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GOOD CLINICAL LABORATORY PRACTICES (GCLP)

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We are…….

PPD Laboratory Services

- Medical Technologists
- GCLP training
- Laboratory Auditing

Why did we develop this program?

- Many requests from site laboratory staff members
- Lack of government standards that apply to clinical research labs
- Past trial problems
- Consistent audit findings

Customized Laboratory Training

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Why for Clinical Research Laboratories?

What is GLP?

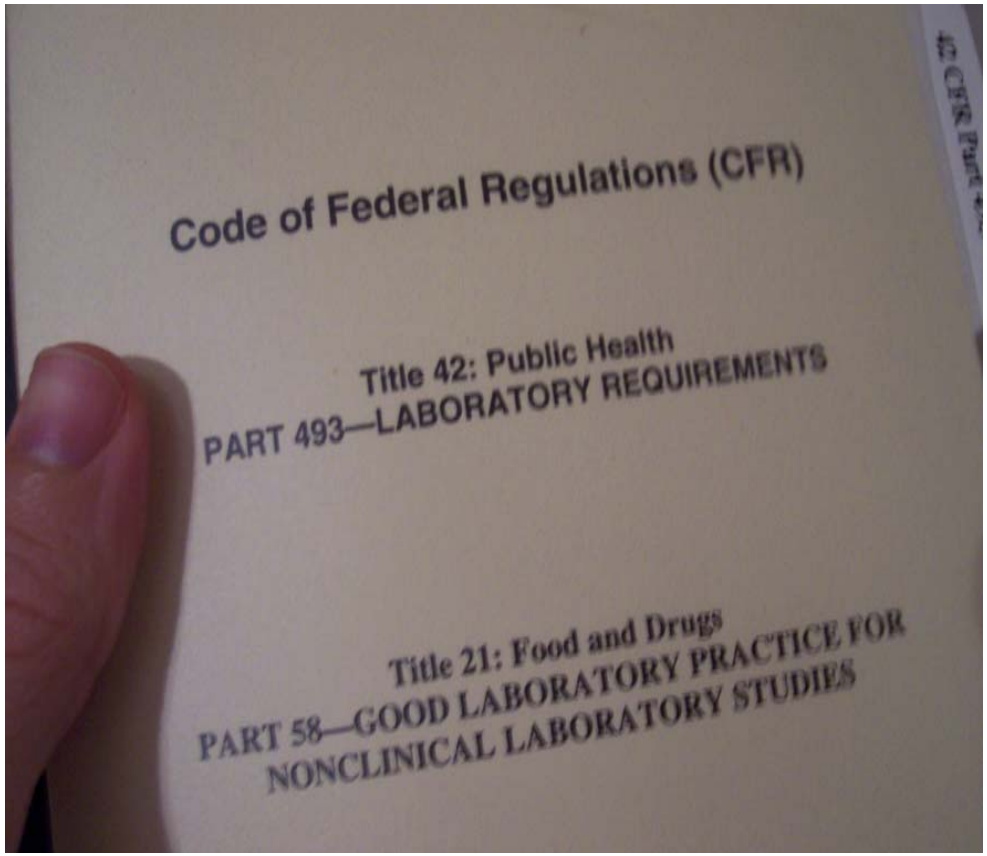
Regulation?

- **Lack of a single set of applicable government regulations/standards**

Regulation?

GLP – Pre-clinical

CLIA – Non-research



OECD?

GLP?

CLIA?

SANAS?

CAP?

Customized Laboratory Training

- Inconsistent laboratory practices potentially compromise study data
- Data set deemed unusable due to problematic laboratory results

Real Examples of Findings

- Discordant peak and trough drug level values
- False positive HIV western blot results
- Broken specimen chain of custody
- Poor Proficiency Testing Performance

Consistently noted audit findings

- Quality Control
- Safety
- Document Control
- Corrective/Preventative Action

Consistently noted audit findings

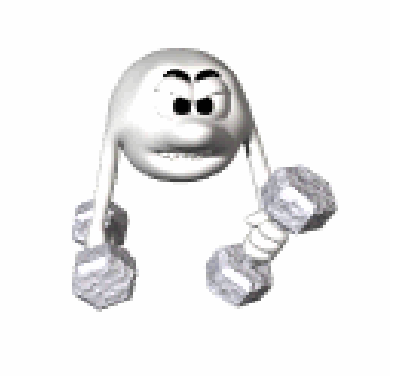
- Equipment Maintenance / Repair
- Organization / Personnel
- Specimen Chain of Custody
- SOP Format / Adherence

Workshop Approach

- **Didactic Presentation**

- **Objectives**

- **Activities and Discussion**



Workshop Modules

- Overview of Good Clinical Laboratory Practice (GCLP)
- Organization and Personnel
- Facilities and Equipment

Workshop Modules (continued)

- Records and Reports
- Testing Facility and Operation
- Specimen Management and Tracking

Workshop Modules (continued)

- Verification of Performance Specification
- Laboratory Safety
- Laboratory Information Systems
- Quality Management Systems

Workshop Materials

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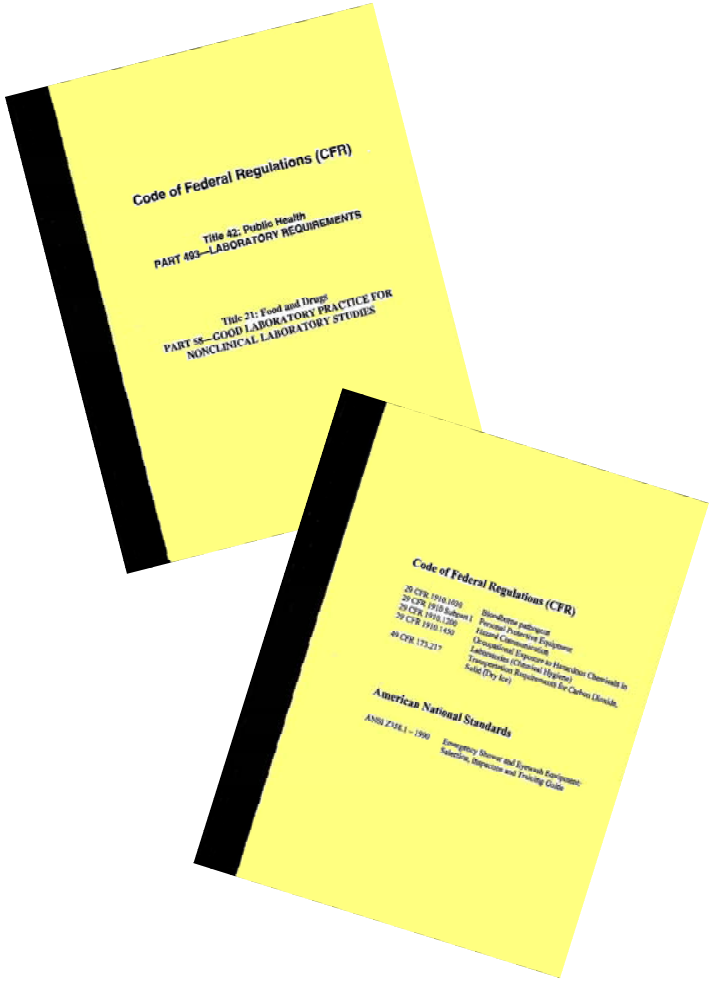
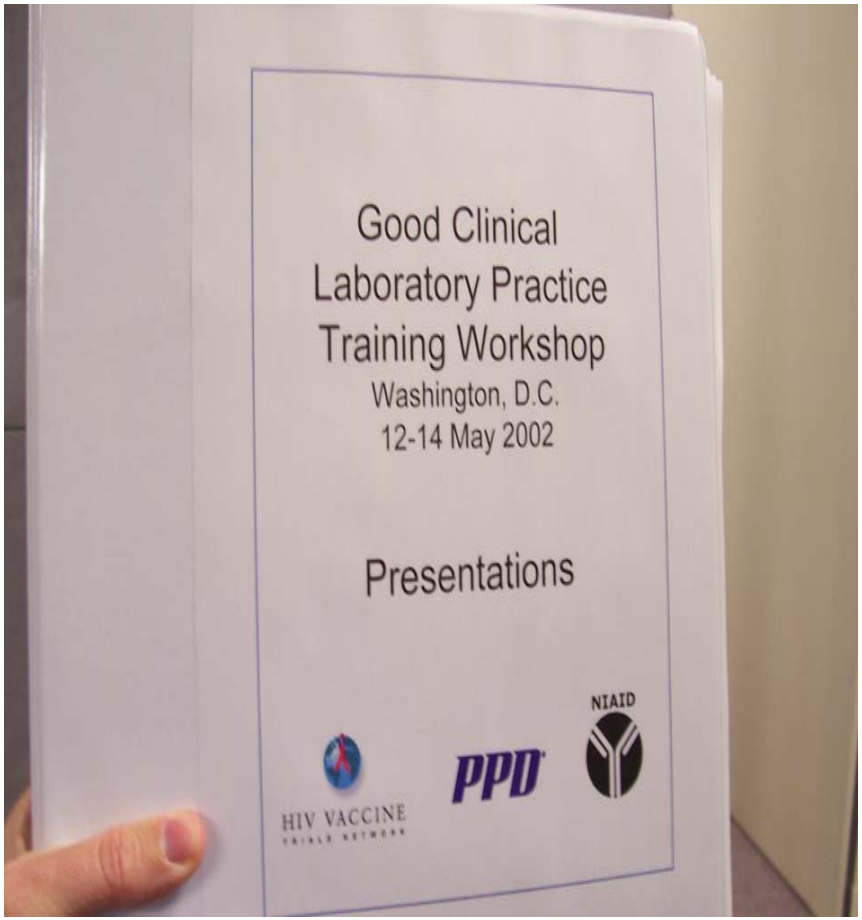
Regulation Booklets

GLP, CLIA and Electronic Records



Workshop Notebook



Reference materials

Module handouts

…and Workshop TRIVA!!!!

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You'll see Favorites like:

NAME THAT PARASITE,
"CELL"ULAR CALLS

and many more!

Workshop Principles

- How will WE succeed?
  - WE must interact
  - WE have to ask questions
  - WE must not sleep!
    - *Teamwork is essential*

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“Teamwork is so important that it is virtually impossible for you to reach the heights of your capabilities or achieve the goals that you want without becoming very good at it.”

Brian Tracy

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Good Laboratory Practices

21 CFR Part 58

History of Good Laboratory Practices (GLP)

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For about 20 years (1950 – 1970), one laboratory performed approximately 40 % of all US toxicology testing.

The Food and Drug Administration audited this laboratory as part of the New Drug Amendments of 1962.

History of Good Laboratory Practices (GLP)

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70% of the data was determined to be invalid because of discrepancies between study conduct and laboratory data

INVALID

Data from guest essay by Dr. Janine Denis Cook, Ph.D. on Westgard QC website (www.westgard.com)

History of Good Laboratory Practices (GLP)

Because of these discrepancies, the FDA decided to regulate laboratory testing.

- **1976 – GLP guidelines were proposed**
- **1978 – GLP guidelines were finalized**
- **1979 – GLP guidelines became effective**
- **1987 – GLP guidelines amended**

History of Good Laboratory Practices (GLP)

Why did the FDA feel the need for the guidelines?

The agency found that not all scientific work was necessarily <u>good</u> scientific work.

History of Good Laboratory Practices (GLP)

- **The FDA intended for the guidelines to:**
  - Assure quality and integrity of safety data
  - Allow accurate reconstruction of experiments
  - Allow for safe, quality products
  - Allow data to be comparable regardless of where generated

Good Laboratory Practices' Goals

GLP's Main Goal:

- To help obtain results that are
  - Reliable
  - Repeatable
  - Auditable
  - Recognizable

Good Laboratory Practices' Goals

- **GLP helps assure sponsors and regulatory authorities that the data submitted:**
  - **is a true reflection of the results obtained during the study**
  - **can be relied upon when making risk/safety assessments**

TRIVIA

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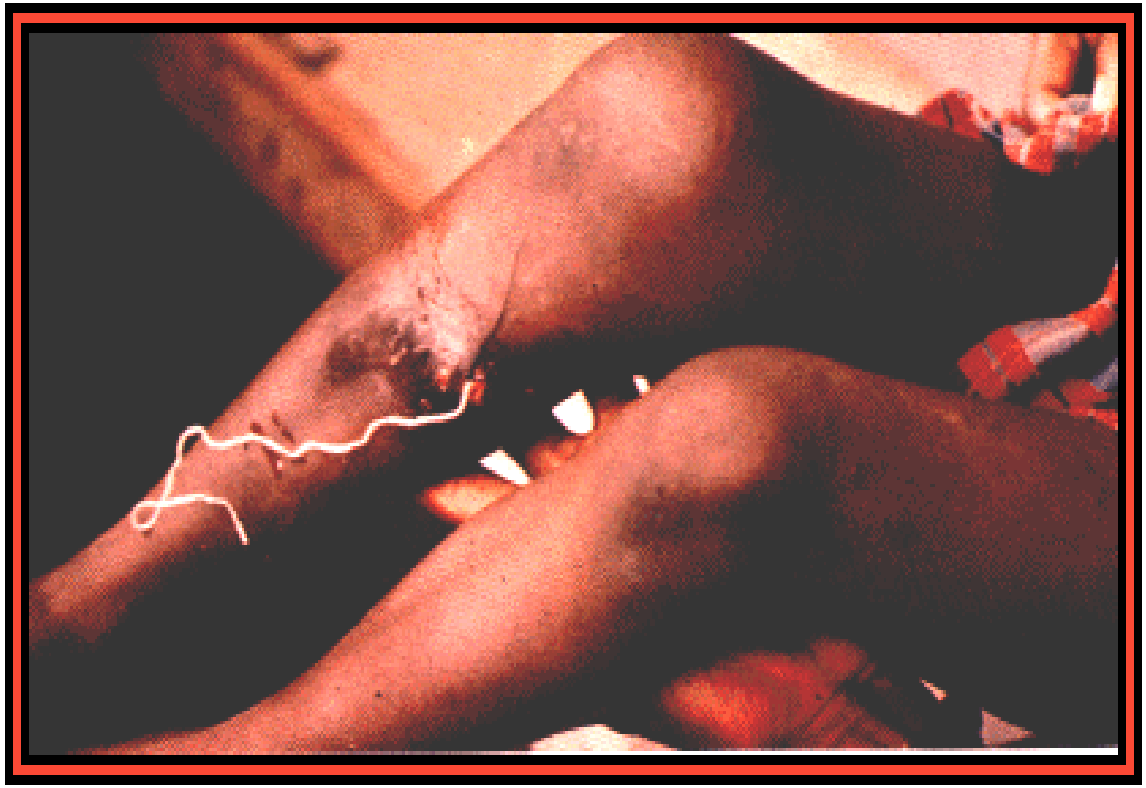
IDENTIFY THIS PARASITE:



GLP Subparts

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Divided into Nine Subparts

A. General Provisions

- **Provides general information such as the scope, definitions, applicability to studies performed under grants and contracts, and inspection of facilities.**

B. Organization and Personnel

- **The structure of the research organization and the responsibilities of the research personnel must be clearly defined.**

C. Facilities

- **Each testing facility shall be of suitable size and construction to facilitate the proper conduct of non-clinic laboratory studies.**

§58.1, 58.3, 58.10, 58.15

GLP Subparts

D. Equipment

- Governs equipment used for:
  - Generation of data, measurement of data, assessment of data, facility environmental control

E. Testing and Facilities Operation

- Sets guidelines for:
  - Standard Operating Procedures, reagents and solutions

F. Test and Control Articles

- Defines requirements for:
  - Labeling and storage of reagents and controls / standards

21 CFR 58 § 58.105 – 58.113

GLP Subparts

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G. Protocol for and Conduct of a Non-clinical Laboratory Study

- Defines:
  - Protocol elements, conduct, monitoring, specimen identification, data generation

J. Records and Reports

- Reporting of non-clinical laboratory study results, storage and retrieval of records and data, retention of records

21 CFR 58 § 58.120 – 58.130 21 CFR 58 § 58.185 - 195

GLP Subparts

K. Disqualification of Testing Facilities

–The purposes of disqualification are:

- Exclude testing facility which has failed to comply with GLP until it can be adequately demonstrated that such noncompliance did not occur during, or did not affect the validity or acceptability of data generated by a particular study.
- Exclude from consideration all studies completed after the date of disqualification until the facility can satisfy the Commissioner that it will conduct studies in compliance with such regulations.

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Why do *WE* need

Good Laboratory Practices

?

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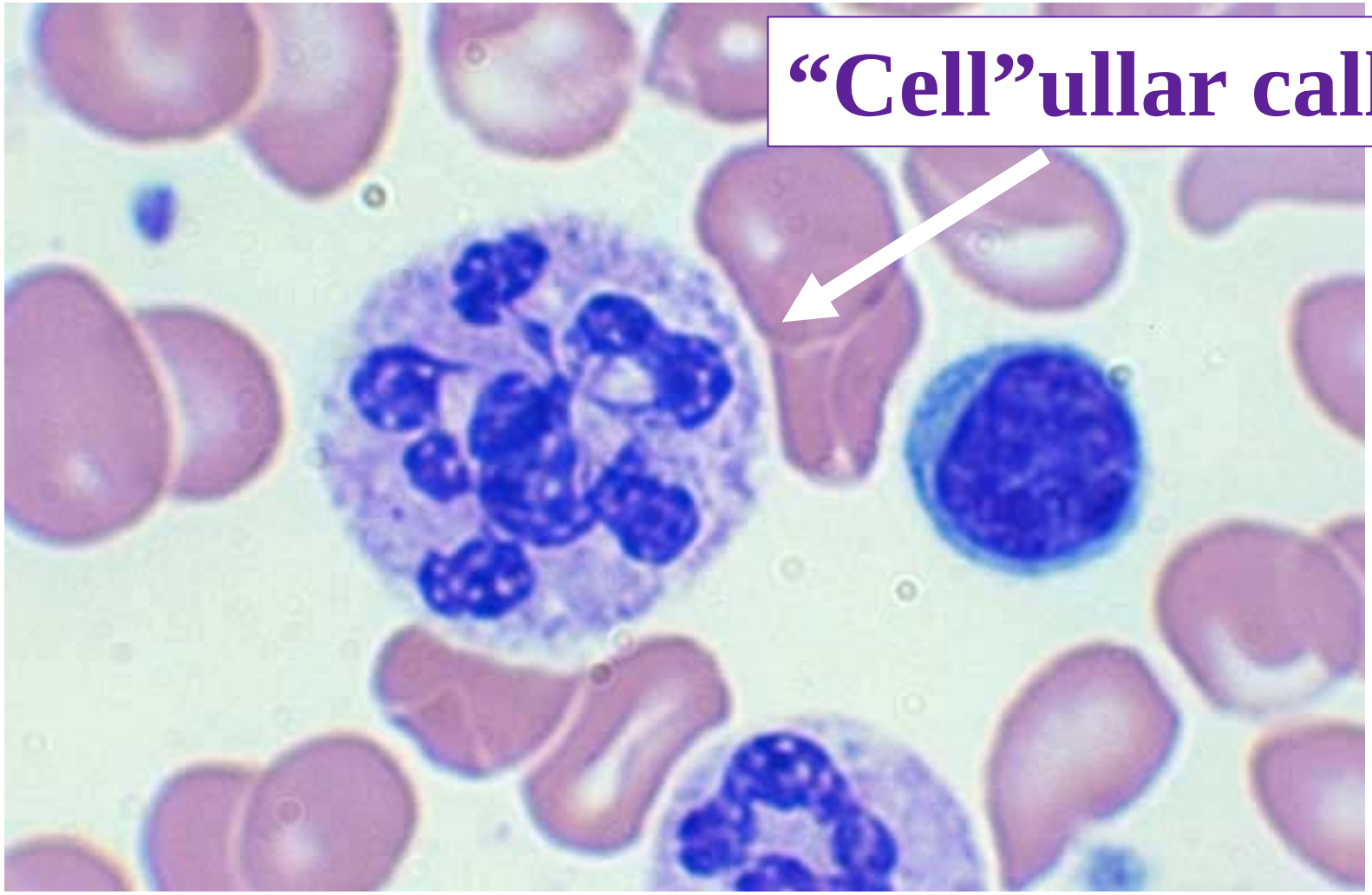
In order to provide data that is

- **Reliable**
- **Repeatable**
- **Auditable**
- **Recognizable**

we must have certain core practices.

Trivia!



History of CLIA

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GLP regulations, as they are written, offer few suggestions for compliance.

However, there is another set of regulations very similar to GLP utilized by clinical laboratories:

These regulations may be found in

42 CFR Part 493

Also known as:

Clinical Laboratory Improvement Amendments of 1988

or more simply, CLIA

History of CLIA

1967 - CLIA ’67 enacted

- **Regulated laboratories engaged in interstate commerce.**
- **Pertained to approximately 12,000 laboratories (mainly commercial and hospital).**

History of CLIA

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1987 – News media coverage

- "Pap mills"
- Quality of laboratory testing
- Number of labs lacking federal / state regulation
- Congressional Hearings

History of CLIA

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October 1988 - Congress passed the Clinical Laboratory Improvement Amendments

- **Site neutral**
- **Regulation determined by complexity of tests**
- **Also covered:**
  - **Physician office labs**
  - **Dialysis units**
  - **Health fairs**
  - **Nursing homes**

History of CLIA

- **February 28, 1992**
  - Final regulations published in Federal Register
- **September 1, 1992**
  - Implementation date
- **March 24, 1995**
  - Regulations for Provider-Performed Microscopy procedures published

Overview of CLIA

- **Established quality standard ensuring**
  - **Accuracy**
  - **Reliability**
  - **Timeliness of patient test results**

…regardless of where the test was performed.

Overview of CLIA

- Testing divided into three categories
  - Waived
  - Moderate
    - Provider-Performed Microscopy
  - High

Overview of CLIA

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- Personnel requirements
- Proficiency testing
- Inspection

Overview of CLIA

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Part 493, while designed for clinical laboratories, reflects all of the elements of GLP – but provides no direction on how to achieve them.

Other Agencies

- In addition to GLP and CLIA, there are several additional accrediting agencies
  - Examples:
    - College of American Pathologists
    - South African National Accreditation System

Program Construction

GLP, CLIA and accrediting bodies…….

Re-invent the wheel…no way!

We call this enhancement…….

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Good Clinical Laboratory Practices

GCLP

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Organization and Personnel

Characteristics of a Good Organization

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Qualities:

- Provision of adequate facilities
- Allocation of resources
- Definition of staff responsibilities

Characteristics of a Good Organization

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Qualities:

- Training of staff
- Good record keeping
- Organized archives

Personnel

- Lab required to demonstrate that its personnel:
  - Possess appropriate education
  - Are qualified
  - Are trained
  - Are experienced

…to perform the assigned tasks.

Personnel

- Personnel organization is reflected in:
  - **Organizational charts**
  - **Job Descriptions**
  - **CVs and Educational records**
  - **Training and Competency records**

Tasks and Responsibilities

Any quality system should be based on making laboratory personnel responsible for their actions.

Tasks and Responsibilities

Don’t do something where you don’t understand the reason, the context, and the consequences.

Tasks and Responsibilities

Each person signs his/her work and feels responsible for its correct completion.

Topics to Cover

- **Organizational Charts**
- **Job Descriptions**
- **Educational Records**

Topics to Cover

- Curriculum Vitae
- Training Records
- Personnel Competency
- Record Keeping

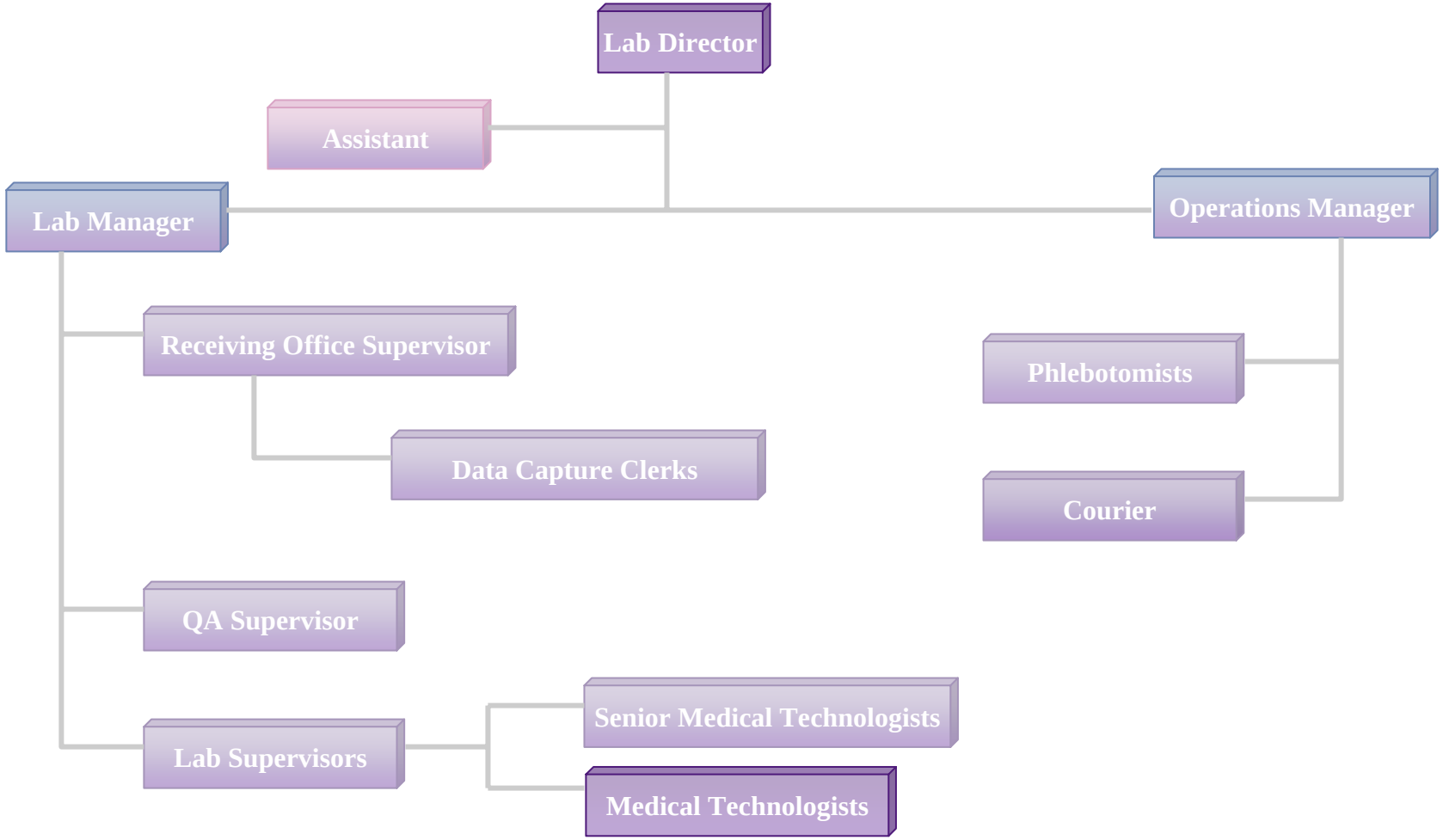
Organizational Charts

- **Reflects overall organization of a test facility**
- **Indicates reporting relationships between sections and personnel positions**

Organizational Charts

- **Outlines communication network**
  - Information
  - Decisions
  - Policies
- **“Organogram”**
  - Clearly outlined
  - Inclusive of all employees

Organizational Charts



TRIVIA

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Identify the trematode ova to *species* level

- Organizational Charts
- Job Descriptions
- Educational Records
- Curriculum Vitae
- Training Records
- Personnel Competency
- Record Keeping

Job Descriptions

- Describe the nature and level of work performed
- Reflect essential job duties, responsibilities, and major job functions
- Hold laboratory personnel accountable for performing duties

Job Descriptions

- Required for all personnel
- Outlines duties and responsibilities
- Updated regularly
- Signed and dated by:
  - Employee
  - Management

- Organizational Charts
- Job Descriptions
- Educational Records
- Curriculum Vitae
- Training Records
- Personnel Competency
- Record Keeping

Educational Records

- **Maintain copies of:**
  - **Educational certificates**
  - **Professional registrations**
  - **National or local licenses**

- Organizational Charts
- Job Descriptions
- Educational Records
- Curriculum Vitae
- Training Records
- Personnel Competency
- Record Keeping

Curriculum Vitae

- **Written summary of personal, educational records, and work history.**
- **Verify:**
  - **Sufficient theoretical knowledge**
  - **Practical experience**

Curriculum Vitae

- **Ensure CVs:**
  - **Exist for all laboratory personnel**
  - **Are documented in a standard format**
  - **Are current**

Curriculum Vitae

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Contents of a CV:

- **Name**
- **Education**
  - **Diplomas**
  - **Qualifications**

Curriculum Vitae

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Contents of a CV:

- **Professional experience**
  - **Affiliation with institutions**
- **Any publications**
- **Membership in associations**

- Organizational Charts
- Job Descriptions
- Educational Records
- Curriculum Vitae
- Training Records
- Personnel Competency
- Record Keeping

Training Records

- **The laboratory should:**
  - **Provide support for continuing education and professional development for the staff**
  - **Establish specific training requirements for all its personnel**

Training Records

- **Important that the laboratory identifies:**
  - **Institutional and facility training**
  - **Job training**
  - **Task-specific training**

Training Records

- **Training programs and other training-related activities should then be:**
  - **Developed,**
  - **Assigned to the employees,**
  - **Conducted, and**
  - **Documented.**

Training Records

Types of Training

Initial Training

Training that develops trainee's knowledge and skills to initially perform specific jobs.

Continuing Training

Training that maintains, enhances, or increases the proficiency of employees.

Retraining

The process of providing remediation or tutoring for employees deficient in specific job functions

Training Records

- **All training shall be documented and tracked in the employee personnel files.**
- **Training records format**
  - **Training logs**
  - **Training certificates**

Trivia

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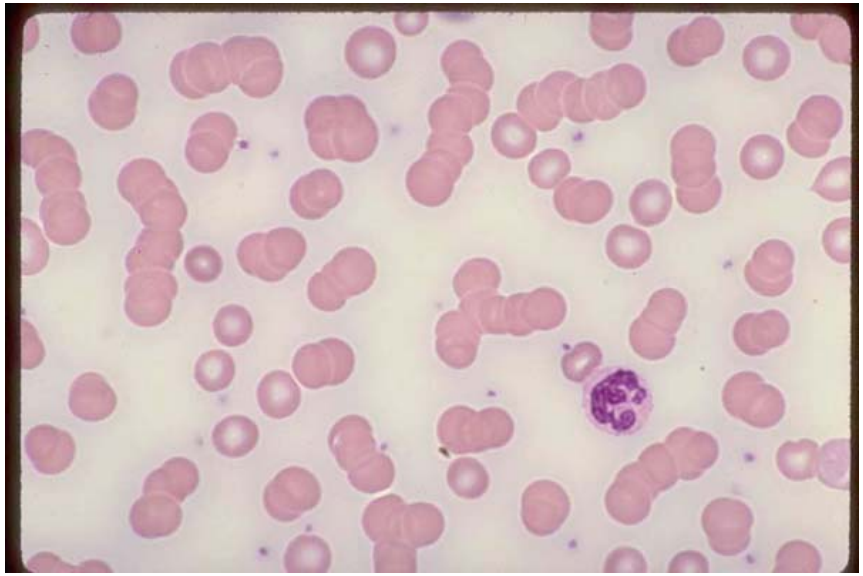
Name the RBC phenomenon on the slide

-AND-

make a differential diagnosis



ACTIVITY

Design a laboratory training log

- Organizational Charts
- Job Descriptions
- Educational Records
- Curriculum Vitae
- Training Records
- Personnel Competency
- Record Keeping

Personnel Competency

- Asks the question:
  - **Is this staff member able to do his/her assigned job properly?**
- And provides an answer:
  - **By comparing employee's performance against a set of criteria.**

Personnel Competency

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“Developing a highly visible, competency program is a key to organizational success”.

Demystifying the Competency Conundrum

Facilitated by: ***Sylvia McKee, MN, RN, BC***

Coordinator, Clinical Staff Development & Education, VA Salt Lake City Health Care System

Personnel Competency

Competent staff

=

Quality and accurate results

Personnel Competency

- **Assessments should:**
  - **Verify employees are competent to perform testing and report accurate and timely results,**
  - **Be able to effectively evaluate competency as well as identify areas for improvement,**
  - **Be meaningful and instructive.**

Personnel Competency

- **Training vs. Competency**
  - **Training:** the process or experience becoming proficient or qualified
  - **Competency:** the state of being adequately qualified

Personnel Competency

Competency is determined by comparing the actual performance against a performance standard.

Personnel Competency

- **Evaluation methods**
  - **Direct observations of specimen handling, processing, and testing**
  - **Monitoring of recording of results (data entry)**

Personnel Competency

- **Evaluation methods**
  - **Review of intermediate test results or worksheets, quality control records, proficiency testing results, and preventive maintenance records**
  - **Direct observation of instrument function and maintenance**

Personnel Competency

- **Evaluation methods**
  - **Assessing performance through testing previously analyzed specimens (blind samples)**
    - **CAP surveys**
    - **UKNEQAS**
  - **Written assessments / problem solving skills**

TRIVIA

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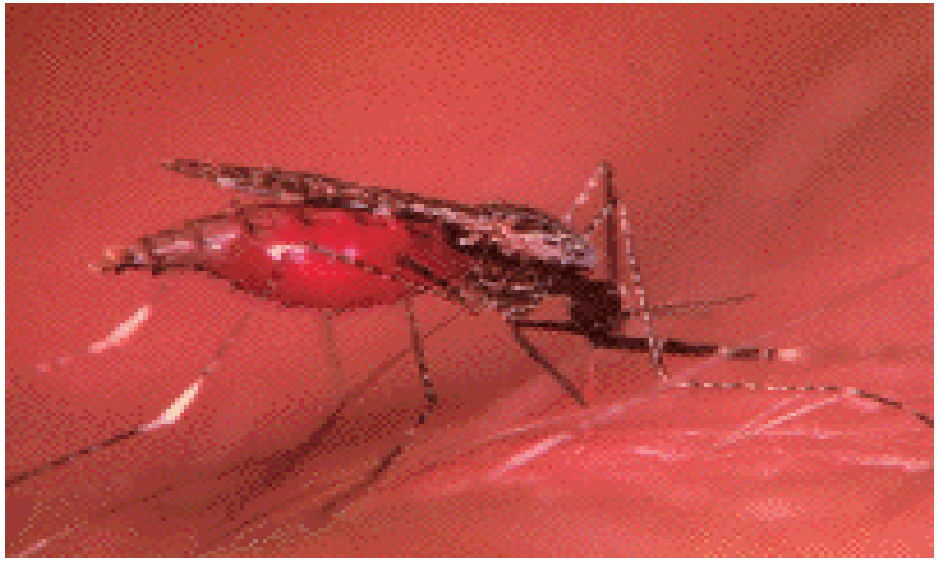
Name this insect that transmits malaria.

Name three other diseases transmitted by species of mosquitoes.



Personnel Competency

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ACTIVITY

- Enrique works in microbiology. His only duty is to inoculate (set up) cultures.
  - List two methods that can be used to evaluate Enrique's competency.

Personnel Competency

- Assess
  - Document
- Re-train, if necessary
  - Document
  - Retraining must occur when problems are identified with employee performance.
- Re-assess, if necessary
  - Document

Personnel Competency

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ACTIVITY

- **List five items to include on the competency evaluation document.**

Personnel Competency

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ACTIVITY

- Jill's competency evaluation was completed last week. The assessment showed she has difficulty differentiating immature WBC cell lines (e.g., myelocytes, metamyelocytes, etc.)
  - What should Jill's manager do next?

Personnel Competency

- **Evaluation Frequency**
  - **Competency must be assessed following training, and periodically thereafter.**
  - **Records must show what skills were assessed and how those skills were measured.**

Personnel Competency

- **To be competent, an employee must:**
  - **know how to perform a test**
  - **be able to perform the test without supervision**
  - **know when there is a problem with the test that must be solved**

TRIVIA

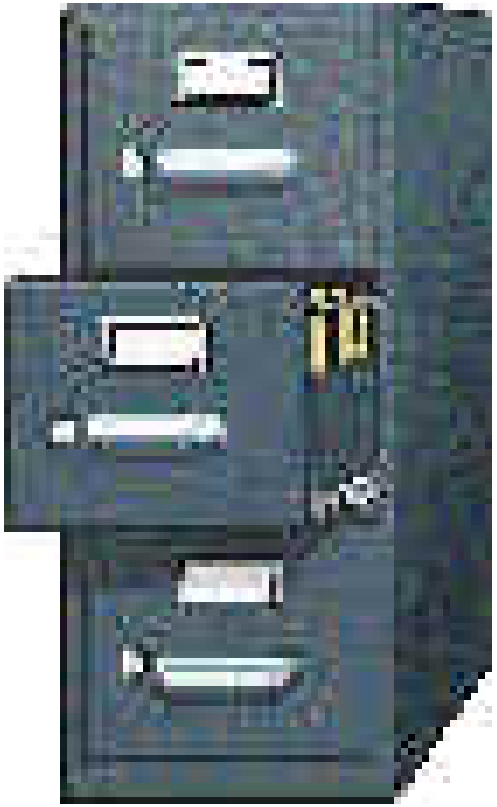
PPD

What is the national airline of Hong Kong?

- Organizational Charts
- Job Descriptions
- Educational Records
- Curriculum Vitae
- Training Records
- Personnel Competency
- Record Keeping

Personnel Record Keeping

- **Records should:**
  - **Document evidence of education, training, experience, and ongoing assessment of competence**
  - **Be maintained through the use of a record keeping system**
  - **Maintained for all laboratory employees**
  - **Be reviewed regularly**



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“When done properly, competency assessment will reward our organizations and assist us in providing the best possible results.”

Competency Assessment in the Clinical Microbiology Laboratory
Susan E. Sharp and B. Laurel Elder

References

- "Technical Criteria for Laboratory Accreditation (Medical Laboratories)," Hong Kong Accreditation Service, June 2003
- SANAS Accreditation Checklist
- College of Physicians and Surgeons of Saskatchewan Checklist
- Johns Hopkins Malawi College of Medicine Laboratory
- BOTUSA HIV Prevention Research Laboratories
- Kilimanjaro Reproductive Health Program Laboratory
- Makerere University – Johns Hopkins University Research Laboratory

Facilities and Equipment

Overview

- Laboratory Facilities
- Data Storage Facilities
- Environmental Control
- Equipment Maintenance
- Equipment Inventory
- Reagents
- Reagents Inventory

Facilities

The testing facility must be suitable in

- Size
- Construction
- Location

to meet study requirements and minimize disturbances that would interfere with the validity of the study

- OECD GLP -

Facilities

- **Suitability of facilities and environmental conditions for the range of tests affect:**
  - **Integrity of the samples tested**
  - **Performance of the equipment**
  - **Competent performance of lab staff**
  - **Compliance with the conditions set in the test**

Facilities

- **Should be set up provide a logical flow of work to prevent:**

  - Risk of specimen mix up
  - Accidents (e.g. sample spillage or loss)

Facilities

- **Should provide for:**
  - **Comfortable working environment for staff**
  - **Appropriate conditions to be maintained for sample and reagent integrity**
  - **Adequate ventilation**
  - **Control of personnel traffic**

Facilities

- **Essential to maintain a high standard of cleanliness**
  - **Necessary to provide work areas which are easily cleaned and impervious to spillages.**
  - **Ensure regular and thorough housekeeping**

Facilities - Data Storage

- **Data should be stored in a safe and secure manner prior to archiving**
- **The archive area should be:**
  - **Restricted and kept locked at all times**
  - **Installed with smoke detectors**

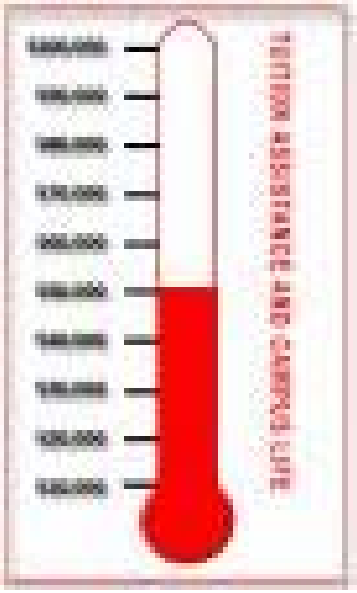
Environmental Control

- The facility should permit test methods to be conducted in an environment controlled for temperature, moisture and other interferences.
  - Ambient room temperature
  - Humidity (if applicable per manufacturer specifications)
  - Dust

Environmental Control

- Good practice to monitor and document temperature of all the temperature sensitive equipment and room temperature.

Why?



Environmental Control

- Predetermined limits

- How are you aware that the temperature limits have been exceeded?

Temperature logs

Temperature Monitoring Chart - Refrigerators

Refrigerator #:_____ Month:_____ Year:_____

Acceptable Range: 2 - 8°C

	Day																													
Reading °C	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
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Reviewed by:_____ Date:_____

Comments:_____
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TRIVIA

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What is the medieval name for China?

