



# THIRD PARTY CONTROLS IN LABORATORY MEDICINE

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## Laboratory medicine is the back bone of all clinical discipline

**In the area of laboratory medicine unreliable performance can result in**

- 1.misdiagnosis,**
- 2.delayed treatment**
- 3.increased costs due to retesting**
- 4.Loss of confidence and trust with stake holders.**

it is therefore of great importance to ensure that all results provided are both accurate and reliable



# Quality Control Considerations

The purpose of quality control in laboratory medicine(QC) is to

- 1.monitor the **analytical quality** of a technical *procedure*,
- 2.detect changes and eliminate reporting results with medically important errors.
- 3.ensure both the reliability and accuracy of test results in order to provide the best possible results

For the laboratory this means controls should be used to detect analytical errors that could pose harm to the patients treatment outcome.



## What are Third Party Controls and Why are they Important?

Third Party Laboratory Quality Controls means a quality control that provide an unbiased, independent assessment of analytical performance.

Use of a single multi-analyte third party control help in eliminating the need to purchase individual controls for each laboratory system/instrument.

Fewer controls to manage and fewer vendors to deal with.

**alternative to third party controls and to reduce costs many laboratories use pooled sera**



## USING POOLED SERA

Analyte levels will be in the patient NORMAL range and NOT HELP when evaluating performance at clinically significant levels

- The stability NOT validated like a true third party control
- Increased risk of infection as pooled sera may not have been tested at donor level for infectious diseases.
- Not having assured and consistent long term supply,

Third party controls with an extended shelf life enable long term QC monitoring and Allow the detection of shifts upon change of reagent or calibrator lot.



## **Please make a note that**

- Many equipment and IVD manufacturers provide their own control values evaluated from a limited number of test results, which leads to unacceptable standard deviations and accompanied by unrealistic wide ranges.
- Ranges provided are so wide that the laboratory in spite of poor performance will not fall outside them regardless of their performance
- Manufacturers use the same raw materials for their kit reagents, quality controls and calibrators which results in an increased risk that a shift in patient results will be unnoticed



## Quality Control Considerations an example

- Controls comply with manufacturer, accreditation and regulatory agency, and Good Laboratory Practices (GLP) requirements for quality control

FDA, CLIAA, NCCLS. Internal Quality Control Testing: Principles and Definitions Doc. C24-A

- Multi-constituent controls reduce risk of confusion
- Control need to be supplied in a ready to use liquid format – no reconstitution required.

### In-Kit Controls

- May be same material as calibrators
- Specific to each kit/reagent lot
- May not identify shifts between reagent lots
- Can be used to calculate assay cut-off
- Levels typically well above or below assay cut-off
- Frequent lot changes don't allow for long-term monitoring
- May not be similar to patient sample

### Third Party / Independent Controls

- Different from kit calibrators
- Independent of kit/reagent lot
- Identify shifts between reagent lots
- Designed to monitor the precision of the test system
- Levels are typically targeted to be reactive within a relevant range
- Same control lot can be used across multiple reagent lots allowing long-term monitoring of assay performance
- Control may be treated same as a patient sample



## **QC Requirements for Assays; Interpretation of Test Results.**

### **Minimum Standards for Laboratory Practice and Quality**

1. CLIA '88 - 42 CFR 493.1218 Law
2. Test / Run QC Definitions and Terminology
  - A. Manufacturer's Assay Criteria: Valid & Invalid QC Criteria
  - B. Laboratory's Supplemental QC Criteria: Acceptance & Rejection Rules
  - C. Manufacturer's control and calibrators: When Assay Kit Controls are Calibrators





# Laboratory QC Required by Law

1. Regulatory/Reimbursement Health Care Financing Administration (HCFA)
2. Regulatory/Advisory FDA Guidance for Industry Blood borne Pathogens Centers for Disease Control & Prevention (CDC)

3. Accreditation/Advisory

COLA

CAP

CLSI (NCCLS)

JCAHO

State Certification Requirements CA, NY Dept of Health

## **Laws, Rules & Regulations**

**CLIA '88**

**Clinical Laboratory Improvement Act 1988**

**42 CFR 493.121B**

**Minimum Standards for Laboratory**

**Practice and Quality**

International Standards & Directives ISO 15189:2003



# Assay QC: Valid and Invalid Test Runs

## Valid Test Run

- Performed in accordance with QC manufacturer's package insert instructions for run QC...
- All supplied internal, in – kit controls and/or calibrators qualify per acceptance criteria defined by manufacturer – “a valid test run”

## Invalid Test Run

- Not performed per manufacturer's package insert instructions
- Error: Manufacturer's internal controls and/or calibrators do not meet criteria and requirements specified in kit package insert - “a failed test run”

## Assay QC: Course of Action For Invalid Test Run

- Void all patient specimen test results
- Repeat entire test run with specimens



## Supplemental Assay QC: Acceptance & Rejection Rules

Tests could be accepted or rejected **HOW?**

Based on additional QC parameters whereby acceptance or rejection rules and procedures established by the laboratory to supplement test kit QC criteria.

