VITROS Products Immunodiagnostic

Intended for Use in the United States

INSTRUCTIONS FOR USE HAV M

VITROS Immunodiagnostic Products Anti-HAV IgM Reagent Pack	REF	680 1812
VITROS Immunodiagnostic Products Anti-HAV IgM Calibrator	REF	137 2101

Rx ONLY

Intended Use

For *in vitro* diagnostic use only.

VITROS Immunodiagnostic Products Anti-HAV IgM Reagent Pack

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

The assay is indicated for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis. Assay results, in conjunction with other clinical information, may be used for the laboratory diagnosis of individuals with acute or recent hepatitis A.

WARNING: ***This assay is not intended for screening blood or solid or soft tissue donors.***

VITROS Immunodiagnostic Products Anti-HAV IgM 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 determination of IgM antibody to hepatitis A viral antigen (HAV) in human serum and plasma (EDTA, heparin or citrate).

Summary and Explanation of the Test

IgM antibodies against HAV are detected soon after the onset of symptoms. [1, 2] Persistence of the IgM response is extremely variable, with specific IgM detected for less than one month in some cases to greater than one year in others. [3, 4] In most cases, IgM antibodies against HAV persist for a period of three to six months after which they decline to levels that are below detection. The VITROS Anti-HAV IgM assay is designed to detect anti-HAV IgM as a laboratory diagnosis of acute or recent hepatitis A infection. The detection of anti-HAV IgM can be useful for the differential diagnosis of hepatitis A from other forms of viral hepatitis. Testing with other hepatitis markers is required.

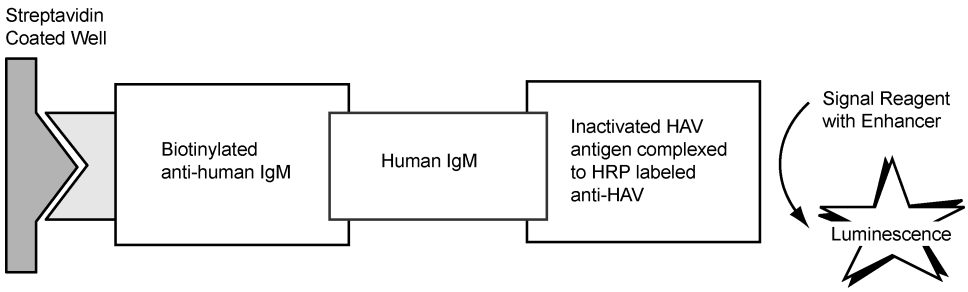
Principles of the Procedure

The VITROS Anti-HAV IgM test is performed using the VITROS Immunodiagnostic Products Anti-HAV IgM Reagent Pack and the VITROS Anti-HAV IgM Calibrator on the VITROS ECi/ECiQ Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System using Intellicheck® Technology. An antibody class capture technique [5] is used which involves the simultaneous reaction of human IgM in the sample with biotinylated antibody (mouse monoclonal anti-human IgM). The antigen-antibody complex is captured by streptavidin on the wells. Unbound materials are removed by washing.

The bound HRP conjugate is measured by a luminescent reaction. [6] 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 bound is indicative of the presence of anti-HAV IgM.

Test Type	System	Incubation Time	Time to first result	Test Temperature	Reaction Sample Volume
Immunometric (Antibody Class capture)	ECi/ECiQ, 3600, 5600	32 minutes	43 minutes	37 °C	10 µL

Reaction Scheme



Warnings and Precautions

WARNING: *Potentially Infectious Material*

The VITROS Anti-HAV IgM Reagent Pack contains formaldehyde inactivated hepatitis A virus. Human blood products provided as components of the VITROS Anti-HAV IgM Calibrator have been obtained from donors who were tested individually and who were found to be negative for hepatitis B surface antigen, 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). [7, 8]

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

The VITROS Anti-HAV IgM Reagent Pack contains 1% 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; binds ≥3 ng biotin/well)
- 19.4 mL biotinylated antibody reagent [biotin-mouse monoclonal anti-human IgM, (K2), 0.5 µg/mL] in buffer with antimicrobial agent
- 20.6 mL conjugate reagent [HRP-mouse monoclonal anti-HAV (21D4), 36 ng/mL with inactivated hepatitis A antigen (HM175), titer ≥ 0.1%] in buffer with antimicrobial agent

Note: Contains bovine serum albumin and bovine gamma globulin.

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	≤8 weeks
Opened	Refrigerated	2–8 °C (36–46 °F)	≤8 weeks

- The VITROS Anti-HAV IgM 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 VITROS Anti-HAV IgM Calibrator (human anti-HAV IgM plasma, 0.8 mL) in buffer with antimicrobial agent
- Lot calibration card
- Protocol card
- 8 calibrator bar code labels

Note: Contains bovine serum.

