration ranges of 0.5-2.0 µg/mL. The sponsor stated in the package insert that each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference range. Test findings should always be assessed in conjunction with patient's medical history, clinical examination and other medical findings. The following ranges for peak and trough were taken from the literature and included in the package insert:

Investigator	Peak µg/mL	Trough µg/mL
Baselt and Cravey	6-10	1.1-4.3
Sande and Mandell	5-8	2.1-4.3
Dipersio	4-8	2.1-4.3

Lew	5-10	-

Baselt RC, Cravey RH. Disposition of Toxic Drugs and Chemicals in Man. 3rd ed, 1990:805-807.
Sande MA, Mandell GL. Antimicrobial agents, the aminoglycosides. In: Gilman AG, Goodman LS, Gilman A, eds. The Pharmacological Basis of Therapeutics. NEW, NY: MacMillan 1980:1162-1180.
Dipersio JR. Gentamicin and other aminoglycosides. In: Pesce AJ and Kaplan LA eds. Methods in Clinical Chemistry. St. Louis, MO: CV Mosby Co. 1987.
Lew M. Interpretation of aminoglycoside serum levels. Hosp. Pharm 1979; 14:465-472.

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.