# AIA-360 Assay Specifications
# ST AIA-PACK SHBG Test Code 124

| No. | Item | Data |
|---|---|---|
| 1 | Calib. Req | SHOW |
| 2 | Cal 1 | 0.0000 |
| 3 | Cal 2 | 0.1000 (Example) |
| 4 | Cal 3 | 0.3000 (Example) |
| 5 | Cal 4 | 1.2500 (Example) |
| 6 | Cal 5 | 6.2500 (Example) |
| 7 | Cal 6 | 15.0000 (Example) |
| 8 | Cal Lot L | |
| 9 | Cal Lot R | |
| 10 | Unit | nmol/L |
| 11 | Smpl. Vol | 15 |
| 12 | Dil. Vol | 135 |
| 13 | Assay L | 0.0100 |
| 14 | Assay H | 12.5000 |
| 15 | Ref. L | |
| 16 | Ref. H | |
| 17 | Decimal | 4 |
| | **Visible only in Test Mode** | |
| 18 | Test Name | #SHBG |
| 19 | Calib. No | 6 |
| 20 | Calib. Mul | 3 |
| 21 | Calib. Equ | 3 |
| 22 | Calib. CV | 90 |
| 23 | Assay Prtl | 1 |
| 24 | Factor1 A | 1.000000 |
| 25 | Factor1 B | 0.000000 |
| 26 | Factor2 A | 20.000000 |
| 27 | Factor2 B | 0.000000 |
| 28 | V. Conc | 0.000000 |
| 29 | G Origin | 0.000000 |

# AIA-900 Assay Specifications
# ST AIA-PACK SHBG Test Code 124

| No. | Item | |
|---|---|---|
| 1 | Code | 124 |
| 2 | ACT | 1 |
| 3 | Analyte | #SHBG |
| 4 | Lot | |
| 5 | CAL 1 | 0.00000 |
| 6 | CAL 2 | 0.1000 (Example) |
| 7 | CAL 3 | 0.3000 (Example) |
| 8 | CAL 4 | 1.2500 (Example) |
| 9 | CAL 5 | 6.2500 (Example) |
| 10 | CAL 6 | 15.0000 (Example) |
| 11 | Cal lot L | |
| 12 | Cal lot R | |
| 13 | Unit | nmol/L |
| 14 | Decimal | 4 |
| 15 | Assay Low | 0.0100 |
| 16 | Assay High | 12.5000 |
| 17 | Reference Low | |
| 18 | Reference High | |
| 19 | Reschedule Low | 0.2000 |
| 20 | Reschedule High | 250.000 |
| 21 | Factor A | 1.000000 |
| 22 | Factor B | 0.000000 |
| 23 | Sample Volume | 15 |
| 24 | Diluent Volume | 135 |
| 25 | 2 Step reagent dispensing volume | 0 |
| 26 | Calibration code | 124 |
| 27 | CAL. No. | 6 |
| 28 | CAL. MUL. | 3 |
| 29 | CAL. EQU. | 3 |
| 30 | CAL. CV | 90 |
| 31 | DIL. SP1 | 20 |
| 32 | DIL. SP2 | 1 |
| 33 | DIL. CAL. (Calculation of dil ratio of conc.) | 1 |
| 34 | DIL. CNTL. | 20 |
| 35 | DIL. DO | 10 |
| 36 | DIL. AH. | 5 |
| 37 | DIL. CALC. | 1 |
| 38 | DIL. CODE | 124 |
| 39 | DIL. NAME | #SHBG |
| 40 | DIL. PRTY | 3 |
| 41 | PRE. SPVOL (Vol. of pretreated sample) | 0 |
| 42 | PRE. 1VOL (Vol. of pretreatment sol-1) | 0 |
| 43 | PRE. 2 VOL (Vol. of pretreatment sol-2) | 0 |
| 44 | PRE. CODE (pretreated sol. code) | 000 |
| 45 | PRE. NAME (pretreated sol. name) | - |
| 46 | Protocol | 1 |
| 47 | SYS. F_A | 1.000000 |
| 48 | SYS. F_B | 0.000000 |
| 49 | V. CONC. | 0.000000 |
| 50 | G. ORIGIN | 0.000000 |

# AIA-2000 Assay Specifications
# ST AIA-PACK SHBG Test Code 124

| No. | Item | |
|---|---|---|
| 1 | Unit | nmol/L |
| 2 | Decimal places | 4 |
| 3 | Reference low | |
| 4 | Reference high | |
| 5 | Reschedule low | 0.2000 |
| 6 | Reschedule high | 250.000 |
| 7 | Assay range low | 0.0100 |
| 8 | Assay range high | 12.5000 |
| 9 | Specimen diluent code | 124 |
| 10 | Specimen diluent name | #SHBG |
| 11 | Dilution factor for Sp. 1 | 20 |
| 12 | Dilution factor for Sp. 2 | 1 |
| 13 | Dilution factor for Control | 20 |
| 14 | Default multiplier for DO | 10 |
| 15 | Default multiplier for >H | 5 |
| 16 | Factor A | 1.000000 |
| 17 | Factor B | 0.000000 |
| 18 | Calibration code | 3 |
| 19 | Calibrator replicates | 3 |
| 20 | Calibrator lot | |
| 21 | Calibrator Concentration | |
| 22 | Cal - 01 | 0.00000 |
| 23 | Cal - 02 | 0.1000 (Example) |
| 24 | Cal - 03 | 0.3000 (Example) |
| 25 | Cal - 04 | 1.2500 (Example) |
| 26 | Cal - 05 | 6.2500 (Example) |
| 27 | Cal - 06 | 15.0000 (Example) |
| 28 | | |
| 29 | | |
| 30 | | |
| 31 | | |
| 32 | | |
| 33 | | |
| 34 | Dilution factor for calibrator | 1 |
| 35 | Calibration period | 90 |
| 36 | Incubation time (10/40) | 10 |
| 37 | Assay protocol | 1 |
| 38 | Specimen volume | 15 |
| 39 | Diluent volume | 135 |
| 40 | Conjugate volume | 0 |
| 41 | Diluted conjugate volume | 0 |
| 42 | Pretreatment | No |
| 43 | Pretreatment specimen volume | 0 |
| 44 | Pretreatment Reagent code | 0 |
| 45 | Pretreatment Reagent name | 0 |
| 46 | Pretreatment Reagent 1 volume | 0 |
| 47 | Pretreatment Reagent 2 volume | 0 |
| 48 | System Factor | 1.000000 |
| 49 | Calibration Code Check | 124 |
| 50 | Virtual Concentration | 0.0000 |
| 51 | Graph Origin | 0.0000 |
| 52 | Calculation with Dilution Factor | Yes |

# SHBG
# ST AIA-PACK SHBG

## Name and Intended Use

ST AIA-PACK SHBG is designed for In Vitro Diagnostic Use Only for the quantitative measurement of sex hormone binding globulin (SHBG) in human serum or Na heparinized plasma on Tosoh AIA System Analyzers. The ST AIA-PACK SHBG assay is intended for use as an aid in the diagnosis of androgen disorders.

