# Anti-HBc IgM

cobas®

**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

REF 11820567 160 — 100 tests

• Indicates analyzers on which the kit can be used

| cobas e 411 |
|---|
| • |

*English*

**Warning**
- Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and use is restricted by or on the order of a physician.
- Assay performance characteristics have not been established in patients under the age of 21, pregnant women, or in populations of immunocompromised or immunosuppressed patients.
- This assay has not been FDA licensed for the screening of blood, plasma and tissue donors.

**Intended use**
The Elecsys Anti-HBc IgM immunoassay is intended for the in vitro qualitative determination of IgM antibodies to hepatitis B core antigen (anti-HBc IgM) in human serum or plasma (potassium EDTA, lithium heparin, sodium heparin, sodium citrate) in adult patients with symptoms of hepatitis or who may be at risk for hepatitis B (HBV) infection. The presence of anti-HBc IgM, in conjunction with other laboratory results and clinical information, is indicative of acute or recent hepatitis B virus (HBV) infection. The Elecsys Anti-HBc IgM immunoassay's performance has not been established for the monitoring of HBV disease or therapy.
The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e** 411 immunoassay analyzer.

**Summary**[1,2,3,4,5,6,7,8,9]
Hepatitis B core antigen (HBcAg) is a non-glycosylated protein (p22) which forms the nucleocapsid (virus core) of the hepatitis B virus. The virus core encloses the HBV-DNA (virus genome) and the DNA-polymerase. In the cytosol of virus-producing hepatocytes the nucleocapsid is enveloped by the hepatitis B surface antigen (HBsAg) to form virions. Free HBcAg or non-enveloped virus cores are not detectable in serum.
IgM antibodies to HBcAg occur in serum during proliferation of active hepatitis B virus and can still be detected weeks to months after viral proliferation has ceased. High anti-HBc IgM concentrations can be found in acute hepatitis B and in attacks during chronic hepatitis B.
Tests for detecting anti-HBc IgM antibodies are used, in conjunction with HBsAg determinations, to identify acute hepatitis B viral infections. An acute attack of hitherto non-diagnosed chronic hepatitis B clinically resembles an acute hepatitis B infection and cannot be distinguished from this with certainty by determining the anti-HBc IgM. Follow-up studies, imaging procedures and liver biopsies are useful in differentiating between these two clinical pictures.

**Test principle**
μ-Capture test principle. Total duration of assay: 18 minutes.
- 1st incubation: Pretreatment of 10 μL of sample (automatically prediluted 1:400 with Elecsys Diluent Universal) with anti-Fdγ reagent to block specific IgG.
- 2nd incubation: Biotinylated monoclonal h-IgM-specific antibodies, HBcAg labeled with a ruthenium complex[a] and streptavidin-coated microparticles are added to the pretreated sample. Anti-HBc IgM antibodies present in the sample react with the ruthenium-labeled HBc antigen and the biotinylated anti-h-IgM to form a sandwich complex which becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the Elecsys software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by anti-HBc IgM calibration.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

**Reagents - working solutions**

| | |
|---|---|
| M | Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative. |
| R1 | Pretreatment anti-HBc IgM (gray cap), 1 bottle, 10 mL: Sample pretreatment reagent: Anti-human-Fdγ-antibody (sheep) > 0.05 mg/mL; phosphate buffer 100 mmol/L, pH 7.4; preservative. |
| R2 | Anti-h-IgM-Ab~biotin; HBcAg~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL: Biotinylated monoclonal anti-h-IgM antibody (mouse) > 600 ng/mL; HBcAg (*E. coli*, rDNA), labeled with ruthenium complex > 200 ng/mL; phosphate buffer 100 mmol/L, pH 7.4; preservative. |
| Cal1 | Negative calibrator 1 (white cap), 2 bottles of 1.0 mL each: Human serum, preservative. |
| Cal2 | Positive calibrator 2 (black cap), 2 bottles of 1.0 mL each: Anti-HBc IgM (human) > 100 PEI U/mL[b] in human serum; preservative. |

b) Paul-Ehrlich-Institute units

**Precautions and warnings**
For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.
All human material should be considered potentially infectious.
The negative calibrator (Cal1) has been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.
Positive calibrator (Cal2): Materials of human origin were tested for HIV and hepatitis C. The findings were negative. The serum containing anti-HBc IgM was inactivated using β-propiolactone and UV-radiation.
However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[10,11]
The reagents may not be used after the stated expiration date.
Avoid foam formation in all reagents and sample types (specimens, calibrators, and controls).

**Reagent handling**
The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.
All information required for correct operation is read in from the respective reagent barcodes.
The calibrators are supplied ready-for-use in bottles compatible with the system. The calibrators should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store at 2-8 °C. Ensure that no calibrator solution is left in the opened snap-cap. Due to possible evaporation effects, not more than 5 calibration procedures per calibrator bottle set should be performed.

**Storage and stability**
Store at 2-8 °C.
Store the Elecsys Anti-HBc IgM reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

| Stability of the reagent rack pack: | |
|---|---|
| unopened at 2-8 °C | up to the stated expiration date |
| M, R1, R2 after opening at 2-8 °C | 8 weeks |
| on the analyzer | 8 weeks if stored continuously onboard |

| Stability of the calibrators: | |
|---|---|
| Cal1, Cal2 after opening at 2-8 °C | 6 weeks |
| on the analyzer | up to 5 hours |

# Anti-HBc IgM

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**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

Store the calibrators **upright**! Ensure that no calibration solution is left in the opened snap-cap.