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)	≤10 weeks
Opened	Frozen	≤-20 °C (≤-4 °F)	≤10 weeks

- VITROS Anti-HAV IgM Calibrator is supplied ready for use.
- The VITROS Anti-HAV IgM 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 IgM test uses 10 µL of calibrator for each determination. The VITROS Anti-HAV IgM Calibrator may be used directly on the VITROS Immunodiagnostic amd VITROS Integrated Systems. Alternatively, transfer an aliquot of each 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 IgM 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.* [10] *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. [11, 12]
- 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 IgM 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. 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 determination.
- The Clinical and Laboratory Standards Institute (CLSI) [formerly the National Committee for Clinical Laboratory Standards (NCCLS)] provides the following recommendations for storing specimens: [13]
  - 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 7 days.
- If the test will not be completed within 7 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 IgM Reagent Pack
- VITROS Immunodiagnostic Products Anti-HAV IgM Calibrator

Materials Required but Not Provided

- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- VITROS Immunodiagnostic Products High Sample Diluent B Reagent Pack
- Quality control materials such as VITROS Immunodiagnostic Products Anti-HAV IgM 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.

Ensure sufficient VITROS High Sample Diluent B Reagent Pack is loaded onto the VITROS Immunodiagnostic and VITROS Integrated Systems before processing samples. Refer to the VITROS High Sample Diluent B Reagent Pack instructions for use.

For detailed instructions on the operation of the VITROS Immunodiagnostic and VITROS Integrated Systems refer to the operating instructions for your system.

Note:	Do not use visibly damaged product.

Caution:	**For this test, do not use Reflex Processing in the VITROS ECi/ECiQ Immunodiagnostic System with system software below Version 3.1. Reflex processing will result in an extra dilution of the specimen, causing a negatively biased result. The VITROS ECi/ECiQ Immunodiagnostic System must be manually programmed if a specimen requires retesting.**

Default Test Name

The default test name which will appear on patient reports is Anti-HAV IgM. The default short name that will appear on the test selection menus and laboratory reports is HAV M. 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 the calibrator in the same manner as samples. Load sufficient for the automatic duplicate determination. Calibration need not be programmed if bar code labels are used; 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 14 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 IgM 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 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 IgM Controls are recommended for use with the VITROS Immunodiagnostic and VITROS Integrated Systems. There are 2 VITROS Anti-HAV IgM Controls (anti-HAV IgM negative and anti-HAV IgM 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 IgM 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 IgM test.

Quality Control Procedure Recommendations

- Good laboratory practice requires that controls be processed to verify the performance of the test.
- Choose control levels that check the clinically relevant concentrations. The recommendation is to run a negative control and a positive control close to the anti HAV IgM 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 or maintenance to critical parts or subsystems that might influence performance of the test
- 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.
- Analyze quality control materials in the same manner as patient specimens.
- If control results fall outside your acceptable range, investigate the cause before deciding whether to report patient 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 system. Results are automatically calculated by the VITROS Immunodiagnostic and VITROS Integrated Systems.

$$\text{Result} = \frac{\text{Signal for test sample}}{\text{Signal at the cutoff (cutoff value)}}$$

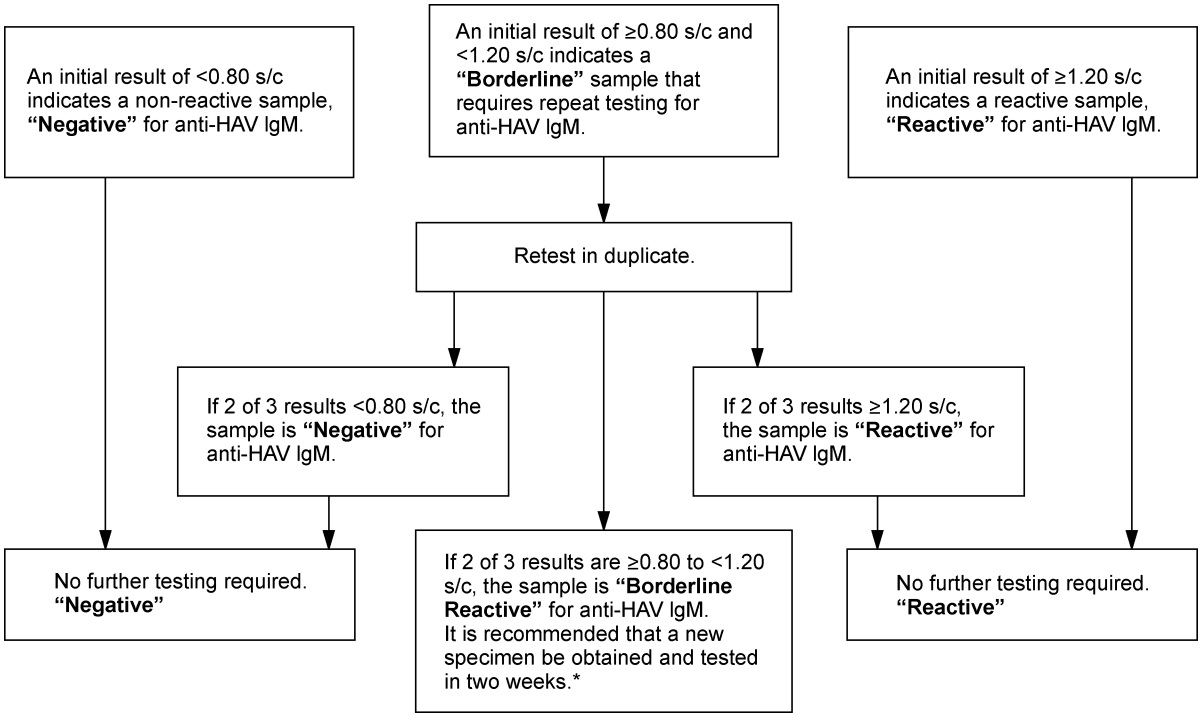
Patient sample results will be displayed with a "Negative", "Borderline" or "Reactive" label. An initial result labeled "Borderline" indicates a sample that requires duplicate repeat testing for anti-HAV IgM in order to determine a final reactive or negative result relative to the cutoff.