## Summary and Explanation of Test

Sex hormone-binding globulin (SHBG), one of blood transport proteins, is a large homodimeric glycoprotein that especially binds testosterone and estradiol *(1)*. It is mostly synthesized in the liver and is released into the bloodstream. The biological activities of these sex steroids in plasma are regulated by plasma SHBG, since its high binding affinity to the steroids limits their access to target cells *(2)*.

It is suggested that SHBG concentrations are influenced by various factors, such as thyroid hormones, estrogens, insulin, and several growth factors. Increases in SHBG levels are found in hyperthyroidism, hepatic cirrhosis, and pregnancy. High SHBG values are also seen with oral estrogen treatment, tamoxifen administration, and Klinefelter's syndrome. Decreases in SHBG levels are observed in female patients with hirsutism, hyperandrogenism, or insulin resistance syndrome. In hypothyroidism, SHBG is often lowered *(3, 4)*.

SHBG is widely measured together with testosterone assays to calculate the "Free Androgen Index" (FAI), the ratio of total testosterone level derived by SHBG level. The FAI is known as a useful indicator to determine abnormal androgen status *(5, 6)*.

## Principle of the Assay

The ST AIA-PACK SHBG is a two-site immunoenzymometric assay which is performed entirely in the ST AIA-PACK SHBG test cups. SHBG present in the test sample is bound with monoclonal antibody immobilized on a magnetic solid phase and enzyme-labeled monoclonal antibody in the test cups. The magnetic beads are washed to remove unbound enzyme-labeled antibody and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled monoclonal antibody that binds to the beads is directly proportional to the SHBG concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using this curve.

## Material Provided (ST AIA-PACK SHBG, Cat. No. 0025238)

5 trays x 20 test cups (ST AIA-PACK SHBG Test Cup)

Unit dose test cups containing twelve lyophilized magnetic beads coated with anti-SHBG mouse monoclonal antibody and 100 µL of anti-SHBG mouse monoclonal antibody conjugated to bovine alkaline phosphatase with sodium azide as a preservative.

## Materials Required But Not Provided

The following materials are required to perform SHBG analysis using the ST AIA-PACK SHBG (Cat. No. 0025238) on the Tosoh AIA System Analyzer. The following are available separately from Tosoh.

| Materials | | | Cat. No. |
|---|---|---|---|
| AIA-2000 ST | | | 0022100 |
| AIA-2000 LA | | | 0022101 |
| AIA-900 | | | 0022930 |
| AIA-360 | | | 0019945 |
| AIA-PACK Substrate Set II | | | 0020968 |
| AIA-PACK Substrate Reagent II | | | |
| AIA-PACK Substrate Reconstituent II | | | |
| ST AIA-PACK SHBG Calibrator Set | | | 0025338 |
| ST AIA-PACK SHBG Calibrator (1) | 0 | nmol/L | |
| ST AIA-PACK SHBG Calibrator (2) | 0.10 | nmol/L (approx.) | |
| ST AIA-PACK SHBG Calibrator (3) | 0.30 | nmol/L (approx.) | |
| ST AIA-PACK SHBG Calibrator (4) | 1.25 | nmol/L (approx.) | |
| ST AIA-PACK SHBG Calibrator (5) | 6.25 | nmol/L (approx.) | |
| ST AIA-PACK SHBG Calibrator (6) | 15.0 | nmol/L (approx.) | |
| ST AIA-PACK SHBG Sample Diluting Solution | | | 0025538 |
| AIA-PACK WASH Concentrate | | | 0020955 |
| AIA-PACK DILUENT Concentrate | | | 0020956 |
| Sample Cups | | | 0018581 |
| AIA-PACK Detector Standardization Test Cup | | | 0020970 |
| AIA-PACK Sample Treatment Cup | | | 0020971 |

Additional Requirements for AIA-900 and AIA-2000:

| | |
|---|---|
| Pipette Tips | 019215 |
| Tip Rack | 019216 |
| Preloaded Pipette Tips (96 Tips X 50 Racks) | 996010 |
| Preloaded Pipette Tips (96 Tips X 5 Racks) | 996005 |

Only materials obtained from Tosoh should be used. Materials obtained elsewhere should not be substituted since assay performance is characterized based strictly on Tosoh materials.

## Warnings and Precautions

- The ST AIA-PACK SHBG is intended for in vitro diagnostic use only.
- ℞ only. US Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.
- Inspect the packaging and the exterior of the aluminum pouch for any sign of damage before use. If any damages are visible, contact your local Tosoh sales representative.
- Test cups from different lots or different assays shall not be mixed within a tray.
- The ST AIA-PACK SHBG contains sodium azide, which may react with lead or copper plumbing to form potentially explosive metal azides. When disposing of such reagents, always flush with large volumes of water to prevent azide build-up.

- The material derived from human origin is not used in the preparation of this product; however, since human specimens will be used for samples and other quality control products in the lab may be derived from human origin, please use standard laboratory safety procedures in handling all specimens and controls.
- Do not use beyond the expiration date.
- The ST AIA-PACK SHBG has been designed so that the high dose "hook effect" is not a problem for the vast majority of samples. Sample with SHBG concentration between 250 and 10,000 nmol/L will read > 250 nmol/L. The "hook effect" phenomenon may occur only at SHBG concentrations > 10,000 nmol/L.
- For safe waste disposal, it is recommended that each laboratory complies with established laboratory procedures and local, state, and federal regulations.
- After opening, the bottle of ST AIA-PACK SHBG Sample Diluting Solution should be kept tightly sealed with a clean cap. Sealing with dirty material may cause deterioration of the reagent.
- The remaining sample diluting solution after use should not be mixed with another bottle but be discarded to avoid contamination.
- Serum, dust, metal, or microorganism contamination may cause degradation of reconstituted substrate solution. Store in a clean environment, away from direct sunlight and ultraviolet light.
- Tosoh Automated Immunoassays utilizing alkaline phosphatase-based technologies should not be used with samples from patients under Asfotase Alfa treatment.

