SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name:	In vitro nucleic acid amplification assay for the detection of hepatitis C virus (HCV) RNA in human plasma or serum.
Device Trade Name:	VERSANT ™ HCV RNA Qualitative Assay
Applicant's Name and Address:	Gen-Probe Incorporated 10210 Genetic Center Drive San Diego, CA 92121

Premarket Approval Application (PMA) Number: P020011

Date of Panel Recommendation: None

Date of Notice of Approval to Applicant: November 7, 2002

II. INDICATIONS FOR USE

The VERSANT HCV RNA Qualitative Assay is an *in vitro* nucleic acid amplification assay for the detection of hepatitis C virus (HCV) RNA in human plasma (EDTA, sodium heparin, sodium citrate, and ACD) or serum. The VERSANT HCV RNA Qualitative Assay is indicated for use with fresh or frozen specimens from the following populations: individuals with antibody evidence of HCV infection with evidence of liver disease, and individuals suspected to be actively infected with HCV with antibody evidence, and individuals at risk for HCV infection with antibodies to HCV. Detection of HCV RNA is evidence of active HCV infection.

Detection of HCV RNA does not discriminate between an acute and chronic state of infection or indicate the presence of liver disease. A negative result does not exclude active HCV replication. It is not known if performance is affected by the state of HCV infection (acute or chronic) or by the presence or absence of liver disease. Performance has not been demonstrated for monitoring HCV infected patients.

WARNING: This assay has not been FDA-approved for the screening of blood or plasma donors.

III. DEVICE DESCRIPTION

The VERSANT HCV RNA Qualitative Assay is a target amplification-based nucleic acid probe test that detects HCV RNA in human plasma and serum. The VERSANT HCV RNA Qualitative Assay utilizes Transcription-Mediated Amplification (TMA) to amplify conserved regions within the 5' untranslated region (5'-UTR) of the HCV genome. TMA utilizes Moloney Murine Leukemia Virus (MMLV) reverse transcriptase (RT) and T7 RNA polymerase to generate multiple RNA copies from the viral nucleic acid template. Assay performance is monitored by means of an internal nucleic acid control that is added to each specimen with the Target Capture Reagent.

The VERSANT HCV RNA Qualitative Assay has three main steps, all of which are performed within a single tube: sample preparation, target amplification, and amplicon detection.

The VERSANT HCV RNA Qualitative Assay consists of the following kits:

The HCV RNA Qualitative Assay Master Kit

The Auto Detect Reagent Kit

The HCV RNA Qualitative Assay Control Kit

Each kit contains labeled reagents assembled according to storage temperature requirements (frozen [-15° to -35°C]; refrigerated [2° to 8°C] and controlled room temperature [15° to 30°C]).

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

There are no known contraindications for the VERSANT HCV RNA Qualitative Assay.

Refer to the Package Insert for a listing of warnings and precautions.

V. ALTERNATE PRACTICES AND PROCEDURES

Currently, the diagnosis of HCV infection is largely established using serologic screening with EIA for anti-viral antibodies followed by supplemental testing with RIBA. The technology for detection of anti-HCV has progressed to third generation EIA and RIBA assays. Detection of HCV antibody is primarily limited due to the elapsed time from acute infection to seroconversion, which may take from three to six months. Furthermore, in patients who are immunosuppressed or immunocompromised, such as by infection with human immunodeficiency virus (HIV) or chronic renal failure (i.e., dialysis patients), evidence of anti-HCV seroconversion may never occur. Additionally, anti-HCV serology tests cannot distinguish between active and inactive viral replication.

Recently, nucleic acid amplification tests (NAATs) have been developed, which can detect HCV RNA in serum or plasma within one to two weeks after exposure to the virus and weeks before the onset of ALT elevations or the appearance of anti-HCV.

VI. MARKETING HISTORY

The VERSANT HCV RNA Qualitative Assay received approval outside the U.S. to be marketed in France, Japan, and Canada.

The VERSANT HCV RNA Qualitative Assay has not been withdrawn from marketing for any reason related to the safety or effectiveness of the product.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The only adverse effect of the Versant HCV RNA, as with all *in vitro* diagnostic assays, is the possibility of misdiagnosis due to a an erroneous test result, which is likely due to a false positive or a false negative test result.