CATHAY

Environmental Control

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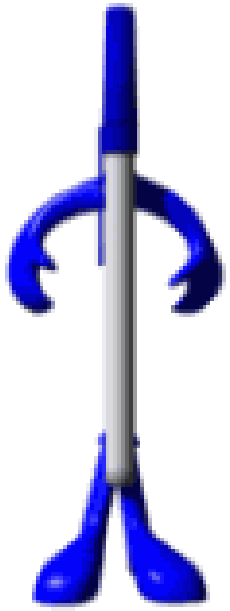
Ideal to have policy on temperature monitoring

- **What should a temperature monitoring policy include?**
  - **Provisions for 24 hour coverage ideally**
  - **Electronic or personnel coverage**

Environmental Control

- **Evaluation of temperature monitoring data**
  - **Ensure appropriate corrective / preventative action is taken when problems occur**



Environmental Control

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Back-up plan in the event of equipment failure

Calibration vs. Calibration Verification

- **Calibration** is the process of testing and adjusting the instrument or test system readout to establish a correlation between the instrument's measurement of the substance being tested and the actual concentration of the substance

Calibration vs. Calibration Verification

- **Calibration Verification** means testing materials of known concentration in the same manner as patients specimens to assure the test system is accurately measuring samples throughout the reportable range

Environmental Control

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Is there a National Institute of Standards and Technology (NIST) certified thermometric device available?

- The laboratory must have access to an appropriate thermometric standard device (reference thermometer) and all non-certified thermometers must be checked against it.

Environmental Control

- **If the NIST certified thermometric device is available…….**

Keep the traceable certificate.

Environmental Control

- Frequency of thermometer validation
- Correction factors

Environmental Control

ACTIVITY

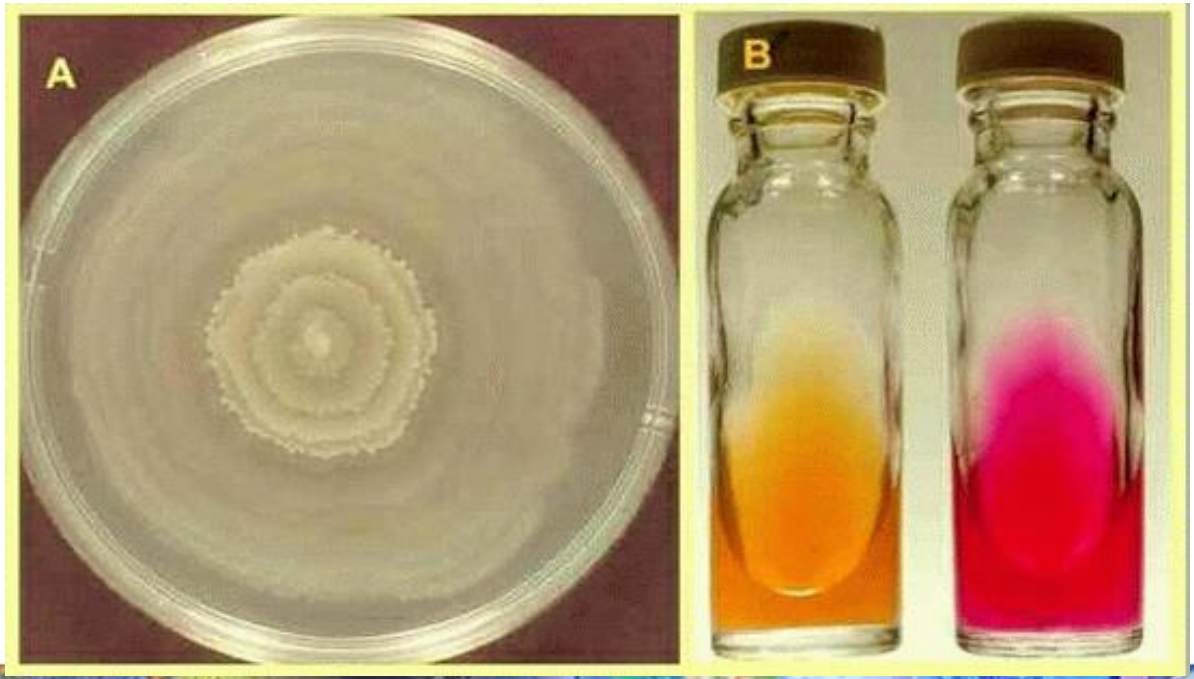
Design a log for the validation of non-certified thermometers

TRIVIA

What gram negative rod typically

“SWARMS”

culture plates?



Equipment

“It is Ideal to establish and implement a program which regularly monitors and demonstrates proper calibration and function of instruments”

-HOKLAS QM Policy

Program should follow manufacturer’s recommendations.

Equipment

Therefore, all instrumentation and equipment must be adequately

- Operated,
- Inspected,
- Cleaned,
- Maintained,
- Tested, and
- Standardized

Equipment

- **Equipment performance, use and maintenance should be documented and records kept.**

Equipment

- Daily, weekly, or monthly maintenance plans should exist for all equipment
- Preventative Maintenance should be conducted per manufacturer specifications
- Preventative Maintenance logs have to be retained

Equipment

PPD

It is ideal for PM logs to be reviewed by the supervisor at monthly intervals

WHY ?

Equipment

- **An equipment service schedule should be maintained**
  - **The list should include all equipment and the accompanying due dates of service and calibration**
  - **Ideal for the list to displayed**
- **Service records should be maintained as well**

PM / Calibration Plans

ABC Laboratory

Equipment Preventative Maintenance and Calibration Plans

Equipment	Calibration / Service/ Validation Frequency	Schedules			
		Due Date	Performed? (Sign/Date)	Due Date	Performed? (Sign/Date)
Cobas Integra 400 plus	Semi Annual	May 2006		November 2006	
Coulter AcT-5 Diff	Semi Annual	February 2006		July 2006	
Bio Safety Cabinets	Annual	June 2006			
Pipettes	Semi Annual	March 2006		August 2006	
Mettler Balance	Annual	July 2006			
ELx 808 Plate Reader	Semi Annual	January 2006		June 2006	

Equipment

Challenge

Is it necessary to document an analyzer SOP if the manufacturer's operator manual is available?

ACTIVITY

- **Design a BD FACS Calibur maintenance checklist using the Operator manual information provided**

Equipment - Pipettes

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Adjustable and fixed-volume automatic pipettes and dispensers

- **Calibration / Calibration Verification of pipettes must be performed before being placed in service initially, and at specific defined intervals and the results of such testing documented.**

Equipment - Pipettes

- **CAP:** Check pipettes prior to putting into service

  At defined intervals, every six months minimum

- **ASTM E:1154-89 11.23:**

  Evaluate pipettes at least quarterly

Equipment - Pipettes

- **CAP:** Check pipettes prior to putting into service

  At defined intervals, every six months minimum

- **Other Standards:**

  Evaluate pipettes at least quarterly

Equipment - Adjustable and fixed-volume pipettes

PPD

- **Factors in Determining Calibration/Calibration Checks Frequency**
  - ✓ Accuracy required
  - ✓ Frequency of use
  - ✓ Skill and training of the operator
  - ✓ Proper and careful handling
  - ✓ Type of liquid dispensed by the pipette

Equipment

- Pipette Methods (check/calibration)
  - Gravimetric
  - Colorimetric

- Outside service representatives (Calibrator Providers)
- All pipettes that fail calibration should be removed from the work areas

Equipment - Pipettes

Gravimetric Method

- **Principle:** Given a certain mass of water with a known specific gravity, its volume can then be calculated.

Equipment - Pipettes

PPD

Gravimetric Method

- **Requirements:**
  - ✓ Controlled environment
  - ✓ High precision balance
  - ✓ Skilled pipette technician
  - ✓ Use of statistics

Equipment - Pipettes

- **Colorimetric or Photometric Method**
- **Principle:** Based on Beer's Law - The color density of a solution is directly proportional to the concentration of a test substance or coloring reagent in that solution.

Equipment - Pipettes

- **Colorimetric or Photometric Method**
- **Requirements:**
  - ✓ Spectrophotometer
  - ✓ Reagent dyes
- **Recommended:**
  - ✓ When optimal accuracy is required
  - ✓ For extremely low-volume pipette calibration, in the 2 microliter range

Equipment - Pipettes

- **Calibrator Providers**
  - ✓ Retain the services of an accredited testing laboratory
  - ✓ Accredited to a national or international standard ISO/IEC 17025
  - ✓ Proven ability to adhere to rigid regulation and protocols

Equipment - Centrifuges

PPD

Centrifuges

- Should be kept clean
- Properly maintained (regular service)
- Operating speed should be checked periodically (tachometer)
- Advisable to have safety buckets to minimize exposure to aerosol.

Equipment - Analytical Balances

PPD

Balances

- Check weights to be used at a predetermined frequency (manufacturer suggestions)
- Serviced and calibrated periodically by qualified personnel (per manufacturer's instruction)
- Placed so that vibration does not affect the readings.

ACTIVITY

- **Design a balance calibration check log**

Balance Calibration Check Log

ABC Laboratory

Weight Verification Log – Mettler Balance

Date:_____ Performed by:_____

	Reference Weights					
	0.100 g	0.200g	0.500g	1.0g	5.0g	10.0g
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
Mean						
SD						
%CV						
Pass/Fail						

Reviewed by:_____ Date:_____

Comments:_____

_____

_____

Laminar Flow Hood

- Annual certification
- Trained Technician
- Daily air flow checks

Laminar Flow Hood

- **How should flow hood certification be documented?**
  - **Must a sticker be affixed to the unit?**
  - **Is a sticker good enough?**

Trivia

Identify the countries, Mongolia and Myanmar from the map of Asia

Trivia

Equipment - Generator

- Records to verify that the back-up generator system is in place and operational need to be maintained by the laboratory.
- Ideal to have an SOP for generator maintenance, which include the frequency and procedure of maintenance and testing

Equipment - Generator

- Logs should document periodic checks on;
  - Oil, coolant fuel levels
  - battery
  - start-up and functional checks etc.

Equipment

- **How should failures and corresponding corrective / preventative action be captured?**
  - Documentation of the entire process (failure through resolution)

Examples?

Corrective Action Logs

PPD

ABC Laboratory

Corrective Action Report

Section/Analyzer:_____

Problem Statement/Non Conformity
Completed by:_____ Date:_____

Root Cause
Completed by:_____ Date:_____

Corrective Action
Completed by:_____ Date:_____

Effectiveness of Corrective Action
Reviewed by:_____ Date:_____
Review Comments:

Corrective Action Logs

PPD

ABC Laboratory

Corrective Action Log

Section/Equipment:_____

Date	Problem/Non-Conformance	Initials	Corrective Action	Initials	Date

Reviewed By:_____ Date:_____

Comments:_____

_____

_____

Inventory

- **All laboratory equipment should be managed by an inventory system.**
  - **Electronic or Manual**

Inventory

- **What should an inventory include?**
  - Equipment make and model
  - Serial number
  - Facility ID number

Inventory

- **What should an inventory include?**
  - Location
  - Disposition information
  - Service contract information
  - Date acquired

Inventory

- **Inventory updates**
- **Frequency?**
  - Whenever new equipment is acquired or retired?
  - Annually?
  - Facility move?

Reagents

Reagents - Storage

PPD

- ✓ Procedures shall be established…to ensure that there is proper storage.

Reagents and kit materials should be stored as required by the manufacturer.

§58.107

Reagents

- They must be properly labeled:
  - Contents
  - Open / Reconstitution date
  - Expiration date
  - Storage requirements
  - Initials of personnel who made up the reagent

Reagents

- **And…….**
  - Safety information as required by your local regulatory agency.
  - Hazard of the chemical/Target Organ

Inventory Control

- **Inventories make reagent management easier**
  - Helps in identifying expired materials
  - Helps with ordering needs

Water Quality

- **Monitoring water quality:**
  - ✓ **Documented statement of policies**
  - ✓ **Procedures that specify schedules and methods of quality checks**
  - ✓ **Tolerance limits**
  - ✓ **Records of corrective action taken when tolerance limits exceeded**

Storage

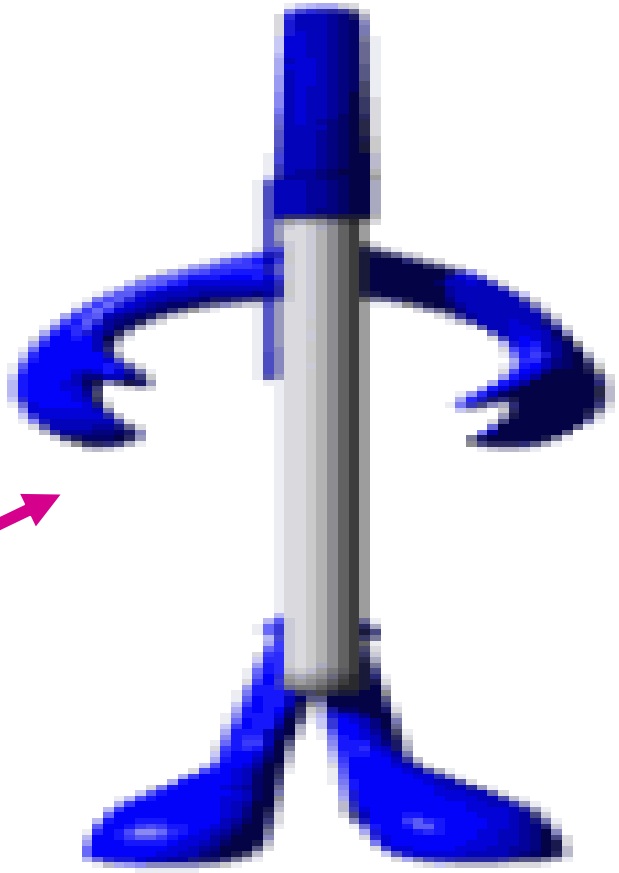
PPD

Reagents and kit materials should be stored as required by the manufacturer.

PPD

Whatever you do,

PLEASE



TRIVIA

- **If the centrifugation and separation of whole blood components is delayed for greater than an hour, what chemistry analytes could be effected?**

PPD

“Maintaining your equipment is paramount in maintaining the quality of your product”

Frank Rabey

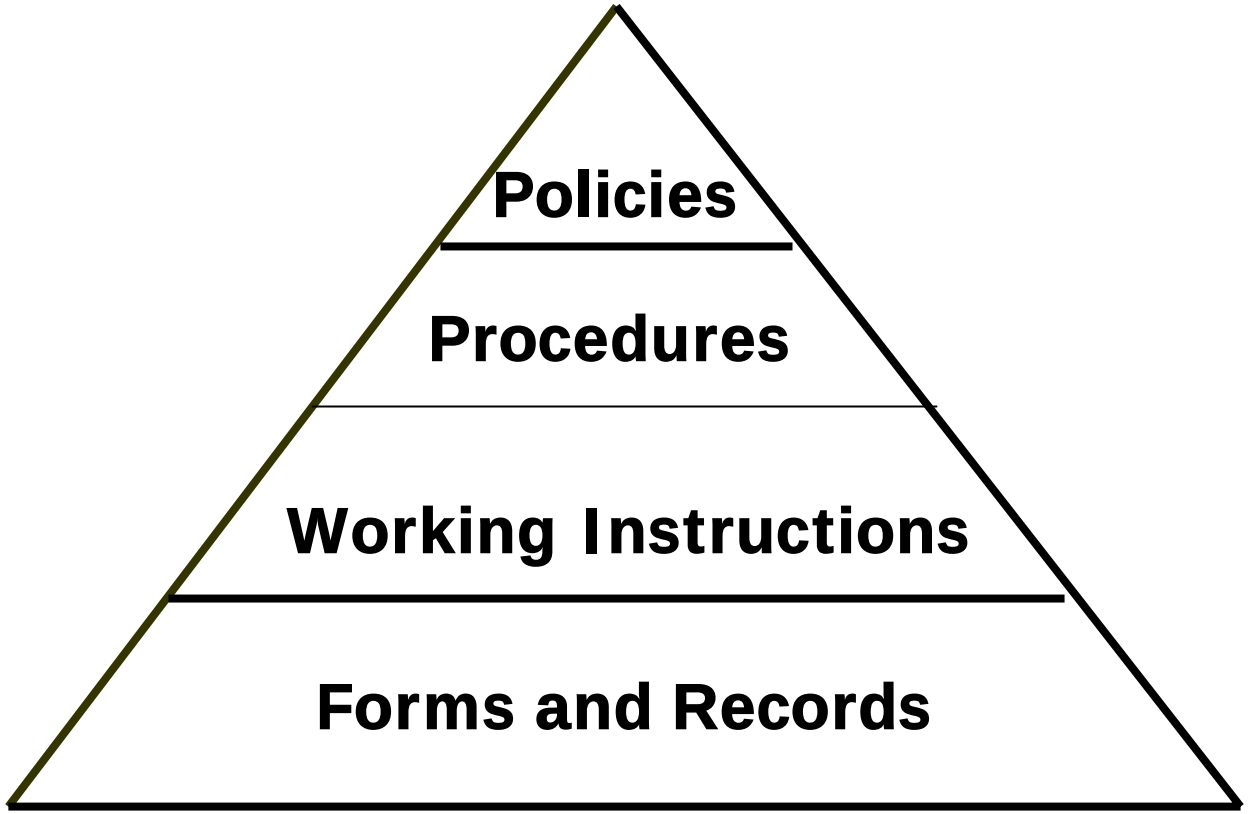
Review

- **Any issues or concerns you have regarding implementing these practices in your laboratories?**

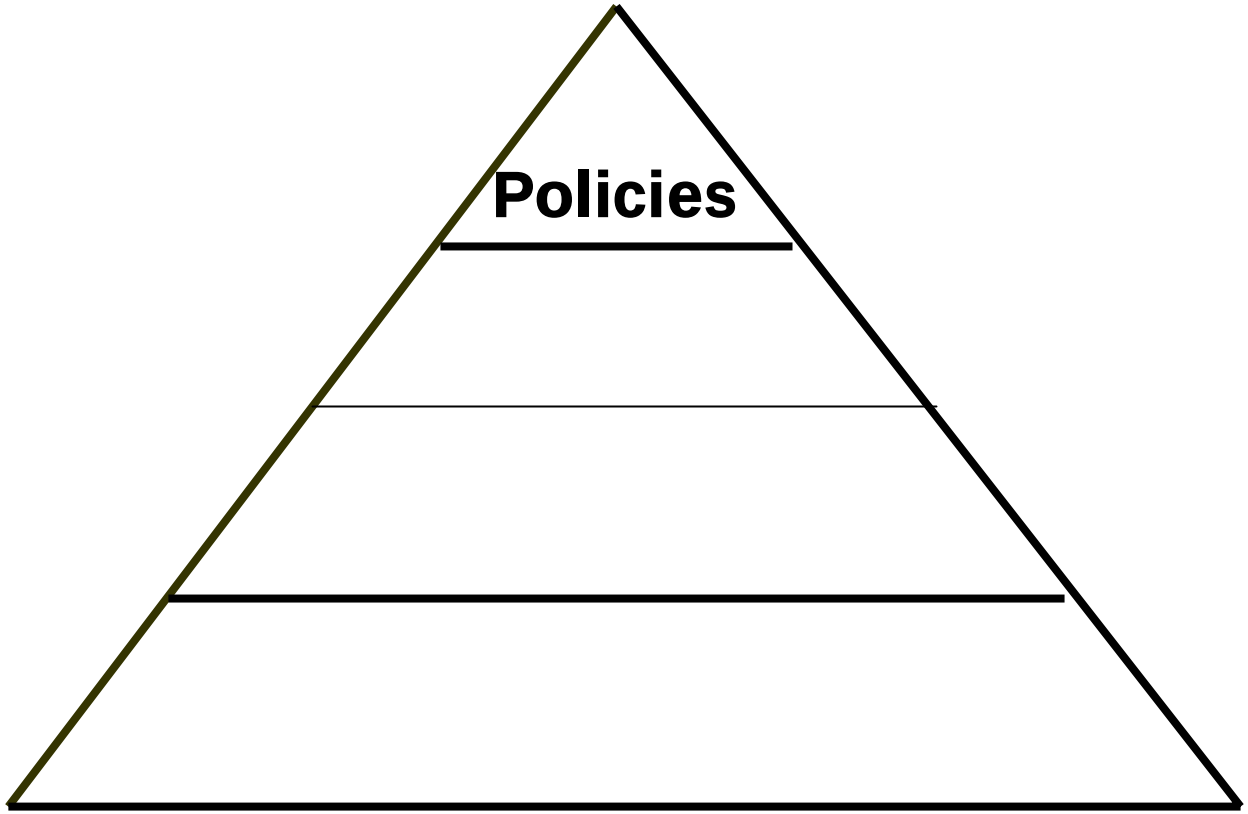
PPD

Records and Reports

Approach to Laboratory Documentation



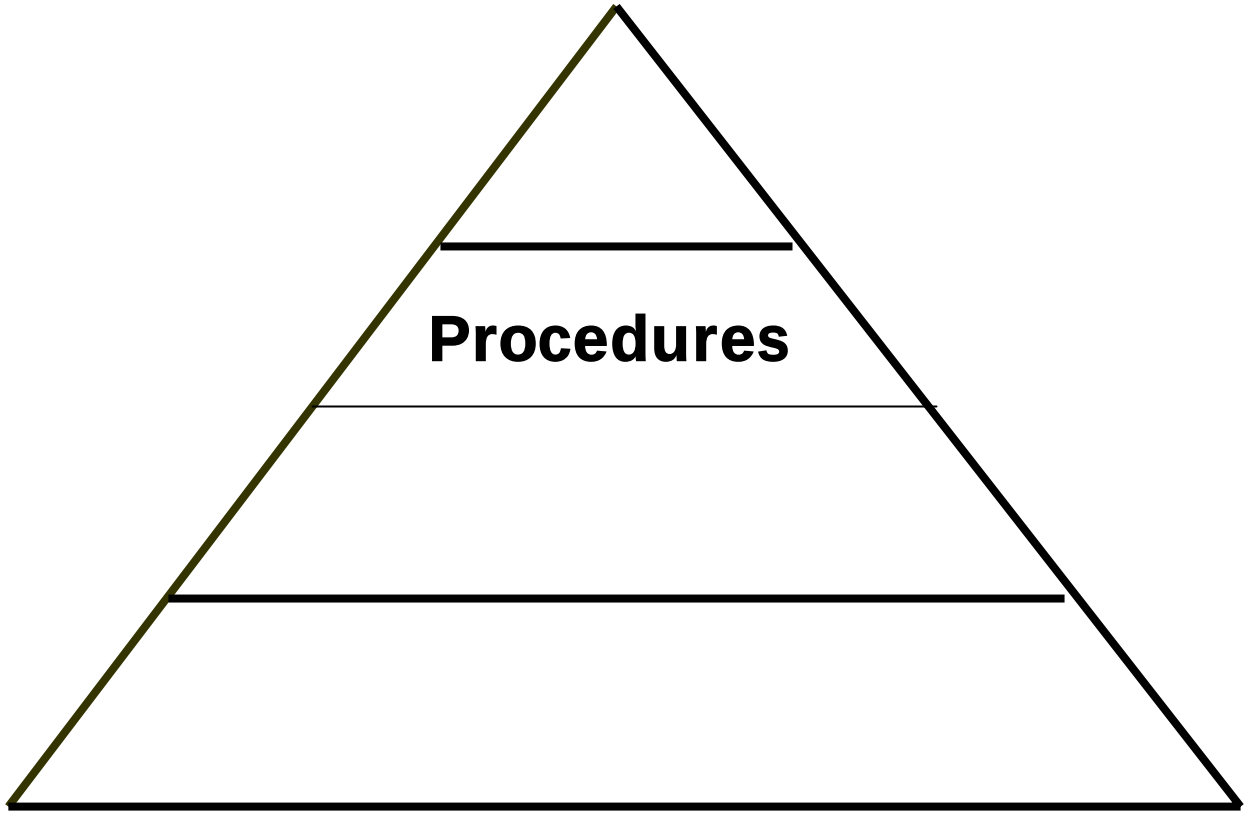
Approach to Laboratory Documentation



Policies

- **Provide a statement of intent that an organization will follow a particular course of action**

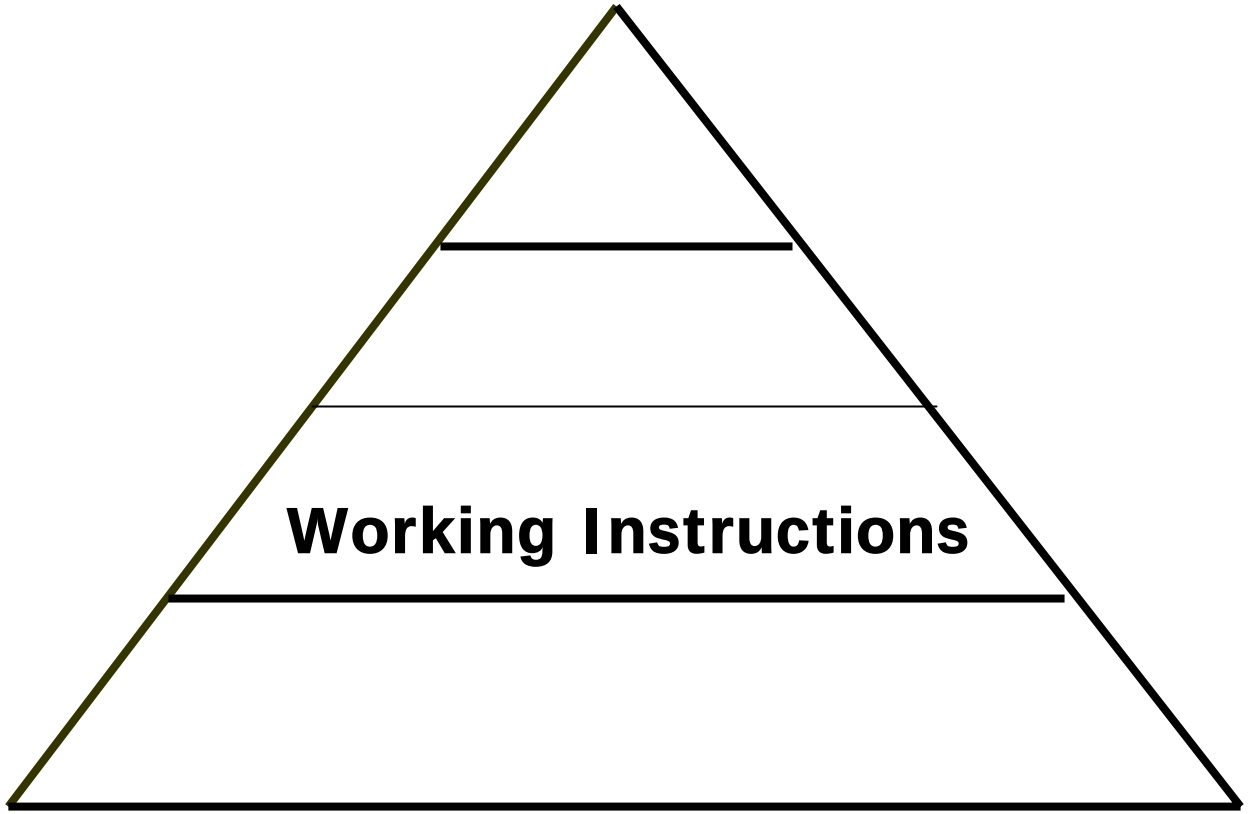
Approach to Laboratory Documentation



Procedures

- Practical way in which a policy is translated into action
- Provide information to carry out an intent
- Called SOPs

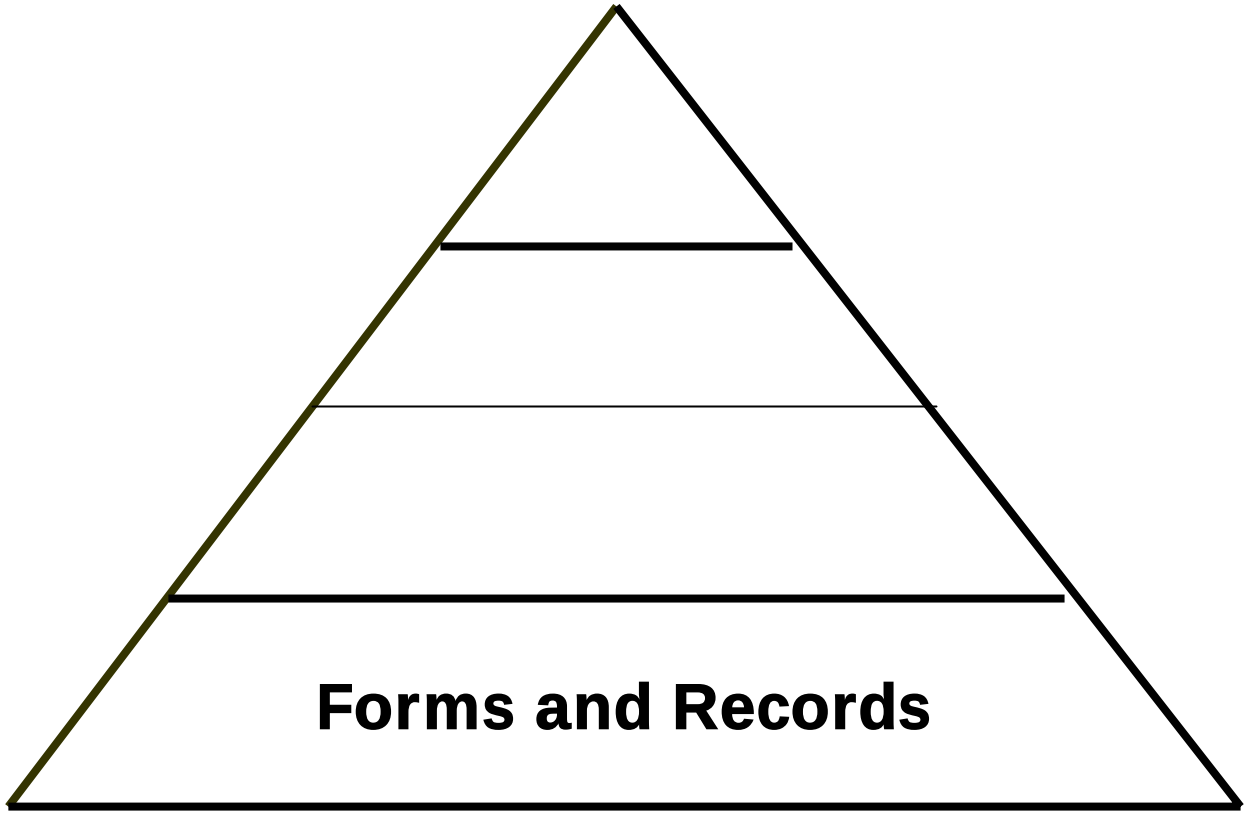
Approach to Laboratory Documentation



Working Instructions

- Procedures can refer to working instructions
- Practical day to day instructions
  - **Can be embedded in a procedure**
  - **Can be referred to in the procedure**

Approach to Laboratory Documentation



Forms and Records

- **Provide evidence of fulfilment of intent**

Forms and Records

Laboratory Records should easily demonstrate:

- **Why**
- **How**
- **By whom**

…the work was done

Forms and Records

PPD

Laboratory Records should easily demonstrate:

- **What equipment was used?**
- **Who was in charge?**
- **Where there any problems encountered?**
- **How were they resolved?**

Records and Reports

Examples of Laboratory Records and Reports

- Pre-analytical?
- Analytical?
- Post-analytical?

Records and Reports Maintenance

- Records must be filed in a manner that allows for prompt retrieval when required

Handwritten Records

- **All handwritten records should comply with GLP guidelines:**
  - Recorded promptly
  - Indelible
  - Legible
  - Signed/initialled and dated by the person
  - Making the entry

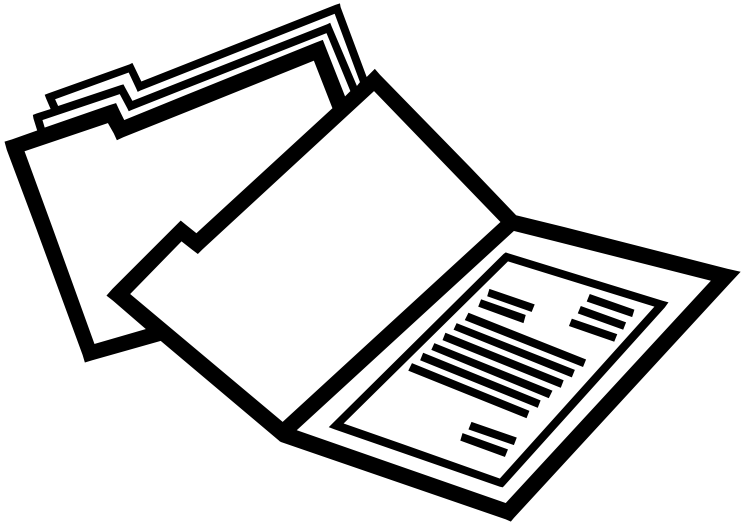
§ 606.160

Reporting of Results

PPD

Information on Laboratory Report:

- Name of Lab
- Participant Identification
- Demographics
- Collection Date and Time

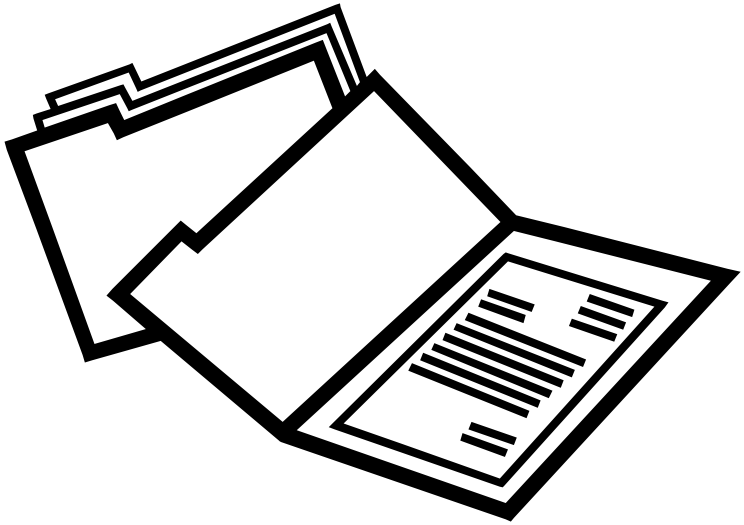


Reporting of Results

PPD

Information on Laboratory Report:

- Test Identification
- Primary Sample Type
- Visit Identification
- Study ID

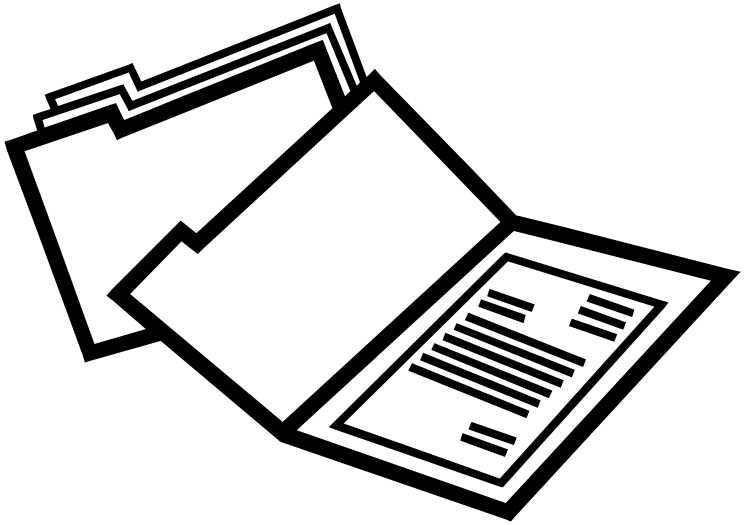


Reporting of Results

PPD

Information on Laboratory Report:

- **Result**
- **Unit of Measurement**
- **Result Flags**
- **Reference Range**

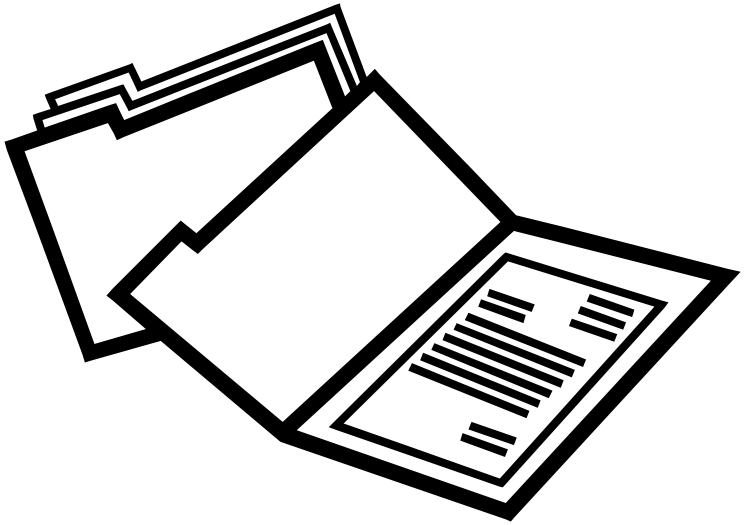


Reporting of Results

PPD

Information on Laboratory Report:

- Date and Time of Report Release
- Identification of Reporting Tech
- Comments



Data Corrections

- **When amending data, the following procedure MUST be followed:**

1. **Draw a single line through the original entry**
2. **Record the correct value**
3. **Sign and date the change**
4. **Document the reason for the change**
5. **Do not use white out/correction fluid**

ICH GCP 4.9.3

Data Corrections (Electronic)

- **Revised Laboratory Reports should:**
  - **Clearly identify report as Revised, Corrected, or Amended.**
  - **Clearly indicate that the new result is a change from a previously reported result.**
- **Ideal to have an audit trail within the system permitting the identification of personnel editing data.**

Data Retention

- The length of time that reported data are retained in the laboratory may vary per regulating Organization

Data Retention

- **Per ICP GCP:**
  - ✓ **2 years after clinical discontinuation of the Investigational Product**
  - ✓ **2 years after the last approval of the marketing application of the Investigational Product**

ICH GCP 4.9.5

Data Retention

- **Service / Maintenance / Validation Records:**
  - **Retained for the life of instrument / method**
  - **Set a reasonably conservative standard for data archival**

Document Storage

PPD

Storage area should be:

- Secure
- Locked
- Accessible only to authorized laboratory personnel
- Easily retrievable when required

CFR § 58.190

Testing Activities

- **Documented list of all the testing activities performed by the laboratory**
- **Defined policy of turnaround times for each test performed**
  - **Turnaround time is defined as the interval between specimen receipt by laboratory personnel and result reporting.**

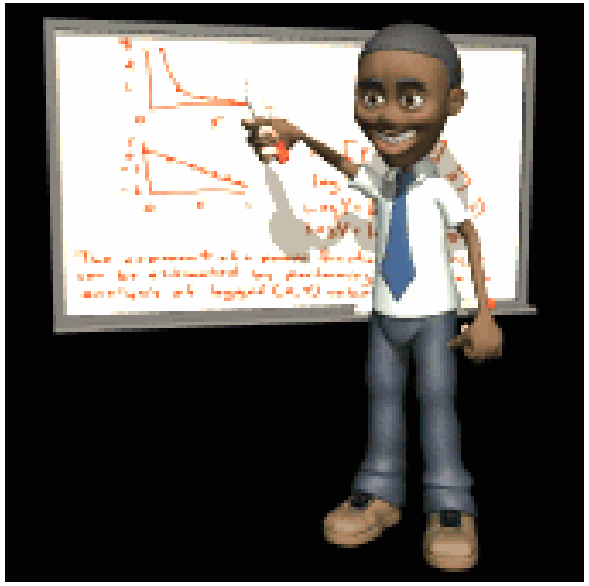
Testing Activities

- Turnaround time should be monitored periodically to determine if there are delays in the testing and reporting of results.

TRIVIA

PPD

What differentiates competency assessment from training?