- All negative specimen test results can be repeated singularly
- A positive specimen test result must remain as an initial test of record
- All positive specimens **MUST** be repeated in duplicate to confirm initial test result

Guidance for Industry  
Revised Recommendations Regarding Invalidation of Test Results of Licensed and  
510(s) Cleared Bloodborne Pathogen Assays Used to Test Donors  
U.S. Department of Health and Human Services  
Food and Drug Administration (CDER)  
July 2001  
<http://www.fda.gov/cber/guidelines.htm>



## CLIA '88 Defines Controls and Calibrators for Qualitative Tests

### Controls

- Any kit manufacturer supplied reagent of a known reactive level **not used** to calculate assay cut-off.

### Calibrators

- Any reagent supplied by the kit manufacturer **used** to calculate the assay cutoff; controls could be calibrators.



## CLIA '88 Clarification

Qualitative tests must have a calibrator & two controls

- At least one Calibrator
- At least one Positive control
- At least one Negative control

**In-Kit Controls may be Calibrators but Calibrators cannot be controls**

- Any additional controls needed are “external” or “independent” of the test kit. The laboratory may choose to prepare their own **in-house controls** or purchase commercial **third party controls** to include with test runs.



## List of Commercial Test Kits where Controls are Calibrators

### HIV Ab

- Abbott HIV-1/2
- Bio-Rad Genscreen EIAs
- Genetic Systems HIV-1 rLAV
- Genetic Systems HIV-1/2 + O
- Murex HIV EIA
- Organon Teknika HIV-1

