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Quality control made easy.

Calibration Verification - Guidelines and Regulations

Presentation Topics & Objectives

- ***Define difference between Calibration and Calibration Verification***
- ***What are <u>acceptable</u> Calibration Verification materials***
- ***How and when Calibration Verification is to be performed***
- ***Troubleshooting for a failed Calibration Verification***

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Let's Start From the Beginning

- ***January 24th, 2003 Centers for Disease Control and Prevention (CDC) and the Centers for Medicare & Medicaid (CMS) publish laboratory regulations (CLIA) to become effective April 24th, 2003***
  - ***Include requirements for Calibration and Calibration Verification for nonwaived tests***
  - ***Nonwaived tests include moderately and high complexity tests***

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Discussion of Terminology

- ***Definitions and applications of following:***
  - ***Calibration***
  - ***Calibration Verification***
  - ***Reportable Range***
  - ***Analytical Measurement Range (AMR)***

Definitions

- ***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***
  - ***Basically "Tells" the instrument how to read a certain level of the analyte being tested***

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Definitions Continued

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

Definitions Continued

- ***Reportable Range: the span of test result values over which the laboratory can establish or verify the accuracy of the instrument or test system measurement response***

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Definitions Continued

- ***Analytical Measurement Range (AMR):***

  Defined by CAP (College of American Pathologists) as the range of numeric results a method can produce without any special specimen pre-treatment, such as dilution, that is not part of the usual analytic process. (Same as reportable range in CLIA terminology.)

Definitions Continued

- ***Linearity As defined by CLSI's (formerly NCCLS) EP06-A guideline: The ability (within a given range) to provide results that are directly proportional to the concentration (amount) of the analyte in the test sample.***

Note: "Linearity" does not appear in CLIA regulations.

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Calibration Vs. Calibration Verification

- ***Calibration Verification essentially checks the Calibration of the analyzer by confirming that the test system is able to provide accurate results throughout the Analytical Measurement Range of the instrument for that particular analyte.***

In a Nutshell

- ***Calibration "tells" the instruments how to read certain analyte concentrations***

- ***Calibration Verification tests to make sure the calibrators are accurate across the instrument's reportable range***

Calibration Overview

Calibration Requirements

- ***Laboratory is responsible for performing calibration as directed by the manufacturer's test system instructions AND when Calibration Verification does not produce acceptable results***

- ***Make sure to document each time calibration is performed***

- ***More frequent calibration may be required if the test system's calibration is less stable than instrument manufacturer's suggested frequency***

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Exceptions to Calibration

- *Manual procedures in which an instrument is not used*
  - *Microbiology cultures*
  - *Tilt-tube prothrombin times*
  - *ABO group and D (Rho) typing*

Exceptions to Calibration Continued

- *Microscopic procedures*
  - *Urine sediment examination*
  - *KOH and pinworm preparations*
  - *All manual cell differential procedures*
  - *Manual Cytology screening procedures*

- *Procedures which involve instruments in which calibration is not practical*
  - *Prothrombin procedures*

How to Perform Calibration

- *The manufacturer's instructions of the test system should explain the process for calibration*
  - *Frequency*
  - *Replicates*
  - *Analyte concentration*
  - *Acceptable material*

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Calibration Materials

- ***Calibration materials, also called calibrators are solutions of known analyte concentrations***

