VITROS Products Immunodiagnostic

Intended for Use in the United States

INSTRUCTIONS FOR USE HAV T

VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack	REF	680 1823
VITROS Immunodiagnostic Products Anti-HAV Total Calibrator	REF	680 1462

Rx ONLY

Intended Use

For *in vitro* diagnostic use only.

VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack

For the qualitative detection of total antibody (IgG and IgM) to hepatitis A virus (total anti-HAV) in human adult and pediatric serum and plasma (EDTA, heparin or citrate) using the VITROS ECi/ECi Q Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System.

The assay is indicated, in conjunction with other serological and clinical information, as an aid in the clinical laboratory diagnosis of individuals with acute or past hepatitis A virus infection, or as an aid in the identification of HAV-susceptible individuals prior to HAV vaccination. The detection of HAV-specific antibodies in human serum or plasma is laboratory evidence of acute or recent HAV infection.

WARNING: ***This assay is not intended for screening blood or solid or soft tissue donors. Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients. The user is responsible for establishing their own assay performance characteristics in these populations.***

VITROS Immunodiagnostic Products Anti-HAV Total Calibrator

For use in the calibration of the VITROS ECi/ECiQ Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System for the qualitative detection of antibodies to hepatitis A virus (anti-HAV) in human serum and plasma (EDTA, heparin or citrate).

Summary and Explanation of the Test

Hepatitis A virus (HAV) infection is a cause of morbidity and socio-economic loss in many parts of the world. [1, 2] Transmission is typically via the fecal-oral route associated with contaminated water or food. [1 - 3] In areas where sanitation is poor, infections often occur early in life. In childhood, HAV infection is generally mild or asymptomatic and results in lifelong immunity. With improved sanitation and hygiene, infections are delayed and consequently the number of adolescents and adults susceptible to the virus increases. In adolescents and adults, HAV infection is more serious leading to hepatitis and an increased mortality rate. [4]

Anti-HAV IgM is detectable during the acute stage of illness, while anti-HAV IgG may be present for many years after recovery [1, 2, 4] or following vaccination. The presence of anti-HAV (IgG or IgM) in human serum or plasma is indicative of past or present infection with hepatitis A virus (HAV) or vaccination against HAV. The test for total anti-HAV is primarily used to determine exposure to HAV either naturally or due to vaccination.

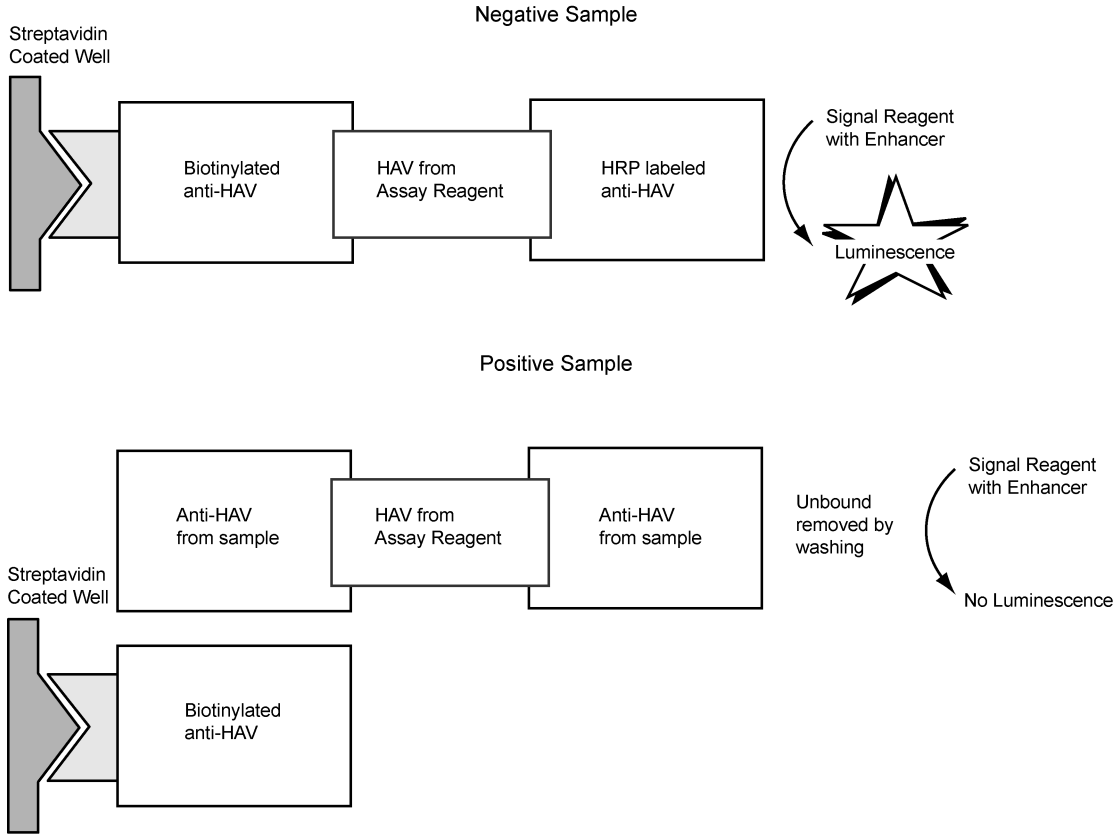
Principles of the Procedure

The VITROS Anti-HAV Total test is performed using the VITROS Anti-HAV Total Reagent Pack and the VITROS Anti-HAV Total Calibrators on the VITROS ECi/ECiQ Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System using Intellicheck® Technology. A competitive immunoassay technique is used, which involves pre-incubation of anti-HAV in the sample with HAV antigen in the test reagent followed by incubation with a conjugate reagent that contains biotinylated mouse monoclonal anti-HAV antibody and horseradish peroxidase (HRP)-labeled mouse monoclonal anti-HAV antibody. Unbound materials are removed by washing.

The bound HRP conjugate is measured by a luminescent reaction. [5] A reagent containing luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent, is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The binding of HRP conjugate is indicative of the absence of anti-HAV antibody.

Test Type	System	Incubation Time	Time to first result	Test Temperature	Reaction Sample Volume
Competitive	ECi/ECiQ, 3600, 5600	45 minutes	53 minutes	37 °C	10 µL

Reaction Scheme



Warnings and Precautions

WARNING: ***Potentially Infectious Material***

The VITROS Anti-HAV Total Reagent Pack contains formalin inactivated HAV virus. Treat as if capable of transmitting infection.

Human anti-HAV positive and anti-HAV negative plasma provided as components of the VITROS Anti-HAV Total Reagent Pack and the VITROS Anti-HAV Total Calibrators have been obtained from donors who were tested individually and who were found to be negative for hepatitis B surface antigen, (HBsAg) and for antibodies to human immunodeficiency virus (HIV 1+2) and hepatitis C virus (HCV), using FDA approved methods (enzyme immunoassays). Treat as if capable of transmitting infection.

