TRAINING UPDATE

Lab Location:	SGMC & WAH	**Date Distributed:**	10/12/2017
Department:	Core Lab	**Due Date:**	10/30/2017
		Implementation:	**10/30/2017**

DESCRIPTION OF PROCEDURE REVISION

Name of procedure:

Digoxin by Dimension Vista® System SGAH.C94 v3

Theophylline by Dimension Vista® System SGAH.C97 v2

These have been converted to system SOPs

Description of change(s):

(note QC change is already in effect)

Section	Reason
4,5,6	Remove individual section labeling instructions and add general one
6.1, 6.2	Update QC material and storage
7.2	Change freezer upper limit to -50C
10.5	Move patient review from section 6
10.6	Remove repeat value below AMR/CRR *
15	Update to new standard wording, digoxin only - move hazard statement from 4.2
17	Update QC product and PI dates

* This change will be made to Vista assays as SOPs are revised

The revised SOPs will be implemented on October 30, 2017

Document your compliance with this training update by taking the quiz in the MTS system.

Technical SOP

Title	**Digoxin by Dimension Vista® System**	
Prepared by	Ashkan Chini	Date: 6/25/2012
Owner	Robert SanLuis	Date: 10/21/2013

Laboratory Approval	**Local Effective Date:**	
Print Name and Title	**Signature**	**Date**
Refer to the electronic signature page for approval and approval dates.		

Review		
Print Name	**Signature**	**Date**

Form revised 2/02/2007

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1. TEST INFORMATION

Assay	Method/Instrument	Local Code
Digoxin	Dimension Vista® System	DIG

Synonyms/Abbreviations
Lanoxin

Department
Chemistry

Form revised 2/02/2007

2. ANALYTICAL PRINCIPLE

The DIGXN method is a homogeneous, sequential, chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead reagents and a biotinylated F(ab′)2 fragment of an anti-digoxin mouse monoclonal antibody. The first bead reagent (Chemibeads) is coated with ouabain, a weaker binding analog of digoxin, and contains a photosensitizer dye. In a first step, sample is incubated with biotinylated F(ab′)2 which allows digoxin from the sample to saturate a fraction of the biotinylated F(ab′)2 that is directly related to the digoxin concentration. In a second step, ouabain chemibeads are added and form bead/biotinylated F(ab′)2 immunocomplexes with the non-saturated fraction of the biotinylated F(ab′)2. Sensibeads are then added and bind to the biotin to form bead pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is an inverse function of the digoxin concentration in the sample.

3. SPECIMEN REQUIREMENTS

3.1 Patient Preparation

Component	Special Notations
Fasting/Special Diets	N/A
Specimen Collection and/or Timing	Collect at any time requested by a physician, or at least 6-8 hours after last dose, regardless of route of administration (optimally 12-24 hours after a dose)
Special Collection Procedures	N/A
Other	N/A

3.2 Specimen Type & Handling

Criteria		
Type -Preferred	Plasma (Lithium Heparin)	
-Other Acceptable	Serum	
Collection Container	Plasma: Mint green top tube (PST) Serum: Red top tube, Serum separator tube (SST)	
Volume - Optimum	1.0 mL	
- Minimum	0.5 mL	
Transport Container and Temperature	Collection container or Plastic vial at room temperature	
Stability & Storage Requirements	Room Temperature:	8 hours
	Refrigerated:	7 days
	Frozen:	6 months

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Criteria	
Timing Considerations	Serum or plasma should be physically separated from cells as soon as possible with a maximum limit of two hours from the time of collection.
Unacceptable Specimens & Actions to Take	Specimens that are unlabeled, improperly labeled, or those that do not meet the stated criteria are unacceptable. Request a recollection and credit the test with the appropriate LIS English text code for "test not performed" message. Examples: Quantity not sufficient-QNS; Wrong collection-UNAC. Document the request for recollection in the LIS.
Compromising Physical Characteristics	Gross hemolysis. Reject sample and request a recollection. Credit the test with the appropriate LIS English text code explanation of HMT (Specimen markedly hemolyzed)
Other Considerations	Allow Red Top or SST to clot completely prior to centrifugation.

NOTE: Labeling requirements for all reagents, calibrators and controls include: (1) Open date, (2) Substance name, (3) Lot number, (4) Date of preparation, (5) Expiration date, (6) Initials of tech, and (7) Any special storage instructions. Check all for visible signs of degradation. When placed onboard the analyzer, the instrument captures the date / time loaded and calculates and tracks the opened expiration.

4. REAGENTS

The package insert for a new lot of kits must be reviewed for any changes before the kit is used. A current Package Insert is included as a Related Document.

4.1 Reagent Summary

Reagents	Supplier & Catalog Number
Digoxin	Siemens, Flex® reagent cartridge, Cat. No. K6435

4.2 Reagent Preparation and Storage

Reagent	**Digoxin**
Container	Reagent cartridge
Storage	Store at 2-8°C
Stability	• Stable until expiration date stamped on reagent cartridges. • Sealed wells on the instrument are stable for 30 days. • Once wells 1 - 12 have been entered by the instrument, they are stable for 6 days.
Preparation	All reagents are liquid and ready for use.