### HTLV Ab

- Abbott HTLV-I/II
- Murex HTLV EIA
- Organon Teknika HTLV-I/II

### HBcore Ab

- Bio-Rad Monolisa EIA
- Ortho HBcore

### HCV Ab

- Abbott HCV-2.0
- Ortho HCV 3.0

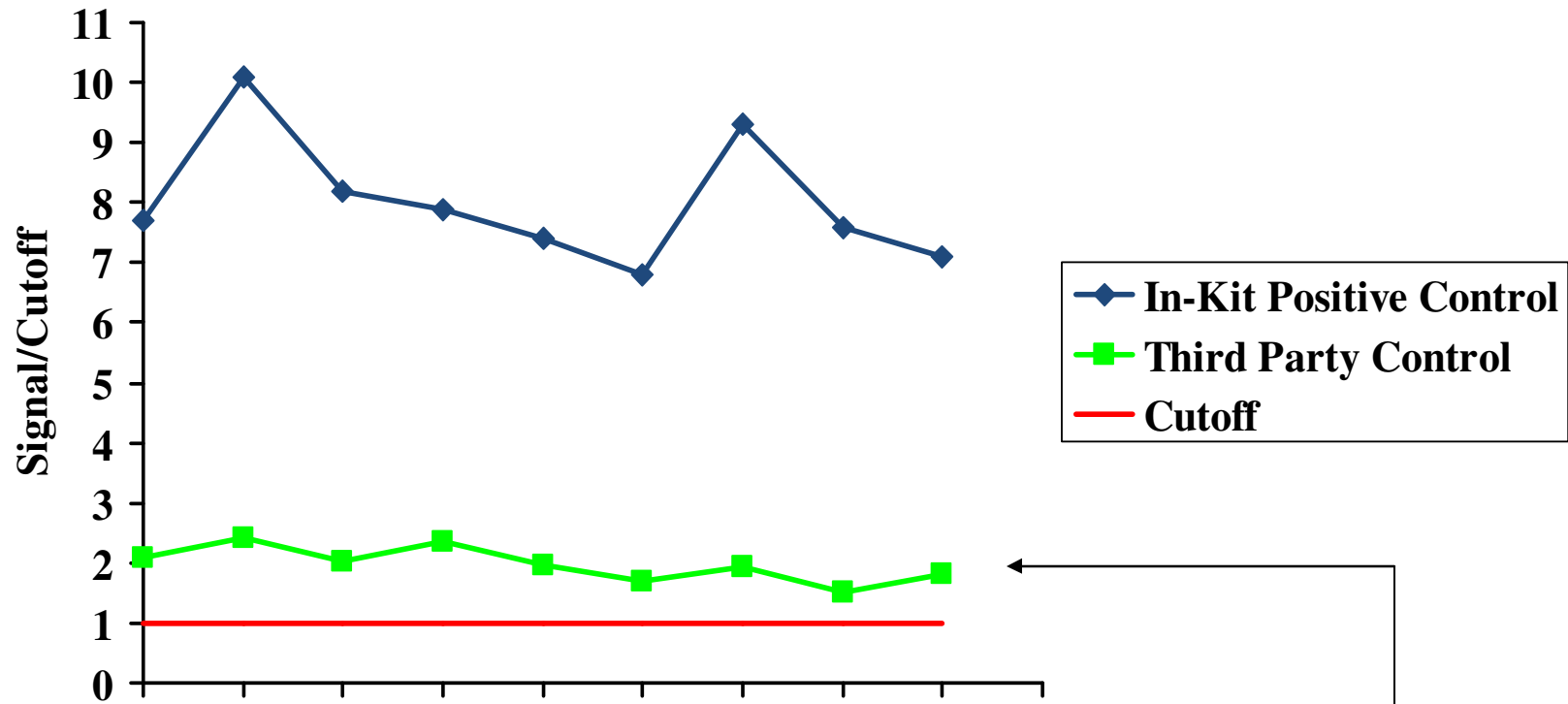
### HBsAg

- Bio-Rad Monolisa EIA
- Ortho HBsAg
- Genetic Systems HBsAg



## Third Party Control Requirements for Manufacturer's Assays

Manufacturer	Methodology	Manufacturers Kit Control(s)	Cut-off Calculation	QC Requirements
<b>Abbott EIA</b>	ELISA	Included	Formula Derived from Pos and Neg	Required
<b>Abbott AxSYM / ARCHITECT</b>	MEIA	Ancillary	Program Derived	Suggested
<b>Bayer Centaur</b>	MEIA	Ancillary	Program Derived	Suggested
<b>Bio-Rad</b>	ELISA	Included	Formula Derived from Pos and Neg	Required
<b>BioMerieux VIDAS</b>	SPR EIA		Program Derived	Suggested
<b>Dade Behring Ezygnost</b>	ELISA	Included	Formula Derived from Pos and Neg	Required
<b>DiaSorin</b>	ELISA	Included	Calibrator Derived	Suggested
<b>DPC Immulite</b>	EIA	Included	Program Derived	Suggested
<b>Fujirubio Lumipulse</b>	EIA			Suggested
<b>BioMerieux EIA (Vironostika)</b>	ELISA	Included	Formula Derived from Pos and Neg	Suggested
<b>Ortho EIA</b>	ELISA	Included	Formula Derived from Pos and Neg	Required
<b>Ortho Vitros ECI</b>	MEIA	Ancillary	Program Derived	Suggested



Third Party Controls yield low and/or weak reactive results with values typically in the 1.5 – 3.0 S/CO range





## Technical Principles Data Report Schemes: QUALITATIVE RESULT

Qualitative Assay results are interpreted/reported as:

- Positive or Negative
- Reactive or Non-reactive

Results interpreted from Assay Value are expressed in:

- Optical Density (Absorbance)
- INDEX; Antibody INDEX (AI); ISR;
- Sample to Cut-off Ratio (S/CO or S/N)



## Technical Principles Data Report Schemes : QUANTITATIVE RESULTS

### Quantitative Assays

Results are reported in units of measurement:

- AU/mL (Arbitrary Unit)
- IU/mL (International Unit – Standardized)
- mIU/mL (International Unit)

Value may be interpreted relative to recognized standard(s) as:

- Positive or Negative
- Reactive or Non-reactive



## General Infectious Disease Quality Control The Quality System

### **Programs and Practices in Today's Modern Laboratory combine both:**

#### **Error Prevention**

“Involves the development and implementation of a laboratory process which is capable of meeting a quality specification.”