Use caution when handling material of human origin. Consider all samples potentially infectious. No test method can offer complete assurance that hepatitis B virus, HCV, HIV 1+2 or other infectious agents are absent. Handle, use, store and dispose of solid and liquid waste from samples and test components, in accordance with procedures defined by appropriate national biohazard safety guideline or regulation (e.g. CLSI document M29). [6, 7]

WARNING: ***Contains ProClin 300 (CAS 55965-84-9)*** [8]

The VITROS Anti-HAV Total Reagent Pack contains 0.5% ProClin 300. H317: May cause an allergic skin reaction. P280: Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P363: Wash contaminated clothing before reuse.

WARNING

WARNING: *Contains Kathon or ProClin 200 (CAS 55965-84-9)*[8]

The VITROS Anti-HAV Total Calibrator contains 2% Kathon or ProClin 200. H317: May cause an allergic skin reaction. P280: Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P363: Wash contaminated clothing before reuse.

Refer to www.orthoclinical.com for the Safety Data Sheets and for OCD contact information.

WARNING

Reagents

Reagent Pack Contents

1 reagent pack containing:

- 100 coated wells (streptavidin, bacterial; binding capacity ≥3 ng biotin/well)
- 8.7 mL assay reagent (inactivated HAV antigen [pHM175], cell culture; 2-20 mg/mL) in buffer with bovine serum albumin, mouse serum and antimicrobial agent
- 12.0 mL conjugate reagent (HRP-mouse monoclonal anti-HAV [21D4]; 1.5 µg/mL, and biotin-mouse monoclonal anti-HAV, 1.5 µg/mL) in buffer with bovine serum albumin and antimicrobial agent

Reagent Pack Handling

- The reagent pack is supplied ready for use.
- The reagent pack contains homogeneous liquid reagents that do not require shaking or mixing prior to loading onto the system.
- Handle the reagent pack with care. Avoid the following:
  - allowing condensation to form on the pack
  - causing reagents to foam
  - agitation of the pack

Reagent Pack Storage and Preparation

Reagent	Storage Condition		Stability
Unopened	Refrigerated	2–8 °C (36–46 °F)	expiration date
Opened	On system	System turned on	≤12 weeks
Opened	Refrigerated	2–8 °C (36–46 °F)	≤12 weeks

- The VITROS Anti-HAV Total Reagent Pack is suitable for use until the expiration date on the carton when stored and handled as specified. Do not use beyond the expiration date.
- Do not freeze unopened reagent packs.
- Load reagent packs directly from refrigerated storage to minimize condensation.
- Store opened refrigerated reagent packs in a sealed reagent pack storage box that contains dry desiccant.

Calibrator Contents

- 1 vial of VITROS Anti-HAV Total Calibrator (human anti-HAV plasma, 2.0 mL) with antimicrobial agent
- Lot calibration card
- Protocol card
- 8 calibrator bar code labels

Calibrator Handling

- Use only with reagent packs of the same lot number. Mix thoroughly by inversion and bring to 15–30 °C (59–86 °F) before use. Each pack contains sufficient volume for a minimum of 6 calibration events.
- Handle calibrators in stoppered containers to avoid contamination and evaporation. To avoid evaporation, limit the amount of time calibrators are on the system. Refer to the operating instructions for your system. Return to 2–8 °C (36–46 °F) as soon as possible after use, or load only sufficient volume for a single determination.

Calibrator Storage and Preparation

Calibrator	Storage Condition		Stability
Unopened	Refrigerated	2–8 °C (36–46 °F)	expiration date
Opened	Refrigerated	2–8 °C (36–46 °F)	≤13 weeks
Opened	Frozen	≤-20 °C (≤-4 °F)	≤13 weeks

- The VITROS Anti-HAV Total Calibrator is supplied ready for use.
- The VITROS Anti-HAV Total Calibrator is suitable for use until the expiration date on the carton when stored and handled as specified. Do not use beyond the expiration date.
- Opened calibrators may be stored frozen (with no more than 1 freeze-thaw cycle).
- The VITROS Anti-HAV Total test uses 10 µL of calibrator for each determination. The VITROS Anti-HAV Total Calibrator may be used directly on the VITROS Immunodiagnostic and VITROS Integrated Systems. Alternatively, transfer an aliquot of the calibrator into a sample container (taking account of the minimum fill volume of the container), which may be bar coded with the labels provided. For details on minimum fill volume of sample cups or containers, refer to the operating instructions for your system.
- The VITROS Anti-HAV Total Calibrator is automatically processed in duplicate.

Specimen Collection, Preparation and Storage

Patient Preparation

No special patient preparation is necessary.

Specimens Recommended

- Serum
- EDTA plasma
- Heparin plasma
- Citrate plasma

Note: The differences between serum and citrate samples may be larger than 10% due to the liquid anticoagulant in the tube. There is approximately a 10% dilution of the blood by the liquid anticoagulant in the citrate tubes. (Refer to Matrix Comparison.)

Specimens Not Recommended

- Do not use turbid specimens. Turbidity in specimens may affect test results.
- Do not use heat-inactivated samples.

Special Precautions

IMPORTANT: *Certain collection devices have been reported to affect other analytes and tests.* [9] *Owing to the variety of specimen collection devices available, Ortho-Clinical Diagnostics is unable to provide a definitive statement on the performance of its products with these devices. Confirm that your collection devices are compatible with this test.*

Specimen Collection and Preparation

- Collect specimens using standard procedures. [10, 11]
- Samples should be thoroughly separated from all cellular material. Failure to do so may lead to an erroneous result.

- Thoroughly mix samples by inversion and bring to 15–30 °C (59–86 °F) before use.
- The VITROS Anti-HAV Total test uses 10 µL of sample for each determination. This does not take account of the minimum fill volume of the chosen sample container. For details on minimum fill volume of sample cups or containers, refer to the operating instructions for your system.

Handling and Storage Conditions

- Handle samples in stoppered containers to avoid contamination and evaporation.
- The amount of time samples are on the system prior to analysis should be limited to avoid evaporation. This time should not exceed two hours. Refer to the operating instructions for your system.
- Return to 2–8 °C (36–46 °F) as soon as possible after use, or load sufficient volume for a single volume determination.
- Serum and plasma samples may be stored for up to 5 days at 2–8 °C (36–46 °F) or 4 weeks at -20 °C (-4 °F).
- The Clinical and Laboratory Standards Institute (CLSI) provides the following recommendations for storing specimens: [12]
  - Store samples at 22 °C (72 °F) for no longer than 8 hours.
  - If the test will not be completed within 8 hours, refrigerate samples at 2–8 °C (36–46 °F) for up to 5 days.
- If the test will not be completed within 5 days, or for shipment, freeze samples at or below -20 °C (-4 °F).
- Samples are not to be repeatedly frozen and thawed because this can cause analyte deterioration. Samples are to be thawed only once.