5. CALIBRATORS/STANDARDS

5.1 Calibrators/Standards Used

Calibrator	Supplier and Catalog Number
DRUG 4 CAL	Siemens Dimension Vista®, Cat. No. KC460A

5.2 Calibrator Preparation and Storage

Calibrator	DRUG 4 CAL
Preparation	Calibrator is ready for use. No preparation is required.
Storage/Stability	• Store at 2-8°C • **Unopened calibrator** is stable until expiration date stamped on the box. • **Opened Calibrator:** once the stopper of the vial is punctured, assigned values are stable for 14 days when stored on board the Dimension Vista System. • **Opened Calibrator:** once cap is removed, assigned values are stable for 31 days when recapped immediately after use and stored at 2-8° C. **Do not use this vial on board the instrument.**

5.3 Calibration Parameter

Criteria	Special Notations
Reference Material	DRUG 4 CAL
Assay Range	0.06 – 5.00 ng/mL
Suggested Calibration Level	See Reagent Package Insert for lot specific assigned values in ng/mL
Frequency	• Every new reagent cartridge lot. • Every 30 days for any one lot • When major maintenance is performed on the analyzer. • When control data indicates a significant shift in assay.
Calibration Scheme	5 levels, n = 2

5.4 Calibration Procedure

Auto Calibration:

1. Place the required calibrator vials in a carrier. Make sure the barcode labels are entirely visible through the slots.
2. Place the carrier in the loading area.
3. Position the carrier with the labels facing away from the user.
4. Press the **Load** button.

5. Automatic calibration requires that calibrators be on the instrument. As the time for processing approaches, the instrument reviews onboard inventory for the appropriate calibrators.

Manual Calibration:

1. Verify that calibrators and reagents are in inventory on the instrument.
2. Press **System > Method Summary > Calibration**.
3. Select a method from the sidebar menu. Press the **Order Calibration** button on the screen.
4. Verify that the information on the screen is correct. Verify that the calibrator lot is correct using the drop-down menu.
   a. When calibrating using Vials press **OK**.
   b. When calibrating using Cups, check the Use Cups box. This displays the rack and cup position fields. For additional cups use the positions in ascending order. Be sure to use the number of calibration levels and cups as specified in the method IFU. Scan the rack barcode and place calibrator cups in an adapter in position 1 on a rack. Press **OK** and load the rack on the instrument.
5. The status field in the calibration screen changes sequentially to Awaiting Scheduling, Preparing Calibrators and Processing.

5.5 Tolerance Limits

IF……	THEN……
If result fall within assay-specific specification, and QC values are within acceptable limits,	proceed with analysis
If result falls outside assay-specific specification, or QC values are out of Acceptable limits,	troubleshoot the assay and/or instrument and repeat calibration

6. QUALITY CONTROL

6.1 Controls Used

Controls	Supplier and Catalog Number
Liquichek™ Immunoassay Plus Control Levels 1, 2 and 3	Bio-Rad Laboratories Cat. No. 267, 268 and 269

6.2 Control Preparation and Storage

Control	Liquichek Immunoassay Plus Controls, Level 1, 2 and 3
Preparation	Allow the vials to stand at room temperature (18-25° C) until it is completely thawed. Before sampling, gently swirl the vials several times to ensure homogeneity. After each use, promptly replace the stopper and return to 2-8° C storage.

Storage/Stability	Once thawed, all analytes will be stable for 4 days at 2-8°C. Unthawed controls are stable until the expiration date at -20 to -50°C.

6.3 Frequency

Analyze all levels of QC material after every calibration and each day of testing (notated on the QC frequency sheets posted on the instruments).

Refer to the Dimension Vista® QC Schedule in the Laboratory policy Quality Control Program and in the Dimension Vista® Quick Reference Guide.

6.4 Tolerance Limits and Criteria for Acceptable QC

Step	Action
1	Acceptable ranges for QC are programmed into the instrument's Quality Control software system and Unity Real Time, and may be posted near the instrument for use during computer downtime.
2	**Run Rejection Criteria** • Anytime the established parameters are exceeded (if one QC result exceeds 2 SD), the run is considered out of control (failed) and patient results must not be reported. • The technologist must follow the procedure in the Laboratory QC Program to resolve the problem.
3	**Corrective Action**: • All rejected runs must be effectively addressed through corrective action. Steps taken in response to QC failures must be documented. Patient samples in failed analytical runs must be reanalyzed according to the Laboratory QC Program. Supervisors may override rejection of partial or complete runs only with detailed documentation and criteria for overrides that are approved by the Medical Director. Consult corrective action guidelines in Laboratory QC Program. Follow corrective action guidelines in the Laboratory QC Program. • Corrective action documentation must follow the Laboratory Quality Control Program.
4	**Review of QC** • QC must be reviewed weekly by the Group Lead or designee and monthly by the Supervisor/Manager or designee. • If the SD and/or CV are greater than established ranges, investigate the cause for the imprecision and document implementation of corrective actions.

6.5 Documentation

- QC tolerance limits are programmed into the instrument and Unity Real Time; it calculates cumulative mean, SD and CV and stores all information for easy retrieval.
- Quality control records are reviewed daily at the bench, weekly by the Group Lead or designee, and monthly by the Supervisor/Manager or designee.
- Refer to complete policies and procedures for QC documentation and for record retention requirements in the Laboratory QC Program.