Caution:	**For this test, do not use Reflex Processing in the VITROS ECi/ECiQ Immunodiagnostic System with system software below Version 3.1. Reflex processing will result in an extra dilution of the specimen, causing a negatively biased result. The VITROS ECi/ECiQ Immunodiagnostic System must be manually programmed if a specimen requires retesting.**

Result s/c	<0.80	≥0.80 and <1.20	≥1.20
Result Text	Negative	Borderline	Reactive

Final results of repeat testing should be manually interpreted using the algorithm below.

Testing Algorithm



*Patients with specimens exhibiting presumptively reactive results should be re-tested at approximately two-week intervals. These patients may be at the beginning or the end of the acute infection. Anti-HAV IgM testing at two-week intervals will distinguish between an early acute or a recovering individual. A rapid rise in s/c is associated with an early acute infection. A gradual decrease or plateau in s/c is normally associated with a late acute stage of infection.

Interpretation of Results

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

VITROS Anti-HAV IgM Test Result (s/c)	Result Text (Testing Algorithm Instruction)	Clinical Interpretation
<0.80	Negative (No further testing)	Indicates a non-reactive sample, "Negative" for anti-HAV IgM. A negative test result does not exclude the possibility of infection with hepatitis A virus. Levels of anti-HAV IgM may be below the cutoff in early infection.
≥0.80 and <1.20	Borderline (Retested in duplicate)	If 2 of 3 results are ≥0.80 and <1.20 s/c sample is "Borderline Reactive" for anti-HAV IgM. It is recommended that a new specimen be obtained in two weeks and retested.
≥1.20	Reactive (No further testing)	Indicates a "Reactive" sample and the presence of anti-HAV IgM. A reactive anti-HAV IgM result does not rule out other hepatitis infections.

Detection of anti-HAV IgM does not necessarily imply an acute HAV infection due to the longevity of anti-HAV IgM. The detection of anti-HAV IgM can be useful for the differential diagnosis of hepatitis A from other forms of viral hepatitis. Testing with other hepatitis markers is required.

Limitations of the Procedure

Known Interferences

The VITROS Anti-HAV IgM test was evaluated for interference consistent with NCCLS Protocol EP7. [15] Of the compounds tested, none was found to interfere with the clinical interpretation of the test at the concentrations indicated at a anti-HAV IgM result of 2 s/c. Refer to “Substances that do not Interfere” for a list of compounds tested that did not show interference.

Other Limitations

- 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 IgM may be below the cutoff in early infection and late after infection.
- A reactive anti-HAV IgM result does not necessarily rule out other hepatitis infections.
- Heterophilic antibodies in the serum or plasma samples can cause interference with immunoassays. [16] Heterophilic antibodies might be present in blood samples from individuals who have been regularly exposed to animals or with animal proteins during immunotherapy.
- Cord blood and neonate samples may give a positive bias in the VITROS Anti-HAV IgM test.
- Some anticoagulants (e.g. liquid citrate) have a dilutional effect on samples and results should be interpreted accordingly.
- 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 IgM test to detect anti-HAV IgM was determined in presumably healthy individuals from both high (Western US) and low (Eastern US) HAV disease prevalence areas in the United States. The population was 50% male and 50% female, with ages that ranged from 18 to 89. 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 below. Two individuals of the low prevalence population produced a positive result in the VITROS Anti-HAV IgM test (0.3%).