Testing Procedure

Materials Provided

- VITROS Immunodiagnostic Products Anti-HAV Total Reagent Pack
- VITROS Immunodiagnostic Products Anti-HAV Total Calibrator

Materials Required but Not Provided

- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- VITROS Immunodiagnostic Products High Sample Diluent B
- Quality control materials such as VITROS Immunodiagnostic Products Anti-HAV Total Controls
- VITROS Immunodiagnostic Products Reagent Pack Storage Box (optional) with desiccant

Operating Instructions

Check the inventory regularly to aid the management of reagents and ensure that sufficient VITROS Signal Reagent, VITROS Universal Wash Reagent and calibrated reagent lots are available for the work planned. When performing panels of tests on a single sample, ensure that the sample volume is sufficient for the tests ordered.

For detailed information refer to the operating instructions for your system.

Note: Do not use visibly damaged product.

Sample Dilution

Rare patient samples occur that give high result ratios beyond the normal negative population, and which may be negative or positive for anti-HAV. The results of these samples are flagged “Retest?” and may be resolved by manually diluting the sample 1 in 20 with High Sample Diluent B and retesting. Refer to the High Sample Diluent B instructions for use.

Default Test Name

The default test name which will appear on patient reports is Anti-HAV Total. The default short name that will appear on the test selection menus and laboratory reports is HAV T. These defaults may be reconfigured, if required. For detailed information refer to the operating instructions for your system.

Calibration

Calibration Procedure

- Calibration is lot specific; reagent packs and calibrators are linked by lot number. Reagent packs from the same lot may use the same calibration.
- A Master Calibration is established for each new reagent lot by performing multiple tests. This is the process by which a lot-specific parameter [a] which links the signal at the cutoff (cutoff value) to the calibrator signal is determined.

Cutoff value = (a x Signal of Cal 1).

- Ensure that the Master calibration for each new reagent lot is available on your system.

- Process calibrators in the same manner as samples. Calibration need not be programmed if bar code labels are used; load the calibrators in any order, calibration will be initiated automatically.
- When the calibrator is processed the validity of the calibration is assessed against quality parameters which compares the actual signal of the calibrator with the expected signal. If the calibration is acceptable the cutoff value is calculated and stored for use with any reagent pack of that lot.
- The quality of calibration cannot be completely described by a single parameter. The calibration report should be used in conjunction with acceptable control values to determine the validity of the calibration.
- Recalibration is required after a pre-determined calibration interval, or when a different reagent lot is loaded.
- Calibration results are assessed against a range of quality parameters. Failure to meet any of the defined quality parameter ranges will be coded in the calibration report. For actions to be taken following a failed calibration, refer to the operating instructions for your system.

Refer to the operating instructions for your system for detailed instructions on the calibration process.

When to Calibrate

- Calibrate when the reagent pack and calibrator lot changes.
- Calibrate every 28 days.
- After specified service procedures have been performed.
- If quality control results are consistently outside of your acceptable range.

For additional information on when to calibrate, refer to the operating instructions for your system.

Traceability of Calibration

The calibration of the VITROS Anti-HAV Total test is traceable to an in-house reference calibrator which has been value assigned to optimize the clinical sensitivity and specificity performance.

Calibration Model

Results are calculated as a normalized signal, relative to a cutoff value. During the calibration process a lot-specific parameter, encoded on the lot calibration card, is used to determine a valid stored cutoff value for the VITROS Immunodiagnostic and VITROS Integrated Systems.

Quality Control

Quality Control Material Selection

VITROS Anti-HAV Total Controls are recommended for use with the VITROS Immunodiagnostic and VITROS Integrated Systems. There are 2 VITROS Anti-HAV Total Controls (anti-HAV negative and anti-HAV positive). The performance of other commercial control fluids should be evaluated for compatibility with this test before they are used for quality control.

Control materials may show a difference when compared with other anti-HAV methods if they contain high concentrations of preservatives, stabilizers, or other nonphysiological additives, or otherwise depart from a true human sample matrix.

Appropriate quality control value ranges must be established for all quality control materials used with the VITROS Anti-HAV Total test.

Choose control material that has a composition similar to or identical with the patient sample matrix being analyzed. [13]

Quality Control Procedure Recommendations

- Good laboratory practice requires that controls be processed to verify the performance of the test.
- Choose control levels that check performance at clinically relevant points. The recommendation is to run a negative control and a positive control close to the anti-HAV decision point [signal/cutoff (s/c) <1.00].
- To verify system performance, analyze control materials:
  - After calibration
  - According to local regulations or at least once each day that the test is being performed
  - After specified service procedures are performed or maintenance to critical parts or subsystems that might influence performance of the test

If quality control procedures within your laboratory require more frequent use of controls, follow those procedures.

- Analyze quality control materials in the same manner as patient specimens.
- If control results fall outside the stated range or outside your established acceptable range, patient results should not be reported. Investigate and determine the cause for the unacceptable control results. When the condition is corrected, retest the controls and confirm that results are within acceptable limits. It is recommended to repeat some or all patient samples, processed after the last acceptable QC results.
- Refer to the published guidelines for general quality control recommendations. [14]

Additional controls may be tested according to guidelines or requirements of local, state, and/or federal regulations or accrediting organizations.

For more detailed information, refer to the operating instructions for your system.

Quality Control Material Preparation and Storage

Refer to the manufacturer's product literature for preparation, storage, and stability information.

Results

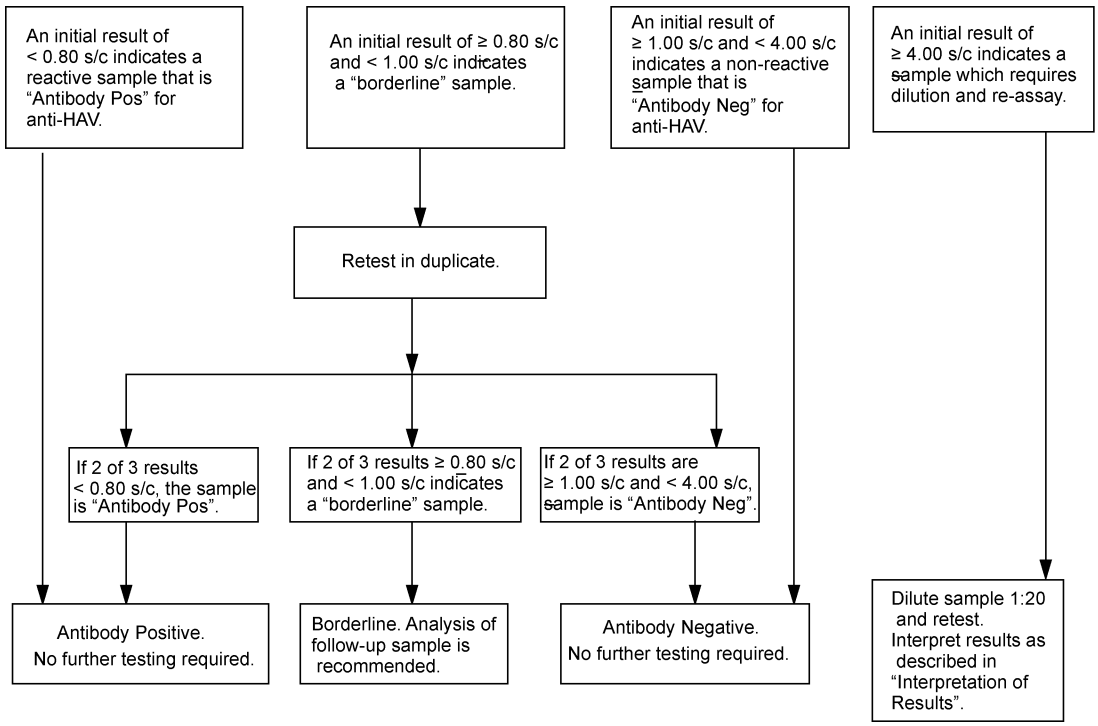
Results are calculated as a normalized signal, relative to a cutoff value (signal/cutoff, s/c). During the calibration process a lot-specific parameter is used to determine a valid stored cutoff value for the VITROS Immunodiagnostic and Integrated Systems.

