Document Control Legend

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Analytical Process Control Management

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TOTAL QUALITY CONTROL MANAGEMENT

Policy

Developing a comprehensive quality control management policy that will guarantee the evaluation of all day-to-day and month-to-month variability of all analytical control of tests.

Purpose

The purpose of quality control of analytical testing is to ensure the reliability of each measurement performed on patient samples. A quality control program is effective if it can be used to provide consistently precise and accurate biochemical control data. Because a technologist's actions should end with decisions based not only on the analytical significance but also on the medical significance of the quality control data.

This analytical quality control policy includes the following areas:

I. Key elements for quality planning
II. Assignment of responsibility for QC data
III. Validation of the analytical measurement range (AMR)
IV. Method calibration
V. Evaluation of daily control results
VI. Validation and reporting of patient test results

I. KEY ELEMENTS FOR QUALITY PLANNING

The aim of quality planning is to develop a structured approach in designing a quality control system that will ensure that each analytical process meets the defined specifications. This will be achieved by validating all tests, calibrating test when needed and running and reviewing controls every day. This will help us develop QC strategies that will alert us to changes in method performance that may affect patient test results. Also, this will allow us to minimize instances where our QC system identifies problems that may not exist and maximize the chances that a significant error will be detected quickly.

II. ASSIGNMENT OF RESPONSIBILITIES FOR QC DATA

Technologist:
The technologist that performs the analysis (calibrations, controls, and patient samples) is responsible for reviewing the control data in Schuylab. Each technologist is responsible for the daily evaluation of all Levy-Jenning's plots, in order to:

- Detect any shifts, trends or other unusual behavior in the data.
- Systematic or random error should be reevaluated by taking corrective action or consulting with the supervisor or quality control coordinator (Figure: 1).
- All corrective action will be recorded in Schuylab by adding a note and/or remark.
- Additionally, all technologists are obligated to add the date opened on all reagents, controls, calibrators etc. in the lab.

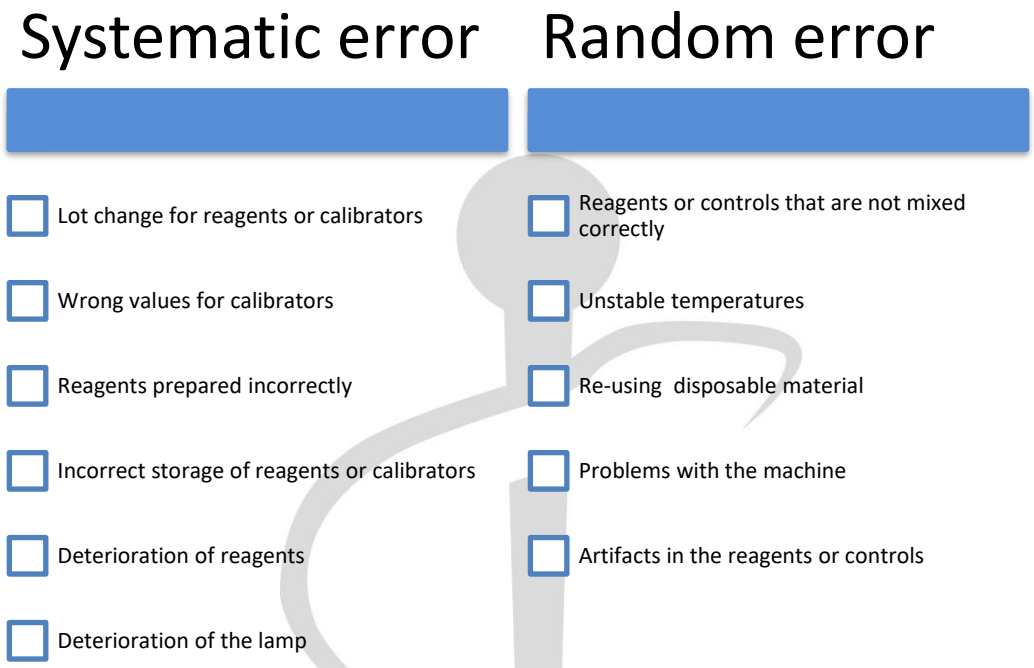


Figure 1: Causes for Systematic and Random Errors (Source: Course: Como hacer un buen control de calidad from Dr. Andreas Rothstein)

Analytical Quality Coordinator:
The Analytical Quality Coordinator (AQC) will monitor the quality assurance program and facilitates the entire quality assurance system by,

- Adding new controls in Schuylab when new controls, or new lot numbers are introduced.
- Reviewing all the daily controls for test violating the Westgard rules in collaboration with the technologist.
- Making the technologist re-evaluate a result and take corrective action if the value is out of range. This corrective action, as previously indicated, will be recorded in Schuylab.
- Has the final check of the day to ensure all records are complete and that the right corrective action has been taken for out of range control results.
- Reports on a weekly basis to the Process Manager the actions undertaken in response to the QC-flags.