PPD

Laboratory Study Plan

Study Protocols

- **Protocol** – Document describing the objectives, design, methodology, and organization of a trial
  - **Details of laboratory analytical procedures to be followed are often inadequate**
- Important to design a **laboratory study plan** describing all aspects of the study-specific laboratory procedures
  - **Technical protocol**
  - **Analytical plan**

Laboratory Study Plan Components

The following may be included in an analytical plan:

- Study title and number
- Sponsor
- PI and Study Coordinator names and contact details

Laboratory Study Plan Components

PPD

The following may be included in an analytical plan:

- Names and address of Clinics participating in the study
- Laboratory coordinator
- Version number / effective date of document

Laboratory Study Plan Components

The following may be included in an analytical plan:

- Approximate Start and Completion Dates of study
- Number of participants to be enrolled
- List of investigations to be performed by the lab

Laboratory Study Plan Components

PPD

The following may be included in an analytical plan:

- Equipment list
- Referred laboratory tests
- Summary of Laboratory investigations performed at each visit

Laboratory Study Plan Components

PPD

The following may be included in an analytical plan:

- Processing shipping summary guide
- Analytical Methods
  - List the analytical method for each assay to be performed
  - List the reference ranges, reporting units, alert and panic ranges

Lab Study Summary Guide

PPD

HVTN 998 LABORATORY STUDY SUMMARY GUIDE

Test	Container	Visit							
		Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 32
WCC, Hb, Hct, Plt, Neutrophil, Lymphocyte	5ml EDTA	X	X	X	X	X	X	X	X
CD4 count	5ml EDTA	X			X		X		
BUN, K, Na, GGT, ALT, AST, Lipase	5ml SST	X	X	X	X	X	X		
Urine dipstick	Universal container	X		X		X		X	
HIV-1 RNA	10ml PPT	X			X		X		X
PBMC isolation	9x 8.5 ACD	X		X			X		X
Serum Storage	2x5ml SST	X		X		X		X	
Anti VEE Antibodies	1x6ml SST	X							

Processing / Shipping Summary Guide

PPD

HVTN 998 LABORATORY PROCESSING SHIPPING GUIDE

Test	Container	Processing Lab	Processing/ Shipping Instructions
WCC, Hb, Hct, Plt, Neutrophil, Lymphocyte	5ml EDTA	ZZ HVTU Lab	Process per Coulter AcT 5 Diff SOP
CD4 count	5ml EDTA	ZZ HVTU Lab	Process per FACS Calibur SOP
BUN, K, Na, GGT, ALT, AST, Lipase	5ml SST	ZZ HVTU Lab	Process Per Cobas Integra CI400 SOP
Urine dipstick	Universal container	ZZ HVTU Lab	Process per Urine Dipstick SOP
HIV-1 RNA	10ml PPT	ZZ HVTU Lab	Process per Cobas Amplicor SOP
PBMC isolation	9x 8.5 ACD	Immunology Lab	Forward samples to the Immunology Lab in a biohazard cooler box at room temperature.
Serum Storage	5ml SST	ZZ HVTU Lab	Centrifuge specimens at 3000rpm for 10 minutes. Aliquot samples in 3x 1ml cryo tubes. Store samples in Freezer 1 (-70°C)
Anti VEE Antibodies	1x6ml SST	Central Lab	Centrifuge specimens at 3000rpm for 10 minutes. Aliquot samples in 3x 1ml cryo tubes. Ship 2 cryo tubes to the central Lab. Refer to appendix for shipping details.

Effective Date:_____ **Signature:_____**

Analytical Method List

PPD

Biochemistry

ANALYTE	METHOD	METHOD REFERENCE
S-Alanine Aminotransferase	IFCC without pyridoxal-5-phosphate	Roche Integra 400 Method Manual
S-Albumin	Modified bromocresol green binding assay (Doumas et al.)	Roche Integra 400 Method Manual
S-Alkaline Phosphatase	IFCC	Roche Integra 400 Method Manual
S-Amylase	Enzymatic Colorimetric (IFCC)	Roche Integra 400 Method Manual
S-Aspartate Aminotransferase	IFCC without pyridoxal-5-phosphate	Roche Integra 400 Method Manual
S-Bilirubin Total	Diazo Method	Roche Integra 400 Method Manual
S-Calcium	Schwarzenbach with o-cresolphthalein complexone	Roche Integra 400 Method Manual
S-Chloride	Ion-selective electrodes using automatically diluted specimens (ISE Indirect)	Roche Integra 400 Method Manual
S-Creatinine	Buffered kinetic Jaffe' reaction without deproteinization	Roche Integra 400 Method Manual
S-γ- Glutamyltransferase	Kinetic procedure described by Szasz-Persijn, using the carboxy substrate L-γ-glutamyl –3-carboxy-4-mitroanilide	Roche Integra 400 Method Manual
S-Glucose	Enzymatic reference method with hexokinase	Roche Integra 400 Method Manual

Effective Date :_____ **Signature:_____**

Reference Ranges

PPD

HVTN 998						Chemistry
			Reference Values			
			Reference Range		Critical Values	
	Assay	Units	Lower Limit	Upper Limit	<	>
	Urea (BUN)	mmol/L	3.3	8.3		18.1
	Creatinine	µmol/L M	0	301		550
		F	0	250		525
	AST	U/L	0	100		200
	ALT	U/L	0	100		200
	Bilirubin, Total	µmol/L	0	51		100
	Bilirubin, Direct	µmol/L	0	21		100
	GGT	U/L M	0	75		200
		F	0	55		150
	LDH	U/L	100	600		1000
	Glucose, Fasting	mmol/L	2.8	16.7		30.1
	CK	U/L	0	250		500
	β-HCG, Qualitative			Negative		Positive

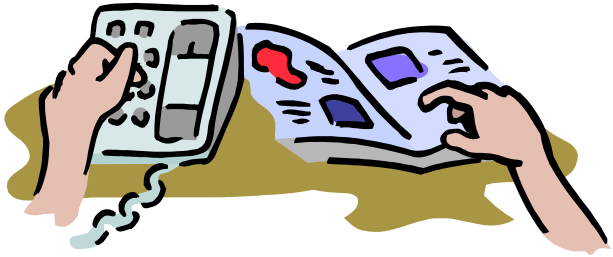
Effective Date:_____ **Signature:_____**

Laboratory Study Plan Components

PPD

The following may be included in an analytical plan:

- Reagent and consumable supply
- Supplier details
- Reagent catalogue numbers



Laboratory Study Plan Components

The following may be included in an analytical plan:

- Referral Laboratory shipping details
- Shipping Schedules
- Packaging and shipping instructions
- Courier Details

Laboratory Study Plan Components

The following may be included in an analytical plan:

- Results report format to the clinic
- Data transmission requirements to the data centers
- Archiving requirements
- List of all SOPs to be used in the study

SOP Control Log

PPD

Doc. No.	Document title	Reviewer	Next Review	Master File	Chemistry	Haem	PCR	Specimen Reception
SOP01	Procedure for writing SOPs	John	Nov-05	X	X	X	X	X
SOP02	Cobas Integra Operation	John	Jun-05	X	X			
SOP03	Reporting abnormal results	John	Jun-05	X				X
SOP04	Turn around times for lab tests	Claire	Feb-06	X	X	X	X	
SOP05	Rejection criteria SOP	Claire	Feb-06	X	X	X	X	X
SOP06	Coulter AcT 5 Diff SOP	Claire	Oct-05	X		X		
SOP07	How to print and Despatch results	Claire	Jan-06	X				X
SOP08	Procedure for labelling Specimens	Jean	Jul-05	X				X
SOP09	Obtaining the audit trail of a specimen	Jean	Sep-05	X				X
SOP10	Haematology SOP	Jean	Oct-05	X		X		
SOP11	FACS Count Operation SOP	Jean	Feb-06	X		X		
SOP12	Standard Operating Procedure for IQC	Jean	Feb-06	X		X		
SOP13	EQA programme assessments	John	Feb-06	X	X	X	X	
SOP14	Corrective action	John	Feb-06	X	X	X	X	X
SOP15	Archiving of laboratory results	John	Jan-06	X		X		X
SOP16	Document control Policy	Jean	Sep-05	X	X	X	X	X
SOP17	Procedure for review of SOP's	Jean	Sep-05	X	X	X	X	X

Laboratory Study Plans

- **Plans should be:**
  - **Approved**
  - **Distributed to all the relevant work areas**

TRIVIA

PPD

What is the molecular weight of Na?

References

- Clinical Pathology Accreditation UK, www.cpa-uk.com
- ICON Laboratories Investigator Manuals
- BARC Laboratory Manual
- Contract Lab Services
- CapioDiagnostic Lab Manual

PPD®

Testing Facilities Operations

A testing facility shall have standard operating procedures in writing setting forth non-clinical laboratory study methods that management are satisfied are adequate to insure the quality and integrity of the data generated in the course of a study...

21 CFR § 58.81 – 58.90

PPD

Okay….

But what does it all mean?

Testing Facilities Operation

- Each laboratory should have SOPs for <u>ALL</u> procedures being performed.
- They should be written in a manner and language that is appropriate to the lab personnel conducting the procedures.

Testing Facilities Operation

- SOPs are written for the benefit of the laboratory employees, not auditors.
- Current SOPs must be available in the work areas and accessible to staff.

Standard Operating Procedures

What should go in an SOP?

Standard Operating Procedures

Title of the Procedure

Should include:

–Name of the analyte
–Type of specimen
–Specific method and / or instrumentation

Example:

Serum/Plasma Glucose Determination using the Olympus AU 600

Standard Operating Procedures

Additional information useful in document control:

- SOP number
- Approval signatures with dates
- Revision number and date
- Number of pages
- Names, signatures and dates of all personnel involved in the procedure, who have read and understood the SOP

Standard Operating Procedures

- **Signature and Initial List**

Employee Name	Sig	Init	Date
Jason Ezzelle	*Jason Ezzelle*	*JE*	6-Jan-00
Tiri Towindo	*Tiri Towindo*	*TT*	12-Jul-02

Trivia

Which country will Host the next Olympic games?

In which year will the games be held?

Standard Operating Procedures Elements

1. Principle and/or purpose
2. Specimen requirements / collection methods
3. Reagents, Standards, Controls and Media used

Standard Operating Procedures Elements

4. Instrumentation

5. Procedural steps

6. Calculations

Standard Operating Procedures Elements

7. Quality Control
8. Reporting Results
9. Limitations

Standard Operating Procedures Elements

10. References

11. Effective Date / Review Schedule

12. Distribution

13. Author

SOP Elements

1. Principle and/or purpose

- List in paragraph form the type of reaction and the reasons for performing the test.

SOP Elements

1. Principle and/or purpose

– **Example**:

The glucose method is an adaptation of the hexokinase-glucose-6-phosphate dehydrogenase method, presented as a general clinical laboratory method by Kunst, et al.[1] This method is more specific than general reducing methods and will give results lower than those obtained by such reducing methods[2]...

SOP Elements

PPD

2. Specimen requirements / collection methods

- Conditions for patient preparation
- Specific specimen type
- Handling conditions

SOP Elements

PPD

2. Specimen requirements / collection methods

- Rejection criteria
  - Mislabeled
  - Leaking / broken
  - Hemolysed, lipemic, icteric

SOP Elements

2. Specimen requirements / collection methods

– **Example:**

Normal procedures for collecting and storing serum, plasma, urine and cerebrospinal fluid may be used for samples to be analyzed by this method.

SOP Elements

3. Reagents, Standards and Media used

- List reagents, standards and media employed
- Indicate directions for preparation
- List parameters that determine acceptable performance.

SOP Elements

3. Reagents, Standards and Media used

– **Example**:

All reagents and test materials for this test are stored in the glass door refrigerator (at 2 – 8°C) located in the chemistry department. Overflow reagents are stored in the gray door refrigerator (at 2 – 8°C) located in the chemistry department.

SOP Elements

4. Instrumentation

- List equipment used in the procedure
- Include calibration protocols and schedules

SOP Elements

4. Instrumentation

– **Example:**

The following information should be considered when calibrating the GLU method:

- **Assay Range: 0–500 mg/dL**
- **Reference Material: Primary standards or secondary calibrators such as CHEM I Calibrator (Cat. No. DC18)**
- **Suggested Calibration Levels: 0, 250, 425 mg/dL**
- **Calibration Scheme: Three levels in triplicate**
- **Calibration Frequency: Every new reagent cartridge lot. Every 3 months for any one lot**
- **Assigned Coefficients: C0 0.000 C1 0.880**

SOP Elements

5. Procedural steps

- Detailed
- Stepwise
- Appropriate for personnel conducting the procedure

SOP Elements

5. Procedural steps

– **Example:**

Instructions for Processing Samples

<u>Bar Coded Tubes</u>

1. **Place bar code labels on tube. 10 mL tubes may be put directly in a segment with the bar code facing the bar code reader. 7 mL and 5 mL tubes must be placed in appropriate adaptors. Brown adaptors are for 7 mL tubes; green adaptors are for 5 mL tubes. Check for sufficient sample volumes using the tube fill gauge…**

SOP Elements

6. Calculations

- Give stepwise instructions
- List any applicable equations
- Give precise examples

SOP Elements

6. Calculations

- Examples:
  - To manually calculate LDLC, use the following equation:
    - LDLC = [TC] - [HDLC] - [TG/5]
  - N/A

SOP Elements

7. Quality Control

- Identify the control material used
- List preparation and handling instructions
- List frequency of analysis
- Establish and explain tolerance limits
- State corrective action for values outside tolerance limits

SOP Elements

7. Quality Control

– **Example:**

At least once daily run solutions at two levels of a quality control material with known concentrations...

SOP Elements

8. Reporting Results

- State the reference range
- Identify procedures for reporting abnormal results
- Give guidelines on acceptable report format

SOP Elements

8. Reporting Results

- **Example:**

  Serum and Plasma results are reported in mg/dL and are rounded to the nearest tenth.

  Normal range: 72-112 mg/dL

  Panic values:

  <50 or >350 mg/dL for adults

  <40 or >350 mg/dL for babies

SOP Elements

9. Limitations

- State linearity and / or detection limits
- State known interferences

SOP Elements

9. Limitations

- **Example:**

LIMITATIONS:

1. **Assay Range: 0–500 mg/dL**
2. **Hemoglobin of 500 mg/dL falsely depresses GLU results by 20 mg/dL at 131 mg/dL of glucose.**
3. **Bilirubin of 20 mg/dL falsely depresses GLU results by 12 mg/dL at 124 mg/dL glucose.**
4. **Lipemic (triglyceride 600 mg/dL) samples falsely elevate GLU results by 10 mg/dL at 129 mg/dL of glucose.**

SOP Elements

10.References

- **List items used as sources of information. Should include:**
  - Literature references
  - Manufacturer product literature
  - Textbooks
  - Written personal communications
  - Standards publications
- **Use Standard Bibliographical format**

SOP Elements

10.References

– **Example**:

REFERENCES:

1. Kunst A, Draeger B, Ziegenhorn J. UV-methods with hexokinase and glucose-6-phosphate dehydrogenase, Methods of Enzymatic Analysis, Vol VI, Bergmeyer HU (ed.) Verlag Chemie, Deerfield, FL 1983:163-172.
2. Henry RJ. Clinical Chemistry Principles and Technics. New York: Harper and Row, 1974:1283...

SOP Elements

11. Effective Date / Review Schedule

- Performed by authorized personnel
- Review when changes are made
- Review annually
- Document review
- Remove obsolete or superseded procedures

SOP Elements

11.Effective Date / Review Schedule

- **Example:**

Review Date	Revision Date	Signature

TRIVIA

PPD®

What is the analyte of interest in the *ELISpot* assay?

SOP Elements

12. Distribution

- Document control
- Keeps track of number of copies

SOP Elements

12.Distribution

- **Example:**

Distributed to	# of Copies	Distributed to	# of Copies

SOP Elements

13. Author

- Take credit for your work
- Defines contact person for questions

Document Control Plan

- The SOP's should be reviewed periodically, and revised where necessary
- Superseded documents should be identified appropriately and archived to prevent their inadvertent use

Document Control Plan

- **Authorization process**
  - **Establish who has authority to conduct a review**
  - **May vary based on the administrative structure**

Document Control Plan

- **Annual reviews**
  - Ensures procedures are current
  - Practice vs. procedure
  - Document the review

Document Control Plan

- **Discontinuation of procedures**
  - **Remove from manuals and designate "obsolete"**
  - **Store in retired procedure file**
    - **Historical**
    - **Liability**
  - **Keep minimum 2 years**

SOP Training

All personnel need to be instructed on new procedures or changes to procedures

Documentation **that all personnel are knowledgeable of the contents of the SOP**

SOP Training

“The best way to become acquainted with a subject is to write a book about it”.

– **Benjamin Disraeli (1804 - 1881)**

PPD®

Specimen Management and Tracking

What is
Specimen Integrity?

Specimen Quality

The reliability and accuracy of all laboratory test results depends on the quality of the specimen submitted.

Specimen Quality

- **Specimens should be properly:**
  - **Collected**
  - **Labelled**
  - **Stored**

Specimen Quality

- **Specimens should be properly:**
  - **Packaged**
  - **Transported to the laboratory.**

These instructions, when properly followed, ensure specimen integrity.

Topics to Cover

- **Rejection Criteria**
- **Critical Values**
- **Specimen Storage**
- **Specimen Transport**

Topics to Cover

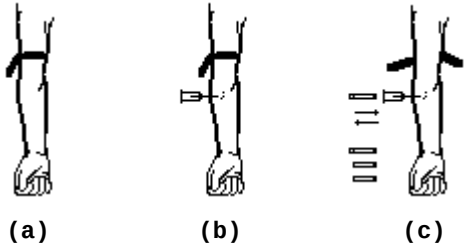
- **Specimen Collection**
- **Specimen Receipt**
- **Audit Trail / Chain of Custody**

Specimen Collection

- **Policies should be available for:**
  - **Specimen collection**
  - **Labeling**
  - **Preservation**
  - **Conditions for transportation**
  - **Storage**

Specimen Collection Manual

- **May contain the following:**
  - **Guidelines on performing venipuncture including labeling**
  - **Guidelines on handling specimens**



•CHEMISTRY, SST tube (6ml) – Yellow Stopper 1.Completely fill the collection tube included in the visit specific kit. 2.Stick a Participant ID label and a specimen Collection Date Label on the vacutainer tube. 3.Allow the blood to clot for 30 minutes in a vertical position, and centrifuge the tube for 10 minutes at 3000rpm. After centrifugation, the gel separates the serum form the cells. DO NOT aliquot serum. 4.Forward the samples immediately to CLS the same day of collection.	

TRIVIA

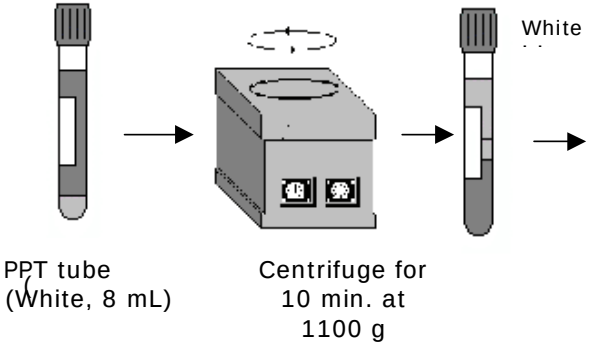
PPD

Name two enzymes that may be measured to assist with the diagnosis of heart disease.

Specimen Collection Manual

May contain the following:

- **Guidelines for sample preparation**
- **Guidelines for sample transfer**
- **Specimen rejection criteria**



ADD TO FROZEN SHIPMENT

Labeling

- **Standard labeling practices must be implemented and enforced with all users of the laboratory services.**

- **All specimen tubes must be properly identified with the PTID.**

Collection Forms

- **Requisition forms**
- **Specimen tracking forms**

Requisition Form

PPD®

ABC Laboratory

[illegible] y: AA2[illegible]345

LABORATORY REQUISITION FORM

PARTICIPANT DEMOGRAPHICS

ABC Laboratory

Study: AA26345

LABORATORY REQUISITION FORM

Tube Qty	Tube Type	Assay	Collection Instructions	Collected? [√]
1	5ml EDTA	CBC	Mix tube immediately by gentle inversion. Keep at Room temperature	
1	6ml SST	Na, K, ALT, AST, GC[illegible] A[illegible] B Bili C[illegible]	Kee[illegible] a[illegible] m temperature	
1	8.5ml PPT	HIV-1 RNA	Mix ub[illegible] ie[illegible]nediately by gentle inversion. Keep at Room temperature	
12	10ml Na Hep	PBMC processing and Cropreservation	Mix tube immediately by gentle inversion. Keep at Room temperature	

Laboratory Use Only

Specimen Receipt Confirmation

Tube	5ml EDTA	6ml SST	8.5ml PPT	10ml Na H
Received (#)				

Accession #: _____

Receipt Date/Time: _____ Rec'd by: _____

Receipt Comments: _____

Requisition Form

ABC Laboratory

Study: AA2634J

LABORATORY REQUISITION FORM

PARTICIPANT DEMOGRAPHICS

Participant ID: ___ – __ – ___ – __

PARTICIPANT DEMOGRAPHICS

Participant ID: ___ – __ – ___ – __

Gender: M F

Birth Date: Day | Month | Year

1	6ml SST	Na, K, ALT, AST, GGT, ALB. Bili, Ca	Keep at Room temperature	
[illegible]	[illegible]	HIV-1 RNA	Mix tube immediately by gentle inversion. Keep at Room temperature	
12	10ml Na Hep	PBMC processing and Cropreservation	Mix tube immediately by gentle inversion. Keep at Room temperature	

- PID Number
- Initials (Optional)
- Gender
- Date of Birth

Laboratory Use Only

Specimen Receipt Confirmation

Tube	[illegible]	6ml SST	8.5ml PPT	10ml Na H
Received (#)				

Accession #: _____

Receipt Date/Time: _____ Rec'd by: _____

Receipt Comments: _____

Requisition Form

ABC Laboratory

Study: AA26345

LABORATORY REQUISITION FORM

PARTICIPANT DEMOGRAPHICS

VISIT

	Day	Month	Year
Sp Coll Date:			

Sp Coll Time: :

Visit: Wk: 4 8 12 16 24 32

Collected by: _____

1	5ml EDTA	CBC	Mix tube immediately by gentle inversion. Keep at Room temperature	
1	6ml SST	Na, K, ALT, AST, GGT, ALB. Bili, Ca	Keep at Room temperature	
[illegible]	[illegible]	[illegible]	Mix tube immediately by gentle inversion. Keep at Room temperature	
12	10ml Na Hep	[illegible] and Cropreservation	Mix tube immediately by gentle inversion. Keep at Room temperature	

Laboratory Use Only

Specimen Receipt Confirmation

Tube	5ml EDTA	6ml SST	8.5ml PPT	10ml Na H
Received (✓)				

Accession #: _____

Receipt Date/Time: _____ Rec'd by: _____

Receipt Comments: _____

- Specimen Collection Date
- Specimen Collection Time
- Visit
- Phlebotomist
- Site details

Requisition Form

ABC Laboratory

PPD

Study: AA26345

COLLECTION DETAILS

Tube Qty	Tube Type	Assay	Collection Instructions	Collected? [√]
1	5ml EDTA	CBC	Mix tube immediately by gentle inversion. Keep at Room temperature	
1	6ml SST	Na, K, ALT, AST, GGT, ALB. Bili, Ca	Keep at Room temperature	
1	8.5ml PPT	HIV-1 RNA	Mix tube immediately by gentle inversion. Keep at Room temperature	
12	10ml Na Hep	PBMC processing and Cropreservation	Mix tube immediately by gentle inversion. Keep at Room temperature	

1	6ml SST	GGT, ALB. Bili, Ca	Keep at Room temperature	
1	8.5ml PPT	HIV-1 RNA	Mix tube immediately by gentle inversion. Keep at Room temperature	
12	10ml Na Hep	PBMC processing and Cropreservation	Mix tube immediately by gentle inversion. Keep at Room temperature	

- Tube Quantity and type
  - Visit specific investigations listed
- Collection instructions

Laboratory Use Only

Specimen Receipt Confirmation

Tubes Received	5ml EDTA	6ml SST	8.5ml PPT	10ml Na H

Accession #: _____

Receipt Date/Time: _____ **Rec'd by:** _____

Receipt Comments: _____

Requisition Form

ABC Laboratory

PPD

Study: AA26345

LABORATORY REQUISITION FORM

Laboratory Use Only

Specimen Receipt Confirmation

Tube	5ml EDTA	6ml SST	8.5ml PPT	10ml Na H
Received (#)				

Accession #: _____

Receipt Date/Time: _____ Rec'd by: _____

Receipt Comments: _____

12	10ml Na Hep	and Cropreservation	Keep at Room temperature

- Specimen Receipt confirmation
- Receipt comments

Laboratory Use Only

Specimen Receipt Confirmation

Tube	5ml EDTA	6ml SST	8.5ml PPT	10ml Na H
Received (#)				

Accession #: _____

Receipt Date/Time: _____ Rec'd by: _____

Receipt Comments: _____

Specimen Sampling Kits

Each kit contains all the specimen collection materials needed for that particular visit, including the appropriate:

- **Specimen collection tubes**
- **Laboratory requisition forms (Duplicate)**

Specimen Transfer

- Procedures for specimen transport
  - from the clinic to the laboratory
  - within the facility
- Specimen transport log

Specimen Receipt

- Specimen Verification
- Assessment of specimen quality and volume
- Specimen receipt date and time
- ID of recipient

Rejection Criteria (General)

- Unlabeled specimen
- Mislabeled specimen
- Incompletely labeled specimen
- Hemolysis, lipemia

Rejection Criteria (General)

- Inadequate or Insufficient information on request form
- Specimen collected in wrong tube, container or preservative
- Insufficient specimen for testing

Specimen Receipt

- **Any discrepant or missing information should be communicated to the clinic and verified promptly before specimens are processed, stored, or results issued.**
- **Any contact with the clinic personnel should be documented.**

Clarification / Notification Form

PPD

LABORATORY DATA CLARIFICATION FORM

URGENT

From: _____

Date: _____

Protocol #: _____

LABORATORY DATA CLARIFICATION FORM

URGENT

From: _____

Date: _____

Protocol #: _____

To:
Site #:: _____ Contact: _____

Fax #: _____

☐ More than ____days after collection date ☐ Unfrozen ☐ _____ tube broken in transit

☐ The following tubes were not received _____

☐ Other _____

_____ _____ _____
Print Name (Clinic Representative) Sign (Clinic Representative) Date

Data Clarification / Notification F

LABORATORY DATA CLARIFICATION FORM

Subject:
The Lab has received a study visit from your clinic with conflicting information. Some Data are missing or inconsistent with previously obtained Data. Please verify, complete and /or confirm the data below and fax it back to us as soon as possible to : **FAX – 123 4567**

Visit Information

PID	Initials	Visit ID	Item in Question	Information Received	Correct Information

Comments: **Specimens Received**

☐ More than ____days after collection date ☐ Unfrozen ☐ _____ tube broken in transit

☐ The following tubes were not received_____

☐ Other_____

_____ _____ _____
Print Name (Clinic Representative) Sign (Clinic Representative) Date

Comments: **Specimens Received**

☐ More than ____days after collection date ☐ Unfrozen ☐ _____ tube broken in transit

☐ The following tubes were not received_____

☐ Other_____

_____ _____ _____
Print Name (Clinic Representative) Sign (Clinic Representative) Date

Monitoring Specimen Quality

The lab should monitor transportation of samples, to ensure that they are transported:

1. **Within the timeframe appropriate for the nature of the requested specimen**
2. **Within the temperature interval specified**

Monitoring Specimen Quality

The lab should monitor transportation of samples, to ensure that they are transported:

3. **Within the designated preservatives to ensure specimen integrity**
4. **In a manner that ensures safety for the carrier, public and your lab**

Specimen Processing

- **The lab should have documented, protocol specific procedures for specimen analysis.**

- **A policy should be available documenting the length of time and temperature the specimens to be retained for potential re-evaluation.**

Specimen Processing

- **Policy / procedure for notifying the clinic when testing is delayed**

Chain of Custody

- **Paper Trail – including date, time, and identity of personnel performing each activity**
  - **Examples of Activities:**
    - **Phlebotomy**
    - **Shipping**
    - **Specimen receipt**
    - **Maintenance procedures**
    - **Specimen analysis**
    - **Storage**
    - **Results reporting**

Trivia

An infection with A gram negative rod almost wiped almost half of the population of Central Asia, Europe, Middle east and North Africa in 4th, 6th and 8 - 14th century.

It was harboured in infected rodents and transmitted to other rats and humans by fleas. The bacillus infects lymphoid tissue causing bubos.

Name the Bacteria

Critical values

- **Results that require prompt and rapid clinical attention to avert significant patient morbidity or mortality.**
- **Values should be defined by the Laboratory Director, in consultation with clinicians served.**
- **Policy for immediate contact of key study personnel**

Critical values

- **Notification records should include:**
  - **Date and time**
  - **Responsible laboratory individual**
  - **Person notified and test results.**
  - **Problems encountered in accomplishing the task**

Critical Values

- An emergency telephone contact list for the key study personnel should available in the laboratory
- Suggestion
  - The laboratory should implement a policy that personnel receiving verbal or phone orders must read back the entire order to verify accuracy of transcription.

Specimen Storage

Specimen Storage

- Ideal for Research Labs to have dedicated sample storage facilities.
- 24-hour monitoring of storage conditions to ensure the integrity of samples is maintained.
- Fully documented disaster recovery procedures should be implemented.

Specimen Storage

- Sample repositories should be created by storing the samples suitably.
- All relevant records for repositories should be traceable and accessible.
- Specimen aliquots must be properly labelled before storage

Specimen Transport

- **Proper organization, packaging, shipping and handling of specimens ensure specimen integrity, while maintaining timely and safe transfer of specimens.**
- **All federal, and in country Transportation of Dangerous Goods regulations must be met for the transportation of specimens.**

Specimen Transport

- **Before dispatch of samples, ensure that:**
  - **Number of specimens in the box corresponds to that on the shipping manifest**
  - **ID numbers on specimen tubes correspond to those on the shipping manifest**

Specimen Transport

- **Before dispatch of samples, ensure that:**
  - **Accompanying list contains the necessary data for each PID**
  - **Shipping date and the particulars of the lab are on the shipping manifest**

Specimen Transport

- Personnel who ship specimens must be trained in hazardous materials/ dangerous goods transportation safety regulations
- Training must be renewed every 2 years
- Certification must be on file and available for inspection

TRIVIA

PPD

Name any 2 components of Method Validation that must be performed before implementing a new unmodified FDA-approved assay.

References

- CapioDiagnostic Lab Manual
- ICON Laboratories Lab Manual
- www.legacyhealth.org
- www.csmc.edu
- www.uhl.uiowa.edu
- www.vh.org

PPD

WHY?

WHY?

WHY?

WHY?

WHY?

WHY?

WHY?

WHY?

WHY?

WHY?

WHY?

Verification of Performance Specifications

Verification of Performance Specifications Overview

PPD

Verification assures that the test:

- **When used in *your* laboratory**
- **By *your* testing personnel**
- **For *your* patient population**

is performing as the manufacturer intended at *your* institution with *your* instruments.

Verification of Performance Specifications Overview

PPD

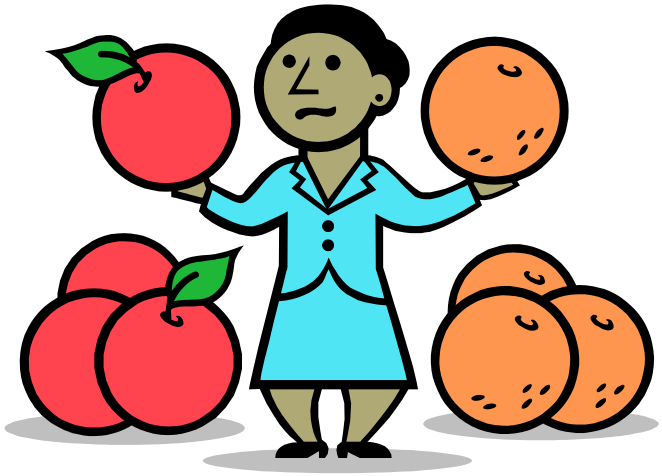
Elements of the Verification

1. Accuracy
2. Precision
3. Analytical Sensitivity
4. Analytical Specificity
5. Reportable Range
6. Reference Intervals

Verification of Performance Specifications Overview

- **Method Validation is simply…**

an Error and Bias Assessment.



Verification of Performance Specifications Overview

PPD®

When do I verify?

Before reporting patient results!

Verification of Performance Specifications Overview

PPD

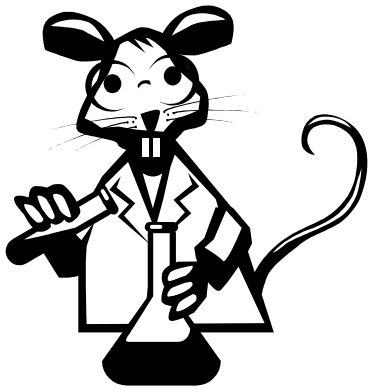
Criteria for validation:

- Introduction of a new analyte to the test repertoire
- Change of analytic methodology or reformulation
- Change in patient population (Reference Intervals)

Verification of Performance Specifications Overview

PPD

- **Which tests do I verify?**
  - **Waived tests**
    - **Do *not* require verification/validation**



42 CFR § 493.15

Verification of Performance Specifications Overview

PPD

- **Which tests do I verify?**
  - Non-waived tests
    - **Require verification/validation**
      - Unmodified, FDA-approved tests (e.g., Sodium on Dade Dimension Max Suite analyzer)
      - Modified FDA-approved tests (altered method, different clinical indication, etc.)
      - Non-FDA-approved tests (e.g., ELISPOT)

Verification of Performance Specifications Overview

- **Which tests do I verify?**
  - **Unmodified FDA-approved non-waived tests must have the following verified:**
    - **Accuracy**
    - **Precision**
    - **Reportable Range (linearity, AMR, CRR)**
    - **Reference intervals**

Verification of Performance Specifications Overview

PPD

- **Which tests do I verify?**
  - **Modified FDA-approved or Non-FDA approved tests must have the following verified:**
    - **All components of Unmodified FDA-approved**
      - **Accuracy**
      - **Precision**
      - **Reportable Range (linearity, AMR, CRR)**
    - ***Establish* Reference Intervals**
    - **Analytical Sensitivity**
    - **Analytical Specificity**

Verification of Performance Specifications Overview

PPD

It's *crucial* to consult appropriate reference guides:

- Westgard's website
- Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS)
- Manufacturer's literature
- Package inserts
- Evaluation and validation manuals

Verification of Performance Specifications Overview

PPD

Evaluation software available via internet includes:

- www.analyse-it.com (purchase)
- www.dgrhoads.com (purchase)

Online tools available at:

- www.westgard.com (free!)

Verification of Performance Specifications

The Elements in Detail

1. Accuracy
2. Precision
3. Analytical Sensitivity
4. Analytical Specificity
5. Reportable Range
6. Reference Intervals

1. Accuracy

- **Are your test results correct?**
- **How close to the "true" value the test system value falls**
- **Provides information about the average *systematic error* (bias)**

Accuracy Estimates

- **Systematic errors (SE)**
  - **are in one direction and are predictable**
  - **produce a result that differs from the true value by a relatively fixed amount**
  - **result from biases introduced by instrumental method, or human factors**

Accuracy Estimates

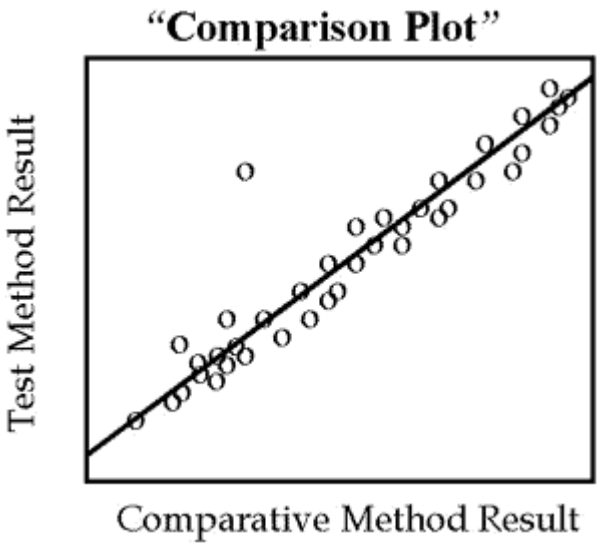
- **Running method comparison**
  - **Testing Methods**
    - **New (Test) method vs. Established (Reference, Comparative) method**
    - **Commercially available calibrators with known values**
    - **Proficiency samples with established values**
  - **Minimum 40 samples, performed in duplicate**
  - **Perform testing over 5 to 20 days**

Accuracy Estimates

- **Running method comparison**
  - **Comparisons should be performed within 2 hours of original testing, maximum**
  - **Patients should span range of disease states for routine application**

Accuracy Estimates

- **Data Analysis of method comparison**
  - Graph the data
  - Visually inspect graphs
  - Calculate Statistics



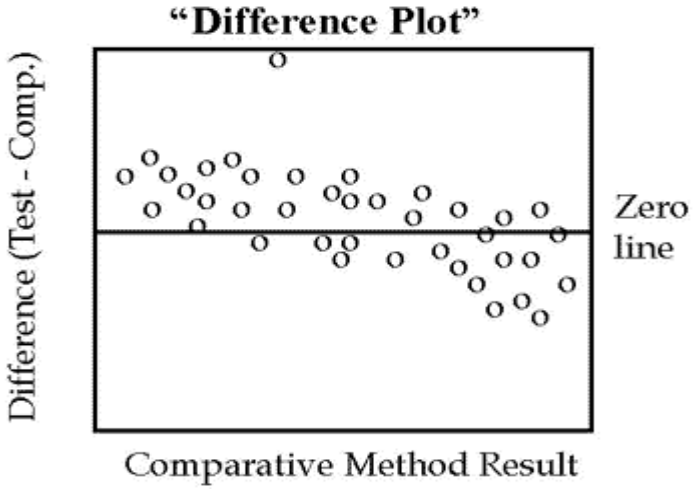
Graphing the Data

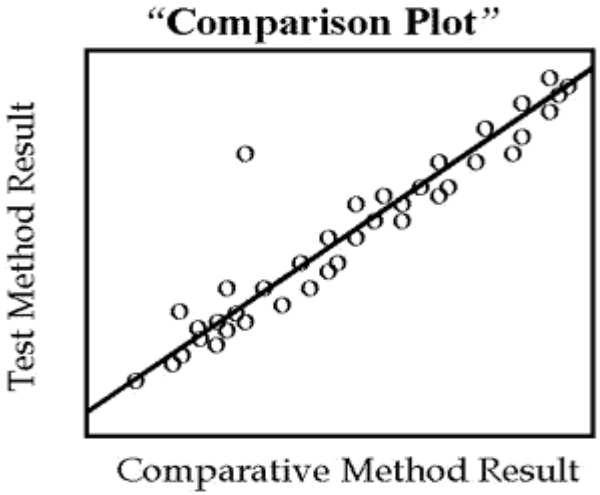
Graphing is *always* necessary!