Patient sample results will be displayed as "Antibody Pos", "Borderline", "Antibody Neg", or "Retest?"*. An initial result labeled with "Borderline" indicates a sample that requires duplicate repeat testing for anti-HAV. An initial result labeled "Retest?" indicates a sample which requires dilution and re-assay.

Result s/c	< 0.80	≥0.80 and <1.00	≥1.00 and <4.00	≥4.00
Result Text	Antibody Pos	Borderline	Antibody Neg	Retest?*

Final results should be interpreted using the algorithm below.

Testing Algorithm



*Retest? indicates the sample will require retesting following the testing algorithm.

Interpretation of Results

The following table summarizes the interpretation of results obtained with the VITROS Anti-HAV Total test upon completion of all testing steps required in the testing algorithm.

VITROS Anti-HAV Total Test Result	Result Text	Clinical Interpretation
<0.80	Antibody Pos	Indicates a reactive sample and the presence of anti-HAV. Indicates individual has been previously infected with or is presumed to be immune to HAV infection.
≥0.80 and <1.00	Borderline	Indicates a borderline sample. It is recommended that a new specimen be collected within 2–4 weeks and retested.
≥1.00 and <4.00	Antibody Neg	Indicates a non-reactive sample, negative for anti-HAV. Indicates that the individual has not been infected and is presumed not to be immune to HAV infection.
≥4.00	Retest?	Indicates a sample which requires dilution and retesting.

Limitations of the Procedure

Known Interferences

The VITROS Anti-HAV Total test was evaluated for interference consistent with CLSI document EP7. [15] Commonly encountered substances were tested on 3 lots of reagents. Of the compounds tested, none was found to interfere with the clinical interpretation of the test.

Refer to “Substances that do not Interfere” for a list of compounds tested that did not show interference.

Other Limitations

- This device is more sensitive for anti-IgG than IgM.
- The results from this or any other diagnostic kit should be used and interpreted only in the context of the overall clinical picture. A negative test result does not exclude the possibility of exposure to hepatitis A virus. Levels of anti-HAV antibody may be below the cutoff in early infection and many years after infection. It has been shown that a viremic window exists with individuals infected with HAV where the individual may be symptomatic for hepatitis, but anti-HAV total and anti-HAV IgM nonreactive.
- A reactive anti-HAV total result does not necessarily rule out other hepatitis infections.
- Heterophilic antibodies in serum or plasma samples may cause interference in immunoassays. [16] These antibodies may be present in blood samples from individuals regularly exposed to animals or who have been treated with animal serum products. Results which are inconsistent with clinical observations indicate the need for additional testing.
- Cord blood and neonate samples may give a negative bias in the VITROS Anti-HAV Total test. (See Recommended Specimen Types.)
- The magnitude of a VITROS Anti-HAV Total test result cannot be correlated to an endpoint titer.
- Some anticoagulants (e.g. liquid citrate) have a dilutional effect on samples and results should be interpreted accordingly. Refer to Matrix Comparison.)
- Biotin levels in serum remain elevated for up to 24 hours after oral or intravenous biotin administration. [17]

Expected Results

HAV Prevalence Population

The expected results of the VITROS Immunodiagnostic Products Anti-HAV Total test to detect anti-HAV IgG and IgM were determined in presumably healthy individuals from areas of both high (Western US) and low (Eastern US) HAV disease prevalence in the United States. The population was 50% male and 50% female, with ages that ranged from 18 to 89 years. The majority of the subjects were White/Caucasian (72.0%). Other ethnic groups tested were African American (12.0%), Hispanic/Latino (15.0%) and Asian (1.0%). The expected results for presumably healthy individuals living in either high or low prevalence areas are presented in the table below.

Expected Results for the VITROS Anti-HAV Total Test in Subjects From Low Prevalence Areas for Hepatitis A (N=648)

Age Range	Gender	VITROS Anti-HAV Total Result						Total
		Reactive		Borderline		Negative		
		N	Percent	N	Percent	N	Percent	
18–20	Female	0	0	0	0	11	100	11
	Male	0	0	0	0	6	100	6
21–30	Female	5	18.5	0	0	22	81.5	27
	Male	6	15.4	0	0	33	84.6	39
31–40	Female	5	19.2	0	0	21	80.8	26
	Male	5	11.1	1	2.2	39	86.7	45
41–50	Female	25	33.3	1	1.3	49	65.3	75
	Male	12	21.8	0	0	43	78.2	55
51–60	Female	21	20.6	0	0	81	79.4	102
	Male	29	23.4	0	0	85	74.6	114
61–70	Female	12	54.5	0	0	10	45.5	22
	Male	19	57.6	0	0	14	42.4	33
71–80	Female	22	71	0	0	9	29	31
	Male	17	81	0	0	4	19	21
81–90	Female	6	85.7	0	0	1	14.3	7
	Male	7	87.5	0	0	1	12.5	8
Total		191	30.7	2*	0.3	429*	69	622

* Three subjects had initial results in the Borderline region.

Expected Results for the VITROS Anti-HAV Total Test in Subjects From High Prevalence Areas for Hepatitis A (N=378)

Age Range	Gender	VITROS Anti-HAV Total Result						Total
		Reactive		Borderline		Negative		
		N	Percent	N	Percent	N	Percent	
16–20	Female	3	100.0	0	0.0	0	0.0	3
	Male	0	0.0	0	0.0	6	100.0	6
21–30	Female	23	57.5	1	2.5	16	40.0	40
	Male	17	43.6	0	0.0	22	56.4	39
31–40	Female	21	61.8	2	5.9	11	32.4	34
	Male	14	35.9	0	0.0	25	64.1	39
41–50	Female	9	50.0	0	0.0	9	50.0	18
	Male	11	45.8	0	0.0	13	54.2	24
51–60	Female	25	34.7	0	0.0	47	65.3	72
	Male	13	34.2	0	0.0	25	65.8	38
61–70	Female	8	40.0	0	0.0	12	60.0	20
	Male	6	40.0	0	0.0	9	60.0	15
71–80	Female	2	28.6	0	0.0	5	71.4	7
	Male	6	46.2	0	0.0	7	53.8	13
81–90	Female	5	100.0	0	0.0	0	0.0	5
	Male	3	60.0	0	0.0	2	40.0	5
Total		166	43.9	3*	0.8	209	55.3	378

* Three subjects had initial results in the Borderline region.

