

101 年度行政院衛生署食品藥物管理局委託業務計畫
建立藥物非臨床試驗優良操作規範(GLP)之輔導及查核體系

實驗室品質管理系統研討會（一）

講師：房君章博士／石藥集團美國德豐公司
曾嶽元主任／國泰醫院分子醫學科

指導單位：衛生署食品藥物管理局

主辦單位：國立陽明大學、台北榮總生物暨生物實驗安全委員會

協辦單位：台灣生醫品質保證協會

時間：101 年 7 月 2 日

地點：台北榮民總醫院致德樓 1 樓第一會議室

實驗室品質管理系統研討會（一）

101 年 7 月 2 日

時 間	課 程	講 師	服務機構
09:00-09:30	報到		
09:30-11:30	GLP 國際發展趨勢- 法規面探討	房君章博士	石藥集團美國德豐公司 前美國 FDA 官員
11:30-13:00	Lunch		
13:00-15:00	GLP 國際發展趨勢- 實務面探討	房君章博士	石藥集團美國德豐公司 前美國 FDA 官員
15:00-15:15	Tea Break		
15:15-17:15	分子檢驗品質管理實務	曾嶽元主任	國泰醫院分子醫學科
17:15-17:30	綜合討論		

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房君章博士/石藥集團美國德豐公司副總經理

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PROFESSIONAL EXPERIENCE

CSPC Dophen Corporation, New Jersey, USA

October,

2010 – Present

President

- Facilitate China Shijiazhuang Pharmaceuticals Ltd. Co. (CSPC, parent company) IND, NDA, and ANDA applications.
- Manage generic drugs, OTC drugs, APIs, and Dietary Supplement Ingredients sales in USA.
- Support CSPC regulatory compliance activities in China.
- Plan a sales and regulatory office in Europe.

Food and Drug Administration, Alameda and Irvine, CA

2003

– September, 2010

Compliance Officer (February, 2006 – July, 2006)

- Performed compliance works of import dietary supplement at San Pedro in Import Operation of Los Angeles District.

Analyst/Investigator/Foreign Inspection Cadre

- Perform analytical works to check drugs, color additives, pesticides and heavy metals in drugs, food, seafood, and food ware using FAA, FTIR, GC/MSD, GFAAS, HPLC, ICP-MS, UV/Vis. and Dissolution instrument.
- Conduct inspections domestically and internationally of drug firms for API, ANDA (abbreviated new drug application), for verifying CGMP compliance, and recommending regulation actions.
- Participated in “Third Party Audit” program. Visited private and government laboratories in foreign countries. Verified their scientific as well as process capabilities of drug residues testing in shrimp and melamine in food products.
- Research and develop new analytical methods (for example: Diethylene Glycol in Glycerin by GC and Erythromycin Ointment by HPLC/UV) for agency to fulfill with the new technology challenges coming from food and pharmaceutical industries.
- Participate “Bait and Switch” operation, lead a group of chemists to perform drug analysis, and perform check analysis with HPLC method validation process.
- Built a team of chemists to perform analytical works for metal program in San Francisco District Laboratory in 2003. Productivity was increased by 33%.

Chem-Rite Consulting Group, Thousand Oaks, CA

1994

- 2003

Chemical Process Consultant

Provided business and technical project management works involving: business strategy, product development and formulation, process design and improvement, etc. consulting services for more than 20 clients from Taiwan, China, Indonesia, and USA in various industries with diverse groups of engineers, managers, and executives.

For example:

- Biotechnology (designed a process to isolation active anti-cancer ingredient(s) from natural products for Ambryx Biotechnology Inc. in USA)
- Chemicals (modified a furfural production process for P. T. Intan Prima Group in Indonesia)
- Fibers (designed and developed a production process of Ultra High Molecular Weight Polyethylene high strength fiber for Union Chemical Laboratory of Industrial Technology Research Institute in Taiwan)
- Health (developed medical device coating products using biocompatible polymers (Polyvinylpyrrolidone (PVP) based hydrogels for Gelwell International, Inc. in Taiwan)
- Pharmaceutical (identified active pharmaceutical ingredients (API) using GC, HPLC, and NMR etc. from natural products with Ambryx Biotech. in USA)
- Plastics (designed and established polyester and polyether polyols based biocompatible thermoplastic polyurethane (TPU) production facility for Crown luggage Ltd. in China.)

Great Lakes Chemical Corporation, West Lafayette, IN

1989

- 1994

Process Development Engineer

EDUCATION

The Ohio State University, Columbus, Ohio - Ph.D., **Physical Chemistry**, 1989 and
M.S., **Chemical Engineering**, 1985.

University of Houston, Houston, Texas - M.S., **Petroleum Engineering**, 1982.

Tung Hai University, Taichung, Taiwan - B.S., Major: **Chemistry**, 1978.

TRAININGS

Food and Drug Administration trainings:

“Industrial Sterilization for Drugs and Devices” August, 2010

“Mobile Laboratory” March, 2009

“Third Party Audit” March, 2009

“Introduction to Inspections of Pharmaceutical Laboratories for Analysts” January, 2009

“Advance Elemental Analysis”, July, 2008
“Active Pharmaceutical Ingredient Manufacturing”, July, 2008
“Orientation of International Inspection”, May, 2008
“Pre-Approval Inspection”, April, 2008
“Basic Drug School”, August 2007
“Basic Medical Device School”, April 2007
“Infectious Disease Prevention and Food Inspection”, March 2006
“Investigative Interviewing / Situation Planning / Verbal Judo”, April 2005
“Basic Mass Spectrometry Workshop”, March 2005,
“Turbo EIR for Inspection Team Members”, November 2004
“Regulatory Science”, February 2004,
“Analytical Method Validation”, October 2003,
“Basic Food and Drug Law” and **“Evidence Development”**, September 2003,
“Investigation and Interrogation”, July 2003,
“Advanced Chromatography Techniques”, July 2003,

FedEx Ground Package System, Inc.

“Ship Safe, Ship Smart, Hazardous Material Training Program”, October 2006.

Association of Official Analytical Chemist (AOAC) International,

“Collaborative Study Design and Management”, April, 2006.

“Single Laboratory Validation of Analytical Methods for Dietary Supplements”, March, 2004.

Institute of Compliance, Training & Technology Solutions

“Methods Development, Validation Procedures, and Conformity Assessment in the Analytical Laboratory”, October 2003.

John E. Reid and Associates,

“The Reid Technique of Interviewing and Interrogation”, July 2003

American Society of Testing and Materials (ASTM), Philadelphia, PA

“Instrumental Analysis of Polymers” training course, October 1999

PROFESSIONAL MEMBERSHIP

Member of American Chemical Society (ACS)

Member of American Institute of Chemical Engineers (AIChE)

Member of Taiwan Society of Quality Assurance (TSQA)

講師簡歷

一、基本資料				
中文姓名	曾嶽元	性別	男	
聯絡電話	(02) 2690-7965 #2519	傳真	(02) 2691-9800	
電子信箱	jeffbucknell@gmail.com			
聯絡地址	22174 新北市汐止區建成路 160 巷 32 號 3 樓			
二、學歷				
學校名稱	國別	主修學門系所	學位	起迄年月
美國梅爾研究所 (Mayo Graduate School)	美國	實驗病理學	博士	1985 年 8 月至 1989 年 5 月
高雄醫學院	台灣	醫學系	醫學士	1974 年 9 月至 1981 年 6 月
三、現職及相關之經歷				
服務機關	服務部門	職稱	起迄年月	
國泰綜合醫院	病理暨檢驗醫學部	主任	2009 年 迄今	
輔仁大學	醫學系	專任教授	2009 年 迄今	
社團法人台灣分子醫學會		理事長	2006 年 迄今	
內政部警政署	刑事警察局	諮詢委員	2007 年 迄今	
行政院衛生署食品藥物管理局	醫療器材諮詢委員會	委員	2010 年 1 月至 2010 年 12 月	
行政院衛生署食品藥物管理局	醫療器材諮議會	副召集人	2011 年 1 月 迄今	
行政院衛生署食品藥物管理局	醫療器材安全評估諮議小組	副召集人	2011 年 7 月 迄今	
財團法人保險犯罪防制中心		諮詢委員	2011 年 迄今	
馬偕醫院	病理科	主任	2001 年-2009 年	
四、專長				
分子醫學、病理學				

GLP國際發展趨勢
GOOD CLINICAL LABORATORY PRACTICES
STANDARDS

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GLP Revision Status

- 2007 – GLP Working Group Charged to Re-Evaluate GLP Regulations
- GLP Working Group Participants
 - FDA: CSFAN, CBER, CDER, CVM, CDRH, and CTP
 - FDA: OCC, NCTR, ORA, and OGCP
 - EPA
 - USDA – Animal Plant Health Inspection Service
 - NIH

GLP Revision Status

- Advance Notice of Proposed Rulemaking (ANPRM) was suggested instead to solicit comments and ideas from stakeholders
- ANPRM published in December 2010
- Comment period closed in February 2011
- Received 89 comments (77 from public and 12 from private individuals)

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ANPRM Points

- GLP Quality Systems
- Multisite Studies
- Electronic/Computerized Systems
- Sponsor Responsibilities
- Animal Welfare
- Information about QAU inspection findings
- Process-based System Inspections
- Test and Control Articles Information
- Sample Storage Container Retention

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Good Clinical Laboratory Practices

- BARQA (2003)
- WHO (2006)
 - <http://www.who.int/tdr/publications/tdr-research-publications/gclp-web/en/index.html>
- NIH (2011)
 - <http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf>

WHO - GCLP

- Only 28 pages
- More listed like regulation
- The major difference from NIH GCLP is “SUB-CONTRACTING”.

