VITROS Products Immunodiagnostic

Not Intended for Use in Canada

INSTRUCTIONS FOR USE HBsAg

VITROS Immunodiagnostic Products HBsAg ES Reagent Pack	REF	680 2131
VITROS Immunodiagnostic Products HBsAg ES Calibrator	REF	680 2132

Rx ONLY

Intended Use

For *in vitro* diagnostic use only.

VITROS Immunodiagnostic Products HBsAg ES Reagent Pack

For the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum and plasma (heparin) using the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems.

VITROS Immunodiagnostic Products HBsAg ES Calibrator

For use in the calibration of the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems for the qualitative detection of hepatitis B surface antigen (HBsAg) in human serum and plasma (heparin).

Summary and Explanation of the Test

Hepatitis B is a major public health problem of global importance with an estimated 300 million persistent carriers of the hepatitis B virus (HBV) worldwide. [1] [2] Infection with HBV results in a wide spectrum of acute and chronic liver diseases. Epidemiological studies have clearly linked the virus with the development of hepatocellular carcinoma. [3] HBV infection produces an array of unique antigens and antibodies which follow distinct and individual serological patterns. By monitoring these markers, it is possible not only to diagnose infection, but also to determine the stage of the disease and probable prognosis. HBsAg is the first marker to appear following infection, and is the best indirect indicator of potentially infectious sera.

Principles of the Procedure

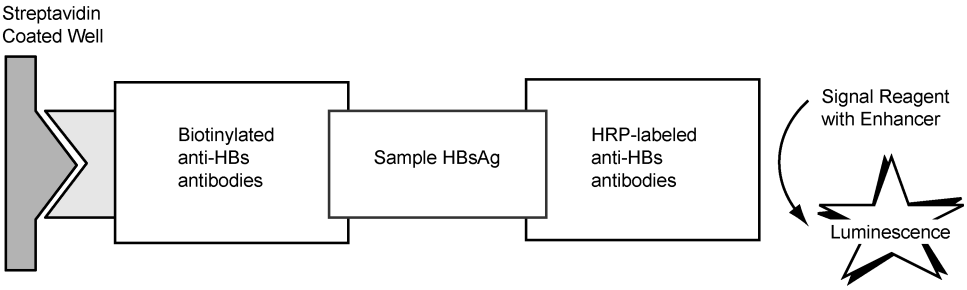
An immunometric immunoassay technique is used, which involves the simultaneous reaction of HBsAg present in the sample with biotinylated antibodies (mouse anti-HBs) and horseradish peroxidase (HRP)-labeled antibody conjugates (mouse anti-HBs) that provide broad reactivity across the a-determinant region. [4] The antigen-antibody complexes are captured by streptavidin on the wells. 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 amount of HRP conjugate bound is directly proportional to the concentration of HBsAg present.

Test Type	System *	Incubation Time	Time to first result	Test Temperature	Reaction Sample Volume
Immunometric	ECi/ECiQ, 3600, 5600, XT 7600	30 minutes	37 minutes	37 °C	80 µL

* Not all products and systems are available in all countries.

Reaction Scheme



Warnings and Precautions

WARNING: Potentially Infectious Material

Human blood products provided as components of the VITROS HBsAg ES Reagent Pack 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 approved methods (enzyme immunoassays). Treat as if capable of transmitting infection.

The VITROS HBsAg ES Calibrator contains human HBsAg purified from donors who were tested individually and who were found to be negative for antibodies to HIV 1+2 and HCV, using approved methods (enzyme immunoassays). The purified HBsAg has been heat inactivated (10 hours at 60 °C). 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 assay components, in accordance with procedures defined by appropriate national biohazard safety guideline or regulation (e.g. CLSI document M29). [6]

WARNING: Contains Kathon or ProClin 200 (CAS 55965-84-9) [7]

The VITROS HBsAg ES Reagent Pack and VITROS HBsAg ES Calibrator contain 1.0% 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.Orthoclinicaldiagnostics.com for the Safety Data Sheets and for Ortho contact information.