Adult Subjects at High Risk for Hepatitis

Expected results from asymptomatic individuals from the multi-center study described in “Performance Characteristics” are provided below. Approximately 74.3% (648) of the 872 prospective subjects enrolled in the US reported no recent or current signs or symptoms of hepatitis. Of these 648 asymptomatic individuals, 8.0% were enrolled in Miami, FL, 46.3% were enrolled in Dallas, TX, and 45.7% were enrolled in Chicago, IL. The group was Caucasian (25.6%), African American

(55.0%) Hispanic (15.0%), and Asian (1.1%) with the remaining 3.3% represented by other ethnic groups. The group was 58.5% male and 41.5% female and ranged in age from 16 to 81 years. All were at risk for viral hepatitis due to lifestyle, behavior, occupation or known exposure event. The VITROS Anti-HAV Total test was reactive in 50.2% of the individuals in this group. The percent VITROS Anti-HAV Total reactive results observed in the asymptomatic population at each collection site was 4.2% at Miami, FL, 28.2% at Chicago, IL, and 17.8% at Dallas, TX. The expected results for the VITROS Anti-HAV Total test in subjects at high risk for viral hepatitis are presented in the following table. None of the samples in this group yielded Borderline results

Expected Results for the VITROS Anti-HAV Total Test in Subjects at High Risk for Viral Hepatitis Without Signs or Symptoms of Hepatitis (N=648)

		VITROS Anti-HAV Total Result						
		Reactive		Borderline		Negative		
Age Range	Gender	N	Percent	N	Percent	N	Percent	Total
16–20	Female	5	45.5	0	0.0	6	54.5	11
	Male	2	28.6	0	0.0	5	71.4	7
21–30	Female	21	35.0	0	0.0	39	65.0	60
	Male	14	26.4	0	0.0	39	73.6	53
31–40	Female	32	40.5	0	0.0	47	59.5	79
	Male	54	39.1	0	0.0	84	60.9	138
41–50	Female	38	64.4	0	0.0	21	35.6	59
	Male	65	55.6	0	0.0	52	44.4	117
51–60	Female	26	74.3	0	0.0	9	25.7	35
	Male	21	61.8	0	0.0	13	38.2	34
61–70	Female	14	73.7	0	0.0	5	26.3	19
	Male	22	91.7	0	0.0	2	8.3	24
71–80	Female	5	100	0	0.0	0	0	5
	Male	5	83.3	0	0.0	1	16.7	6
81–90	Female	1	100	0	0.0	0	0	1
Total		325	50.2	0	0.0	323	49.8	648

There were no initial Borderline results observed in these subjects.

Pediatric Subjects at Low Risk for Hepatitis

Expected results for the VITROS Anti-HAV Total test were also determined using unlinked, randomly collected samples from pediatric subjects at low risk for viral hepatitis (N=109). The group was 31.2% male and 68.8% female, and the subjects' ages ranged from 2 to 19 years. The expected results for the VITROS Anti-HAV Total test in pediatric subjects are presented in the following table.

Expected Results for the VITROS Anti-HAV Total Test in Pediatric Subjects At Low Risk for Viral Hepatitis (N=109)

		VITROS Anti-HAV Total Result						
		Reactive		Borderline		Negative		
Age Range	Gender	N	Percent	N	Percent	N	Percent	Total
2–4	Female	0	0.0	0	0.0	6	100	6
	Male	2	16.7	0	0.0	10	83.3	12
5–9	Female	2	8.7	0	0.0	21	91.3	23
	Male	2	22.2	0	0.0	7	77.8	9
10–14	Female	6	22.2	0	0.0	21	77.8	27
	Male	1	20.0	1	20.0	3	60.0	5
15–19	Female	3	15.8	0	0.0	16	84.2	19
	Male	0	0.0	0	0.0	8	100	8
Total		16	14.7	1	0.9	92	84.4	109

Sixteen of 109 specimens were reactive and one had a borderline result with the VITROS Anti-HAV Total test. The remaining 92 specimens were negative with both the VITROS and reference tests.

Performance Characteristics

Clinical Performance

A multi-center prospective study was conducted to evaluate the clinical performance of the VITROS Anti-HAV Total test among individuals with signs or symptoms or biochemical manifestations (elevated liver function tests) of hepatitis and those at high risk of hepatitis infection due to lifestyle, behavior, occupation, or known exposure events. Specimens were evaluated from 872 subjects prospectively enrolled at three geographically separated collection sites within the United States (Population 1) located in Miami, FL (12.6%), Dallas, TX (37.5%) and Chicago, IL (49.9%). Specimens were also evaluated from 313 subjects prospectively enrolled in an area in India with a high prevalence of viral hepatitis (Population 2). Statistical testing performed to evaluate the homogeneity of the distribution of VITROS Anti-HAV Total test s/c values across the four collection sites indicated that the data from Population 1 and Population 2 could be pooled for statistical analysis.

The subjects in Population 1 were Caucasian (25.6%), African American (53.1%), Hispanic (17.0%), with the remaining 4.3% represented by other ethnic groups. The group was 57.3% male and 42.7% female, and ranged in age from 16 to 81 years. Testing of these specimens with the VITROS Anti-HAV Total test occurred at diagnostic laboratories located in Miami, FL (12.6%), Port Jefferson, NY (49.9%) and Minneapolis, MN (37.5%).

The subjects in Population 2 were Indian (100.0%). The group was 72.8% male and 27.2% female, and ranged in age from 18 to 90 years. Testing of these specimens with the VITROS Anti-HAV Total test occurred at diagnostic laboratories located in Miami, FL (43.8%), Minneapolis, MN (43.8%) and Port Jefferson, NY (12.5%).

Agreement of the VITROS Anti-HAV Total test was assessed relative to the reference anti-HAV total test using serum samples from Population 1, Population 2, and Populations 1 and 2 combined.

Percent Agreement

A comparison of the VITROS Anti-HAV Total test and the reference anti-HAV Total test results is presented in the following tables. Data are listed by site and population. Positive and negative percent agreement and 95% exact confidence intervals are also shown.

VITROS and Reference Anti-HAV Total Test Results in Population 1: Prospective Samples from the U.S. (N=872)

VITROS Anti-HAV Total Test Result	Reference Anti-HAV Total Test Result							
	Site 1		Site 2		Site 3		All Sites	
	Reactive	Negative	Reactive	Negative	Reactive	Negative	Reactive	Negative
Reactive	61	2	267	3	121	4	449	9
Borderline	0	0	0	0	0	0	0	0
Negative	0	47	1	164	1	201	2	412
Total	61	49	268	167	122	205	451	421
Positive Percent Agreement	100% (61/61)		99.63% (267/268)		99.18% (121/122)		99.56% (449/451)	
95% Exact Confidence Interval	94.13%–100%		97.94%–99.99%		95.52%–99.98%		98.41%–99.95%	
Negative Percent Agreement	95.92% (47/49)		98.20% (164/167)		98.05% (201/205)		97.86% (412/421)	
95% Exact Confidence Interval	86.02%–99.50%		94.84%–99.63%		95.08%–99.47%		95.98%–99.02%	

There were no initial borderline results observed in these populations.