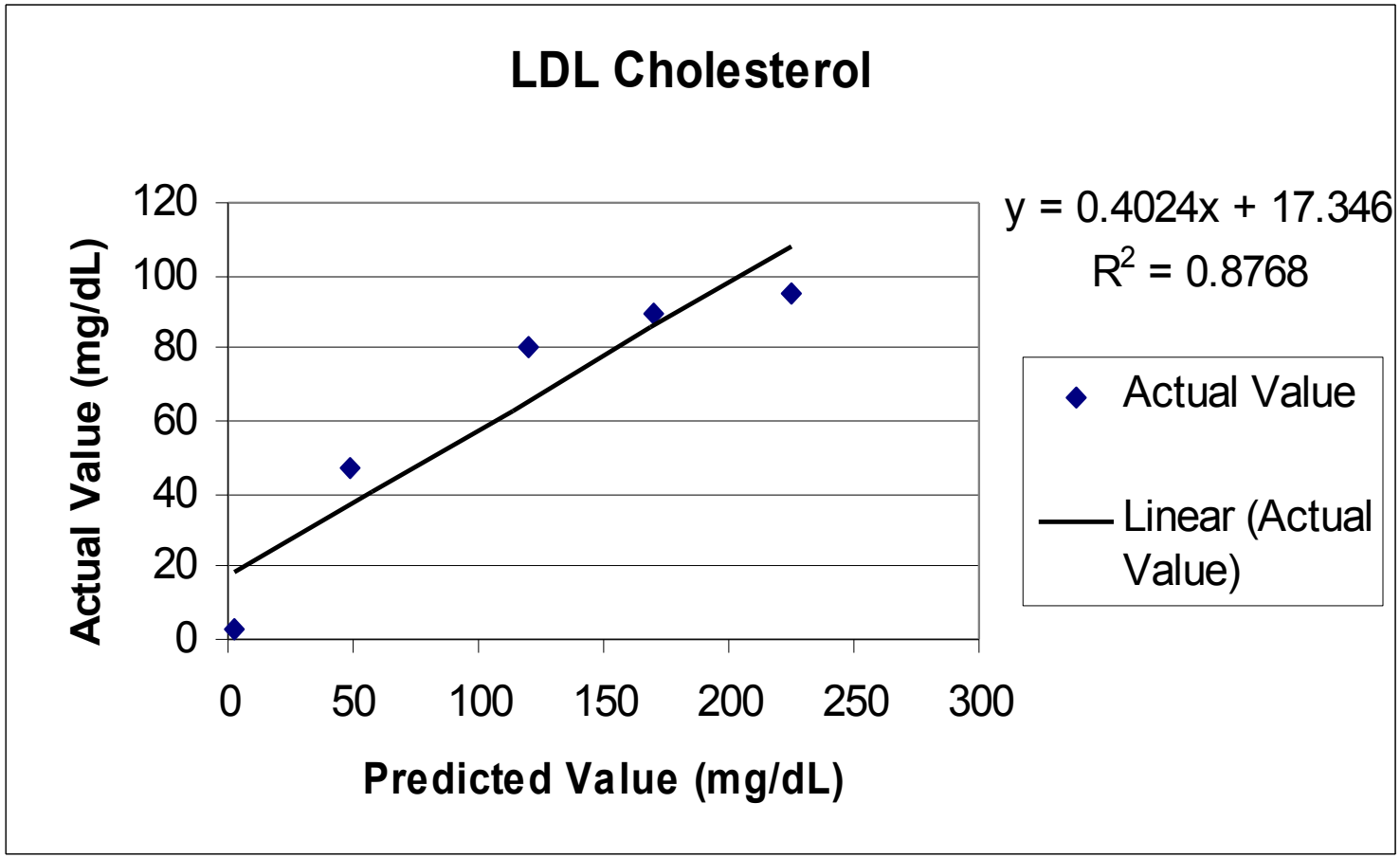
- ***May contain more than a single analyte***

- ***The term "standards" generally used to refer to calibration material***

Calibration Verification Overview

Reasons to Perform Calibration Verification

- *Can Detect Hook Dose Effect*



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Reasons to Perform Calibration Verification Continued

- *Test method may have limited number of calibrators*
  - *May have only one or two calibrators*
- *Test method calibrators may not span the instrument's reportable range*
  - *Even if the test method has three calibrators (minimum number of calibrators required to be exempt from Calibration Verification, may not adequately span AMR)*

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Reasons to Perform Calibration Verification Continued