6.6 Quality Assurance Program

- Each new lot number of reagent or new shipment of the same lot of reagent must be tested with external control materials and previously analyzed samples. Performance of the new lot must be equivalent to the previous lot; utilize published TEA for acceptability criteria.
- Training must be successfully completed and documented prior to performing this test. This procedure must be incorporated into the departmental competency assessment program.
- The laboratory participates in CAP proficiency testing. All proficiency testing materials must be treated in the same manner as patient samples.
- Monthly QC must be presented to the Medical Director or designee for review and signature.
- Monthly QC mean and SD are sent to Bio-Rad Laboratories for peer group comparison.
- Consult the Laboratory QC Program for complete details.

7. EQUIPMENT and SUPPLIES

7.1 Assay Platform

Dimension Vista® System

7.2 Equipment

- Refrigerator capable of sustaining 2–8°C.
- Freezer capable of sustaining range not to exceed -20 to -50°C.
- Centrifuge

7.3 Supplies

- Aliquot Plates
- System Fluids
- Assorted calibrated pipettes (MLA or equivalent) and disposable tips

8. PROCEDURE

DIGXN Flex® reagent cartridge Cat. No. K6435 is required to perform this test.

Digoxin is performed on the Dimension Vista® System after the method is calibrated (see Reference Material in Calibration section) and Quality Controls are acceptable.

NOTE: For all procedures involving specimens, buttoned lab coats, gloves, and face protection are required minimum personal protective equipment. Report all accidents to your supervisor.

8.1	Sample Processing
1.	A sample rack holding tubes or cups is placed on the rack input lane.
2.	The sample shuttle moves the rack to the barcode reader which identifies the rack and samples to the system.
3.	The rack moves into the sample server and to the rack positioner.
4.	At the same time, aliquot plates move from the aliquot loader into position.
5.	The aliquot probe aspirates the sample from the tubes or cups and dispenses it into the wells of the aliquot plates.
6.	After each aspirate-dispense action, the probe is thoroughly rinsed inside and out to prevent sample carryover.
7.	When sample aspiration is completed, the sample server moves the rack back to the sample shuttle, where it is placed on the output lane and can be removed by the operator.

8.2	Specimen Testing
1.	For QC placement and frequency, refer to the Dimension Vista® QC Schedule in the Laboratory QC Program.
2.	Follow the instructions, outlined in the Dimension Vista® Operator's Manual
3.	The instrument reporting system contains error messages to warn the user of specific malfunctions. Results followed by such error messages should be held for follow-up. Refer to the Dimension Vista® system manual "Error messages" section for troubleshooting.
4.	Follow protocol in Section 10.5 "Repeat criteria and resulting" for samples with results above or below the Analytical Measurement Range (AMR). Investigate any failed delta result and repeat, if necessary.
5.	Append the appropriate English text code qualifier messages to any samples requiring a comment regarding sample quality and/or any other pertinent factors.

Test Conditions	
Sample Volume:	10 µL
Reagent 1 Volume:	40 µL
Reagent 2 Volume:	20 µL
Reagent 3 Volume:	60 µL

Reaction Time:	20.7 minutes
Test Temperature:	37° C
Wavelength:	680 and 612 nm
Type of measurement:	Chemiluminescence

NOTE: In the event that the test system becomes inoperable, notify supervision or designee for further direction. Patient specimens must be stored in a manner that maintains the integrity of the specimen.

9. CALCULATIONS

The instrument automatically calculates the concentration of Digoxin in ng/mL.

10. REPORTING RESULTS AND REPEAT CRITERIA

10.1 Interpretation of Data

None required

10.2 Rounding

No rounding is necessary. Instrument reports results up to two decimal points.

10.3 Units of Measure

ng/mL

10.4 Clinically Reportable Range (CRR)

0.06 – 50.00 ng/mL

10.5 Review Patient Data

Each result is reviewed for error messages. Refer to the Dimension Vista system manual “Error messages” section for troubleshooting. Resolve any problems noted before issuing patient reports.

10.6 Repeat Criteria and Resulting

All repeats must replicate the original result within the total allowable error (TEa) of the assay. Refer to TEa listing for specific information.

Values that fall below or within the AMR or CRR may be reported without repeat. Values that exceed the upper ranges must be repeated.

IF the result is …	THEN…
< 0.06 ng/mL	Assure there is sufficient sample devoid of bubbles, cellular debris, and/or fibrin clots. Report as: < 0.06 ng/mL
≥ 5.00 ng/mL	**Manual Dilution:** Using the primary tube, make the smallest dilution possible to bring the raw data within the AMR. Maximum allowable dilution: x 10 **Diluent**: Digoxin free serum or level 1 drug 4 cal. Enter dilution factor as a whole number. Re-assay. Readout is corrected for dilution.
> 50.00 ng/mL	If the recommended dilution does not give results within the clinically reportable range, report as: "> 50.00 ng/mL-REP" Bring to the attention of your supervisor prior to releasing result.

Message	Code
Verified by repeat analysis	Append –REP to the result.

