cobas TaqScreen West Nile Virus Test for use with the **cobas** s 201 system Summary of Basis for Approval

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COBAS TAQSCREEN WEST NILE VIRUS TEST, SUMMARY OF BASIS FOR APPROVAL

Trade Name	**cobas** TaqScreen West Nile Virus Test for use with the **cobas** s 201 system
Proper Name (Licensed Name)	West Nile Virus / Nucleic Acid, Pooled Testing/Synthetic [**cobas** TaqScreen West Nile Virus Test]
Applicant/Manufacturer	Roche Molecular Systems, Inc. 4300 Hacienda Drive Pleasanton, CA 94588 FDA Registration No: 3004141078
Biological License Application (BLA) Reference Number(s)	BL125245
Report Date	August 24, 2007

I. INTENDED USE

The **cobas** TaqScreen West Nile Virus Test, for use with the **cobas s** 201 system, is a qualitative in vitro test for the direct detection of West Nile Virus (WNV) RNA in human plasma.

This test is intended as a donor screening test to detect WNV RNA in plasma specimens from individual human donors, including donors of whole blood and blood components and other living donors. This test is also intended for use in testing plasma specimens to screen individual organ donors when specimens are obtained while the donor's heart is still beating. This test is not intended for use on samples of cord blood.

Plasma from all donors may be screened as individual specimens. For donations of whole blood and blood components, plasma specimens may be tested in pools comprised of not more than six equal aliquots of individual specimens.

This test is not intended for use as an aid in diagnosis.

II. BRIEF DESCRIPTION OF DEVICE AND PRINCIPLES

A. Summary and Explanation of the Test

West Nile Virus is a member of the Flaviviridiae family, the genus Flavivirus and the Japanese encephalitis virus serocomplex. Viruses in this complex are arboviruses with the potential to cause meningitis, encephalitis and meningoencephalitis. Other members of the Japanese encephalitis group include Japanese encephalitis virus, Murray Valley encephalitis virus, Kunjin (now known to be a variant of WNV) and St. Louis encephalitis virus; the latter caused an epidemic of encephalitis in the US in the mid-1970s.

The **cobas** TaqScreen West Nile Virus Test is a qualitative test that enables the screening and detection of WNV RNA in infected pooled and individual specimen donations. The **cobas** TaqScreen West Nile Virus Test uses a generic nucleic acid preparation technique on the **COBAS** AmpliPrep Instrument. WNV RNA is then detected by automated, real time PCR amplification on the **COBAS** TaqMan Analyzer. The test incorporates an Internal Control for monitoring test performance in each individual test as well as the AmpErase enzyme to reduce potential contamination by previously amplified material (amplicon).

B. Description of Kit and Component Formulations

Three kits are required for the detection of WNV RNA in plasma specimens: (1) **cobas** TaqScreen West Nile Virus Test, (2) **cobas** TaqScreen West Nile Virus Control Kit, and (3) **cobas** TaqScreen Wash Reagent.

cobas TaqScreen West Nile Virus Test	96 Tests
WNV CS1	2 x 48 Tests
MGP	
(Magnetic Glass Particles)	2 x 7.0 mL
Magnetic glass particles	
93% Isopropanol	
WNV CS2	2 x 48 Tests
LYS	
(Lysis Reagent)	2 x 78 mL
Sodium citrate dihydrate	
42.5% Guanidine thiocyanate	
< 14% Polydocanol	
0.9% Dithiothreitol	

WNV CS3	2 x 48 Tests
Pase	
(Proteinase Solution)	2 x 3.8 mL
TRIS buffer	
< 0.05% EDTA	
Calcium chloride	
Calcium acetate	
≤ 7.8% Proteinase	
Glycerol	
WNV EB	
(WNV Elution Buffer)	2 x 7.0 mL
TRIS buffer	
< 0.005% Poly rA RNA (synthetic)	
EDTA	
0.09% Sodium azide	
WNV CS4	2 x 48 Tests
WNV MMX	
(WNV Master Mix)	2 x 2.5 mL
Tricine buffer	
Potassium acetate	
Glycerol	
< 17% Dimethylsulfoxide	
< 0.07% dATP, dCTP, dGTP, dUTP	
< 0.002% Upstream and downstream WNV primers	
< 0.002% Fluorescent-labeled WNV probe	
< 0.002% Fluorescent-labeled Internal Control probe	
< 0.002% Oligonucleotide aptamer	
< 0.05% Z05 DNA Polymerase (microbial)	
< 0.1% AmpErase [uracil-N-glycosylase] enzyme (microbial)	
0.08% Sodium azide	
WNV Mn^{2+}	
(WNV Manganese Solution)	2 x 19.8 mL
< 0.6% Manganese acetate	
Glacial acetic acid	
0.08% Sodium azide	
WNV IC	
(WNV Internal Control)	2 x 3.6 mL
TRIS buffer	
≤ 0.002% Poly rA RNA (synthetic)	
EDTA	
0.05% Sodium azide	
< 0.001% Non-infectious, synthetic internal control RNA encapsulated in MS2 bacteriophage coat protein.	