NIH - GCLP background

- July 25, 2011
- Final version 2.0
- Minimal requirements that clinical research laboratories should follow.
- Embraces both the research/pre-clinical and clinical aspects of GLP
 - 21 CFR part 58 (GLP)
 - 42 CFR part 493 (Clinical Laboratory Improvement Amendments [CLIA])

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GCLP to ensure

- The 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

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GCLP contents

- Organization and Personnel
- Equipment
- Testing Facility Operation
- Test and Control
- Verification of Performance Specifications
- Records and Reports
- Physical Facilities
- Specimen Transport and Management
- Personnel Safety
- Laboratory Information Systems
- Quality Management

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Study (Analytical) Plan

- Written and Approved by the laboratory director (or designee).
- A valuable source of information for
 - Trial sponsor
 - Laboratory director
 - Laboratory personnel
 - Specimen management coordinator
 - The Statistical Center
 - Quality Assurance Unit

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Study (Analytical) Plan

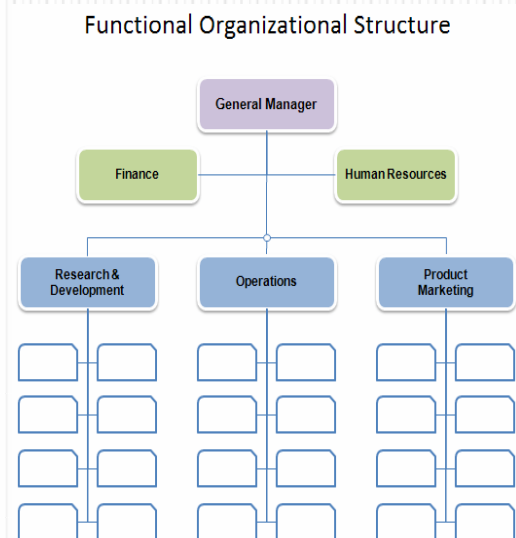
- Must include detailed information on (see Appendix 1)
 - Title of the study
 - Purpose
 - Authority and Responsibility
 - Key contacts
 - Introduction and Background
 - Instructions for specimen collection
 - Chain of custody and shipping instructions
 - Instrumentation and analytical methods to be used
 - Reference ranges
 - Referral laboratory information
 - Transmission of results

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Organization and Personnel

- Documentation
 - Personnel policies
 - Organization and/or Department policies
 - Job descriptions
 - Personnel files
 - Organization chart(s)
- Staff education and evaluations
- Staff numbers
- Staff identification (see Appendix 3)



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Organization and Personnel

- Personnel Files
 - Orientation and Training
 - Experience
 - Education
 - Applicable licensure/certification (if required)
 - Competency assessments
 - Continuing education records
 - Curriculum Vitae
 - Safety training
 - Attendance at job-related workshops and seminars (see Appendix 2)

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Organization and Personnel

- Job-specific Training, Education, and Assessments
 - Competency assessments must be conducted and recorded ... upon completion of initial training.
 - Competency must be assessed every six months during the first year of employment, annually thereafter, and/or as laboratory management deems necessary.
 - Competency assessment must compare employee performance against a documented standard and clearly verify competency.
 - Example of training:
 - Blood-borne pathogens
 - Shipping of dangerous goods based on International Air Transportation Association (IATA) regulations
 - Laboratory safety

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Equipment

- SOPs and Maintenance Logs must exist
- To demonstrate and provide evidence of
 - Qualified, Validated, Inspected, Cleaned, Maintained, Tested, and standardized to ensure optimal quality of assay results
- Preventive Maintenance and Calibrations must be scheduled and performed at least as frequently as suggested by the equipment manufacturers
- There must be evidence that equipment performance, use, and maintenance are consistently and routinely documented and **reviewed by the laboratory director or designee**

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Equipment

- Documentation Guidelines
 - Must keep documentation of all scheduled preventive maintenance, unscheduled maintenance, service records, and calibrations for all equipment
 - A supervisory staff member must review, sign, and date all documentation of equipment maintenance at least monthly
 - All laboratory equipment should be listed on an inventory document
- General Guidelines
 - Must employ and adhere to documented daily, weekly, and/or monthly routine maintenance plans for all equipment utilized

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Equipment

- Service Guidelines
 - Adjustable and fixed-volume automatic pipettors
 - At least once every six months
 - Strongly recommend that laboratory performs checks for accuracy and reproducibility and recalibrations four times per year, with at least two of the four performed by an external contracted service provider
 - Thermometers
 - Against NIST-certified (or equivalent) thermometric device annually

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Equipment

- Refrigerators and freezers
 - Establish tolerance limits for temperatures and/or liquid nitrogen level
 - Maintain daily (at a minimum) record of temperatures
 - Maintain appropriate documentation of corrective action for out-of-range temperatures
- Incubators and water baths
 - Establish tolerance limits for temperatures, carbon dioxide level, and humidity
 - Maintain daily (or “date of use”) record of temperatures
 - Maintain appropriate documentation of corrective action for out-of-range temperatures

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Equipment

- Centrifuges

- Measure operating speeds periodically (annually at a minimum, recommend every six months) with tachometer
- Maintain daily (or “date of use”) record of temperature for refrigerated centrifuges
- Verify performance of centrifuge timers

- Autoclaves

- Verify content processing using heat-sensitive tape with each autoclave batch
- Verify effective sterilization with an appropriate biological indicator weekly
- Perform autoclave maintenance (temperature and pressure) annually



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Equipment

- Analytical balances

- Place the analytical balance so that vibration does not affect the readings

- Biosafety cabinets / laminar air flow hoods

- Verify air intake grills are not obstructed
- Certify cabinets/hoods annually by a trained service technician
- Check daily for air flow and document the results to verify the effectiveness of the hood's personnel and environmental protective functions
- Clean the work surfaces after each use with 70% ethanol
- Clean the UV lamp weekly with 70% ethanol
- Document daily and weekly cleaning

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Testing Facility Operation

- SOP Format
 - See example of SOP in Clinical and Laboratory Standards Institute (CLSI) format in Appendix 4
- SOP Distribution
 - Must document that lab personnel have reviewed and understood all new and revised SOPs
- Document Control Plan
 - Maintain a master list of SOPs
 - Review SOPs annually and document the review
 - Remove retired or obsolete SOPs from circulation and identify them
 - Archive retired or obsolete SOPs for a period of time

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Testing Facility Operation

- SOP Categories
 - Documentation Control
 - Organization and Personnel
 - Personnel Training
 - Equipment Calibration and Maintenance
 - Specimen Management and Chain-of-Custody
 - Test Procedures
 - QC
 - QA
 - Test Reporting and Records Management
 - Safety
 - Laboratory Communications
 - Operations and Laboratory Information System (LIS)

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Test and Control

- Standards for Test and Quality Control
 - Quality Control Program
 - Must have a site-specific, written QC plan which clearly defines procedures for monitoring analytical performance
 - Laboratory Director should be actively involved in the design, implementation, and oversight of the QC program
 - Evaluation Criteria
 - The laboratory must establish and document the tolerance limits for acceptance of control results
 - The laboratory should establish local means and QC ranges based on historical method CVs

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Test and Control

- Frequency of Quality Control Testing and Types of Control Materials
 - The laboratory director and/or designee must determine the appropriate number and frequency of QC tests
 - For quantitative tests, use control materials at more than one level
 - For qualitative tests, include positive and negative controls with each run
 - For staining procedures, gram stains require both Gram positive and Gram negative control organisms to be used once per week and with each change of a lot number of any component in the stain procedure

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Test and Control

- Frequency of Quality Control Testing and Types of Control Materials
 - Recommend the external QC be conducted weekly during the patient samples are tested
 - Recommend the daily QC be run for testing used for primary endpoint of non-FDA approved tests.
 - QC should be done in seven listed situations. E.g.: If there are changes to device reagents, study populations and/or analytes; new operator(s) performing testing on patient specimens; with each new kit lot; whenever a new shipment of test kits is received; the temperature of the test kit storage area falls outside manufacturer's recommended range; the temperature of the testing area falls outside the recommended range; and at periodic intervals as specified in laboratory's QA program.

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Test and Control

- Review of Quality Control Data
 - QC must be run and reviewed prior to reporting results and after a change of analytical critical reagents, major preventive maintenance/service, or change of a critical instrument component
 - If the QC data falls outside the tolerance limits, corrective action must be taken and be documented with initial and date
 - If the QC data is determined to be unacceptable, the laboratory must re-evaluate all study-participant test results since the last acceptable test run

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Test and Control

- Quality Control Logs
 - Control records must be readily available to the staff performing the test
 - Results of controls must be recorded or plotted ...
 - Appropriate charts must be utilized by personnel to document quantitative QC data to allow... and to aid in detection of shifts and trends in the control data
 - QC records should contain detailed information
 - See Appendix 5 for Levy Jennings chart example
- Corrective Action Logs
 - Must ensure a corrective action log is present to facilitate documentation and resolution of QC failures

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Test and Control

- Supervisor Review of Quality Control Documentation
 - Laboratory manager or designee must review, sign, and date the corrective action log at least monthly
 - Laboratory director or designee must review, sign, and date QC data at least monthly
- Quality Control Record Retention
 - Instrument printouts, all QC records including worksheets, package inserts, and CoA must be retained by the laboratory in a secured fire-proof (preferred), fire-resistant, or fire-protected (least preferred) storage area/facility for a period of time that has been defined by the laboratory

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Test and Control

- Labeling and Storage of Quality Control

Materials and Reagents

- All QC materials and reagents currently in use must be prepared and stored as required by the manufacturers
- If ambient storage temperature is indicated, there must be documentation that the defined ambient temperature is maintained and corrective action taken when tolerance limits are exceeded
- Date opened, prepared, or reconstituted by the laboratory
- Initial(s) of personnel who prepared/reconstituted the QC material and reagents
- Expiration date

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Test and Control

- Inventory Control

- Parallel Testing

- For each new lot of reagents, the laboratory must document that samples (study-participant specimens are preferred) are tested in parallel with each current lot and the comparable results are obtained before or concurrently with being placed in service
- For quantitative tests, it should be performed by assaying the same study-participant specimens or reference materials with both the old and new lot numbers to assess comparability
- For qualitative tests, minimum parallel testing must include re-testing at least one known positive(abnormal) and one negative (normal) study-participant sample

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Test and Control



- Water Quality Testing

- Laboratory water is classified as Type 1, 2, or 3 (defined by NCCLS guideline C3-CA) and each type has different specifications for maximum microbial content, resistivity, maximum silicate contents, and particulate matter
- Laboratory must ensure that records of water quality testing are complete and/or indicate that the required standards are consistently met
- Laboratory must document evidence of corrective action taken when water testing does not meet defined tolerance limits

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Verification of Performance Specifications

- All validation experiments should occur prior to testing study-participant specimens; documentation of experiment results and approval should be readily accessible.
- Methods that are defined as waived by CLIA do not require method validation.