VITROS and Reference Anti-HAV Total Test Results in Population 2: Prospective Samples from India (N=313)

VITROS Anti-HAV Total Test Result	Reference Anti-HAV Total Test Result							
	Site 1		Site 2		Site 3		All Sites	
	Reactive	Negative	Reactive	Negative	Reactive	Negative	Reactive	Negative
Reactive	135	2	39	0	133	4	307	6
Borderline	0	0	0	0	0	0	0	0
Negative	0	0	0	0	0	0	0	0
Total	135	2	39	0	133	4	307	6
Positive Percent Agreement	100% (135/135)		100% (39/39)		100% (133/133)		100% (307/307)	
95% Exact Confidence Interval	97.30%–100%		90.97%–100%		97.26%–100%		98.81%–100%	
Negative Percent Agreement	0% (0/2)		N/A		0% (0/4)		0% (0/6)	
95% Exact Confidence Interval	0%–84.19%		N/A		0%–60.24%		0%–45.93%	

There were no initial borderline results observed in these populations.

The positive percent agreement of the VITROS Anti-HAV Total test with the reference anti-HAV total test was 99.56% (449/451) for Population 1 and 100% (307/307) for Population 2. The negative percent agreement of the VITROS Anti-HAV Total test with the reference test was 97.86% (412/421) for Population 1 and 0% (0/6) for Population 2.

The overall positive percent agreement for the VITROS Anti-HAV Total test with the reference test was 99.74% (756/758), with a 95% exact confidence interval of 99.05% to 99.97% for the prospective samples in Populations 1 and 2 combined. The overall negative percent agreement for the VITROS Anti-HAV Total test with the reference test was 96.49% (412/427), with a 95% exact confidence interval of 94.27% to 98.02% for the prospective samples in Populations 1 and 2 combined.

Performance of the VITROS Anti-HAV Total Test in Known Anti-HAV IgM Reactive Subjects

The performance of the VITROS Anti-HAV Total test was evaluated among serum samples from subjects known to be anti-HAV IgM positive.

A total of 77 samples collected in Egypt (N=50) and India (N=27) from subjects with a medical history and laboratory results indicative of acute hepatitis A were tested concurrently with the VITROS and reference anti-HAV IgM and anti-HAV total tests.

The VITROS Anti-HAV Total test was reactive in 100% of the 77 anti-HAV IgM reactive samples. The percent agreement of the VITROS Anti-HAV Total test with the reference test and the 95% exact confidence interval are 96.1% (74/77) and 89.0%–99.2% respectively.

The reference anti-HAV total test was negative in three subjects. The three reactive results with VITROS Anti-HAV Total test was considered falsely reactive for purposes of the analysis.

Performance of the VITROS Anti-HAV Total Test in Pediatric Subjects

The VITROS Anti-HAV Total test was also evaluated using residual laboratory serum samples from pediatric subjects at low risk for viral hepatitis. The samples were unlinked to the subjects' identities, and were included based on age, gender and available volume remaining after all testing ordered for that sample had been completed. Samples were selected such that the following age ranges (in years) were represented (2–4, 5–9, 10–14, and 15–19).

The positive and negative percent agreement of the VITROS Anti-HAV Total test with the reference anti-HAV total test, and the 95% exact confidence intervals are presented in the following table. One sample, negative with the reference test, was Borderline with the VITROS Anti-HAV Total test and was considered falsely reactive for purposes of the analysis.

Agreement of the VITROS and Reference Anti-HAV Total Tests in Pediatric Subjects

Population	Positive Percent Agreement	95% Exact Confidence Intervals	Negative Percent Agreement	95% Exact Confidence Intervals
Pediatric Subjects	93.75% (15/16)	69.77%–99.84%	97.85% (91/93)	92.45%–99.74%

The positive percent agreement for the VITROS Anti-HAV Total test with the reference test was 93.75% (15/16), with a 95% exact confidence interval of 69.77% to 99.84% for the pediatric samples. The negative percent agreement for the VITROS Anti-HAV Total test with the reference test was 97.85% (91/93), with a 95% exact confidence interval of 92.45% to 99.74% for the pediatric samples.

Performance of the VITROS Anti-HAV Total Test in Cord Blood

A total of 20 cord blood (as a surrogate for neonate serum) and 10 adult serum samples were tested in the VITROS Anti-HAV Total test. None of the samples gave a reactive result in the VITROS Anti-HAV Total test. Forty-five (45) µl of anti-

HAV positive material was added to 255 µl of cord blood and adult serum. A negative bias* was observed in the cord blood results when compared to the adult serum.

Anti-HAV Total Cord Blood Study

Sample Type	N	Mean Response (S/C)	St Dev
Cord Blood - Neat	20	2.17	0.205
Cord Blood - Spiked	20	0.89	0.151
Adult Serum - Neat	10	2.19	0.073
Adult Serum- Spiked	10	0.77	0.022

* Due to the competitive nature of the VITROS Anti-HAV Total test a positive numerical bias indicates a negative functional bias.

Seroconversion Panels

Three seroconversion panels each having at least 5 individual samples with a known predetermined result were measured in the VITROS Anti-HAV Total test and in a reference test. The results were compared with the published results for the reference test. The VITROS Anti-HAV Total test gave seroconversion sensitivity equivalent to or more sensitive than a reference test in the three panels tested.

	VITROS Anti-HAV Total		Anti-HAV Total Reference Test		Difference in Days to Reactive Result
Panel ID	Post bleed day of last non-reactive result	Post bleed day of first reactive result	Post bleed day of last non-reactive result	Post bleed day of first reactive result	
PHT902	3	16	3	16	0
RP-013	6	9	6	9	0
RP-004	P*	1	1	7	6

* P = Positive in first bleed

Potentially Cross-Reacting Subgroups

The specificity of the VITROS Anti-HAV Total test was evaluated by testing 283 samples from the following potentially cross-reacting sub-groups: SLE, anti-HIV, Cirrhosis, Non-viral Liver Disease, anti-HCV, anti-CMV, anti-HSV I & II, anti-EBV, anti-syphilis, anti-Rubella, anti-Toxoplasma, anti-HBs, anti-HTLV, HBsAg, Rheumatoid Factor, Pregnancy (1st – 3rd Trimester), HAMA, Rubeola, Mumps, VZV and ANA. All initially reactive samples were tested with a reference test for confirmation. None of these categories were found to interfere with the VITROS Anti-HAV Total test.