In the case of a false positive result, patients may be subjected to unnecessary medical interventions or faced with undesirable social implications. A false negative result may delay needed intervention to mediate pain and suffering and improve health or allow for the continued transmission of an infectious disease.

A false positive VERSANT HCV RNA Qualitative Assay test result may initiate certain medical interventions associated with the diagnosis and treatment of HCV infection. A presumptive misdiagnosis of HCV infection may occur if the false positive result is coincident with an ALT value that was elevated due to other reasons. As a result, the patient would be subject to undue psychological stress and a liver biopsy with its potential for side effects. False positive results may be caused by the presence of cross-reacting species in the specimen, procedural errors, carryover contamination, specimen misidentification, or transcription errors.

A false negative VERSANT HCV RNA Qualitative Assay test result may delay needed diagnostic procedures to identify those at risk or suspected of having HCV infection. Due to the parenteral means of disease transmission, failure to identify infected individuals may increase the likelihood of new cases of HCV infection. False negative results may be caused by specimen inhibition, interfering substances, procedural deviations, use of the test by unqualified personnel, or transcription errors.

VIII. SUMMARY OF NONCLINICAL STUDIES

Nonclinical studies were conducted to establish the analytical performance and potential limitations of the VERSANT HCV RNA Qualitative Assay. The effects of non-HCV factors on assay performance (non-specificity studies) were also included in the studies. These nonclinical laboratory studies were performed by the Research and Development Department (R&D) at Gen-Probe Incorporated and by the Nucleic Acid Assay Development Laboratory at Bayer Diagnostics, Bayer Corporation.

The performance characteristics determined through the conduct of the nonclinical testing are summarized in the package insert for the VERSANT HCV RNA Qualitative Assay. Brief summaries of the results from the nonclinical studies are also provided in the following sections.

Specificity

The specificity of the VERSANT HCV RNA Qualitative Assay was determined using 1,000 serum and 1,504 EDTA plasma specimens from anti-HCV negative volunteer blood donors. The specimens were negative for antibodies to HCV using FDA approved methods. Of the total samples tested, 2,495/2,504 was nonreactive in the VERSANT HCV RNA Qualitative Assay, yielding a specificity of 99.6%.

Analytical Sensitivity

1. Limit of Detection (WHO International Standard)

The Limit of Detection (LOD) for the VERSANT HCV RNA Qualitative Assay was determined by testing serial dilutions of the WHO International Standard for HCV genotype 1 RNA (NIBSC code 96/790). The tables in the package insert present the percent detection of each panel member. Each panel member was tested in replicates ranging from 60 to 240.

Serial dilutions of the WHO International Standard for HCV genotype 1 RNA were detected ≥95% of the time as low as 7.5 IU/mL. Linear regression analysis determined 5.3 IU/mL (95% probability) as the limit of detection for the VERSANT HCV RNA Qualitative Assay.

2. Detection of HCV Genotypes Using RNA Transcripts

Transcripts of HCV genotypes 1, 2a, 2b, 3a, 4a, 5a, and 6a made from the 5'-untranslated region of the HCV genome were tested using the VERSANT HCV RNA Qualitative Assay. All transcripts were quantitated using phosphate analysis and confirmed using hyperchromicity and OD_{260}. The copies/mL were converted to IU/mL using an in-house conversion factor: 5.2 copies/mL = 1 IU/mL.

Dilutions of each transcript were tested at 9.6 IU/mL (50 copies/mL) for genotypes 1, 2a, 3a, 4a, 5a, and 6a. Genotype 2b was diluted to 14.4 IU/mL (75 copies/mL). Each transcript was tested in replicates ranging from 360 to 720. The results are presented in the package insert.

With the exception of genotype 2b, all genotype transcripts were detected ≥95% of the time at 9.6 IU/mL (50 copies/mL). Genotype 2b was detected ≥95% of the time at 14.4 IU/mL (75 copies/mL).