**Specimen collection and preparation**

Serum should be collected using standard sampling tubes or tubes containing separating gel.
Only the specimens listed below were tested and found acceptable.
Lithium heparin, sodium heparin, $K_2$-EDTA and sodium citrate plasma.
Serum and plasma should be separated from the cells within 2 hours from the time of collection. Test samples as soon as possible after collection.
Store samples at 2-8 °C if not tested immediately.
Serum and plasma samples are stable for 7 days at 2-8 °C and for 3 months at -20 °C. The samples may be frozen and thawed up to 6 times.
The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.
Do not use samples and controls stabilized with azide.
Centrifuge samples containing precipitates and previously frozen samples before performing the assay.
Ensure the samples, calibrators and controls are at ambient temperature (20-25 °C) before measurement.
Due to possible evaporation effects, samples, calibrators and controls on the analyzer should be analyzed/measured within 2 hours.

**Materials provided**

See "Reagents - working solutions" section for reagents.

**Materials required (but not provided)**

- REF 11876333160, PreciControl Anti-HBc IgM, 8 x 1.0 mL each of PreciControl Anti-HBc IgM 1 and 2
- REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment
- **cobas e** 411 analyzer

Accessories for **cobas e** 411 analyzer:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips
- REF 11298500160, Elecsys SysClean, 5 x 100 mL system cleaning solution

**Assay**

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.
Resuspension of the microparticles takes place automatically prior to use.
Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

The calibrators Cal1 and Cal2 should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store at 2-8 °C. Ensure that no calibration solution is trapped in the opened snap-cap. Because of possible evaporation effects, not more than 5 calibration procedures per calibrator bottle set should be performed.

**Calibration**

Traceability: This method has been standardized against the "HBc Reference Serum 84 (anti-HBc IgM)" of the Paul-Ehrlich-Institute, Langen (Germany).

*Calibration frequency:* Calibration must be performed once per reagent lot using Elecsys Anti-HBc IgM Cal1, Cal2, and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).
Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the defined limits
- more frequently when this is required by pertinent regulations

Range for the electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (Cal1): 600-3500
Positive calibrator (Cal2): 24000-150000

**Quality control**

For quality control, use Elecsys PreciControl Anti-HBc IgM.
Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration. The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits.
Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.
If necessary, repeat the measurement of the samples concerned.
Follow the applicable government regulations and local guidelines for quality control.

**Note:**

For technical reasons re-assigned target values valid for a specific reagent and control lot combination only, must be entered manually. Therefore, always consider the value sheet included in the rackpack or PreciControl kit to make sure that the correct target values are used.
When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

**Results**

The analyzer automatically calculates the cutoff based on the measurement of Cal1 and Cal2.
The result of a sample is given in the form of a cutoff index (signal sample/cutoff) with a result interpretation of:

- "non-reactive" (COI < 0.9)
- "border"[c] (0.9 ≤ COI < 1.1)
- "reactive" (COI ≥ 1.1)

c) border = borderline

*Interpretation of results:*

| Initial Elecsys Anti-HBc IgM assay result | | | |
|---|---|---|---|
| COI | Result | Interpretation of results | Retest procedure |
| < 0.9 | Non-reactive[d] | No IgM antibodies to HBc were detected | No retest required |
| 0.9 ≤ COI < 1.1 | Border | Borderline zone (undetermined) | Retest in duplicate with the Elecsys Anti-HBc IgM assay |
| ≥ 1.1 | Reactive | IgM antibodies to HBc detected | Presumptive evidence of IgM antibodies to HBc. Follow CDC recommendations for ancillary testing. No retest required. |

d) Please note: A negative anti-HBc IgM result can indicate that the patient is either susceptible to HBV infection due to no past exposure, is chronically infected with HBV, or is immune to HBV infection due to a resolved past infection or vaccination.

# Anti-HBc IgM

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**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

| Final Elecsys Anti-HBc IgM assay result | | | |
|---|---|---|---|
| Initial result (COI) | Result after retest (COI) | Final results | Interpretation of results |
| < 0.9 | No retest required | NON-REACTIVE[e] | IgM antibodies to HBc were not detected; does not exclude the possibility of exposure to HBV |
| 0.9 ≤ COI < 1.1 | If 2 of the 3 results have a COI < 1.0 | NON-REACTIVE | IgM antibodies to HBc were not detected; does not exclude the possibility of exposure to HBV |
| | If 2 of the 3 results have a COI ≥1.0 | REACTIVE | Presumptive evidence of IgM antibodies to HBc. Follow CDC recommendations for ancillary testing. |
| ≥ 1.1 | No retest required | REACTIVE | Presumptive evidence of IgM antibodies to HBc. Follow CDC recommendations for ancillary testing. |

e) Please note: A negative anti-HBc IgM result can indicate that the patient is either susceptible to HBV infection due to no past exposure, is chronically infected with HBV, or is immune to HBV infection due to a resolved past infection or vaccination.

**Cutoff determination**

The cutoff value was established with in-house studies by measuring a panel of 168 samples. For the Elecsys Anti-HBc IgM immunoassay, the cutoff (cutoff index 1.0) was set to approx. 45 PEI U/mL.
A Receiver Operator Curve (ROC) analysis was used to verify the cutoff. Validation of the cutoff was performed by external clinical studies.