Expected Results for the VITROS Anti-HAV IgM Test in Subjects From Low Prevalence Areas for Hepatitis A (N=622)

Age Range	Gender	VITROS Anti-HAV IgM Result						Total
		Reactive		Borderline		Negative		
		N	Percent	N	Percent	N	Percent	
18–20	Female	0	0.0	0	0.0	11	100.0	11
	Male	0	0.0	0	0.0	6	100.0	6
21–30	Female	0	0.0	0	0.0	27	100.0	27
	Male	0	0.0	0	0.0	39	100.0	39
31–40	Female	0	0.0	0	0.0	26	100.0	26
	Male	0	0.0	0	0.0	45	100.0	45
41–50	Female	0	0.0	0	0.0	75	100.0	75
	Male	0	0.0	0	0.0	55	100.0	55
51–60	Female	0	0.0	0	0.0	102	100.0	102
	Male	0	0.0	0	0.0	114	100.0	114
61–70	Female	1	4.5	0	0.0	21	95.5	22
	Male	0	0.0	0	0.0	33	100.0	33
71–80	Female	0	0.0	0	0.0	31	100.0	31
	Male	1	4.8	0	0.0	20	95.2	21
81–90	Female	0	0.0	0	0.0	7	100.0	7
	Male	0	0.0	0	0.0	8	100.0	8
Total		2*	0.3	0	0.0	620	99.7	622

* Two subjects from New Jersey giving initial results of 1.16 and 1.21 s/c, also had strong VITROS Anti-HAV Total results (s/c 0.01). One subject gave an initial Borderline result.

Expected Results for the VITROS Anti-HAV IgM Test in Subjects From High Prevalence Areas for Hepatitis A (N=378)								
Age Range	Gender	VITROS Anti-HAV IgM Result						Total
		Reactive		Borderline		Negative		
		N	Percent	N	Percent	N	Percent	
18–20	Female	0	0.0	0	0.0	3	100.0	3
	Male	0	0.0	0	0.0	6	100.0	6
21–30	Female	0	0.0	0	0.0	40	100.0	40
	Male	0	0.0	0	0.0	39	100.0	39
31–40	Female	0	0.0	0	0.0	34	100.0	34
	Male	0	0.0	0	0.0	39	100.0	39
41–50	Female	0	0.0	0	0.0	18	100.0	18
	Male	0	0.0	0	0.0	24	100.0	24
51–60	Female	0	0.0	0	0.0	72	100.0	72
	Male	0	0.0	0	0.0	38	100.0	38
61–70	Female	0	0.0	0	0.0	20	100.0	20
	Male	0	0.0	0	0.0	15	100.0	15
71–80	Female	0	0.0	0	0.0	7	100.0	7
	Male	0	0.0	0	0.0	13	100.0	13
81–90	Female	0	0.0	1*	20.0	4	80.0	5
	Male	0	0.0	0	0.0	5	100.0	5
Total		0	0.0	1	0.3	377	99.7	378

* One subject gave an initial Borderline result.

Adult Subjects at High Risk for Viral Hepatitis

Expected results of asymptomatic individuals from the multi-center study described in “Performance Characteristics” are provided below. Approximately 74.2% (650) of the 876 prospective subjects enrolled in the US reported no recent or current signs or symptoms of hepatitis. Of these 650 asymptomatic individuals, 8.0% were enrolled in Miami, FL, 46.2% were enrolled in Dallas, TX, and 45.8% were enrolled in Chicago, IL. The group was Caucasian (25.5%), African American (55.1%) and Hispanic (14.9%), with the remaining 4.5% represented by other ethnic groups. The group was 58.8% male and 41.2% 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 IgM test was reactive in 0.5% of the individuals in this group. The percent VITROS Anti-HAV IgM reactive results observed in the asymptomatic population at each collection site was 0.31% at Chicago, IL, and 0.15% at Dallas, TX. The expected results for the VITROS Anti-HAV IgM test in subjects at high risk for viral hepatitis are presented in the following table.

Expected Results for the VITROS Anti-HAV IgM Test in Study Subjects at High Risk for Viral Hepatitis Without Signs or Symptoms of Hepatitis (N=650)								
Age Range	Gender	VITROS Anti-HAV IgM Result						Total
		Reactive		Borderline		Negative		
		N	Percent	N	Percent	N	Percent	
18–20	Female	0	0	0	0.0	11	100	11
	Male	0	0	0	0.0	7	100	7
21–30	Female	0	0	0	0.0	60	100	60
	Male	0	0	1	1.9	52	98.1	53
31–40	Female	0	0	1	1.3	78	98.7	79
	Male	0	0	0	0.0	139	100	139
41–50	Female	1	1.7	0	0.0	58	98.3	59
	Male	1	0.8	0	0.0	117	99.2	118
51–60	Female	0	0	0	0.0	35	100	35
	Male	0	0	0	0.0	34	100	34
61–70	Female	0	0	0	0.0	19	100	19
	Male	0	0	0	0.0	24	100	24
71–80	Female	0	0	0	0.0	5	100	5
	Male	0	0	0	0.0	6	100	6
81–81	Female	0	0	0	0.0	1	100	1
Total		2	0.31	2*	0.31	646	99.4	650

* Two subjects gave an initial Borderline result.