11. EXPECTED VALUES

11.1 Reference Ranges

0.80 – 2.00 ng/mL

11.2 Critical Values

> 1.99 ng/mL

11.3 Standard Required Messages

None established

12. CLINICAL SIGNIFICANCE

Digoxin, a cardiac glycoside, is used as an antiarrhythmic agent, both alone and in conjunction with other drugs. Absorption from the gastrointestinal tract is variable: 60 – 80% of the administered dose is absorbed. Digoxin is excreted by the kidney almost entirely unchanged. Therefore the patient's renal function is an important consideration in determining dosage. In persons with normal kidney function the half-life is about 1.5 days. The most serious complications of digoxin toxicity are ventricular arrhythmias: ventricular tachycardia and ventricular fibrillation.

13. PROCEDURE NOTES

- **FDA Status:** FDA Approved/cleared
- **Validated Test Modifications:** None

The instrument reporting system contains error messages to warn the operator of specific malfunctions. Any report slip containing such error messages should be held for follow-up. Refer to your Dimension Vista Operator's Guide.

The expected maximum observed standard deviations for repeatability using n = 5 replicates at the following Digoxin concentrations are:

DIGXN Concentration	Acceptable S.D. Maximum
0.6 ng/mL	0.05 ng/mL
2.5 ng/mL	0.13 ng/mL

14. LIMITATIONS OF METHOD

14.1 Analytical Measurement Range (AMR)

0.06 – 5.00 ng/mL

14.2 Precision

Material	Mean ng/mL	Standard Deviation (%CV)	
		Repeatability	Within-Lab
Liquichek Immuno. Control			
Level 1	0.67	0.01 (1.5)	0.01 (1.7)
Level 2	1.63	0.02 (1.2)	0.02 (1.4)
Level 3	3.31	0.05 (1.4)	0.05 (1.5)

14.3 Interfering Substances

HIL Interference:
The DIGXN method was evaluated for interference according to CLSI/NCCLS EP7-A2. Bias, defined as the difference between the control sample (does not contain interferent) and the test sample (contains interferent), is shown in the table below. Bias exceeding 10% is considered "interference".

Substance tested	Substance Concentration	DIGXN ng/mL	Bias %
Hemoglobin (hemolysate)	1000 mg/dL	0.4, 2.0	<10
Bilirubin (unconjugated)	20 mg/dL	0.4, 2.0	<10
Bilirubin (conjugated)	20 mg/dL	0.4, 2.0	<10
Lipemia Intralipid®	2000 mg/dL	0.4, 2.0	<10

14.4 Clinical Sensitivity/Specificity/Predictive Values

Not available

15. SAFETY

Refer to your local and corporate safety manuals and Safety Data Sheet (SDS) for detailed information on safety practices and procedures and a complete description of hazards.

DIGXN Flex® Reagent Cartridge may cause an allergic skin reaction. Contains: 2-chloro-2-methyl-3(2h)-isothiazolone mixture with 2-methyl-3(2h)-isothiazolone. Wear protective gloves/protective clothing/eye protection/face protection.
IF ON SKIN: Wash with plenty of soap and water. If skin irritation or rash occurs: Get medical advice/attention.

16. RELATED DOCUMENTS

1. Dimension Vista® Clinical Chemistry System Operator's Manual
2. Dimension Vista® Calibration/Verification Procedure
3. Dimension Vista® Cal Accept Guidelines
4. Dimension Vista® Calibration summary
5. Dimension Vista® Sample Processing, Startup and Maintenance procedure
6. Laboratory Quality Control Program
7. QC Schedule for Siemens Dimension Vista®
8. Laboratory Safety Manual
9. Safety Data Sheets (SDS)
10. Dimension Vista® Limits Chart (AG.F200)
11. Quest Diagnostics Records Management Procedure
12. Dimension Vista® System Error Messages Chart
13. Centrifuge Use, Maintenance and Functions Checks (Lab policy)
14. Hemolysis, Icteria and Lipemia Interference (Lab policy)
15. Repeat Testing Requirement (Lab policy)
16. Therapeutic Drug Monitoring, (Chemistry SOP)
17. Current Allowable Total Error Specifications
    at http://questnet1.qdx.com/Business_Groups/Medical/qc/docs/qc_bpt_tea.xls
18. Current package insert DIGXN Flex® Reagent Cartridge K6435

17. REFERENCES

1. Package Insert, DIGXN Flex® Reagent Cartridge K6435, Siemens Healthcare Diagnostics Inc., 03/27/2015.
2. Package Insert, DRUG 4 CAL, Siemens Healthcare Diagnostics Inc., 02/2011.
3. Package Insert, Liquichek Immunoassay Plus Control, Bio-Rad Laboratories, 12/2015.