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Verification of Performance Specifications

Performance Specifications	Unmodified FDA-Approved	Modified FDA-Approved
Reportable Range	√	√
Linearity	√	
Precision	√	√
Accuracy	√	√
Analytical Sensitivity		√
Analytical Specificity		√
Reference Interval	√	√

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Verification of Performance Specifications

- Reportable range
 - A useful analytical range of a laboratory method
 - Verification and documentation of normal responses for each test system, including reportable range and normal range(s), must be established to determine the usable and reliable range of results produced by that system
 - Verification and documentation of both the Analytical Measurement Range (**AMR**) and the Clinically Reportable Range (**CRR**) must be performed when establishing the reportable range
 - See Appendix 7 for an example of how to determine the reportable range

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Verification of Performance Specifications

- AMR: Verifies the lowest and highest test results that may be reliably reported by an assay without additional steps beyond the routine procedure, such as dilutions or concentrations
 - Matrix of purchased materials for AMR should not interfere or otherwise bias results of the method
 - The validation materials must have analyte values which span the range of the AMR
 - Each laboratory must defined limits for accepting or rejecting validation tests of the AMR

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Verification of Performance Specifications

- CRR: Takes into consideration the need for dilutions or changes in concentrations
 - The CRR must be determined during initial verification of a method and not revised/updated until the method changes
 - Values lower than the CRR must be reported as “less than” the limit
 - The upper limit of the CRR will usually not be indicated
 - The lower limit of the CRR will often be represented by the lower limit of the AMR

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Verification of Performance Specifications

- Analytical sensitivity (lower detection limit): estimate of the lowest concentration of an analyte that can be measured
 - Analytical sensitivity of each assay must be verified or
 - For FDA-cleared/approved tests, one can use data from manufacturers or the published literature
 - For non-FDA approved methods, the laboratory must establish and document analytical sensitivity
 - See Appendix 8 for an example of how to determine analytical sensitivity

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Verification of Performance Specifications

- Precision: measurement of the scatter or random error between repeated measurements
 - Must verify the precision of each test by assessing day-to-day, run-to-run, and within-run variation. Can be accomplished by the one or a combination of the followings:
 - Repeat testing of known study-participant samples over a period of time
 - Test QC material in duplicate and over time
 - Repeat testing of calibration materials over time

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Verification of Performance Specifications

- Precision validation for qualitative tests:
 - Validation of a test's precision should be performed if the manufacturer's package insert mentions precision testing AND if value will be gained with such testing
 - See Appendix 9 for an example of precision experiment

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Verification of Performance Specifications

- Analytical Specificity (Analytical Interferences): To estimate the systematic error caused by non-analyte materials that may be present in the specimen being analyzed
 - For FDA-cleared/approved tests, one can use data from manufacturers or the published literature
 - For non-FDA approved methods, the laboratory must establish and document interfering substances
 - See Appendix 10 for an example of how to determine analytical specificity

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Verification of Performance Specifications

- Accuracy: Measure of how close a measured value is to the true value
 - Use reference materials with known concentrations or activities
 - Compare results of tests performed by the laboratory against the results of a reference method
 - Compare split-sample results with the results obtained from a method which is shown to provide clinically valid results
 - See Appendix 11 for an example of accuracy experiment results

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Verification of Performance Specifications

- Reference (Normal) Ranges: specified interval bound by two limiting values that contains 95% of the values found in healthy individuals
 - The reference range must be established or verified for each analyte and specimen source/type
 - Use the manufacturer's reference range when appropriate specimens are difficult to obtain provided the range is appropriate for the study-participant population
 - If the appropriate specimens are difficult to obtain and the manufacturer has not provided reference ranges appropriate for the laboratory's study-participant population, the laboratory may use published reference range(s)

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Verification of Performance Specifications

- 20 fresh, “normal”, and representative of the population (age, gender, etc.) specimens is the minimum number to verify the claimed reference range
- Typically, 120 specimens per demographic group is the minimum number to establish reference ranges
- Reference intervals must be evaluated at the following times:
 - Upon introduction of a new analyte to the test offerings by a lab
 - With a change of analytic methodology
 - With a change in study-participant population
- See Appendix 12 for an example of how to determine reference values

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Recent 483s in GLP areas

- Data Integrity and Reliability
- Focus on scientific adequacy of validation and stability experiments
- SOPs were not followed
- No Written Procedures
- Lack of Documentation

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Recent 483s in GLP areas

- Failure to evaluate for matrix effects
- Failure to evaluate dilution linearity
- Method used for sample analysis was not the method validated
- Failure to use freshly prepared calibration standards
- Failure to establish written procedure for the following: “assessment of instrumental carryover during chromatographic analysis of study samples...”

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Records and Reports

- The following are records and reports:
 - Specimen tracking form/laboratory requisitions
 - Chain of custody documents
 - Laboratory reports
 - QC data (proficiency testing, QC, and CAPA)
 - Equipment service and maintenance logs (repair, temperature monitoring, and validation.)
 - Analyte results with reference intervals
 - Raw data source documentation (21CFR §58.3(k))
 - Other operational documentation (SOPs, safety policies, safety incident reports, specimen management, protocols/manuals, Laboratory Information System, and specimen storage documentation.)



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Records and Reports

- Record retention
 - 21 CFR §58.33(f)
 - 21 CFR §58.190
 - 21 CFR §58.195
 - ... at least two years...
 - ... at least five years...
 - ... at least two years...

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Records and Reports

- Data integrity
 - Adequate manual or electronic systems must be in place to ensure assay results and other data are accurately and reliably sent from the point of data entry to the final report destination in an accurate and timely manner
- Report format
 - Eleven items (e.g. the date and time of specimen receipt into the lab, the assay report date, and the name of the test performed, etc.) are required to be included in the report

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07/02/2012

Records and Reports

- Pertinent reference ranges
 - Determined by the laboratory performing tests, must be available to the authorized person who ordered the tests
- Laboratory assays and performance specifications
 - This list may also contain expected time-to-result (turnaround time) for each assay.
 - See Appendix 13 for an example of Laboratory Test Method List

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07/02/2012

Records and Reports

- Assay results
 - Information that may affect the interpretation of assay results must be provided upon request
 - Assay results must be released only to authorized persons
 - Laboratories should maintain a list of locations to which results are reported
 - All test reports and records must be maintained by the laboratory in a manner that permits ready identification and timely accessibility

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07/02/2012

Records and Reports

- Assay results
 - Alter and critical values
 - Laboratory Director must define alert or critical values
 - Complete procedures must be in place for immediate notification of key study personnel/responsible clinic staff when assay results fall within established alert or critical ranges
 - Communication logs (date and time of notification, responsible lab individual performing notification, name and credentials of person notified at the clinic and test results given, and any problem encountered in accomplishing this task) must be maintained

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07/02/2012

Records and Reports

- Results modification log and errors in test results
 - A log must be kept for result modifications
 - New reports must clearly indicate the changes from a previously reported
 - Must have a system to know who, when, and what of modification has been done. Supervisor (Lab Director) or designee must review, sign, and date (review) the Result Modifications/Corrective Action Logs at least monthly.

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07/02/2012

Records and Reports

- When errors are detected, do the following:
 - Must promptly notify the appropriate clinician and/or clinic staff member
 - Must issue corrected reports promptly to the authorized person ordering the test and, if applicable, the individual using the test results
 - Must maintain copies of the original reports as well as the corrected report

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07/02/2012

Records and Reports

- Archiving reports or records
 - Must remain readily available (within 24 hours)
 - Maybe either on- or off-site
 - Access to archived records must be limited to authorized personnel
 - Use proper error correction techniques, e.g. single line through error, signature, and date
 - Protect from damage (causing by fire, water, wind, humidity, etc.) of sole copies of research (defined as documents not having any back-up copy)

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07/02/2012

Physical Facilities

- General Space
 - Must have sufficient space
 - Walkways must be unobstructed
- Temperature and Humidity Controls
 - Laboratory room (ambient) temperature and humidity must be **controlled**
- Cleanliness of Facilities
 - All floors, walls, ceilings, and bench tops of the laboratory must be clean and well maintained



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Physical Facilities

- Archiving and Storage Spaces
 - Space must be allocated to the archiving of data in a secured fire-proof (preferred), fire-resistant, or fire-protected (least preferred) environment which is accessible only to authorized personnel.
 - Laboratory storage areas must be allocated to adequately preserve the identity, purity, and stability of laboratory reagents, control materials, calibrators, and other laboratory materials.

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07/02/2012

Physical Facilities

- Molecular Amplification Work Areas
 - Molecular amplification procedures within the laboratory that are not contained in closed systems must have a uni-directional workflow.
 - This must include separate areas for specimen preparation, amplification, detection, and as applicable, reagent preparation.

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07/02/2012

Specimen Transport & Management

- Standards Operating Procedure
 - Specimen collection,
 - Tracking,
 - Labeling,
 - Preservation,
 - Conditions for transportation, and
 - Storage.

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07/02/2012

Specimen Transport & Management

- Specimen Labeling
 - All specimen containers must be properly identified with the unique participant identifiers
- Laboratory Testing Request Form (Requisition)
 - A properly completed request form/log sheet must accompany each study-participant sample to the laboratory
 - Must document unique study-participant identifiers, collection date and time, demographics, specimen type, and collector's identity
 - Any discrepant or missing information must be verified promptly, before specimens are processed or stored by laboratory personnel

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07/02/2012

Specimen Transport & Management

- Specimen Acceptance/Rejection Criteria
 - Must have in place documented instructions for receipt and inspection of samples (including rejection criteria) and demonstrate evidence of adherence in order to ensure positive identification, adequacy, and integrity
 - Inspection process must involve verification of container label information with the request form or log sheet
 - Must also checking for the volume and quality of the samples

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Specimen Transport & Management

- Audit Trails
 - Must maintain a complete audit trail for every specimen from collection to disposal or storage
 - Must verify the date and time an activity was performed and the personnel responsible for the activity

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Specimen Transport & Management

- Chain-of-Custody
 - Collection site, date, and time of collection and shipping
 - Name, date, and signature of collector
 - Name, date, time, and signature of driver
 - Type of sample
 - Types of testing requested
 - Project, site, and collection site names
 - Identity of the receiver and inspector of the specimens
 - Date and time of sample receipt
 - Laboratory sample receiver name and signature
 - Observed sample condition and documentation of other factors
 - Sample and/or cooler temperature at time of receipt
 - Transporter name and signature

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Specimen Transport & Management

- Specimen Transportation and Shipment
 - Transportation of samples must be monitored
 - Shipping procedure (of proper organization, labeling, packaging, shipping, and handling of specimens for integrity, safety, and timely) must be documented
 - Personnel who ship specimens must be trained and certified in hazardous materials/dangerous goods transportation safety regulations
 - Regulation training must be renewed every two years
 - Certification of regulation training must be on file and ready available

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07/02/2012

Specimen Transport & Management

- Specimen Preparation, Analysis and Retention
 - Documented procedures for preparation and analysis must be available and address:
 - Any specimens which must be retained for potential reanalysis; and/or
 - The length of time the specimens must be retained, appropriate for the type of specimen and test
 - 24 hours monitoring of storage conditions and SOPs for response to alerts
 - A documented disaster recovery procedure must be available to ensure the continued integrity of specimens.