Pediatric Subjects at Low Risk for Hepatitis

Expected results for the VITROS Anti-HAV IgM test were also determined using unlinked, randomly collected samples from pediatric subjects at low risk for viral hepatitis (N=110). The group was 30.9% male and 69.1% female, and the subjects' ages ranged from 2 to 19 years. The expected results for the VITROS Anti-HAV IgM test in pediatric subjects are presented in the following table.

Age Range	Gender	VITROS Anti-HAV IgM Result						Total
		Reactive		Borderline Reactive		Negative		
		N	Percent	N	Percent	N	Percent	
2–4	Female	0	0	0	0	7	100	7
	Male	0	0	0	0	12	100	12
5–9	Female	0	0	0	0	23	100	23
	Male	0	0	0	0	9	100	9
10–14	Female	0	0	0	0	27	100	27
	Male	0	0	0	0	5	100	5
15–19	Female	0	0	0	0	19	100	19
	Male	0	0	0	0	8	100	8
Total		0	0	0	0	110	100	110

The reference anti-HAV IgM test was also negative in this group of samples.

Performance Characteristics

Clinical Performance

A multi-center prospective study was conducted to evaluate the clinical performance of the VITROS Anti-HAV IgM 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 876 subjects prospectively enrolled at three geographically separated collection sites within the United States (Population 1) located in Miami, FL (12.8%), Dallas, TX (37.3%) and Chicago, IL (49.9%). Specimens were also evaluated from 315 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 IgM 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 (25.5%), African American (53.1%), and Hispanic (17.1%), with the remaining 4.3% represented by other ethnic groups. The group was 57.4% male and 42.6% female, and ranged in age from 16 to 81 years. Testing of these specimens with the VITROS Anti-HAV IgM test occurred at diagnostic laboratories located in Miami, FL (12.8%), Port Jefferson, NY (49.9%) and Minneapolis, MN (37.3%).

The subjects in Population 2 were Indian (100.0%). The group was 73.0% male and 27.0% female, and ranged in age from 18 to 90 years. Testing of these specimens with the VITROS Anti-HAV IgM test occurred at diagnostic laboratories located in Miami, FL (44.1%), Minneapolis, MN (43.5%) and Port Jefferson, NY (12.4%).

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

Percent Agreement

A comparison of VITROS Anti-HAV IgM test and reference anti-HAV IgM 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 IgM Test Results in Population 1: Prospective Samples from the U.S. (N=876)

VITROS Anti-HAV IgM Test Result	Reference Anti-HAV IgM Test Result *											
	Site 1			Site 2			Site 3			All Sites		
	R	GZR**	N	R	GZR**	N	R	GZR**	N	R	GZR**	N
Reactive	1	0	0	1	1	0	0	0	0	2	1	0
Borderline Reactive***	0	0	0	0	0	2	0	0	0	0	0	2
Negative	0	0	111	0	0	433	0	0	327	0	0	871
Total	1	0	111	1	1	435	0	0	327	2	1	873
Positive Percent Agreement	100% (1/1)			100% (2/2)			N/A			100% (3/3)		
95% Exact Confidence Interval	2.5%–100%			15.81%–100%			N/A			29.24%–100%		
Negative Percent Agreement	100% (111/111)			99.54% (433/435)			100% (327/327)			99.77% (871/873)		
95% Exact Confidence Interval	96.73%–100%			98.35%–99.94%			98.88%–100%			99.17%–99.97%		

* Reference test result: R = Reactive; GZR = Grayzone Reactive; N = Negative

** Reference test Grayzone Reactive (GZR) samples are interpreted as anti-HAV IgM reactive.

*** Two subjects from Population 1 had initial results in the Borderline region. VITROS Borderline reactive results are considered anti-HAV IgM reactive in the positive and negative percent agreement calculations.

VITROS and Reference Anti-HAV IgM Test Results in Population 2: Prospective Samples from India (N=315)

VITROS Anti-HAV IgM Test Result	Reference Anti-HAV IgM Test Result *											
	Site 1			Site 2			Site 3			All Sites		
	R	GZR**	N	R	GZR**	N	R	GZR**	N	R	GZR**	N
Reactive	12	0	0	3	0	0	8	3	0	23	3	0
Borderline Reactive***	0	1	0	0	0	5	0	2	3	0	3	8
Negative	0	0	126	0	0	31	0	0	121	0	0	278
Total	12	1	126	3	0	36	8	5	124	23	6	286
Positive Percent Agreement	100% (13/13)			100% (3/3)			100% (13/13)			100% (29/29)		
95% Exact Confidence Interval	75.29%–100%			29.24%–100%			75.29%–100%			88.06%–100%		
Negative Percent Agreement	100% (126/126)			86.11% (31/36)			97.58% (121/124)			97.20% (278/286)		
95% Exact Confidence Interval	97.11%–100%			70.50%–95.33%			93.09%–99.50%			94.56%–98.78%		

* Reference test result: R = Reactive; GZR = Grayzone Reactive; N = Negative

** Reference test Grayzone Reactive (GZR) samples are interpreted as anti-HAV IgM reactive.

*** Eleven subjects from Population 2 had initial results in the Borderline region. VITROS Borderline reactive results are considered anti-HAV IgM reactive in the positive and negative percent agreement calculations

The positive percent agreement of the VITROS Anti-HAV IgM test with the reference anti-HAV IgM test was 100% (3/3) for Population 1 and 100% (29/29) for Population 2. The negative percent agreement of the VITROS Anti-HAV IgM test with the reference test was 99.77% (871/873) for Population 1 and 97.20% (278/286) for Population 2.