18. REVISION HISTORY

Version	Date	Section	Reason	Reviser	Approval
000	10/21/13		Update owner	L Barrett	R SanLuis
000	10/21/13	11.1	Change range	L Barrett	R SanLuis
000	10/21/13	16	Update titles	L Barrett	R SanLuis
000	10/21/13	Footer	Version # leading zero's dropped due to new EDCS in use as of 10/7/13.	L Barrett	R SanLuis
1	8/24/15	3.2	Change preferred specimen to plasma	L. Barrett	R. SanLuis
1	8/24/15	4.2	Add hazard statement	L. Barrett	R. SanLuis
1	8/24/15	6.4,6.6	Replace LIS with Unity Real Time	L. Barrett	R. SanLuis
1	8/24/15	11.2	Reformat value to eliminate ≥ sign	L. Barrett	R. SanLuis
2	10/2/17	Header	Add WAH	L Barrett	R SanLuis
2	10/2/17	3.2	Remove specimen onboard stability	L Barrett	R SanLuis
2	10/2/17	4,5,6	Remove individual section labeling instructions and add general one	L Barrett	R SanLuis
2	10/2/17	6.1, 6.2	Update QC material and storage	L Barrett	R SanLuis
	10/2/17	7.2	Change freezer upper limit to -50C	L Barrett	R SanLuis
2	10/2/17	10.5	Move patient review from section 6	L Barrett	R SanLuis
2	10/2/17	10.6	Remove repeat value below AMR/CRR	L Barrett	R SanLuis
2	10/2/17	15	Update to new standard wording, move hazard statement from 4.2	L Barrett	R SanLuis
2	10/2/17	17	Update QC product and PI dates	L Barrett	R SanLuis

19. ADDENDA

None

Technical SOP

Title	**Theophylline by Dimension Vista® System**	
Prepared by	Ashkan Chini	Date: 6/25/2012
Owner	Robert SanLuis	Date: 6/25/2012

Laboratory Approval	**Local Effective Date:**	
Print Name and Title	**Signature**	**Date**
Refer to the electronic signature page for approval and approval dates.		

Review		
Print Name	**Signature**	**Date**

TABLE OF CONTENTS

1. TEST INFORMATION

Assay	Method/Instrument	Local Code
Theophylline	Dimension Vista® System	THEO

Synonyms/Abbreviations
Aminophylline, THEO

Department
Chemistry

2. ANALYTICAL PRINCIPLE

The methodology for THEO is based on a homogeneous particle enhanced turbidimetric inhibition immunoassay (PETINIA) technique which uses a synthetic particle theophylline conjugate (PR) and monoclonal theophylline specific antibody (Ab). Theophylline present in the sample competes with theophylline on the particles for available antibody, thereby decreasing the rate of aggregation. Hence, the rate of aggregation is inversely proportional to the concentration of theophylline in the sample. The rate of aggregation is measured using a turbidimetric rate at 340 nm.

Theophylline + PR + Ab ----------> PR-Ab complex + Theophylline-Ab
(scatters light at 340 nm)

3. SPECIMEN REQUIREMENTS

3.1 Patient Preparation

Component	Special Notations
Fasting/Special Diets	N/A
Specimen Collection and/or Timing	After IV infusion loading dose and anytime during infusion **Trough**: Immediately before dose (within thirty (30) minutes) **Peak**: Two (2) hours after immediate release oral dose and four (4) hours after sustained release oral dose
Special Collection Procedures	N/A
Other	N/A

3.2 Specimen Type & Handling

Criteria	
Type -Preferred **-Other Acceptable**	Plasma (Lithium Heparin) Serum
Collection Container	Plasma: Mint green top tube (PST) Serum: Red top tube, Serum separator tube (SST)
Volume - Optimum **- Minimum**	1.0 mL 0.5 mL
Transport Container and Temperature	Collection container or Plastic vial at room temperature
Stability & Storage Requirements	Room Temperature: 8 hours
	Refrigerated: 7 days
	Frozen: 3 months

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Criteria	
Timing Considerations	Serum or plasma should be physically separated from cells as soon as possible with a maximum limit of two hours from the time of collection.
Unacceptable Specimens & Actions to Take	Specimens that are unlabeled, improperly labeled, or those that do not meet the stated criteria are unacceptable. Request a recollection and credit the test with the appropriate LIS English text code for "test not performed" message. Examples: Quantity not sufficient-QNS; Wrong collection-UNAC. Document the request for recollection in the LIS.
Compromising Physical Characteristics	Gross hemolysis. Reject sample and request a recollection. Credit the test with the appropriate LIS English text code explanation of HMT (Specimen markedly hemolyzed)
Other Considerations	Allow Red Top or SST to clot completely prior to centrifugation.

NOTE: Labeling requirements for all reagents, calibrators and controls include: (1) Open date, (2) Substance name, (3) Lot number, (4) Date of preparation, (5) Expiration date, (6) Initials of tech, and (7) Any special storage instructions. Check all for visible signs of degradation. When placed onboard the analyzer, the instrument captures the date / time loaded and calculates and tracks the opened expiration.

4. REAGENTS

The package insert for a new lot of kits must be reviewed for any changes before the kit is used. A current Package Insert is included as a Related Document.

4.1 Reagent Summary

Reagents	Supplier & Catalog Number
Theophylline	Siemens, Flex® reagent cartridge, Cat. No. K4071

4.2 Reagent Preparation and Storage

Reagent	Theophylline
Container	Reagent cartridge
Storage	Store at 2-8° C
Stability	• Stable until expiration date stamped on reagent cartridges. • Sealed wells on the instrument are stable for 30 days. • Once wells 1 - 12 have been entered by the instrument, they are stable for 3 days.
Preparation	All reagents are liquid and ready to use.