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07/02/2012

Personnel Safety



- Safety Equipment
 - Plumbed eye wash must be flushed weekly
 - Portable eye wash must be inspected monthly and replace prior to expiration date. Must be cleaned and refilled weekly
 - Emergency shower must be flushed weekly
 - Fire extinguishers must be inspected monthly
 - Sharps containers must be inspected daily and replaced when three-fourths full
 - Document those activities

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07/02/2012

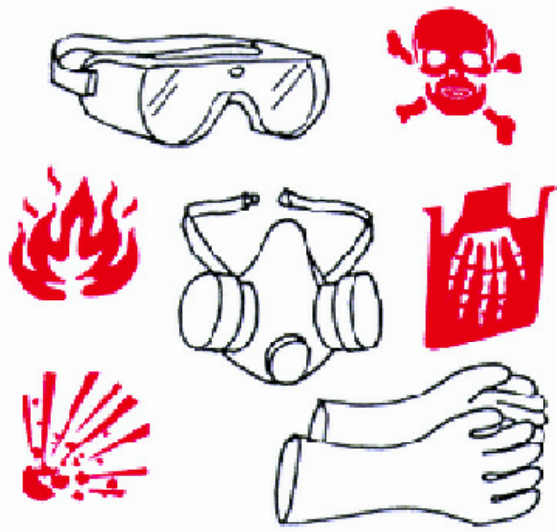
Personnel Safety

- Personal Protective Equipment
 - Gloves (both latex and non-latex)
 - Gowns or laboratory coats (fluid resistant)
 - Eye protection (goggles, face shield, laminar flow hoods)
 - Masks
- Material Safety Data Sheets
 - Must maintain each MSDS in the local language
 - Personnel must be trained on reading the MSDS
 - Can be maintained electronically as long as no barriers for immediate access

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Personnel Safety



- Safety Policies
 - Standard Precautions/Universal Precautions Policy
 - Chemical Hygiene/Hazard Communication Plan
 - Waste Management Policy
 - General Safety Policies
 - Safety Equipment

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07/02/2012

Personnel Safety



- Safety Training
 - Everyone needs to be trained
 - Documentation of completion of training
- Safety Incident Reporting
 - Safety-related incidents (such as injuries, chemical exposure, malfunctioning equipment) must be documented and submitted to the laboratory manager or designee
 - Safety reports must be incorporated into the Quality Management program

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Laboratory Information Systems

- Laboratory Information System (LIS) Validation
 - Must maintain documented validation data for the LIS
 - Document the installation of new computer programs
 - Document testing of all possible anticipated permutations of processes
 - Document testing and validation of all calculations
 - Document the validation of all data transmitted from LIS to other computer systems and their output devices
 - Document the verification of reference ranges, comments, and actual testing results
 - Document a validated emergency preparedness system

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Laboratory Information Systems

- Audit Trails
 - Computer time-stamped audit trails must be used by the LIS
 - Ensure every individual test performed is entered into the LIS system
 - If auto-verification is used, the audit trail must reflect that the result was verified automatically at a given time and date

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Laboratory Information Systems

- Access and Security
 - LIS access is limited to authorized individuals
 - Training records
 - LIS policies must define who may only access study-participant data and users who are authorized to enter results and/or modify results
 - Laboratory must establish user codes for authorized individuals to access data or alter programs
- Documentation
- Technical Support and Preparedness

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Quality Management

- Quality Management Plan (Quality Assurance Plan)
 - Developed and maintained by an individual or a group of individuals that is (are) separate and distinct from the testing personnel of the laboratory
 - Detail an operational plan that describes the goals and objectives of the QM program
 - Be accessible to all staff
 - Be designed to monitor, assess, and (when indicated) correct problems in all systems

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Quality Management

- Address monitoring to include complaints and incidents
- Include all aspects of the laboratory's scope of care
- Address any problem that could potentially interfere with study-participant care or safety while addressing risk assessment
- Include information on how the quality and safety information is to be collected and communicated
- Include control activities (e.g. QC and EQA)
- Include any measurable key indicators of quality that are related to the lab operations that are explicitly targeted for improvement

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Quality Management

- Include results of ongoing measurement activities of these key indicators compared with internal or external benchmarks and trended over time
- Must use this QM for guidance when conducting annual appraisals of effectiveness.
- QM program documentation must demonstrate regular review by the laboratory director or designee(s)
- Must provide evidence (minutes of committee meetings, results of ongoing measurements, and documentation-related complaint investigation) of implementation of the QM plan

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Quality Management

- Internal Audits
 - All findings (of both compliance and noncompliance, or deficiencies) resulting from the internal audit should be documented in an organized format to allow for appropriate corrective actions and follow-up through resolutions
- Testing Turnaround Times
 - Must have a list of assay turnaround times readily available to all laboratory staff as well as to customers of the laboratory

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Quality Management



- Laboratory Communication Plan
 - Must have a non-retaliatory policy for employees to communicate concerns regarding testing quality or laboratory safety to laboratory management.

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Quality Management

- External Quality Assurance (EQA)
 - Laboratory should enroll in EQA programs that cover all study protocol analytes
 - EQA specimen testing should be rotated among staff members
 - Laboratory director (or equivalent) or designee must review all external quality assurance data
 - Regular supervisory review of EQA program results must be evidenced by Signature and date of review of all results, and documentation of corrective action and appropriate preventive action taken.





分子檢驗品質管理實務

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品質管理

- 全面品質管制 (total quality control; TQC)
- 全面品質領導 (total quality leadership; TQL)
- 持續品質改善 (continuous quality improvement; CQI)
- 品質管理科學 (quality management science; QMS)
- 工業品質管理 (industrial quality management; IQM)
- 全公司品質管制 (company-wide quality control; CWQC)

品質管制 (Quality Control)

- 品管 (QC)原先指的是以檢視(inspection)方法淘汰不良品(outlier),使得出廠之產品能達到一定的品質水準。
 - 這是根據「壞蘋果理論(the theory of bad apples)」所建立的工具。
 - 這種手段固然能減少顧客買到爛蘋果的機會,但會增加成本。

品質保證(Quality Assurance)

- 避免或減少錯誤最好的方法就是,從一開始每個步驟都是由優秀的工作人員根據已通過驗證的方法,在最佳的情況下,使用最好的技術做檢驗。
- 檢驗品質在這種情況下可獲得充分的保證。

品質管制 (Quality Control)

- 就醫學檢驗而言,因技術人員發現檢驗品質不良而重覆檢驗,一樣會增加成本
- 因臨床醫師對檢驗報告質疑而重覆申請檢驗,更是一種浪費。

品質管制(Quality Control)

- QC強調及定義檢驗的過程面。每一步驟都必須分別描述、建立、監督,才足以讓每次的操作達到一致,因而結果有再現性。

臨床實驗室品管

- QC就是運用統計和非統計的方法(如標準品的核對、溫度的監控等),來監控日常檢驗的精確度與準確度,以達到既定的品質水準。
- QC監控性能參數的技術或流程。它常常是一種量化的技巧,而能指出錯誤的來源及錯誤的程度。

Quality Control

- QC只能偵測出「目前的操作(present operation)」與原先所建而欲達到之「穩定的操作 (stable operation)」有何不同。
- 只能偵測出「隨機錯誤(random error)」和基準(baseline)中未有的「系統錯誤(systemic error)」。

臨床實驗室品管

- CAP: 結合流程及技術以用來偵測、減少、及矯正分析過程中的缺陷

Quality Assurance

- 承諾
- 設備與資源
- 技術能力
- 技術流程
- 解決問題的機制

承諾

- 團隊必須把有品質的服務列為中心目標, 否則無法達到品質的目標。
- 每一個管理階層都應把品質視為主要考量, 因為每一個決策都有可能危害到品質。

設備與資源

- 實驗室必須得到足夠的行政資源以達到設定的品質水準。
- 亦即要有足夠的空間、儀器、耗材、備料、人員、指導、經費。

技術能力

- 高水準的人員才能提供高品質的服務。
 - 人員的教育背景和經驗以及在職訓練都非常重要。
 - 在職訓練更是落實品管所必要的。
- 所有的人員中扮演最重要角色的就是第一線的工作人員;至於位於上階的經理人,他們所扮演的是支持性的角色,以及授權給第一線的工作人員去發掘問題。

技術流程

- 約85%左右的品質問題出自於流程錯誤(另外15%的品質問題來自人員素質)。所以優良的技術流程是品質保證中最重要的一環。
- 雖然近年來CLIA愈來愈強調分析前和分析後階段的重要性,但最困難的部分還是在分析階段。

解決問題的機制

- 此為對應於已發生之錯誤的一種回饋路徑,可使危害變小或避免再度發生。
- 實驗室必須養成除錯的能力,邀請QC專家指導及在職訓練,是啟動此機制所必要的。有時還需要成立品質改善小組來執行全面品質管理。

QA:在人員方面

- 在職教育必須是持續性的,以確保技術及知識都能保持在最先進的狀態。
 - RCPA認為實驗室每年至少要有150例的經驗,判讀的醫師每年要有50例的經驗。
 - 人員的能力必須定期重新評估,通常為每年一次。
- 病理醫師應與外科醫師充分溝通以便檢體傳送能符合HER2檢驗的規程。