3. Detection of HCV Genotypes Using Clinical Specimens

Clinical specimens representing HCV genotypes 1 to 6 at different concentrations were used to determine the percent detection of the VERSANT HCV RNA Qualitative Assay. The specimens were quantitated using the VERSANT HCV RNA 3.0 Assay (bDNA). The genotypes of the specimens were provided by the specimen vendor and confirmed using the VERSANT HCV Genotype Assay (LiPA) and sequencing. The results are presented in the package insert. The overall percent detected across all HCV genotypes tested was ≥95% at 9.6 IU/mL (50 copies/mL).

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In a supplemental study, 61 clinical specimens representing genotypes 1 to 6 were tested at 1,00, 300 and 100 c/mL; no testing was performed at 50 c/mL. With the exception of specimens representing HCV genotype 2, all specimens were detected at all levels. All clinical specimens containing HCV genotypes 1 to 6 showed reactivity in the VERSANT HCV RNA Assay. These included 8 specimens in the transcript testing, 6 in the clinical specimen testing, and 61 in the supplemental testing.

Analytical Specificity

1. Cross Contamination Frequency

The potential cross-contamination frequency was determined by testing replicates of a high titer HCV genotype 1 positive specimen and replicates of an HCV negative specimen. HCV positive samples (1×10^6 copies/mL) were alternated with HCV negative samples using a "checkerboard" pattern. Forty-five (45) replicates each of HCV negative and HCV positive samples were tested in each of five runs, for a total of 225 replicates of the HCV positive samples and 225 replicates of the HCV negative samples. No false results were obtained; two negative samples were invalid. Combined results across all runs yielded a cross-contamination frequency of 0% (0/223).

2. Microorganisms and Viruses

The potential cross-reaction and interference of other microorganisms and viruses was evaluated by adding selected microorganisms and viruses to HCV negative specimens and specimens spiked with HCV genotype 1 at 9.6 IU/mL (50 copies/mL); skin flora microorganisms that may contaminate a blood sample or microorganisms and viruses that can co-infect individuals with HCV infection were tested.

The microorganisms and viruses were pooled and tested at final concentrations of 5×10^4 CFU/mL or 5×10^4 copies/mL, respectively. Pool 1 contained *E. coli, P. aeruginosa, K. pneumoniae, H. influenzae,* and cytomegalovirus (CMV) (Towne). Pool 2 contained *E. cloacae, P. fluorescens, S. aureus, S. marcescens,* and *S. pneumoniae.* Pool 3 contained *S. epidermidis,* Streptococcus group B, *C. albicans,* hepatitis B virus (HBV), and HIV-1 B. Pool 4 contained HIV-1 A, HIV-1 C, and HIV-1 D. Pool 5 contained HIV-1 E, HIV-1 F, HIV-1 O and *P. acnes*. Hepatitis G virus (HGV) also was tested both in the presence and absence of spiked HCV 1a at 9.6 IU/mL (50 copies/mL) using five HGV-positive specimens. HGV titers were not known due to the lack of an HGV quantitative assay. For all microorganisms and viruses tested, no cross-reactions or interference were observed in the VERSANT HCV RNA Qualitative Assay.

Potentially Interfering Substances

1. Endogenous Substances

Potentially interfering endogenous substances were tested by adding these substances to HCV negative specimens and specimens spiked with HCV genotype 1 at 9.6 IU/mL (50 copies/mL). The concentrations of potentially interfering endogenous substances were tested according to NCCLS Document EP7-P.

The following endogenous substances were tested: 500 mg/dL hemoglobin, 60 mg/dL bilirubin (conjugated), 60 mg/dL bilirubin (unconjugated), 3,000 mg/dL triglycerides, and 8 g/dL protein. None of the endogenous substances tested interfered with the sensitivity and specificity of the VERSANT HCV RNA Qualitative Assay.

2. Therapeutic Drugs

The potential interference of commonly prescribed drugs to treat HCV or other viral diseases was tested by adding these substances to HCV negative specimens and specimens spiked with HCV genotype 1 at 9.6 IU/mL (50 copies/mL). The drugs were pooled and tested at final concentrations five times the reported peak serum or plasma concentrations in the therapeutic range. Pool 1 contained Intron A, Ribavirin, and Azathioprine. Pool 2 contained Cyclosporine, Aldactone, and Prednisone. Pool 3 contained Roferon A, Tacrolimus, and Amantadine HCl. Pool 4 contained Fluoxetine HCl, Peginterferon Alfa-2b, and Azidothymidine. Pool 5 contained Ganciclovir and Dideoxycytidine, and Pool 6 contained Didanosine and Didehydrodeoxythymidine. None of the drugs tested interfered with the sensitivity and specificity of the VERSANT HCV RNA Qualitative Assay.