Process Manager
In collaboration with the AQC:

- The Process Manager will review all quality assurance records with the Technologist's.
- Reviews all the preventative maintenance records at least once a month so that any discrepancies can be spotted as soon as possible.
- On a monthly basis meeting with management team. To prepare for this meeting, the AQC uses a checklist titled: "Quality Meeting Prep Sheet".

Quality Control Flow Chart

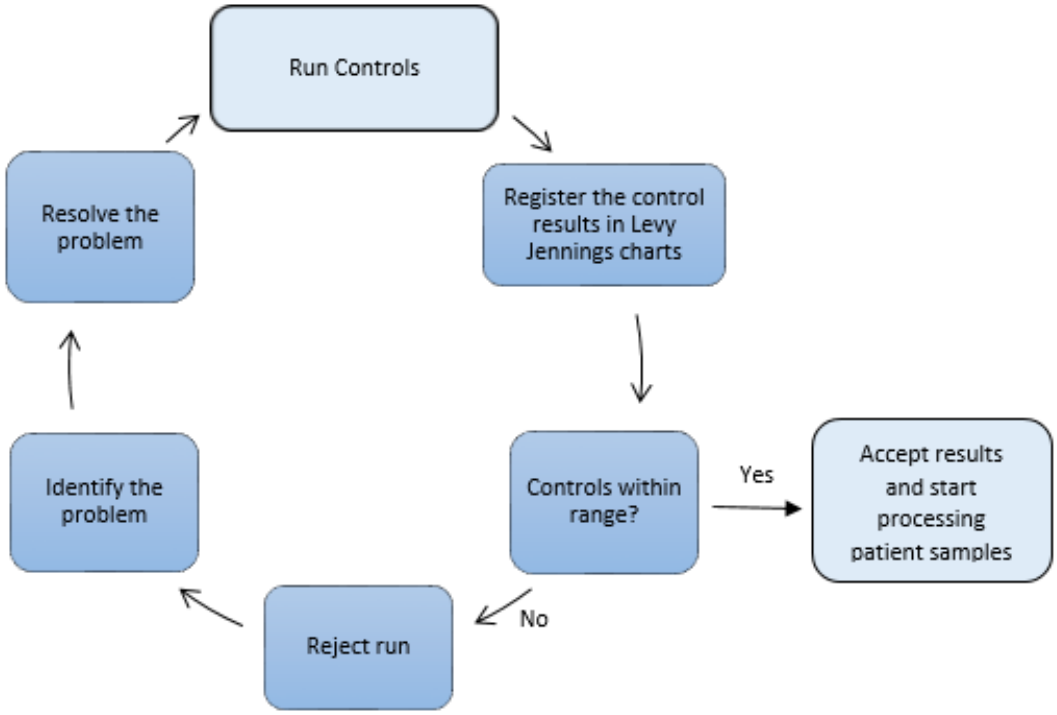


Figure 2: Chart indicating the actions that should be taken when a control result is not within range (Source: Course: Como hacer un buen control de calidad from Dr. Andreas Rothstein)

III. VALIDATION OF THE ANALYTICAL MEASUREMENT RANGE (AMR)

AMR validation is the process of confirming that the assay system will correctly recover the concentration or activity of the analyte over all the AMR. The AMR is the range of analyte values

that a method can directly measure on the specimen without any dilution, concentration, or other pretreatment not part of the usual assay process.

At LABdeMED, the AMR has been determined based on:

1. Manufacturer recommendations
2. Experimental evaluation

The AMR will be validated:

- At least once a year
- At changes in mayor system components as indicated by the managerial team
- When a complete change in reagent for a procedure is introduced.

In situations where more than one instrument is used for a given test for a analyte, these instruments will be checked against each other at least once a year for correlation of patient results.

IV. DETERMINATION OF METHOD CALIBRATION AND RECALIBRATION

Calibration is the process of testing and adjusting of an instrument, kit, or test system, to provide a known relationship between the measurement response and the value of the substance being measured. The reliability of the analytical values obtained with this procedure depends on the quality of the calibrators and calibration procedure used.