WARNING

Reagents

Reagent Pack Contents

1 reagent pack containing:

- 100 coated wells (streptavidin, bacterial; binds ≥3 ng biotin/well)
- 6.0 mL conjugate reagent (HRP-mouse monoclonal anti-HBs, 2.1 µg/mL) in buffer with bovine serum albumin, goat serum and antimicrobial agent

- 8.2 mL biotinylated antibody reagent (biotin-mouse monoclonal anti-HBs, 4.3 µg/mL) in buffer with calf serum 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 HBsAg ES 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 HBsAg ES Calibrator, (human HBsAg ad subtype, inactivated, 2.0 mL; 0.90 ± 0.39 IU/mL [8]) in buffer with antimicrobial agent and bovine serum albumin
- 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 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 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 HBsAg ES Calibrator is supplied ready for use.
- The VITROS HBsAg ES 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 HBsAg ES test uses 80 µL of calibrator for each determination. The VITROS HBsAg ES Calibrator may be used directly on the VITROS Immunodiagnostic and 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 HBsAgES Calibrator is automatically processed in duplicate.

Specimen Collection, Preparation and Storage

Patient Preparation

No special patient preparation is necessary.

Specimens Recommended

- Serum
- Heparin plasma

Note:	The anticoagulant tested had no clinically significant effects on negative samples. However, heparin has been shown to lower the signal/cutoff values in some HBsAg reactive samples. High negative results (0.80–0.99) obtained on samples collected with this anticoagulant should be interpreted accordingly. Supplemental tests may be required.

Specimens Not Recommended

- Do not use turbid specimens. Turbidity in specimens may affect test results.
- Citrate and EDTA plasma are not recommended sample types.

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 HBsAg ES test uses 80 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 cross-contamination and evaporation.
- Follow procedures within your laboratory to avoid cross-contamination of patient specimens.
- 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.
- Serum and plasma samples may be stored for up to 5 days at 2–8 °C (36–46 °F). Serum and plasma samples tested initially and after 4 weeks storage at -20°C (-4 °F) showed no performance differences.
- Avoid repeated freeze-thaw cycles.

Testing Procedure

Materials Provided

- VITROS Immunodiagnostic Products HBsAg ES Reagent Pack
- VITROS Immunodiagnostic Products HBsAg ES Calibrator

Materials Required but Not Provided

- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- Quality control materials such as VITROS Immunodiagnostic Products HBsAg 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.

Default Test Name

The default test name which will appear on patient reports is HBsAg ES. The default short name that will appear on the test selection menus and laboratory reports is HBsAg. 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 compare 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 two quality parameters. Failure to meet either of the defined quality parameter range 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 test reagent 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 HBsAg ES 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 HBsAg Controls are recommended for use with the VITROS Immunodiagnostic and VITROS Integrated Systems. There are 2 VITROS HBsAg Controls (a negative control and a HBsAg positive control). 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 HBsAg 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 HBsAg ES 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.

- 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

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 your acceptable range, investigate the cause before deciding whether to report patient results.
- Refer to published guidelines for general quality control recommendations. [12]

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 automatically calculated by the VITROS Immunodiagnostic and VITROS Integrated Systems.

Result Calculation

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

A result of ≥1.00 indicates a reactive sample and the possible presence of HBsAg.
A result of <0.90 indicates a non-reactive sample, negative for HBsAg.
A result of ≥0.90 and <1.00 indicates a borderline sample.

Interpretation of Results

A sample found borderline or reactive in the VITROS HBsAg ES test should be retested in duplicate to verify its status. Before retesting, the sample should be centrifuged to ensure freedom from cells, cellular debris or fibrin. If results on repeat testing are <0.90 for both replicates, the sample should be considered negative. If either duplicate retest result is ≥0.90, the sample should be tested by supplemental tests to confirm the result. A repeatedly reactive sample confirmed by supplemental tests should be considered positive for HBsAg. In the case of repeatedly borderline results, analysis of follow-up samples is recommended.