Graphing reveals:

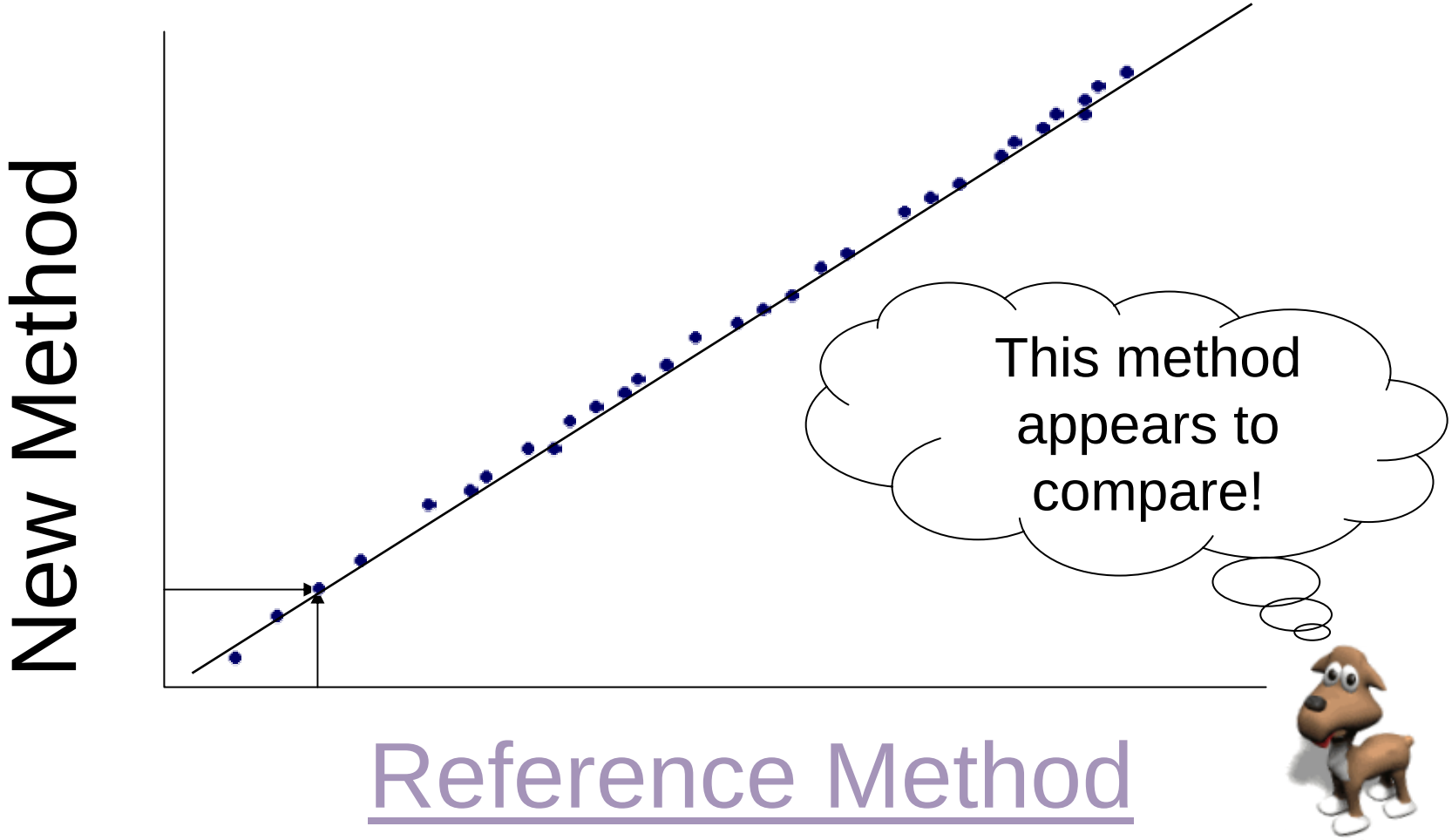
- –Degree of dispersion
- –Disagreement
- –Nonlinearity
- –Gross errors

Statistical evaluation alone is insufficient

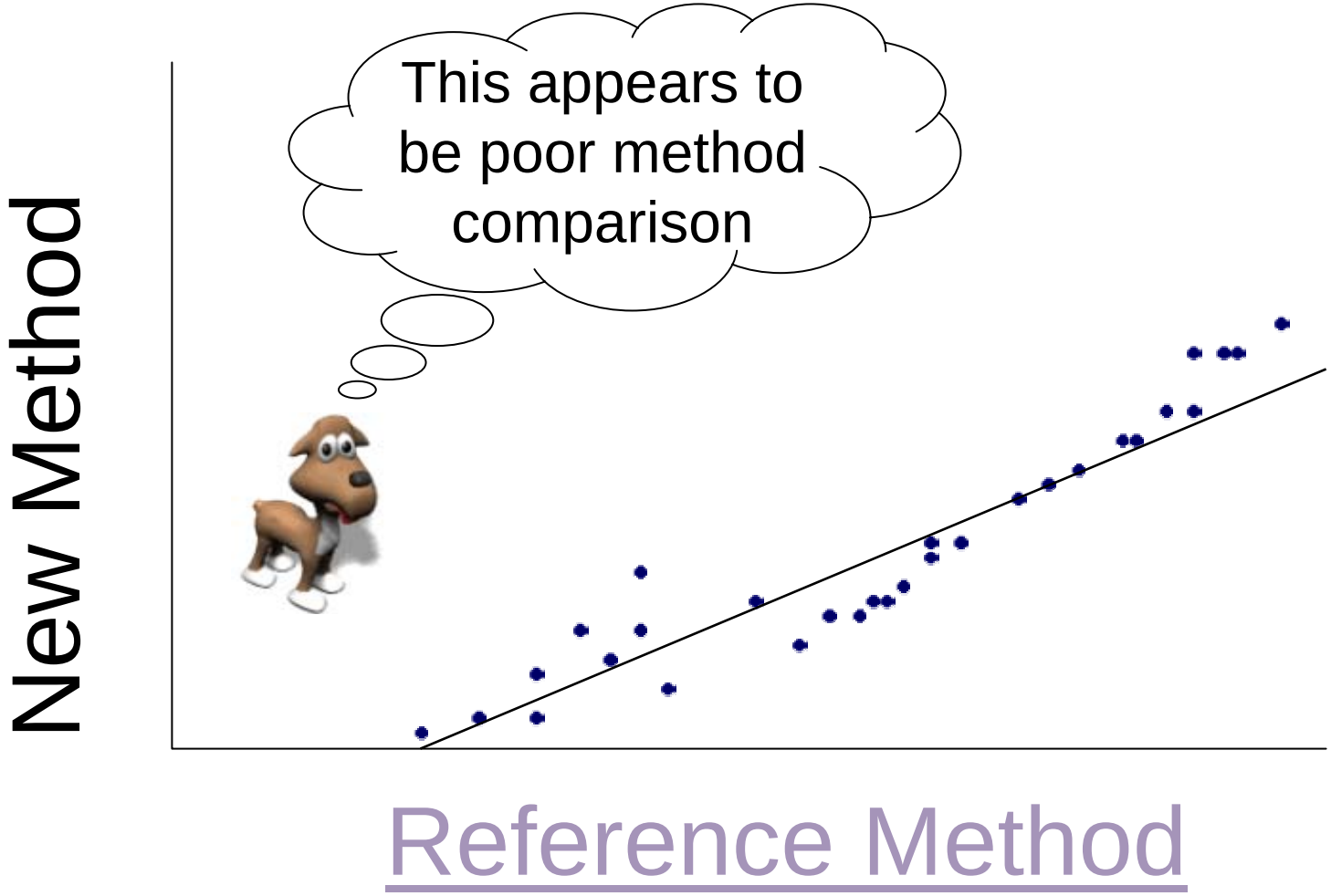




Visual Inspection for Accuracy



Visual Inspection for Accuracy



Calculate Appropriate Statistics

- **Westgard and Hunt evaluated the commonly performed statistical tests**
  - Slope
  - Intercept
  - Standard Error
  - Correlation Coefficient
- **Linear Regression Analysis is available on most statistical programs and calculators**

$$Y = mX + b$$

Calculate Appropriate Statistics

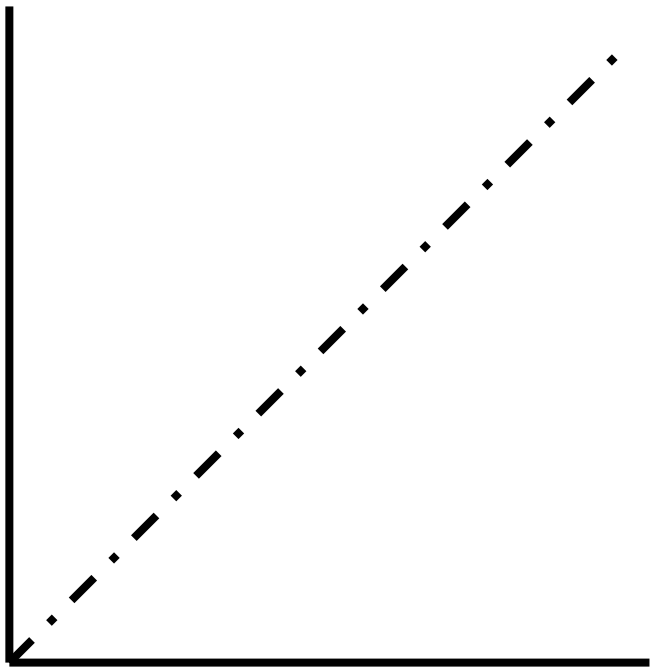
- **Slope**
  - **Measure of *proportional* bias**
    - $m = (y_1 - y_2) / (x_1 - x_2)$ **or "rise / run"**
    - **Slope greater than 1 means the Y (Test) values are generally higher than the X (Comparative) values**
    - **Slope of 1.11 means the Y (Test) values are on average 11% higher than the X (Comparative) values**

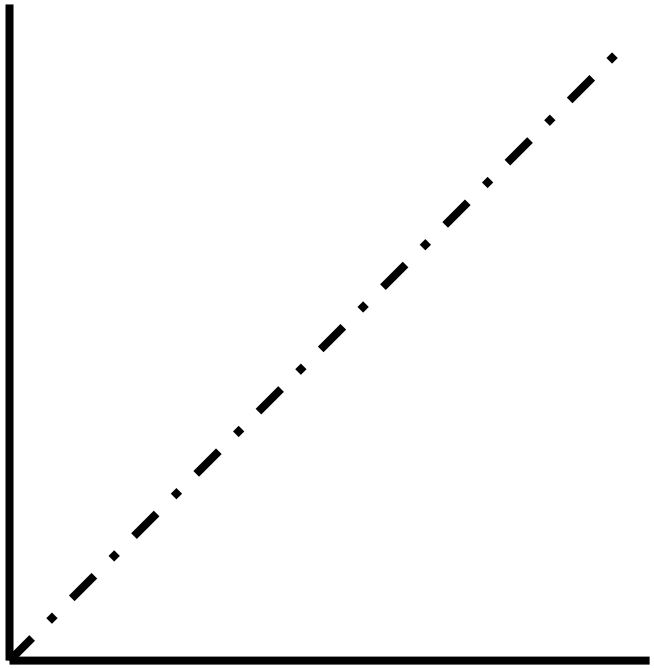
Calculate Appropriate Statistics

- **Intercept of the Line**
  - **Measure of *constant* bias between two methods**
    - **Y (Test) value at the point where the line crosses the Y axis**
    - **If Y intercept is 12, then all Y (Test) values are at least 12 units higher than the X (Comparative) values**

Accuracy

What type of bias do you see?

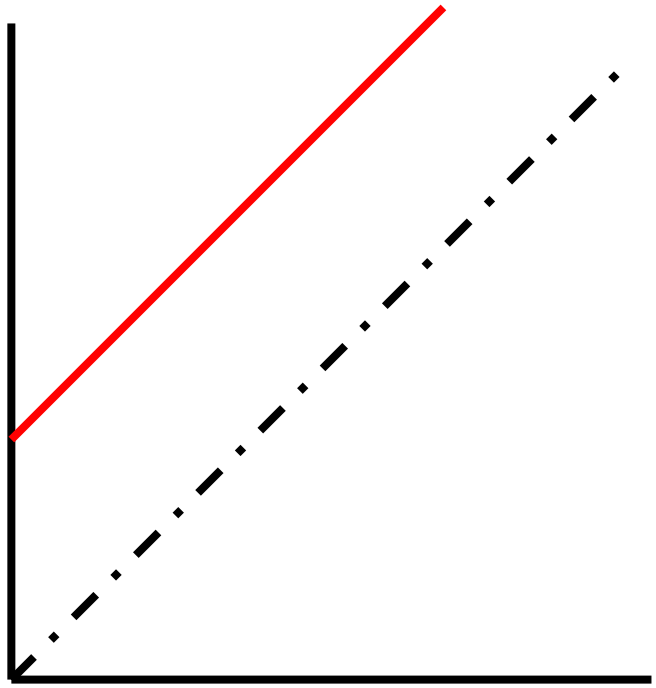




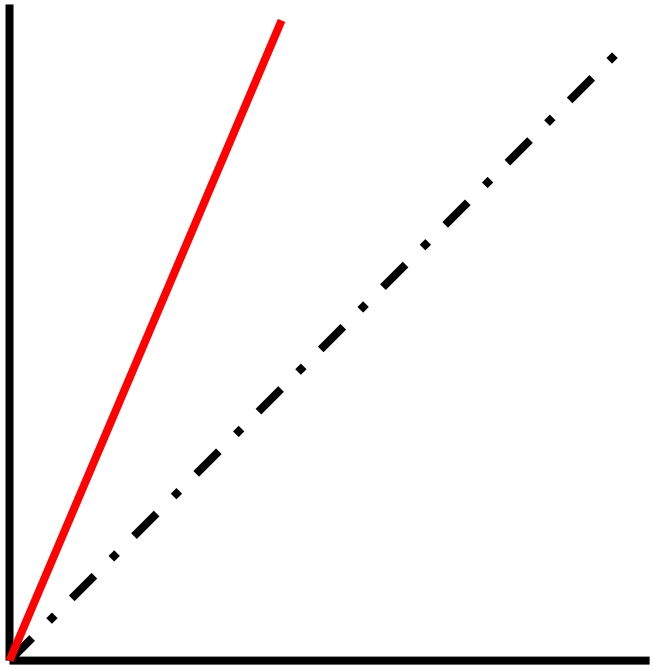
Accuracy

PPD

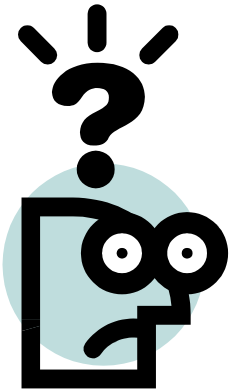
Constant Bias

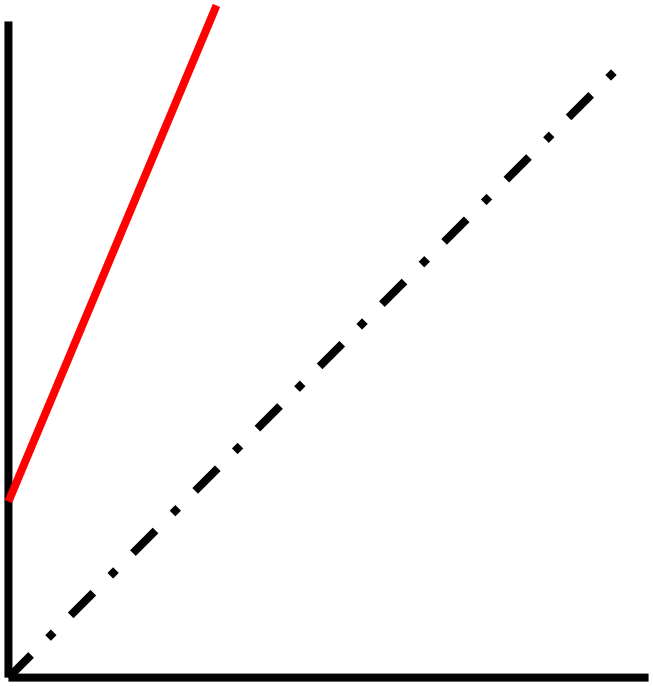


Proportional Bias



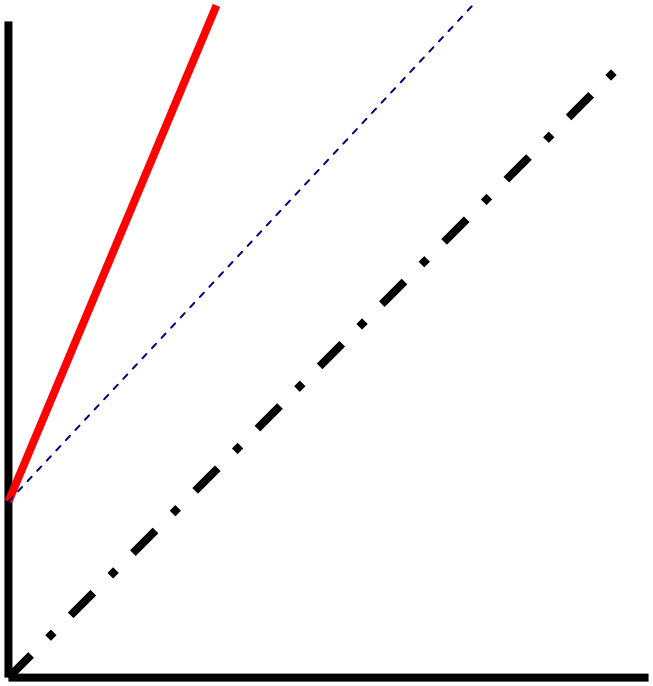
Accuracy





Accuracy

Constant and Proportional Bias



Accuracy

ACTIVITY!

- **Practice with Cholesterol Package Insert and Sample Data**

COBAS INTEGRA 400/700/800

Roche Diagnostics

Cholesterol

Order information

COBAS INTEGRA* Cholesterol	400 Tests	Cat. No. 20763012 System-ID 07 6301 2	
Calibrator f.a.s.	10 × 3 mL	Cat. No. 10759350 System-ID 07 3718 6	
Precinorm* U	20 × 5 mL	Cat. No. 10171743 System-ID 07 7997 0	
Precipath* U	20 × 5 mL	Cat. No. 10171778 System-ID 07 7998 9	
Precinorm* U plus	10 × 3 mL	Cat. No. 12149435 System-ID 07 7999 7	
Precipath* U plus	10 × 3 mL	Cat. No. 12149443 System-ID 07 8000 6	

● Indicates analyzer(s) on which cassette can be used

INTEGRA 400/ 400 plus	INTEGRA/ INTEGRA 700	INTEGRA 800
●	●	●

Intended use

The cassette COBAS INTEGRA Cholesterol (CHOLL) contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of total cholesterol in serum and plasma in clinical laboratories. This method sheet describes the application for total cholesterol (test CHOLL, 0-001).

Summary

Measurements of serum cholesterol levels are important in the diagnosis and classification of hyperlipoproteinemias. Elevated cholesterol levels may occur with hypothyroidism, nephrotic syndrome, diabetes, and various liver diseases. There is a correlation between elevated serum cholesterol levels and the incidence of coronary artery diseases. Normal cholesterol levels are affected by stress, diet, age, gender, hormonal balance, and pregnancy. Nonfasting sample results are slightly lower than fasting results. Comparable nonfasting results were observed with beta quantification method.[1,2]

Depressed levels are associated with hyperthyroidism and severe liver diseases.

Test principle

Enzymatic, colorimetric method (CHOD/PAP) with cholesterol esterase, cholesterol oxidase, and 4-aminoantipyrine.[3,4]

Cholesterol esterase (CE) hydrolyzes cholesterol esters to form free cholesterol and fatty acids. Cholesterol oxidase (CHOD) then catalyzes the oxidation of cholesterol to form cholest-4-ene-3-one and H_2O_2. In presence of peroxidase (POD), the hydrogen peroxide formed effects the oxidative coupling of phenol and 4-amino-antipyrine (4-AAP) to form a red-colored quinoneimine dye.

$$\text{Cholesterol esters} + H_2O \xrightarrow{CE} \text{cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{CHOD} \text{cholest-4-ene-3-one} + H_2O_2$$

$$2\,H_2O_2 + \text{4-AAP} + \text{phenol} \xrightarrow{POD} \text{quinoneimine dye} + 4\,H_2O$$

The color intensity of the red quinoneimine dye formed is directly proportional to the cholesterol concentration. It is determined by measuring the increase in absorbance at 520 nm.

Reagents - working solutions

R Mono reagent in vial A (liquid).

Active ingredients

Components	Concentrations R	Test	
Phosphate	70	17	mmol/L
Sodium cholate	13	3.1	mmol/L
Phenol	97	23	mmol/L
4-Aminoantipyrine	1.7	0.4	mmol/L
CE (microbial)	≥8	≥1.9	µkat/L (≥0.1 kU/L)
CHOD (microbial)	≥5	≥1.2	µkat/L (≥0.07 kU/L)
POD (horseradish)	≥50	≥12	µkat/L (≥0.7 kU/L)
pH	6.8	6.8	

The reagent contains nonreactive surfactant and stabilizer. Please see cassette label for reagent filling volume.

Precautions and warnings

Pay attention to all precautions and warnings listed in Chapter 1, Introduction.

Reagent handling

Ready for use.

Storage and stability

Shelf life at 2 to 8°C	See expiration date on cassette
INTEGRA 400	
On-board in use at 10 to 15°C	8 weeks
INTEGRA 700/800	
On-board in use at 8°C	8 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.
Serum: Collect serum using standard sampling tubes.
Plasma: Li-heparin plasma.
Fasting and non-fasting samples can be used. Collect blood by using an evacuated tube or syringe. Specimens should preferably be analyzed on the day of collection.
When processing samples in primary tubes, follow the instructions of the tube manufacturer.

Calculate Appropriate Statistics

- **Standard Error**
  - **Measure of *Random Error***
    - **“Sy·x”**
    - **Measure of the vertical scatter about the line (SD)**
    - **If all points fit exactly in the line, “Sy·x” would be zero**

Calculate Appropriate Statistics

- **Correlation Coefficient**
  - **Another measure of *Random Error***
    - **"r"**
    - **An "r" close to 1 does not mean agreement; only that the values go up and down in tandem**
    - **Can have huge proportional or constant bias and still have a near-perfect "r"**
    - **Highly dependent on distribution of data, difficult to evaluate**

Calculate Appropriate Statistics

PPD

Correlation

Regression Statistics [i]

Comparative Method	Slope	Intercept	Correlation Coefficient	n[j]
Dimension® GLU (Serum/Plasma)	1.01	0.01 [0.001]	0.999	162
Dimension® GLU (Urine)	1.01	-1.05 [-0.058]	1.000	64
Dimension® GLU (CSF)	1.00	-0.54 [-0.030]	1.000	70

f. All specific performance characteristics tests were run after normal recommended equipment quality control checks were performed (Refer to your Dimension® System Manual).

g. Reproducibility testing was done in accordance with the NCCLS Approved Guideline for Evaluation of Precision Performance of Clinical Chemistry Devices (EP5-A, Feb. 1999).

h. Specimens at each level were analyzed in duplicate, twice a day, for 20 days. The within-run and total standard deviations were calculated by the analysis of variance method.

i. Model equation for regression statistics is: Result of D mension® analyzer = [Slope x Comparative method result] + Intercept.

j. The range of glucose values in the correlation study was 2 to 465 mg/dL [0.11 to 25.81 mmol/L] for serum/plasma, 3 to 480 mg/dL [0.17 to 26.64 mmol/L] for urine, and 2 to 397 mg/dL [0.11 to 22.03 mmol/L] for CSF.

Qualitative Method Comparison

- **Compare two methods that report results as Positive or Negative**
- **Key statistic is Agreement**
  - **Do the two methods give the same diagnosis?**
  - **Percent of total cases in which the two methods give the same result**

Qualitative Method Comparison

Assuming the reference method is accurate,

- **True Positive:**
  - **Specimen that tests positive by both methods**
- **True Negative:**
  - **Specimen that tests negative by both methods**

Qualitative Method Comparison

Assuming the reference method is accurate,

- **False Positive:**
  - **Specimen that is positive by the test method, but negative by the reference method**
- **False Negative:**
  - **Specimen that is negative by the test method, but positive by the reference method**

Trivia

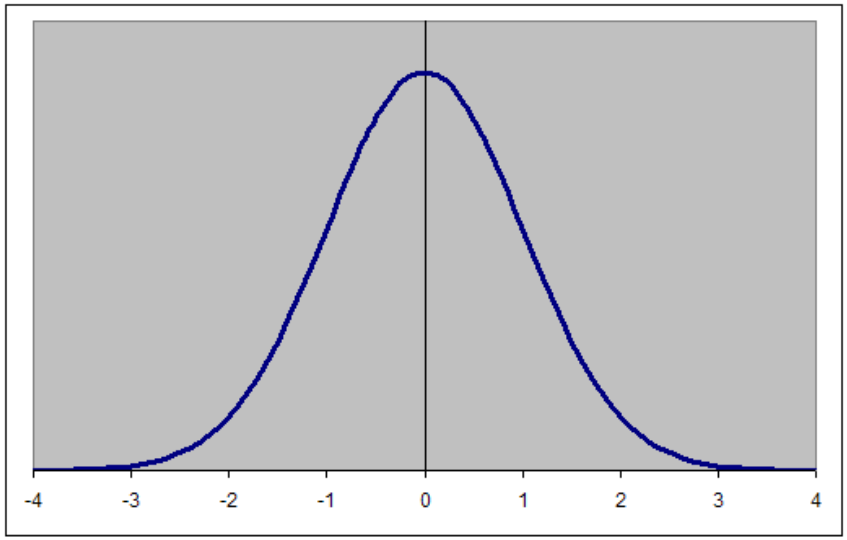
- **The average human body contains enough: _____ to make a 3 inch nail, sulfur to kill all fleas on an average dog, carbon to make 900 pencils, _____ to fire a toy cannon, fat to make 7 bars of soap, _____ to make 2,200 match heads, and _____ to fill a ten-gallon tank**

2. Precision

- **Can you obtain the same test result time after time?**
- **The agreement between replicate measurements**
- **Provides more information about *random error***

Precision

- **Random Error**
  - **Can either be positive or negative and the direction is not predictable**
  - **Distribution of random errors follows a Gaussian-shape "bell" curve**



Precision Measurement

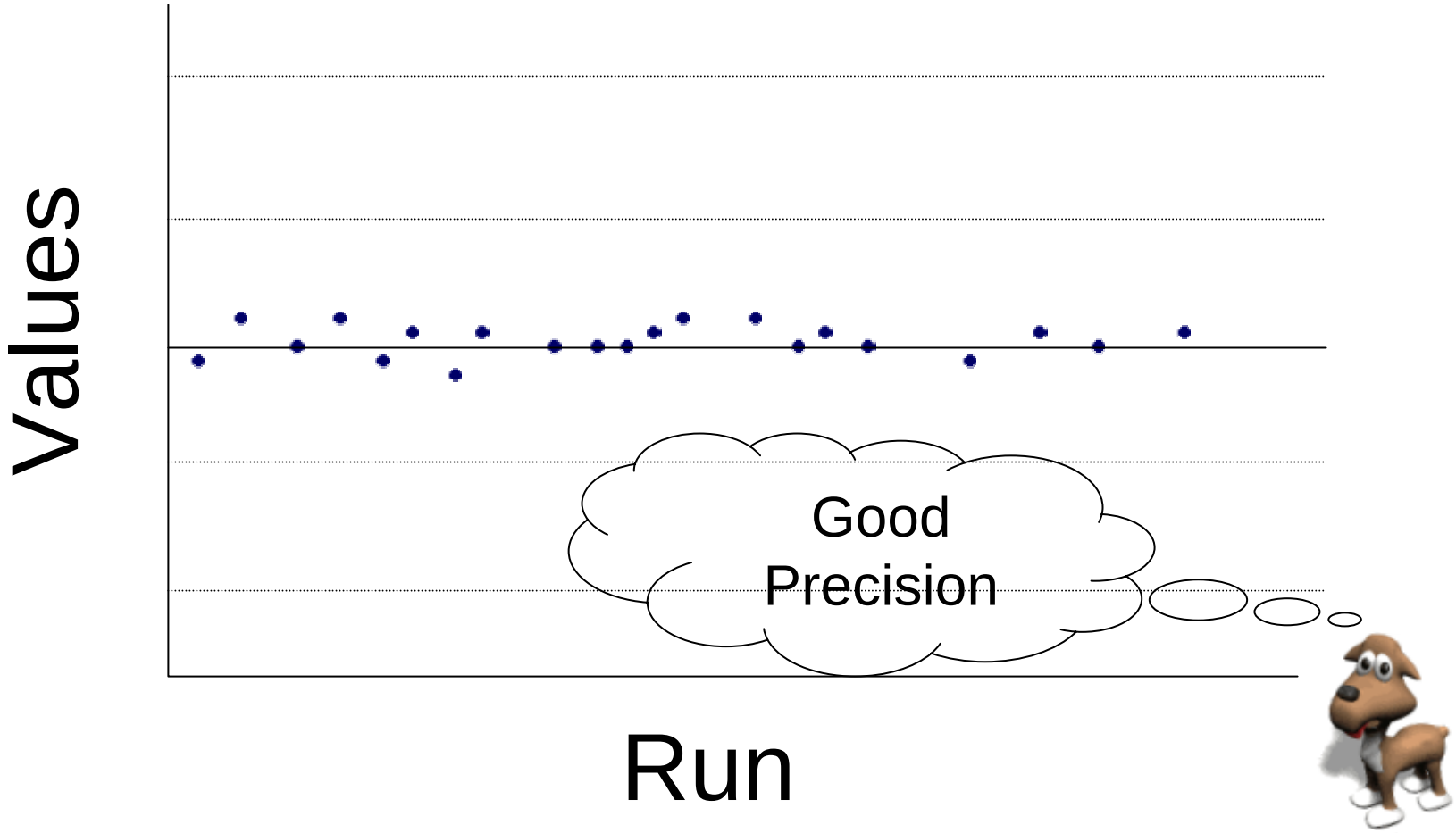
- **Replicate testing**

- **Two phases of precision experiment**
  - **Within-run precision**
  - **Between-run precision**

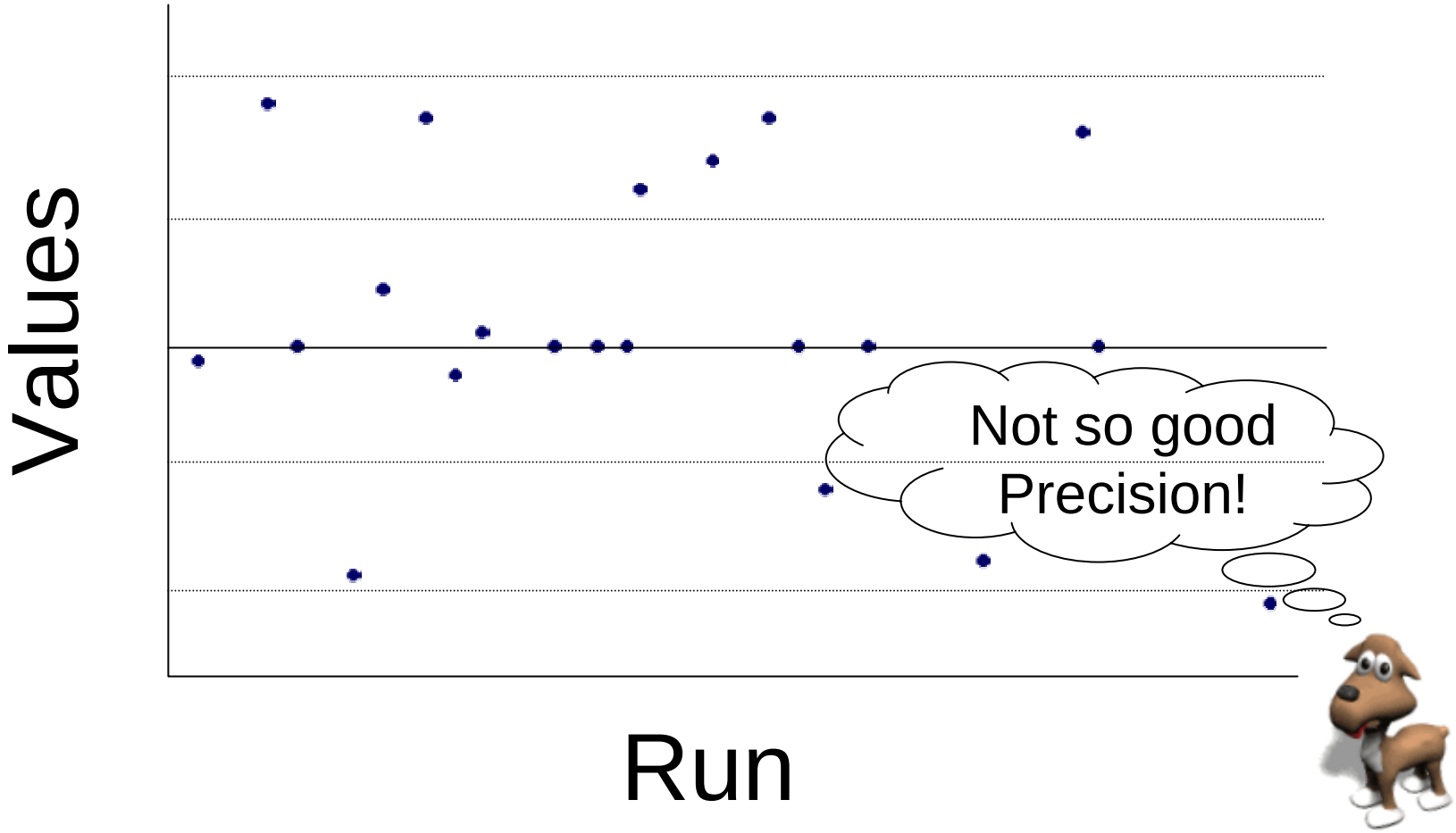
Precision Measurement

- **Easiest Method:**
  - **Control materials**
    - **At two or more concentrations**
    - **Preferably near decision points**
    - **Between Run: Analyzed at least 2 times on each of 10 successive days.**
  - **The mean, within-run and between-run SDs and coefficients of variation are calculated.**
  - **Levy Jennings (LJ) charts are prepared and analyzed.**

Precision – LJ Charts



Precision – LJ Charts



Precision Calculations

- **Mean** $\overline{X} = \sum X_i / n$

- **Standard Deviation** $SD = \sqrt{\frac{\sum (Xi - X)2}{(n-1)}}$

- **Coefficient of Variation** $CV = SD / \overline{X}$

Precision Criteria

- **The judgment on acceptability depends on what amount of analytical error is allowable without affecting or limiting the use and interpretation of a test result.**
- **Compare with precision data from manufacturer**
- **Use the CLIA criteria as a guide for defining the amount of error that is allowable.**

Precision Criteria

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Specific Performance Characteristics[f]

Reproducibility[g,h]

Material	Mean mg/dL [mmol/L]	Standard Deviation (% CV) Within-run	Total
BioRad® MULTIQUAL® Serum Control			
Level 1	55 [3.05]	0.6 [0.03] (1.0)	0.9 [0.05] (1.6)
Level 2	118 [6.55]	0.6 [0.03] (0.5)	1.4 [0.08] (1.2)
Level 3	350 [19.43]	1.8 [0.05] (0.5)	5.0 [0.27] (1.4)
BioRad® Liquichek™ Urine Control			
Level 1	31 [1.72]	0.5 [0.03] (1.5)	0.5 [0.03] (1.7)
Level 2	286 [15.87]	1.4 [0.08] (0.5)	3.3 [0.18] (1.1)
BioRad® Liquichek™ Spinal Fluid Control			
Level 1	59 [3.27]	0.4 [0.02] (0.6)	0.8 [0.04] (1.4)
Level 2	29 [1.61]	0.4 [0.02] (1.5)	0.6 [0.03] (2.2)
Serum Pool	191 [10.60]	1.0 [0.06] (0.5)	1.9 [0.11] (1.0)
Urine Pool	139 [7.71]	0.7 [0.04] (0.5)	1.4 [0.08] (1.0)
CSF Pool	192 [10.66]	0.9 [0.05] (0.4)	2.7 [0.15] (1.4)
Plasma Pool	193 [10.71]	0.8 [0.04] (0.4)	2.0 [0.11] (1.0)

MULTIQUAL® is a registered trademark of Bio-Rad Laboratories Diagnostics Group, Irvine, CA 92618

Liquichek™ is a registered trademark of Bio-Rad Laboratories Diagnostics Group, Irvine, CA 92618

Precision Criteria

- **For short-term imprecision:**
  - **Total standard deviation should be ¼ or less of the defined allowable total error to be acceptable.**
- **For long-term imprecision:**
  - **Total standard deviation should be ⅓ or less of the defined total error.**

(Federal Register February 28, 1992;57(40):7002-186)

Precision

PPD

ACTIVITY!

- **Analyte: Cholesterol, total**
- **Acceptable Value: Target value ± 10% (from CLIA criteria)**
- **We want to start using Analyzer Y to perform Cholesterol analysis.**

Precision Activity

Our Experiments' Results:

- **A control serum analyzed for cholesterol 20 times during one run with Analyzer Y yeilds a mean of 154 ± 4.0 (2SD) mg/dL.**
- **The same control serum analyzed for cholesterol 40 times over 1 month with Analyzer Y yeilds a mean of 155 ± 4.5 (2SD) mg/dL.**
- **Is this acceptable performance for this level?**

Precision Activity

Is the method acceptable for precision study?

- Short Term:
- At 154 mg/dL
  - Total allowable error = 15.4 mg/dL (10 % x 154)
  - Random error = 2 (1 SD), less than 1/4 of total allowable error
- Must compare with manufacturer's expected Standard Deviations or Coefficient of Variations.

Putting it all together

Is the method acceptable for precision study?

- Long-term:
- At 155 mg/dL
  - Total allowable error = 15.5 mg/dL (10 % x 155)
  - Random error = 2.25 (1 SD), less than 1/3 of total allowable error
- Again, must compare with manufacturer's expected Standard Deviations or Coefficient of Variations.

Putting it all together

PPD

Accuracy

- **Method Comparison**
  - Linear regression analysis of the test method with the reference method on 50 patient specimens gives:
    - Y(test) = mX(ref) + b
    - Y = 1.02 X + 3.0
  - Therefore, the test method has a proportional bias of 2% (slope of 1.02) and a constant bias of 3.0 mg/dL (intercept of 3.0)

3. Analytical Sensitivity

- **The lowest concentration that can be reliably measured**
  - **Provides information about the assay's lower detection limit**
- **Can be obtained from the manufacturer for FDA-approved tests**

Analytical Sensitivity

PPD

Analytical Sensitivity

The sensitivity of the GLUC method is 1 mg/dL [0.056 mmol/L] and represents the lowest concentration of glucose that can be distinguished from zero. This sensitivity is defined as the concentration at two standard deviations above the mean (n=20) of Level 1 Chem I calibrator (0 mg/dL) [0 mmol/L].

4. Analytical Specificity

- Relates how good the assay is at discriminating between analyte and interfering substances
- Can be obtained from manufacturer for FDA-approved tests
  - Checking for the effect of hemolysis, lipemia, and icterus is good laboratory practice

Analytical Specificity

PPD

Known Interfering Substances[b]

Serum

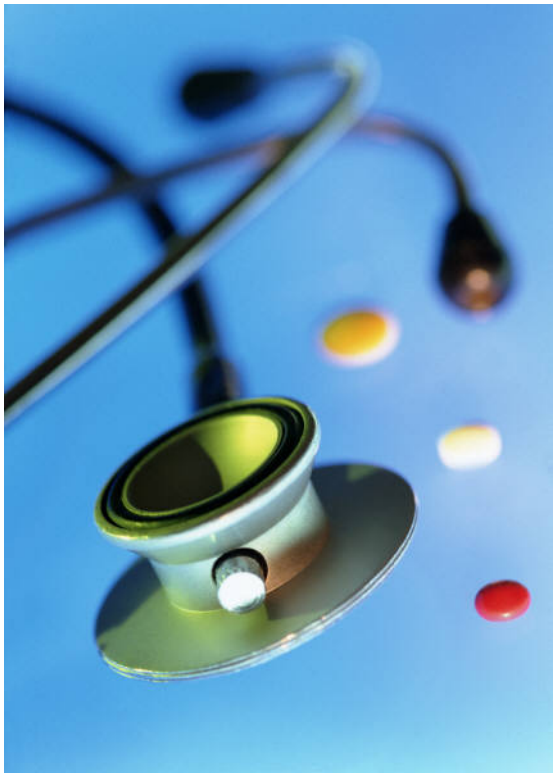
- Unconjugated bilirubin of 60 mg/dL [1026 mmol/L] increases the GLUC result by 6.5 mg/dL [0.36 mmol/L] at a GLUC concentration of 50 mg/dL [2.78 mmol/L].
- Cholesterol of 500 mg/dL [12.9 mmol/L] increases the GLUC result by 9.0 mg/dL [0.50 mmol/L] at a GLUC concentration of 50 mg/dL [2.78 mmol/L]. No significant interference (<10%) from triglycerides of 4000 mg/dL [45.2 mmol/L] was observed at a GLUC concentration of 50 mg/dL [2.78 mmol/L].
- Hemoglobin of 1000 mg/dL [0.62 mmol/L] decreases the GLUC result by 5.5 mg/dL [0.31 mmol/L] at a GLUC concentration of 50 mg/dL [2.78 mmol/L]. No significant interference (<10%) from hemoglobin of 500 mg/dL [0.31 mmol/L] was observed at a GLUC concentration of 50 mg/dL [2.78 mmol/L].