3. Other Potentially Interfering Substances

The effect of other potentially interfering substances was determined by testing HCV negative specimens and specimens spiked with HCV genotype 1 at 9.6 IU/mL (50 copies/mL). The disease categories tested were: myeloma IgG (n=12) positive specimens, anti-nuclear antibody positive specimens (n=10), anti-doublestranded DNA positive specimens (n=6), rheumatoid factor positive specimens (n=19), and specimens from subjects with systemic lupus erythematous (n=10).

With the exception of a subset of the myeloma specimens, none of the tested samples from subjects with HCV-like disease states interfered with the performance of the VERSANT HCV RNA Qualitative Assay. Refer to the Limitations section of the package insert for information on myeloma specimens.

4. Specimen Collection (Commonly Used Anticoagulants)

HCV-negative specimens and specimens spiked with HCV genotype 1 at 9.6 IU/mL (50 copies/mL) were collected in serum separator tubes (SST PLUS, plastic), K_2 EDTA (PLUS, plastic), K_2 EDTA (PPT), sodium citrate (glass, 4%), ACD-solution A (glass) and sodium heparin (PLUS, plastic 60 USP units) tubes. None of the anticoagulants tested affected the sensitivity and specificity of the VERSANT HCV RNA Qualitative Assay.

IX. SUMMARY OF CLINICAL STUDIES

Performance characteristics for the VERSANT HCV RNA Qualitative Assay were established in a multi-center study at four geographically diverse clinical sites. In the study, serum or plasma specimens from 1,511 subjects enrolled in hepatology clinics, intravenous drug abuse clinics, transfusion centers and AIDS clinics were evaluated. The study population included 938 (62.1%) subjects with a medical history of liver disease or positive anti-HCV serology and 741 (49.0%) subjects diagnosed with chronic HCV hepatitis. A history of one or more risk factors was reported by 1,175 (77.8%) subjects. Symptoms associated with HCV infection were reported by 741 (49.0%) subjects and 112 (7.4%) subjects were infected with HIV or another hepatitis virus. No patients were on anti-viral therapy at the time of enrollment into the study.

Of the 1,511 total subjects, 544 (36.0%) were female and 967 (64.0%) were male. Subject age ranged from 17 years to 89 years with a mean of 47 years. Ethnicity representation included: White, Non-Hispanic, 689 (45.6%); Black, Non-Hispanic, 588 (38.9%); White, Hispanic, 149 (9.9%); Asian/Pacific Islander, 23 (1.5%); Black, Hispanic, 19 (1.3%); Native American, Alaskan, 8 (0.5%); and unknown or other, 35 (2.3%).

CLINICAL STUDY RESULTS

A total of 5,542 EIA, RIBA, PCR and VERSANT HCV RNA Qualitative Assay results were used in the clinical data analysis. Performance characteristics were based on calculations of Positive and Negative Percent Agreement and 95% Confidence Intervals of VERSANT HCV RNA Qualitative Assay results compared to anti-HCV serology results and to PCR results in three different populations: subjects with or without anti-HCV, subjects with anti-HCV with or without biochemical (i.e., elevated ALT) or histological evidence of liver disease, and subjects at risk for HCV with or without anti-HCV. Liver histopathology was characterized by cirrhosis, fibrosis, hepatocelluar carcinoma, or other histopathological diagnosis. Subjects were classified as "at risk for HCV" if they were exposed to needle-stick accidents or another occupational exposure, blood or blood product transfusion, past or current injection-drug use or use of shared drug tools, multiple sex partners, sex with an HCV-positive partner, men having sex with men, dialysis, or a history of a sexually transmitted disease (STD).

For assay comparisons made within each population, performance of the VERSANT HCV RNA Qualitative Assay was similar across the four study sites and for each specimen type. Summary data are provided in Tables IX-1 and IX-.2 for each population and overall. Serum and plasma data are shown combined.