## Storage and Stability

All unopened materials are stable until the expiration date on the label when stored at the specified temperature.

| Materials | Cat. No. |
|---|---|
| **Refrigerator Temperature (2 - 8 °C):** | |
| ST AIA-PACK SHBG | 0025238 |
| ST AIA-PACK SHBG Calibrator Set | 0025338 |
| ST AIA-PACK SHBG Sample Diluting Solution | 0025538 |
| AIA-PACK Substrate Set II | 0020968 |
| AIA-PACK WASH Concentrate | 0020955 |
| AIA-PACK DILUENT Concentrate | 0020956 |
| **Room Temperature (18 - 25 °C):** | |
| AIA-PACK Detector Standardization Test Cup | 0020970 |
| AIA-PACK Sample Treatment Cup | 0020971 |

After opening the aluminum pouch, ST AIA-PACK SHBG test cups can be left on-board the Tosoh AIA System Analyzer (18 - 25 °C) for a maximum of 7 days (7 x 24 hours). When stored over night at 2 - 8 °C, the test cups can be used for up to 21 days (21 cycles of 8 hours on board and 16 hours in the refrigerator). Once the aluminum pouch is opened, even if the test cups are stored in the refrigerator, they must be used within 30 days.

ST AIA-PACK SHBG Calibrator Set must be kept tightly sealed and refrigerated at 2 - 8 °C. After opening or reconstituting, the calibrators should be used within 1 day.

After opening, ST AIA-PACK SHBG Sample Diluting Solution can be left on-board the Tosoh AIA System Analyzer (18 - 25 °C) for a maximum of 10 days (10 x 24 hours). When stored over night at 2 - 8 °C, the sample diluting solution can be used for up to 30 days (30 cycles of 8 hours on

board and 16 hours in the refrigerator). The sample diluting solution should not be used beyond 90 days after opening, even if it is sealed and stored in the refrigerator.

Reconstituted substrate solution is stable for 3 days at 18 - 25 °C or 30 days at 2 - 8 °C. Working diluent and wash solutions are stable for 30 days at 18 - 25 °C.

Reagents should not be used if they appear cloudy or discolored.

## Specimen Collection and Handling

- Serum or Na heparinized plasma is required for the assay. EDTA plasma or citrated plasma SHOULD NOT BE USED.
- When using serum, a venous blood sample is collected aseptically with or without additives. Store at 18 - 25 °C until a clot has formed (usually 15-45 minutes), then centrifuge to obtain the serum specimen for assay.
- When using heparinized plasma, a venous blood sample is collected aseptically with the designated additive. Centrifuge and separate plasma from the packed cells as soon as possible.
- Inadequate centrifugation or the presence of fibrin or particulate matter in the sample may cause an erroneous result.
- Samples containing inhibitors of alkaline phosphatase may cause erroneous results.
- Inspect all samples for air bubbles and foaming. Remove any air bubbles prior to assay.
- Specimen types should not be used interchangeably during serial monitoring of an individual patient. Measured concentrations may vary slightly between sample types in certain patients.
- Samples may be stored at 2 - 8 °C for up to 7 days prior to analysis. If the analysis cannot be done within 7 days, the sample should be stored frozen at -20 °C or below for up to 60 days.
- Repeated freeze-thaw cycles should be avoided. Turbid serum samples or samples containing particulate matter should be centrifuged prior to testing. Prior to the assay, slowly bring frozen samples to 18 - 25 °C and mix gently.
- All patient specimens require dilution prior to analysis. Samples are diluted by 20 fold with ST AIA-PACK SHBG Sample Diluting Solution. The AIA-2000 will automatically perform dilutions and calculate the results. . The AIA-900 and AIA-2000 will automatically perform dilutions and calculate the results. For further information regarding instrument operation, consult the specific Tosoh AIA System Operator's Manual. ST AIA-PACK SHBG Calibrator materials do not require dilution prior to assay.
- Diluted sample should be used within 24 hours and should not be stored.
- The diluted sample required for analysis is 15 µL.

## Procedure

For the AIA-2000 please refer to their Operator's Manual for detailed instructions. For the AIA-900, AIA-2000, and AIA-360, please refer to their Operator's Manual for detailed instructions.

### 1) Reagent Preparation

#### 1a) Substrate Solution

Bring all reagents to room temperature (18 - 25 °C) before preparing the working reagent. Add the entire contents of the AIA-PACK Substrate Reconstituent II (100 mL) to the lyophilized AIA-PACK Substrate Reagent II and mix thoroughly to dissolve the solid material.

#### 1b) Wash Solution

Add the entire contents of the AIA-PACK Wash Concentrate (100 mL) to approximately 2.0 L of CAP Class I water or the clinical laboratory reagent water, mix well, and adjust the final volume to 2.5 L.

#### 1c) Diluent

Add the entire contents of the AIA-PACK Diluent Concentrate (100 mL) to approximately 4.0 L of CAP Class I water or the clinical laboratory reagent water, mix well, and adjust the final volume to 5.0 L.

### 2) Calibration

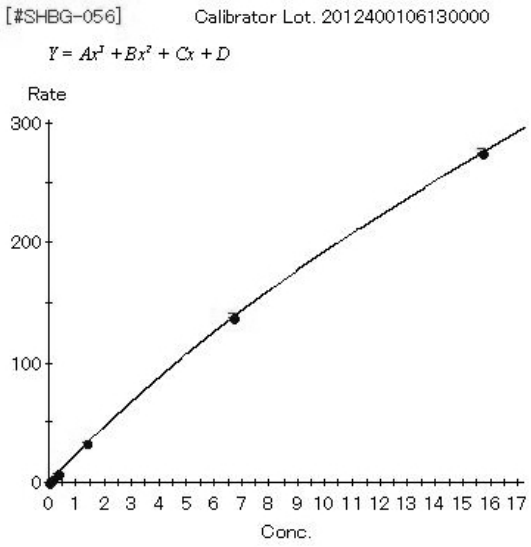
#### 2a) Calibration Curve

The calibrators for use with the ST AIA-PACK SHBG are referred to the 2nd International Standard for SHBG from the National Institute for Biological Standards and Control (NIBSC) code 08/266.

The calibration curve for the ST AIA-PACK SHBG is stable for up to 90 days. Calibration stability is monitored by quality control performance and is dependent on proper reagent handling and Tosoh AIA System maintenance according to the manufacturer's instructions.

Recalibration may be necessary more frequently if controls are out of the established range for this assay or when certain service procedures are performed (e.g. temperature adjustment, sampling mechanism changes, maintenance of the wash probe, or detector lamp adjustment or change). For further information regarding instrument operation, consult the Tosoh AIA System Operator's Manual.

A sample calibration curve from the AIA-2000 follows and shows the algorithm used for calculating results. The concentration range of the calibration curve is displayed in 1/20 of the assay range in patient specimens. The concentrations of patient specimens are calculated by multiplying the concentrations obtained on the calibration curve with the dilution factor. The AIA-900 and AIA-2000 will automatically calculate the concentrations of patient specimens using the dilution factor and report the results.