**Limitations - Interference**

Current methods for the detection of IgM antibodies to hepatitis B core (HBc) antigen may not detect all infected individuals. A non-reactive test result does not exclude the possibility of exposure to HBV.
Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.
Drug interference studies were performed in vitro, and may not assess the potential interferences that might be seen after the drugs are metabolized in vivo.
A reactive anti-HBc IgM result does not exclude co-infection by another hepatitis virus.
The detection of anti-HBc IgM antibodies indicates either an acute infection with hepatitis B virus or an acute attack in an individual with chronic Hepatitis B infection.
False negative results may occur due to antibody levels below the detection limit of this assay or if the patient's antibodies do not react with the antigen used in this test.
False positive results due to non-specific reactivity cannot be ruled out with the Elecsys Anti-HBc IgM assay.
In rare cases, interference due to extremely high titers of antibodies to immunological components, streptavidin and ruthenium can occur.
Results obtained with the Elecsys Anti-HBc IgM immunoassay may not be used interchangeably with values obtained with different manufacturers' assay methods.
For diagnostic purposes, the results obtained should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

**Endogenous interferences**

To evaluate the effect of elevated levels of hemoglobin, bilirubin, intralipid, biotin and total protein on the Elecsys Anti-HBc IgM assay, the following samples were tested. The results are presented below:

| Interferent tested | No interference up to: |
|---|---|
| Hemoglobin | 2 g/dL or 1.2 mmol/L |
| Bilirubin | 25 mg/dL or 428 µmol/L |
| Lipemia | 1000 mg/dL |
| Biotin | 100 ng/mL or 409 nmol/L |
| Total protein | 12 g/dL |

**Limits and ranges**

Detection limit: ≤ 3.0 PEI-U/mL
The detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the negative calibrator (negative calibrator + 2 SD, repeatability study, n = 21).

**Dilution**

Use Elecsys Diluent Universal for automatic sample predilution.

**Specific performance data**

Representative performance data on the analyzer are given below. Results obtained in individual laboratories may differ.

**Precision**

Precision was determined with 1 **cobas e** 411 analyzer at 1 site using 1 lot of Elecsys reagent to test 4 serum pools and 2 controls in accordance with CLSI (Clinical and Laboratory Standards Institute) guideline EP5-A2. The following results were obtained.

| **cobas e** 411 analyzer | | | | | | |
|---|---|---|---|---|---|---|
| | | Repeatability[f] | | | Intermediate precision[g] | |
| Sample | N | Mean COI[h] | SD COI | CV % | SD COI | CV % |
| HS[i], negative | 48 | 0.101 | 0.001 | 1.1 | 0.003 | 3.2 |
| HS, high negative | 48 | 0.944 | 0.034 | 3.7 | 0.050 | 5.5 |
| HS, low positive | 48 | 1.23 | 0.052 | 4.2 | 0.090 | 7.3 |
| HS, positive | 48 | 2.60 | 0.127 | 4.9 | 0.160 | 6.2 |
| PC[j]A-HBCIGM1 | 48 | 0.104 | 0.001 | 0.95 | 0.003 | 2.4 |
| PC A-HBCIGM2 | 48 | 3.06 | 0.211 | 6.9 | 0.220 | 7.2 |

f) Repeatability = within-run precision
g) Intermediate precision = within-laboratory
h) COI = cutoff index
i) HS = human serum
j) PC = PreciControl

**Reproducibility study**

Precision was further evaluated incorporating between-run, between-day, between-lot, and between-site variation. A reproducibility study was conducted following CLSI EP5-A2 and CLSI EP15-A2 at 3 sites incorporating a 4 member panel consisting of 3 near cutoff human serum pools, 1 moderately reactive human serum pool, and PreciControl Anti-HBc IgM 1 and 2 that were assayed for 5 days, 2 runs per day, 3 replicates per run. The analysis of data was based on guidance from CLSI documents EP5-A2 and EP15-A2. Data from all 3 reagent lots were combined to achieve SD and percent CV for repeatability (within-run), between-run, between-day, between-lot, between-site and reproducibility. The overall imprecision data are summarized in the following table:

| Elecsys Anti-HBc IgM reproducibility on the **cobas e** 411 analyzer | | | | | | | |
|---|---|---|---|---|---|---|---|
| Sample | | HS1 | HS2 | HS3 | HS4 | PC[k]1 | PC2 |
| N | | 180 | 180 | 180 | 180 | 180 | 180 |
| Mean | COI | 0.799 | 1.04 | 1.48 | 1.19 | 0.093 | 3.11 |
| Repeatability | SD | 0.032 | 0.056 | 0.070 | 0.047 | 0.003 | 0.155 |
| | % CV | 4.0 | 5.4 | 4.7 | 4.0 | 3.3 | 5.0 |
| Between-run | SD | 0.015 | 0.018 | 0.016 | 0.036 | 0.002 | 0.102 |
| | % CV | 1.9 | 1.8 | 1.1 | 3.0 | 1.7 | 3.3 |
| Between-day | SD | 0.021 | 0.014 | 0.038 | 0.021 | 0.001 | 0.000[l] |
| | % CV | 2.6 | 1.4 | 2.5 | 1.8 | 1.3 | 0.0 |
| Between-lot | SD | 0.037 | 0.030 | 0.038 | 0.036 | 0.022 | 0.090 |
| | % CV | 4.6 | 2.9 | 2.5 | 3.0 | 23.8 | 2.9 |
| Between-site | SD | 0.014 | 0.028 | 0.048 | 0.039 | 0.000[l] | 0.068 |
| | % CV | 1.8 | 2.7 | 3.2 | 3.3 | 0.0 | 2.2 |
| Reproducibility | SD | 0.057 | 0.073 | 0.101 | 0.082 | 0.023 | 0.217 |
| | % CV | 7.1 | 7.0 | 6.8 | 6.9 | 24.2 | 7.0 |

k) PC = PreciControl Anti-HBc IgM
l) SD of zero due to variance contributed by particular component was below stated significant figure.