QA: 在硬體方面

- 持續的儀器校正與維護
 - 需要校對的儀器包括吸注器、保溫箱、水浴箱、溫度計及計時器
- 實驗室的環境條件良好
 - 溫度及溼度的變化都有可能影響檢驗結果

QA: 在流程方面

- 持續的定期評估、分析缺點、以及建立矯正措施。
 - 監控陽性及陰性率並與文獻所記載的數據相比。
- 驗證任何修改過的檢驗方法,並依據此新的規程操作。

品質管制 (Quality Control)

- 如果「系統錯誤」在實驗室開始建立基準時就已存在,那麼QC很可能無法偵測此錯誤。
- 如果此「基準中未有的系統錯誤」非常輕微,以致例行之QC不會發覺,那麼錯誤就可能慢慢地累積,而大到讓實驗室出現有害的檢驗,但卻躲過QC的偵測。

內部品質評量

- 「內部品質評量」是長期的工作,可用來判斷實驗室的整體表現,例如陽性率、陰性率、再檢率,這些數據和別的實驗室比起來是否過高。
- 每年重驗5%的陽性及陰性案例
 - 不管是陽性或是陰性樣本,檢驗正確率要達到95%才可驗收。

外部品質評量

- 如果「系統錯誤」在實驗室開始建立基準時就已存在,那麼QC很有可能無法偵測此錯誤。如果此「基準中未有的系統錯誤」非常輕微,以致例行之QC不會發覺,那麼錯誤就可能慢慢地累積,而大到讓實驗室出現有害的檢驗,但卻躲過QC的偵測。
- 因此,實驗室若能和別的實驗室作比對,會是一個很好的反省機制。這個機制就是所謂的「外部品質評量」。

外部品質評量

- 「外部品質評量」就是外部監控,亦即和其他實驗室作比對。這可用來確定實驗室內部的程序與外面其他實驗室的標準程序一致。

外部品質評量

- Sources of proficiency testing material must be selected.
- The laboratory subscribed to the commercially available proficiency challenges from the CAP.

外部品質評量

- 外部品質評量固然相當有用,但只考慮到分析層面 (analytic phase)而已。由於檢驗錯誤可發生在分析前(preanalytic)、分析中(analytic)、分析後(postanalytic)各層面,而分析層面發生錯誤的比率卻是最低的。
- 分析層面發生的錯誤佔全部檢驗錯誤的 7.3-13.3%。

Example

- **Testing and documentation of new lots and shipments of test kits are established according to standard laboratory practices.**

Example

- **Controls are selected to provide a realistic assessment of all steps of the assay.**

Example

- **Protocols to minimize the risk of contamination include cleaning of all countertop surfaces with 10% bleach followed by 70% ethanol, soaking racks in 10% bleach followed by wiping with 70% ethanol, and wiping of pipettes with 10% bleach and 70% ethanol before and after each run.**

Example

- **Sampling is performed from instrument surfaces, countertops, and racks used in the specimen preparation area and frequently touched surfaces, such as handles and keyboards.**

LDT vs. IVD

- **The FDA is responsible for the oversight of IVD in the US, but the number of laboratories or manufactures that have acquired FDA approval for molecular tests is rather limited when one considers the wide range of molecular test that are presently offered clinically.**

LDT vs. IVD

- **Because of the cost and time commitments involved in gaining FDA approval, those tests are generally limited to high-volume test.**
- **FDA approval is not required for clinical implementation of molecular tests as long as other regulations are met.**

LDT

- To date, the **FDA** has generally chosen not to enforce the rule as it applies to LDTs (sometimes referred to as “home brew tests”), at least in part because the FDA is already regulating the primary ingredients of most LDTs (the ASRs), and also because “**CLIA** regulated laboratories qualified to perform high complexity testing have demonstrated expertise and ability to use ASRs in test procedures and analyses.”

Regulation of clinical laboratory tests in the US

- Federal regulation of clinical laboratory tests began in 1976 with the Medical Device Amendment to the Food, Drug, and Cosmetic Act. This amendment covered all reagents, test, and equipment manufactured for the diagnosis or treatment of disease.

CLIA

- **In 1988, Congress passed the Clinical laboratory Improvement amendment (CLIA), which was enacted in 1992 to establish quality standards for all aspects of clinical laboratory testing.**
- **The CLIA is overseen by the Centers for Medicare & Medicaid Services (CMS), which publishes regulations and assumes primary responsibility for financial management operations of the CLIA program.**

FDA

- **The FDA has primary responsibility for categorizing the complexity of laboratory tests into 1 of 3 CLIA regulatory categories.**
- **The Centers for Disease Control serves an advisory role and provides scientific support.**

FDA

- **The Code of Federal Regulations (CFR) is a compilation of the general and permanent rules published in the Federal Register by the executive departments and agencies of the US federal government. Title 21 of the CFR is reserved for rules of the FDA.**

ASR

- **In 1997, the FDA published 3 rules that were intended to ensure the quality of and control the risks associated with reagents used in LDTs. These rules (21 CFR 864.4020) defined and classified analyte-specific reagents (ASRs), which the FDA defines as “antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.” The rules imposed restrictions on the sale, distribution, and use of ASRs (21 CFR 809.30) and established requirements for ASR labeling (21 CFR 809.10(e)). These rules, collectively known as the “ASR Rule,” hold that “clinical laboratories that develop tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction.”²**

LDT

- The steps involved in test validation are meant to answer one main question—is a given test ready to be implemented in the clinical laboratory? In order to answer this question, the clinical utility (ie, usefulness) of the test must be established, along with its analytic performance characteristics and limitations.

分子檢驗品質管理實務

- CLIA requires that **laboratories** performing LDTs, and modified FDA-cleared/approved tests, “establish’ the same 4 performance characteristics that are required for FDA-cleared/approved tests, as well as determine analytic sensitivity, analytic specificity, and any additional performance characteristics that may be important to establish (eg., specimen stability, linearity).

分子檢驗品質管理實務

- For LDTs or modified FDA-cleared/approved test it is **PARR+AS+AS** (precision, accuracy, reportable range, and reference range, analytic sensitivity, and analytic specificity).
 - It should be noted that there may be additional parameters that a laboratory needs to address beyond the 4 or 6 respective performance characteristics. For example, the laboratory may find it important to assess specimen stability, linearity, and carryover.

Precision

- The closeness of agreement between independent test results obtained under stipulated conditions.

International Organization for Standardization. International Vocabulary of Basic and General Terms in Metrology (VIM). Geneva, Switzerland: International Organization for Standardization; 2004

- It encompasses
 - **repeatability** (agreement between independent test results for the same analyte under the same conditions such as intrarun assay) and
 - **reproducibility** (agreement between independent test results for the same analyte under different conditions such as interrun, interoperator, or interlaboratory assay).

Qualitative assays

- **For qualitative assays, precision refers to the reproducibility of test results.**
- **Reproducibility is defined by how well independent test results for the same sample agree with one another.**
- **Reproducibility of within-run, between-run, between-technologist, and between-instrument results should be assessed.**

Accuracy

- **The purpose of determining the accuracy of an assay is to provide evidence that the test produces the expected results.**

Accuracy

- The closeness of the agreement between the result of a measurement and a true value of the measurand.

Genet Med 2004;6:387-391

Accuracy

- Accuracy may be determined by comparing the experimental methods to well-established reference or gold standard methods. When this is not possible (eg, no gold standard exists), then spiking studies may be used in which positive control material is spiked into a suitable matrix.

Reportable range

- The reportable range is defined as the range of test result values for which the laboratory can establish or verify the accuracy of the instrument or test system measurement response. This definition is more applicable to quantitative assays than it is to qualitative assays, such as the KRAS assay, which is simply reported as positive or negative for mutation.

Reportable range

- The reportable range is defined as the range of values “over which the acceptability criteria for the method have been met; this is, where errors due to nonlinearity, impression, or other sources are within defined limits.”

Tholen DW. Evaluation of the linearity of quantitative measurement procedure: A statistical approach: approved guideline. Wayne, PA: NCCLS; 2003. CLSI document EP6-A.

Reference range

- The reference range is the range of test values expected to occur in 95% of a healthy or reference population.
- Ideally, the reference range of an assay is determined by testing a panel of “normal” donor samples to determine the number of positives in a healthy population.

Analytic sensitivity

- Analytic sensitivity is the ability of an assay to detect a given analyte or the limit of detection.
- LOD: lowest concentration of analyte with an informative result that is distinguishable from background.

Analytic sensitivity

- For molecular genetic testing, analytic sensitivity is considered as “the proportion of biological samples that have a positive test result or known mutation and that are correctly classified as positive.”

International Organization for Standardization. ISO/IEC Guide 2: Standardization and Related Activities-General Vocabulary. Geneva, Switzerland: International Organization for Standardization; 2004

Analytic sensitivity

- One definition of analytical sensitivity is the ability to obtain positive results in concordance with positive results obtained by a reference method.

Analytic Specificity

- **Analytic specificity is the ability of the assay to detect only the target analyte, or, in molecular genetic testing, the a**

Analytic Specificity

- **Analytic specificity may be defined as negative agreement when compared with the results obtained by the reference method.**
- **Measures that laboratories can take to ensure high analytical specificity include “BLASTing” (using the Basic Local Alignment Search Tool) their primers against the human genome to make sure that they do not cross-hybridize to other regions in the genome, and PCR optimization experiments to ensure that a specific PCR product is generated.**

附件

DAIDS Guidelines for Good Clinical
Laboratory Practice Standards



DAIDS Guidelines for Good Clinical Laboratory Practice Standards

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National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

Dear Site Principal Investigator and Laboratory Director:

All National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS-supported clinical trials involving human subjects must ensure compliance with federal regulations including procedures to protect the safety of all participants. These studies must be conducted in a manner to assure the sponsor and regulatory agencies that all data submitted are a true reflection of the results obtained during a study and that this data can be relied upon when making risk and/or safety assessments of study products.

DAIDS has determined that Good Clinical Laboratory Practices (GCLP) are the minimal requirements that clinical research laboratories should follow, as GCLP embraces both the research/pre-clinical and clinical aspects of Good Laboratory Practices (GLP). Complying with GCLP is an ongoing process that is central to optimal clinical research laboratory operations. DAIDS will monitor the progress toward GCLP compliance through annual audits and/or site visits. GCLP compliance will ensure that consistent, reproducible, auditable, and reliable laboratory results that support clinical trials will be produced in an environment conducive to study reconstruction.