Of the 283 samples tested, four (4) were observed to be discordant. The incidence of discordant samples is not significantly different from the claimed sensitivity and specificity.

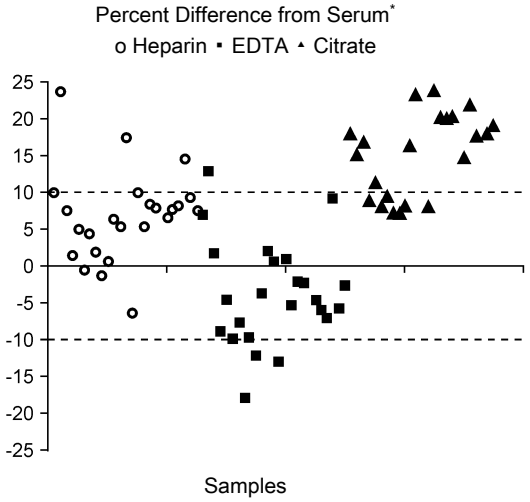
Summary of Data from Potentially Cross-Reacting Sub-Groups

		VITROS Anti-HAV Total Test		Reference Test	
Sample Category	No. Samples Tested	No. Negatives	No. Initial Reactives/ Borderlines	No. Initial Reactives/ Borderlines	No. Discordants
Toxo IgM	4	3	1	1	0
Toxo IgG	20	6	14	13	1
RF	50	24	26	25	1
SLE	10	5	5	5	0
HIV	10	7	3	2	1
aHBs	10	2	8	8	0
HCV	10	7	3	3	0
Cirrhosis	10	7	3	3	0
Syphilis	10	9	1	1	0
HTLV	10	8	2	2	0
Non Viral Liver	12	4	8	8	0
HBsAg	10	4	6	6	0
HAMA	9	5	4	4	0
EBV	10	9	1	0	1

Sample Category	No. Samples Tested	VITROS Anti-HAV Total Test		Reference Test	
		No. Negatives	No. Initial Reactives/ Borderlines	No. Initial Reactives/ Borderlines	No. Discordants
1st Trimester	18	10	8	8	0
2nd Trimester	16	7	9	9	0
3rd Trimester	16	7	9	9	0
HSV 1	3	3	0	N/A	N/A
HSV 2	2	2	0	0	0
CMV	8	8	0	N/A	N/A
VZV	5	5	0	0	0
Mumps	5	5	0	0	0
Rubella	15	12	3	3	0
Rubeola	5	3	2	2	0
ANA	5	3	2	2	0
Total	283	165	118	114	4

Matrix Comparison

A total of 25 donors had blood drawn which was spiked with anti-HAV total positive plasma to a level close to the test cutoff. The spiked blood was then aliquoted into serum and plasma collection tubes and tested in the VITROS Anti-HAV Total test. The percent difference in the plasma from serum was calculated. Mean percent differences from serum are represented below for each plasma type tested.



* Due to the competitive nature of the VITROS Anti-HAV Total test a positive numerical bias indicates a negative functional bias.

Some anti-coagulants (e.g. liquid citrate) have a dilutional effect on samples and results should be interpreted accordingly.

Precision

VITROS ECi/ECiQ Immunodiagnostic System

Precision was evaluated according to the Clinical and Laboratory Standards Institute (formerly NCCLS) protocol EP5-A2. [18] The precision panel consisting of 4 samples (a negative, a negative close to the cutoff, a positive close to the cutoff and a positive) was prepared and shipped to 3 different sites. Two replicates of each of 4 panel samples were tested at each of the 3 different sites once per day for at least 20 different days, over one calibration interval. The experiment was performed using 1 reagent lot on three different VITROS Immunodiagnostic Systems at three different sites. The data presented is a summary of the product performance.

Clinical Site	Mean VITROS Anti-HAV Total S/C (Ratio)	Within Day*		Between Day**		Total***		No. of Observ	No. of Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
Site 1	1.74	0.015	0.9	0.041	2.3	0.043	2.5	40	20
	1.08	0.018	1.6	0.026	2.4	0.031	2.9	40	20
	0.73	0.008	1.1	0.019	2.6	0.020	2.8	40	20
	0.52	0.006	1.1	0.012	2.3	0.013	2.6	40	20
Site 2	1.93	0.054	2.8	0.029	1.5	0.061	3.2	40	20
	1.14	0.015	1.3	0.033	2.9	0.036	3.2	40	20
	0.74	0.011	1.5	0.028	3.8	0.030	4.0	40	20
	0.51	0.007	1.3	0.026	5.1	0.027	5.3	40	20
Site 3	1.93	0.029	1.5	0.068	3.5	0.074	3.8	40	20
	1.18	0.030	2.5	0.038	3.2	0.048	4.1	40	20
	0.77	0.013	1.6	0.030	3.8	0.032	4.2	40	20
	0.55	0.012	2.2	0.030	5.4	0.032	5.8	40	20

* Within Day: variability of the assay performance from replicate to replicate

** Between Day: variability of the assay performance from day to day

*** Total: variability of the assay performance combining the effects of within day and between day

Mean VITROS Anti-HAV Total S/C (Ratio)	Between Site *		Total		No. Obs.
	SD	CV (%)	SD	CV (%)	
1.87	0.108	5.8	0.124	6.7	120
1.13	0.048	4.2	0.062	5.5	120
0.75	0.023	3.1	0.036	4.9	120
0.52	0.020	3.7	0.032	6.1	120

* Between Site: Variability of the test performance from site to site.

** Total: Variability of the test incorporating factors of site and day.

VITROS 3600 Immunodiagnostic System and VITROS 5600 Integrated System

Precision was evaluated consistent with NCCLS document EP5. [18] Two replicates of each 4 patient sample pools were tested on 2 separate occasions per day on at least 20 different days. The experiment was performed using 1 reagent lot on each system. The data presented are a representation of the product performance.

System	Units = S/C (Ratio)							No. Observ.	No. Days
	Mean VITROS Anti-HAV Total S/C (Ratio)	Within Day*		Between Day**		Total***			
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
ECi/ECiQ	2.35	0.026	1.1	0.026	1.1	0.039	1.7	80	20
	1.25	0.014	1.1	0.015	1.2	0.037	3.0	80	20
	0.92	0.015	1.6	0.006	0.7	0.023	2.5	80	20
	0.61	0.010	1.6	0.005	0.8	0.019	3.1	80	20
3600	2.37	0.018	0.8	0.024	1.0	0.037	1.6	84	21
	1.30	0.018	1.4	0.012	0.9	0.039	3.0	84	21
	0.97	0.014	1.4	0.014	1.4	0.023	2.4	84	21
	0.64	0.009	1.4	0.014	2.2	0.020	3.1	84	21
5600	2.32	0.022	0.9	0.000	0.0	0.030	1.3	80	20
	1.27	0.018	1.4	0.000	0.0	0.036	2.8	80	20
	0.94	0.015	1.6	0.002	0.2	0.022	2.3	80	20
	0.62	0.013	2.1	0.012	1.9	0.019	3.1	80	20

* Within Day: variability of the assay performance from replicate to replicate

** Between Day: variability of the assay performance from day to day

*** Total: variability of the assay performance combining the effects of within day and between day

Substances that do not Interfere

Serial dilutions were made for bilirubin, triolein, hemoglobin and biotin, and point estimates were made for sodium azide and dipyrone. The mean result of 3 determinations of a solution of each test substance was compared with that of a control pool, for both a negative and positive sample. For each substance, the highest concentration which was considered not to impact results are shown in the table below.