## 2b) Calibration Procedure

Refer to the appropriate Tosoh AIA System Operator's Manual for the procedural instructions.

1. Verify that both the calibrator lot and concentration numbers have been correctly entered into the software.

2. The ST AIA-PACK SHBG Calibrator (1) is provided ready for use.

3. The ST AIA-PACK SHBG Calibrators (2) - (6) are lyophilized. Lyophilized calibrators should be reconstituted with 1.0 mL of CAP Class I water or the clinical laboratory reagent water.

4. Tosoh recommends that all calibrators be run in triplicate.

## 2c) Calibration Acceptability criteria

1. The mean rate for the ST AIA-PACK SHBG Calibrator (1) should be </= 1.5 mol/(L.s).

2. Since there is a direct relationship between concentration and rate, the rate should increase as the concentration increases.

3. The replicate values should be within a 10% range.

## 2d) Calibration Review and Acceptance

1. Review the calibration curve carefully, using the criteria listed above.

2. Edit the calibration if necessary, then accept the calibration.

For further information regarding calibration, consult the specific AIA System Operator's Manual.

## 3) Quality Control

### 3a) Commercially Available Controls

Commercially available controls shall be run at least once per day. It is recommended that at least two levels of controls, normal and abnormal, be used. Laboratory policy for this particular assay designates the following:

Control Material: _____

Frequency: _____

Lot number of control material, acceptable limits, and corrective action to be taken if controls do not meet laboratory criteria will be found in a separate quality control document maintained by the laboratory.

### 3b) Quality Control Procedure

1. Assay quality control specimens as instructed in the specific Operator's Manual for your analyzer. In addition, refer to the Tosoh AIA System Operator's Manual for detailed instructions on defining and editing the files.
2. Quality control material to be run with this assay is defined by individual laboratory policy. Follow federal, state and local guidelines for testing quality control materials.

## 4) Specimen Processing

### 4a) Preparation

All patient specimens require dilution prior to analysis and are diluted 20 fold with ST AIA-PACK SHBG Sample Diluting Solution. Either diluted or undiluted patient specimens are placed in appropriate positions on the Tosoh AIA System Analyzers. For the AIA-360, the samples must be manually diluted in sample cups and the sample cups should be placed on the AIA-360. For further information regarding sample preparation and instrument operation, refer to the SPECIMEN COLLECTION AND HANDLING section and consult the specific Tosoh AIA System Operator's Manual, respectively. Barcoded primary tubes as well as sample cups can be run on the AIA-900 and AIA-2000.

### 4b) Assay Procedure

1. Ensure a sufficient quantity of ST AIA-PACK SHBG test cups for the number of samples to be run.
2. Load patient samples as instructed in the Operator's Manual and proceed with analysis. Note: The AIA-900 and AIA-2000 will require AIA-PACK Sample Treatment Cups if onboard dilutions are utilized.

# Procedural Notes

1. Lyophilized substrate must be completely dissolved.
2. Ligand assays performed by the Tosoh AIA System Analyzer require that the laboratory use water designated by the CAP Class I or by the clinical laboratory reagent water. Water should be tested at least once per month and should be free of particulate matter including bacteria. The pH of the water should also be routinely tested. For further

information, consult the CLSI document GP40-A4-AMD, Preparation and Testing of Reagent Water in the Clinical Laboratory; Approved Guideline - Fourth Edition.

3. If a specimen SHBG concentration is found to be greater than 250 nmol/L, the specimen should be diluted with the ST AIA-PACK SHBG Sample Diluting Solution and reassayed according to the Assay Procedure. The recommended dilution for specimens containing greater than 250 nmol/L is a 10 fold dilution. It is desirable to dilute the specimen so that the diluted specimen reads between 0.2 and 250 nmol/L. The dilution factor should be entered into the software. For further information on the dilution of specimens, refer to the Tosoh AIA System Operator's Manual.
4. The Tosoh AIA System Analyzer can store two different calibration curves for each analyte at one time. Therefore, up to two different lots of ST AIA-PACK SHBG test cups can be used during the same run.
5. If the assay specifications for this test are not in the system software, the specifications must be entered under test code 124.

## Calculation of Results

The Tosoh AIA System Analyzer performs all sample and reagent handling operations automatically. The Tosoh AIA System Analyzer reads the rate of fluorescence produced by the reaction and automatically multiplies the result by the original 1:20 dilution factor and converts the rate to SHBG concentration in nmol/L.

For samples requiring dilution, the AIA-900 and AIA-2000 will automatically perform dilutions and calculate results if the dilution factors are entered into the software. For detailed information regarding programming dilutions, consult the appropriate Tosoh AIA System Operator's Manual.

## Evaluation of Results

### Quality Control

In order to monitor and evaluate the precision of the analytical performance, it is recommended that commercially available control samples shall be assayed according to the local regulations.

The minimum recommendations for the frequency of running internal control material are:

- After calibration, two levels of the internal control are run in order to accept the calibration curve.
- The two levels of controls are repeated when certain service procedures are performed (e.g. temperature adjustment, sampling mechanism changes, maintenance of the wash probe, or detector lamp adjustment or change).
- After daily maintenance, two levels of the control shall be run in order to verify the overall performance of the Tosoh AIA System Analyzer.

If one or more control value(s) is out of the acceptable range, it is necessary to investigate the validity of the calibration curve before reporting patient results. Standard laboratory procedures should be followed in accordance with the strict regulatory agency under which the laboratory operates.

## Limitations of the Procedure

For diagnostic purposes, the results obtained from this assay should be used in conjunction with other data (e.g. symptoms, results of other tests, clinical impressions, therapy, etc.).

Using ST AIA-PACK SHBG, the highest concentration of SHBG measurable by a 20-fold dilution with ST AIA-PACK SHBG Sample Diluting Solution is 12.5 nmol/L, which corresponds to 250 nmol/L in specimens, and the lowest measurable concentration is 0.01 nmol/L which corresponds to 0.2 nmol/L (lowest reportable concentration) in specimens.

Although the approximate value of the highest calibrator is 15.0 nmol/L, the exact concentration may be slightly different. The assay specification, ASSAY RANGE HIGH, should be defined as the upper limit of the assay range, 12.5 nmol/L, which corresponds to approximately 250 nmol/L in original specimens (dilution factor 20).

Although hemolysis has an insignificant effect on the assay, hemolyzed samples may indicate mistreatment of a specimen prior to assay and results should be interpreted with caution.

Lipemia has an insignificant effect on the assay except in the case of gross lipemia where spatial interference may occur.