# Anti-HBc IgM

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**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

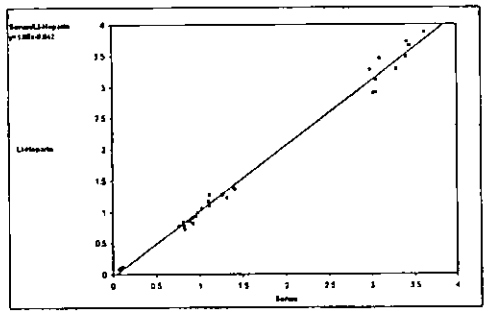
**Drug interferences**

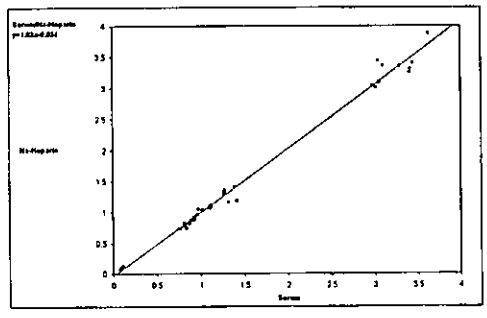
A drug interference study was performed with 18 common therapeutic drugs. Each drug was tested three-fold spiked into a negative, a low positive and a positive sample.
Each drug was found to be non-interfering at the following claimed concentrations:

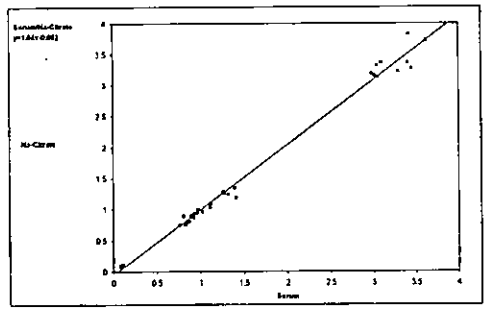
| Compound | Concentration |
|---|---|
| Acetyl cysteine | 150 mg/L |
| Ampicillin-Na | 1000 mg/L |
| Ascorbic acid | 300 mg/L |
| Ca-Dobesilate | 200 mg/L |
| Cyclosporine | 5 mg/L |
| Cefoxitin | 2500 mg/L |
| Heparin | 5000 U |
| Intralipid | 10000 mg/L |
| Levodopa | 20 mg/L |
| Methyldopa+ 1.5 | 20 mg/L |
| Metronidazole | 200 mg/L |
| Phenylbutazone | 400 mg/L |
| Tetracycline | 50 mg/L |
| Acetylsalicyclic acid | 1000 mg/L |
| Rifampicin | 60 mg/L |
| Acetaminophen | 200 mg/L |
| Ibuprofen | 500 mg/L |
| Theophylline | 100 mg/L |

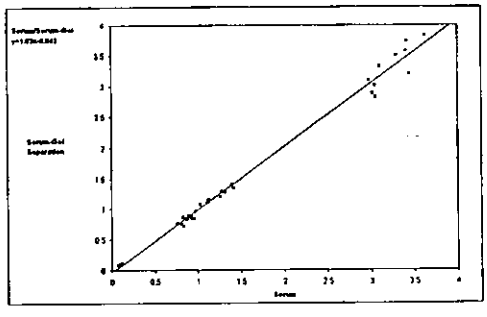
**Matrix effects**

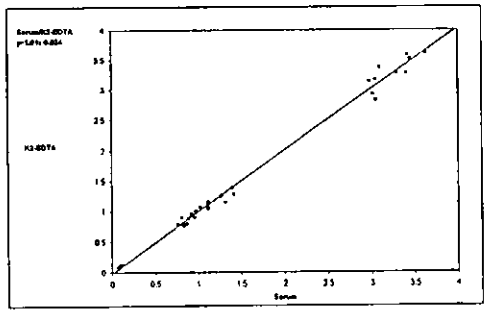
Studies were conducted to evaluate the suitability of the following 5 types of blood collection tubes: serum/gel separation tubes, lithium heparin plasma, sodium heparin plasma, $K_2$-EDTA plasma and sodium citrate plasma. Samples were collected into matched serum and plasma collection tubes and assayed in triplicate. The study was conducted using negative, high-negative, low-positive and positive samples for anti-HBc IgM. The studies support the use of serum/gel separation tubes and the following plasma types: lithium heparin plasma, sodium heparin plasma, $K_2$-EDTA plasma and sodium citrate plasma. The results are shown below:











**Analytical specificity**

A study was conducted to evaluate the Elecsys Anti-HBc IgM assay for potential cross-reactivity in specimens from individuals with medical conditions unrelated to hepatitis B infection. All specimens in the study were evaluated with the Elecsys Anti-HBc IgM and the reference assay. The results are summarized in the following table:

# Anti-HBc IgM

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**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

**Reactivity of the Elecsys Anti-HBc IgM assay in individuals with medical conditions unrelated to hepatitis B infection**