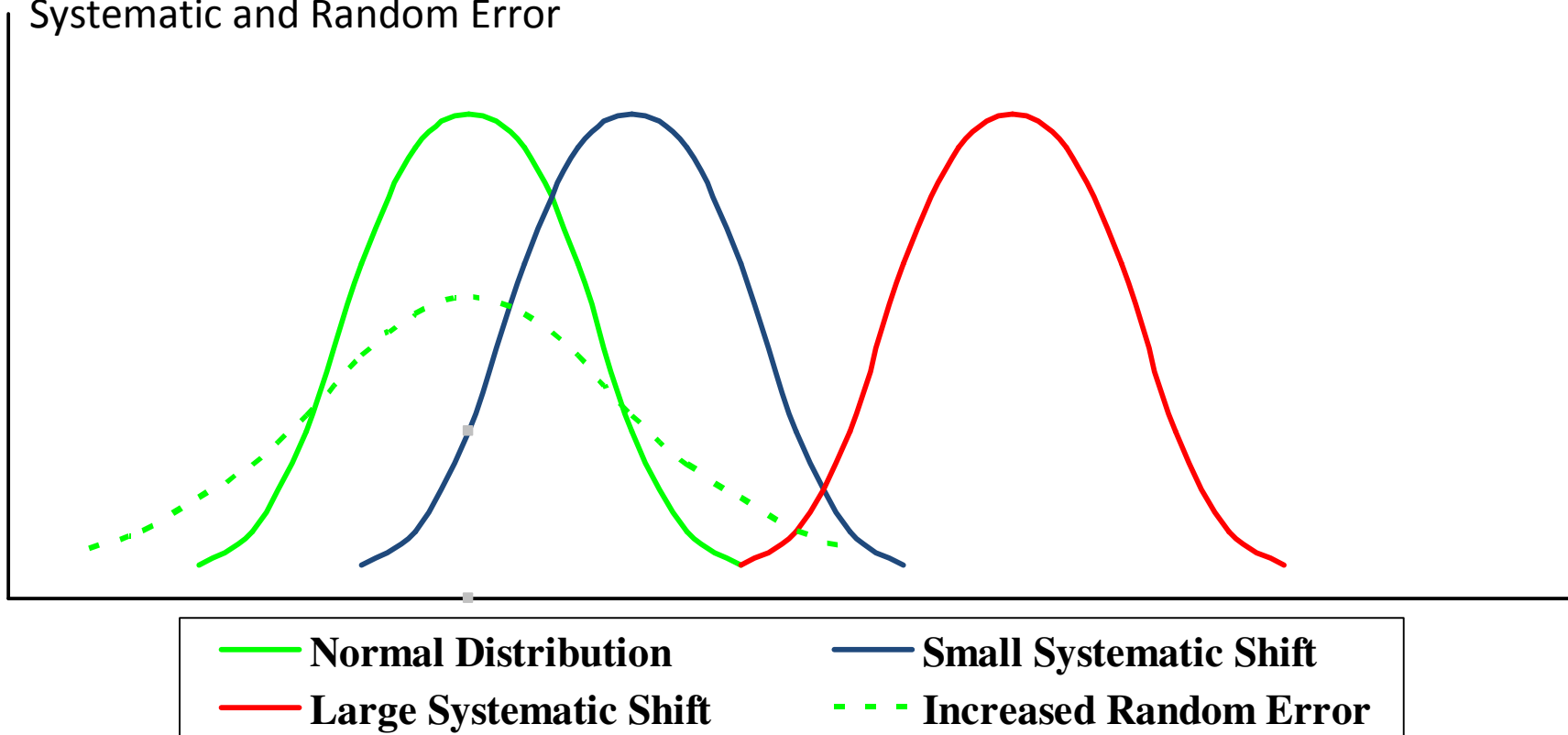
#### **Error Detection**

“Involves the monitoring of the process for the presence of error and is the monitoring activity of quality control.”

Cembrowski GS, Carey RN. Quality Control of the Testing Process In: Laboratory Quality Management QC and QA. Chicago IL.: American Society of Clinical Pathologists Press; 1989



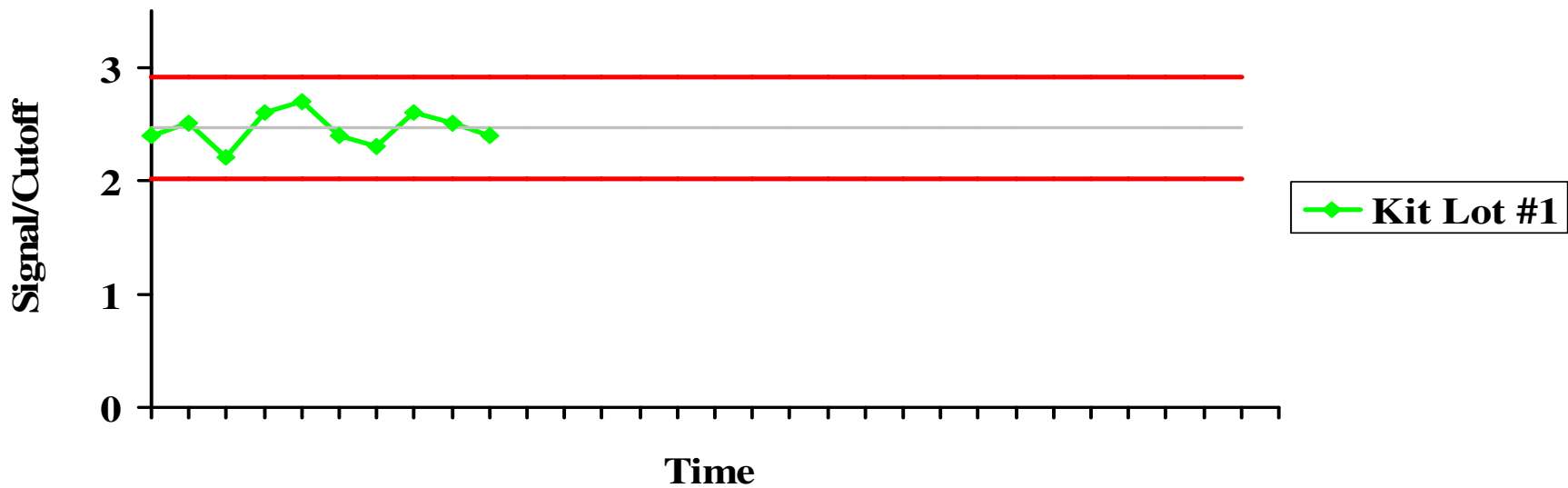
## Systematic and Random Error





### Case Study #1: Incorrect Range Established

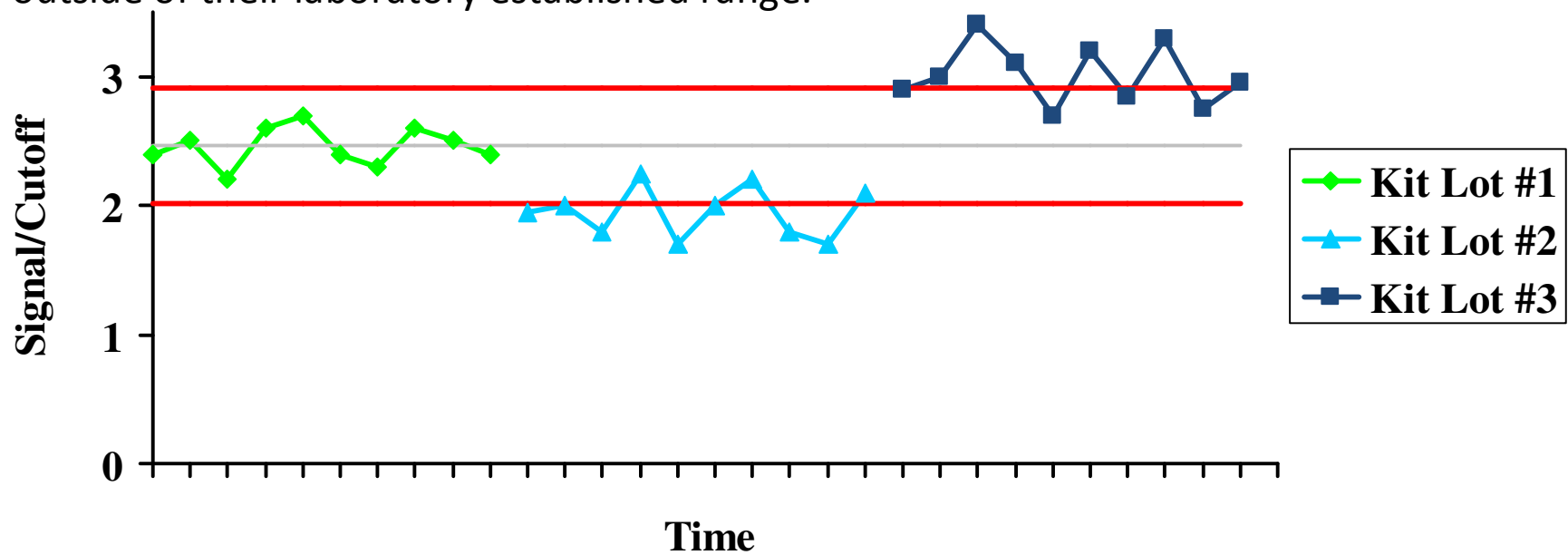
Laboratory establishes range for their VIROTROL control with data from one reagent kit lot.