To support the many laboratories that conduct quality laboratory testing for clinical trials around the world, DAIDS has developed, in collaboration with PPD, the attached "DAIDS Guidelines for Good Clinical Laboratory Practices (GCLP) Standards." This guidance document is provided to clearly define the standards that encompass GCLP to include applicable portions of 21 Code of Federal Regulations (CFR) part 58, or GLP, and 42 CFR part 493, or Clinical Laboratory Improvement Amendment (CLIA) rules. Due to the ambiguity of some parts of these regulations, the attached document also includes guidance from accrediting bodies such as the College of American Pathologists and South African National Accreditation System. These GCLP standards should be applied to all laboratories performing testing that supports a clinical trial sponsored by the DAIDS. Institutions must also meet sponsor-specific requirements as outlined in the Sponsor Statement of this document.

The first 40 pages of the document provide the GCLP standards. The next 60 pages are appendices that offer additional information and guidelines on how to implement some of these standards. This document can also be accessed on the DAIDS Clinical Research Policies and Standard Procedures Documents as an appendix to the Laboratory policies for Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials (<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Laboratories.aspx>).

I hope these GCLP Guidelines become a useful resource for your clinical research laboratory operations. This document has been vetted through the DAIDS Management Group, Regulatory Affairs Branch, Office of Policy for Clinical Research Operations, DAIDS Clinical Laboratory Oversight Team (DCLOT), and the Cross Network Laboratory Groups. If you have any questions about the content of this document please contact your Network Coordinator or the DAIDS Clinical Lab Oversight Team (DCLOT's e-mail: NIAIDDCLOT@niaid.nih.gov).

Sincerely,

Carl W. Dieffenbach, Ph.D.
Director, Division of AIDS, NIAID, NIH

DAIDS Guidelines for Good Clinical Laboratory Practice Standards

The development of these GCLP standards was a collaborative effort between PPD and the Division of AIDS (DAIDS). The authors that have contributed to this document are listed below:

PPD, Inc.:

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DAIDS:

DAIDS Clinical Laboratory Oversight
Team

The authors would also like to thank the following groups for their review and comments:

Cross Network Laboratory Groups

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Good Clinical Laboratory Practices Standards

1. Sponsor Statement

Introduction

The mission of the Division of AIDS (DAIDS) is to help ensure an end to the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of HIV, supporting the development of therapies for HIV infection and its complications, and supporting the development of vaccines and other prevention strategies. DAIDS accomplishes its mission through planning, implementing, managing, and evaluating programs in: 1) fundamental basic research; 2) discovery and development of therapies and treatment strategies for HIV-infection and its complications; and 3) discovery and development of vaccines, topical microbicides, and other prevention strategies. To achieve its mission, DAIDS actively supports and promotes public and private-sector alliances to maximize available research opportunities and resources. DAIDS supports all phases of the discovery and evaluation of new drugs and preventive strategies such as vaccines including basic research, preclinical testing, and human clinical testing of candidate products. Clinical evaluation in humans provides the only means of determining whether a candidate product is safe and effective. DAIDS-supported clinical trials and studies involving human subjects must ensure compliance with federal regulations including procedures to protect the safety of all participants. With regard to clinical trials of HIV-1 preventive vaccines, there are multiple organizations conducting HIV-1 vaccine trials globally. In the absence of a single central laboratory that can perform endpoint and safety assays, it is imperative that the data from multiple laboratories performing assays are reliable and reproducible so that clinical trial data can be effectively compared. As an example, no standards or regulations exist for conducting immunogenicity assays for vaccine studies in Phase 1 and 2 studies. To bridge this gap, DAIDS, as the Investigational New Drug (IND) application sponsor, has determined that the Good Clinical Laboratory Practices (GCLP) are minimal requirements that must be followed. Institutions must also meet sponsor-specific requirements as outlined in the sections below.

Food and Drug Administration's Form FDA 1572

Before permitting an investigator to participate in a clinical trial for an Investigational New Drug (IND), the sponsor must obtain a completed Food and Drug Administration's Form FDA 1572, Statement of Investigator. This form serves to capture demographic information of the investigator, the specific protocol(s) to be conducted, information on the research facility where the trial will be conducted, and identification of the clinical laboratories to be used in the trial. In addition, the Form FDA 1572 provides documentation of the commitment of the investigator regarding compliance and the conduct of the trial. Form FDA 1572, Section 4 requires the entry of "Name and Address of any Clinical Laboratory Facilities to be used in the Study." Section 4 must list the name(s) and complete physical address of ALL clinical laboratories or testing facilities that will be used for the clinical trial to process study related and/or study defined samples, which will directly contribute to or support the clinical trial. The official name of the laboratory

(i.e. Department of Pathology) should be included. If multiple Clinical Research Sites (CRSs) and/or locations are listed on the Form FDA 1572, the corresponding clinical laboratories must be listed for each CRS and/or location. If a central laboratory is sending samples to its own satellite laboratories for additional testing, the satellite laboratories do not need to be listed as long as the central laboratory can trace, through written records, the samples to the satellite laboratories where the tests were performed. This information is necessary to ensure that the FDA and DAIDS can monitor the activities of all laboratories that provide data to support a DAIDS-sponsored trial. For clinical trials that are not conducted as an IND, a DAIDS Investigator of Record agreement must be completed.

Study Plans and Analytical Plans

Often, study protocols may not be adequate in addressing all tasks and processes that must be carried out by laboratory personnel when working with clinical trial specimens; in this case, a formal laboratory-specific supplement in the form of an analytical or study plan should be developed. This plan is a technical document that describes all laboratory-specific components of the trial, defining study objectives and design for the conduct of the study within the laboratory setting. The study plan is a valuable source of information for many parties involved in the clinical trial (e.g. trial sponsor, laboratory director, laboratory personnel, specimen management coordinator, the Statistical Center, and the Quality Assurance Unit [QAU]). This comprehensive plan is written and approved by the laboratory director or designee and must include detailed information on the title of the study, purpose, authority and responsibility, key contacts, introduction and background, instructions for specimen collection, chain of custody and shipping instructions, instrumentation and analytical methods to be used, reference ranges, referral laboratory information, and transmission of results. This version-controlled document must conform to an approved study protocol and its appendices, be updated as required by protocol revisions, and be in compliance with the U.S. FDA requirements and the Organization for Economic Cooperation and Development (OECD) regulations for Good Laboratory Practices (GLP).

Note: Please refer to Appendix 1 for an example template for a study plan.

Enrollment in External Quality Assurance Programs

The DAIDS requires all laboratories receiving funding to be enrolled in External Quality Assurance (EQA) programs for all testing used to support clinical trial research. Laboratories should enroll in EQA programs that cover all study protocol analytes. These programs must be approved by the DAIDS and serve to 1) compare a laboratory's performance with that of its peers performing the same type of testing, 2) ensure the sponsor and regulatory agencies that the data generated is accurate and reliable to properly manage clinical trial volunteers' safety, and 3) that testing is performed with a rigor that will support product licensure in the USA. Laboratory performance in DAIDS-approved proficiency-testing programs will be monitored for successful performance by DAIDS or its designee.

Retention of Records

Laboratory records are paramount in reconstructing trial execution. There are regulations, such as 21 CFR 312.62 and ICH GCP 4.9.5, which address record retention

periods. DAIDS policy on Record Retention <http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/recordretention.pdf> states that clinical trial records belong to the Institution that conducts the DAIDS sponsored and/or funded trial. To determine how long to retain laboratory records refer to the DAIDS policy and the requirements of your Institution. Section 8. of these GCLP standards provides additional guidance on the types of laboratory documentation that should be archived.

Performance Specifications – Validation of Test Methods

The DAIDS requires that all methods undergo testing activities to verify their performance specifications. This includes verification of accuracy, precision, sensitivity, specificity, linearity and reference ranges. It is recommended that FDA-approved testing methods be employed when possible, as validation exercises are less intensive and do not include verification of sensitivity and specificity performance.

Good Clinical Laboratory Practices

These Good Clinical Laboratory Practice (GCLP) standards should be applied to all laboratories performing testing that supports a clinical trial sponsored by the DAIDS to include safety, diagnostic, and endpoint laboratory assays. Safety assays are those tests that are performed to both monitor potential adverse events and to verify the study participants' continued satisfaction of study inclusion/exclusion criteria, as appropriate, for each protocol. Endpoint assays are performed to aid in the monitoring of the trial's efficacy for treatments and prophylaxis/prevention. The DAIDS will audit all laboratories that are involved with its clinical trials on an annual basis (or as deemed necessary) to confirm GCLP compliance.

2. Introduction

Most laboratories in the clinical research arena do not fall under the oversight of any government regulatory authority. Often, in areas outside of Europe, Australia, and North America, there is no regulatory body devoted to laboratory science. In the areas where regulation exists, the targeted laboratories are either strictly "clinical" or "research" oriented. This type of scenario presents difficulties in discerning which regulations apply to laboratories engaging in clinical research.

GCLP is a relatively new approach to laboratory guidance which has been adopted by some European quality associations. The GCLP concept possesses a unique quality, as it embraces both the research/pre-clinical and clinical aspects of Good Laboratory Practices (GLP). The DAIDS recognizes that consistent GCLP application is paramount in the success of any clinical trial. In most cases, clinical trial data is largely laboratory in nature to include study endpoints and participant safety data. Hence, if this laboratory data is called into question due to inconsistent practices, an entire trial effort could be deemed as a failure. As a precautionary element, and to ensure the sponsor's confidence in the good quality of data produced by any laboratory performing study testing, the DAIDS has overseen the development of GCLP standards which encompass applicable portions of 21 Code of Federal Regulations (CFR) part 58, or GLP; and 42 CFR part 493, or the Clinical Laboratory Improvement Amendments (CLIA). These

regulations were intended to ensure the quality and integrity of safety data, allow accurate reconstruction of experiments, allow for safe, quality products, and allow data to be comparable regardless of where generated. These guidelines also help assure sponsors and regulatory agencies that all data submitted are a true reflection of the results obtained during a study and that this data can be relied upon when making risk and/or safety assessments. Due to the ambiguity of some parts of these regulations, these GCLP standards also include guidance from other organizations and accrediting bodies, such as the College of American Pathologists (CAP) and The International Organization for Standardization (ISO), which better define the intent of GCLP that is presently undefined by a single regulatory body. By recognizing these standards as the minimum requirements for DAIDS-funded laboratory operations, the expectation is that GCLP compliance will ensure that consistent, reproducible, auditable, and reliable laboratory results that support clinical trials will be produced in an environment conducive to study reconstruction.