The overall positive percent agreement for the VITROS Anti-HAV IgM test with the reference test was 100% (32/32), with a 95% exact confidence interval of 89.11% to 100% for the prospective samples in Populations 1 and 2 combined. The overall negative percent agreement for the VITROS Anti-HAV IgM test with the reference test was 99.14% (1149/1159), with a 95% exact confidence interval of 98.42% to 99.59% for the prospective samples in Populations 1 and 2 combined.

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

The performance of the VITROS Anti-HAV IgM 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 tests.

The VITROS Anti-HAV IgM test was reactive and in 100% agreement with the reference anti-HAV IgM test in all 77 anti-HAV IgM reactive samples. The positive percent agreement of the VITROS Anti-HAV IgM test with the reference anti-HAV IgM test and the 95% exact confidence interval are presented in the following table.

Agreement of the VITROS and Reference Anti-HAV IgM Tests in Known Anti-HAV IgM Reactive Subjects

Population	Positive Percent Agreement	95% Exact Confidence Interval
Anti-HAV IgM Reactive Subjects	100% (77/77)	95.32%–100%

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

The VITROS Anti-HAV IgM 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 IgM test with the reference anti-HAV IgM test, and the 95% exact confidence intervals are presented in the following table.

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

Population	Negative Percent Agreement	95% Exact Confidence Interval
Pediatric Subjects	100% (110/110)	96.70%–100%

The negative percent agreement for the VITROS Anti-HAV IgM test with the reference test was 100% (110/110), with a 95% exact confidence interval of 96.70% to 100% for the pediatric samples. None of the samples were reactive with the VITROS or reference anti-HAV IgM tests.

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

A total of 20 cord blood samples (as a surrogate for neonate serum) and 10 adult serum samples were tested in the VITROS Anti-HAV IgM test. None of the samples were found to give a reactive result in the VITROS Anti-HAV IgM test. Thirty microliters (30 µl) of anti-HAV IgM positive material was added to 270 µl of cord blood and adult serum.

Anti-HAV IgM Cord Blood Study

Sample Type	N	Mean Response (s/c)	SD
Cord Blood - Neat	20	0.08	0.018
Cord Blood - Spiked	20	2.24	0.134
Adult Serum - Neat	10	0.07	0.010
Adult Serum - Spiked	10	1.88	0.218

A 16% positive bias was observed with the cord blood when compared to adult serum.

Seroconversion Panels

Three seroconversion panels each having at least 5 individual samples with a known predetermined result were measured in the VITROS Anti-HAV IgM test and in a reference test. The VITROS and reference anti-HAV IgM test results are summarized below. The VITROS Anti-HAV IgM test gave seroconversion sensitivity equivalent to or more sensitive than a reference test in the three panels tested, although it appears to detect IgM for a longer period than the comparator test for qualitative determination of IgM antibody to hepatitis A.

Panel ID	VITROS Anti-HAV IgM		Anti-HAV IgM Reference Test		
	Post bleed day of last non-reactive result	Post bleed day of first repeatedly reactive result.	Post bleed day of last non-reactive result	Post bleed day of first repeatedly reactive result	Difference in Days to Repeatedly Reactive Result
PHT902	3	16	3	16	0
RP-004	0	6	0	6	0

Panel ID	VITROS Anti-HAV IgM		Anti-HAV IgM Reference Test		
	Post bleed day of earliest reactive result	Post bleed day of last positive result*	Post bleed day of earliest reactive result	Post bleed day of last positive result	Difference in Days from Last Repeatedly Reactive Result
RP-6201	0	42	0	28	14

* Only positive results from both VITROS and Reference tests were used. Borderline Reactive results were not used to determine a positive result.

Potentially Cross-Reacting Subgroups

The specificity of the VITROS Anti-HAV IgM test was evaluated by testing 189 samples from the following potentially cross-reacting sub-groups (see table below). 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 IgM test.

Of the 189 samples tested, two (2) were observed to be discordant.