- *Daily Quality Controls generally do not challenge lower and upper limits*
  - *Daily QC normally targets Normal and Abnormal patient ranges only*
  - *It is possible to have "Passing" Daily QC, but "Failing" Calibration Verification since controls may not span entire analyzer range*
    - *Especially important in Therapeutic Drug Monitoring*

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Calibration Verification Requirements

- ***Labs must perform every 6 months (or more frequently if specified in the test system's instructions) or if:***
  - ***There is a change in reagent lot numbers for a particular analyte—unless the laboratory can show that the new lot of reagent does not affect the range of the patient test results and that daily quality control results are not adversely affected by changing reagent lots***

Calibration Verification Requirements Continued

- *There is major preventative maintenance or replacement of critical instrument components which may affect test patient results*
  - *Includes analyzer being sent to manufacturer for repairs*

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Calibration Verification Requirements Continued

- ***Quality control materials begin to shift or are out of the laboratory's acceptable limits and other methods of checking the accuracy of the control results are not able to ascertain and resolve the problem***

- ***The individual laboratory has determined the reportable range for patient test results are to be monitored more frequently***

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Calibration Verification Requirements Continued

- ***Document each time Calibration Verification is performed***

- ***<u>IMPORTANT NOTE</u>: The laboratory must also be able to verify calibration on factory-calibrated instruments that cannot be calibrated by the end user***

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What Are Acceptable Calibration Verification Materials?

- *Materials of Known Concentrations*
  - *Calibration Materials*
  - *Proficiency Testing samples with known results*
  - *Commercially available material*
  - *Controls with known values*
  - *Patient samples with known values*

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Calibration Verification Exceptions

- ***For Automated Cell Counters:***
  - ***Follow manufacturer's instructions for analyzer operation and tests two levels of control each day of patient testing and results are within lab's acceptable range***
- ***Calibration Verification is met if:***
  - ***Running 3 or more levels of calibrator and includes a low, mid, and high value, and is performed at least once every 6 months***

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Calibration Verification Exceptions Continued

- *If laboratory follows manufacturer's instruction for analyzer operation and runs three levels of control material:*
  - *on a routine basis (low, mid, and high)*
  - *more than once each day patient results are reported*
  - *and the control results meet the lab's criteria for acceptability*
  - *and the controls are NIST traceable, the calibration verification requirements have been met*

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Calibration Verification Review

- ***When: Every 6 Months or whenever the following occurs:***
  - ***New lot of reagent used (unless lab can verify that there is no change in results)***
  - ***Major preventative maintenance or replacement of critical test method components***
  - ***Controls indicate shift or are out of the laboratory's acceptable range***
  - ***Laboratory determines more frequent verification required***

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How to Perform Calibration Verification – Tools and Resources

How To Perform Calibration Verification

- *Document*
  - *Date, Analyte, and Calibration Verification material used*
- *Run 3 levels of material*
  - *Run low, mid, and high levels as if running patient samples*
  - *Record data*
  - *CLIA does not state minimum number of replicates*
- *Compare results to expected values*
- *Document results and determine if results meet laboratory's acceptable criteria*

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Sample Calibration Verification Results Worksheet

Worksheet and Documentation Form for Calibration Verification

Analyte _____ Date _____

Instrument _____ Serial Number _____

Reagent/Strip/Cassette Lot# _____ Expires: _____

Materials used _____

Source of Acceptable Limits _____

	Low Level	Mid Level	High Level
Lot Number			
Expiration Date			
Expected Value			
Acceptable Limits			

Calibration Verification Results

	Low Level	Mid Level	High Level
Results Obtained Repetition 1			
Optional: Repetition 2			
Repetition 3			
Mean			
Results Acceptable?			
Comments and/or Corrective Actions			

Performed by _____

Reviewed by _____ Date _____

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How To Perform Calibration Verification Continued