Re-calibration interval:

Manufacturers of method systems often recommend a standard interval when the method system is stable. The re-calibration interval may be extended if calibration verification is performed and the results meet the established criteria of the laboratory. Criteria for re-calibration include:

- QC fails to meet established criteria
- After major maintenance or service
- A change in lot number or new technique of reagent
- When recommended by the manufacturer
- A change of chemically or physically active or critical reagents

Calibration (or recalibration) should be recorded in Schuylab and also indicate the reason for (re-) calibration.

V. EVALUATION OF DAILY CONTROL RESULTS

Before analyzing patient specimens, the technologist runs daily control samples. Control samples act as a surrogate for patient specimens. They are processed like a patient sample to monitor the ongoing performance of the entire analytical process.

Daily quality control tasks include:

Preparation/adequate storage of the control samples.

Analysis of the control samples.

Evaluation of all control sample results by using the Levy Jennings plots.

Fill in control checklist.

Protocol for Accepting Assay Control Results

At least two levels of controls will be analyzed in the morning before the analysis of patient specimens. Depending on the analyte testing system and the established QC requirements, controls may also be run more frequently in one day.

Both level of controls should be within the established range, as determined from previous quality evaluation studies. This can be monitored by reviewing the Levy Jennings plot.

If both levels of control values are within the established range, accept the run as valid, and analysis on patient specimens can be performed.

If one of the controls is within the established range and one is outside the limits; bring this to the attention of the AQC or the Process Manager, who will decide whether to accept or reject an assay run. This decision will be noted in Schuylab.

If both controls are out of range, reject that run and check the controls for contamination (make new controls) or re-calibrate that test. Other steps that can be taken are mentioned in the next paragraph named '*Corrective Action for Control Values Outside of Established Range'.* Whichever decision was taken has to be recorded in Schuylab by AQC or the Process Manager using remark codes, if necessary, a note can also be written.

Review each assay procedure to determine if there are any unique actions to follow for that assay, instrumentation tolerance limits, and patient normal ranges.

QC data may be excluded from the database only under the following circumstances:

When QC values obtained is greater than 4 SD.

Data were obtained from QC material that were demonstrated to have been stored incorrectly.

Incorrect QC data has been introduced from clerical mix-ups.

Significant errors were identified in reagent constitution and/or handling.

Corrective Action for Control Values Outside of Established Range

If the results of the internal controls are outside of the established range:

Inspect the Levy-Jenning's plots to determine the rule that has been violated and the type of error (Figure: 1 & 3):

Systematic error

2_{2S}

4_{1S}

10_{X}

Random error

1_{3S}

R_{4S}

Correlate the type of error with potential causes.

Check reagent solutions (lot number, expiration date etc.).

Check calibration solutions.

Repeat calibration and controls.

Check mechanical and flow systems of instrument for proper delivery of reagents and sample. When the source of the error is identified repeat the analysis of the control specimen.

Check to see if clots interfere with the assay.