Analytical Specificity

PPD

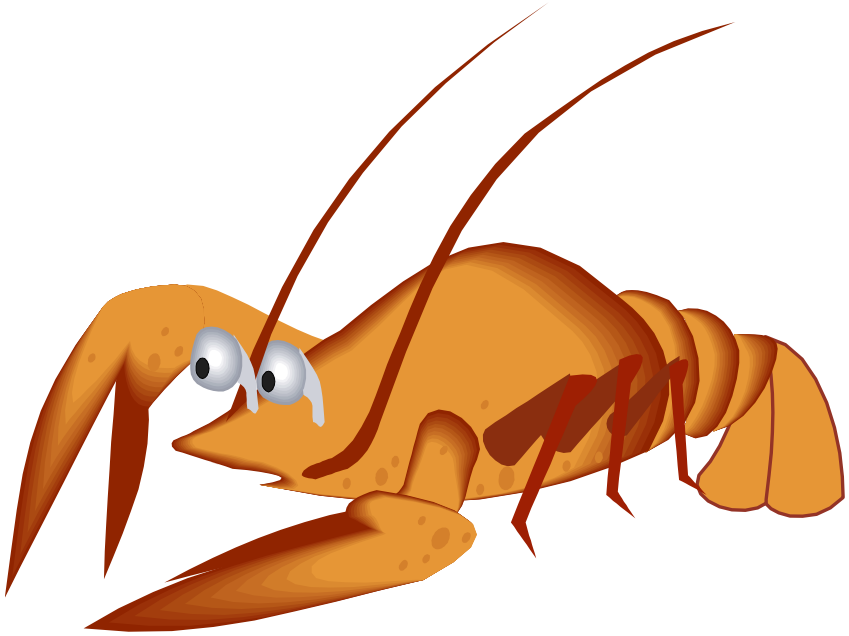
If your laboratory must evaluate Analytical Specificity, consider:

- **The number of drugs in common use**
- **Seriously ill individuals receive 8 to 12 different drugs!**



Trivia

- ***Humans have 46, peas have 14 and crayfish have 200. What are they?***



Verification of Performance Specifications

5. Reportable Ranges

- **Perform Reportable Range experiments (linearity)**
  - Also referred to as Linearity Determination
  - Standard solutions with known values
  - Cover the entire range
  - Replicates

Reportable Ranges

Reportable Range validation consists of two components:

- **Analytical Measurement Range (AMR)**
- **Clinically Reportable Range (CRR)**
  - **The CRR is dependent on the AMR**

Reportable Ranges

Analytical Measurement Range (AMR)

- **The range of analyte values that a method can directly measure *without***
  - **Dilution**
  - **Concentration**
  - **Other pretreatment**

(that is not part of the usual assay process)

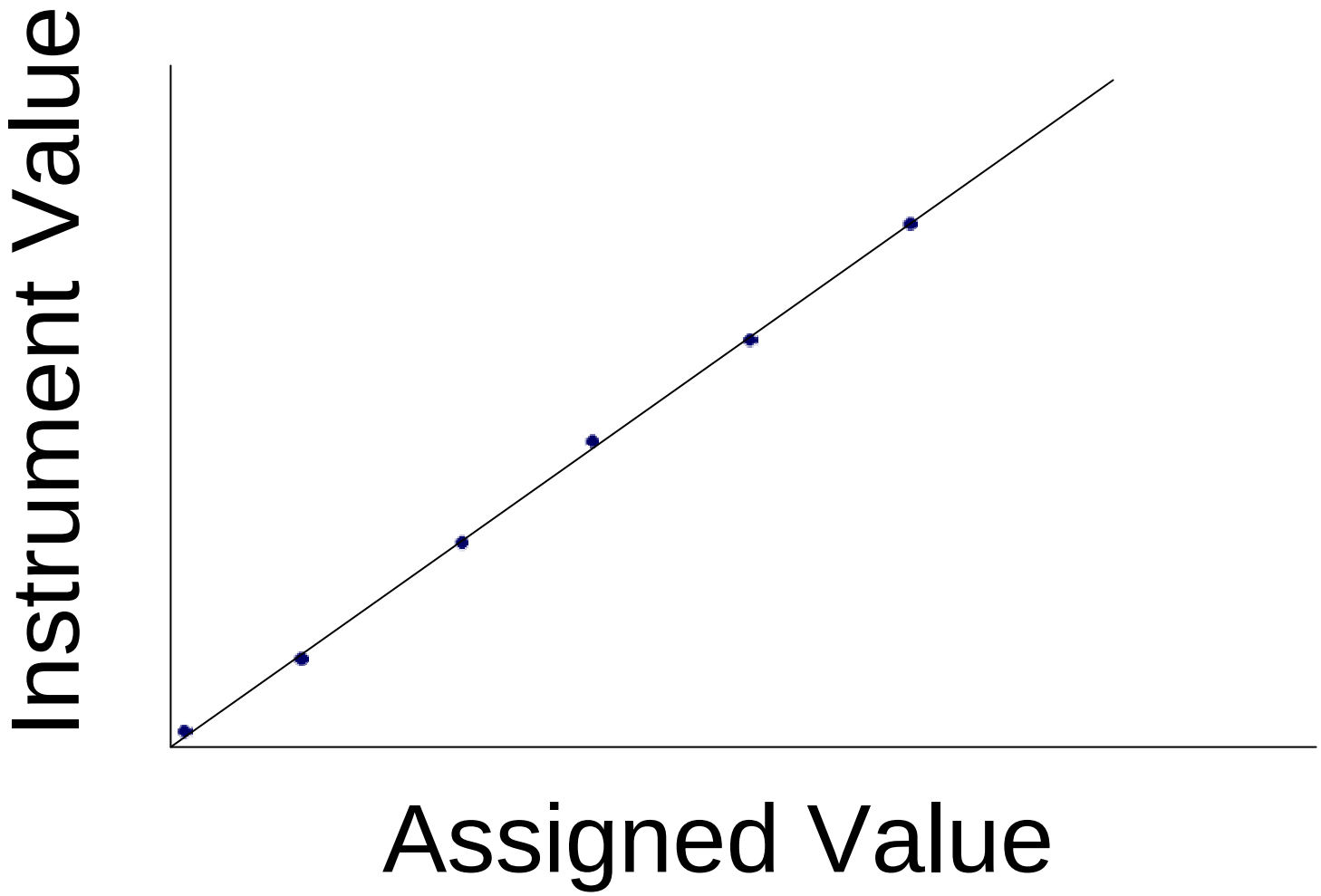
Reportable Ranges

PPD

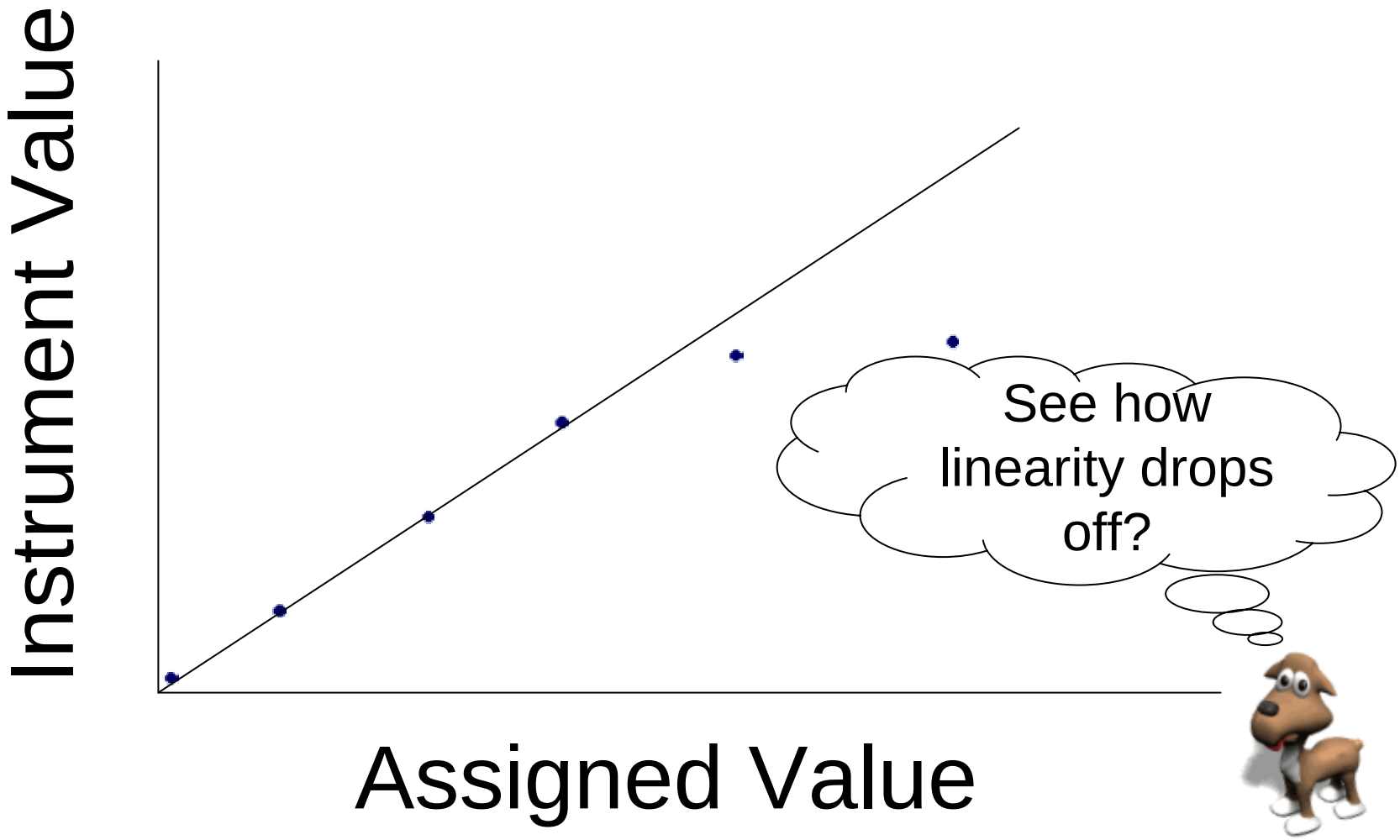
Analytical Measurement Range (AMR) - Minimum Requirements

- Establish AMR initially
  - Minimum of 3 points
    - Span range of manufacturer's published linear range (e.g. low range, mid-range and high range values)
  - Evaluate results against pre-determined acceptance criteria

Reportable Ranges



Reportable Ranges



Reportable Ranges

Activity!

Plot the following results of a Cholesterol Reportable Range experiment on a graph and draw the "best fit" line.

Is the method linear or not? How can you tell?

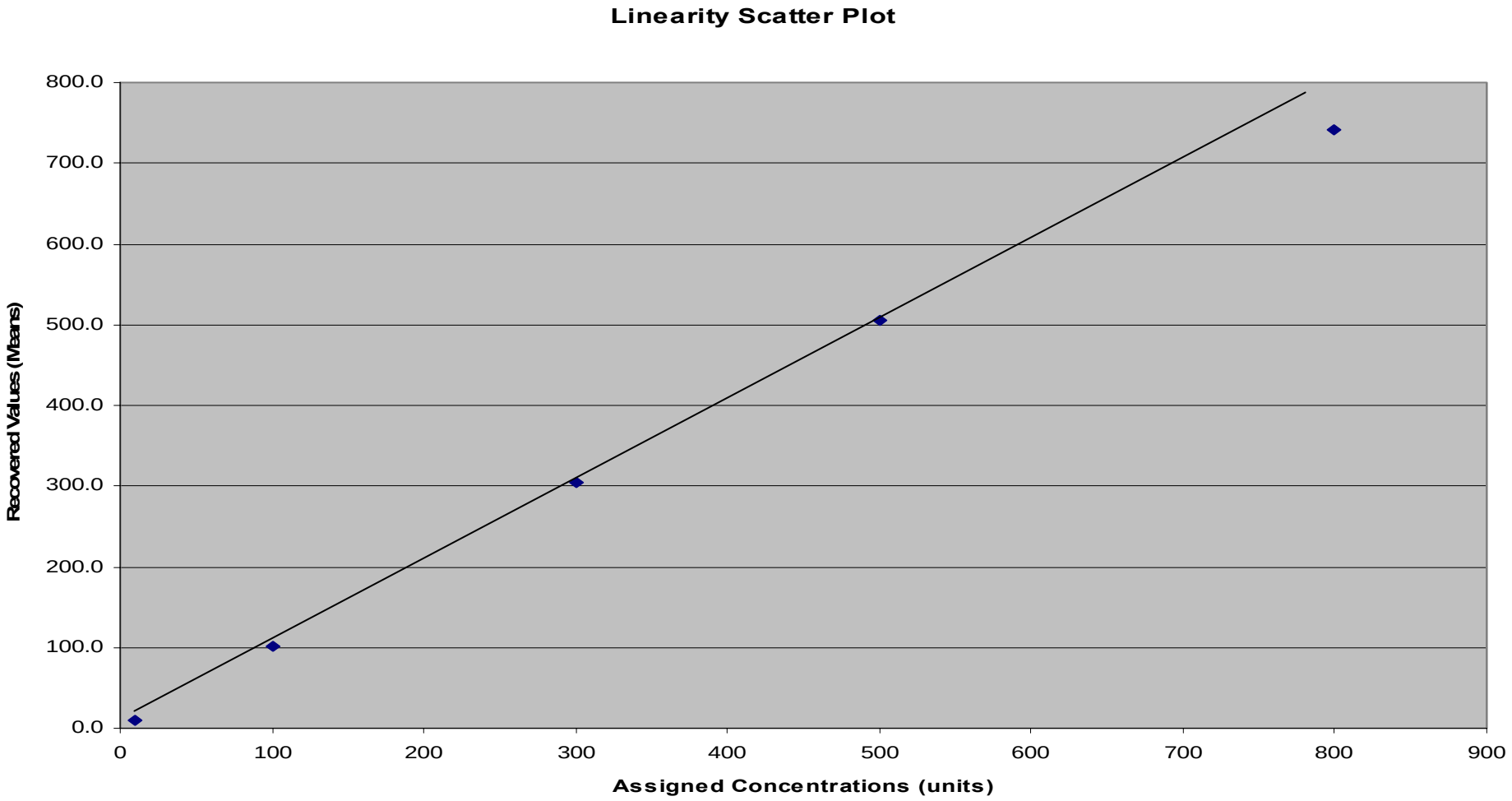
Reportable Ranges Activity

Assigned Value	Experimental Results				
	Average	Rep #1	Rep #2	Rep #3	Rep #4
10.0	____	11.0	10.0	11.0	10.0
100.0	____	99.0	103.0	103.0	101.0
300.0	____	303.0	305.0	304.0	306.0
500.0	____	505.0	506.0	505.0	506.0
800.0	____	740.0	741.0	744.0	742.0

Reportable Ranges Activity

Assigned Value	Experimental Results				
	Average	Rep #1	Rep #2	Rep #3	Rep #4
10.0	**10.5**	11.0	10.0	11.0	10.0
100.0	**101.5**	99.0	103.0	103.0	101.0
300.0	**304.5**	303.0	305.0	304.0	306.0
500.0	**505.5**	505.0	506.0	505.0	506.0
800.0	**741.8**	740.0	741.0	744.0	742.0

Reportable Ranges Activity



Reportable Ranges

Clinically Reportable Range (CRR)

- **The range of analyte values that a method can report as a quantitative result that *allows for***
  - **Specimen dilution**
  - **Concentration**
  - **Other pretreatment**

  (that is not part of the usual assay process)

- **Used to extend the direct AMR**

Reportable Ranges

PPD

Clinically Reportable Range (CRR) – Minimum Requirements

- Document the CRR in procedure
  - Dilution protocols
    - Highest acceptable dilution
    - Diluent to be used
  - When to report “>” or “<”

Reportable Ranges

Example:

Makeitbetter Medical Center uses the following test with both low and high measurable limits.

The test is cholesterol.

Reportable Ranges

- Assume that the ***AMR*** is **0 - 800 mg/dL**
- The Laboratory Director establishes that, for proper patient/client care, the ***CRR*** is **5 - 1,600 mg/dL**
  - **The lower CRR is based on medical judgment that lower values or higher values are not useful for diagnostic or prognostic purposes.**

Reportable Ranges

PPD

How would you report . . .

- **An instrument result of 1 mg/dL?**
- **An <u>undiluted</u> result of 1,000 mg/dL?**
- **A <u>diluted</u> result of 2,000 mg/dL?**

Reportable Ranges

- Patient/client specimens with analytical measured results of 1, 2, 3, or 4 mg/dL are reported as:

"<5 mg/dL"

- In this case, specimens with analytic results greater than 800 mg/dL would be diluted; but without a dilution, we can only report as:

“>800 mg/dL”

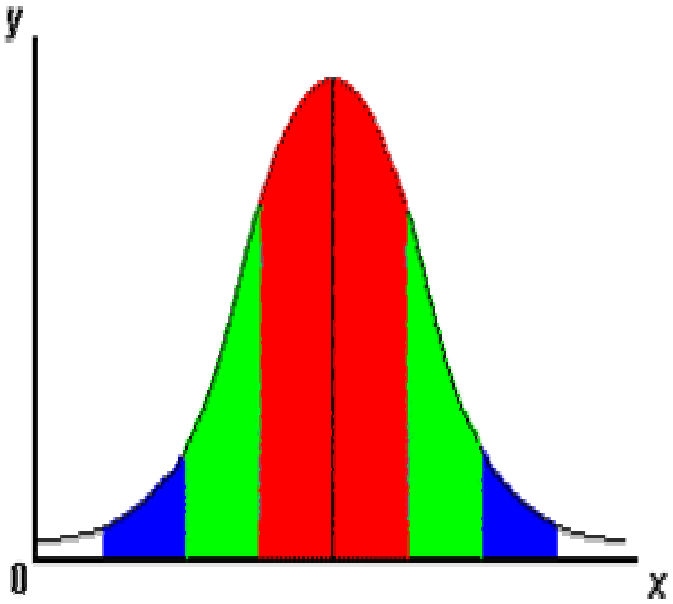
- Specimens with analytic results >1,600 mg/dL are reported as

">1,600 mg/dL"

6. Reference Intervals

- **Defined as the range where 95% (the range from +2 standard deviations to -2 standard deviations) of the healthy population fall**

- **Used to assist with interpretation of participant results**



Reference Intervals

- **Generally studied last**
  - Doesn't enter into the decision of method acceptability
  - Isn't needed if method performance is unacceptable
- **May vary from lab to lab**
  - Affected by population, climate, altitude, etc.

Reference Intervals

- ***Establishing*** **Reference Ranges**
  - **Very resource-intensive**
    - **Define normal population using protocols, such as developed by CLSI (NCCLS)**
    - **Minimum of 120 *normal* individuals from each group (i.e., gender dependent 2 x 120 = 240 reference individuals)**
  - **Non-FDA approved or modified FDA approved methodology**

Reference Intervals

- *Transferring* Reference Ranges
  - "Measurement of the same analyte by the same analytical method for which reference value studies from another laboratory or the manufacturer are available" -CLSI
  - Methods
    - Verification with 20 samples
  - Unmodified FDA-approved methods

Reference Intervals

- *Transferring* Reference Ranges
  - Of 20 samples from healthy individuals
    - If 2 or fewer fall outside claimed reference interval – considered verified
    - If more than 2 fall outside of claimed reference interval, must analyze 20 more

Getting Started

PPD

How do I do all of this?

Getting Started

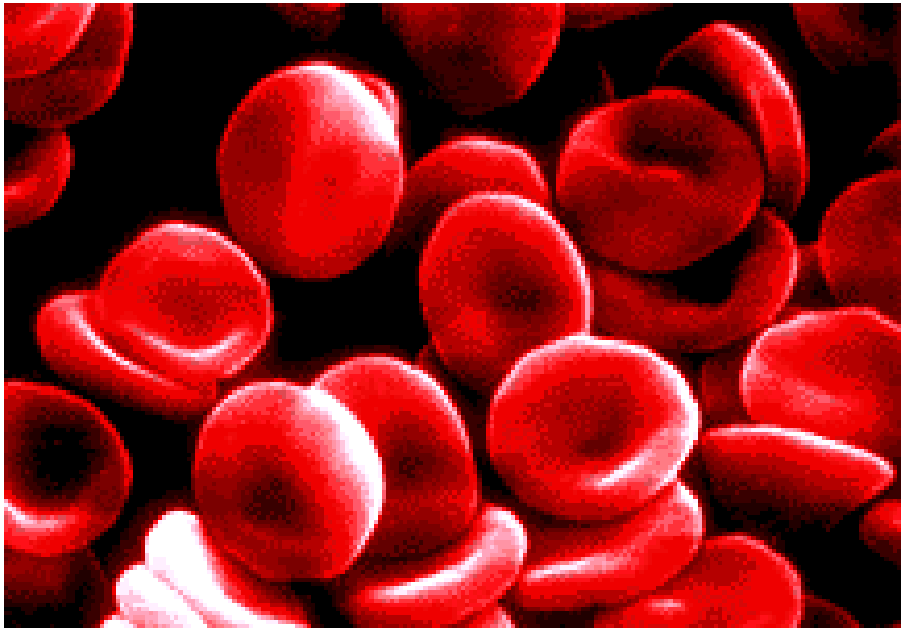
PPD

Method Validation steps:

1. Familiarization period
2. Preliminary validation
3. Final validation
4. Implementation

Trivia

What is the
smallest cell
in the human body?
Largest cell?



Familiarization Period

- Set up the instrument
- Prepare the reagents
- Learn how to perform the method properly

Familiarization Period

- Establish a “working” procedure
  - Refer to Manufacturer’s package insert
  - Ensures validation follows a standardized format
- Check calibration
  - Critical Step!
  - Ensures the method is working properly
    - Otherwise, errors will adversely affect all validation experiments

Preliminary Validation

- **Perform reportable range experiments (linearity)**

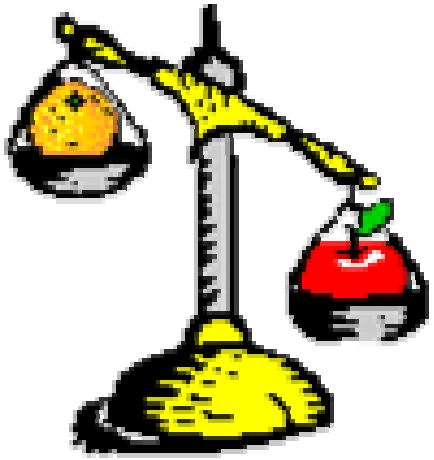
- **Check detection limit (sensitivity) if applicable**
  - **Not necessary for unmodified FDA-approved methods**

Preliminary Validation

- **Perform within-run precision**
- **Perform specificity experiments (interfering substances) if applicable**
  - **Not necessary for unmodified FDA-approved methods**

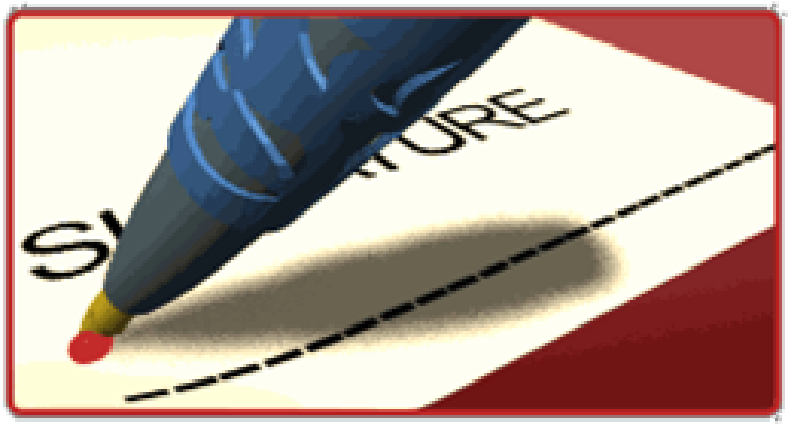
Final Validation

- **Perform between-run precision**
- **Perform method comparison**
- **Verify reference interval (normal range)**



Final Validation

- **Document studies**
  - **Compile raw and calculated statistical results of each experiment**
    - precision, accuracy, etc.
  - **Verify record of dates of performance**
  - **Obtain approval signatures**



Question

Is it *acceptable* to take *your* reagents and samples to *another* laboratory and analyze them for any portion of method validation?

PPD

NO!

Method validation must be performed utilizing *your* instrument, *your* reagents, and *your* patient samples in order to be valid.

Implementation

Write Operating Protocol / Procedure

- **Based on your experience with validation experiments.**

Implementation

PPD

Train analysts

- Everyone that is expected to use instrument and/or assay must be trained
- Training *must* be documented
  - Provide post-training assessment (also serves as competency assessment)
  - Maintain training attendance logs (Sign-in sheet)

Implementation

PPD

Train analysts

- File completed documentation
  - With Validation documentation
    - Easily accessed if needed
  - In employee file
    - Cumbersome to find all trained personnel

Implementation

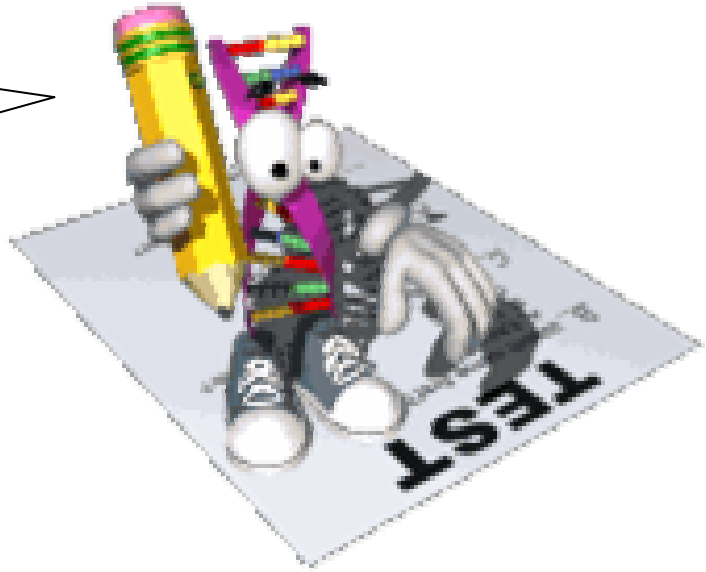
- **Introduce method for service**
  - **Notify appropriate individuals and groups**
    - **Physicians**
    - **Regulatory body (if required)**
    - **DAIDS**
  - **Document notification!**

Implementation

- **Monitor routine performance for at least the first 30 days of use**
  - **Identify / correct sources of problems**
    - **Specimen Integrity**
    - **Reagent Stability**
  - **Improve Preventive Maintenance Procedures and Documentation**
  - **Update Quality Control data; inform analysts**

PPD

How often do I need to validate?



Validation Frequency

- **Validate prior to reporting patient test results when initiating a new procedure or instrument**
- **Validate at periodic intervals to assess on-going system performance**
  - **e.g., reportable ranges, reference ranges**
- **Validate when troubleshooting questionable system performance**

Validation Frequency

- **Validate following a MAJOR reformulation by the manufacturer of a reagent**
  - **Usually notified by manufacturer**
    - **Certified letter**
    - **Highly visible notice on packaging**

How can I learn more?

PPD

Several good websites are available for use as references. Elements from this presentation were based on information at:

www.westgard.com

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Evaluation software available via internet includes:

www.analyse-it.com (purchase)

www.dgrhoads.com (purchase)

Online tools available at:

www.westgard.com (free!)

Science is a system of statements based on direct experience, and controlled by experimental verification. Verification in science is not, however, of single statements but of the entire system or a sub-system of such statements.

Rudolf Carnap (1891–1970), AustrianAmerican philosopher. trans. by Max Black, K. Paul, Trench, Trubner & Co. (1934). Unity of Science, p. 42.

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Questions?

References

- www.westgard.com
- www.cap.org
- www.dgrhoads.com
- Burtis, C.A., & Ashwood E.R. (Eds.).(1999). *Tietz Textbook of Clinical Chemistry, 3rd Edition.*
- Snyder, J. R., & Wilkinson, D.S. (Eds.). (1998). *Laboratory Management, 3rd Edition*.

Laboratory Safety

Objectives

- **Gain knowledge of basic safety practices relating to:**
  - **Fire safety**
  - **Chemical safety**
  - **Bloodborne pathogens**
- **Basic knowledge relating to Dangerous Goods Regulations**

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You should always follow <u>your</u> institution's policies regarding safety

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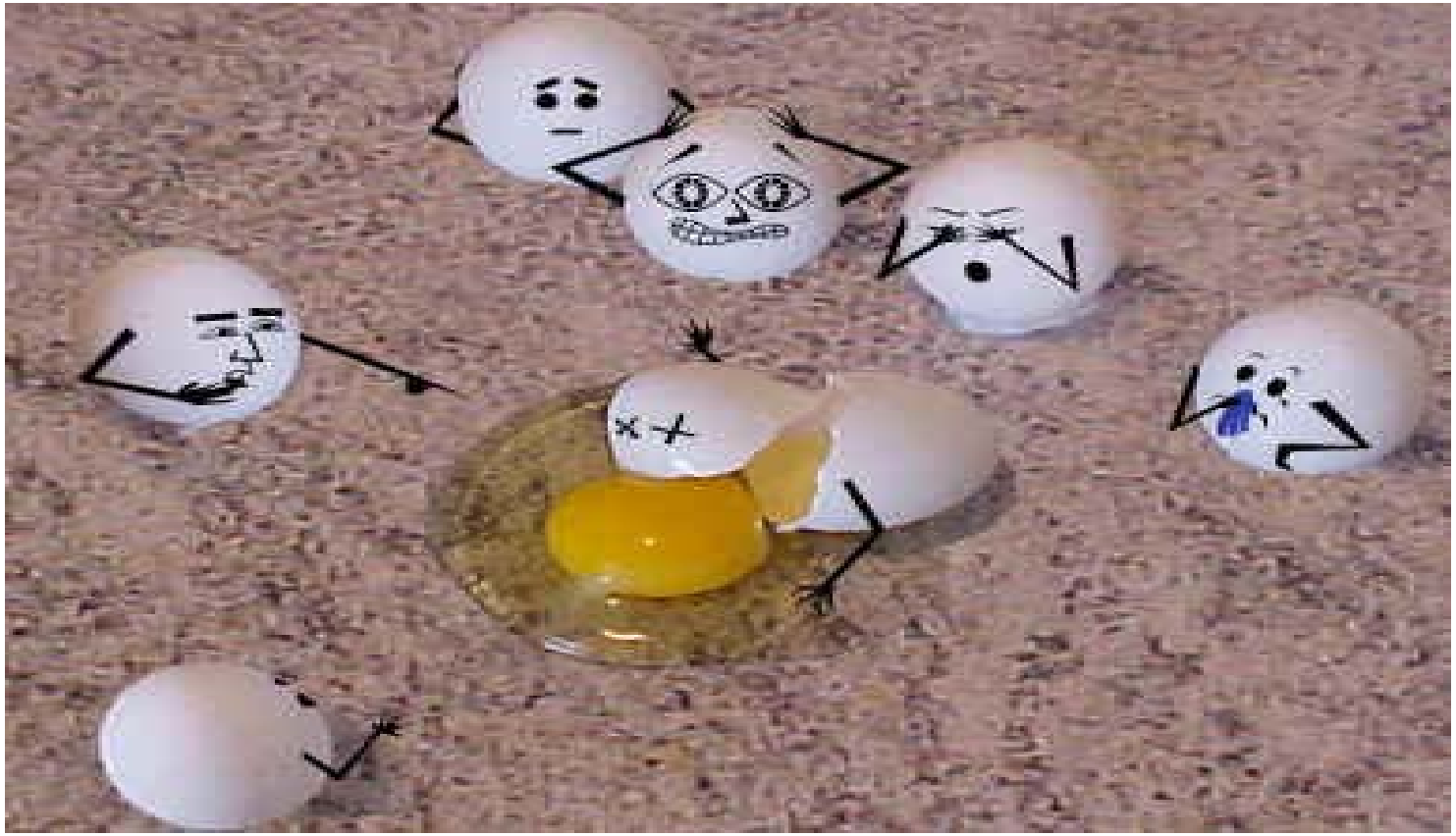

Responsibility

Who's responsibility is safety

?

Responsibility

Employer

- Provides
  - Necessary policies
  - Engineering and work practice controls
  - Personal Protective Equipment
- Ensures compliance with policies

Responsibility

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Employee

- Important to know your institution's health and safety practices
- Follow those health and safety practices

Responsibility

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Safety

is

a

TEAM

event

Responsibility

You are not only protecting yourself, but also those around you.

Four main elements…

- **Fire Safety**

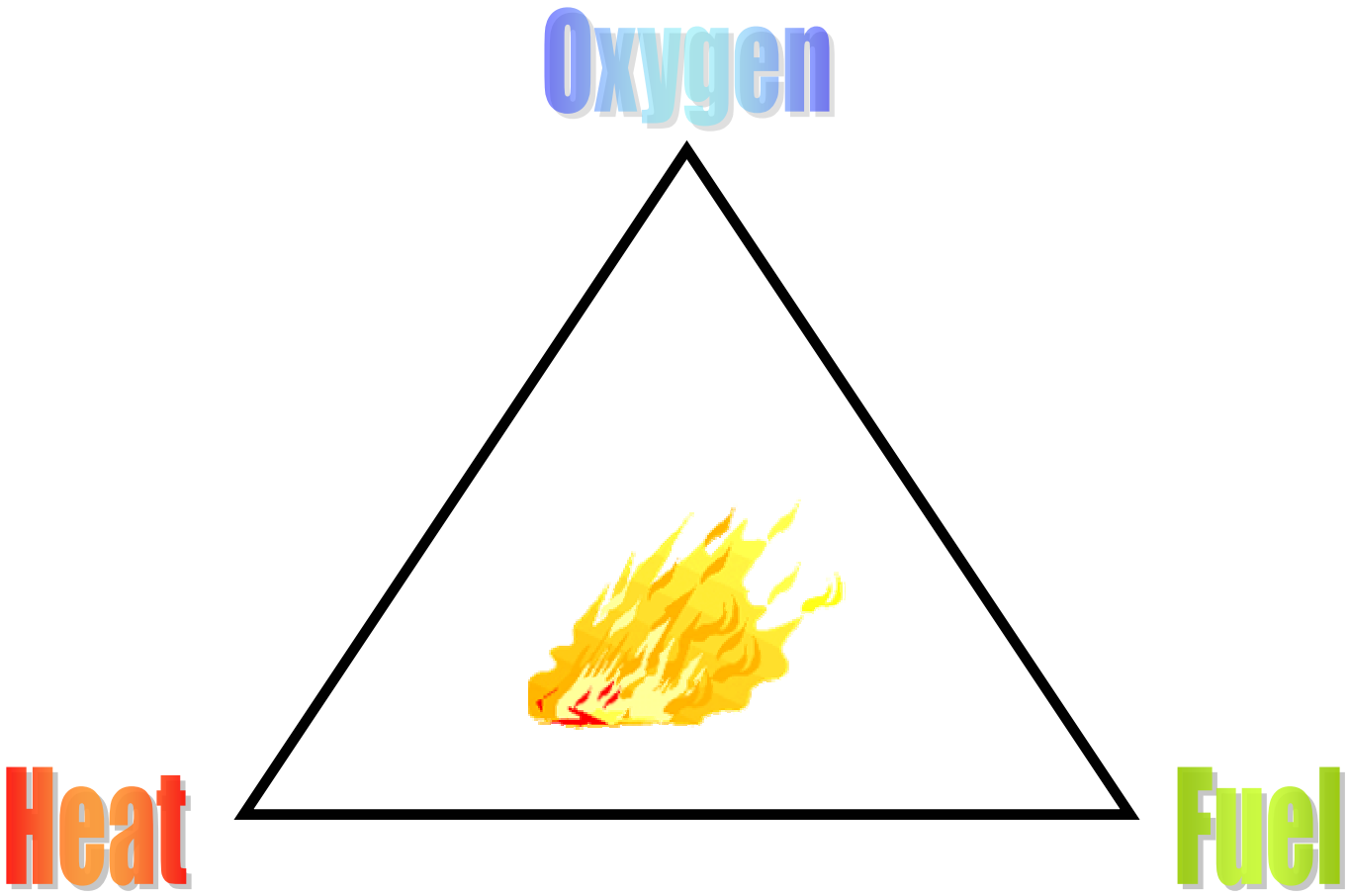
- **Chemical Safety**

- **Bloodborne Pathogens**

- **Dangerous Goods**

Fire Safety

Elements of fire



Fire Safety

- **RACE**

  Rescue – any people in danger

  Alarm – activate the fire alarm

  Contain – contain the fire by closing the door

  Extinguish – if it's small enough

Types of Fire Extinguishers

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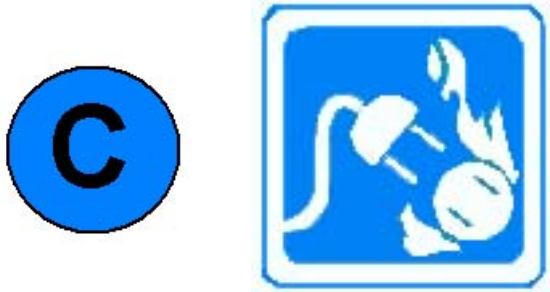
Ordinary Combustibles

Flammable Liquids

Electrical Equipment

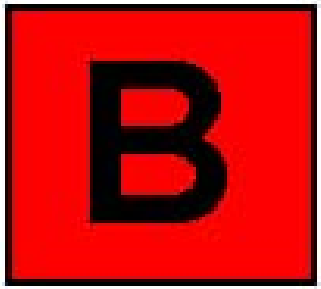


Fire Safety

Typically filled with water

- **Wood**
- **Paper**
- **Cloth**
- **Rubber**

Fire Safety



Typically filled with dry chemical

- **Gas**
- **Oil**
- **Tar**
- **Lacquer**
- **Flammable gases**

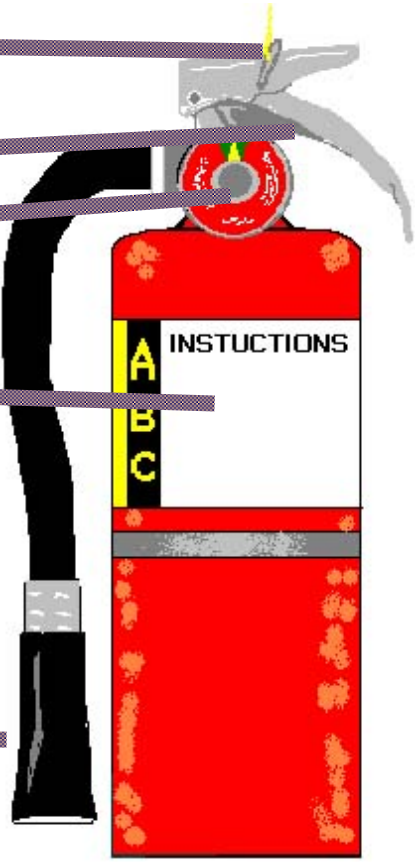
Fire Safety

Typically filled with CO2 or Halon

- **Wiring**
- **Fuse boxes**
- **Circuit breakers**
- **Machinery**
- **Appliances**

Fire Safety

- Locking pin
- Carrying handle / operating lever
- Pressure gauge
- Label :
  - **Type (Water, C02, Dry Chemical)**
  - **Classification (A, B, C)**
  - **Instructions**
- Discharge nozzle or horn



Fire Safety

- **PASS**

  Pull – the pin

  Aim – at the base of the fire

  Squeeze – the handle

  Sweep – to cover the fire

- **Plan Your Exit**
  - Always position yourself with an exit to your back when using an extinguisher

Fire Extinguisher Maintenance

Portable fire extinguishers must be visually inspected monthly. The inspection should assure that extinguishers are/have:

- Wall-mounted
- In their assigned place
- Not blocked or hidden

Fire Extinguisher Maintenance

Portable fire extinguishers must be visually inspected monthly. The inspection should assure that extinguishers are/have:

- Pin and seals are in place
- No visual sign of damage
- Nozzles that are free of blockage
- Pressure gauges that show adequate pressure

Fire Safety

Pressure gauge should be within the green area

Fire Safety

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Review:

- Three elements of fire
- RACE
- PASS

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STORY TIME!!!!!

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Do you have a fire story????

Chemical Safety

Chemical Safety

- **1992** International mandate adopted at the Earth Summit
- **Goal:** The development of a world-wide system for Hazard Communication
- **Result:** The Globally Harmonized System (GHS) for Hazard Classification and Labeling

- Adopted in 2002 by the United Nations

Chemical Safety

- **Ways chemicals can enter the body**
  - **Inhalation : breathing in (e.g., powders, fumes)**
  - **Absorption : on skin or mucus membranes**
  - **Ingestion : entry through mouth**
  - **Injection : through skin by foreign body**

Chemical Safety

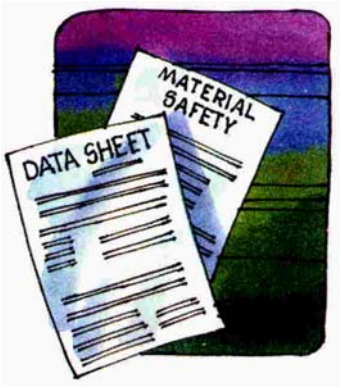
- **Examples of chemical hazards**
  - **Carcinogens : cancer**
  - **Corrosives : burns**
  - **Hepatotoxins : liver damage**
  - **Mutagens : damage genetic material in cells**

Chemical Safety

- *More* Examples of chemical hazards
  - Nephrotoxins : kidney damage
  - Neurotoxins : damage to the nervous system
  - Teratogens : birth defects

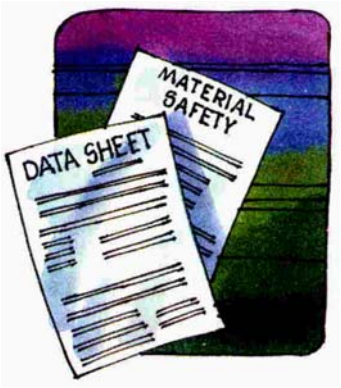
Chemical Safety

- **MSDS**
  - **Material Safety Data Sheets**
  - **Product specific information for chemicals**
    - **Name of Chemical**
    - **Physical Characteristics and Hazards**
    - **Health Related Info**



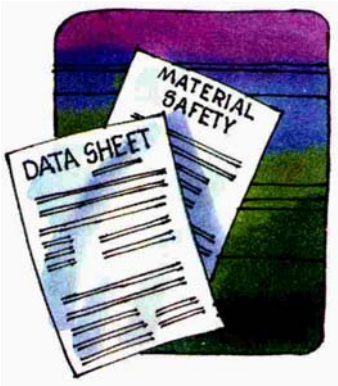
Chemical Safety

- **MSDS**
  - **Product specific information for chemicals**
    - **First Aid**
    - **Spill and Disposal**
    - **Date of most recent change**
    - **Name and address of party responsible for MSDS**



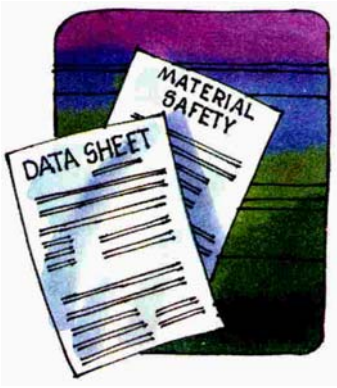
Chemical Safety

- **MSDS, continued:**
  - **Need to check for updates annually**
  - **Highlight the chemical name (also recommend highlighting the first aid section, too)**



Chemical Safety

- **MSDS, continued:**
  - **Organize in alphabetical order**
  - **Index of all MSDS may also serve as chemical inventory**
  - **Must be accessible to everyone all of the time (not locked in manager's office)**



Chemical Safety

- **Spills**

Rescue
Avoid the chemical
Find the MSDS
Telephone for help

Chemical Safety

First Aid for Chemical Exposure

- **Flush with plenty of water**
  - At least 15 minutes
  - Remove contaminated clothing
- **Seek medical attention**
- **Document**

Trivia!