3. Organization and Personnel

A. Introduction to Organization and Personnel

Laboratory management and staff share the responsibility of thorough documentation of the structure of the organization and the respective job descriptions and qualifications, as well as an ongoing documentation of an individual's professional experience, training, and skill-assessment. This ensures an employee's ability to adequately and safely perform his/her job.

B. Standards for Organization and Personnel

Documentation: The testing laboratory must have the following documents stored in the laboratory or readily available (e.g. within 24 hours) to authorized personnel, as appropriate:

- **Personnel policies** must be available that address such topics as orientation, training, continuing education requirements, performance evaluations, dress codes, and security. These policies detail employer and employee responsibilities as they relate to continued employment, employee and employer legal requirements, and protections.
- **Organizational and/or departmental policies** that describe how personnel can communicate existing issues which may affect quality of testing or safety of personnel must be available to ensure a non-retaliatory environment that encourages communication vital to the integrity of the study and the institution.
- **Job descriptions** that define qualifications and delegation of duties for all positions within the laboratory must be available to staff and other appropriate individuals (as defined below).
- **Personnel files** must be available to appropriate individuals (as defined below) that include a summary of the following items as they relate to each employee:
 - a. Orientation and training

- b. Experience
- c. Education
- d. Applicable licensure/certification (if required)
- e. Competency assessments
- f. Continuing education records
- g. Curriculum Vitae
- h. Safety training
- i. Attendance at job-related workshops and seminars; see *Appendix 2* for an example of a Training Attendance Log.

Note: Personnel files must be readily available (e.g. within 24 hours) only to authorized personnel such as Laboratory Director, Quality Assurance (QA)/Quality Control (QC) Manager, Primary Investigator of protocol, and DAIDS officials and auditors.

- **Organizational chart(s)** that represent the formal reporting and communication relationships that exist among personnel and management and between the main laboratory unit and satellite units, as applicable, must be available. These charts provide the current communication structure within the laboratory and help to ensure that the staff understands communication path options and requirements.

Staff education and evaluations: Managerial and technical personnel engaged in the conduct of laboratory testing related to clinical research must have the education, training, and experience commensurate with their assigned functions.

Job-specific Training, Education, and Assessments

- All personnel must receive direct and detailed training for the performance of all duties and tasks that they perform.
- Competency assessments must be conducted and recorded for all components of the employee's training and functional responsibilities upon completion of initial training. Competency must be assessed every six months during the first year of employment, annually thereafter, and/or as laboratory management deems necessary. Competency assessments must compare employee performance against a documented standard and clearly verify competency or lack of competency for each evaluated task.
 - Examples of methods utilized to evaluate competency include, but are not limited to: direct observation of test performance, direct observation of equipment maintenance, monitoring test result production, assessment of performance of analysis on known specimens, and external proficiency testing performance.
- A clinical laboratory continuing education program that is adequate to meet the needs of all personnel must be documented, and evidence of ongoing adherence by all laboratory personnel must be readily available. This documentation should include scheduling information such as how frequently personnel should attend a given course, the type of courses required, and the number of educational sessions personnel are required to attend over a given time period. Examples of training include, but are

not limited to, topics such as blood-borne pathogens, shipping of dangerous goods based on International Air Transportation Association (IATA) regulations, and laboratory safety.

GCLP Training

- At this time, GCLP training is not a DAIDS requirement. However, it is recommended that all laboratory personnel receive training in GCLP. The frequency of this training must be sufficient to ensure that employees remain familiar with the GCLP requirements applicable to them.

Job Performance Evaluations

- Annual performance evaluations must be given to all laboratory personnel. These evaluations compare the employee's overall performance of job responsibilities, duties, and tasks as outlined in the job description. These evaluations often take into consideration many aspects of job performance in addition to technical competency, such as quality of interpersonal communication, attendance, and behavioral expectations.

Staff numbers: The laboratory must employ an adequate number of qualified personnel to perform all of the functions associated with the volume and complexity of tasks and testing performed within the laboratory. The number of employees needed for optimal laboratory operations is determined by upper management in consultation with staff; this number is adjusted based on the scope and amount of workload.

Staff identification: If signatures, initials, or codes are used as staff identifiers on any laboratory documentation, a documented list that links these identifiers to a printed name must be in place. Changes in staff signatures, initials, or codes, as well as identifiers for new staff must be immediately recorded in the laboratory's documented list. The laboratory's documented list should be a "controlled version" document that must be updated when applicable changes described occur in the laboratory. Signature logs should be archived so that those individuals who performed trial testing throughout the length of a trial may be identified. As an example, staff signatures, initials, or codes included in results from assays should be traceable to printed names available in the laboratory. (Please see example of signature sheet in Appendix 3.)

C. Record Retention

Personnel records should be retained as outlined in Section 8 of these GCLP Guidelines.

References:

College of American Pathologists Commission on Laboratory Accreditation, Laboratory General Checklist, April 2006.

Clinical and Laboratory Standards Institute. *Developing a Training Verification Program*. NCCLS document SC16-L, Clinical and Laboratory Standards Institute, Wayne, PA USA, 1996.

42 CFR § 493.1413

42 CFR § 493.1451

4. Equipment

A. Introduction to Equipment

The laboratory staff must have regular access to all the equipment required to perform all the analyses within the scope of the laboratory. Standard Operating Procedures (SOPs) and supporting documentation such as maintenance logs must exist that demonstrate and provide evidence that all instrumentation and equipment are adequately validated, operated, inspected, cleaned, maintained, tested, and standardized to ensure optimal quality of assay results. All preventive maintenance and calibrations must be scheduled and performed at least as frequently as suggested by the equipment manufacturers to ensure continued accuracy, precision, and extended usable life of the equipment.

There must be evidence that equipment performance, use, and maintenance are consistently and routinely documented and reviewed by the laboratory director or designee.

B. Standards for Equipment

Documentation Guidelines

- The laboratory must keep documentation of all scheduled preventive maintenance, unscheduled maintenance, service records, and calibrations for all equipment utilized, as defined by the laboratory or institution. This documentation should be readily accessible.
 - Retain preventive maintenance and service logs as outlined in Section 8 of these GCLP guidelines or until otherwise instructed.
- A supervisory staff member must review, sign, and date all documentation of equipment maintenance at least monthly.
- All laboratory equipment should be listed on an inventory document.

General Guidelines

Staff must conduct all preventive maintenance and service per manufacturer specifications by following these guidelines:

- Staff must keep all equipment clean, avoiding any buildup of dust, dirt, and spills that may adversely affect personnel safety or equipment performance.
- The laboratory must employ and adhere to documented daily, weekly, and/or monthly routine maintenance plans for **all** equipment utilized, and record completion of these tasks on the appropriate logs in a timely fashion.

Temperature monitoring in absence of staff:

- There should be a written policy/procedure in place, explaining how temperatures are monitored during the absence of laboratory staff.

Service Guidelines

In addition to the above general guidelines, the laboratory must observe and document the following specific service guidelines described below. Trained laboratory staff or certified contractors should perform the following:

- **Adjustable and fixed-volume automatic pipettors**
Check for volumetric accuracy and reproducibility, and recalibrate as necessary before placing in service initially and at specific defined intervals. DAIDS requires that pipettors be checked for accuracy and reproducibility and recalibrated at least once every six months. Pipettor malfunction is one of the most common sources of laboratory error. Therefore, DAIDS strongly recommends that laboratories perform checks for accuracy and reproducibility and recalibrations four times per year, with at least two of the four performed by an external contracted service provider.
- **Thermometers**
Test thermometers against a standardized National Institute of Standards and Technology (NIST)-certified (or equivalent) thermometric device annually. For NIST-certified (or equivalent) thermometers, follow manufacturer's recommendations for calibration and expiration date.
- **Refrigerators and freezers**
 - Establish tolerance limits for temperatures and/or for liquid nitrogen level, as appropriate. For example, a given refrigerator's temperature tolerance limits must reflect the most stringent needs of all reagents, supplies, and specimens stored within it. If Reagent A's acceptable storage temperature range is 2-8°C, and Reagent B's acceptable storage temperature range is 3-10°C, the tolerance limit for the refrigerator must be 3-8°C.
 - Place liquid nitrogen freezers in facilities that are well ventilated or monitored for oxygen content.
 - Maintain daily (at a minimum) record of temperatures and/or levels of liquid nitrogen' as appropriate.
 - Maintain appropriate documentation of corrective action for out-of-range temperatures and liquid nitrogen levels.
- **Incubators and water baths**
 - Establish tolerance limits for temperatures, carbon dioxide level, and humidity, as applicable.
 - Maintain daily (or "dates of use") record of temperatures.
 - Maintain appropriate documentation of corrective action for out-of-range temperatures.

- **Centrifuges**
 - Measure operating speeds (appropriate for use in specimen processing) periodically (annually at a minimum; DAIDS recommends every six months) with a tachometer. Document the readings.
 - Maintain daily (or “date of use”) record of temperatures for refrigerated centrifuges.
 - Verify performance of centrifuge timers by comparing to a known standard (i.e. NIST traceable timer).

- **Autoclaves**
 - Verify content processing using heat-sensitive tape with each autoclave batch.
 - Verify effective sterilization with an appropriate biological indicator weekly.
 - Perform autoclave maintenance annually, or as per manufacturer, including a pressure check and calibration of temperature device.
 - Check autoclave mechanical timing device periodically.
 - Maintain records of autoclave operation and maintenance in the equipment log.

- **Timers**
 - Check for accuracy by comparing to a known standard (i.e. NIST traceable timer) every six months.

- **Analytical balances**
 - Check accuracy with standard weights of the appropriate ANSI/ASTM (American National Standards Institute/American Society for Testing and Materials) class at a predetermined frequency (based on manufacturer suggestions). Document the results with an evaluation of their acceptability.
 - Service and calibrate periodically using qualified personnel (per manufacturer’s instruction). Maintain records of service and calibrations.
 - Place the analytical balance so that vibration does not affect the readings.