Comparison with Anti-HCV Serology

Performance of the VERSANT HCV RNA Qualitative Assay compared to anti-HCV serology was similar for each population and overall as shown in Table IX-1. Of the 1,511 VERSANT HCV RNA Qualitative Assay and anti-HCV results available in subjects with or without evidence of HCV, ten (10) anti-HCV serology results were indeterminate. Of the remaining 1,501 VERSANT HCV RNA Qualitative Assay and conclusive anti-HCV results available in this population, 93.6% were in agreement between the two assays. The VERSANT HCV RNA Qualitative Assay detected HCV RNA in 930 of 1,014 (91.7% Positive Agreement) anti-HCV

serology positive specimens, but not in 475 of 486 (97.7% Negative Agreement) anti-HCV serology negative specimens. Sixteen (16) results were RIBA indeterminate or negative, however, five (5) of the 16 were PCR positive. Therefore, these five (5) subjects were infected. The VERSANT HCV RNA Qualitative Assay agreed with all 5 of these results (100%).

Of the 522 specimens collected from subjects with anti-HCV and biochemical or histological evidence of liver disease, the VERSANT HCV RNA Qualitative Assay detected HCV RNA in 486 (93.1%) specimens. HCV RNA was detected in: (a) 368 (98.7%) of 373 specimens from subjects with elevated ALT and liver histopathology, (b) 92 (74.8%) of 123 specimens from subjects with normal ALT and liver histopathology, and (c) 26 (100%) of 26 specimens from subjects with elevated ALT and no liver histopathology. Of the 129 specimens collected from subjects without anti-HCV with evidence liver disease, the VERSANT HCV RNA Qualitative Assay did not detect HCV RNA in 127 (98.4%) specimens. Six (6) results were RIBA indeterminate or negative; however, three (3) of the six (6) were PCR positive. Therefore, these three (3) subjects were infected. The VERSANT HCV RNA Qualitative Assay agreed with all three (3) of these results (100%).

Of the 1,175 subjects at risk for HCV, the VERSANT HCV RNA Qualitative Assay detected HCV RNA in 765 of 831 (92.1%) anti-HCV serology positive specimens, but not in 328 of 336 (97.6%) anti-HCV serology negative specimens. Nine (9) results were RIBA indeterminate or negative; however, PCR was positive for four (4) of the nine (9) subjects, indicating that they were infected. The VERSANT HCV RNA Qualitative Assay agreed with all four (4) of these results (100%).

Table IX-1. Agreement of the VERSANT HCV RNA Qualitative Assay and Anti-HCV Serology for Each Study Population

	N	VERSANT+ Serology+	VERSANT+ Serology-	VERSANT- Serology+	VERSANT- Serology-	% Negative Agreement	95% C.I.	% Positive Agreement	95% C.I.
Total	1511	935	11	84	481	97.8	96.0-98.9	91.8	89.9-93.4
Anti-HCV Serology	1511	935	11	84	481	97.8	96.0-98.9	91.8	89.9-93.4
EIA R / RIBA Pos	1014	930	0	84	0	N/A	N/A	91.7	89.8-93.3
EIA R / RIBA Neg	6	1[1]	0	0	5	100	47.8- 100	100	2.5- 100
EIA R / RIBA Ind	10	4[1]	0	0	6[3]	100	54.1- 100	100	39.8- 100
EIA NR[2]	481	0	11	0	470	97.7	95.9-98.9	N/A	N/A
Anti-HCV Serology, ALT, Liver Histological Findings									
Total	658	490	2	37	129	98.5	94.6-99.8	93.0	90.5-95.0
Elevated ALT and Liver Histopathology	425	371	0	5	49	100	92.7- 100	98.7	96.9-99.6
EIA R / RIBA Pos	373	368	0	5	0	N/A	N/A	98.7	96.9-99.6
EIA R / RIBA Neg	3	1[1]	0	0	2	100	15.8- 100	100	2.5- 100
EIA R / RIBA Ind	3	2[1]	0	0	1[3]	100	2.5- 100	100	15.8- 100
EIA NR[2]	46	0	0	0	46	100	92.3-100	N/A	N/A