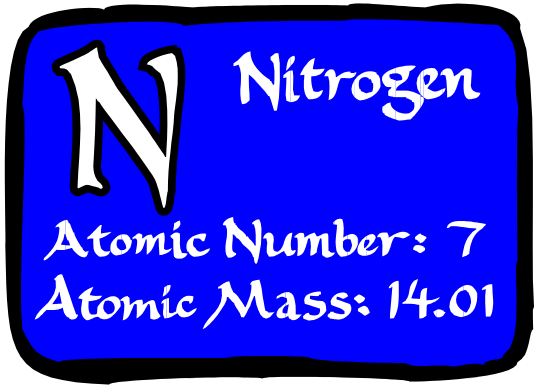
- **What class of antibody is initially produced by the immune system in an immune response to a pathogenic virus?**

Chemical Safety

Liquid Nitrogen

– Characteristics of Nitrogen

- 78% of Atmosphere
- Colorless, Odorless, Tasteless, Nontoxic
- Boils at -320 degrees F (-196 C)
- Nonflammable



Chemical Safety

Liquid Nitrogen

- **Why be concerned?**
  - **It displaces oxygen from the air**
    - **WILL NOT SUPPORT LIFE**
    - **Can lead to asphyxiation**
  - **It can cause frostbite or worse**

Liquid Nitrogen – Precautions

- Always wear safety equipment (PPE)
- Avoid use in small enclosed areas
- Avoid prolonged breathing of vapors
- Avoid rough handling of containers
- Provide adequate ventilation

Chemical Safety

Liquid Nitrogen – PPE

- Full Face Shield with Safety Glasses or Safety Goggles
- Cryogenic Gloves
- Arm Protection
- Lab Coat
- Cuff-less pants

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Liquid Nitrogen – Emergencies

- Inhalation – Immediately remove to fresh air
- Eyes – flush with water for 15 minutes
- Skin – soak affected area in tepid water
- SEEK MEDICAL ATTENTION
- Document Incident

Chemical Safety

What's wrong with this picture?

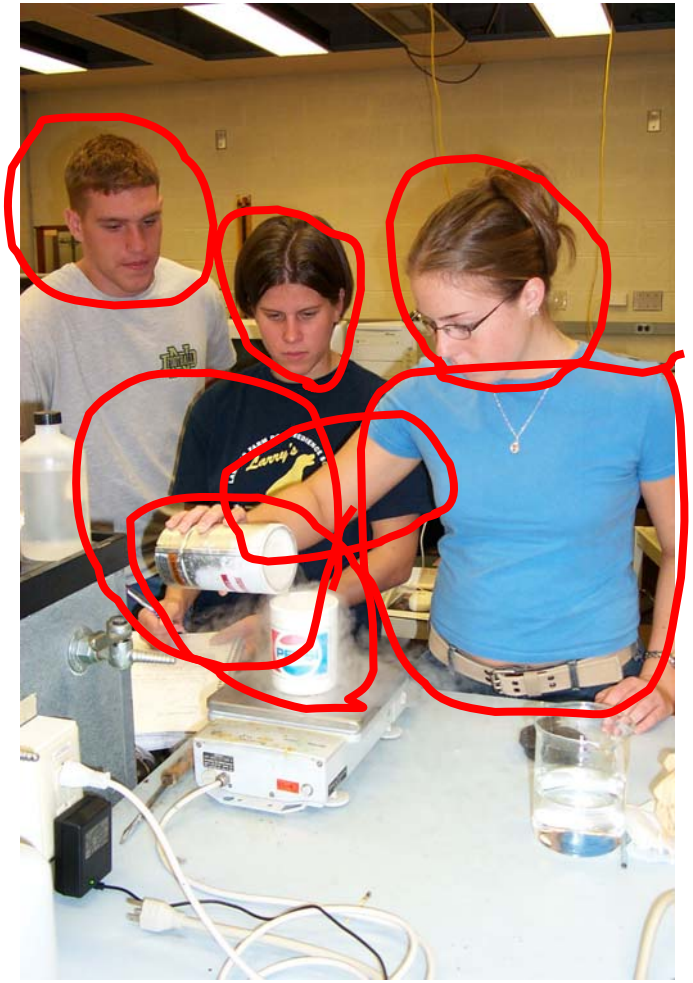
That's liquid nitrogen they are working with.

Chemical Safety

PPD

What's wrong with this picture?

- **No cryogenic gloves**
- **No face protection**
- **No arm protection**
- **No lab coat**
- **Not an approved container**



Chemical Safety

Solid Carbon Dioxide – Dry Ice

– Characteristics of Carbon Dioxide

- Colorless, Odorless, Tasteless, Nontoxic
- Nonflammable
- Can only be solid when temperature is < -78° C

PPD

Solid Carbon Dioxide – Dry Ice

- It also displaces oxygen from the air
  - WILL NOT SUPPORT LIFE
  - Can lead to asphyxiation

Chemical Safety

Solid Carbon Dioxide – Dry Ice

- **High concentrations may cause rapid circulatory insufficiency**
  - **Headache**
  - **Nausea**
  - **Vomiting**
  - **Unconsciousness**

Chemical Safety

Solid Carbon Dioxide – Dry Ice

- Always wear safety equipment (PPE)
- Ensure adequate ventilation
- Avoid prolonged breathing of vapors

Chemical Safety

Solid Carbon Dioxide – PPE

- Full Face Shield with Safety Glasses or Goggles
- Cryogenic Gloves
- Lab Coat

Chemical Safety

Solid Carbon Dioxide– Emergencies

- Inhalation – Immediately remove to fresh air
- Eyes – flush with water for 15 minutes
- Skin – soak affected area in tepid water
- SEEK MEDICAL ATTENTION
- Document Incident

Chemical Safety

Management of Chemicals in the laboratory

- SOPs
  - Hazard Communication
  - Chemical Hygiene
- Annual Chemical Inventory / MSDS updates
- Periodic Safety Assessments

Chemical Safety

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Review:

- **MSDS**
- **RAFT**
- **Cryogenics**

Nicely Done!

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Story Time!

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Who has a chemical safety story?

Intermission

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- **Bloodborne Pathogens**

Bloodborne Pathogens

What are bloodborne pathogens?

Viruses, bacteria or other micro-organisms that are carried in a person's blood stream and can cause disease.

Bloodborne Pathogens

- **Other body fluids can also spread bloodborne pathogens such as:**
  - **Blood products (plasma, platelets, etc.)**
  - **Abdominal and chest fluids**
  - **Amniotic fluid**
  - **Cerebrospinal Fluid (CSF)**
  - **Joint fluids**
  - **Vaginal Secretions**
  - **Semen**

Bloodborne Pathogens

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Most common pathogens

- Hepatitis B
  - Active or chronic
  - Can lead to cirrhosis, liver cancer and death
  - EFFECTIVE VACCINE AVAILABLE

Bloodborne Pathogens

PPD

Most common pathogens

- Hepatitis C
  - Milder symptoms than Hepatitis B or no symptoms at all
  - More likely to develop into chronic carrier state
  - Can lead to cirrhosis, liver cancer and death
  - NO VACCINE CURRENTLY AVAILABLE

Bloodborne Pathogens

PPD

Most common pathogens

- HIV
  - May demonstrate no symptoms for years after infection
  - Variety of symptoms including rapid weight loss, fever, etc.
  - NO VACCINE CURRENTLY AVAILABLE

Bloodborne Pathogens

Standard precautions

Treat everyone's **blood** and **body fluids** as **infectious all of the time**

Bloodborne Pathogens

- **Use Personal Protective Equipment (PPE)**
  Includes, but not limited to:
  - **Gloves**
  - **Fluid resistant gowns or coats**
  - **Goggles and masks or face shields**

Bloodborne Pathogens

You should wear as much or as little PPE as you anticipate you will need to prevent blood and other infectious materials from contact with your skin, mucus membranes and clothing

Bloodborne Pathogens

PPD

What type of PPE do you recommend for the performing the following?

- **Drawing blood?**
- **HIV ELISA?**
- **Clerical work, such as a receptionist?**

Bloodborne Pathogens

- **Handle sharps with care**
  - **Do not recap needles or other sharps**
  - **Do not bend, shear or break off needles**
  - **Dispose of sharps in puncture resistant container**

Bloodborne Pathogens

Things that should not be done in areas where you are working with blood or body fluids:

- Eat or drink
- Smoke
- Apply cosmetics
- Handle contact lenses

Bloodborne Pathogens

- **MOST IMPORTANT!!!!!**

WASH HANDS

  – **Very basic but important practice to reduce your risk of infection. The <u>sooner</u> you wash infectious material off your hands, the less your chance of infection.**

Trivia!

What is the human body's

***heaviest organ*?**

Dangerous Goods

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What

Are

Dangerous

Goods

?

IATA

International Air Transport Association

Regulates international air transport, including the transport of Dangerous Goods

Dangerous Goods

Articles / substances that pose

Significant risk to

- **Health**
- **Safety**
- **Property**
- **Environment**

When

Transported by

- **Sea**
- **Air**
- **Road**
- **Rail**

Dangerous Goods

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Includes...

- Dry ice
- Infectious substances
- Poisons
- Firearms
- Ammunition
- Paint

To name a few...

Dangerous Goods

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The regulations state:

"No person shall handle, offer for transport, or transport Dangerous Goods…unless they are trained."

(In accordance with IATA 1.5, 49 CFR Sec.172.700)

Dangerous Goods

Training sources:

Saf-T-Pak Compliance Training

www.saftpak.com

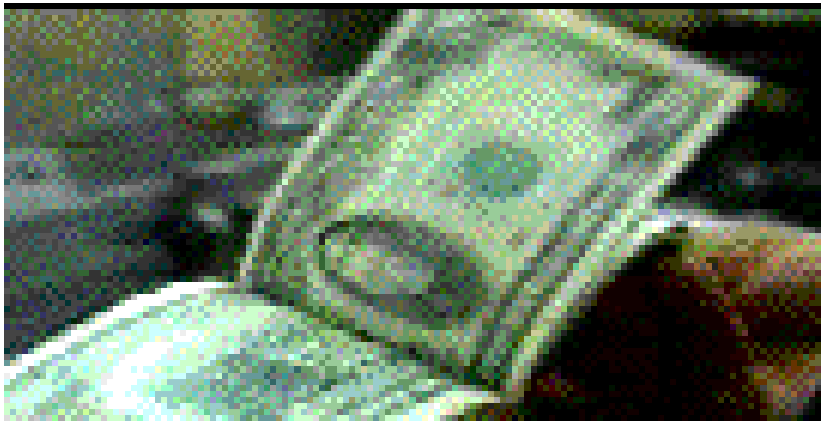
IATA website

www.iata.org

Dangerous Goods

So what do you think happens if you don’t follow the regulations for dangerous goods transportation?

Fines for Violations



Fines for Violations

- Individual civil penalty between $250 and $25,000 per violation

- Willful individual violators may be fined up to $250,000 and/or receive up to 5 years in prison

- Business entities or institutions may be fined up to $500,000 per violation

Fines for Violations

- Shippers from NY and Georgia in the US and from the UK, each have fines of $51,000 and higher pending against them for tendering shipments later found leaking at a sorting facility.

- A shipper faces a civil penalty of $59,000 for allegedly offering five fiberboard boxes, each containing four cans of paint, a flammable liquid.

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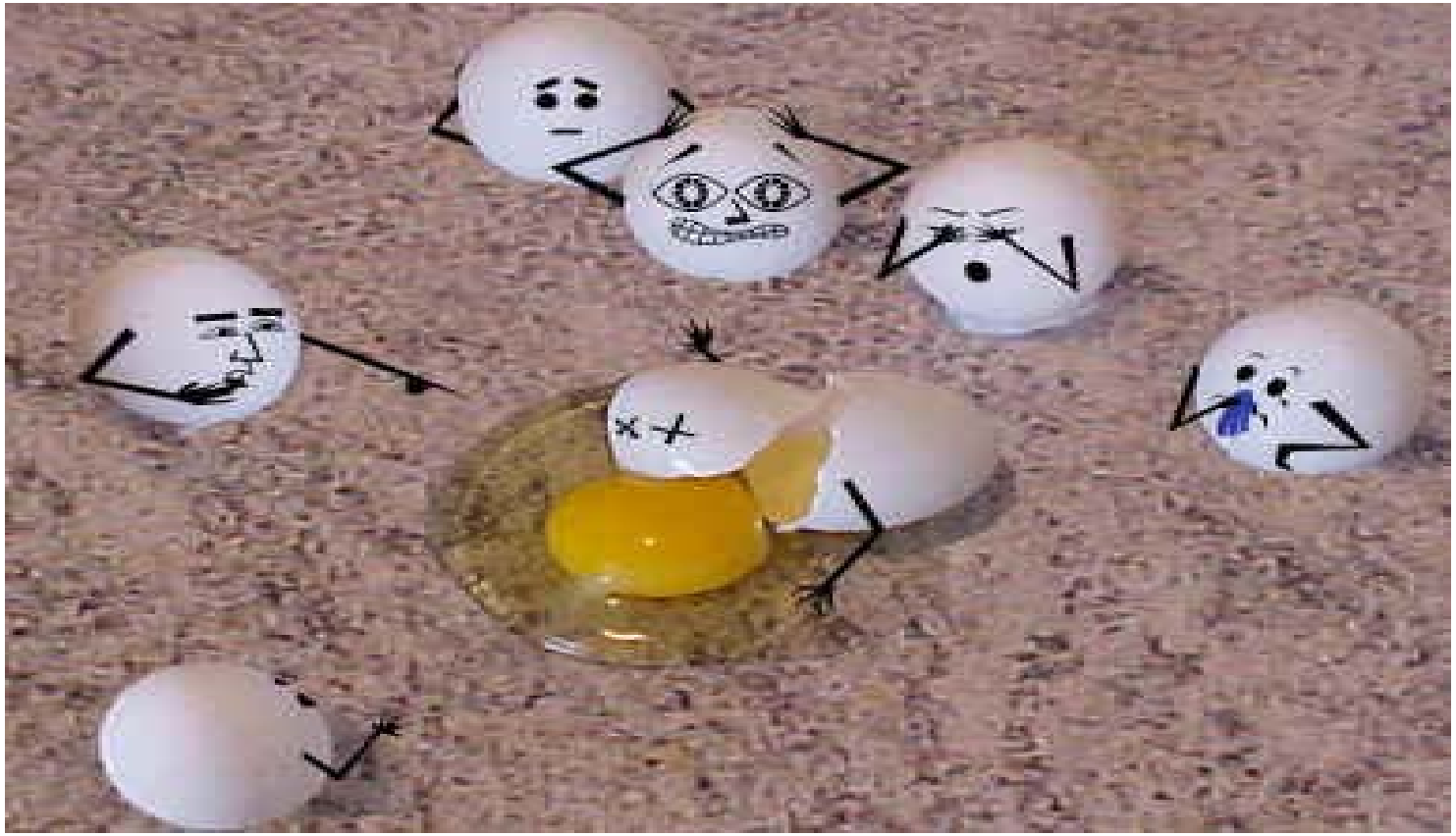

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Out of this nettle, danger, we pluck this flower, safety.

-William Shakespeare
King Henry IV. Part I.
Act ii. Scene 3

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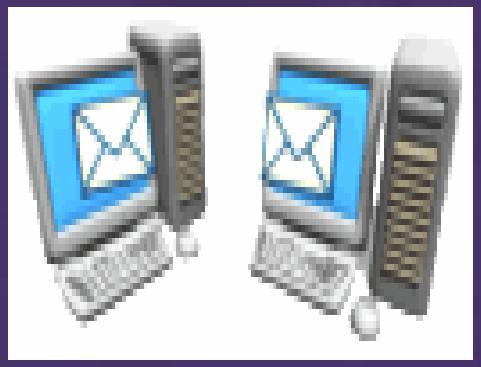
Laboratory Information Systems



Laboratory Information Systems

- Often referred to as LIS
- Usually comprised of host server and network
  - Not applicable to:
    - Laptops
    - Purchased services, such as *EP Evaluator*
    - PCs for word processing
    - Data-management systems for analyzers

Laboratory Information Systems

Topics of discussion within this Module

- Environment
- Procedures / Procedure Manuals
- Validation

Laboratory Information Systems

Topics of discussion within this Module

- Policies / Security / Access Codes
- Auto-verification
- Data Entry / Reports
- Data Retrieval / Storage

Laboratory Information Systems

Topics of discussion within this Module

- Hardware and Software
- System Maintenance
- Regulations

21 CFR Part 11

- **Regulations surrounding electronic records**
- **What does this regulation entail?**

21 CFR Part 11

- **VALIDATION**
  - **Studies to ensure:**
    - **System accuracy**
    - **Reliability**
    - **Consistent intended performance**
    - **Ability to discern invalid or altered records**

Sec. 11.10 (a)

Validation

- **The primary purpose of system validation is to ensure that the LIS is performing in a manner for which it was designed.**
- **System validation ensures that the entire system has been properly tested, and will maintain data integrity**
- **Reproducibility and accuracy must be quantifiable and verifiable.**

Re-validation

- **When would re-validation occur?**

  The system must be revalidated whenever the end user, vendor or laboratory adds modifications or customizations to the LIS.

LIS – Altered Records

- There should be a documented system to ensure that all revised reports for previously reported incorrect (erroneous) patient results are identified as revised, corrected, or amended on the laboratory reports
- When revised reports are issued, the laboratory must have a mechanism to ensure that both the new result and previous incorrect result are reported together

21 CFR Part 11

- **The LIS must have the ability to generate accurate and complete copies that are:**
  - **Readable**
  - **Suitable for:**
    - **Inspection**
    - **Review**
    - **Copying**

Sec. 11.10 (b)

LIS – Data Entry and Reports

- **The reporting system must provide for comments on specimen quality that might compromise the accuracy of analytic results (e.g., lipemic, hemolyzed).**

LIS – Data Entry and Reports

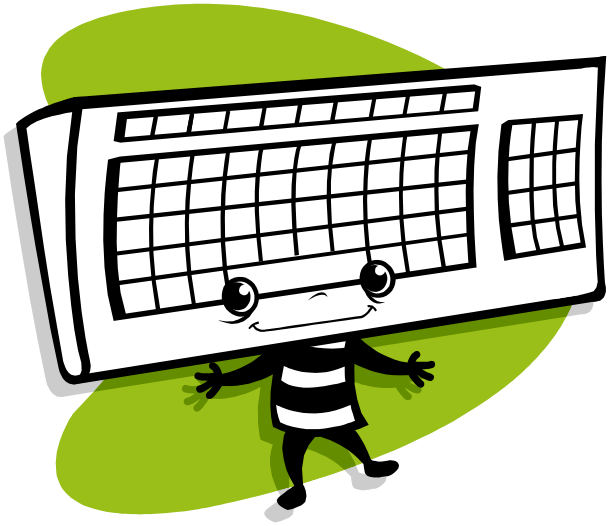
- **Calculations, algorithms, and/or rules involving reportable patient results must be periodically rechecked and documented to ensure accuracy.**

- **Data entered into the computer system manually must be reviewed by an authorized individual who verifies the accuracy of the input data before final acceptance and reporting by the computer**

LIS - Data Entry and Reports

Auto-verification

- Process by which the computer performs the initial verification of test results.



Auto-verification

- Any data that fall outside of set parameters should be reviewed by the human operator.
- If the procedure is used, the results of auto-verification must be thoroughly tested, appropriately documented and signed by the director before implementation

21 CFR Part 11

- **The LIS must protect all electronic records to enable accurate and ready retrieval throughout the retention period.**

Sec. 11.10 (c)

Protection of Electronic Records: Environment

- **The computer facilities and equipment should be:**
  - clean
  - well-maintained
  - in a location that is well-ventilated, humidity-controlled, and temperature-controlled
  - kept as required by vendor specifications.

Protection of Electronic Records: Environment

- All wires and computer cables should be properly located and/or protected from traffic

- The entire computer system should be adequately protected against electrical power interruptions and surges

Protection of Electronic Records: Written Procedures

- **The laboratory should maintain the following procedures:**
  - for the preservation of data and equipment in case of
    - **unexpected destructive event (e.g., fire, flood),**
    - **software failure,**
    - **hardware failure**

Protection of Electronic Records: Written Procedures

- **More LIS Procedures**
  - protocols for periodic backing up and storing of information
  - procedures for off-site storage of backup data
  - protocols/procedures for restoring information from backed up media

Protection of Electronic Records: Backup

- How often should you backup?
- Archival of backup materials
  - Organization and duplication

Protection of Electronic Records: Data Retrieval and Storage

- **Stored patient result data and archival information must be easily and readily retrievable.**

- **The LIS must be able to reproduce archived test results completely, including the reference range originally given for that test, and any flags, footnotes, or interpretive comments that were attached to that result at the time of the original report.**

Protection of Electronic Records: Data Retrieval and Storage

- **When multiple identical analyzers are used for reporting patient test results, there should be the ability to trace results back to the original instrument on which the test was performed.**

- **The data storage capacity of the LIS should be sufficient to meet the needs of the sponsor**

Protection of Electronic Records: Data Retrieval and Storage

- **Data storage media, such as tapes, disks, etc., must be properly labeled, stored and protected from damage or unauthorized use.**
- **Documented procedures must allow for timely restoration of services utilizing the data storage media after an unexpected destructive event.**

Protection of Electronic Records: System Maintenance

- **There must be documented procedures for handling the shutdown and restarting of LIS to ensure integrity of the data and uninterrupted delivery of laboratory services**

Protection of Electronic Records: System Maintenance

- **All unscheduled computer downtime, periods and other computer problems must be documented, including the reasons for failure and corrective actions taken.**

Protection of Electronic Records: System Maintenance

- **Documented contingency plans must be developed to handle services in the event of a computer system failure such that participant results are reported promptly.**
- **Records must be maintained to document regular maintenance of LIS**

Protection of Electronic Records: Hardware and Software

- A documented procedure and a complete, up-to-date record of preventive maintenance must be readily available for all computer hardware.
- There must be active review of computer system maintenance records by the laboratory manager or designee.

Protection of Electronic Records: Hardware and Software

- **Errors detected during computer system usage or backup must be documented, along with corrective action taken and communicated to the responsible person in the laboratory**

Trivia

NAME THAT PARASITE

21 CFR Part 11

- **The LIS must have access limited to authorized individuals.**

Sec. 11.10 (d)

System Access and Security

- **Policies must be established stating who may use the computer system.**
- **Access levels should be defined to identify:**
  - **who may access patient data**
  - **who is authorized to enter patient results**
  - **who is authorized to change results**
  - **who is authorized to alter computer programs**

System Access and Security

Security (user) codes should be established such that only specifically authorized individuals may access patient data or alter programs.

Access Codes

- **Access Codes and passwords should be used in such a manner that they are able to effectively control access to the system should:**
  - **Include numbers, not be real words**
  - **Be deleted when employees leave**
  - **<u>Not</u> be posted on terminals**
  - **<u>Not</u> be loaned**

TRIVIA

- What does the term <u>Auto-verification</u>
- mean?

21 CFR Part 11

- **The LIS must provide secure, computer generated time stamped audit trails that record date and time of operator entries and actions that:**
  - **Create**
  - **Modify**
  - **Delete**

Sec. 11.10 (e)

Audit Trails

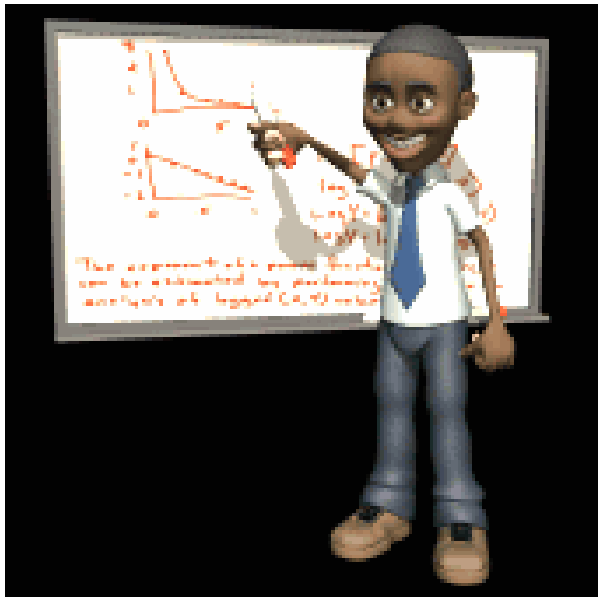
- **The LIS should maintain an audit trail of all activities**
  - **Identification of all personnel responsible for performance and verification of tests should be available on the system**
  - **Time / date stamps of all data entry / manipulation**

Audit Trails

- **There must be an audit mechanism which allows the laboratory to identify all individuals who have modified patient data, results, control files, or computer programs.**

Training of Personnel

- **There should be documentation that all appropriate users of the computer system have received adequate training initially and whenever the computer system is modified.**



Sec. 11.10 (i)

Timeline for Implementation

- Review of Available Systems / Selection
- Acquisition
- Offsite Training: System Admin and Key User(s)
- On-site System Installation of hardware, server, uploading of software
- Configuration / Database Creations
- End-user Training
- Testing
- Announcements
- GO – LIVE!

Story Time!

- **Does anyone have a Laboratory System Implementation experience they would like to share?**

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References

- College of American Pathologists, available at http://cap.org
- Code of Federal Regulations, available at: http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200521

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LABORATORY QUALITY MANAGEMENT

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We should be ambassadors of quality. Most people aren't used to an environment where perfection is expected.

QUALITY WORDS

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- Quality Management (QM)
- Quality Assurance (QA)
- Quality Improvement (QI)
- Quality Control (QC)

Glossary

- ***Quality*: The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs.**

- ***Quality assurance*: All those planned or systematic actions necessary to provide adequate confidence that a product or service will satisfy given requirements for quality.**

Glossary

- ***Quality control*** **: The operational techniques and the activities used to fulfill requirements of quality.**
- ***Quality improvement:*** **Part of quality management focused on increasing the ability to fulfill quality requirements.**

Management vs. Assurance vs. Improvement vs. Control

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Quality Management

- **Factors included:**
  - Quality Control
  - Proficiency Testing / EQA
  - Instrument Maintenance

Quality Management

- ***More*** **Factors included:**
  - **Quality Improvement / Performance Improvement**
  - **Internal Audits**

Quality Management

- **Coordinated activities to direct and control an organization with regard to quality.**
- **For our discussion, Quality Management encompasses all features of Quality Assurance, Improvement, and Quality Control.**

Quality Management

Ensures:

DEFECTIVE PRODUCTS OR SERVICES ARE NOT PRODUCED!

Quality Control (QC)

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What is it?

Quality Control (QC)

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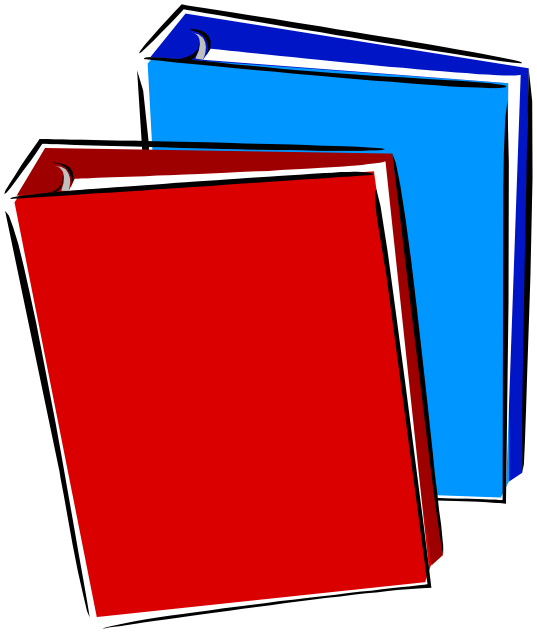
"…procedures for monitoring the work processes, detecting problems, and making corrections prior to delivery of products or services. Statistical process control, or statistical quality control, is the major procedure for monitoring the analytical performance of laboratory methods. "

-James O. Westgard. Ph.D., FACB

Quality Control (QC)

- **Elements of QC**
  - Policies
  - Performance / Documentation
  - Review
  - Corrective Action



Quality Control (QC) - Policies

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For each assay performed:

- **Clearly define procedures for monitoring analytic performance**
- **Establish QC tolerance limits**
- **List number and frequency of control testing**
- **Corrective Action for QC failures**

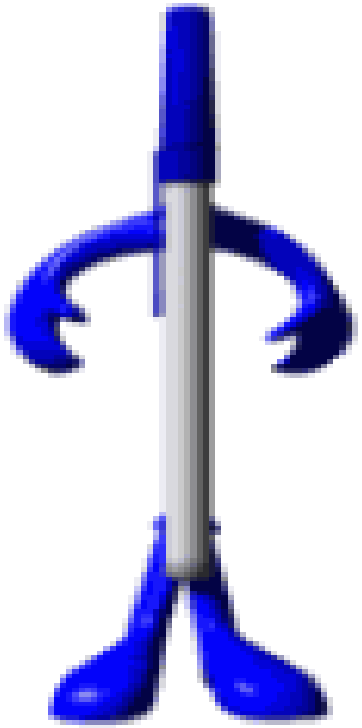
Quality Control (QC) – Performance / Documentation

How many times have you heard,

"If it isn't documented. . .

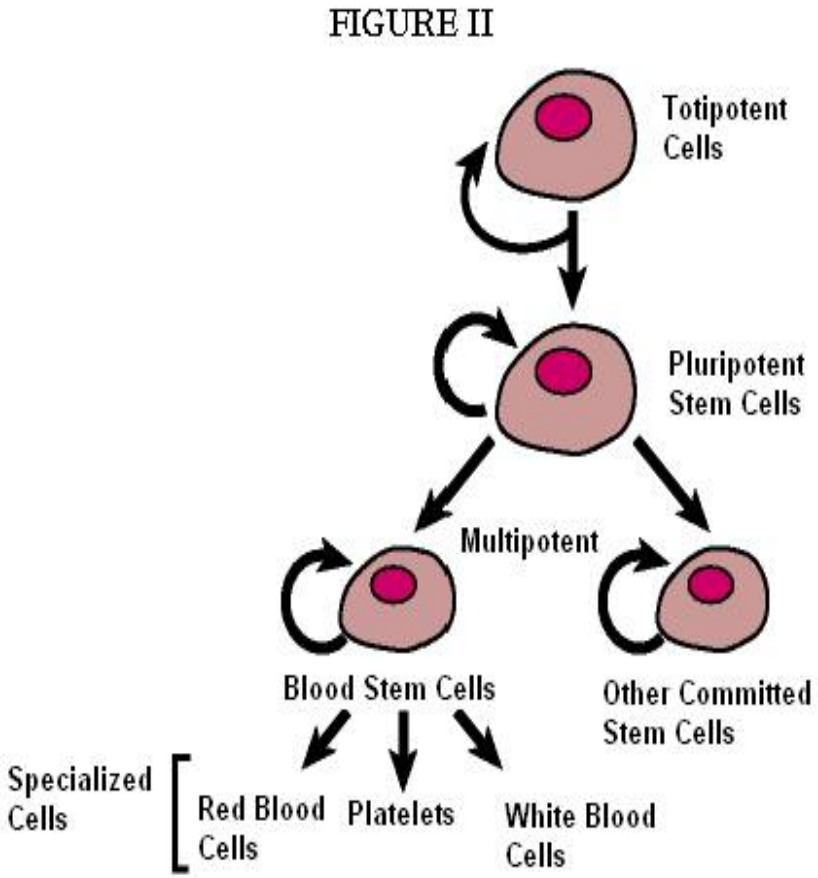
It isn't done"?

DO YOU BELIEVE IT?

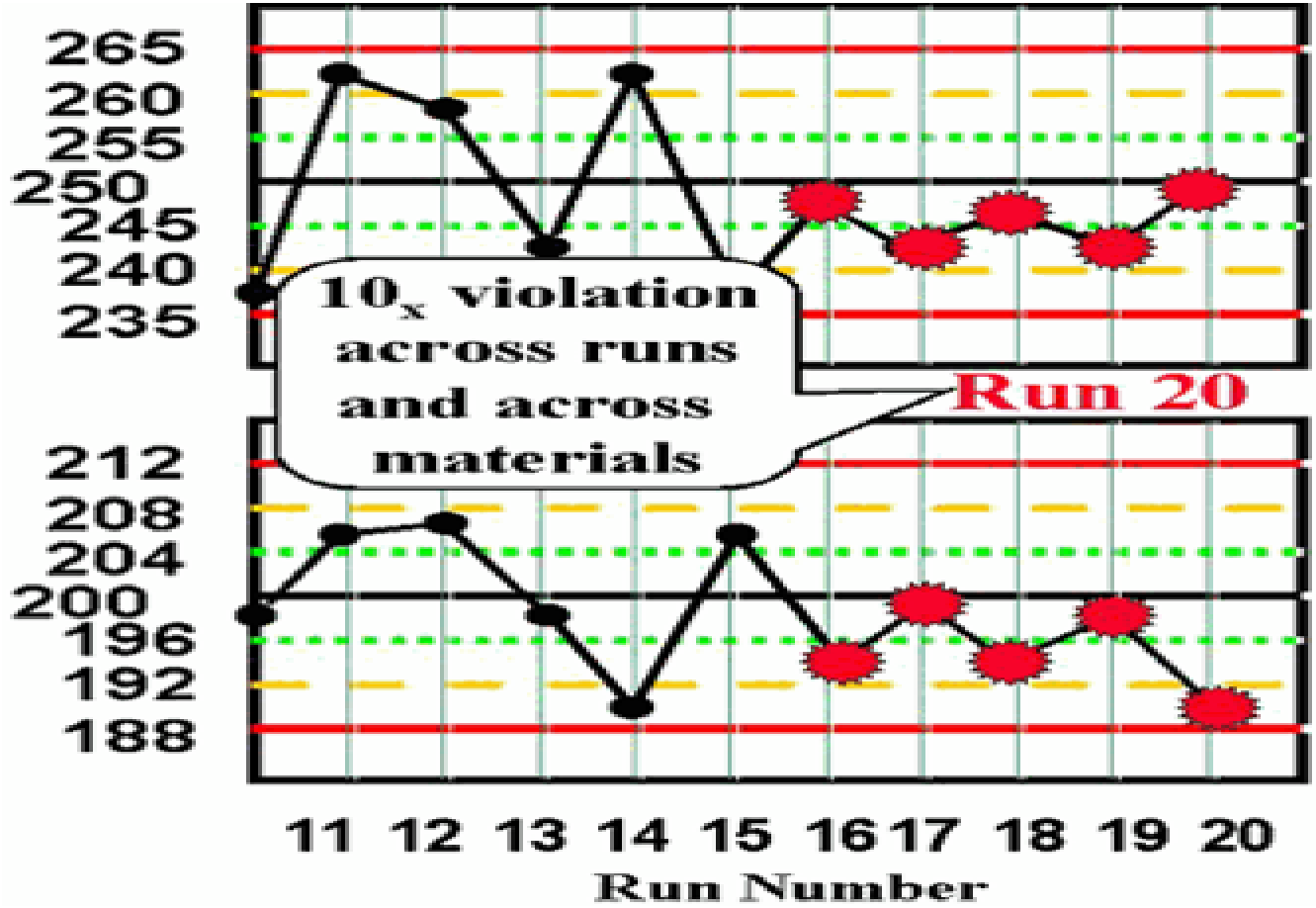


Trivia

- **From which cell do all blood cells begin?**
  - **Totipotent**
  - **Pluripotent**
  - **Verypotent**
  - **Multipotent**

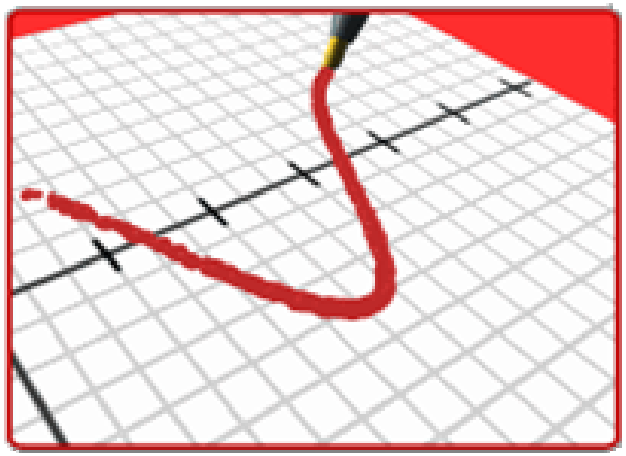


Quality Control Tools – Review and Corrective Action



QC Tools - Levy Jennings Charts

- **How can they be used?**



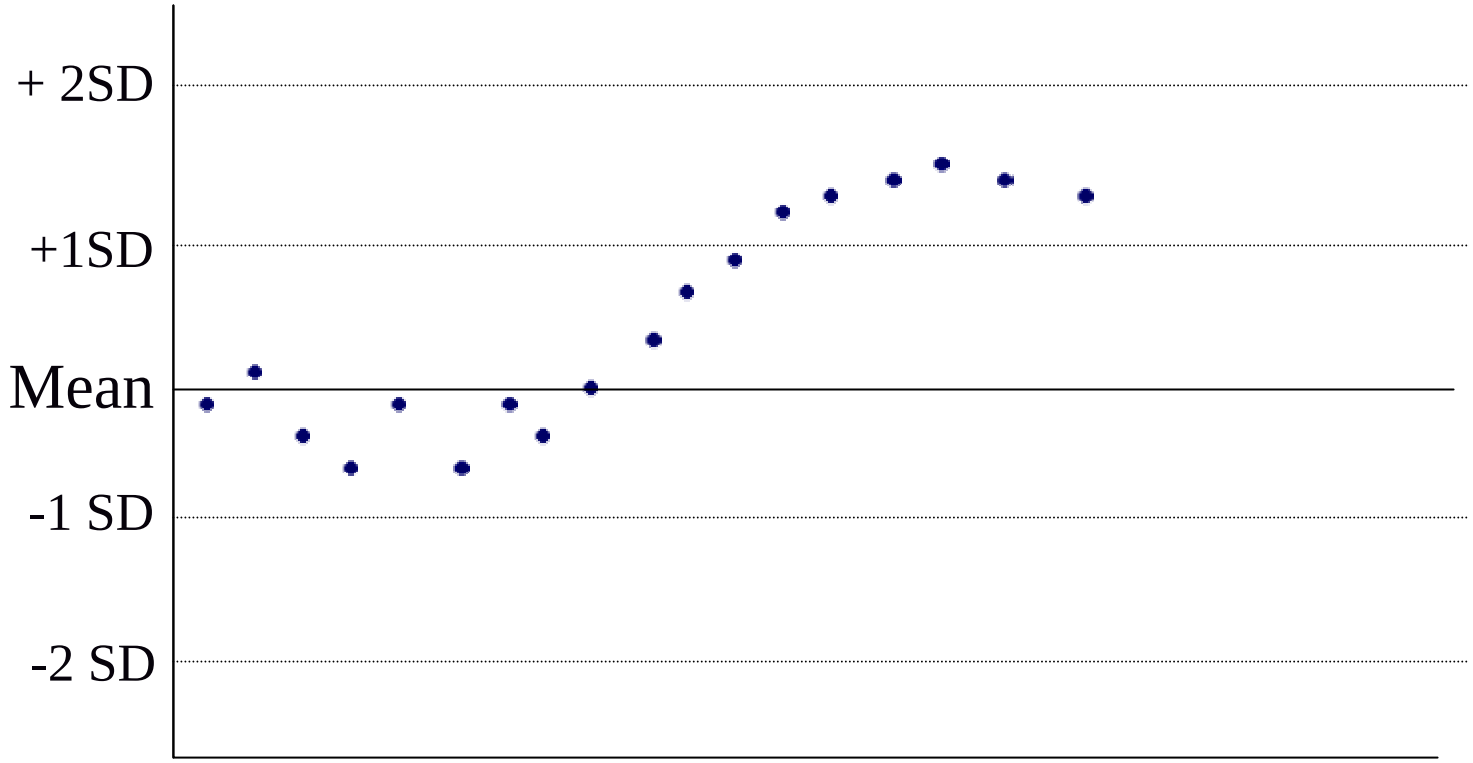
QC Nomenclature

Mean : The average of a data set

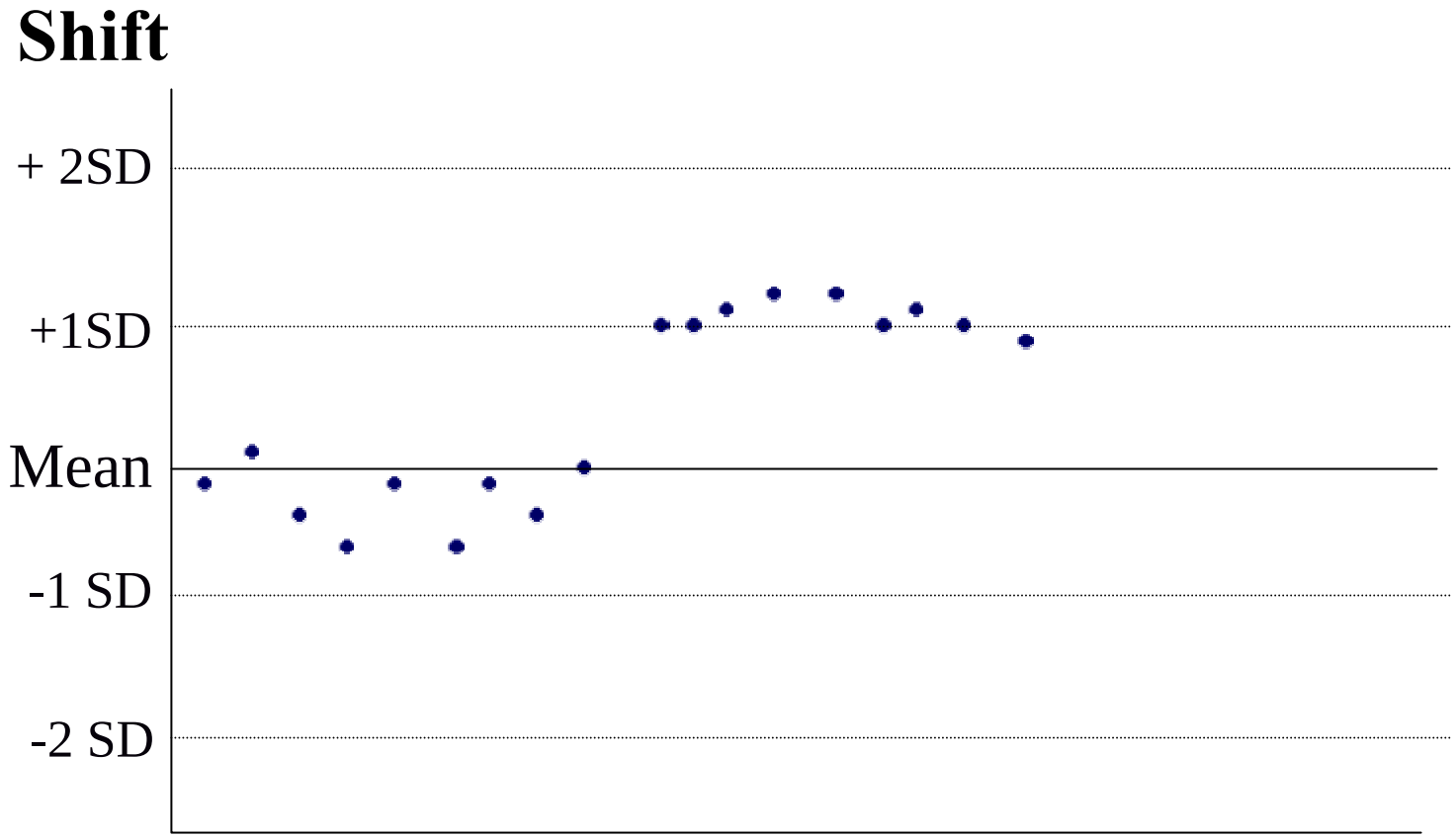
$$\bar{X} = \sum x_i / n$$

QC Nomenclature

Trend



QC Nomenclature



QC Nomenclature

Standard Deviation (SD) : a measure of the dispersion or variation in a distribution.