### Case Study #1: Incorrect Range Established

Using the same lot of VIROTROL with new test kit lots #2 and #3 yielded results outside of their laboratory established range.

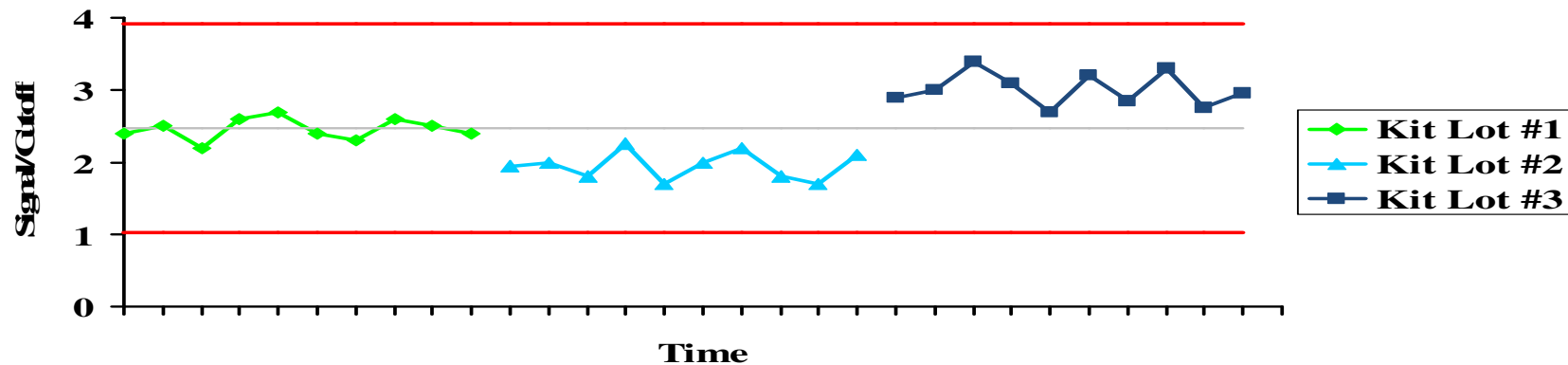




## Case Study #1: Incorrect Range Established

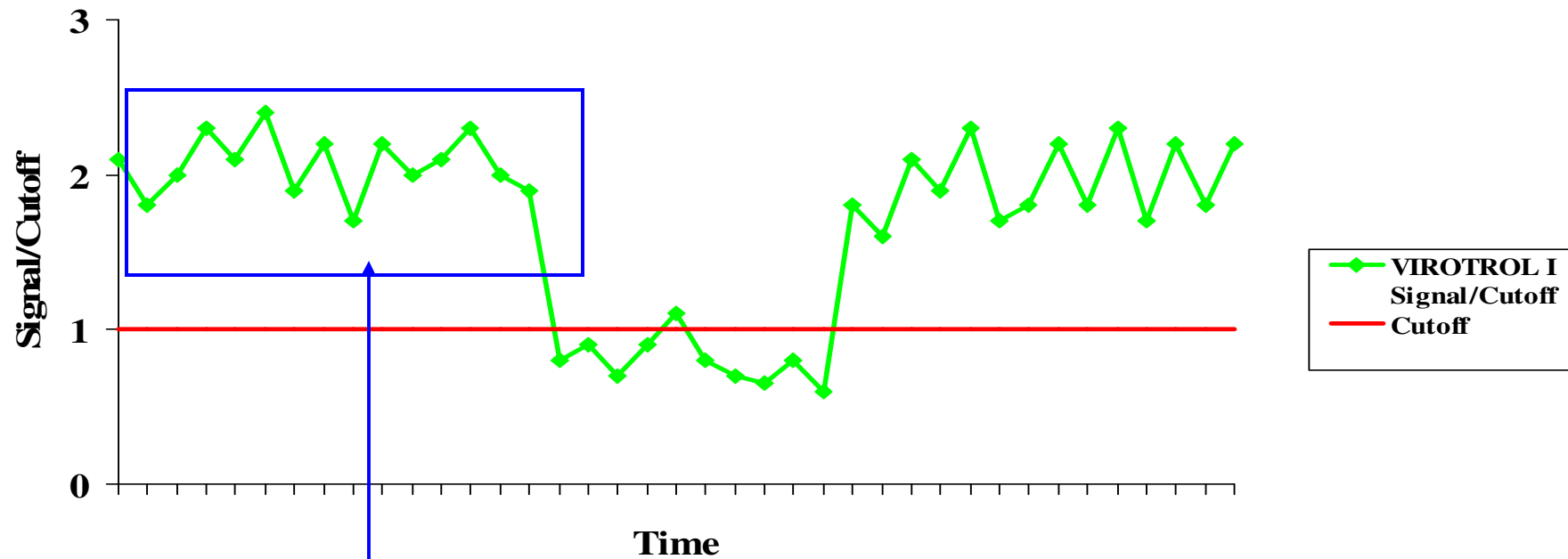
Laboratory uses data from multiple test kit lots to establish correct range for each VIROTROL control lot.