cobas TaqScreen West Nile Virus Control Kit (WNV CTL) 6 Sets

WNV (+) C
(WNV Positive Control) 6 x 1.1 mL
Tris buffer
≤ 0.002% Poly rA RNA (synthetic)
EDTA
0.05% Sodium azide
< 0.001% Non-infectious, synthetic WNV RNA encapsulated in MS2 bacteriophage coat protein

WNV (-) C
[WNV Negative Control (Human Plasma)] 12 x 1.6 mL
Negative Human Plasma, non-reactive by licensed tests for antibody to HCV, antibody to HIV-1/2 and HBsAg; WNV RNA not detectable by PCR methods
0.1% ProClin 300

cobas TaqScreen Wash Reagent (TS WR) 5.1 L

TS WR
(cobas TaqScreen Wash Reagent)
Sodium citrate dihydrate
0.1% Methylparaben

III. MANUFACTURING AND CONTROLS

A. Description of Manufacturing Facilities

The **cobas** TaqScreen West Nile Virus Test is manufactured by Roche Molecular Systems, Inc. (RMS) and prepared under U.S. License 1636. The corporate headquarters is located at 4300 Hacienda Drive, Pleasanton, California. The primary RMS manufacturing facility is located at 1080 US Highway 202, Branchburg, New Jersey. ----------
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----------. Finished, approved product is distributed in the United States from the Roche Diagnostic distribution center located in Indianapolis, Indiana.

The DNA oligonucleotide primers ---------- and probes ---------- used in the **cobas** TaqScreen WNV Test are manufactured synthetically on a ----------.

The Z05 DNA Polymerase and Uracil-N-Gylcosylase (rUNG) enzymes used in the Test are manufactured at RMS. Both enzymes are grown in ----------

The Armored RNA Positive and Internal Controls each include an armored RNA construct ----------. The WNV RNA Positive control ---------- and Internal Control ---------- are purified ----------.

The Negative Control is prepared from Human Plasma pools, which are tested and found to be non-reactive by licensed tests for antibody to HCV, HIV-1/2 and HBsAg; and not detectable for WNV RNA by PCR methods.

The raw materials used in this product are subjected to appropriate quality control evaluations before they are accepted for use in manufacturing. Acceptance criteria and performance specifications have been established for all test kit components. Components are assembled into test kits, each lot of which is subjected to a final performance test.

Each **cobas** TaqScreen WNV Test kit lot is tested with in-house panels of samples with varying WNV copy numbers/mL and must meet the performance requirements.

B. Stability Program

Components of the **cobas** TaqScreen West Nile Virus Test were entered into the stability program in order to define the recommended storage conditions and to establish the expiration dating period (i.e., shelf-life) for each component. The expiration date of the complete Test kit is defined on a lot-by-lot basis as the expiration date of the component lot with the shortest expiration date. In addition, components from the reserve and stability inventory that are at, near or beyond shelf life will be assembled into “virtual kits” and functional testing will be performed.

The results of stability studies completed to date support the shelf-life claims summarized in Table 1 to Table 3, below.