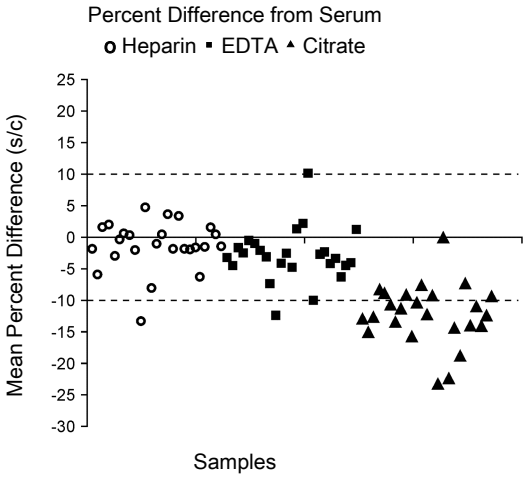
Summary of Data from Potentially Cross-Reacting Sub-Groups

Sample Category	No. Samples Tested	VITROS Anti-HAV IgM Test		Reference Test	
		No. Negatives	No. Initial Reactives/ Borderlines	No. Initial Reactives/ Borderlines	No. Discordants
Acute Hepatits B	20	20	0	0	0
ANA	5	5	0	NT*	-
Anti-HAV IgG	8	8	0	0	0
Anti-HCV	12	12	0	0	0
CMV IgM	11	11	0	0	0
EVB	5	5	0	0	0
HAMA	5	5	0	NT*	-
HIV	10	10	0	0	0
Mumps	5	5	0	NT*	-
Non Viral Liver	10	10	0	1	1
Parvo B-19	3	3	0	0	0
Rheumatoid Factor	52	51	1	0	1
Rubella	5	5	0	NT*	-
Rubeola	5	5	0	NT*	-
SLE	23	23	0	0	0
Toxoplasma	5	5	0	NT*	-
VZV	5	5	0	NT*	-
Total	189	188	1	1	2

* NT = Not Tested

Matrix Comparison

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



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 based on the Clinical and Laboratory Standards Institute (formerly NCCLS) protocol EP5. [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 2 calibration intervals. The experiment was performed using 1 reagent lot on 3 different systems at 3 different sites. The data presented is a summary of the product performance.

Clinical Site	Mean VITROS Anti-HAV IgM S/C (Ratio)	Within Day*		Between Day**		Total***		No. of Observ.	No. of Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
Site 1	0.08	0.025	29.6	0.009	10.4	0.026	31.3	40	20
	0.64	0.034	5.3	0.027	4.3	0.044	6.8	40	20
	0.99	0.044	4.5	0.042	4.2	0.061	6.2	40	20
	2.33	0.112	4.8	0.121	5.2	0.164	7.0	40	20
Site 2	0.07	0.018	27.1	0.010	15.9	0.021	31.4	40	20
	0.53	0.034	6.5	0.046	8.8	0.058	10.9	40	20
	0.84	0.035	4.1	0.072	8.6	0.080	9.6	40	20
	2.13	0.065	3.1	0.142	6.7	0.156	7.3	40	20
Site 3	0.08	0.021	27.4	0.017	22.3	0.027	35.3	40	20
	0.67	0.039	5.9	0.063	9.4	0.074	11.1	40	20
	1.02	0.080	7.8	0.042	4.1	0.090	8.8	40	20
	2.58	0.096	3.7	0.156	6.0	0.183	7.1	40	20

* Within Day: variability of the test performance from replicate to replicate.

** Between Day: variability of the test performance from day to day.

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

Mean VITROS Anti-HAV IgM S/C (Ratio)	Between Site *		Total**		No. Obs.
	SD	CV (%)	SD	CV (%)	
0.08	0.008	10.6	0.026	34.6	120
0.61	0.072	11.8	0.094	15.3	120
0.95	0.099	10.4	0.126	13.2	120
2.35	0.225	9.6	0.281	12.0	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] 2 replicates each of 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 = Result (S/C)							No. Observ.	No. Days
	Mean VITROS Anti-HAV IgM S/C (ratio)	Within Day*		Between Day**		Total***			
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
ECi/ECiQ	0.12	0.019	15.8	0.014	11.7	0.024	20.0	96	24
	0.63	0.041	6.5	0.040	6.3	0.073	11.6	88	22
	0.98	0.057	5.8	0.039	4.0	0.097	9.9	96	24
	2.13	0.104	4.9	0.104	4.9	0.191	9.0	96	24
3600	0.15	0.015	10.0	0.012	8.0	0.021	14.0	92	23
	0.65	0.035	5.4	0.040	6.2	0.062	9.5	92	23
	0.99	0.054	5.5	0.068	6.9	0.100	10.1	92	23
	2.13	0.092	4.3	0.141	6.6	0.186	8.7	92	23
5600	0.16	0.014	8.8	0.000	0.0	0.020	12.5	88	22
	0.72	0.034	4.7	0.000	0.0	0.052	7.2	88	22
	1.09	0.057	5.2	0.027	2.5	0.067	6.1	88	22
	2.39	0.067	2.8	0.000	0.0	0.131	5.5	88	22

* Within Day: Variability of the test performance from replicate to replicate

** Between Day: Variability of the test performance from day to day

*** Total: Variability of the test 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 for both positive and negative samples is shown in the table below.