Limitations of the Procedure

Known Interferences

The VITROS HBsAg ES test was evaluated for interference consistent with CLSI document EP7. [13] 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

- The results from this or any other diagnostic test 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 or infection with hepatitis B virus. Levels of HBsAg may be undetectable both in early infection and late after infection. In rare cases there may also be a lack of antigen reactivity to the antibodies in HBsAg tests. [2] [4]
- Heterophilic antibodies in serum or plasma samples may cause interference in immunoassays. [14] These antibodies may be present in blood samples from individuals regularly exposed to animals or who have been treated with animal serum products. Results that are inconsistent with clinical observations indicate the need for additional testing.
- Biotin levels in serum remain elevated for up to 24 hours after oral or intravenous biotin administration. [15]
- A high dose hook effect was not observed in samples up to 685,000 IU/mL. [8]
- Do not use quality control materials preserved with azide.

Performance Characteristics

Clinical Performance

Sensitivity

Sensitivity was determined by testing serial dilutions of the WHO 2nd International Standard with 9 determinations using 3 reagent lots. The overall sensitivity of the VITROS HBsAg ES test for the 2nd International Standard was <0.10 IU/mL. [8] A linear regression of the mean VITROS HBsAg ES result versus the calculated concentration of each dilution was used to determine the HBsAg concentration at the cutoff. The mean value for the amount of HBsAg present at the cutoff, determined as described above, was 0.066 IU/mL. [8]

In a population of samples positive for HBsAg, 100% (412/412; 95% C.I., 99.3% to 100%) were found to be reactive in the VITROS HBsAg ES test.

In a study of HBsAg positive human samples containing naturally occurring single and multiple amino acid substitutions across the a-determinant region of HBsAg, 67/67 were found to be reactive in the VITROS HBsAg ES test. [16]

25 positive fresh serum and plasma samples, (≤1 day after sampling), were tested in direct comparison with a commercially available CE-marked test. Both tests gave comparable results.

Specificity

Samples from 5040 presumed healthy blood donors, and 497 clinical samples were tested in the VITROS HBsAg ES test and another commercially available test with the same intended use.

Samples	Number of test samples	Initially Reactive	Repeatedly Reactive	Confirmed Positive
Donor	5,040	10	7	1
Clinical	497	46	40	40

The specificity for the VITROS HBsAg ES test for the donor samples was calculated as 99.88% (6/5039; 95% C.I.; 99.74 to 99.96%) based on repeat reactives.

Potentially Cross-Reacting Subgroups

A total of 282 samples from the following 18 potentially cross-reacting sub-groups were tested in the VITROS HBsAg ES test: hepatitis A IgM, hepatitis B vaccine recipients, non viral liver diseases, HCV, HIV, CMV, EBV, SLE, rheumatoid factor positive, HSV (Herpes Simplex), Parvovirus B19, HEV infection, rubella, syphilis, toxoplasmosis, HTLV, heterophilic antibody/HAMA and recent influenza vaccine recipients. Within these categories, 6 out of the 282 samples were found to give reactive results in the VITROS HBsAg ES test. All 6 of these samples were confirmed as positive for HBsAg.

Precision

VITROS ECi/ECiQ Immunodiagnostic System

Precision was evaluated consistent with NCCLS Protocol EP5. [17] 2 replicates each of 5 samples were tested once per day on at least 20 different days. The experiment was performed using 3 reagent lots on 3 different systems. The data presented are a representation of the product performance.

VITROS 3600 Immunodiagnostic System and VITROS 5600 Integrated System

Precision was evaluated consistent with NCCLS document EP5. [17] Two replicates each of 4 samples 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.