Table 1: cobas TaqScreen West Nile Virus Test
Quality Control Component Shelf-Life, Storage Temperature and Stability Tests

Component	Proposed Shelf Life (Months)	Storage Temperature	Real Time Stability Tests
MGP Reagent	--	2-8°C	----------, ----------
WNV Elution Buffer	--	2-8°C	---------- ----------
Proteinase Reagent	--	2-8°C	----------, ----------
Lysis Reagent	--	2-8°C	---------- ----------
WNV Manganese Solution	--	2-8°C	----------, ----------
WNV Master Mix	--	2-8°C	---------- ----------
WNV Internal Control	--	2-8°C	---------- ----------

**Stability testing performed by RAS (Roche Applied Sciences) in Penzberg, Germany*

Table 2: cobas TaqScreen West Nile Virus Control Kit
Quality Control Component Shelf-Life, Storage Temperature and Stability Tests

Component	Proposed Shelf Life (Months)	Storage Temperature	Real Time Stability Tests
WNV Positive Control	--	2-8°C	---------- ----------
WNV Negative Control	--	2-8°C	---------- ----------

Table 3: cobas TaqScreen Wash Reagent
Quality Control Component Shelf-Life, Storage Temperature and Stability Tests

Component	Proposed Shelf Life (Months)	Storage Temperature	Real Time Stability Tests
cobas TaqScreen Wash Reagent	--	2-8°C	---------- ----------

C. Methods of Validation

All test kit components are monitored by in-process testing. ----------

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--------. Product performance is assessed through quality release evaluations of the final test kit against an in-house panel containing negative control specimens and specimens that are known to be positive for WNV and the test kit must meet all performance requirements.

D. Labeling

The product labeling, including immediate container labels, box or package labels, and package insert have been reviewed for compliance with 21 CFR§610.60, 610.61, 610.62, and 809.10 and were found acceptable. The package insert clearly states the intended use as a qualitative *in vitro* test for the direct detection of West Nile Virus RNA in human plasma.

This test is intended as a donor screening test to detect WNV RNA in plasma specimens from individual blood donors, including donors of whole blood and blood components and other living donors. This test is also intended for use to screen individual organ and tissue donors when specimens are obtained while the donor's heart is still beating. This test is not intended for use on samples of cord blood.

Plasma from all donors may be screened as individual specimens. For donations of whole blood and blood components, plasma specimens may be tested in pools comprised of not more than six equal aliquots of individual specimens.

This test is not intended for use as an aid in diagnosis.

E. Establishment Inspection

The last FDA inspection of the RMS manufacturing facilities was conducted from June 18, 2007 through June 22, 2007. This was an FDA pre-license inspection for the **cobas** TaqScreen West Nile Virus Test.

F. Environmental Impact Analysis, Claims for a Categorical Exclusion

Roche Molecular Systems, Inc. claimed a Categorical Exclusion from the submission of an Environmental Impact Statement with the **cobas** TaqScreen West Nile Virus Test, Biologics License Application. This claim for a Categorical Exclusion was made pursuant to 21 CFR 25.31(j). The manufacture of the **cobas** TaqScreen West Nile Virus Test is performed under controlled conditions and in compliance with the appropriate federal, state, and local environmental regulations. The disposal of waste from the use of this product is performed in compliance with appropriate federal, state, and local environmental regulations. Based on the materials, concentration, volumes used in this product, the method(s) of product disposal, it is unlikely that the release of any of the substances of this product at the expected level of exposure will be harmful to the environment or toxic to organisms in the environment.

IV. PERFORMANCE CHARACTERISTICS

A. Pre-clinical Studies Summary

Analytical Sensitivity — Health Canada Standard — Lineage 1

The Limit of Detection (LOD) of the **cobas** TaqScreen West Nile Virus Test was evaluated using the Health Canada West Nile Virus Reference Standard (Infectious Diseases, Canadian Blood Services, 1800 Alta Vista, Ottawa, Ontario, K1G 4J5). Panels were prepared by dilution of the standard into normal, virus-negative human plasma. Each dilution was tested using three different lots of the **cobas** TaqScreen West Nile Virus Test. A total of 30 replicates per kit lot were tested for a total of 90 replicates per concentration. Using the combined data from all replicates tested, the LOD was determined based on the positivity rate with the 95% lower confidence bounds (one sided) as well as calculated by PROBIT analysis to estimate the 95% Limit of Detection and two-sided 95% fiducial confidence intervals for the panel (Table 4). The estimated 95% LOD using the Health Canada Standard – Lineage 1 was 40.3 copies/mL.