Compound	Concentration	
Bilirubin	0.257 mmol/L	15 mg/dL
Biotin	10 ng/mL	1.0 µg/dL
Dipyrone	1.0 mg/mL	100 mg/dL
Hemoglobin	0.31 mmol/L	500 mg/dL
Sodium Azide	1.0 g/dL	1000 mg/dL
Triolein	33.9 mmol/L	3000 mg/dL

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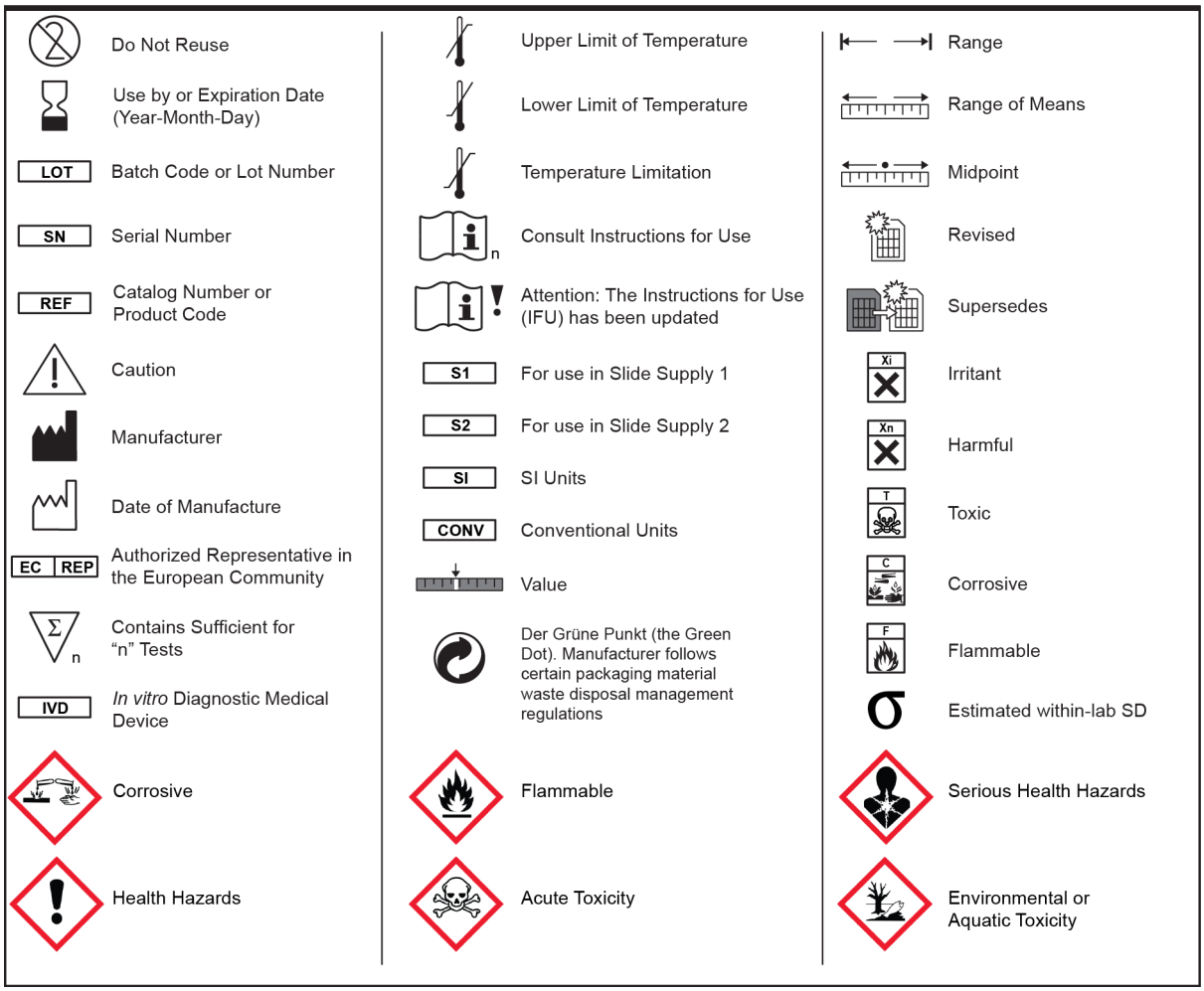
Glossary of Symbols

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	9.1	Address Block: CHIRON logo changed to GRIFOLS logo
2016-06-14	9.0	• Warnings and Precautions: Removed ProClin 300 • Reagent Pack Contents: changed HAV antigen titre to ≥0.1%
2016-03-03	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
2013-01-04	4.1	Results: corrected typographical error
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
2008-11-11	2.0	• New format that combines the following into one document: – Anti-HAV IgM Reagent Pack (GEM1230A_EN_US), version 1.0 – Anti-HAV IgM Calibrators (GEMC230), version 1.0 • Added information for the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System • Updated risk and safety statements • References: updated • Glossary of Symbols: updated
2005-09-16	1.0	New format, technically equivalent to PIGEM1230/106.0 with the following minor changes: • Replaced Symbols used with Glossary of Symbols table • Added Revision History, signature box

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

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