Compound	Concentration	
Bilirubin	0.342 mmol/L	20 mg/dL
Biotin	10 ng/mL	1 µg/dL
Dipyrone	1 mg/mL	10 mg/dL
Hemoglobin	0.078 mmol/L	125 mg/dL
Sodium Azide	1 g/dL	1000 mg/dL
Triolein	33.9 mmol/L	3000 mg/dL

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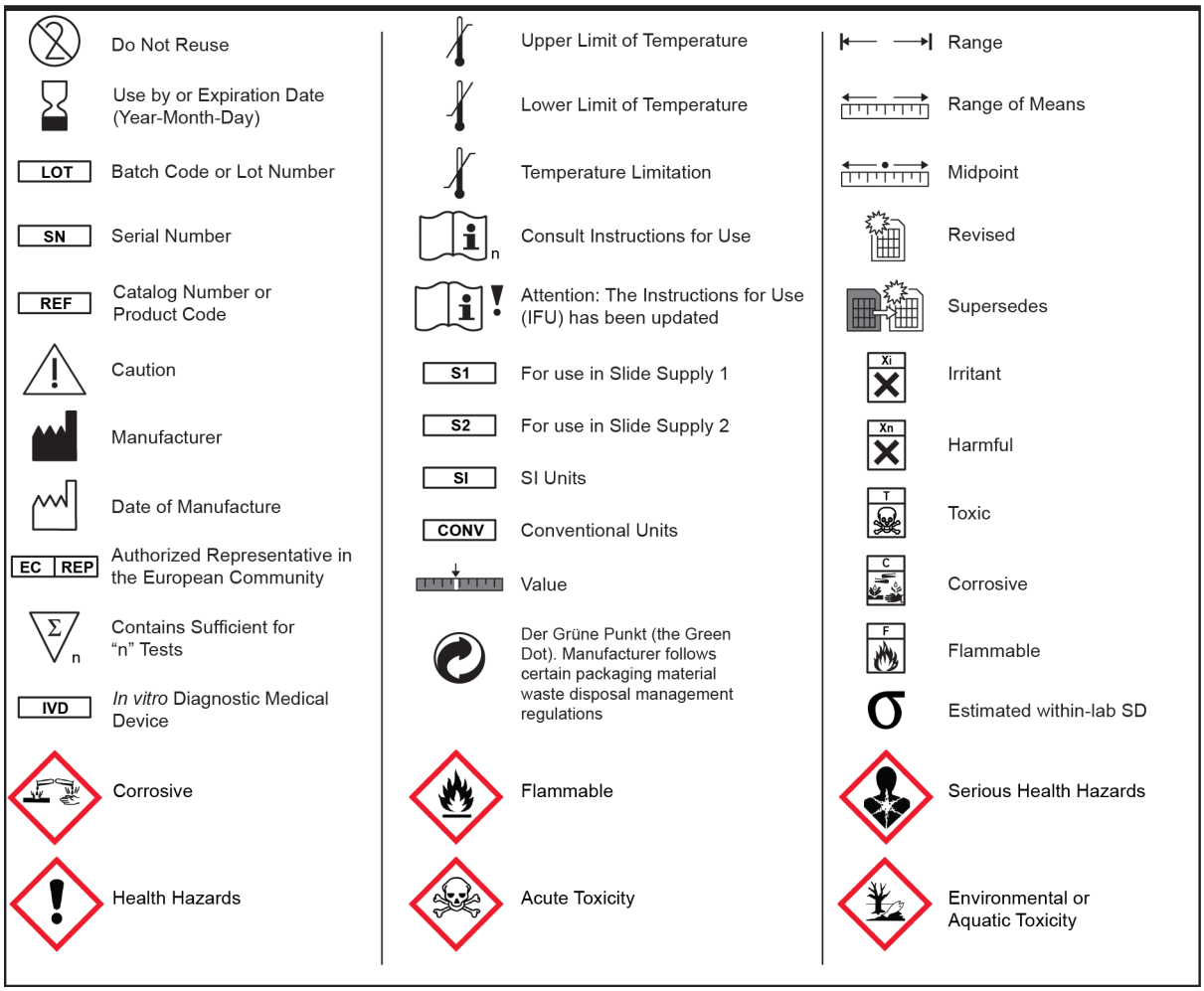
Glossary of Symbols

The following symbols may have been used in the labeling of this product.



Revision History

Date of Revision	Version	Description of Technical Changes*
2016-08-05	8.1	Address Block: CHIRON logo changed to GRIFOLS logo
2016-02-11	8.0	Warnings and Precautions: changed Kathon to Kathon or ProClin 200
2015-06-30	7.0	Updated Legal Manufacturer address

Date of Revision	Version	Description of Technical Changes*
2015-03-13	6.0	• Prescription Use Statement added • Warnings and Precautions: – added reference – updated Hazard and Precaution Statements to align with the new Safety Data Sheets – added Globally Harmonized Symbol to comply with the Classification, Labelling and Packaging (CLP) Regulations • Calibrator Storage and Preparation: clarification of the frozen storage temperature • References: – updated M29 – added reference • Glossary of Symbols: added Globally Harmonized Symbols to comply with the Classification, Labelling and Packaging (CLP) Regulations
2014-02-28	5.0	Glossary of Symbols: added Date of Manufacture
2012-01-22	4.0	Glossary of Symbols: updated
2009-08-18	3.0	• Reagent Pack Storage and Preparation: updated wording • Quality Control Procedure Recommendations: updated wording
2008-11-12	2.0	• New format that combines the following into one document: – Anti-HAV Total Reagent Pack (GEM1235A_EN_US), version 1.0 – Anti-HAV Total Calibrator (GEMC235), version 1.0 • Added information for the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System • Updated risk and safety statements • Other Limitations: added biotin statement • References: updated • Glossary of Symbols: updated
2007-10-04	1.1 (GEM1235A_EN_US)	Address Block: CHIRON Corporation changed to Novartis Vaccines and Diagnostics, Inc.
2006-09-20	1.0 (GEM1235A_EN_US)	Initial version of Instructions for Use.
2005-02-14	1.0 (GEMC235)	New format, technically equivalent to PIGEMC235/100.0 with the following minor changes: • Replaces Symbols used with Glossary of Symbols table • Added Revision History, signature block

* The change bars indicate the position of a technical amendment to the text with respect to the previous version of the document.

When this Instructions For Use is replaced, sign and date below and retain as specified by local regulations or laboratory policies, as appropriate.

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Signature Obsolete Date

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