Table 4: Analytical Sensitivity Summary with the Health Canada West Nile Virus Standard

Nominal Input (copies/mL)	Number of Reactives	Number of Individual Tests	% Reactives	95% Lower Confidence Bound (one sided)
0	0	89*	0	NA
5	10	90	11.1	6.2%
10	43	90	47.8	38.7%
20	70	90	77.8	69.4%
25	74	90	82.2	74.3%
30	76	90	84.4	76.8%
35	85	90	94.4	88.7%
50	89	90	98.9	94.8%
Probit Analysis	Detection Rate (%)	Concentration (copies/mL)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
	95	40.3	35.1	47.8

** One replicate was invalid*

Analytical Sensitivity — Roche Standard — Lineage 1

The Limit of Detection (LOD) of the **cobas** TaqScreen West Nile Virus Test was evaluated using the Roche Secondary Standard (Zeptometrix West Nile Virus Stock, NY 2001-6263, Lot #302142, calibrated to the Health Canada West Nile Virus Reference Standard). Panels were prepared by dilution of the standard into normal, virus-negative human plasma. Each dilution was tested using three different lots of the **cobas** TaqScreen West Nile Virus Test. A total of 64 replicates per kit lot were tested for a total of 192 replicates per concentration. Using the combined data from all replicates tested, the LOD was determined based on the positivity rate with the 95% lower confidence bounds (one sided)as well as calculated by PROBIT analysis to estimate the 95% Limit of Detection and two sided 95% fiducial confidence intervals for the panel (Table 5). The estimated 95% LOD using the Roche Standard – Lineage 1 was 36.9 copies/mL.

Table 5: Analytical Sensitivity Summary with the Roche Secondary Standard

Nominal Input (copies/mL)	Number of Reactives	Number of Individual Tests	% Reactives	95% Lower Confidence Bound (one sided)
0	0	192	0	NA
5	68	192	35.4	29.7%
10	110	191*	57.6	51.4%
20	153	192	79.7	74.3%
25	173	192	90.1	85.8%
30	182	192	94.8	91.3%
35	183	192	95.3	92.0%
50	187	192	97.4	94.6%
Probit Analysis	Detection Rate (%)	Concentration (copies/mL)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
	95	36.9	32.7	42.6

** One replicate was invalid*

Analytical Sensitivity — CBER/FDA West Nile Virus Panel — Lineage 1

The Limit of Detection (LOD) of the **cobas** TaqScreen West Nile Virus Test was evaluated using the CBER/FDA West Nile Virus Panel. The panel contains 14 members derived from one human West Nile Virus Lineage 1 isolate (Hu2002) and one flamingo West Nile Virus Lineage 1 isolate (NY99) (produced for CBER by BBI Diagnostics, 375 West Street, West Bridgewater MA, 02379). Each panel member was tested in duplicate with three different lots of the **cobas** TaqScreen West Nile Virus Test (Table 6).

Table 6: Analytical Sensitivity Summary with the CBER/FDA West Nile Virus Panel

Member ID	Lineage 1 Isolate	Nominal Input (copies/mL)	% Reactive
CBER/FDA – 03	Hu2002	0	0% (0/6)
CBER/FDA – 05	NY99	0	0% (0/6)
CBER/FDA – 09	Hu2002	5	50% (3/6)
CBER/FDA – 10	NY99	5	83% (5/6)
CBER/FDA – 12	Hu2002	10	50% (3/6)
CBER/FDA – 02	NY99	10	33% (2/6)
CBER/FDA -04	Hu2002	50	100% (6/6)
CBER/FDA -13	NY99	50	100% (6/6)
CBER/FDA – 07	Hu2002	100	100% (6/6)
CBER/FDA – 01	NY99	100	100% (5/5)*
CBER/FDA – 14	Hu2002	500	100% (6/6)
CBER/FDA – 11	NY99	500	100% (6/6)
CBER/FDA – 08	Hu2002	1000	100% (6/6)
CBER/FDA - 06	NY99	1000	100% (6/6)

** One replicate was invalid*

Analytical Sensitivity — West Nile Virus RNA Qualification Panel QWN701 — Lineage 2

The Limit of Detection (LOD) of the **cobas** TaqScreen West Nile Virus Test was evaluated using the West Nile Virus RNA Qualification Panel QWN701 (West Nile Virus Stock, Lineage 2, Uganda – BBI Diagnostics, 375 West Street, West Bridgewater MA, 02379). The virus stock was calibrated by the vendor using a TaqMan-based RT PCR assay. Panels were prepared by dilution of the standards into normal, virus-negative human plasma. Each dilution was tested using three different lots of the **cobas** TaqScreen West Nile Virus Test. A total of 30 replicates per kit lot were tested for a total of 90 replicates per concentration. Using the combined data from all replicates tested, the LOD was determined based on the positivity rate with the 95% lower confidence bounds (one sided) as well as calculated by PROBIT analysis to estimate the 95% Limit of Detection and two-sided 95% fiducial confidence intervals for the panel (Table 7).