Normal ALT and Liver Histopathology	205	92	2	31	80	97.6	91.5-99.7	74.8	66.2-82.2
EIA R / RIBA Pos	123	92	0	31	0	N/A	N/A	74.8	66.2-82.2
EIA R / RIBA Neg	1	0	0	0	1	100	2.5-100	N/A	N/A
EIA R / RIBA Ind	1	0	0	0	1[3]	100	2.5- 100	N/A	N/A
EIA NR[2]	80	0	2	0	78	97.5	91.3-99.7	N/A	N/A
Elevated ALT and No Liver Histopathology	26	26	0	0	0	N/A	N/A	100	86.8-100
EIA R / RIBA Pos	26	26	0	0	0	N/A	N/A	100	86.8-100
EIA R / RIBA Neg	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA R / RIBA Ind	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA NR[2]	0	0	0	0	0	N/A	N/A	N/A	N/A
Normal ALT and No Liver Histopathology	2	1	0	1	0	N/A	N/A	50.0	1.3-98.7
EIA R / RIBA Pos	2	1	0	1	0	N/A	N/A	50.0	1.3-98.7
EIA R / RIBA Neg	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA R / RIBA Ind	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA NR[2]	0	0	0	0	0	N/A	N/A	N/A	N/A
At Risk									
Total	1175	769	8	66	332	97.6	95.4-99.0	92.1	90.1-93.8
EIA R / RIBA Pos	831	765	0	66	0	N/A	N/A	92.1	90.0-93.8
EIA R / RIBA Neg	2	1[1]	0	0	1	100	2.5- 100	100	2.5- 100
EIA R / RIBA Ind	7	3[1]	0	0	4[3]	100	39.8- 100	100	29.2- 100
EIA NR[2]	335	0	8	0	327	97.6	95.3-99.0	N/A	N/A

VERS = VERSANT Ser = Serology R = Reactive NR = Nonreactive Pos = Positive
Neg = Negative Agree = Agreement N/A = Insufficient data for meaningful result
Ind = Indeterminate

[1]Subject was designated infected per CDC guidelines if RIBA was indeterminate or negative, and PCR was positive.

[2]Patients who had anti-HCV EIA non-reactive results were studied for approximating the specificity of the AMPLICOR HCV Test, v2.0, but these data do not imply performance for testing of anti-HCV EIA non-infected individuals.

[3]Subject was designated as having uncertain infection per CDC guidelines if RIBA was indeterminant and PCR was negative.

Comparison with PCR

As shown in Table XI-2, performance of the VERSANT HCV RNA Qualitative Assay compared to an FDA-cleared PCR test was similar for each population and overall. Of the

1,013 anti-HCV serology positive specimens, HCV RNA was detected in 921 specimens by both assays (99.7% positive Agreement) and not in 83 specimens (91.2% Negative Agreement). The VERSANT HCV RNA Qualitative Assay was in 100% agreement with PCR for specimens with indeterminate or negative RIBA results. The VERSANT HCV RNA Qualitative Assay and the PCR test detected HCV RNA in 4 of 10 specimens with indeterminate RIBA results and in 1 of 6 specimens with RIBA negative results. Of the 471 anti-HCV serology negative specimens, both assays detected HCV RNA in 6 EIA nonreactive specimens, but not in 459 EIA nonreactive specimens.

Of the 522 VERSANT HCV RNA Qualitative Assay and PCR test results for subjects with anti-HCV and biochemical or histological evidence of liver disease, 520 (99.6%) were in agreement between the two assays: (a) 373 (100%) of 373 specimens from subjects with elevated ALT and liver histopathology, (b) 121 (98.4%) of 123 specimens from subjects with normal ALT and liver histopathology, and (c) 26 (100%) of 26 specimens from subjects with elevated ALT and no liver histopathology. Both assays were in 100% agreement for specimens with indeterminate or negative RIBA results. The HCV TMA Assay and the PCR test detected HCV RNA in 2 of 4 specimens with indeterminate RIBA results and in 1 of 4 specimens with RIBA negative results. Of the 126 specimens collected from subjects without anti-HCV, 125 (99.2%) were in agreement. Both assays detected HCV RNA in 1 EIA nonreactive specimen, but not in 124 EIA nonreactive specimens.