| Category | anti-HBc IgM reference assay | | | | Total samples |
|---|---|---|---|---|---|
| | RX[m] | | NR[n] | | |
| | Elecsys Anti-HBc IgM assay | | | | |
| | RX | NR | RX | NR | |
| Autoimmune (AMA, ANA, SLE) | 0 | 0 | 0 | 12 | 12 |
| Cytomegalovirus (anti-CMV) | 0 | 0 | 0 | 11 | 11 |
| Epstein-Barr virus (anti-EBV) | 0 | 0 | 0 | 9 | 9 |
| *E. coli* infection | 0 | 0 | 0 | 9 | 9 |
| Flu vaccination | 0 | 0 | 0 | 10 | 10 |
| Hepatitis A virus (anti-HAV total) | 0 | 0 | 0 | 9 | 9 |
| HAV vaccination | 0 | 0 | 0 | 9 | 9 |
| HBV vaccination | 0 | 0 | 0 | 7 | 7 |
| Hepatitis C virus (anti-HCV) | 0 | 0 | 0 | 11 | 11 |
| Hepatitis D virus (anti-HDV) | 0 | 0 | 0 | 12 | 12 |
| Hepatitis E virus (anti-HEV) | 0 | 0 | 0 | 10 | 10 |
| Human immunodeficiency virus (anti-HIV-1) | 0 | 0 | 0 | 12 | 12 |
| Herpes Simplex virus (anti-HSV) | 0 | 0 | 0 | 12 | 12 |
| HTLV I/II | 0 | 0 | 0 | 12 | 12 |
| Non-viral liver disease | 0 | 0 | 0 | 33 | 33 |
| Parvovirus $B_{19}$ infection | 0 | 0 | 0 | 11 | 11 |
| Pregnancy | 0 | 0 | 0 | 11 | 11 |
| Rheumatoid factor | 0 | 0 | 0 | 14 | 14 |
| Rubella (anti-Rubella) | 0 | 0 | 0 | 9 | 9 |
| Syphilis | 0 | 0 | 0 | 10 | 10 |
| Toxoplasmosis (anti-Toxo) | 0 | 0 | 0 | 14 | 14 |
| Varicella zoster (Anti-VZV) | 0 | 0 | 0 | 9 | 9 |
| Total | 0 | 0 | 0 | 256 | 256 |

m) RX = reactive
n) NR = non-reactive

**Seroconversion sensitivity**

Seroconversion sensitivity of the Elecsys Anti-HBc IgM assay has been shown by testing 7 commercially-sourced seroconversion panels in comparison to a reference anti-HBc IgM immunoassay. The comparison of the seroconversion detection between the 2 assays is summarized in the following table:

| Panel ID | Reference anti-HBc IgM | | Elecsys Anti-HBc IgM | | Difference in days to Elecsys Anti-HBc IgM reactivity (Reference - Elecsys) |
|---|---|---|---|---|---|
| | NR | RX | NR | RX | |
| 6278 | 37 | 41 | 37 | 41 | 0 |
| 6281 | 41 | 43 | 41 | 43 | 0 |
| 9092 | 82 | 89 | 82 | 89 | 0 |
| 9093 | 42 | 49 | 56 | 74 | 25 (2 draws) |
| PHM933 | 16 | 144 | 16 | 144 | 0 |
| PHM934 | 14 | 84 | 14 | 84 | 0 |
| PHM935(M2) | 66 | 68 | 66 | 68 | 0 |

The Elecsys Anti-HBc IgM assay was reactive in the same bleed as the reference assay in 6 of the 7 panels tested. The Elecsys Anti-HBc IgM assay was reactive 2 draws later than the reference assay in 1 panel, wherein both draws yielded near cutoff testing in both assays before conversion.

**Summary of clinical performance**

A multicenter study was conducted to evaluate the ability of the Elecsys Anti-HBc IgM assay to detect anti-HBc IgM antibodies in specimens from an intended use population.

Of the 1582 specimens tested in the Elecsys Anti-HBc IgM clinical study, 1338 specimens were obtained from individuals at risk of HBV infection due to lifestyle, behavior, occupation, disease state or known exposure event; and 244 specimens were obtained from individuals with signs and symptoms of a hepatitis infection.

The 1582 specimens were collected from 3 collection sites located in California (49.6 %), Florida (19.9 %), and Georgia (30.5 %). A demographic summary of the overall specimen population by age and race/ethnic group is provided in the following tables.

**Demographic summary of overall specimen population by age**

| | Overall | | Asymptomatic | | Symptomatic | |
|---|---|---|---|---|---|---|
| Age group | N | % | N | % | N | % |
| 21 - 30 | 142 | 8.98 | 130 | 9.72 | 12 | 4.92 |
| 31 - 40 | 248 | 15.7 | 220 | 16.4 | 28 | 11.5 |
| 41 - 50 | 674 | 42.6 | 568 | 42.5 | 106 | 43.4 |
| 51 - 60 | 459 | 29.0 | 372 | 27.8 | 87 | 35.7 |
| 61 - 70 | 57 | 3.60 | 46 | 3.44 | 11 | 4.51 |
| 71 - 80 | 2 | 0.13 | 2 | 0.15 | 0 | 0.00 |
| Total | 1582 | 100 | 1338 | 100 | 244 | 100 |

**Demographic summary of overall specimen population by race**

| | Overall | | Asymptomatic | | Symptomatic | |
|---|---|---|---|---|---|---|
| Race | N | % | N | % | N | % |
| African American/Black | 1166 | 73.7 | 997 | 74.5 | 169 | 69.3 |
| American Indian/ Alaska Native | 11 | 0.70 | 11 | 0.82 | 0 | 0.00 |
| Asian | 14 | 0.89 | 10 | 0.75 | 4 | 1.64 |
| Caucasian/White | 384 | 24.3 | 314 | 23.5 | 70 | 28.7 |
| Pacific Islander | 2 | 0.13 | 2 | 0.15 | 0 | 0.00 |
| Other | 4 | 0.25 | 4 | 0.30 | 0 | 0.00 |
| Unknown | 1 | 0.06 | 0 | 0.00 | 1 | 0.41 |
| Total | 1582 | 100 | 1338 | 100 | 244 | 100 |

Of the 1582 at risk subjects, 388 (24.5 %) were female and 1194 (75.5 %) were male. The mean age of the subjects was 45.8 years (age range: 21 - 75 years). Testing of the specimens was performed at 4 clinical testing sites located in St. Louis, MO, Ft. Lauderdale, FL, Boston, MA and South Bend, IN.