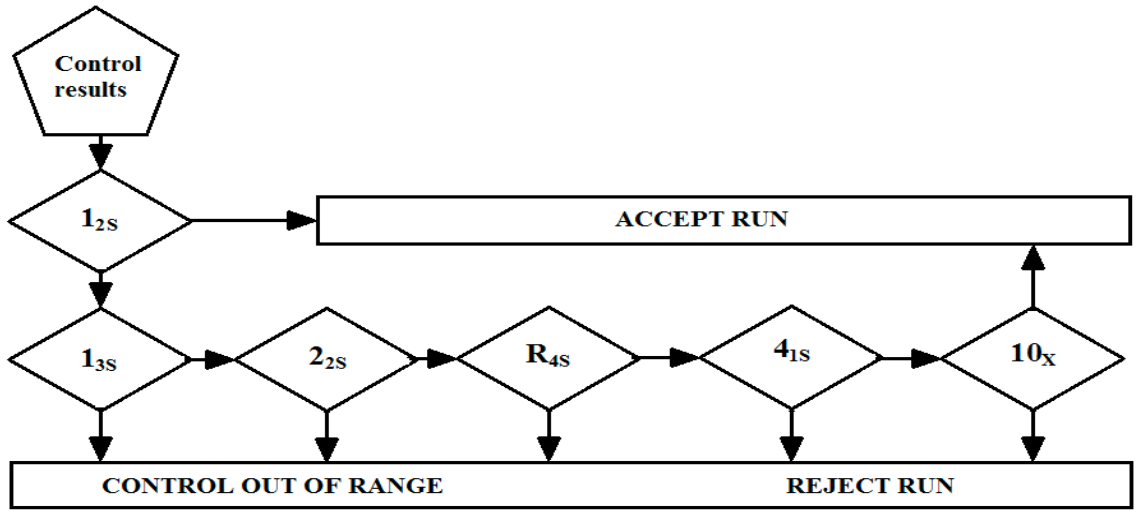


Figure 3: Chart indicating the actions that should be taken when a result violates one of the rules of Westgard. (Source: Course: Como hacer un buen control de calidad from Dr. Andreas Rothstein)

After all of these steps the control checklist has to be filled in and all actions taken should be written down. *(see an example: appendix 1)*

VI. VALIDATION AND REPORTING OF PATIENT TEST RESULTS

Test result validation process:

a. Verify if all controls are within range, and that there are no instrument malfunctions.
b. Separate patient test results in normal and abnormal.
    - In Schuylab, the patients with a result in the (normal) reference range will be accepted automatically.
    - Patients with a delta check or outside of the (normal) reference range will have to be accepted manually.
c. In the abnormal test results, identify the results that are in or out of reference range.
d. Verify if all conditions of the specimens with abnormal test results comply with the established laboratory criteria (lipemia, hemolysis or icteric).
e. Separate samples that need to be rerun (Critical values)
f. Consult Schuylab for the patient history to see if patient is known for any analyte abnormalities.

Critical values

Start by reviewing the result that are outside of the reference intervals. Reference (normal) intervals or interpretations should be reported with patient test results. If a critical value is measured, the following steps should be taken:

- Check the specimen for abnormalities.
- Re-check the controls to see if they are within range.
- Check other patient results within run (to see if there are any consistencies).
- Check patient history, possible diagnosis and/or medicine.
- Check correlations with other tests.
- If necessary, rerun test using another sample after consulting with the Supervisor.
- Additionally, report result and if necessary, re-draw the patient sample after approbation from the Supervisor to compare results.

A critical value will be notified immediately to the Process Manager, and she will decide:

- To re-run the test using another sample tube to confirm the result.
- How the clinical personnel responsible for the patient will be notified (fax and/or phone call).

The actions taken will be recorded in Schuylab by indicating the name of the supervisor and the personnel that was spoken with (Schuylab will save the time and date).

VII. PERFORMANCE EVALUATION AND QUALITY REQUIREMENTS DETERMINATION PRECEDURE

Purpose:

The performance of all quantitative tests will be evaluated in terms of imprecision and inaccuracy, and subsequently expressed in terms of total error of the laboratory (TE) compared to the total allowable error (TEa) and critical systematic error (ΔSE_{crit}).

Procedure:

1. For the initial evaluation, the recommended range by the manufacturer and a bias of 0 will be used.
2. After the initial values are obtained (n=20), a preliminary target and range will be calculated based on replication experiments, the mean (X) and standard deviation (SD).
3. After a month of operation, the preliminary range is evaluated, and a definitive range is assigned.
4. The final X, SD, CV, TE and ΔSE_{crit} will be determined.

Based on the ΔSE_{crit}, the QC performance of all tests may be classified as follows:

Total QC Strategy			
ΔSE_{crit}	**Error Detection**	**QC Rules**	**QC Strategies**
< 1.0	Low	Single rule: 1_{2S} or Multi rules: 1_{2S} / R_{4S} / 4_{1S} / 10_{X}	• Choose QC rules to maximize error detection • Increase N • Increase visual examination of QC chart, SQC, QI and the other QC
1.0-2.0	Intermediate	Single rule: $1_{2,5S}$ or Multi rules: 1_{3S} / 2_{2S} / R_{4S} / 4_{1S}	• Choose QC rules to maximize error detection • Increase N • Increase visual examination of QC chart, SQC, QI and the other QC

> 2.0	High	Single rule: 1_{3S} / $1_{3,5S}$ or Multi rules: 1_{3S} / 2_{2S} / R_{4S} / 4_{1S} / 1_{3S} / 4_{1S}	• Other QC

SQC = Statistical QC
QI = Quality improvement (Improvement of the precision, accuracy, and stability of the measurement)
Other QC = PM (Preventative maintenance), PV (Performance method validation), PD (Patient data QC)

Quality Requirements

At LABdeMED, quality requirements in all departments with qualitative tests will be defined in terms of a TEa for each analyte. The TEa is the amount of error that can be tolerated without invalidating the medical usefulness of the analytical results. The TEa values will be provided by CLIA and if not available this will be deduced from literature (1st CLIA, 2nd BV and 3rd CAP). If the calculated TE were greater than the TEa, this would cause a test result to be of unacceptable quality. Therefore, the TE will be re-evaluated for each quantitative assay at least every 4 months.