Conclusion: Range must accommodate for normal and acceptable test kit lot-to-lot variability





## Case Study #2: Detecting Faulty Equipment

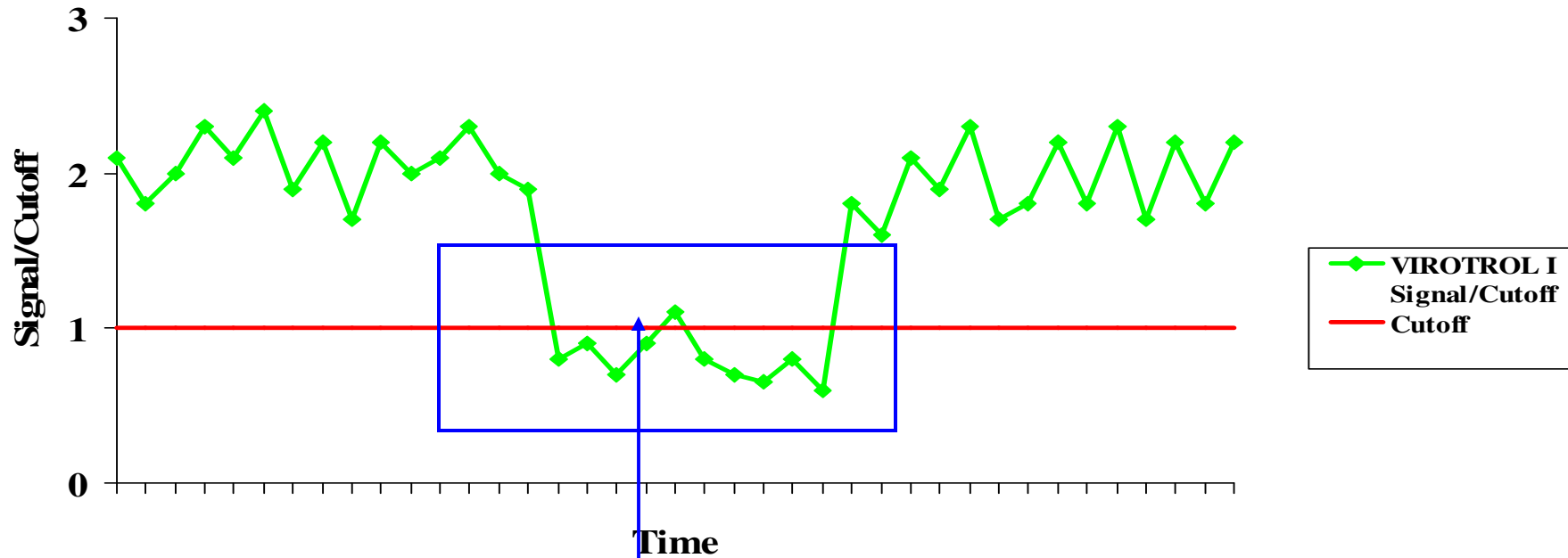


A. Laboratory reports valid in-kit control and calibrator test results with normal and acceptable Bio-Rad VIROTROL I control results on Organon Teknika HTLV I/II EIA.