Grossly hemolyzed and lipemic samples should not be tested.

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show falsely elevated or decreased SHBG values.

Certain medications may interfere with assay performance. Specimens from patients taking medicines and/or medical treatment may show erroneous results. All results should be interpreted with respect to the clinical picture of the patient.

For a more complete understanding of the limitations of this procedure, please refer to the Specimen Collection and Handling, Warnings and Precautions, Storage and Stability, and Procedural Notes in this insert sheet.

## Expected Values

Each laboratory should determine a reference interval corresponding to the characteristics of the population being tested. As with all diagnostic procedures, clinical results must be interpreted with regard to concomitant medications administered to the patient.

## Reference Ranges

The interval given here was determined in serum samples from 494 apparently healthy American and European individuals.

| | n | Range (nmol/L) |
|---|---|---|
| Male (21 to 49 years old) | 124 | 12 - 64 |
| Male (≥50 years old) | 121 | 18 – 99 |
| Females (pre-menopausal ≥ 21 years) | 125 | 19 – 131 |
| Females (post-menopausal) | 124 | 15 – 170 |

**Free Androgen Index**

The free androgen index (% FAI) correlates with the value of free testosterone.[4] Therefore, in addition to SHBG all samples were tested with the Tosoh ST AIA-PACK Testosterone. The free androgen index (% FAI) was calculated on a molar/molar basis. Values for the target populations are summarized in the following table.*

| | | | FAI (%) | |
|---|---|---|---|---|
| | | n | 2.5th percentile | 97.5th percentile |
| Males | 21 - 49 years of age | 124 | 23.2 | 129.9 |
| | 50 - 87 years of age | 121 | 13.2 | 78.5 |
| Females | 21 - 49 years of age, pre-menopausal | 125 | 0.4 | 8.8 |
| | 55 - 80 years of age, post-menopausal | 124 | 0.3 | 9.0 |

Testosterone values were converted from ng/dL to nmol/L by multiplying the testosterone result by 0.03467.

- When the alternate result unit, nmoL/L, is desired, the conversion factor is 0.03467.
- $\text{FAI (\%)} = \frac{\text{Testosterone value (nmol/L)}}{\text{SHBG value (nmol/L)}} \times 100$

# Performance Characteristics

## 1) Linearity

The linearity for ST AIA-PACK SHBG was determined, based on guidance from CLSI Protocol EP06-A. The linearity was measured on the AIA-2000 instrument and has been demonstrated to be linear from 0.2 to 250 nmol/L.

**Serum:**

| Dilution | | Expected Value | Measured Value (nmol/L) | | | |
|---|---|---|---|---|---|---|
| No. | Low : High | (nmol/L) | Mean | SD | CV (%) | Recovery |
| 1 | Low Undiluted | 0.07 | 0.07 | 0.01 | 7.9 | 100.0 |
| 2 | 9 : 1 | 26.12 | 24.00 | 0.67 | 2.8 | 91.9 |
| 3 | 8 : 2 | 52.18 | 49.22 | 0.59 | 1.2 | 94.3 |
| 4 | 7 : 3 | 78.23 | 80.21 | 2.47 | 3.1 | 102.5 |
| 5 | 6 : 4 | 104.28 | 109.80 | 3.74 | 3.4 | 105.3 |
| 6 | 5 : 5 | 130.34 | 136.30 | 5.18 | 3.8 | 104.6 |
| 7 | 4 : 6 | 156.39 | 167.70 | 4.68 | 2.8 | 107.2 |
| 8 | 3 : 7 | 182.45 | 171.00 | 2.16 | 1.3 | 93.7 |
| 9 | 2 : 8 | 208.50 | 219.11 | 5.70 | 2.6 | 105.1 |
| 10 | 1 : 9 | 234.55 | 254.74 | 12.13 | 4.8 | 108.6 |
| 11 | High Undiluted | 260.61 | 260.61 | 3.24 | 1.2 | 100.0 |

**Note:** linear regression equation for serum (y= 1.038x-1.4013, R2=0.9924)

**Na Heparinized Plasma:**

| Dilution | | Expected Value | Measured Value (nmol/L) | | | |
|---|---|---|---|---|---|---|
| No. | Low : High | (nmol/L) | Mean | SD | CV (%) | Recovery |
| 1 | Low Undiluted | 0.09 | 0.09 | 0.00 | 5.3 | 100.0 |
| 2 | 9 : 1 | 27.65 | 26.57 | 0.43 | 1.6 | 96.1 |
| 3 | 8 : 2 | 55.22 | 53.63 | 1.16 | 2.2 | 97.1 |
| 4 | 7 : 3 | 82.78 | 82.55 | 1.17 | 1.4 | 99.7 |
| 5 | 6 : 4 | 110.35 | 111.57 | 1.23 | 1.1 | 101.1 |
| 6 | 5 : 5 | 137.91 | 140.30 | 3.01 | 2.1 | 101.7 |
| 7 | 4 : 6 | 165.47 | 164.41 | 3.89 | 2.4 | 99.4 |
| 8 | 3 : 7 | 193.04 | 196.51 | 4.73 | 2.4 | 101.8 |
| 9 | 2 : 8 | 220.60 | 223.66 | 3.39 | 1.5 | 101.4 |
| 10 | 1 : 9 | 248.17 | 249.98 | 7.52 | 3.0 | 100.7 |
| 11 | High Undiluted | 275.73 | 275.73 | 1.98 | 0.7 | 100.0 |

**Note:** linear regression equation for Na-Heparin (y=1.001x – 0.6649, R2=0.9997)

## 2) Precision

The precision study was developed with reference to the CLSI protocol entitled: Evaluation of Precision Performance of Quantitative Measurement Methods (EP05-A2).

The precision study for the ST AIA-PACK SHBG assay was evaluated utilizing three AIA-2000 Analyzers and three different lots of reagents. Precision was assessed by assaying three levels of serum and Na heparinized plasma specimens. Estimates of total and within run precision were obtained from measurements of 2 replicates in a single run, 2 times a day for 20 non-consecutive days. The mean of each duplicate was used to obtain the pooled standard deviation (SD), which was then used to calculate the coefficient of variation (CV). The study results of one representative lot are provided in the table below. In addition, all of the data were combined to assess the within run, between run, between day, between lot and total precision.