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5. CALIBRATORS/STANDARDS

5.1 Calibrators/Standards Used

Calibrator	Supplier and Catalog Number
DRUG 1 CAL	Siemens Dimension Vista®, Cat. No. KC410

5.2 Calibrator Preparation and Storage

Calibrator	DRUG 1 CAL
Preparation	Calibrator is ready for use. No preparation is required.
Storage/Stability	• Store at 2-8° C • **Unopened product:** Stable until expiration date stamped on the box. • **Opened Calibrator:** once the stopper of the vial is punctured, assigned values are stable for 15 days when stored on board the Dimension Vista System. • **Opened Calibrator:** once cap is removed, assigned values are stable for 31 days when recapped immediately after use and stored at 2-8° C. **Do not use this vial on board the instrument.**

5.3 Calibration Parameter

Criteria	Special Notations
Reference Material	DRUG 1 CAL
Assay Range	2.0 – 40.0 µg/mL
Suggested Calibration Level	See Reagent Package Insert for lot specific assigned values in µg/mL
Frequency	• Every new reagent cartridge lot. • Every 30 days for any one lot • When major maintenance is performed on the analyzer. • When control data indicates a significant shift in assay.
Calibration Scheme	5 levels, n = 4

5.4 Calibration Procedure

Auto Calibration:

1. Place the required calibrator vials in a carrier. Make sure the barcode labels are entirely visible through the slots.
2. Place the carrier in the loading area.
3. Position the carrier with the labels facing away from the user.
4. Press the **Load** button.

5. Automatic calibration requires that calibrators be on the instrument. As the time for processing approaches, the instrument reviews onboard inventory for the appropriate calibrators.

Manual Calibration:

1. Verify that calibrators and reagents are in inventory on the instrument.
2. Press **System > Method Summary > Calibration**.
3. Select a method from the sidebar menu. Press the **Order Calibration** button on the screen.
4. Verify that the information on the screen is correct. Verify that the calibrator lot is correct using the drop-down menu.
   a. When calibrating using Vials press **OK**.
   b. When calibrating using Cups, check the Use Cups box. This displays the rack and cup position fields. For additional cups use the positions in ascending order. Be sure to use the number of calibration levels and cups as specified in the method IFU. Scan the rack barcode and place calibrator cups in an adapter in position 1 on a rack. Press **OK** and load the rack on the instrument.
5. The status field in the calibration screen changes sequentially to Awaiting Scheduling, Preparing Calibrators and Processing.

5.5 Tolerance Limits

IF……	THEN……
If result fall within assay-specific specification, and QC values are within acceptable limits,	proceed with analysis
If result falls outside assay-specific specification, or QC values are out of Acceptable limits,	troubleshoot the assay and/or instrument and repeat calibration

6. QUALITY CONTROL

6.1 Controls Used

Controls	Supplier and Catalog Number
Liquichek™ Immunoassay Plus Control Levels 1, 2 and 3	Bio-Rad Laboratories Cat. No. 267, 268 and 269

6.2 Control Preparation and Storage

Control	Liquichek Immunoassay Plus Controls, Level 1, 2 and 3
Preparation	Allow the vials to stand at room temperature (18-25°C) until it is completely thawed. Before sampling, gently swirl the vials several times to ensure homogeneity. After each use, promptly replace the stopper and return to 2-8°C storage.

Storage/Stability	Once thawed, all analytes will be stable for 4 days at 2-8°C. Unthawed controls are stable until the expiration date at -20 to -50°C.

6.3 Frequency

Analyze all levels of QC material after every calibration and each day of testing (notated on the QC frequency sheets posted on the instruments).

Refer to the Dimension Vista® QC Schedule in the Laboratory policy Quality Control Program and in the Dimension Vista® Quick Reference Guide.

6.4 Tolerance Limits and Criteria for Acceptable QC

Step	Action
1	Acceptable ranges for QC are programmed into the instrument's Quality Control software system and Unity Real Time, and may be posted near the instrument for use during computer downtime.
2	**Run Rejection Criteria** • Anytime the established parameters are exceeded (if one QC result exceeds 2 SD), the run is considered out of control (failed) and patient results must not be reported. • The technologist must follow the procedure in the Laboratory QC Program to resolve the problem.
3	**Corrective Action**: • All rejected runs must be effectively addressed through corrective action. Steps taken in response to QC failures must be documented. Patient samples in failed analytical runs must be reanalyzed according to the Laboratory QC Program. Supervisors may override rejection of partial or complete runs only with detailed documentation and criteria for overrides that are approved by the Medical Director. Consult corrective action guidelines in Laboratory QC Program. Follow corrective action guidelines in the Laboratory QC Program. • Corrective action documentation must follow the Laboratory Quality Control Program.
4	**Review of QC** • QC must be reviewed weekly by the Group Lead or designee and monthly by the Supervisor/Manager or designee. • If the SD and/or CV are greater than established ranges, investigate the cause for the imprecision and document implementation of corrective actions.

6.5 Documentation

- QC tolerance limits are programmed into the instrument and Unity Real Time; it calculates cumulative mean, SD and CV and stores all information for easy retrieval.
- Quality control records are reviewed daily at the bench, weekly by the Group Lead or designee, and monthly by the Supervisor/Manager or designee.
- Refer to complete policies and procedures for QC documentation and for record retention requirements in the Laboratory QC Program.