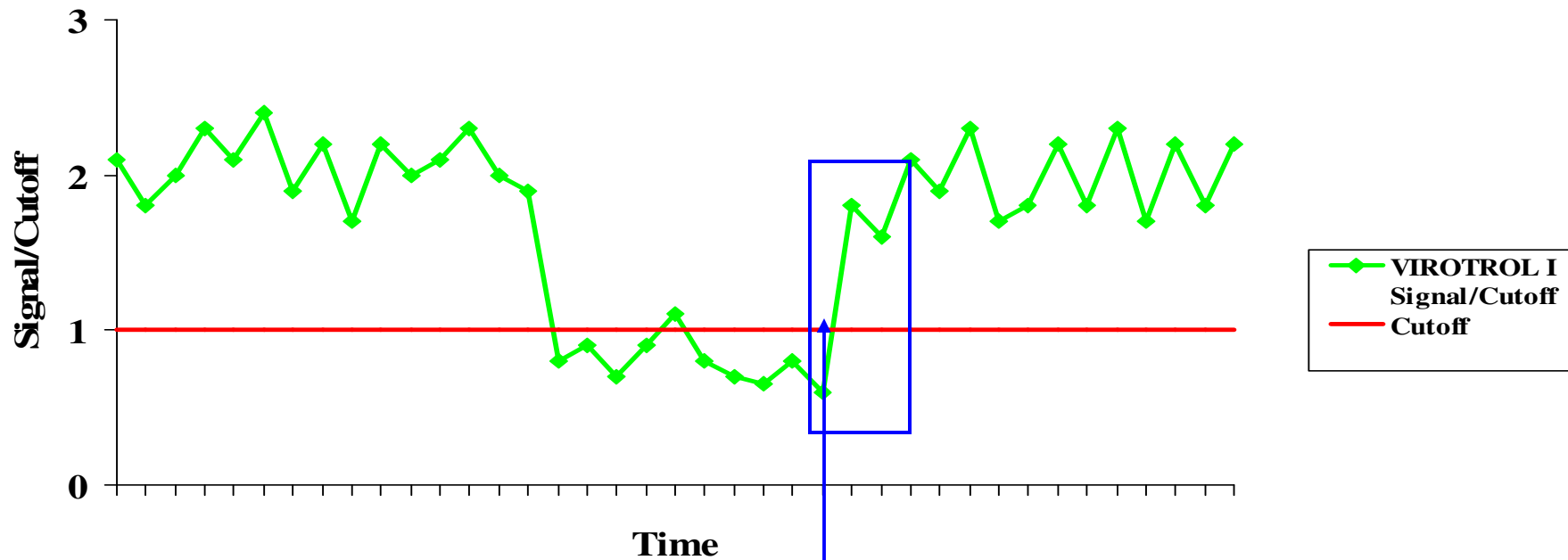
## Case Study #2: Detecting Faulty Equipment



B. Observes unacceptable low and non-reactive VIROTROL I results but continues reporting valid runs with in-kit control and calibrator values found to be within the insert range provided by reagent manufacturer



## Case Study #2: Detecting Faulty Equipment



C. Investigation reveals microwell plate washer programming error.

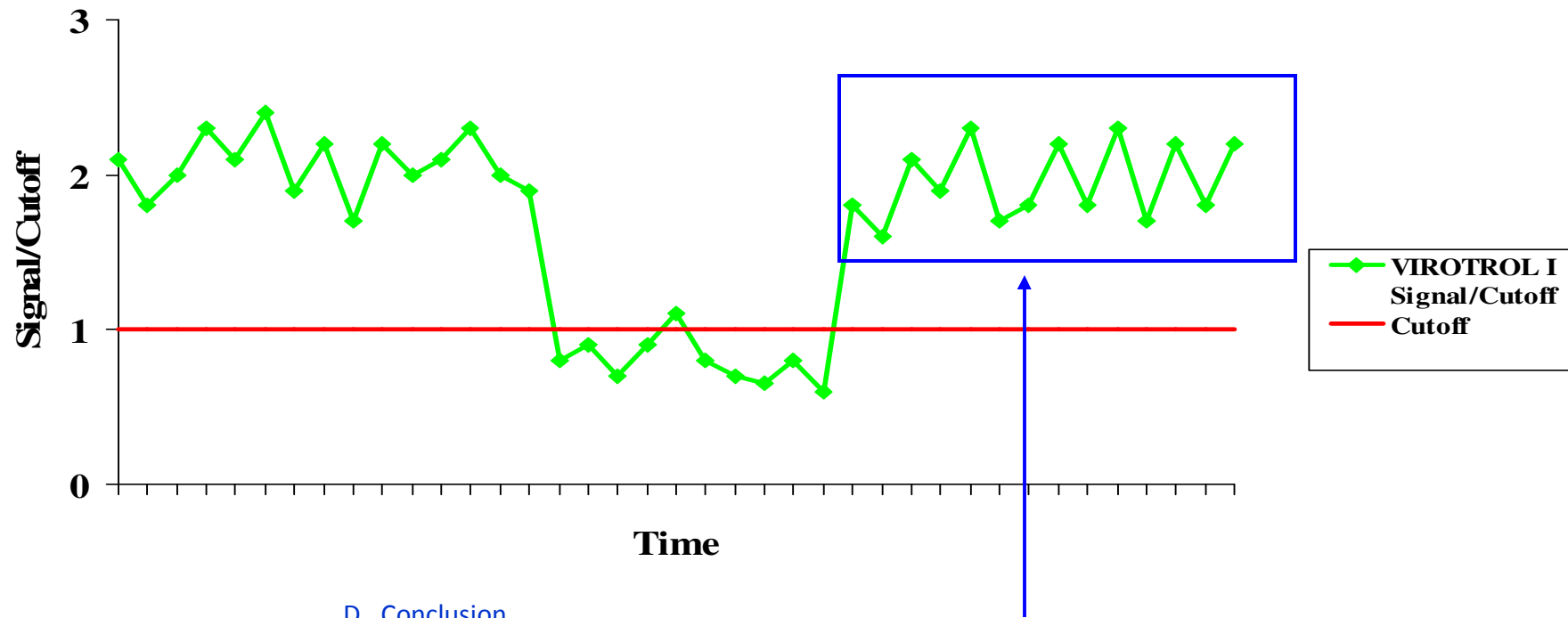
Laboratory corrects program.