**Representative Lot-to-Lot Precision**

| Sample | Mean (n=80) nmol/L | Within-Run | | Between-Run | | Total | |
|---|---|---|---|---|---|---|---|
| | | SD | %CV | SD | %CV | SD | %CV |
| **Serum Low** | 18.0 | 0.39 | 2.1 | 0.37 | 2.0 | 0.53 | 3.0 |
| **Serum medium** | 54.8 | 1.29 | 2.3 | 1.32 | 2.4 | 1.8 | 3.3 |
| **Serum High** | 158.9 | 4.07 | 2.6 | 3.39 | 2.1 | 4.93 | 3.1 |
| | | | | | | | |
| **Hep Plasma Low** | 16.1 | 0.4 | 2.4 | 0.4 | 2.5 | 0.6 | 3.4 |
| **Hep Plasma Medium** | 65.2 | 1.0 | 1.6 | 1.0 | 1.5 | 1.5 | 2.3 |
| **Hep Plasma High** | 142.2 | 3.7 | 2.6 | 2.9 | 2.0 | 4.4 | 3.1 |

**Combined Summary Table**

| Sample | | Serum-1 | Serum-2 | Serum-3 | Hep Plasma-1 | Hep Plasma-2 | Hep Plasma-3 |
|---|---|---|---|---|---|---|---|
| **Mean Conc. (nmol/L)** | | 18.1 | 55.3 | 163.1 | 16.3 | 66.3 | 147.0 |
| **Within Run** | **SD** | 0.47 | 1.39 | 4.79 | 0.43 | 1.47 | 4.21 |
| | **%CV** | 2.6 | 2.5 | 2.9 | 2.7 | 2.2 | 2.9 |
| **Between Run** | **SD** | 0.38 | 1.21 | 4.10 | 0.42 | 1.36 | 3.83 |
| | **%CV** | 2.1 | 2.2 | 2.5 | 2.6 | 2.0 | 2.6 |
| **Between Day** | **SD** | 0.72 | 2.57 | 9.59 | 0.74 | 3.47 | 9.19 |
| | **%CV** | 4.0 | 4.6 | 5.9 | 4.6 | 5.2 | 6.3 |
| **Between Lot** | **SD** | 0.77 | 1.54 | 2.77 | 0.84 | 1.59 | 1.79 |
| | **%CV** | 4.3 | 2.8 | 1.7 | 5.1 | 2.4 | 1.2 |
| **Total** | **SD** | 0.84 | 2.88 | 9.42 | 0.85 | 3.75 | 10.04 |
| | **%CV** | 4.6 | 5.2 | 5.8 | 5.3 | 5.7 | 6.8 |

## Correlation

The methods comparison study was determined based on guidance from EP9-A2.

### a. Method Comparison

A total of 126 serum specimens were assayed in singleton utilizing the ST AIA-PACK SHBG assay on the AIA-2000 analyzer and the predicate SHBG.

| | **Deming** | **Regular** |
|---|---|---|
| **Slope:** | 0.949 (0.926 to 0.972) | 0.940 (0.917 to 0.964) |
| **Intercept:** | -0.64 (-2.61 to 1.34) | -0.09 (-2.06 to 1.89) |
| **Corr Coef (R):** | 0.991 | |
| **Result Ranges:** | Tosoh ST AIA-PACK SHBG 0.6 to 241.0 nmol/L<br>Predicate SHBG 0.5 to 221.6 nmol/L | |

*95% Confidence Intervals are shown in parentheses

### b. Matrix Comparison

The correlation between serum (x) and Na heparinized plasma (y) on ST AIA-PACK SHBG was carried out using 116 patient specimens. Five specimens were diluted to obtain the low end of the measuring range.

| | **Deming** | **Regular** |
|---|---|---|
| **Slope:** | 0.977 (0.964 to 0.991) | 0.975 (0.961 to 0.988) |
| **Intercept:** | 0.269 (-0.629 to 1.168) | 0.415 (-0.483 to 1.313) |
| **Corr Coef (R):** | 0.997 | |
| **Result Ranges** | Serum: 0.2 to 219.1 nmol/L<br>Na heparinized plasma: 0.2 to 219.9 nmol/L | |

*95% Confidence Intervals are shown in parentheses

## Specificity

The following substances were tested for cross-reactivity. Cross-reactivity (%) is the percentage of the compound which will be identified as SHBG.

| Substance | Concentration added | Cross-reactivity (%) |
|---|---|---|
| Alpha-Fetoprotein (AFP) | 48.4 µg/dL | N.D. |
| Cortisol | 100 µg/mL | 0.003 |
| 11-Deoxycortisol | 4 µg/mL | 0.114 |
| 5alpha-Dihydroxytestosterone | 20 µg/mL | 0.007 |
| Estradiol | 3600 pg/mL | N.D. |
| Testosterone | 20 µg/mL | 0.019 |
| Thyroglobulin | 300 µg/mL | 2.544 |
| Thyroxin-Binding Globulin | 200 µg/mL | N.D. |
| Transferrin | 4 mg/mL | N.D. |
| Fibrinogen | 4.5 g/L | 0.120 |
| Plasminogen | 250 mg/L | N.D. |
| Human IgA | 367 mg/dL | 0.072 |
| Human IgG | 335 mg/dL | 0.218 |
| CBG | 35 mg/dL | 0.012 |
| TSH | 180 mIU/L | N.D. |

(N.D.: not detectable)

## Limit of Detection and Limit of Quantification

The LoD and LoQ for ST AIA-PACK SHBG was determined, according to CLSI guideline EP17-A entitled: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline.

The LoB was determined by 60 measurements of 4 different blank specimens. The LoB was the value at the 95$^{th}$ percentile. In this case LoB was determined to be 0.017 nmol/L.

The LoD was determined by 12 measurements of 10 low level samples. The sample range was chosen to be between LoB and 5XLoB. The LoD was determined to be 0.063 nmol/L.

The Limit of Quantification (LoQ) 12 measurements of 5 samples for ST AIA-PACK SHBG. The test results from the LoD study were used to calculate the %TE at that level. The LoQ was determined to be 0.2 nmol/L based on a % total error of 12%.

The reportable range for the assay is 0.2-250 nmol/L.

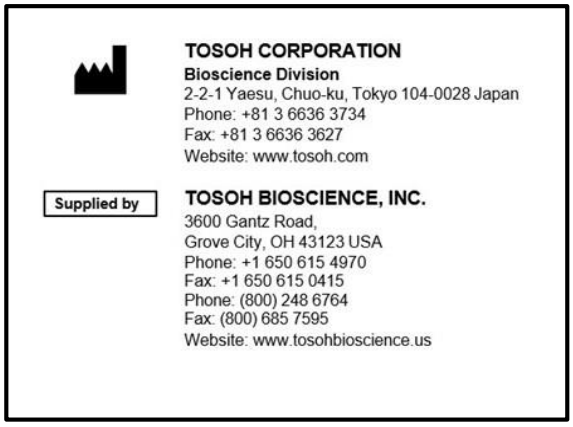
## Interference

Interference is defined, for the purposes of this study, with recovery outside of 10 % of the known concentration of the specimen after the following substances are added to human specimens.