VIII. MONTHLY REVIEW OF DAY-TO-DAY QC VALUES

Purpose:

Monthly evaluation of the internal control values to ensure the precision of all quantitative tests.

Procedure:

Observed internal control values (X_{obs} SD_{obs} and CV_{obs}) will be compared to manufacturers target value or value established after validation procedures. If necessary, the TE will be calculated with these values and compared to the TEa.

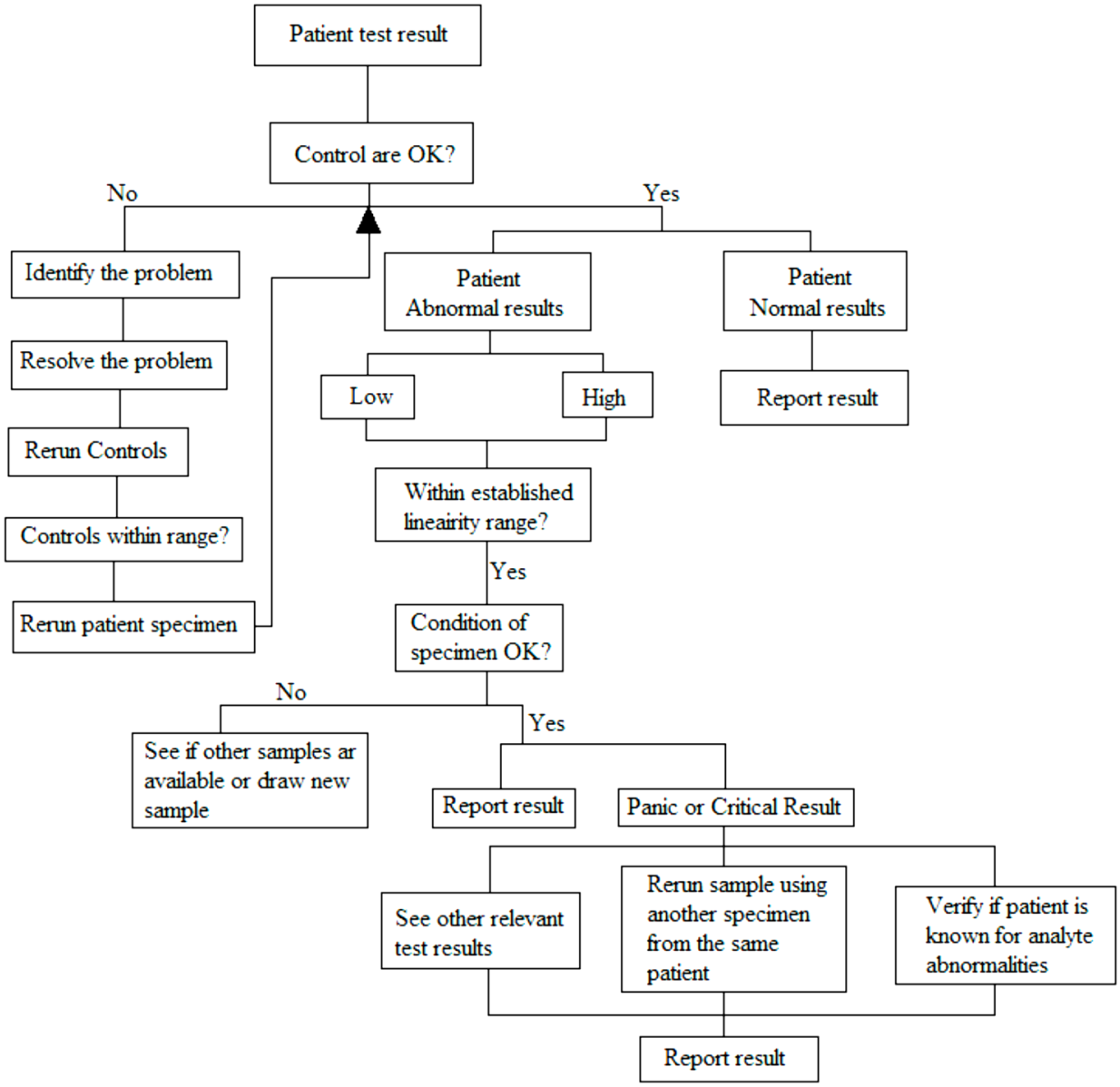
IX. PATIENT TEST RESULT VALIDATION AND REPORTING PROCESS

Purpose:

To ensure that the correct patient results are reported, the patient test results need to be validated.