To supplement the clinical study, a total of 148 samples from subjects with increased risk for hepatitis due to living in areas endemic for hepatitis or who were potential candidates for acute disease or reactive anti-HBc IgM status were tested with the Elecsys anti-HBc IgM assay on the **cobas e 411** analyzer. Results were compared to the reference assay. The reference method value for samples found to be reactive by either method was determined by consensus of results from the reference method and 2 additional FDA approved anti-HBc IgM assays (2 out of 3).

**Results by specimen classification**

HBV classifications were determined based on the constellation of test results from an FDA-approved HBV marker panel. Using the reference anti-HBc IgM assay, the specimens were assigned an HBV status based on the algorithm provided in the following table:

# Anti-HBc IgM

cobas®

**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

**Serological classification by FDA-approved HBV panel**

| | HBsAg | HBeAg | anti-HBc IgM | anti-HBc | anti-HBe | anti-HBs |
|---|---|---|---|---|---|---|
| Acute | (+) | (+) | (-) | (-) | (-) | (-) |
| Acute | (+) | (-) | (-) | (-) | (-) | (-) |
| Acute | (+) | (+) | (+) | (+) | (-) | (-) |
| Acute | (+) | (-) | (+) | (+) | (+) | (-) |
| Acute | (+) | (-) | (+) | (+) | (-) | (-) |
| Acute (late) | (+) | (-) | (+) | (+) | (+) | (+) or eq |
| Chronic | (+) > 6 mo. | | | | | |
| Chronic | (+) > 6 mo. | (-) | (-) | (+) | (+) | (-) |
| Chronic | (+) > 6 mo. | (+) | (-) | (+) | (-) | (-) |
| Chronic | (+) | (+) | (-) | (+) | (-) | (-), (+), eq |
| Chronic | (+) | (-) | (-) | (+) | (+) | (-), (+) |
| Chronic | (+) | (-) | (-) | (+) | (+) | (+) |
| Chronic | (+) | (+) | (-) | (+) | (+) | (-) |
| Chronic | (+) | (+) | (+) | (+) | (+) | (+) |
| Early recovery | (-) | (-) | (+) | (+) | (+) or (-) | (-) |
| Early recovery | (-) | (-) | (+) | (+) | (+) | (+) |
| Early recovery | (-) | (-) | (-) | (+) | (+), eq, (-) | (-) |
| Recovery | (-), rr uncnf | (-) | (-) | (+) | (+) | (+) or eq |
| Recovery | (-) | (-) | (-) | (+) | eq | (+) |
| Recovery | (-) | (-) | (-) | (-) | (+) | (+) |
| Recovered or immune due to natural infection | (-) | (-) | (-) | (+) | (-) | (+) or eq |
| HBV vaccine response | (-), rr uncnf | (-) | (-) | (-) | (-) | (+) |
| HBV vaccination response (?) | (-) | (-) | (-) | (-) | (-) | eq |
| Not previously infected | (-) | (-) | (-) | (-) | (-) | (-) |
| Not previously infected | rr uncnf | (-) | (-) | (-) | (-) | (-) |
| Not interpretable | rr uncnf | (+) | (+) | (+) | (-) | (-) |
| Not interpretable | (-) | (-) | (-) | nd | (+) | (-) |
| Not interpretable | (-) | (-) | (-) | (-) | (+) or eq | (-) |
| Not interpretable | (-) | (-) | (-) | (-) | eq | (+) |
| Not interpretable | (-) | (+) | (-) | (-) | (-) | (+) or (-) |
| Not interpretable | qns | (-) | (-) | (-) | (-) | (-) |
| Not interpretable | rr uncnf | (+) | (-) | (+) | (-) | (-) |
| Not interpretable | (+) | (-) | (-) | (-) | (-) | (+) |

nd = not detected
eq = equivocal or indeterminate or borderline
rr uncnf = repeatedly reactive: did not confirm
qns = incomplete or unconfirmed

**Results of HBV classification**

***Asymptomatic at risk population***

The following table compares Elecsys Anti-HBc IgM results on the **cobas e** 411 analyzer with the results obtained with the reference anti-HBc IgM assay for specimens which have been serologically classified in the asymptomatic at risk of HBV infection cohort.

*Comparison of Elecsys Anti-HBc IgM assay on the* **cobas e** 411 *analyzer to the reference assay results by HBV classification in the asymptomatic at risk cohort*

| HBV classification | Reference anti-HBc IgM assay results | | | | Total |
|---|---|---|---|---|---|
| | + | | - | | |
| | Elecsys Anti-HBc IgM test results | | | | |
| | + | - | + | - | |
| Acute | 3 | 0 | 0 | 3 | 6 |
| Chronic | 0 | 0 | 0 | 35 | 35 |
| Early recovery | 5 | 0 | 0 | 96 | 101 |
| Recovery | 0 | 0 | 0 | 258 | 258 |
| Recovered | 0 | 0 | 0 | 95 | 95 |
| HBV vaccination | 0 | 0 | 0 | 293 | 293 |
| Not previously infected | 0 | 0 | 0 | 537 | 537 |
| Not interpretable | 0 | 0 | 0 | 13 | 13 |
| Total | 8 | 0 | 0 | 1330 | 1338 |

The table below summarizes the percent agreement between the Elecsys Anti-HBc IgM assay and the reference assay with clinically classified samples in the asymptomatic at risk cohort. The table also provides the upper and lower 95 % exact confidence bounds.