- Hemoglobin (up to 446 mg/dL), free bilirubin (up to 17.6 mg/dL), and conjugated bilirubin (up to 18.5 mg/dL) do not interfere with the assay.
- Lipemia, as indicated by triglyceride concentration (up to 1,667 mg/dL), does not interfere with the assay.
- Ascorbic acid (up to 20 mg/dL) does not interfere with the assay.
- Protein, as indicated by human albumin concentration (up to 5.00 g/dL added to samples from apparently healthy subjects), does not interfere with the assay.
- Heparin Sodium (up to 100.0 U/mL) does not interfere with the assay.
- Rheumatoid factor (up to 550 IU/mL) does not interfere with the assay.
- HAMA (up to up to 24,269 ng/mL) does not interfere with the assay.
- Tosoh Automated Immunoassays utilizing alkaline phosphatase-based technologies should not be used with samples from patients under Asfotase Alfa treatment.

## References


1. Anderson D. C., Sex-hormone-binding globulin. Clinical Endocrinology, 3, 69-96 (1974).
2. Déchaud H., et al., In vitro influence of plasma steroid-binding proteins on androgen metabolism in human leukocytes. Steroids, 60, 226-233 (1995).
3. Selby C., Sex hormone binding globulin: origin, function and clinical significance. Ann. Clin. Biochem., 27, 532-541 (1990).
4. Pugeat M., et al., Clinical Utility of sex hormone-binding globulin measurement. Horm. Res., 45, 148-155 (1996).
5. Carlström K., et al., Free testosterone and testosterone/SHBG index in hirsute women: A comparison of diagnostic accuracy. Gynecol. Obstet. Invest., 24, 256-261 (1987).
6. Wilke T. J., et al., Total testosterone, free-androgen index, calculated free testosterone, and free testosterone by analog RIA compared in hirsute women and in otherwise-normal women with altered binding of sex-hormone-binding globulin. Clin. Chem., 33, 1372-1375 (1987).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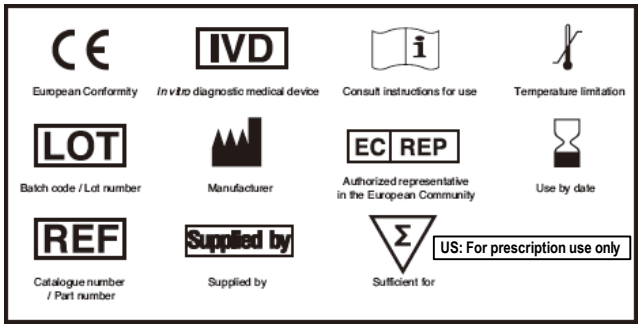

IVD
European Conformity
In vitro diagnostic medical device
Consult instructions for use
Temperature limitation
LOT
EC REP
Batch code / Lot number
Manufacturer
Authorized representative in the European Community
Use by date
REF
Supplied by
Catalogue number / Part number
Supplied by
Sufficient for
US: For prescription use only

# ST AIA-PACK SHBG
# Calibrator Set

## Intended Use

The ST AIA-PACK SHBG Calibrator Set is intended for IN VITRO Diagnostic Use Only for the calibration of the ST AIA-PACK SHBG assay.

## Summary and Explanation

The ST AIA-PACK SHBG Calibrator Set contains a protein matrix with assigned levels of sex hormone binding globulin (SHBG). Calibration should be performed according to the schedule indicated in the Tosoh AIA System Operator's Manual.

## Material Provided (Cat. No. 0025338)

| | | | |
|---|---|---|---|
| 2 x 1 mL | ST AIA-PACK SHBG Calibrator (1) | 0 | nmol/L |
| | Protein matrix containing no detectable concentration of SHBG with sodium azide as a preservative (Ready to Use). | | |
| 2 x 1 mL | ST AIA-PACK SHBG Calibrator (2) | 0.10 | nmol/L (approx.) |
| | ST AIA-PACK SHBG Calibrator (3) | 0.30 | nmol/L (approx.) |
| | ST AIA-PACK SHBG Calibrator (4) | 1.25 | nmol/L (approx.) |
| | ST AIA-PACK SHBG Calibrator (5) | 6.25 | nmol/L (approx.) |
| | ST AIA-PACK SHBG Calibrator (6) | 15.0 | nmol/L (approx.) |
| | Protein matrix containing the assigned concentration of SHBG (described on each vial) (Lyophilized). | | |

## Warnings and Precautions

- The ST AIA-PACK SHBG Calibrator Set is intended for in vitro diagnostic use only.
- For prescription use only.
- Inspect the packaging and the exterior of the vials for any sign of damage before use. If any damages are visible, contact your local Tosoh sales representative.
- The ST AIA-PACK SHBG Calibrator (1) contains sodium azide, which may react with lead or copper plumbing to form potentially explosive metal azides. When disposing of such reagents, always flush with large volumes of water to prevent azide build-up.
- The calibrator material has been tested by FDA-approved methods and found negative for the presence of HBsAg, antibody to HIV-1/2 and HCV. Because no test method can offer complete assurance that products derived from human origin will not transmit infectious agents, it is recommended that this product be handled with the same precautions as used for patient samples.
- Do not use beyond the expiration date.
- For safe waste disposal, it is recommended that each laboratory complies with established laboratory procedures and local, state, and federal regulations.

## Preparation

Bring the calibrators to 18 - 25 °C for use. Using a volumetric pipette or a calibrated adjustable pipette, reconstitute the lyophilized calibrators accurately with 1 mL of CAP Class I water or the clinical laboratory reagent water. Allow the lyophilized material to fully dissolve, then mix the calibrators gently but thoroughly prior to performing the calibration.

ST AIA-PACK SHBG Calibrator materials do not require dilution prior to assay.

## Storage and Stability

Always store the ST AIA-PACK SHBG Calibrator Set in an upright position at 2 - 8 °C when not in use. When stored unopened and refrigerated at 2 - 8 °C, the calibrator set is stable until the expiration date on the label. The calibrators should be used within 1 day of opening or reconstituting, provided the vials are kept tightly sealed and refrigerated at 2 - 8 °C.

## Procedure

Refer to the CALIBRATION PROCEDURE in the AIA-PACK section of this analyte application. For additional procedural instructions regarding calibration, refer to the Tosoh AIA System Operator's Manual.

## Calibration Procedure

1. Verify that both the calibrator lot and concentrations have been correctly entered into the analyzer software.
2. Add the appropriate amounts of each calibrator to sample cups (refer to the instrument worklist for the amount required in each sample cup.)
3. Place the sample cups and the test cups on the analyzer as indicated on the worklist.
4. TOSOH recommends that all calibrators be run in triplicate.