Procedure chart:

When reporting a patient test result, we need to ensure that the controls have been run and that they are within range. But most importantly, the patient sample has to be collected and processed correctly. See flow chart below for an overview of the result validation and reporting process.



X. EVALUATION OF CRITICAL VALUES

Purpose:

A CRITICAL value is of great significance for the physician and the patient. Therefore, the physician should be notified immediately by fax or phone call.

Responsibility:

The technologist and the supervisor are responsible for the correct handling of the CRITICAL values. Such as, reporting, re-running the test and inspecting the sample.

Reported values:

The laboratory must report reference (normal) intervals or interpretations with patient test results, where such exist. If LABdeMED does not have a reference for an analyte, in such cases a range will be used from the literature.

Procedure:

Protocol for reviewing and reporting critical values

Technologist:

- Check the specimen for abnormalities.
- Re-check the controls to see if they are within range.
- Check other patient results within run (to see if there are any consistencies).
- Check patient history, possible diagnosis and/or medicine.
- Check correlations with other tests.
- Rerun test using another sample (verify result in Schuylab).
- Additionally, report result and if necessary, re-draw the patient sample after approbation from the Supervisor to compare results.
- Alert the supervisor of the result.

Supervisor:

1. Accept result in Schuylab.
2. Fill in pop-up:
    a. Check result verified
    b. Call or Fax physician
    c. Fill in physician's name and comment and accept

All this will be stored in Schuylab for future reference.

XI. DAILY, WEEKLY, MONTHY MAINTENANCE CHECKLISTS

Purpose:

Daily, weekly and monthly maintenance is essential for the devices to work properly and leads to less problems.

Procedure:

Each device has its own daily, weekly and monthly maintenance sheet in its logbook. This sheet must be filled out completely, on a daily basis. In case this action cannot be done, the technologists need to obtain previous approval from the Process Manager.

Devices that require a maintenance sheets are:

- Alegria
- IMMULITE 1000
- IMMULITE 2000
- DxC600 -I
- DxC600 -II
- SEBIA Capillaries -I
- SEBIA Capillaries -II
- CL4 (Coagulation)
- Roche COBAS Urine
- VesMatic Cube 30 -I
- VesMatic Cube 30 -II
- DxH600
- DxH800
- URISCAN
- MiniVidas

XII. STAT PATIENT PROCEDURE

Purpose:

STAT test requests, are for those patients that need their test results as soon as possible. With this procedure we want to ensure that these STAT patient results are ready within 4 hours after entering the lab. All STAT patients are marked and are dealt with instantly.

See PROCEDURE STAT Specimen (02-ANA-INT-CLC-205).

XIII. REGISTRATION MANUALLY ENTERED RESULTS

Purpose:

When a devise breaks down or there is no communication with Schuylab, some test results may need to be entered manually into the system. These manually entered results should be recorded to know from which device they came from.

Procedure:

Manually entered results shall be written down on a worklist made in Schuylab. These worklists will be saved in a binder for future reference.

Appendix 1

LAB de MED	DxC 600 DAILY QC MONITORING	
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Instrument: DxC 600 I or II **Technician:** **Date:**

Analyte	Levy-Jenning Chart						New Reagent	New Cal.	No Reagent on Board	ACTIONS
	QC-1		QC-2		QC-3					
	IN	OUT	IN	OUT	IN	OUT				
RF										
CRP										
ASO										
Albumin										
ALP										
ALT										
Amylase										
ASAT										
Ca										
Cholesterol										
Cl										
CPK										
CO2										
Creatinine										
D-Bil.										
Fe										
gGT										
Glucose										
HDL-Chol										
K										
LDLD										
LDH										
LIPASE										
Mg										
Na										
Phosphate										
T-Bil.										
Tot. Protein										
TRANSFERINE										
Triglycirides										
Ureum										
Uric Acid										
G6PD										

I. No flags > Check
II. 2SD flag > write 2SD
III. 3SD flag > write 3SD and action taken (rerun control, use new control, calibrate etc.)
IV. Any other flags, check the charts and take action if necessary