- *Plot data on Linear Graph*
  - *Computer program - spreadsheet*
  - *Commercial Programs*
  - *Manufacturer material and programs*
  - *Third Party control manufacturer and programs*

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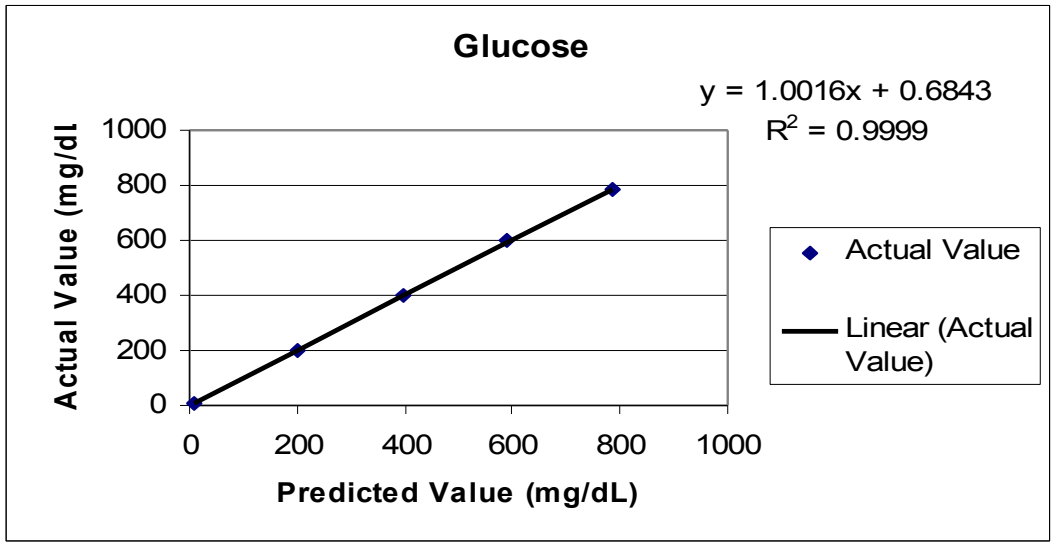
Sample Calibration Verification Results Spreadsheet and Graph

Technician	Analyte		
Terry Smith	Glucose		
Gen. Chem. Lin. Lot	Gen. Chem. Lin. Exp.	Reagent Lot	Reagent Exp.
06107	9/22/2011		
Date Run	Instrument	Method	Units
5/2/2007			mg/dL
Level	Units	Predicted Value	Actual Value
A	mg/dL	8	9
B	mg/dL	202	200
C	mg/dL	397	401
D	mg/dL	591	597
E	mg/dL	785	783
SLOPE	1.0016		
INTERCEPT	0.6843		
COEFFICIENT R	0.9999		



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Sample Calibration Verification Results Spreadsheet and Graph

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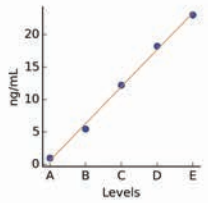
Linearity/Calibration Verification Report

Company Name: General Hospital
Lab Name: Chemistry Lab
Analyzer Model: AnyChem Analyzer
Analyzer Name: AnyChem S/N #12345
Date Of Run: Dec 31, 2014
Technician: Jane Doe

Analyte: Folate
Analyte Units: ng/mL
Reagent: AnyChem Folate Reagent
Product: K714M-5 - Linearity FD Immunoassay
Lot Number: 0111
Lot Expiration Date: Sept 10, 2016

USER DATA SUMMARY



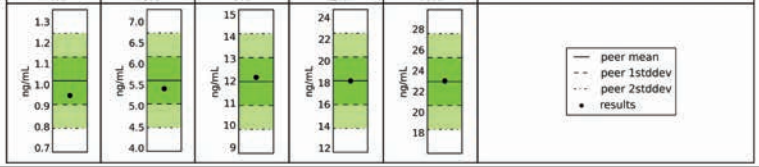
Slope	Y-Intercept	R-Squared
1.032	1.032	0.998