The estimated 95% LOD using the West Nile Virus RNA Qualification Panel QWN701 – Lineage 2 was 3.8 copies/mL.

Table 7: Analytical Sensitivity Summary with the West Nile Virus RNA Qualification Panel QWN701 — Lineage 2

Nominal Input (copies/mL)	Number of Reactives	Number of Individual Tests	% Reactives	95% Lower Confidence Bound (one sided)
0.00	0	90	0	NA
0.25	22	90	24	17.2%
0.50	29	90	32	24.1%
1.00	48	90	53	44.1%
1.50	68	90	76	67.0%
3.00	85	90	94	88.7%
5.00	90	90	100	96.7%
Probit Analysis	Detection Rate (%)	Concentration (copies/mL)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
	95	3.8	2.3	11.1

Analytical Specificity — Potentially Cross Reactive and Interfering Microorganisms

The analytical specificity of the **cobas** TaqScreen West Nile Virus Test was evaluated by testing a panel of 52 microorganisms, including 47 viral isolates, 4 bacterial strains and 1 yeast isolate (Table 8). The microorganisms were added to normal, virus negative, human plasma and tested with and without West Nile Virus added to a concentration of 3x the limit of detection of the **cobas** TaqScreen West Nile Virus Test. With the exception of the 4 isolates of the Japanese Encephalitis Virus family (Japanese encephalitis, Murray Valley encephalitis, Saint Louis encephalitis and Kunjin virus), non-reactive results were obtained with the **cobas** TaqScreen West Nile Virus Test for all microorganism samples without added West Nile Virus and reactive results were obtained for all microorganism samples with added West Nile Virus. The 4 isolates of the Japanese encephalitis Virus family were reactive in all 8 testing replicates. The results were expected because these viruses share nucleotide sequence homology with West Nile Virus and the primers and probes in the **cobas** TaqScreen West Nile Virus Test.

Table 8: Microorganisms Tested

Adenovirus Type 2	Hepatitis C virus, genotype 6	HIV-1 subtype A
Adenovirus Type 3	MJ (G11) cells producing HTLV-I	HIV-1 subtype B
Adenovirus Type 7	(C5/MJ) cells producing HTLV-I	HIV-1 subtype C
Candida albicans	(MoT) cells producing HTLV-II	HIV-1 subtype D
Cytomegalovirus Davis	(DeltaH6H11) full length HTLV-II	HIV-1 subtype E
Cytomegalovirus Towne	Herpes simplex type I, F	HIV-1 subtype F
Epstein-Barr Virus RAJI	Herpes simplex type I, HF	HIV-1 subtype G
Epstein-Barr Virus P3	Herpes simplex type I, MacIntyre	HIV-1 subtype H
Hepatitis A virus (PA 21)	Herpes simplex type II, G	HIV-2
Hepatitis B virus genotype A	Herpes simplex type II, MS	*Pneumocystis carinii* D&D
Hepatitis B virus genotype B	Human Papilloma Virus Type 11	*Propionibacterium acnes*
Hepatitis C virus genotype 1a	Human Papilloma Virus Type 18	*Staphylococcus aureus*
Hepatitis C virus genotype 1b	Human Papilloma Virus Type 6B	*Staphylococcus epidermidis*
Hepatitis C virus genotype 2a	Influenza virus A (A/New Jersey/8/76)	Japanese encephalitis virus
Hepatitis C virus genotype 2b	Influenza virus B (B/Hong Kong/5/72)	Murray Valley encephalitis virus
Hepatitis C virus genotype 3	Varicella-zoster virus Ellen	Saint Louis encephalitis virus
Hepatitis C virus genotype 4	Varicella-zoster virus Oka	Kunjin virus
Hepatitis C virus genotype 5		

Analytical Specificity — Other Disease States

Plasma specimens from 10 – 20 patients from each of the following disease categories (Cytomegalovirus infection, Hepatitis A virus infection, Hepatitis B virus infection, Hepatitis C virus infection, Human Immunodeficiency virus (HIV-1), Epstein Barr virus infection) were tested with and without WNV added to a concentration of 3X the limit of detection of the **cobas** TaqScreen West Nile Virus Test. The **cobas** TaqScreen WNV Test yielded non-reactive results on all of the disease state specimens without added WNV and reactive results on all of the disease state specimens with added WNV. These disease states did not interfere with the sensitivity or specificity of the **cobas** TaqScreen West Nile Virus Test.