*Positive and negative percent agreement in the asymptomatic at risk population*

| HBV classification | Positive percent agreement (n/N) | 95 % Exact confidence interval | Negative percent agreement (n/N) | 95 % Exact confidence interval |
|---|---|---|---|---|
| Acute | 100 (3/3) | 29.2 - 100 | 100 (3/3) | 29.2 - 100 |
| Chronic | N/A | N/A | 100 (35/35) | 90.0 - 100 |
| Early recovery | 100 (5/5) | 47.8 - 100 | 100 (96/96) | 96.2 - 100 |
| Recovery | N/A | N/A | 100 (258/258) | 96.7 - 100 |
| Recovered | N/A | N/A | 100 (95/95) | 96.2 - 100 |
| HBV vaccination | N/A | N/A | 100 (293/293) | 98.8 - 100 |
| Not previously infected | N/A | N/A | 100 (537/537) | 99.3 - 100 |
| Not interpretable | N/A | N/A | 100 (13/13) | 75.3 - 100 |
| Total | 100 (8/8) | 63.1 - 100 | 100 (1330/1330) | 99.7 - 100 |

The positive percent agreement between the Elecsys Anti-HBc IgM assay results and the HBV infected status for the asymptomatic at risk for HBV infection population (n = 1338) was 100 % (8/8) with a 95 % confidence interval of 63.1-100 %. The negative percent agreement between the Elecsys Anti-HBc IgM assay results with the not HBV infected status was 100 % (1330/1330) with a 95 % confidence interval of 99.7-100 %.

# Anti-HBc IgM

cobas®

**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

***Symptomatic at risk population***

The following table compares Elecsys Anti-HBc IgM results on the **cobas e** 411 analyzer with the results obtained with the reference anti-HBc IgM assay for specimens which have been serologically classified in the symptomatic at risk for HBV infection cohort.

*Comparison of Elecsys Anti-HBc IgM assay on the* **cobas e** *411 analyzer to the reference assay results by HBV classification in the symptomatic at risk cohort*

| HBV classification | Reference anti-HBc IgM assay results | | | | Total |
|---|---|---|---|---|---|
| | + | | - | | |
| | Elecsys Anti-HBc IgM test results | | | | |
| | + | - | + | - | |
| Acute | 1 | 0 | 0 | 1 | 2 |
| Chronic | 0 | 0 | 0 | 11 | 11 |
| Early recovery | 2 | 0 | 0 | 26 | 28 |
| Recovery | 0 | 0 | 1 | 33 | 34 |
| Recovered | 0 | 0 | 0 | 25 | 25 |
| HBV vaccination | 0 | 0 | 0 | 45 | 45 |
| Not previously infected | 0 | 0 | 0 | 93 | 93 |
| Not interpretable | 1 | 0 | 0 | 5 | 6 |
| Total | 4 | 0 | 1 | 239 | 244 |

The table below summarizes the percent agreement between the Elecsys Anti-HBc IgM assay on the **cobas e** 411 analyzer and the reference assay with clinically classified samples in the symptomatic at risk cohort. The table also provides the upper and lower 95 % exact confidence bounds.

*Positive and negative percent agreement in the symptomatic at risk population*

| HBV classification | Positive percent agreement (n/N) | 95 % Exact confidence interval | Negative percent agreement (n/N) | 95 % Exact confidence interval |
|---|---|---|---|---|
| Acute | 100 (1/1) | 2.50 - 100 | 100 (1/1) | 2.50 - 100 |
| Chronic | N/A | N/A | 100 (11/11) | 71.5 - 100 |
| Early recovery | 100 (2/2) | 15.8 - 100 | 100 (26/26) | 86.8 - 100 |
| Recovery | N/A | N/A | 97.1 (33/34) | 84.7 - 99.9 |
| Recovered | N/A | N/A | 100 (25/25) | 86.3 - 100 |
| HBV vaccination | N/A | N/A | 100 (45/45) | 92.1 - 100 |
| Not previously infected | N/A | N/A | 100 (93/93) | 96.1 - 100 |
| Not interpretable | 100 (1/1) | 2.50 - 100 | 100 (5/5) | 47.8 - 100 |
| Total | 100 (4/4) | 39.8 - 100 | 99.6 (239/240) | 97.7 - 100 |

The positive percent agreement between the Elecsys Anti-HBc IgM assay results and the HBV infected status for the symptomatic at risk population (n = 244) was 100 % (4/4) with a 95 % confidence interval of 39.8-100 %. The negative percent agreement between the Elecsys Anti-HBc IgM assay results with the not HBV infected status was 99.6 % (239/240) with a 95 % confidence interval of 97.7-100 %.

***Endemic/acute/reactive population***

The following table compares Elecsys Anti-HBc IgM results on the **cobas e** 411 analyzer with the results obtained with the reference anti-HBc IgM assay for specimens from subjects with increased risk for hepatitis due to living in areas endemic for hepatitis or who were potential candidates for acute disease or reactive anti-HBc IgM status. The specimens were acquired from prospective studies or retrospective collections from commercial vendors.

*Comparison of Elecsys Anti-HBc IgM assay on the* **cobas e** *411 analyzer to the reference assay results by HBV classification in the endemic/acute/reactive cohort*

| HBV classification | Reference anti-HBc IgM assay results | | | | Total |
|---|---|---|---|---|---|
| | + | | - | | |
| | Elecsys Anti-HBc IgM test results | | | | |
| | + | - | + | - | |
| Acute | 32 | 1 | 0 | 13 | 46 |
| Chronic | 1 | 0 | 1 | 93 | 95 |
| Early recovery | 4 | 0 | 0 | 0 | 4 |
| HBV vaccination | 0 | 0 | 0 | 1 | 1 |
| Not previously infected | 0 | 0 | 0 | 2 | 2 |
| Total | 37 | 1 | 1 | 109 | 148 |

| HBV classification | Positive percent agreement (n/N) | 95 % Exact confidence interval | Negative percent agreement (n/N) | 95 % Exact confidence Interval |
|---|---|---|---|---|
| Acute | 97.0 (32/33) | 84.2 - 99.9 | 100 (13/13) | 75.3 - 100 |
| Chronic | 100 (1/1) | 2.50 - 100 | 98.9 (93/94) | 94.2 - 100 |
| Early recovery | 100 (4/4) | 39.8 - 100 | N/A | N/A |
| HBV vaccination | N/A | N/A | 100 (1/1) | 2.50 - 100 |
| Not previously infected | N/A | N/A | 100 (2/2) | 15.8 - 100 |
| Total | 97.4 (37/38) | 86.2 - 99.9 | 99.1 (109/110) | 95.0 - 100 |