6.6 Quality Assurance Program

- Each new lot number of reagent or new shipment of the same lot of reagent must be tested with external control materials and previously analyzed samples. Performance of the new lot must be equivalent to the previous lot; utilize published TEA for acceptability criteria.
- Training must be successfully completed and documented prior to performing this test. This procedure must be incorporated into the departmental competency assessment program.
- The laboratory participates in CAP proficiency testing. All proficiency testing materials must be treated in the same manner as patient samples.
- Monthly QC must be presented to the Medical Director or designee for review and signature.
- Monthly QC mean and SD are sent to Bio-Rad Laboratories for peer group comparison.
- Consult the Laboratory QC Program for complete details.

7. EQUIPMENT and SUPPLIES

7.1 Assay Platform

Dimension Vista® System

7.2 Equipment

- Refrigerator capable of sustaining 2–8°C.
- Freezer capable of sustaining range not to exceed -20 to -50°C.
- Centrifuge

7.3 Supplies

- Aliquot Plates
- System Fluids
- Assorted calibrated pipettes (MLA or equivalent) and disposable tips

8. PROCEDURE

THEO Flex® reagent cartridge Cat. No. K4071 is required to perform this test.

Theophylline is performed on the Dimension Vista® System after the method is calibrated (see Reference Material in Calibration section) and Quality Controls are acceptable.

NOTE: For all procedures involving specimens, buttoned lab coats, gloves, and face protection are required minimum personal protective equipment. Report all accidents to your supervisor.

8.1	Sample Processing
1.	A sample rack holding tubes or cups is placed on the rack input lane.
2.	The sample shuttle moves the rack to the barcode reader which identifies the rack and samples to the system.
3.	The rack moves into the sample server and to the rack positioner.
4.	At the same time, aliquot plates move from the aliquot loader into position.
5.	The aliquot probe aspirates the sample from the tubes or cups and dispenses it into the wells of the aliquot plates.
6.	After each aspirate-dispense action, the probe is thoroughly rinsed inside and out to prevent sample carryover.
7.	When sample aspiration is completed, the sample server moves the rack back to the sample shuttle, where it is placed on the output lane and can be removed by the operator.

8.2	Specimen Testing
1.	For QC placement and frequency, refer to the Dimension Vista® QC Schedule in the Laboratory QC Program.
2.	Follow the instructions, outlined in the Dimension Vista® Operator's Manual
3.	The instrument reporting system contains error messages to warn the user of specific malfunctions. Results followed by such error messages should be held for follow-up. Refer to the Dimension Vista® system manual "Error messages" section for troubleshooting.
4.	Follow protocol in Section 10.5 "Repeat criteria and resulting" for samples with results above or below the Analytical Measurement Range (AMR). Investigate any failed delta result and repeat, if necessary.
5.	Append the appropriate English text code qualifier messages to any samples requiring a comment regarding sample quality and/or any other pertinent factors.

Test Conditions	
Sample Volume:	1.54 µL
Buffer Volume:	117.5 µL
Part. Reagent Volume:	15.4 µL
Antibody Volume:	15.4 µL

Reaction Time:	5 minutes
Test Temperature:	37° C
Wavelength:	340 nm
Type of measurement:	Turbidimetric rate

NOTE: In the event that the test system becomes inoperable, notify supervision or designee for further direction. Patient specimens must be stored in a manner that maintains the integrity of the specimen.

9. CALCULATIONS

The instrument automatically calculates the concentration of Theophylline in µg/mL.

10. REPORTING RESULTS AND REPEAT CRITERIA

10.1 Interpretation of Data

None required

10.2 Rounding

No rounding is necessary. Instrument reports results up to one decimal point.

10.3 Units of Measure

µg/mL

10.4 Clinically Reportable Range (CRR)

2.0 – 160.0 µg/mL

10.5 Review Patient Data

Each result is reviewed for error messages. Refer to the Dimension Vista system manual "Error messages" section for troubleshooting. Resolve any problems noted before issuing patient reports.

10.6 Repeat Criteria and Resulting

All repeats must replicate the original result within the total allowable error (TEa) of the assay. Refer to TEa listing for specific information.

Values that fall below or within the AMR or CRR may be reported without repeat. Values that exceed the upper ranges must be repeated.

IF the result is …	THEN…
< 2.0 µg/mL	Assure there is sufficient sample devoid of bubbles, cellular debris, and/or fibrin clots. Report as: < 2.0 µg/mL
≥ 40.0 µg/mL	**On Board Automated Dilution:** Results ≥ 40.0 µg/mL will automatically have repeat testing performed into the instrument using dilution factor of 4. No multiplication is necessary.
> 160.0 µg/mL	If the recommended dilution does not give results within the clinically reportable range, report as: "> 160.0 µg/mL -REP" Bring to the attention of your supervisor prior to releasing result.

Message	Code
Verified by repeat analysis	Append –REP to the result.

11. EXPECTED VALUES

11.1 Reference Ranges

10.0 – 20.0 µg/mL

11.2 Critical Values

> 19.9 µg/mL

11.3 Standard Required Messages

None established

12. CLINICAL SIGNIFICANCE

Theophylline measurements may be used in the diagnosis and treatment of theophylline overdose, and in therapeutic drug monitoring. Theophylline is a methylated xanthine, 1,3-dimethylxanthine. It is structurally related to purines and uric acid, as well as to xanthine itself. The most commonly used compound is aminophylline, the double salt of theophylline and ethylenediamine. About 10% is excreted unchanged in the urine and the remaining 90% of the drug is converted to other compounds before it is eliminated from the body. The biologic half-life of theophylline varies from about 3.5 hours in young children to 8–9 hours in most adults. It is substantially prolonged in the presence of liver disease and/or cardiac decompensation.