VIROTROL I, in-kit controls and calibrators normalize.

Laboratory reports valid and acceptable test runs.



## Case Study #2: Detecting Faulty Equipment



### D. Conclusion

Bio-Rad VIROTROL I control detected a problem that led to the discovery of an equipment related programming error that potentially could have affected patient test results.<sup>1</sup>

<sup>1</sup>Read more stories online at [www.thirdpartyQC.bio-rad.com](http://www.thirdpartyQC.bio-rad.com)



## Troubleshooting

### List of Common Problems:

- Product not used correctly:
  - Incorrect VIROTROL product for assay
  - Manipulated and/or diluted control to extend usage
  - Used product 60 days after opening
  - Contaminated product and/or cross-contaminated sample during assay
  - Removed dropper tip (dangerous and exposes product to contamination!)
- Systematic failure to equipment and/or instrument malfunction and/or improper use
- Test kit lot-to-lot variability
- Differences between various manufacturers' test systems
- VIROTROL lot-to-lot variability
- Incorrect VIROTROL Class for assay

### Storage

- Refrigerate VIROTROL products at (2 to 8°C)
- VIROTROL products are shipped to customers and/or selling entities at ambient temperature. Conditions during transit do not affect product performance.
- Deliveries exceeding seven (7) days should be reported to QSD San Ramon, CA via ICCR
- Refer to package insert for further instruction



## Troubleshooting

### Freezing & Aliquoting

- VIROTROL labeling does not expressly forbid freezing; however, the product labeling clearly states proper storage conditions at **2 to 8°C**.

#### Note:

- If the customer decides to use an alternate storage for VIROTROL controls, they must validate their method/process. Documentation and/or performance data that allow customers to freeze store of control products would be contrary to package insert instructions and should not be provided.
- Refer to package insert for further instructions

### Normal Distribution

- Values within +/- 3 SD (standard deviation) of average (mean)

#### Random Error

- Statistical fluctuations in the amount by which a single value differs from the expected value.
- Causes may be differences in manufacturer's test kit lots, operators, instruments and/or calibrators

#### Systematic Error

- Reproducible and persistent shift in values from the expected value occurring in the same direction (biased shift in values)

**Random and Systematic Errors are easy to identify but difficult to resolve**



## Frequently Asked Questions

Which analytes are in which control?

- Refer to QSD Infectious Disease Product Catalog  
[www.bio-rad.com/qualitycontrol](http://www.bio-rad.com/qualitycontrol)

What is the shelf life of the control?

- A typical shelf life is 18 months from the date of manufacture
- Refer to individual package insert for product expiration date

What is the control made of?

- VIROTROL controls are pooled human plasma which has been stabilized and treated following common methods used in the industry to inactivate infectious agents.

**I tried VIROTROL I with an anti-HIV (HIV-1) assay and it was negative. Why?**

- Manufacturers of HIV test kits use a variety of solid phase antigen sources (viral lysates, purified virus, recombinant peptides, etc.). For this reason and others, the different test kits react differently to a variety of specimen types, including VIROTROL I.
- In particular, diluted specimens, such as VIROTROL I, can react differently due to the fact that they contain manipulated titers of the various epitope specificities found in the original undiluted source material which may achieve endpoint titer at different rates.



**I'm ready to test the VIROTROL control, shall it be treated as an in-kit control or as a test specimen?**

- VIROTROL controls should be handled in the same manner as test specimens (not kit controls) following procedures provided by the kit manufacturer
- Most manufacturer's assays require a pre-dilution step for test specimens but may not for their in-kit controls. Should the customer choose not to follow the manufacturer's procedures, then abnormal VIROTROL results are expected – VIROTROL performance will not be optimal and may yield values higher and/or lower than expected.

**I'm searching for a low-positive third party control for my viral marker testing, will VIROTROL control yield the desired performance?**

- Each class of VIROTROL I, II, III and VIROTROL HAV-IgM is developed to yield low-positive results on most commercial tests with values generally in the representative range of 1.5 to 3.5 S/CO and within the linear range of the assay.
- Review customer's testing requirements and match with suitable VIROTROL class.



## Frequently Asked Questions

### **How often should VIROTROL controls be used?**

- Provider encourages customers to use quality controls in every run or assay. Since runs may be performed in batches or within a specific time frame (e.g. every 8 hour shift, every 24 hours, etc.), the customer will need to determine how to best use their quality controls.

### **VIROTROL controls must not be substituted for the mandatory positive or negative calibrators (mandatory in-kit controls) provided with the manufacturer's test kit**

- Note: Most manufacturers of microwell EIA kits utilize mandatory positive or negative calibrators. Automated assay platforms such as Abbott AxSYM, ARCHITECT, Bayer Centaur and Ortho Vitros ECI have assay positive and negative control which are ancillary and in many cases, optional.





## A Comprehensive QA Program Incorporates Third Party Controls

- **Complements test kit acceptance criteria**
- **Detects and prevents errors**
- **Provides added confidence**
- **Complies with regulatory guidelines**
- **Improves quality and proficiency**
- **Augments blood safety efforts**
- **Enhances health care for patients**



## Issues to Consider in Deciding Between In-House or Third Party Controls

- **Convenience**
- **Safety**
- **Regulatory**
- **Reliability**
- **Cost**



# Thanks