The positive percent agreement between the Elecsys Anti-HBc IgM assay results and the HBV infected status for the endemic/acute/reactive population (n = 148) was 97.4 % (37/38) with a 95 % confidence interval of 86.2-99.9 %. The negative percent agreement between the Elecsys Anti-HBc IgM assay results with the not HBV infected status was 99.1 % (109/110) with a 95 % confidence interval of 95.0-100 %.

# Anti-HBc IgM

cobas®

**IgM antibodies to hepatitis B core antigen (anti-HBc IgM)**

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11. Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.


For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information, and Method Sheets of all necessary components.

**Limited License**

The Elecsys Anti-HBc IgM assay shall not be used by blood banks, donor centers, or other institutions which exclusively or predominantly use the test for the safety or screening of blood and blood products.

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Significant additions or changes are indicated by a change bar in the margin. Changes to reagent barcode test parameters which have already been read in should be edited manually.


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Roche Diagnostics, Indianapolis, IN
US Customer Technical Support 1-800-428-2336


Roche

# PreciControl Anti-HBc IgM *(Draft)* cobas®

REF 11876333 160 16 x 1.0 mL

*English*

**Intended use**
Elecsys PreciControl Anti-HBc IgM is used for quality control of the Elecsys Anti-HBc IgM immunoassay on the **cobas e** 411 immunoassay analyzer.

**Summary**
Elecsys PreciControl Anti-HBc IgM contains control serum based on human serum in the negative and positive concentration ranges. The controls are used for monitoring the accuracy of the Elecsys Anti-HBc IgM immunoassay.

**Reagents - working solutions**
- PC A-HBCIGM1: 8 bottles, each containing 1.0 mL of control serum Human serum, negative for anti-HBc IgM; preservative.
  Target range for the cutoff index: 0.0-0.4
- PC A-HBCIGM2: 8 bottles, each containing 1.0 mL of control serum Anti-HBc IgM antibodies (human) > 130 U/mL (Paul-Ehrlich-Institute units) in human serum; preservative.
  Target range for the cutoff index: 2.0-4.8

The exact ranges, given in the form of a cutoff index, are encoded in the barcodes as well as printed on the enclosed (or electronically available) value sheet.

**Target values and ranges**
The target values and ranges were determined and evaluated by Roche. They were obtained using the Elecsys Anti-HBc IgM assay reagents and analyzers available at the time of testing.
If the target values and control ranges are updated, this information is conveyed either via the reagent barcodes, or control barcodes (or provided electronically) and in an additional value sheet included in the reagent kit. This value sheet lists all control lots to which the new values apply.
If some of the values remain unchanged, the original values conveyed via the CBC (Control Barcode) and in the value sheet included in the control kit (or provided electronically) remain valid.
Results must be within the specified ranges. In the event that increasing or decreasing trends or any other suddenly occurring deviations beyond the range limits are observed, all test steps must be checked.
When necessary, measurement of the patient samples tested should be repeated.
Traceability information is given in the package insert of the relevant Elecsys assay.
Each laboratory should establish corrective measures to be taken if values fall outside the specified limits.

*Note:* For technical reasons, re-assigned target values valid only for a specific reagent and control lot combination, must be entered manually. Therefore, always refer to the value sheet included in the RackPack or PreciControl kit to make sure that the correct target values are used.
When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

**Precautions and warnings**
For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.
All human material should be considered potentially infectious.
All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg (PC A-HBCIgM1 only) and antibodies to HCV and HIV.
The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.
The serum containing anti-HBcIgM used for the positive control (PC A-HBCIGM2) was inactivated using β-propiolactone and UV radiation. However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[1,2]

The controls may not be used after the expiration date.
Avoid foam formation in all reagents and sample types (specimens, calibrators, and controls).
Controls are in a serum matrix made from recalcified plasma. The user should provide alternate control material for plasma when necessary.

**Handling**
The controls are supplied ready-for-use in bottles compatible with the system. The controls should only be left on the analyzer during performance of quality control. After use, close the bottles as soon as possible and store upright at 2-8 °C.
Due to possible evaporation effects, not more than 7 quality procedures per bottle should be performed.

**Storage and stability**
Store at 2-8°C. Store controls **upright** in order to prevent the control solution from adhering to the snap-cap.
Stability:

| | |
|---|---|
| unopened at 2-8 °C | up to the stated expiration date |
| after opening at 2-8 °C | 8 weeks |
| on the analyzer at 20-25 °C | up to 6 hours |

**Materials provided**
- Elecsys PreciControl Anti-HBc IgM

**Materials required (but not provided)**
- **cobas e** 411 immunoassay analyzer and assay reagents. See test package insert and operator's manual for additionally required materials.

**Assay**
Treat the control serum in the system-compatible labeled bottles for analysis in the same way as patient samples. Read the data into the analyzer.
Ensure the controls are at ambient temperature (20-25 °C) before measurement.
Run controls daily in parallel with patient samples, once per reagent kit, and whenever calibration is performed. The control intervals and limits should be adapted to each laboratory's individual requirements.
Follow the applicable government regulations and local guidelines for quality control.

**References**

1. Occupational Safety and Health Standards: bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.
2. Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.


For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information, and the package inserts of all necessary components.

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