Level	Theoretical*	User Mean	Replicates
A	0.953	0.953	0.95, 0.96, 0.95
B	6.473	5.43	4.30, 6.02, 5.97
C	11.993	12.2	12.24, 12.48, 11.88
D	17.513	18.23	18.19,18.07,18.43
E	23.033	23.033	23.37, 22.33, 23.40

*Theoretical values are determined by generating a line between smallest and largest observed values then applying product blend ratios to determine intermediate levels. Blend ratios as follows:
A=1A B=0.75A+0.25E C=0.5A+0.5E D=0.25A+0.75E E=1E

USER VS. PEER COMPARISON
(200 Peers)

	Level A	Level B	Level C	Level D	Level E	
N	200	200	200	200	200	Number of peer data points
Peer Mean	1.023	5.623	12.012	18.230	23.100	Mean of the peer data points
User Mean	0.953	5.43	12.2	18.23	23.033	Mean of user replicates
+/- Diff	-0.07	-0.193	0.188	0	-0.07	Difference between user and peer means
% Diff	-6.8	-3.4	1.6	0.0	-0.3	% difference between user and peer means
Peer Stddev	0.113	0.562	1.081	2.188	2.310	Peer standard deviation
Peer CV (%)	11.0	10.0	9.0	12.0	10.0	Peer coefficient of variation



Approved By: _____ Date: _____

Each lot of product is manufactured such that a linear relationship exists among levels. Actual results obtained may vary depending on instrumentation, methodology, and assay temperature. Results may also be dependent on the accuracy of the instrument/reagent system calibration. The degree of acceptable non-linearity is an individual judgment based on methodology, clinical significance, and medical decision levels of the test analytes. AUDIT MicroControls, Inc. assumes no responsibility for the reading and interpretation of the above data.

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So, Do I Pass???

What are Acceptable Results?

So What Are Acceptable Results?

The Million Dollar Question (drum roll please.....):

How do I know if my results are "Good Enough"?

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What is Acceptable Calibration Verification?—The Ultimate Question

- *Each laboratory is responsible for establishing acceptable parameters*
- *Some labs use CLIA '88 Proficiency Testing Limits*
- *General Rule of Thumb used by some inspectors and laboratory managers:*
  - ***R Coefficient (Also R^2): 0.98 – 1.00***
    - ***Tells you is data is linear***
  - ***Slope: 0.90 – 1.10 (+/- 10%)***
    - ***Tells you how well you match up to the expected data***

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Goal of Calibration Verification

- ***Confirm that the test system is reporting accurate results throughout the test system's reportable range***

What if Calibration Verification Fails?

How to Address Failed Cal Ver

- *As per CLIA guidelines:*
  - *Repeat calibration procedure*
  - *Good Laboratory Practice to run controls after recalibrating and before reporting patient results*
  - *If the instrument is factory-calibrated, contact instrument manufacturer*

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Additional Troubleshooting

- *Calibration Verification Troubleshooting*

- *Number of variables to be considered*
  - *QC Material*
  - *Reportable Range of Instrument*
  - *Changes in Reagent*
  - *Maintenance Logs*
  - *Environmental Conditions*
  - *Instrument Servicing*
  - *Changes in Operators*
  - *Compare on similar instrument*