Potentially Interfering Substances

Endogenous Interfering Substances

Plasma specimens with abnormally high levels of triglycerides (up to 2487 mg/dL), hemoglobin (up to 516 mg/dL), bilirubin (up to 23.5 mg/dL) or albumin (up to 6900 mg/dL), were tested with and without West Nile Virus added to a concentration of 3x the limit of detection of the **cobas** TaqScreen West Nile Virus Test. These endogenous substances did not interfere with the sensitivity or specificity of the **cobas** TaqScreen West Nile Virus Test.

Plasma specimens with defined autoimmune conditions/diseases (Antinuclear Antibody Positive, Rheumatoid Factor positive and Systemic Lupus Erythematosus) were tested with and without West Nile Virus added to a concentration of 3x the limit of detection of the **cobas** TaqScreen West Nile Virus Test. These endogenous substances did not interfere with the sensitivity or specificity of the **cobas** TaqScreen West Nile Virus Test.

Plasma specimens with red blood cells added to abnormally high levels, (up to 10% v/v) were tested with and without West Nile Virus added to a concentration of 3X the limit of detection the **cobas** TaqScreen West Nile Virus Test. Plasma with red blood cells added to 10% (v/v) did interfere with the sensitivity or specificity of the **cobas** TaqScreen West Nile Virus Test.

Exogenous Interfering Substances

Plasma specimens containing abnormally high concentrations of acetaminophen (1324 μmol/L), acetylsalicylic acid (3.62 μmol/L), atorvastatin (600 Eq/L), fluoxetine (11.2 μmol/L), loratadine (0.78 μmol/L), nadolol (3.88 μmol/L), naproxen (2170 μmol/L), paroxetine (3.04 μmol/L), sertraline (1.96 μmol/L), ascorbic acid (284 μmol/L), ibuprofen (2425 μmol/L) and phenylephrine HCl (327.5 μmol/L), were tested with and without West Nile Virus added to a concentration of 3x the limit of detection of the **cobas** TaqScreen West Nile Virus Test. These exogenous substances did not interfere with the sensitivity or specificity of the **cobas** TaqScreen West Nile Virus Test.

B. Clinical Trials Summary

Reproducibility

The reproducibility of the **cobas** TaqScreen West Nile Virus Test using the **cobas** s 201 system was evaluated by testing ----------
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1 Page Determined to be not releasable

Clinical Performance

Clinical Sensitivity — Testing of Known West Nile Virus Positive Specimens

The clinical sensitivity of the **cobas** TaqScreen West Nile Virus Test was evaluated by testing 315 individual West Nile Virus positive clinical specimens. The specimens were determined to be West Nile Virus RNA positive by one of three nucleic acid testing methods. The study was conducted at 3 testing laboratories with each site testing approximately 100 specimens, both neat and diluted 1:6, utilizing three different lots of the **cobas** TaqScreen West Nile Virus Test.
The sensitivity of the **cobas** TaqScreen West Nile Virus Test with neat specimens in this study was 100% (95% CL 98.8-100.0) and with 1:6 diluted specimens was 97.5% (95% CL 95.1-98.9) (Table 9). The eight (8) non-reactive, 1:6 diluted specimens were derived from neat specimens with viral loads determined to be less than 100 copies/mL according to the National Genetics Institute WNV Quantitative PCR assay.

Table 9: Clinical Sensitivity with Known West Nile Virus Positive Specimens

	Number of Specimens Tested	Number of Specimens Reactive	Number of Specimens Non-Reactive	Sensitivity (%)	Sensitivity [95% CL]	
					Lower Limit	Upper Limit
Neat	314*	314	0	100	98.8	100.0
Diluted 1:6	315	307	8	97.5	95.1	98.9

** One neat specimen was invalid*

Clinical Specificity

The clinical specificity of the **cobas** TaqScreen West Nile Virus Test was evaluated by testing randomly selected whole blood donations at six external laboratory sites. Individual specimens and specimens in pools of six were tested. Three different lots of the **cobas** TaqScreen West Nile Virus Test were used in the study. Clinical specificity of the **cobas** TaqScreen West Nile Virus Test was calculated as the percentage (95% exact 2-sided Binomial confidence interval [CI]) of WNV donor status-negative donors who had **cobas** TaqScreen West Nile Virus Test non-reactive

results. There were 86,935 evaluable donors from pooled testing and 10,375 evaluable donors from individual testing.