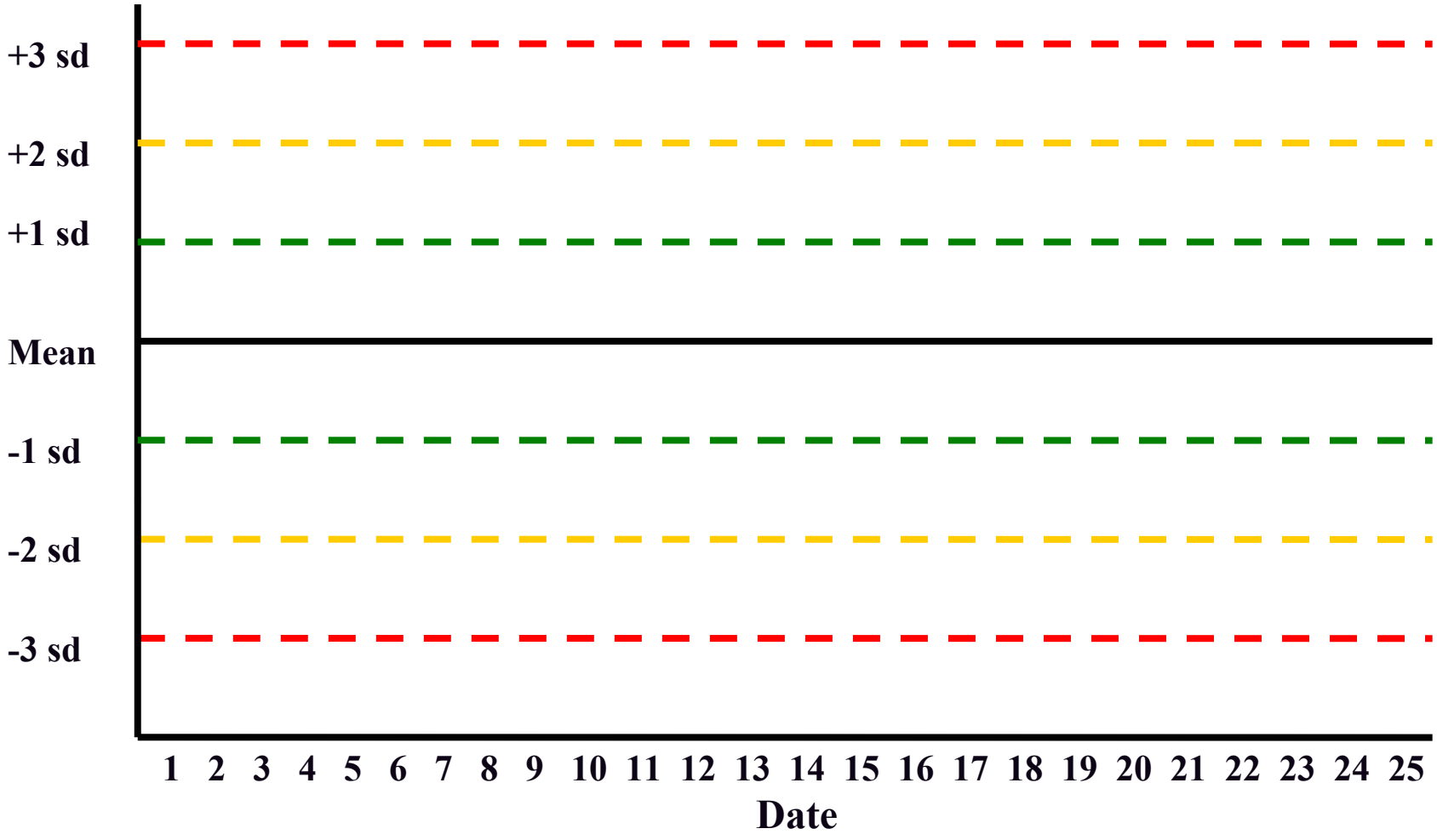
$$SD = \sqrt{\frac{\sum (X_i - \bar{X})^2}{(n-1)}}$$

QC Nomenclature

Coefficient of Variation (CV) : a measure of the dispersion or variation in a distribution.

$$CV = \left(\frac{SD}{\bar{x}} \right)$$

QC Tools - Westgard Rules



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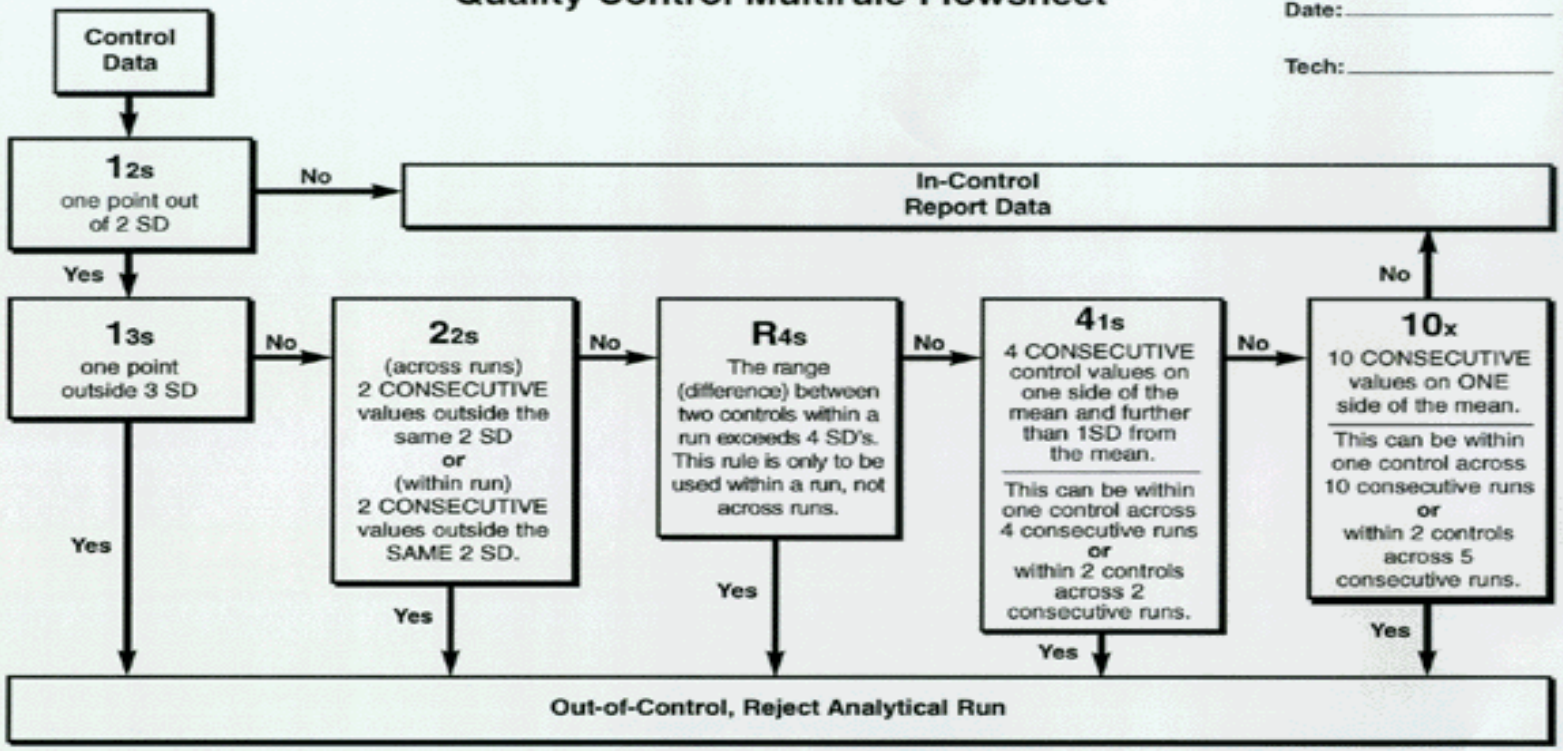
Quality Control Multirule Flowsheet

Date: _____

Tech: _____



Problem: _____

Resolution: _____

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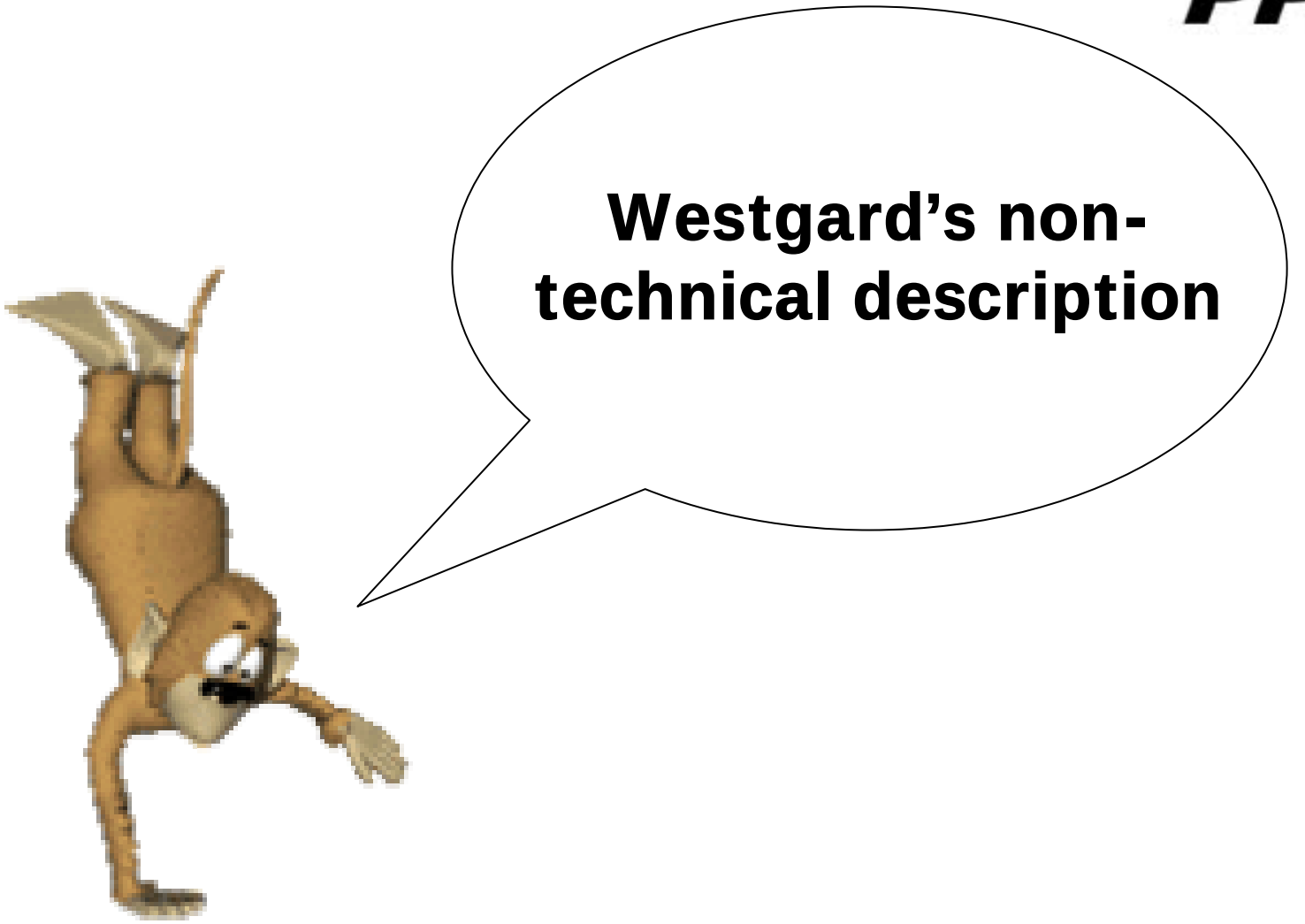
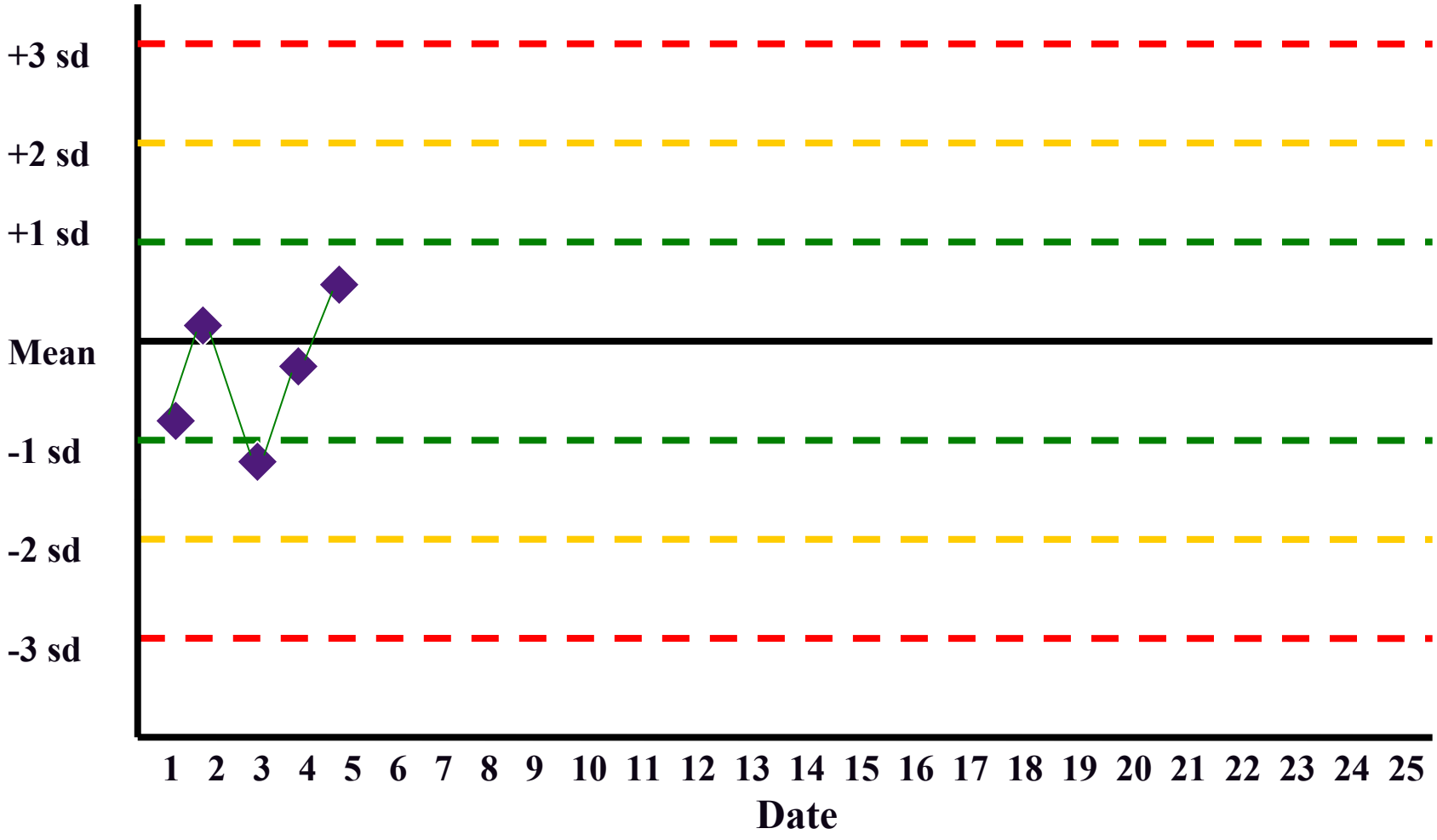
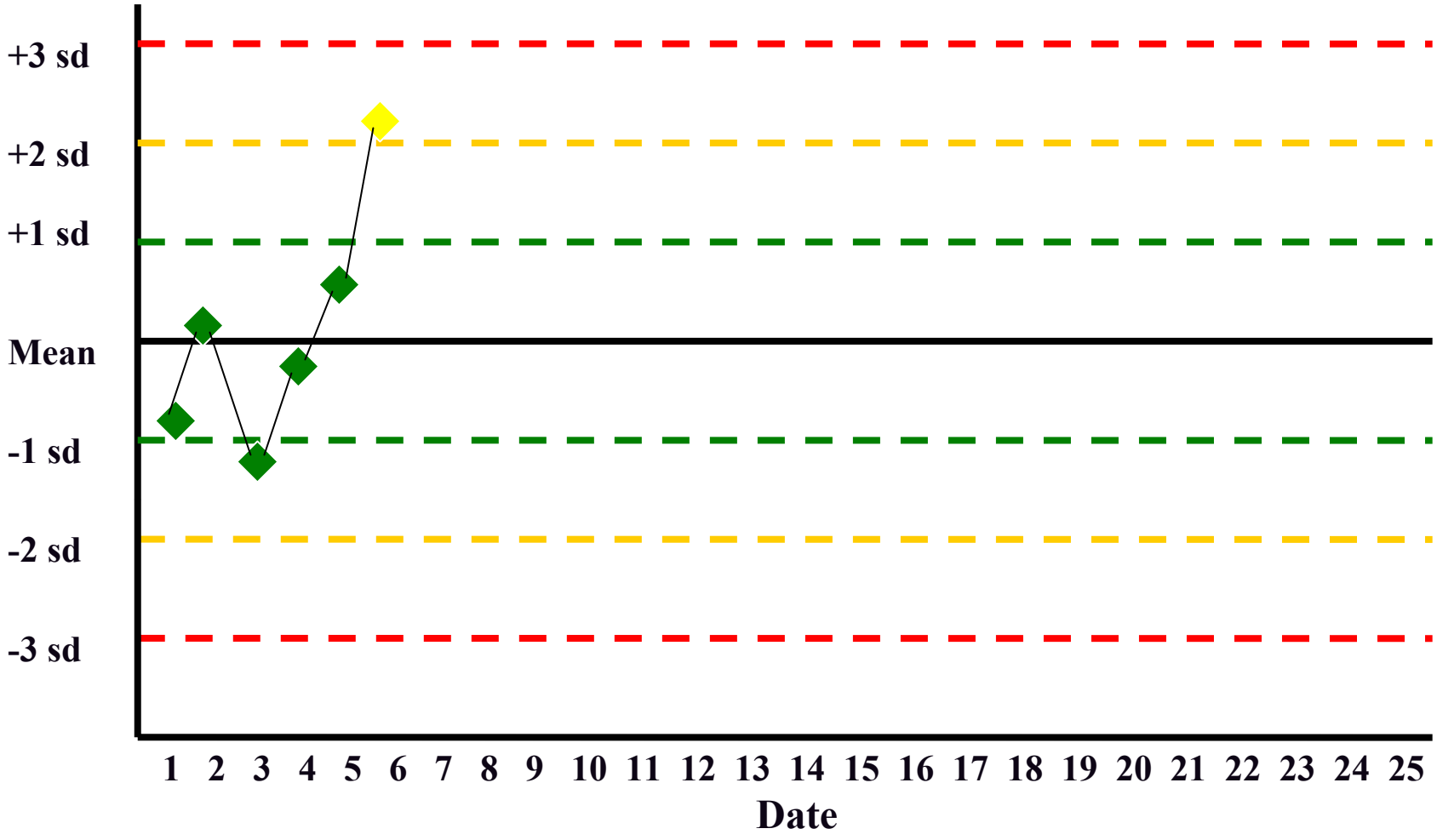


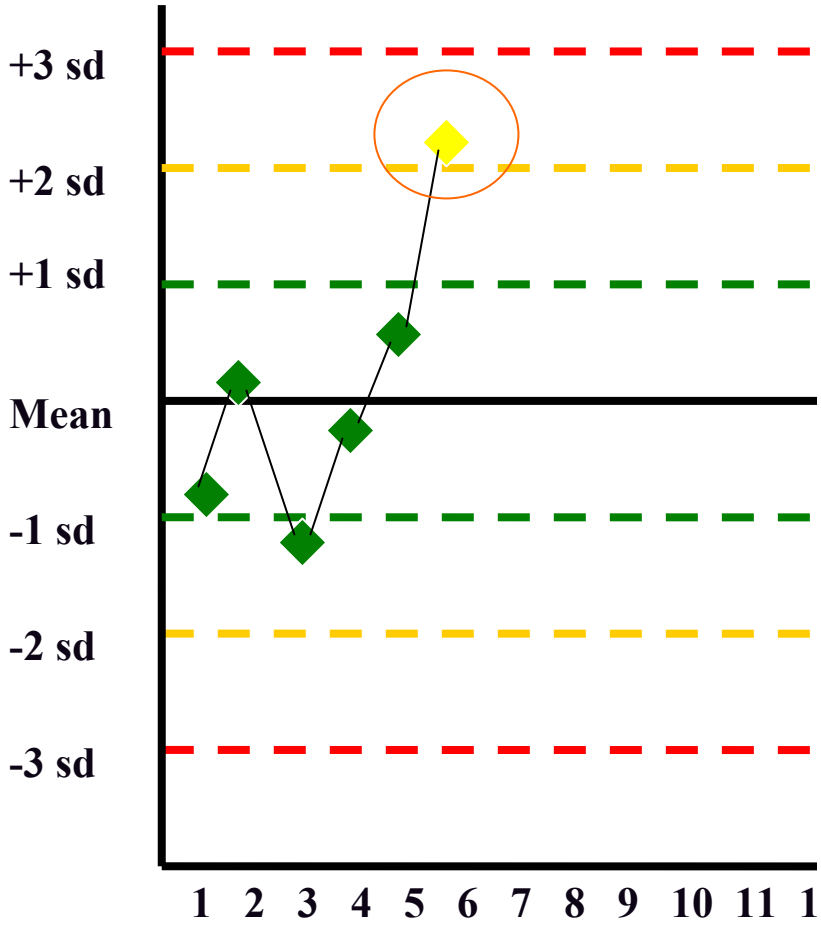
QC Tools - Westgard Rules



QC Tools - Westgard Rules



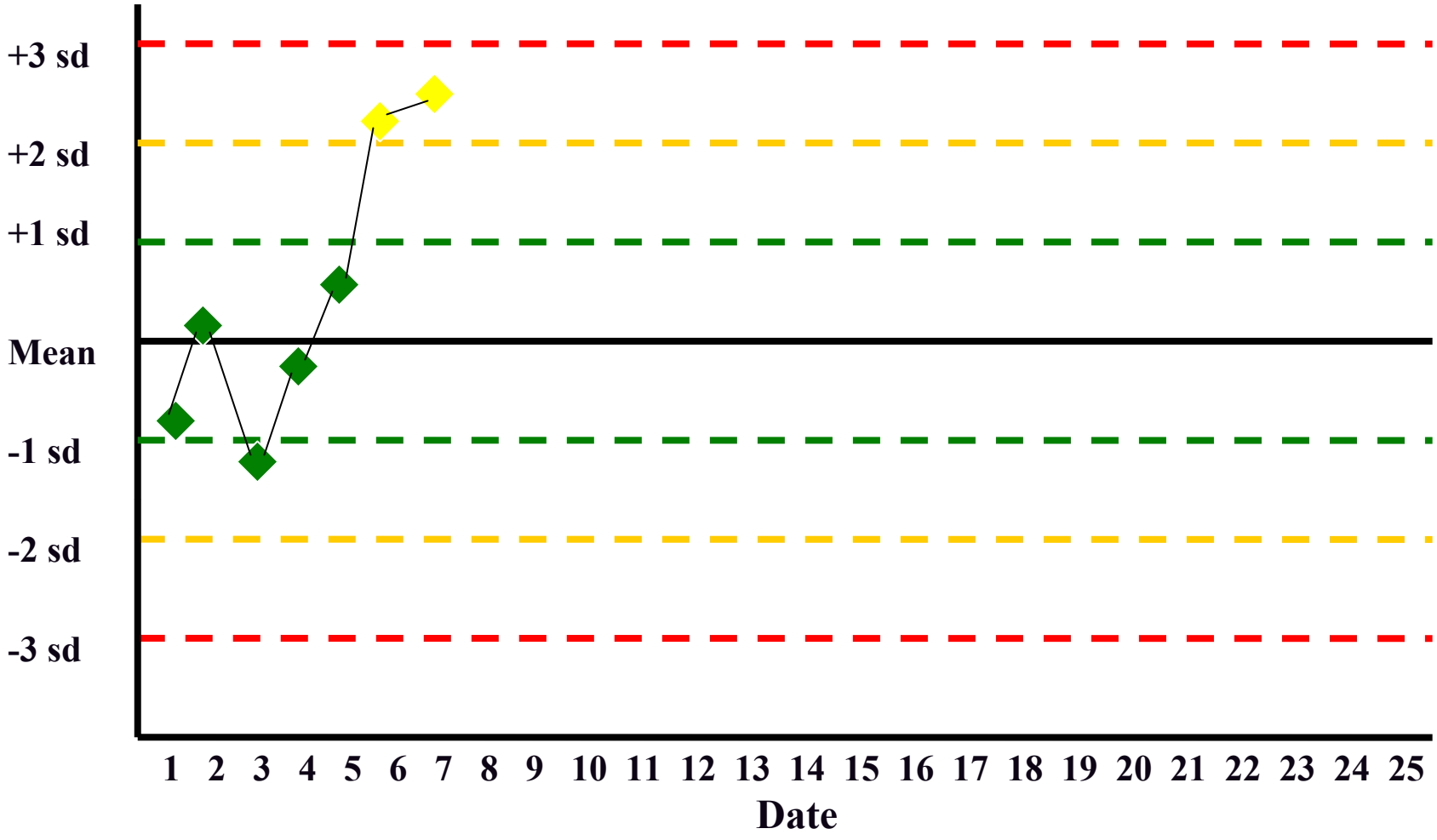
QC Tools - Westgard Rules



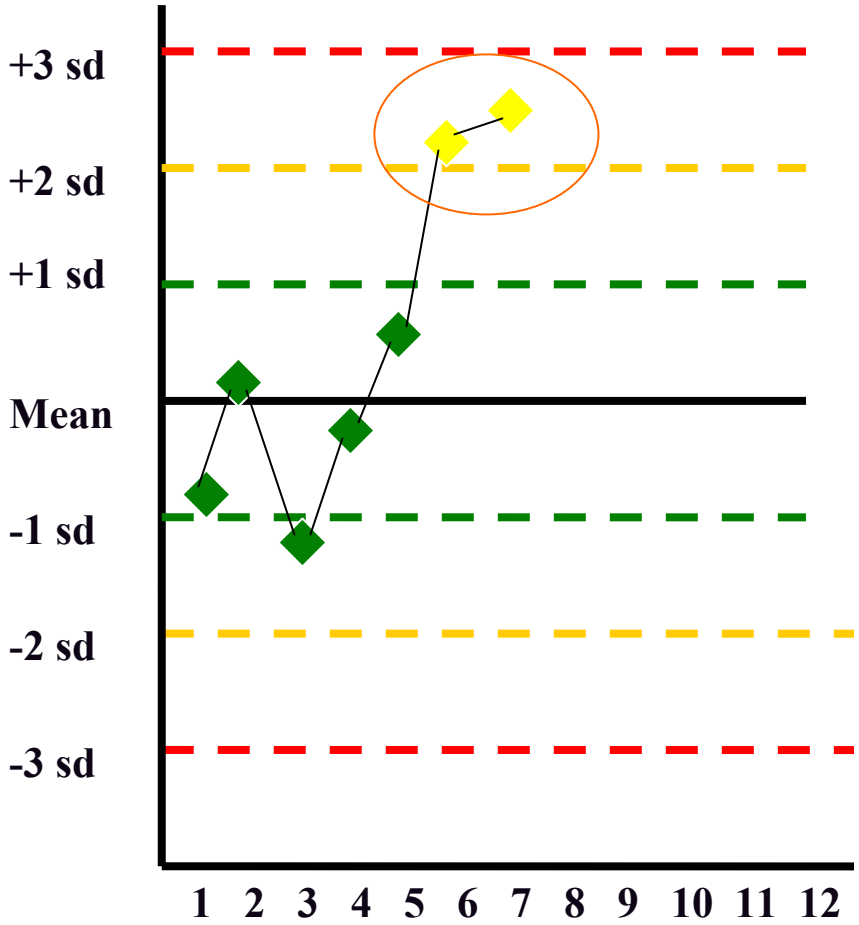
1_{2S} RULE

- **Warning rule**
- **Data must be closely evaluated**

QC Tools - Westgard Rules



QC Tools - Westgard Rules

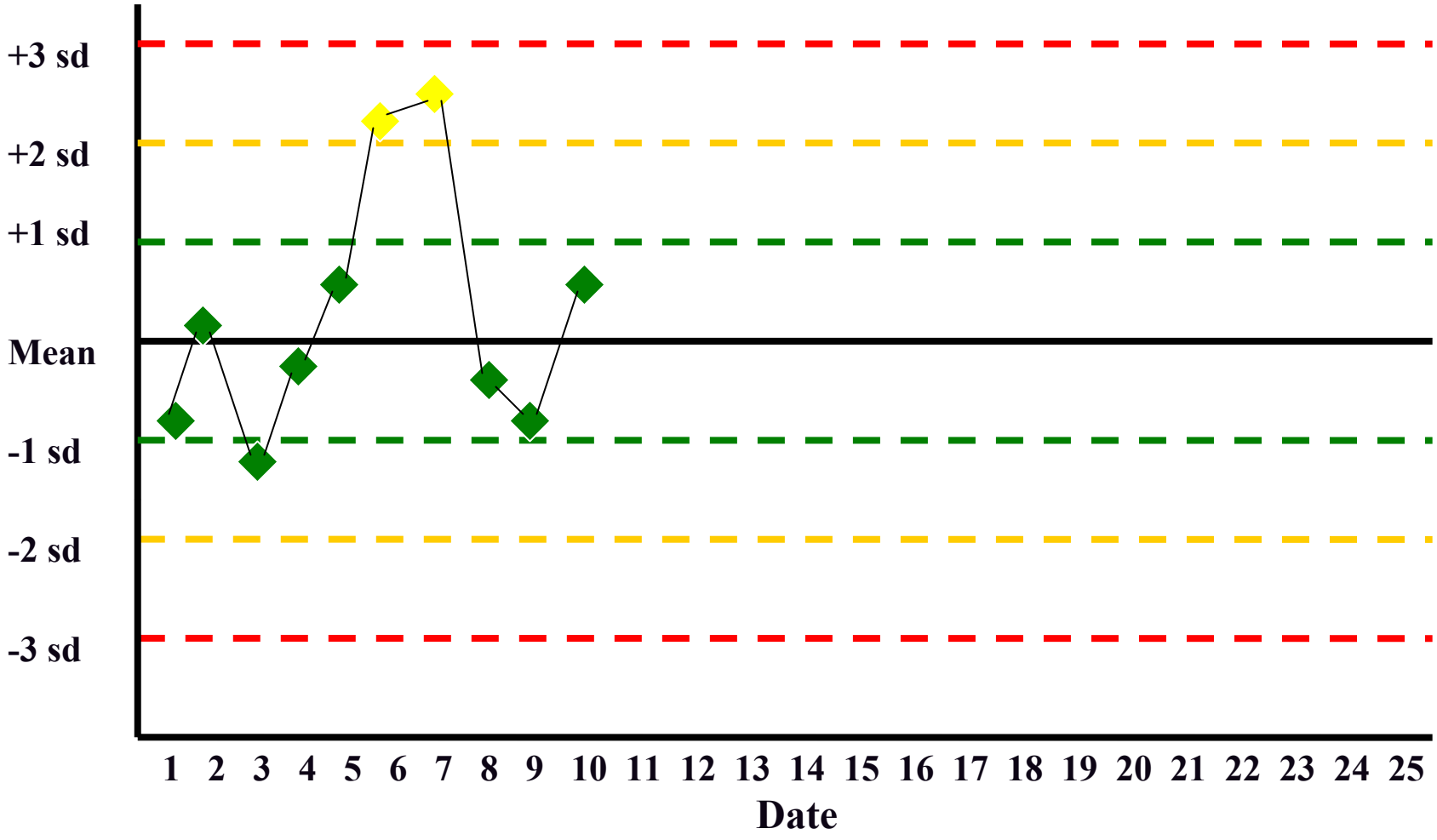


2_{2S} rule

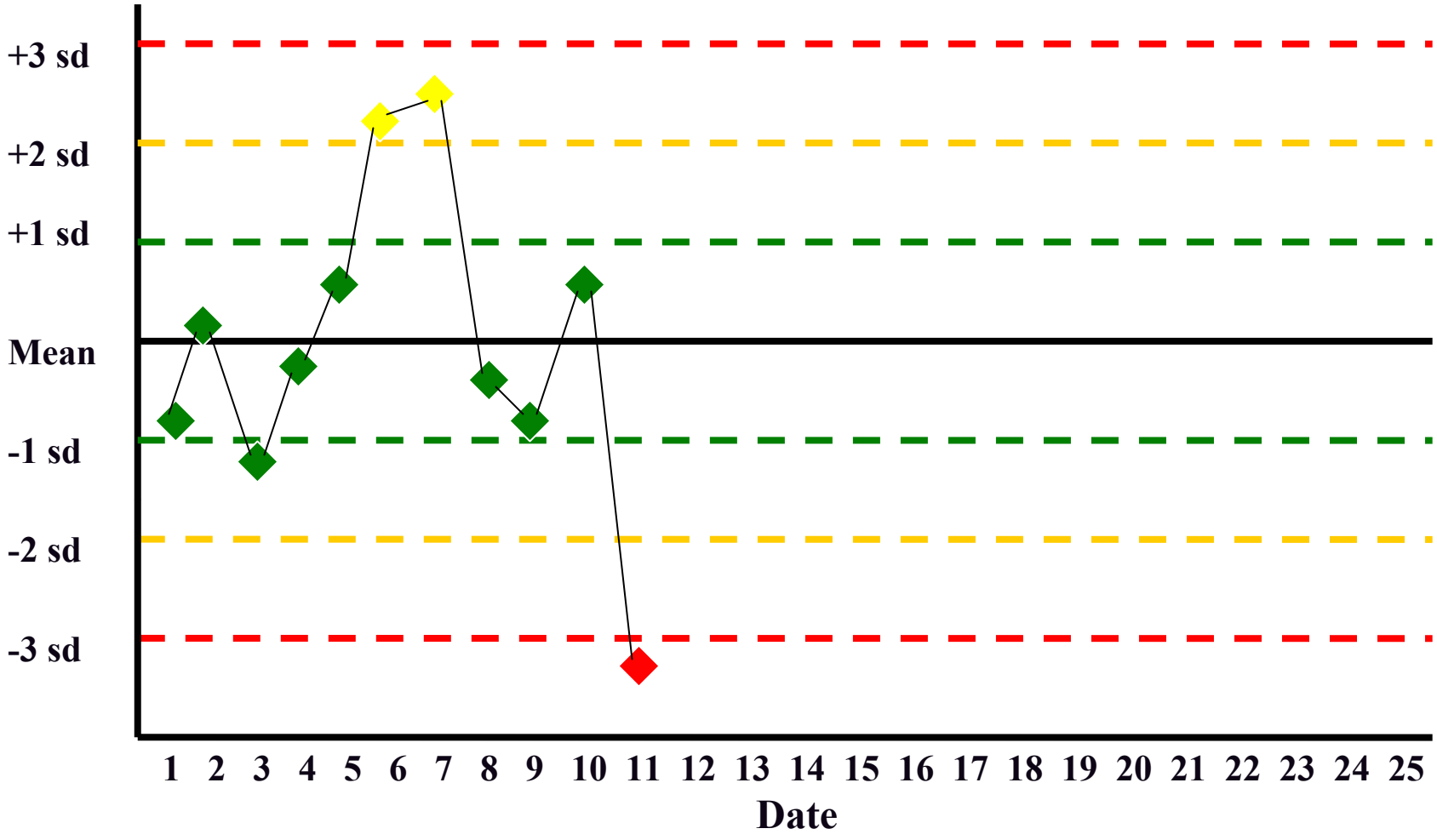
2 consecutive measurements exceeding two SD

Reject run!