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Troubleshooting Checklist

Troubleshooting Checklist for Calibration Verification

Analyte _____ Date _____

Instrument _____ Serial Number _____

1. Check your quality control (QC) results for the analyte	
• Are there any patterns seen in the control results?	
▪ Are all values below the mean?	Yes / No
▪ Are all values above the mean?	Yes / No
• Are there any noticeable shifts or trends over time?	Yes / No
• Are accuracy and precision acceptable?	Yes / No
Comments:	
2. Check your calibration verification material	
• Are the materials used appropriate and in-date?	Yes / No
• Have you properly determined the acceptable limits for the calibration verification material?	Yes / No
Comments:	
3. Check your reagents	
• Have there been any reagent changes?	Yes / No
• Is there a new lot number of reagent?	Yes / No
• Has there been a change in manufacturer?	Yes / No
• Has there been a new formulation (check the package insert) of current reagent?	Yes / No
• Are the reagents in date?	Yes / No
Comments:	
4. Check instrument maintenance	
• Review the daily, weekly, monthly, quarterly, etc. logs. Is there any missing maintenance, problems, or changes?	Yes / No
Comments:	
5. Check the environment	
• Has the instrument been moved recently?	Yes / No
• Have there been any changes to the environment or surroundings of the instrument?	Yes / No
Comments:	
6. Check the service record	
• Has the instrument been serviced recently?	Yes / No
• Has there been any software or hardware upgrades or changes?	Yes / No
Comments:	
7. Check instrument operation	
• Are there new instrument operators?	Yes / No
• Are all operators following established procedures for instrument operation?	Yes / No
• Has there been any recent modification to the technique used to run the test?	Yes / No
Comments:	
8. Check a comparative method	
• Is there another laboratory nearby that can run your calibration verification material so you can compare the results?	Yes / No
Comments:	
9. Will recalibration be performed for the analyte?	Yes / No
Comments:	

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Moving Forward – Current and Future Calibration Verification Topics

Point-of-Care Testing and Calibration Verification

- *If a lab is running nonwaived tests on POCT instruments, Calibration Verification may be required*
  - *Some anlayte panels on the Abbott i-STAT® require Calibration Verification*

Top Reasons for Lab Citations

Excerpt from Advance for Administrators of the Laboratory November 22, 2010:

- ***Fourth most common reason for lab non-compliance citation:***

#4 - “not performing calibration verification according to the manufacturer's instructions including: the number, type and concentration of materials to be used; use of materials at low, medium and high values within the reportable range as determined by the laboratory; acceptable limits for calibration verification, once every 6 months or more often, if required by laboratory procedures;”

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References and Resources

References

- *CLIA Brochure #3: www.cms.hhs.gov/clia*
- *COLA LabGuide, 5/07*
- *"The State Operations Manual," Appendix C-Interpretive Guidelines, Calibration and Calibration Verification Procedures (§ 493.1255)—CMS website at: www.cms.hhs.gov/clia*
- *http://wwwn.cdc.gov/clia/chronol.aspx*
- *http://www.cap.org/apps/docs/laboratory_accreditation/audio_conferences/cvl_webinar_presentation.pdf*
- *www.cygnustechnologies.com/Hook Effect.pdf*
- *http://laboratory-manager.advanceweb.com/Features/Articles/Ten-Most-Frequent-Laboratory-Citations.aspx*

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Resources

- *Article by Kathryn Connolly Quality Management Systems Accreditation Manager for COLA: http://laboratory-manager.advanceweb.com/Editorial/Conte*

- *CLSI (Formerly NCCLS) Document EP6-A – Evaluation of the Linearity of Quantitative Measurment Procedures: A Statistical Approach; Approved Guideline; ISBN 1-56238-498-8; ISSN 0273-3099*

- *dgrhoads website: http://www.dgrhoads.com/*

- *CMS website: http://www.cms.hhs.gov/CLIA/*

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Thank You!!

Thank you for your time and interest in Audit MicroControls. We hope that you find our product offering helpful in meeting your Calibration Verification / Linearity requirements.

Please feel free to contact us by phone at: (866) 252-8348 or via email at: sales@auditmicro.com if you should have any questions.

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AUDIT® MicroControls™, Inc.
222 Technology Parkway
Eatonton, GA 31024

Toll Free: 866.25.AUDIT (28348)
Fax: 706.485.2123
Email: orders@**audit**micro.com

www.**audit**micro.com