Of the 830 VERSANT HCV RNA Qualitative Assay and PCR test results for subjects at risk for HCV infection with anti-HCV, 824 (99.3%) were in agreement between the two assays. Both assays detected HCV RNA in 759 specimens, but not in 65 specimens. Furthermore, both assays were in 100% agreement for specimens with indeterminate or negative RIBA results. The VERSANT HCV RNA Qualitative Assay and the PCR test detected HCV RNA in 3 of 7 specimens with indeterminate RIBA results and in 1 of 2 specimens with RIBA negative results. Of the 325 specimens collected from subjects at risk for HCV infection without anti-HCV, 321 (98.8%) were in agreement. Of the 325 anti-HCV serology negative specimens from subjects at risk for HCV infection, both assays detected HCV RNA in 5 EIA nonreactive specimens, but not in 316 EIA nonreactive specimens.

Table XI-2. Agreement of the VERSANT HCV RNA Qualitative Assay and PCR for Each Study Population

	N	VERSANT+ PCR+	VERSANT+ PCR-	VERSANT- PCR+	VERSANT- PCR-	% Negative Agreement	95% C.I.	% Positive Agreement	95% C.I.
Total	1500[1]	932	12	3	553	97.9	96.3-98.9	99.7	99.1-99.9
Anti-HCV Serology	1500	932	12	3	553	97.9	96.3-98.9	99.7	99.1-99.9
EIA R / RIBA Pos	1013	921	8	1	83	91.2	83.4-96.1	99.9	99.4-100
EIA R / RIBA Neg	6	1	0	0	5	100	47.8-100	100	2.5-100
EIA R / RIBA Ind	10	4	0	0	6	100	54.1-100	100	39.8-100
EIA NR[2]	471	6	4	2	459	99.1	97.8-99.8	75.0	34.9-96.8

Anti-HCV Serology, ALT, Liver Histological Findings

Total	658	489	3	0	166	98.2	94.9-99.6	100	99.2-100
Elevated ALT and Liver Histopathology	425	371	0	0	54	100	93.4-100	100	99.0-100
EIA R / RIBA Pos	373	368	0	0	5	100	47.8-100	100	99.0-100
EIA R / RIBA Neg	3	1	0	0	2	100	15.8-100	100	2.5-100
EIA R / RIBA Ind	3	2	0	0	1	100	2.5-100	100	15.8-100
EIA NR[2]	46	0	0	0	46	100	92.3-100	N/A	N/A
Normal ALT and Liver Histopathology	205	91	3	0	111	97.4	92.5-99.5	100	96.0-100
EIA R / RIBA Pos	123	90	2	0	31	93.9	79.8-99.3	100	96.0-100
EIA R / RIBA Neg	1	0	0	0	1	100	2.5-100	N/A	N/A
EIA R / RIBA Ind	1	0	0	0	1	100	2.5-100	N/A	N/A
EIA NR[2]	80	1	1	0	78	98.7	93.1-100	100	2.5-100
Elevated ALT and No Liver Histopathology	26	26	0	0	0	N/A	N/A	100	86.8-100
EIA R / RIBA Pos	26	26	0	0	0	N/A	N/A	100	86.8-100
EIA R / RIBA Neg	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA R / RIBA Ind	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA NR[2]	0	0	0	0	0	N/A	N/A	N/A	N/A
Normal ALT and No Liver Histopathology	2	1	0	0	1	100	2.5-100	100	2.5-100
EIA R / RIBA Pos	2	1	0	0	1	100	2.5-100	100	2.5-100
EIA R / RIBA Neg	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA R / RIBA Ind	0	0	0	0	0	N/A	N/A	N/A	N/A
EIA NR[2]	0	0	0	0	0	N/A	N/A	N/A	N/A
At Risk									
Total	1164	768	7	3	386	98.2	96.4-99.3	99.6	98.9-99.9
EIA R / RIBA Pos	830	759	5	1	65	92.9	84.1-97.6	99.9	99.3-100
EIA R / RIBA Neg	2	1	0	0	1	100	2.5-100	100	2.5-100
EIA R / RIBA Ind	7	3	0	0	4	100	39.8-100	100	29.2-100
EIA NR[2]	325	5	2	2	316	99.4	97.7-99.9	71.4	29.0-96.3

VERS = VERSANT R = Reactive NR = Nonreactive Pos = Positive Neg = Negative

Agree = Agreement N/A = Insufficient data for meaningful result Ind = Indeterminate

N/A = Insufficient data for meaningful result

Clinical Specimen Storage Study

Specimen storage conditions were evaluated for their effects on assay performance. Specimens from each of 72 subjects were separated into two aliquots. One aliquot was stored at 2° to 8°C and tested within 48 hours. The other aliquot was stored frozen at -20°C or below for up to 44 days. Data indicated no difference in the detection of HCV RNA in specimens stored in the two conditions.