Pooled Testing Results

Table 10 shows the calculation of the clinical specificity of the **cobas** TaqScreen West Nile Virus Test for the 86,935 evaluable donors from pooled testing. The clinical specificity of the **cobas** TaqScreen West Nile Virus Test from pooled testing was 100% (86,935/86,935; 95% CI = 99.996% to 100.000%) in this study.

Table 10: Clinical Specificity of the cobas TaqScreen West Nile Virus Test — Pooled Testing

WNV Endpoint*	WNV Donor Status**				Total
	Positive	Presumed Positive***	Negative	Unknown****	
WNV Reactive	0 (N/A)	0 (N/A)	0 (0.000%)	0 (N/A)	0
WNV Non-Reactive	0 (N/A)	0 (N/A)	86,935 (100.000%)	0 (N/A)	86,935
Total	0	0	86,935	0	86,935
Clinical Specificity (95% CI)			100.000% (99.996%, 100.000%)		

** The WNV Endpoint was derived from the valid **cobas** TaqScreen WNV Test result from testing on the index donation using the Pooled Testing Algorithm.*
*** WNV Donor Status was assigned programmatically based on test reactivity patterns on the index donation and if present, follow-up donation(s).*
**** A WNV Donor Status of 'Presumed Positive' was to be programmatically assigned to donors with no Follow-up Study donation but who had a **cobas** TaqScreen WNV Test reactive result on the index donation and at least 1 reactive/positive result on the Alternate Plasma Source, Alternate NAT, or IgM for the index donation.*
***** Donors classified as WNV Donor Status Unknown would have had insufficient testing results to assign a WNV Donor Status.*

The **cobas** TaqScreen West Nile Virus Test pool specificity for index donations was 99.986% (14,387/14,389; 95% CI = 99.950% to 99.998%). Two pools of 6 were **cobas** TaqScreen West Nile Virus Test reactive, but both resolved to contain **cobas** TaqScreen West Nile Virus Test

non-reactive specimens at the individual specimen level. An invalid rate of 2.3% due to internal control or instrument failures was seen for pooled specimen results.

Individual Testing Results

Table 11 shows the calculation of the clinical specificity of the **cobas** TaqScreen West Nile Virus Test for the 10,375 evaluable donors from individual testing. The clinical specificity of the **cobas** TaqScreen West Nile Virus Test from individual testing was 100% (10,375/10,375; 95% CI = 99.964% to 100.000%) in this study. An invalid rate of 1.1% due to internal control or instrument failures was seen for individual specimen results.

Table 11: Clinical Specificity of the cobas TaqScreen West Nile Virus Test — Individual Testing

WNV Endpoint*	WNV Donor Status**				Total
	Positive	Presumed Positive***	Negative	Unknown****	
WNV Reactive	0 (N/A)	0 (N/A)	0 (0.000%)	0 (N/A)	0
WNV Non-Reactive	0 (N/A)	0 (N/A)	10,375 (100.000%)	0 (N/A)	10,375
Total	0	0	10,375	0	10,375
Clinical Specificity (95% CI)			100.000% (99.964%, 100.000%)		

** The WNV Endpoint was derived from the valid **cobas** TaqScreen West Nile Virus Test result from testing on the index donation using the Pooled Testing Algorithm.*
*** WNV Donor Status was assigned programmatically based on test reactivity patterns on the index donation and if present, follow-up donation(s).*
**** A WNV Donor Status of 'Presumed Positive' was to be programmatically assigned to donors with no Follow-up Study donation but who had a **cobas** TaqScreen West Nile Virus Test reactive result on the index donation and at least 1 reactive/positive result on the Alternate Plasma Source, Alternate NAT, or IgM for the index donation.*
***** Donors classified as WNV Donor Status Unknown would have had insufficient testing results to assign a WNV Donor Status.*

V. PACKAGE INSERT

A copy of the Package Insert (directions for use) for the **cobas** TaqScreen WNV Test for use with the **cobas** s 201 system is provided in this submission.