	Units = S/C (Ratio)								
	Mean VITROS HBsAg S/C (Ratio)	Within-run*		Within-calibration**		Within-lab***		No. Observ.	No. Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
ECi/ECiQ System 1	6.55	0.082	1.2	0.113	1.7	0.117	1.8	52	26
	4.09	0.052	1.3	0.129	3.1	0.131	3.2	52	26
	2.43	0.040	1.6	0.143	5.9	0.145	6.0	52	26
	1.37	0.022	1.6	0.093	6.8	0.092	6.7	52	26
	1.04	0.025	2.4	0.096	9.2	0.094	9.1	52	26

	Units = S/C (Ratio)								
	Mean VITROS HBsAg S/C (Ratio)	Within-run*		Within-calibration**		Within-lab***		No. Observ.	No. Days
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
ECi/ECiQ System 2	5.96	0.090	1.5	0.187	3.2	0.218	3.6	54	27
	3.65	0.090	2.5	0.165	4.6	0.178	4.8	54	27
	2.24	0.036	1.6	0.126	5.7	0.140	6.2	54	27
	1.27	0.023	1.8	0.103	8.2	0.113	8.8	54	27
	0.96	0.025	2.7	0.097	10.2	0.102	10.5	54	27
ECi/ECiQ System 3	6.03	0.074	1.2	0.143	2.4	0.165	2.7	54	27
	3.71	0.065	1.8	0.115	3.1	0.127	3.4	54	27
	2.25	0.043	1.9	0.087	3.9	0.096	4.3	54	27
	1.24	0.028	2.3	0.068	5.5	0.071	5.7	52	26
	0.94	0.025	2.6	0.063	6.7	0.065	6.9	54	27
3600	3.37	0.038	1.1	0.093	2.8	0.094	2.8	92	23
	1.80	0.027	1.5	0.066	3.7	0.069	3.8	92	23
	0.64	0.012	1.9	0.045	7.0	0.016	2.5	92	23
	0.08	0.006	7.5	0.012	15.0	0.013	16.3	92	23
5600****	3.37	0.057	1.7	0.107	3.2	0.121	3.6	92	23
	1.78	0.041	2.3	0.076	4.3	0.085	4.8	92	23
	0.61	0.014	2.3	0.045	7.4	0.048	7.9	92	23
	0.07	0.004	5.7	0.012	17.1	0.013	18.6	92	23

* Within-run (repeatability). Between Duplicate precision averaged over all runs

** Within-calibration. Total precision with weighted components of within-run, between–run and between-day variation

*** Within-lab. A measure of the effect of recalibration on total precision, calculated within reagent lot, using data from at least 4 calibrations

**** Performance characteristics for the VITROS 5600 System are applicable to the VITROS XT 7600 System.

Substances that do not Interfere

The VITROS HBsAg ES test was evaluated for interference consistent with CLSI Protocol EP7. [13] Testing was performed using both negative and positive samples. Of the compounds tested, none was found to interfere with the clinical interpretation of the test at the concentrations indicated.

Compound	Concentration	
Bilirubin	0.342 mmol/L	20 mg/dL
Biotin	20.5 nmol/L	500 ng/dL
Hemoglobin	0.310 mmol/L	500 mg/dL
Triolein	33.9 mmol/L	3000 mg/dL