Signal Analysis

A summary of the VERSANT HCV RNA Qualitative Assay signal analysis for the assay calibrators and controls and the internal control in plasma and serum specimens is shown in the table below:

Calibrator	N	Mean RLU (x 1000)	SD (x 1000)	% CV	Min RLU (x 1000)	Max RLU (x 1000)
Positive	111	1,265	102	8.0	795	1493
Negative	110	5.6	3.0	53.2	0	13.1

Control	N	Mean S/CO	SD	% CV	Min S/CO	Max S/CO
Positive	54	22.5	2.1	9.5	11.2	27.3
Negative	54	0.07	0.04	55.1	0.01	0.2

Internal Control	N	Mean IC S/CO	SD	%CV	Min S/CO	Max S/CO
Serum	355	2.1	0.1	6.1	1.0	3.0
Plasma	210	2.1	0.09	4.3	1.7	2.2

REPRODUCIBILITY

Reproducibility testing was performed at three laboratories (A, B, C) to obtain measures of repeatability and reproducibility during the clinical trial; two of the sites were outside laboratories and one was in-house. Testing was also conducted in-house during the preclinical phase (D). In the clinical testing, the three sites were provided with six identical panels of eight samples containing 0 to 9,615 IU/mL (0 to 50,000 copies/mL) genotype 1 or 0 to 577 IU/mL (0 to 3,000 copies/mL) genotype 2b in serum or plasma. In the preclinical phase testing, six member serum or plasma panels for genotype 1 at 0 to 14.4 IU/mL (0 to 75 copies/mL) and genotype 2b at 0 to 69.2 IU/mL (0 to 360 copies/mL) were tested. At sites A, B, and C, each of two operators performed two days of testing with each of three kit lots for a total of six days of testing. At Site D, three operators tested the genotype 1 panel with each of three kit lots on six separate days. Similarly, Site D tested the genotype 2b panel with each of three kit lots on each of five separate days. Reproducibility testing at or near the assay's limit of detection was not done with genotypes other than genotype 1. The data is presented in the package insert.

X. CONCLUSIONS DRAWN FROM STUDIES

Risk/Benefit Analysis

As a nucleic acid and amplification assay, the VERSANT HCV RNA Qualitative Assay detects the presence of HCV RNA in human plasma or serum. Detection of viral nucleic acid is indicative of viral replication and therefore, active HCV infection. The primary benefit of using this test is the detection of active HCV infection in individuals with antibody evidence of HCV infection with evidence of liver disease, and individuals suspected to be actively infected with HCV with antibody evidence, and individuals at risk for HCV infection with antibodies to HCV.

The potential risks seen for *in vitro* diagnostic assays are not unusual in the laboratory setting, and appropriate warnings and risks are contained in the labeling for these devices. Standard good laboratory practices are recommended to minimize the risks to the end user. The benefits to patients tested with the VERSANT HCV RNA Qualitative Assay exceed the known or potential risks or adverse events for patients or laboratory personnel.

Safety

The VERSANT HCV RNA Qualitative Assay is a diagnostic test that utilizes blood specimens and, as such, requires the withdrawal of blood from individuals being tested. The safety hazards to individuals being tested are no greater than those involved in other diagnostic tests for which blood is drawn.

XI. PANEL RECOMMENDATIONS

Pursuant to Section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not the subject of an FDA Microbiology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by the Panel.

XII. CDRH DECISION

The applicant's manufacturing facility inspected on was found to be in compliance with the Quality Systems Regulation (21 CFR 820).

FDA issued an approval order on November 7, 2002.

XIII. APPROVAL SPECIFICATIONS

Directions for use: See Labeling

Hazards to Health from Use of the Device: See Indications, Contraindications, Warning, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

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