13. PROCEDURE NOTES

- **FDA Status:** FDA Approved/cleared
- **Validated Test Modifications:** None

The instrument reporting system contains error messages to warn the operator of specific malfunctions. Any report slip containing such error messages should be held for follow-up. Refer to your Dimension Vista Operator's Guide.

The expected maximum observed standard deviations for repeatability using n = 5 replicates at the following Theophylline concentrations are:

THEO Concentration	Acceptable S.D. Maximum
5.0 µg/mL	1.0 µg/mL
14.0 µg/mL	2.2 µg/mL

14. LIMITATIONS OF METHOD

14.1 Analytical Measurement Range (AMR)

2.0 – 40.0 µg/mL

14.2 Precision

Material	Mean µg/mL	Standard Deviation (%CV)	
		Repeatability	Within-Lab
Liquichek Immuno. Control			
Level 1	4.7	0.2 (5)	0.3 (6)
Level 2	14.5	0.5 (4)	0.8 (5)
Level 3	28.2	1.1 (4)	1.6 (6)

14.3 Interfering Substances

Theophylline values will be increased by 1.0 µg/mL in the presence of 10 µg/mL of 1,3-dimethyl uric acid.

HIL Interference:
The THEO method was evaluated for interference according to CLSI/NCCLS EP7-A2. Bias, defined as the difference between the control sample (does not contain interferent) and the test sample (contains interferent), is shown in the table below. Bias exceeding 10% is considered "interference".

Substance tested	Substance Concentration	THEO µg/mL	Bias %
Hemoglobin (hemolysate)	1000 mg/dL	25	<10
Bilirubin (unconjugated)	60 mg/dL	25	<10
Bilirubin (conjugated)	60 mg/dL	25	<10
Lipemia Intralipid®	1000 mg/dL 3000 mg/dL	25	<10 -23.7

14.4 Clinical Sensitivity/Specificity/Predictive Values

Not available

15. SAFETY

Refer to your local and corporate safety manuals and Safety Data Sheet (SDS) for detailed information on safety practices and procedures and a complete description of hazards.

16. RELATED DOCUMENTS

1. Dimension Vista® Clinical Chemistry System Operator's Manual
2. Dimension Vista® Calibration/Verification Procedure
3. Dimension Vista® Cal Accept Guidelines
4. Dimension Vista® Calibration summary
5. Dimension Vista® Sample Processing, Startup and Maintenance procedure
6. Laboratory Quality Control Program
7. QC Schedule for Siemens Dimension Vista®
8. Laboratory Safety Manual
9. Safety Data Sheets (SDS)
10. Siemens Dimension Vista® Limits Chart (AG.F200)
11. Quest Diagnostics Records Management Procedure
12. Dimension Vista® System Error Messages Chart
13. Centrifuge Use, Maintenance and Functions Checks (Lab policy)
14. Hemolysis, Icteria and Lipemia Interference (Lab policy)
15. Repeat Testing Requirement (Lab policy)
16. Therapeutic Drug Monitoring (Chemistry SOP)
17. Current Allowable Total Error Specifications at http://questnet1.qdx.com/Business_Groups/Medical/qc/docs/qc_bpt_tea.xls
18. Current package insert THEO Flex® Reagent Cartridge K4071

17. REFERENCES

1. Package Insert, THEO Flex® Reagent Cartridge K4071, Siemens Healthcare Diagnostics Inc., 05/05/2015.
2. Package Insert, DRUG I CAL, Siemens Healthcare Diagnostics Inc., 09/2011.
3. Package Insert, Liquichek Immunoassay Plus Control, Bio-Rad Laboratories, 12/2015.

18. REVISION HISTORY

Version	Date	Section	Reason	Reviser	Approval
000	8/24/15	3.2	Change preferred specimen to plasma	L. Barrett	R. SanLuis
000	8/24/15	6.4,6.6	Replace LIS with Unity Real Time	L. Barrett	R. SanLuis
000	8/24/15	11.2	Reformat value to eliminate ≥ sign	L. Barrett	R. SanLuis
000	8/24/15	16	Update titles	L. Barrett	R. SanLuis
000	8/24/15	Footer	Version # leading zero's dropped due to new EDCS in use as of 10/7/13	L. Barrett	R. SanLuis
1	10/2/17	Header	Add WAH	L Barrett	R SanLuis
1	10/2/17	3.2	Remove specimen onboard stability	L Barrett	R SanLuis
1	10/2/17	4,5,6	Remove individual section labeling instructions and add general one	L Barrett	R SanLuis
1	10/2/17	6.1, 6.2	Update QC material and storage	L Barrett	R SanLuis
1	10/2/17	7.2	Change freezer upper limit to -50C	L Barrett	R SanLuis
1	10/2/17	10.5	Move patient review from section 6	L Barrett	R SanLuis
1	10/2/17	10.6	Remove repeat value below AMR/CRR	L Barrett	R SanLuis
1	10/2/17	15	Update to new standard wording	L Barrett	R SanLuis
1	10/2/17	17	Update QC product and PI dates	L Barrett	R SanLuis

19. ADDENDA

None