## Assignment of Values

The ST AIA-PACK SHBG Calibrator Set contains assigned concentrations of SHBG. The assigned value is determined on a lot-by-lot basis and is designed to provide an assay calibration range of 0.005 to 12.5 nmol/L of SHBG. The calibrators in this set are referred to the 2nd International Standard for SHBG from the National Institute for Biological Standards and Control (NIBSC) code 08/266.

*Note: As each manufactured calibrator concentration corresponds to a unique rate generated by the reaction detected by the instrument, the rate generated by the patient sample (which is diluted 1:20) would correspond to a rate on the curve generated by the manufactured calibrator. The value would then be multiplied automatically by the factor of 20 to generate the actual concentration of SHBG in the sample.*

## Results

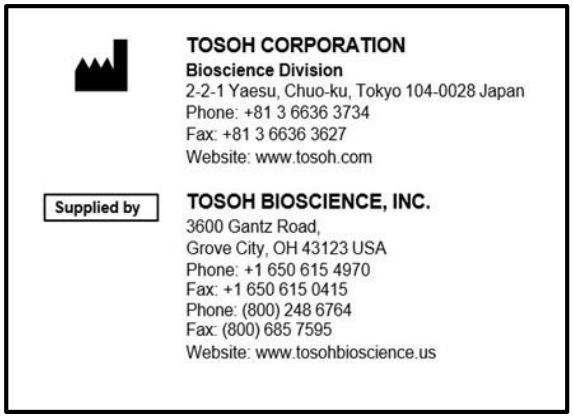
- The mean rate for the ST AIA-PACK SHBG Calibrator (1) should be </= 1.5 mol/(L.s).
- Since there is a direct relationship between concentration and rate, the rate should increase as the concentration increases.
- The replicate values should be within a 10 % range.

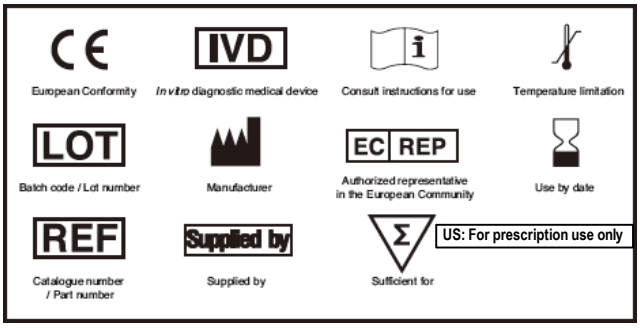
## Limitations

The ST AIA-PACK SHBG Calibrator Set is designed solely for use with ST AIA-PACK SHBG assay procedures. Although the approximate value of the highest calibrator is 15.0 nmol/L, the exact concentration may be slightly different. The assay specification, ASSAY RANGE HIGH, should be defined as the upper limit of the assay range, 12.5 nmol/L, which corresponds to approximately 250 nmol/L in original specimens (dilution factor 20).

## References


1. AIA Analyte Application Manual (AAM). Tosoh Bioscience, Inc., Grove City, OH.
2. AIA-System Operator's Manual. Tosoh Bioscience, Inc., Grove City, OH.

# ST AIA-PACK SHBG
# Sample Diluting Solution

## Intended Use

The ST AIA-PACK SHBG Sample Diluting Solution is intended for In Vitro Diagnostic Use Only to dilute patient samples.

## Material Provided (Cat. No. 0025538)

4 x 100 mL ST AIA-PACK SHBG Sample Diluting Solution

Protein matrix containing no detectable concentration of sex hormone binding globulin (SHBG) with sodium azide as a preservative.

## Warnings and Precautions

- The ST AIA-PACK SHBG Sample Diluting Solution is intended for in vitro diagnostic use only.
- Inspect the packaging and the exterior of the bottles for any sign of damage before use. If any damages are visible, contact your local Tosoh sales representative.
- This material contains sodium azide, which may react with lead or copper plumbing to form potentially explosive metal azides. When disposing of such reagents, always flush with large volumes of water to prevent azide build-up.
- Although material derived from human origin is not used for the sample diluting solution, it is recommended that this product be handled with the same precautions as used for patient samples.
- Do not use beyond the expiration date.
- For safe waste disposal, it is recommended that each laboratory complies with established laboratory procedures and local, state, and federal regulations.
- After opening, the bottle of the sample diluting solution should be kept tightly sealed with a clean cap. Sealing with dirty material may cause deterioration of the reagent.
- The remaining sample diluting solution after use should not be mixed with another bottle but be discarded to avoid contamination.

## Preparation

The ST AIA-PACK SHBG Sample Diluting Solution is provided ready for use. The sample diluting solution should be used after equilibrating to 18 - 25 °C for about 30 minutes.

## Storage and Stability

Always store the ST AIA-PACK SHBG Sample Diluting Solution in an upright position. When stored unopened and refrigerated at 2 - 8 °C, the sample diluting solution is stable until the expiration date on the label. After opening, the sample diluting solution can be left on-board of the Tosoh AIA System Analyzers (18 - 25 °C) for a maximum of 10 days (10 x 24 hours). When stored over night at 2 - 8 °C, the sample diluting solution can be used for up to 30 days (30 cycles of 8 hours on board and 16 hours in the refrigerator). The sample diluting solution should not be used beyond 90 days after opening, even if it is sealed and stored in the refrigerator.

## Procedure

Refer to the Tosoh AIA System Operator's Manual for additional procedural instructions regarding sample dilution.

- Serum or heparinized plasma specimens should be diluted by 20 fold prior to analysis.
- If a specimen SHBG concentration is found to be greater than 250 nmol/L, the specimen should be diluted with the ST AIA-PACK SHBG Sample Diluting Solution and assayed according to the procedure in the AIA-PACK section of the analyte application.
- The AIA-900 and AIA-2000 will perform dilutions automatically if the dilution factors are entered into the software prior to assaying the diluted sample.
- The recommended dilution for specimens containing greater than 250 nmol/L is 10 fold dilution. It is desirable to dilute the specimen so that the diluted specimen reads between 0.1 and 250 nmol/L.

## Results

When an auto-dilution is performed, the Tosoh AIA System Analyzer will calculate the final result.

## Limitations

The ST AIA-PACK SHBG Sample Diluting Solution is designed solely for use with ST AIA-PACK SHBG assay procedures.

## References


1. AIA Analyte Application Manual (AAM). Tosoh Bioscience, Inc., Grove City, OH.
2. AIA-System Operator's Manual. Tosoh Bioscience, Inc., Grove City, OH.

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