References

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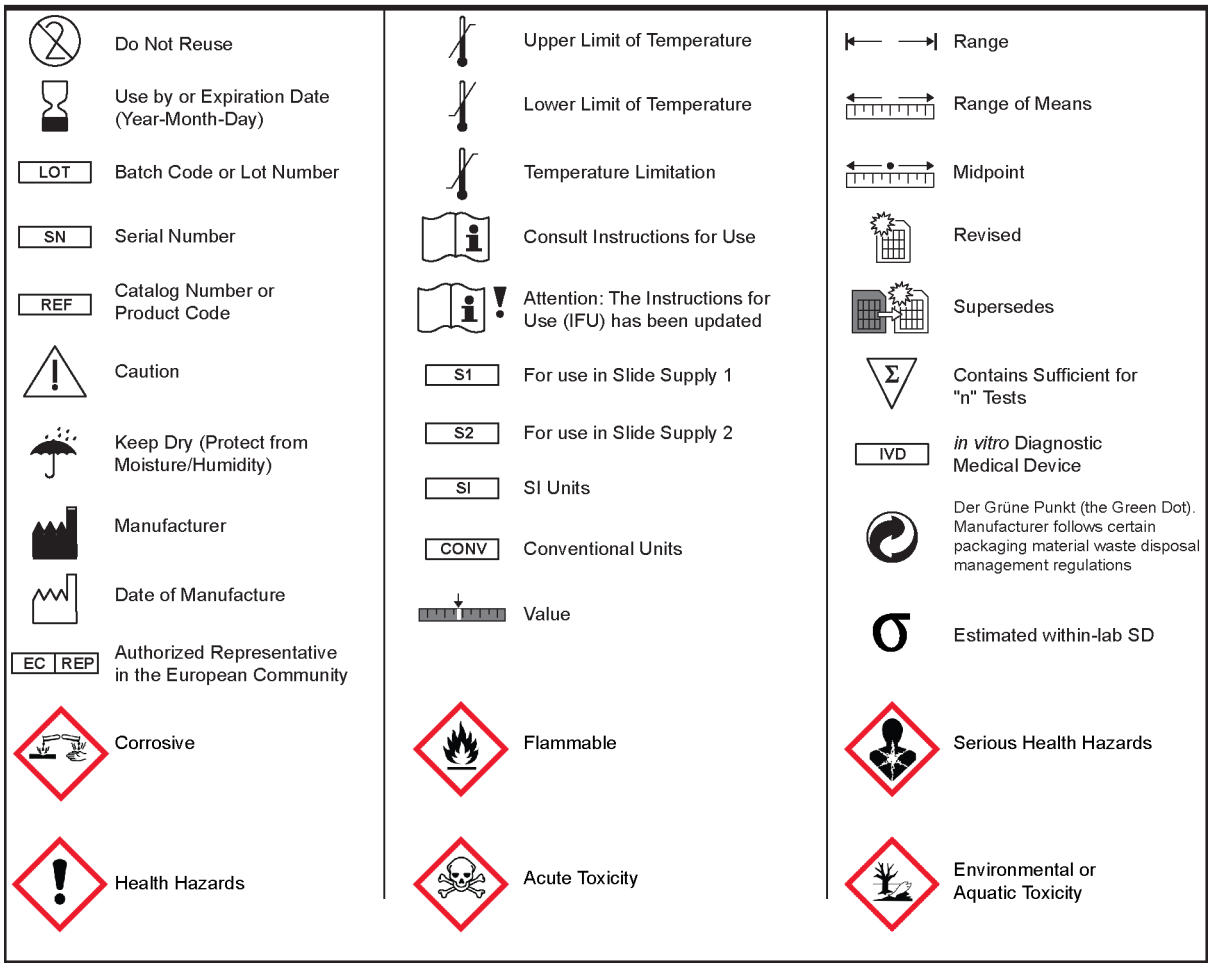
Glossary of Symbols

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



Revision History

Date of Revision	Version	Description of Technical Changes*
2019-09-06	10.1	• Glossary of Symbols: updated • Added EC Representative address
2017-09-29	10.0	• Added information for the VITROS XT 7600 Integrated System • Minor formatting and wording updates • References: updated • Glossary of Symbols: updated

* 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.

Signature

Obsolete Date

Conditions of supply: all supplies are made subject to the standard terms and conditions of Ortho Clinical Diagnostics or its distributors. Copies of these are available on request.

CE
0459

EC REP
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Date: 2022.10.13 12:25:20 EEST
Reason: MoldSign Signature
Location: Moldova

Ortho Clinical Diagnostics

Co-developed with

GRIFOLS