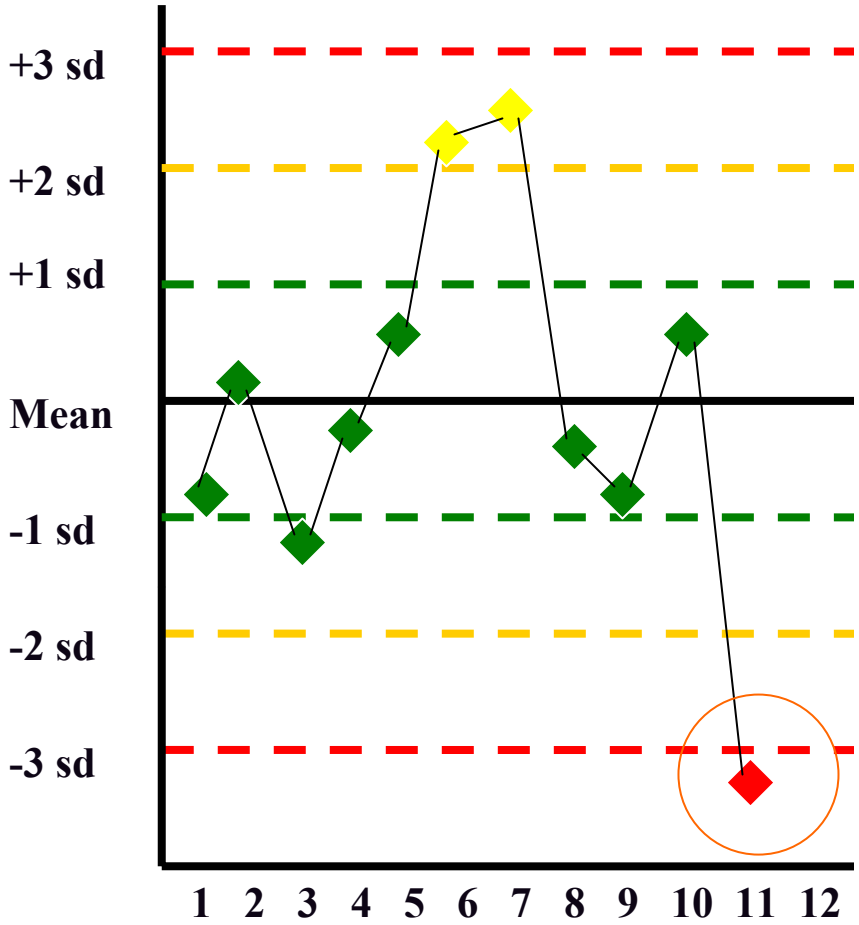
QC Tools - Westgard Rules



QC Tools - Westgard Rules



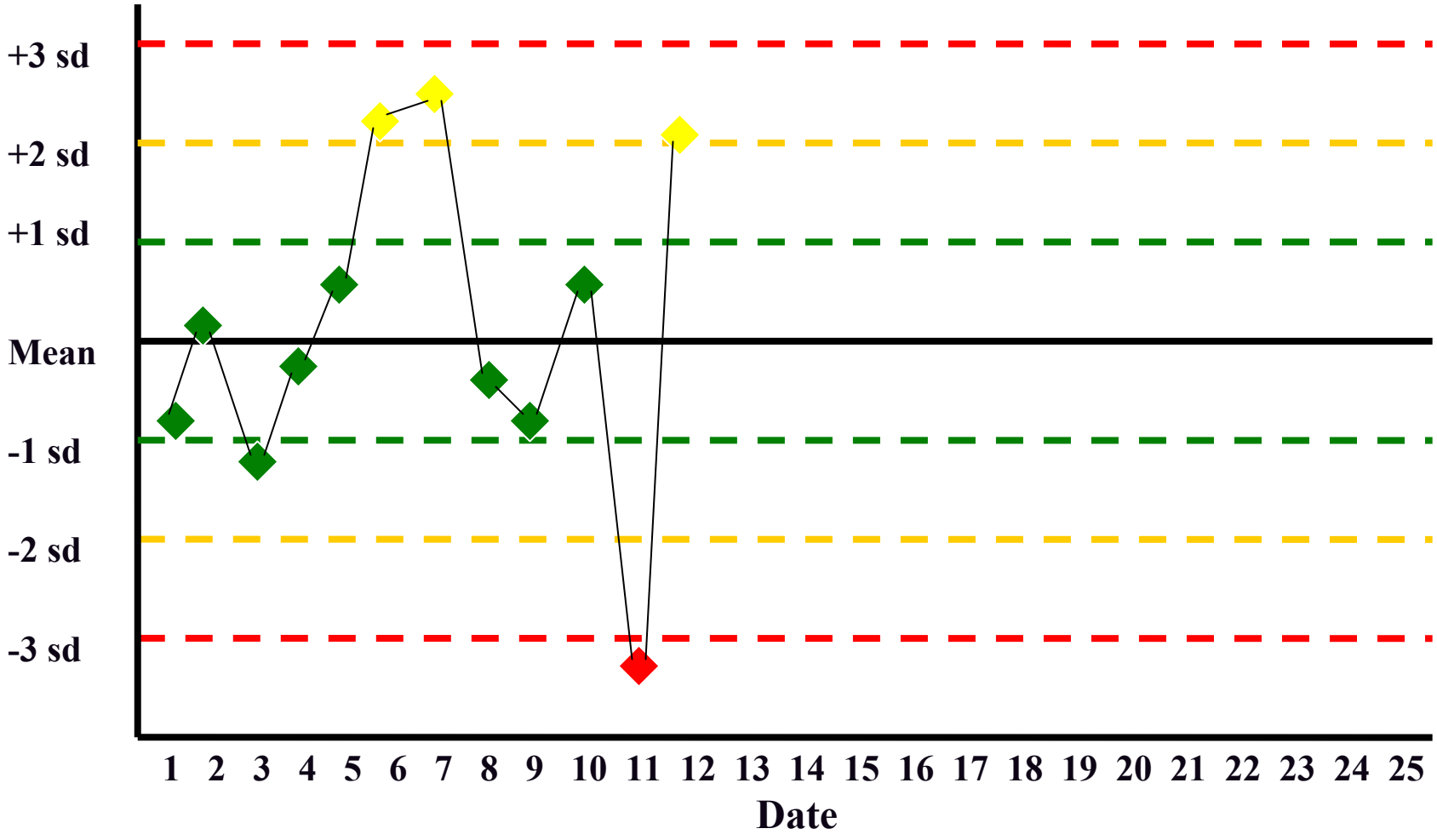
QC Tools - Westgard Rules



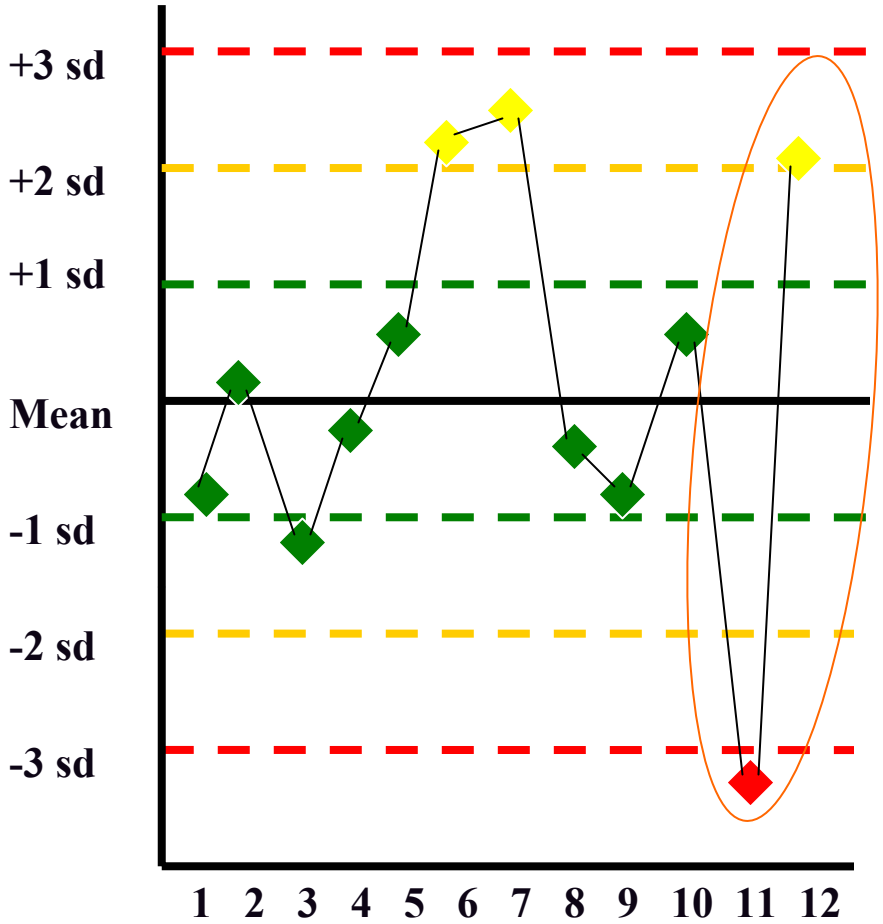
1_{3S} RULE

Reject run!

QC Tools - Westgard Rules



QC Tools - Westgard Rules

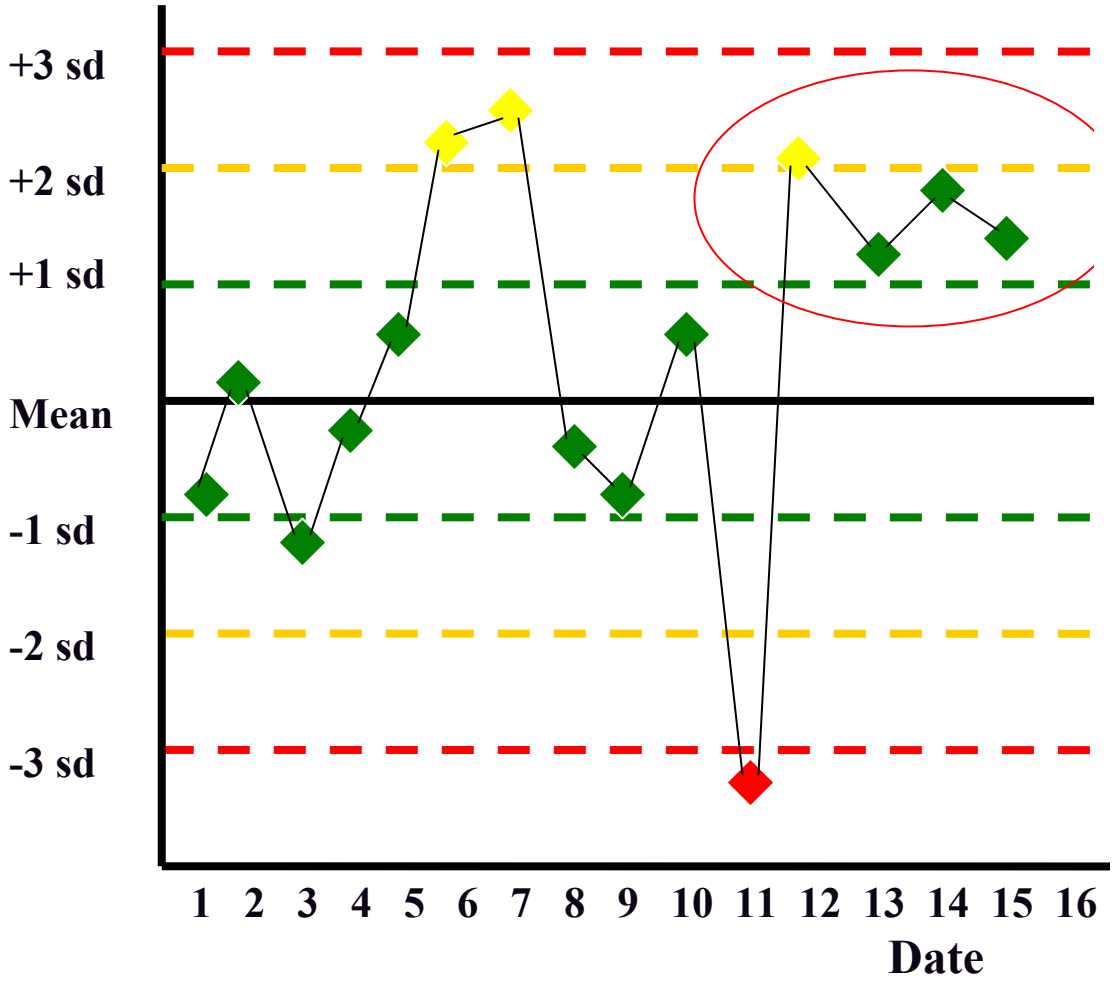


R_{4S} Rule

Within run control results span >4sd

Reject run!

QC Tools - Westgard Rules

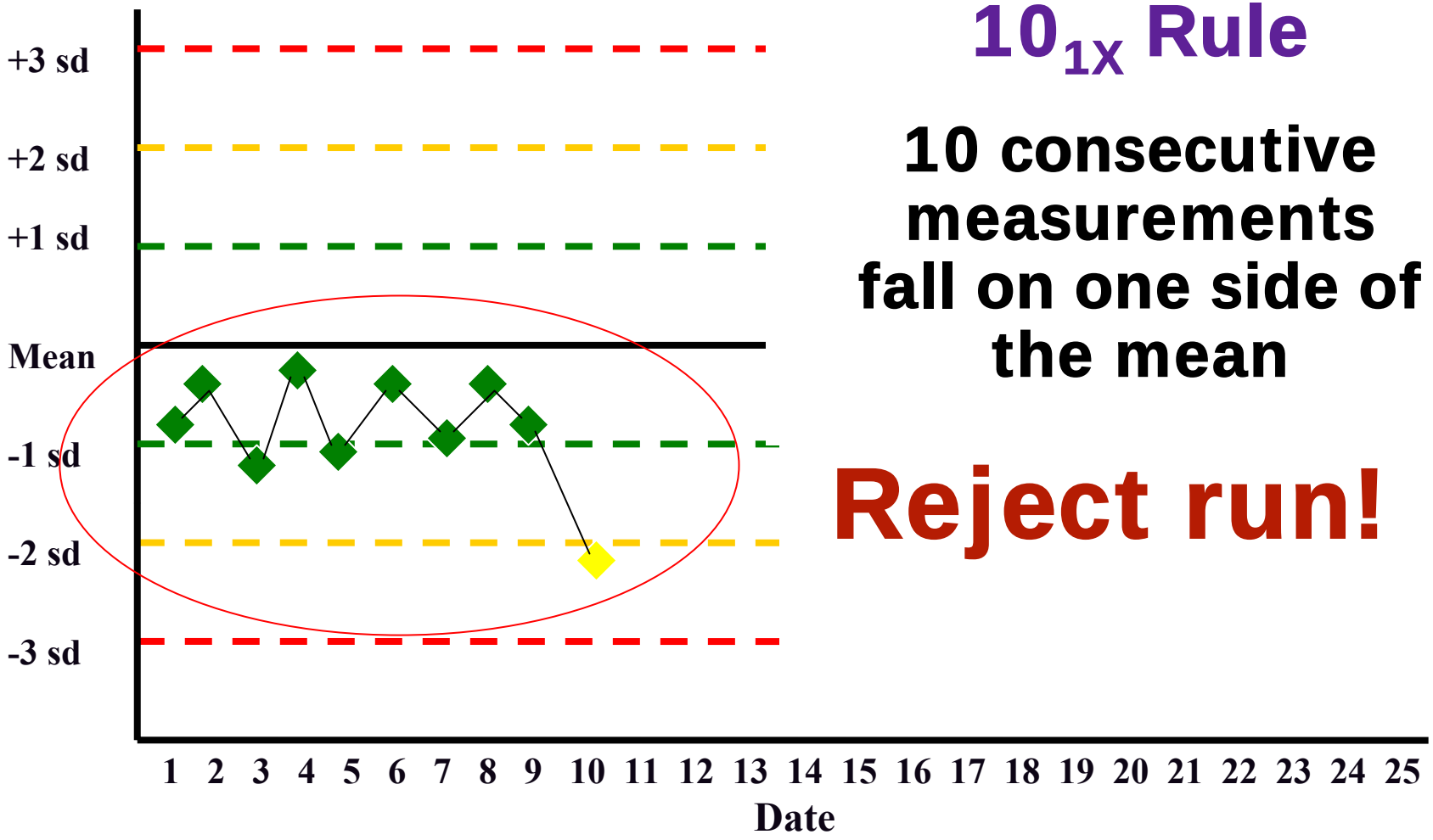


4_{1s} Rule

4 values on one side of the mean further than 1sd from the mean

Reject run!

QC Tools - Westgard Rules



10_{1X} Rule

10 consecutive measurements fall on one side of the mean

Reject run!

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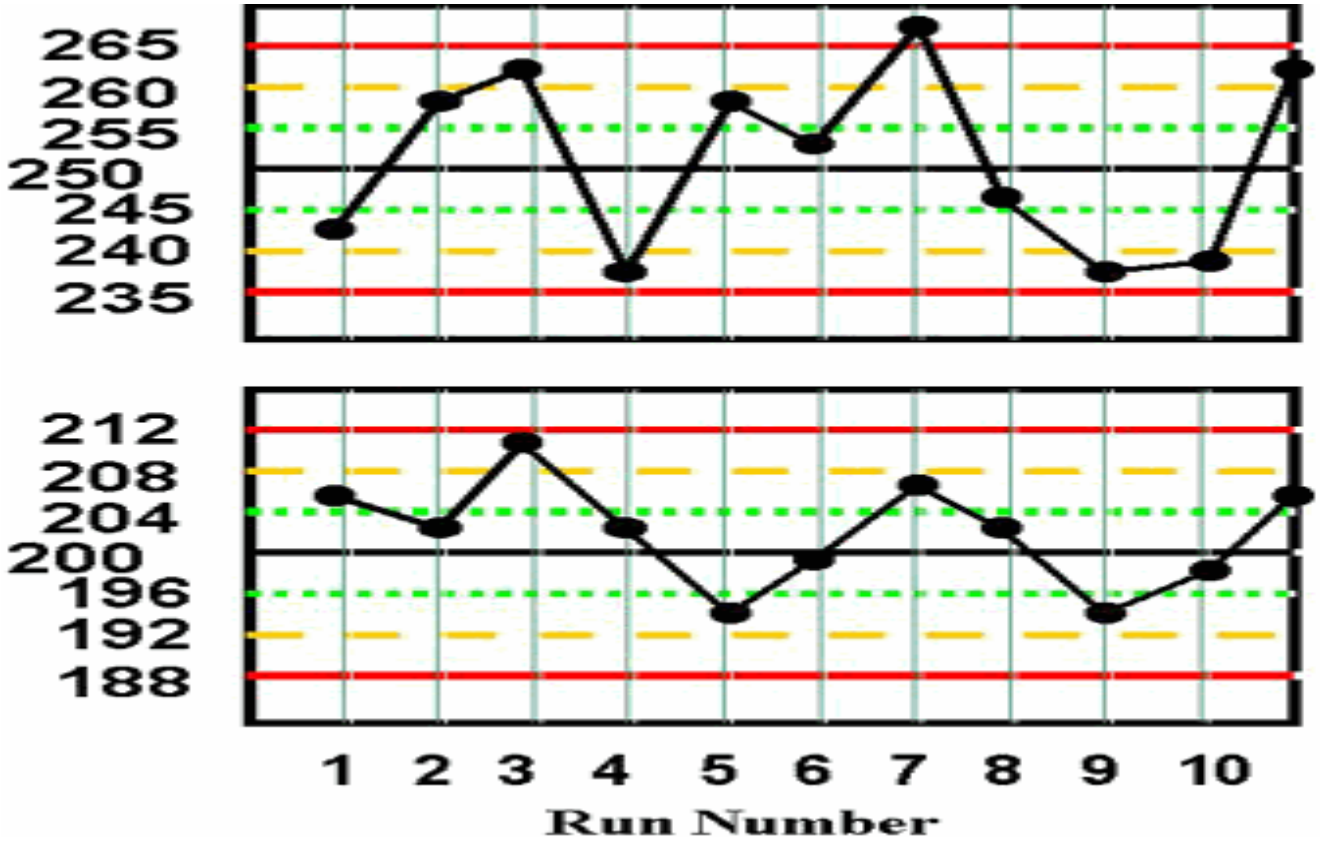
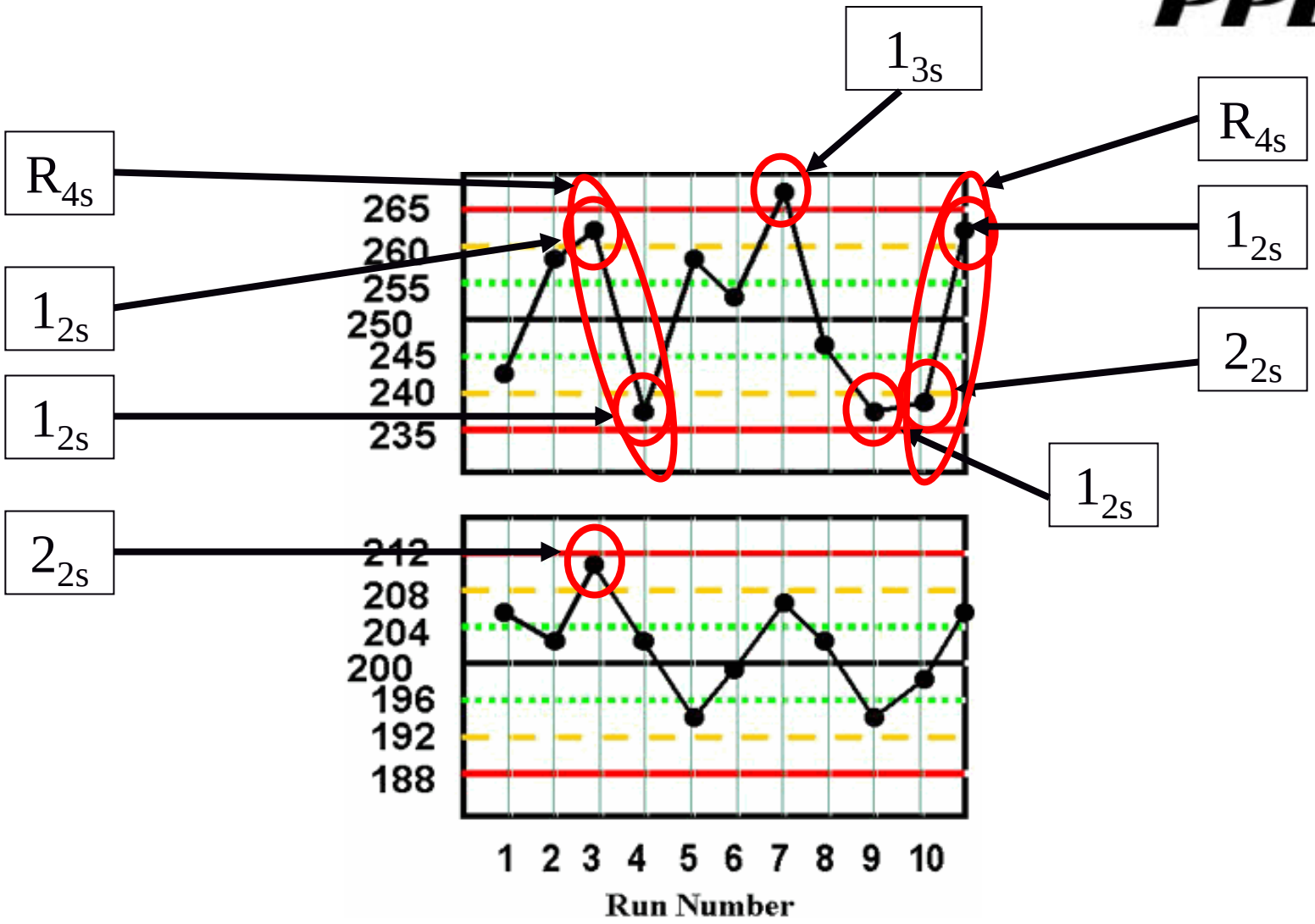
ACTIVITY

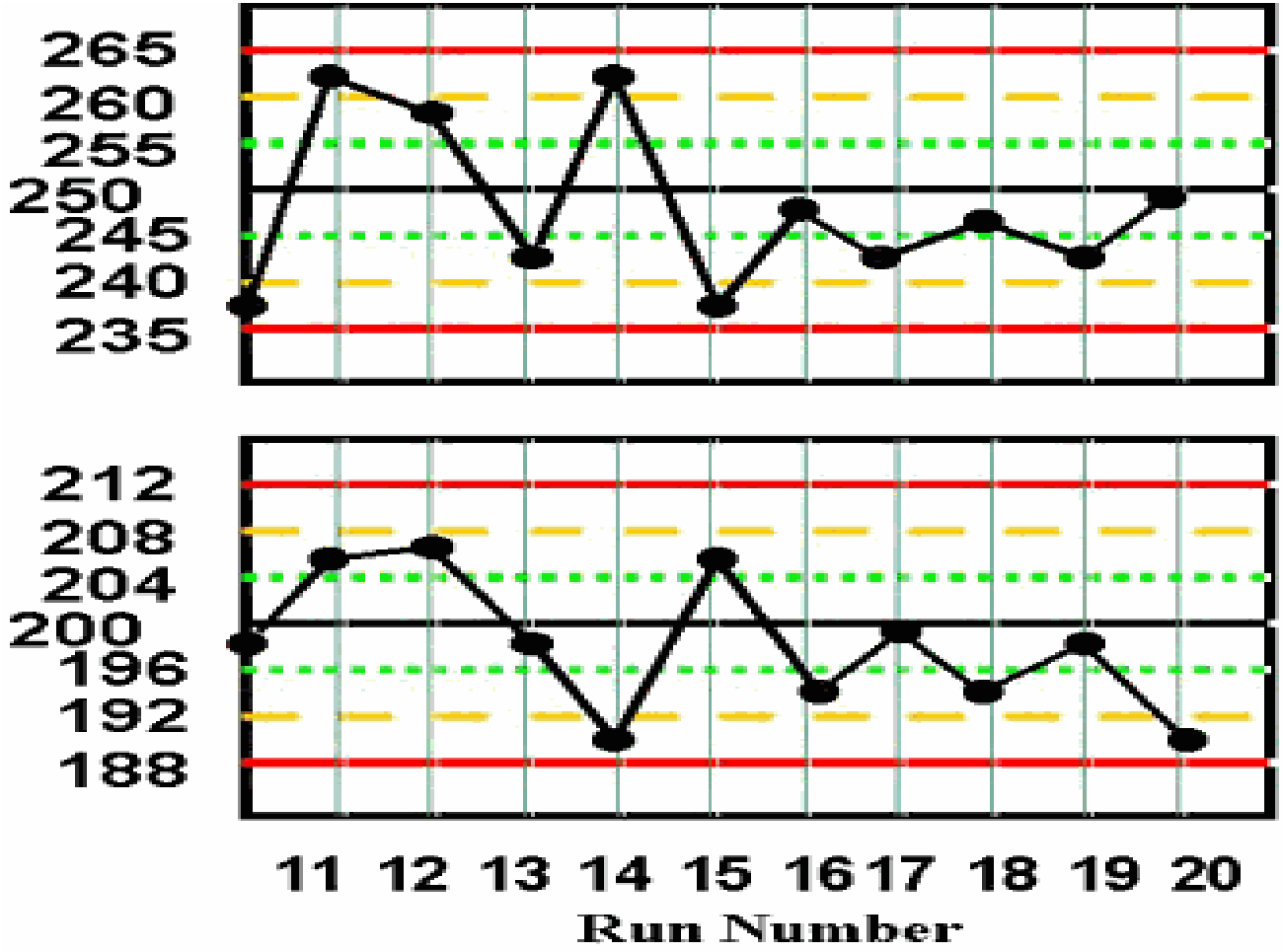
Identify the rule violations

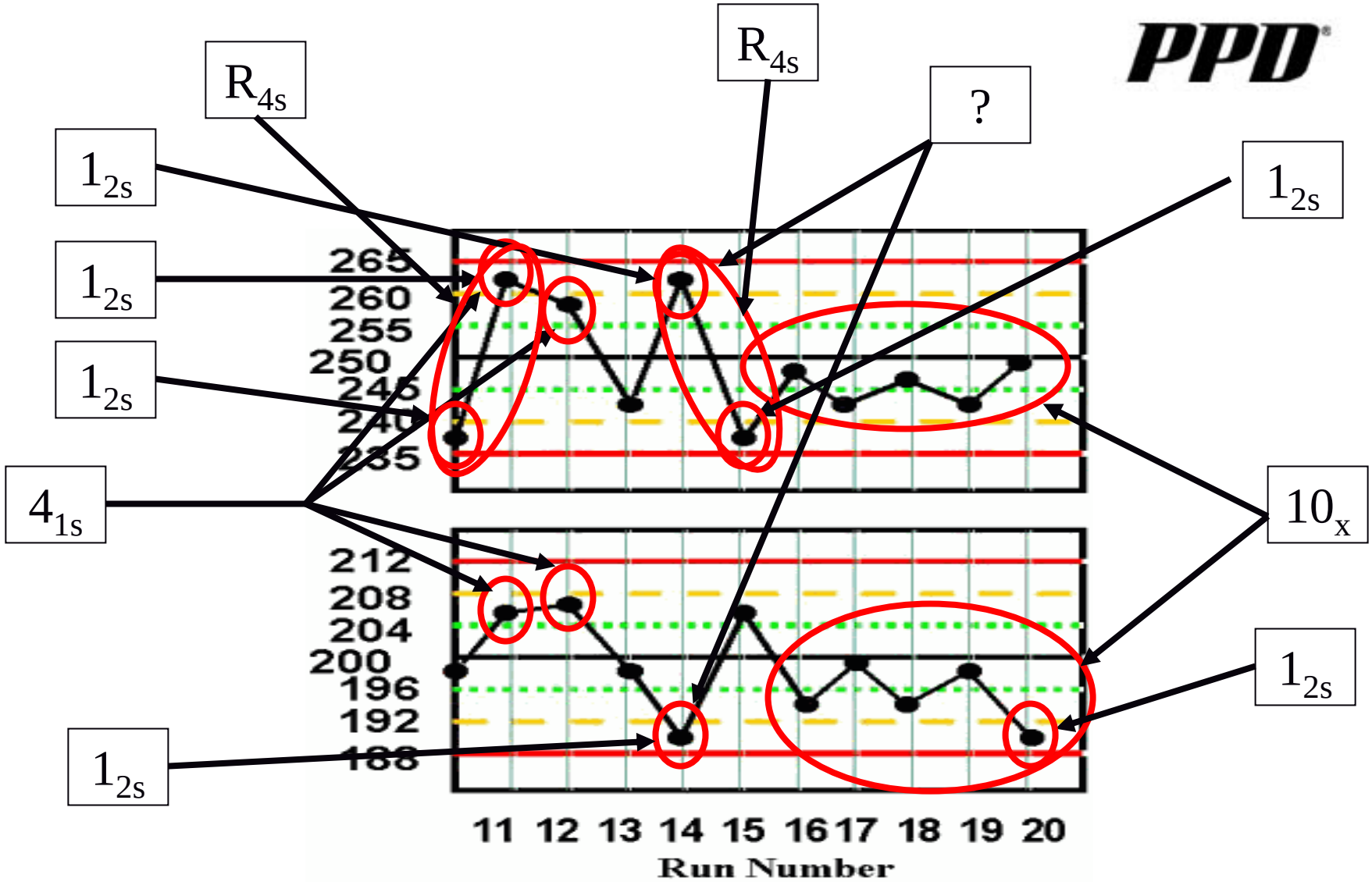
What do you see?



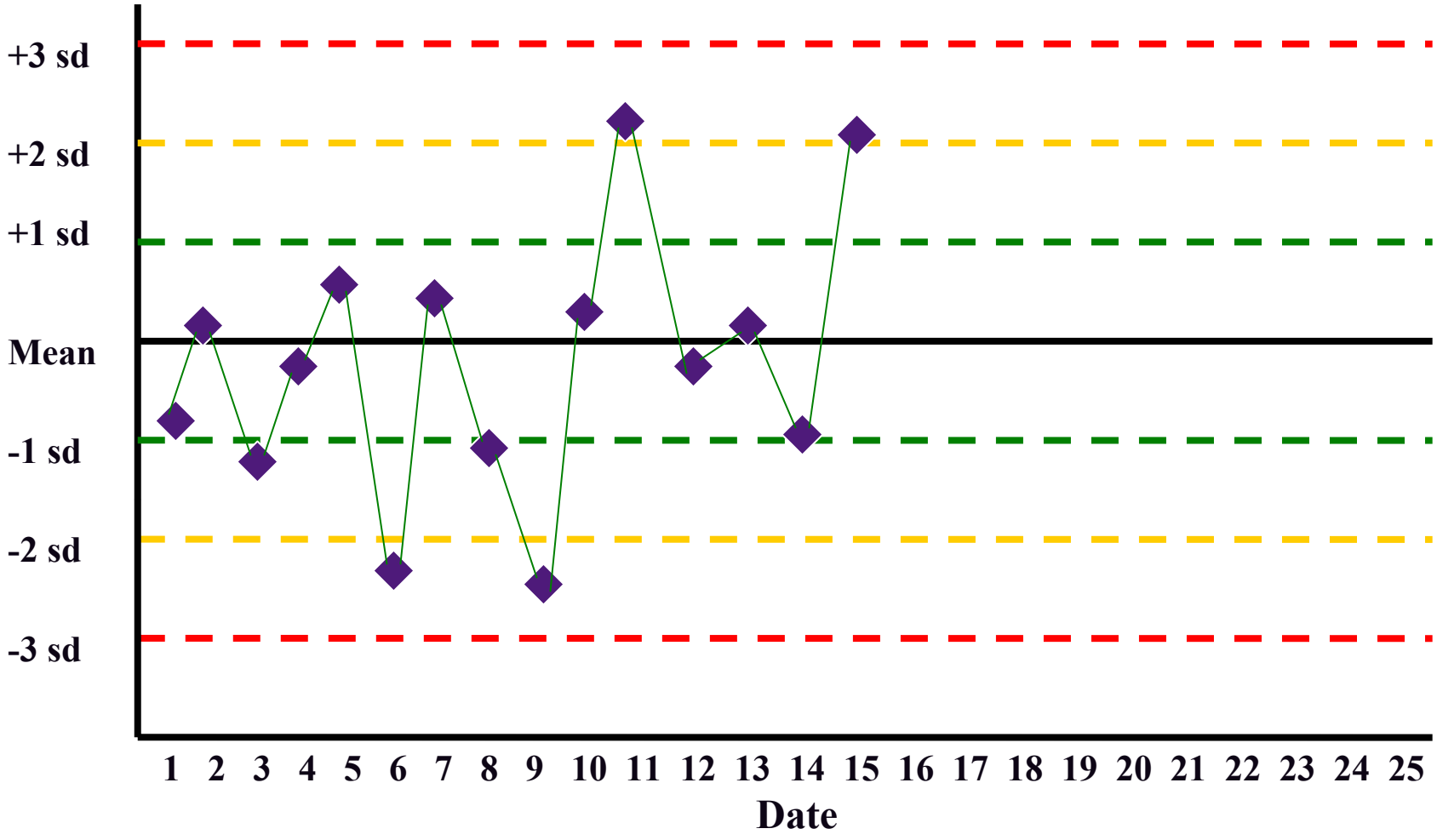

1_{3s}
R_{4s}
R_{4s}
1_{2s}
1_{2s}
2_{2s}
1_{2s}
1_{2s}
2_{2s}
265
260
255
250
245
240
235
212
208
204
200
196
192
188
1 2 3 4 5 6 7 8 9 10
Run Number

What do you see?




R4s
R4s
?
1 2s
1 2s
1 2s
1 2s
1 2s
1 2s
4 1s
10 x
265
260
255
250
245
240
235
212
208
204
200
196
192
188
11 12 13 14 15 16 17 18 19 20
Run Number

What do you see?



Solving QC Failures

- **Systematic Error**
  - Change in reagent / calibrator lot
  - Deterioration of reagent / calibrator
  - Change in temperature of assay environment

Solving QC Failures

- **Random Error**
  - Bubbles
  - Unstable assay environment temperatures
  - Unstable power supply

Solving QC Failures

- **Recent Changes**
  - Systematic Error: Trend vs. Shift
  - Random: Unpredictable

Solving QC Failures

- **Verify and Document**
  - Retest QC
  - Rerun Patient / Subject Specimens
  - DOCUMENT

QC Tools - Westgard Rules

- **Assayed versus Unassayed QC Materials**
  - **For unassayed controls: must establish a valid acceptable range by repetitive analysis in runs that include previously tested control material.**
  - **For assayed controls: must verify the recovery ranges supplied by the manufacturer.**

QC and Parallel Testing

- **Definition**
  - **Performing sample assays with old and new lot numbers of reagents; *documenting*, *comparing* and *evaluating* consistency of results produced**

QC and Parallel Testing

PPD

Examples

- Chemistry and Complete (Full) Blood Count: quality control materials, calculate statistics for comparisons
- HIV EIA, HIV RNA PCR, and Qualitative PCR assays: Minimum of three patient samples (preferably with a range of results) tested with old and new reagents and evaluated for consistent results

QC and Parallel Testing

- **More Examples**
  - **CD4/CD8: Minimum of two patient specimens (preferably with ratio of <1.0 and ratio of >1.0) tested with old and new reagents and evaluated for consistent results**

Quality Assurance (QA)

PPD

QA policies:

- **Outline how internal quality audits are to be performed**
  - **Audit approach and objectives**
  - **Audit report templates/shells**
- **Outline how evaluation of External Quality Assurance (EQA) should take place**

Internal Audits

Practice vs. SOP

- **Evaluates both components**

Internal Audits

Document review

- **QC data**
- **Training records**
- **Safety practices**

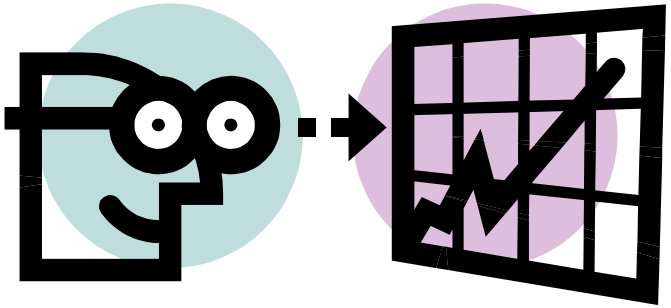
Internal Audits

Audit report

External Quality Assurance (EQA)

PPD

- Measure of Accuracy
- Peer vs. Proficiency
- Reports



  - SDI: Standard Deviation Index

    SDI = (Lab mean – Group mean)/Group SD

  - CVI: CV Index

    CVI = Lab CV/Group CV

External Quality Assurance (EQA)

- **Evaluate it as you would internal QC data**
  - Identify deficiencies
  - Construct corrective/preventative action plans
  - Monitor plans through resolution
  - DOCUMENT
    - **Acceptable results as well as failure results**

Quality Improvement (QI)

- **The determination of causes or sources of problems identified by QC and QA.**
- **Example:**

ROOT CAUSE ANALYSIS

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QUALITY MANAGEMENT (QM) PLAN

How is a QM plan constructed?

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It must be documented

Quality Management Plan

PPD

Functions of QM Plan

- Evaluates Quality and Appropriateness of Lab Services
- Identifies / solves important problems in patient care

Quality Management Plan

More Functions of QM Plan

- Includes all aspects of lab's scope of care
- Documents internal and external lab problems
- ***The QM plan must identify measurable indicators of quality.***

Quality Management Plan

PPD

Measurable Indicators of Quality Properties

- Pre-analytic, Analytic, Post-analytic
- High volume activities
- Problem prone activities

Quality Management Plan

PPD

More **Measurable Indicators of Quality Properties**

- **High risk activities**
- **Client focused activities**

Allow for Systematic Monitoring

Activity

- List some examples of quality indicators.
- List how we can monitor them.

Activity

PPD

Remember: They must identify *measurable* indicators of quality.

- QC failures
- Safety incidents
- External survey/proficiency failures
- Result modifications
- Turn around time (TAT) lapses
- Internal/external audit findings

Quality Management Plan Checklist

Does it……

Mandate key indicators of quality be monitored and evaluated to detect problems and opportunities for improvement?

<u>INTERNAL AUDITS</u>

Quality Management Plan Checklist

Does it……

Mandate that appropriate corrective action and/or preventive actions are taken and documented when opportunities for improvement are identified?

Quality Management Plan Checklist

PPD

Is it…..

Approved by the laboratory director?

Quality Management Plan Checklist

PPD

Is it…..

Overseen by a QM designee / officer ?

Quality Management Plan Checklist

PPD

Is it…..

Reviewed annually for performance and effectiveness?

Additional Features of the Quality Management Plan

- **Don’t forget these vital elements:**
  - QC failures
  - Safety incidents
  - EQA performance
  - Equipment problems
  - Managerial Review of Documentation

Management review

- **What is reviewed?**
  - Preventative Maintenance (PM)
  - Safety Events
  - SOPs
  - EQA Results
  - QC Data

Management review

- **Frequency of Review?**
  - Customized to your needs
- **Designee?**
  - Must be documented and approved

Corrective / Preventative Actions

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Overall Goal:

Implementation of solutions resulting in the reduction or elimination of an identified problem

Discussion…..

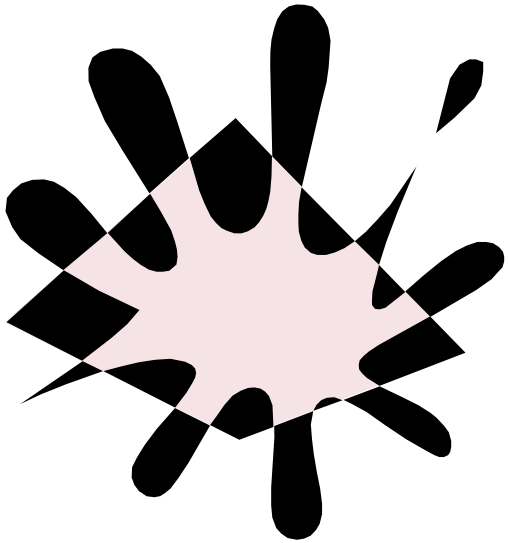
- **The quality management coordinator has identified a trend of specimen spills:**

– **In the hematology lab,**

– **With no exposures,**

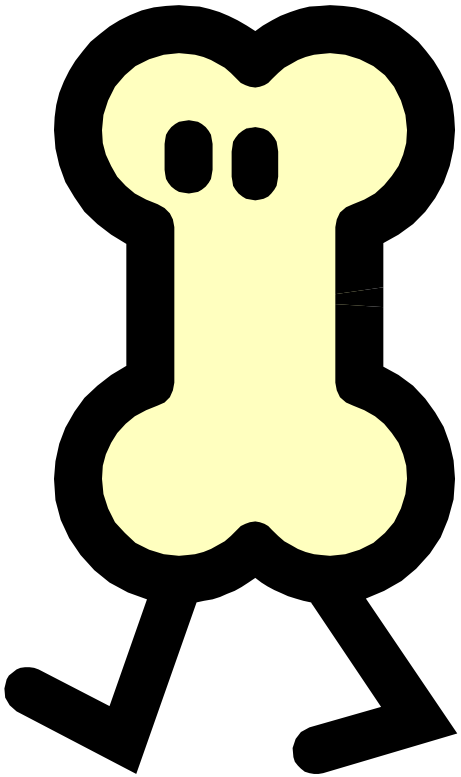
– **At the specimen processing bench,**

– **And each incident report indicates that the individual stumbled and dropped specimen vials.**



Trivia

What is the
largest bone
in the human body?
***Smallest bone*?**



That which remains quiet, is easy to handle.
That which is not yet developed is easy to manage.
That which is weak is easy to control.
That which is still small is easy to direct.
Deal with little troubles before they become big.
Attend to little problems before they get out of hand.
For the largest tree was once a sprout,
the tallest tower started with the first brick,
and the longest journey started with the first step.

From Lao Tsu (c.500BC)

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Questions? Questions? Questions?

THE ULITIMATE QUESTION

- **How will we succeed in our goal to meet or exceed Good Clinical Laboratory Practice standards?**

Final Questions and Comments

References

- College of American Pathologists, available at http://cap.org
- Westgard QC, available at http://westgard.com
- 1stNclass.com, available at http://www.1stnclass.com/

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Good Clinical Laboratory Practices

GCLP