- **Biosafety cabinets/laminar air flow hoods**
 - Verify air intake grills are not obstructed.
 - Certify cabinets/hoods annually by a trained service technician, certified maintenance department, or company.
 - Check daily for air flow as instructed by manufacturer and document the results to verify the effectiveness of the hood’s personnel and environmental protective functions. For example, a Class 2 biosafety cabinet will likely have an inflow velocity meter. The manufacturer of the cabinet may state that the cabinet must maintain a minimum of 75 FPM inflow velocity. The actual airflow obtained on a daily basis would be documented and compared to this limit, with corrective action taken as required.

- Clean the work surfaces after each use with 70% ethanol or other disinfectant as recommended by the manufacturer.
 - Clean the Ultraviolet (UV) lamp, if used, weekly with 70% alcohol.
 - Use of UV is recommended only when personnel are out of the room.
 - Document daily and weekly cleaning.
- **Generators**
 - Maintain and keep readily accessible records to verify that the back-up generator system is in place and operational.
 - Follow SOPs that detail generator maintenance.
 - Procedures should list the frequency and procedural steps of maintenance and testing.
 - Supporting logs should document monthly checks on critical generator components, including fluid levels (oil, coolant, and fuel), belts, battery, testing of start-up, and operation.

References:

- College of American Pathologists Commission on Laboratory Accreditation, Accreditation Checklists, April 2006.

5. Testing Facility Operation

A. Introduction to Testing Facility Operation

A testing facility must have written Standard Operating Procedures (SOPs) to ensure the consistency, quality, and integrity of the data generated from the laboratory. Policies provide a statement of intent that an organization will follow a particular course of action, while SOPs detail practical ways in which policies are translated into action. All SOPs must be readily available for use by testing personnel at the workbench. These SOPs must be of uniform format as determined by the laboratory director and must include items such as test principles and clinical significance. A Document Control Plan must exist to facilitate the review for accuracy and relevance of all SOPs.

B. Standards for Testing Facility Operation

Current SOPs must be available in the work areas and accessible to staff.

The laboratory must write SOPs in a manner and language that is appropriate to the lab personnel conducting the corresponding procedures.

SOP Format

The laboratory must write SOPs in a standard format such as the format recommended by the Clinical and Laboratory Standards Institute (CLSI). This format may include the following:

- Document number;
- Revision number and date;
- Effective date of the document;
- Number of pages;

- Title, to include name of analyte, type of specimen, and method/assay and/or instrumentation;
- Principal and/or purpose;
- Scope;
- Specimen requirements/collection methods;
- Reagents, standards, controls, and media used;
- Instrumentation, Calibration procedures;
- QC;
- Procedural steps;
- Attachments (e.g. product inserts);
- Calculations;
- Reporting results;
- Reference ranges/critical values;
- Limitations;
- References;
- Definitions;
- Distribution;
- Author;
- Approval signatures and dates; and/or
- Document change history.

Note: Example of SOP in CLSI format is contained in Appendix 4.

SOP Distribution

The laboratory must distribute all new and revised SOPs to the appropriate laboratory staff who will be responsible for performing their routine tasks in accordance with the content of those SOPs.

- The laboratory personnel must document that they have reviewed and understood all new and revised SOPs by signing and dating the SOP after their review.
- The laboratory must maintain this documentation in a system that readily allows for verification that personnel are knowledgeable of the new or revised SOPs.

Document Control Plan

The laboratory must maintain a current document control plan that addresses and ensures the following vital elements of SOPs:

- Maintain a master list of SOPs currently used in the laboratory.
- Ensure SOPs are procedurally accurate and relevant.
- Keep the authorization process standardized/consistent, limiting approvals to laboratory management.
- Review SOPs annually and document the review.
- Remove retired or obsolete SOPs from circulation and identify them as retired or obsolete.
- Archive retired or obsolete SOPs for a period defined by the laboratory or institution.

Note: Retention time periods established by the laboratory or institution must meet or exceed the requirements set forth by the sponsor and/or any applicable regulatory bodies such as the U.S. FDA.

SOP Categories

The laboratory must have SOPs for **all** procedures being performed. Comprehensive lists of categories for SOPs may be found in reference literature.

General categories of SOPs within the department may include:

- Documentation Control: describe a plan that ensures relevance of all SOPs, as described earlier in this section.
- Organization and Personnel: detail policies that govern communication and administrative components of all employees of the organization, as described in Section 3.
- Personnel Training: explain required training and supporting documentation, as detailed in Section 3.
- Equipment Calibration and Maintenance: govern the physical maintenance and calibration of laboratory assets, as described in Section 4.
- Specimen Management and Chain-of-Custody: feature specimen transportation and handling steps required to maintain specimen integrity, positive identification of specimens, and audit trails from point of collection to delivery of results, as detailed in Section 5.
- Test Procedures: include the steps describing the performance of tasks, processes, and assays (safety, diagnostic, and end-point), formatted consistently as described earlier in this section.
- QC: express the components of establishing, performing, evaluating, troubleshooting, and documenting QC processes, as described in Section 6.
- QA: explain the systematic approach to ensuring continued improvement of the operations within the laboratory, as detailed in Section 13.
- Test Reporting and Records Management: oversee the format, reproduction, and delivery of final information generated by laboratory assays to appropriate individuals; also governs archiving of source documents, as found in Section 8.
- Safety: describe the engineering controls, personal protective equipment (PPE), and processes to reduce risks to personal safety within the laboratory environment, as detailed in Section 11.
- Laboratory communications: detail steps to take if an individual has concerns regarding how personnel can communicate existing issues which may affect quality of testing or safety of personnel.
- Operations of Laboratory Information System (LIS): describe procedural stepwise details of routine operation, as defined in Section 12.

C. Record Retention

Procedural documents should be retained as outlined in Section 8 of these GCLP Guidelines.

References:

42 CFR § 493.1251

42 CFR § 493.1407

42 CFR § 493.1105

College of American Pathologists Commission on Laboratory Accreditation, Accreditation Checklists, April 2006.

Clinical and Laboratory Standards Institute. *Laboratory Documents: Development and Control; Approved Guideline-Fifth Edition*, CLSI document GP2-A5. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2006.

- NCCLS. *Continuous Quality Improvement: Integrating Five Key Quality System Components; Approved Guideline-Second Edition*. NCCLS document GP22-A2. NCCLS, Wayne, PA USA, 2004.

6. Test and Control

A. Introduction to Test and Control

The management of Quality Control (QC) must include a process of identification and documentation of analytical problems as they occur, with the ultimate goal of evaluating the accuracy and reliability of the analytical testing process. The laboratory must establish and follow written quality control procedures for each test system to detect both immediate errors and the changes that happen over time. Frequency of performance, number of materials to be used, as well as the type of QC materials must be determined by the laboratory. All failed QC results must be investigated and handled according to a documented QC program.

B. Standards for Test and Quality Control

Quality Control Program

The laboratory must have a site-specific, written QC plan which clearly defines procedures for monitoring analytic performance; this program ensures the consistent identification, documentation, and resolution of QC issues. The laboratory director should be actively involved in the design, implementation, and oversight of the QC program.

Evaluation Criteria

Manufacturers' tolerance limits or ranges tend to be set wide to accommodate the various operating systems present in different laboratory settings. The laboratory must establish and document the tolerance limits for acceptance of control results.

For example, a laboratory may choose to utilize Westgard multirule QC procedures to judge the acceptability of an analytical run. This laboratory should establish the means of new lot numbers of QC materials over a period of a few weeks, running the new lot in parallel with the current lots in use. Once they have acquired a minimum of 20 replicates of each level of new QC material, the laboratory can then calculate the new mean and use the method's historic coefficient of variation (CV) to calculate the new standard deviation. The laboratory should establish local means and QC ranges based on historical method CVs.

Frequency of Quality Control Testing and Types of Control Materials

QC samples must be tested in the same manner as study-participant specimens and by the personnel who routinely perform study-participant testing.

The laboratory director and/or designee must determine the appropriate number and frequency of QC tests using the following guidelines:

- For quantitative tests, use control materials at more than one level, such as a "high" and "low" control.

Note: Controls must verify assay performance at result levels where clinical or study decisions are made. For example, medical decisions may be made for study-participant's glucose levels at 45 mg/dL and 180 mg/dL; two levels of control materials should be representative of these results.

- For qualitative tests, include positive and negative controls with each run.
- For staining procedures, gram stains require both Gram positive and Gram negative control organisms to be used once per week and with each change of a lot number of any component in the stain procedure. Other stains require daily or day of use QC, using a positive reacting organism and a negative, which could include the patient sample.

Note: An analytical run spans the time interval over which the accuracy and precision of the assay is expected to be stable, must be based upon manufacturers' instructions, and must not exceed 24 hours. For example, a given chemistry analyzer's manufacturer may state that glucose reagents on their platform are stable for eight hours; in this case, QC must be performed every eight hours, or three times per day if operated 24 hours per day.

For FDA-approved, CLIA-waived tests, the manufacturer package insert instructions should be followed. In addition, it is recommended that sites conduct external QC weekly during any week in which patient samples are tested.

For non-FDA approved tests, it is recommended that daily QC be run for testing used for primary endpoint and critical safety determinations. In addition, QC should be done in the following situations:

- If there are changes to device reagents, study populations and/or analytes
- When there are new operators performing testing on patient specimens
- With each new kit lot
- Whenever a new shipment of test kits is received

- If the temperature of the test kit storage area falls outside manufacturer's recommended range
- If the temperature of the testing area falls outside manufacturer's recommended range
- At periodic intervals as specified in a laboratory's Quality Assurance program

At a minimum, laboratories should perform external QC weekly, whenever patient samples are tested in that week.

Review of Quality Control Data

QC must be run and reviewed prior to reporting study-participant results and after a change of analytically critical reagents, major preventive maintenance/service, or change of a critical instrument component.

QC results must be performed and acceptable results obtained (as defined in the written QC program) before test results are reported.

The laboratory personnel performing the testing must determine the appropriate corrective action to take for QC data that falls outside of established tolerance limits, using the QC program as a guide. Corrective action should be documented with the technician's initials and date.

In the event the QC data is determined to be unacceptable, the laboratory must re-evaluate all study-participant test results since the last acceptable test run. The laboratory should evaluate study-participant results to determine if a significant clinical difference has occurred, in which case, the instrument QC should be re-established and the affected testing repeated.

Quality Control Logs

- QC logs must be present documenting control results assayed with each test, as described in each specific assay procedure.
 - Control records must be readily available to the staff performing the test.
 - Results of controls must be recorded or plotted to readily detect a malfunction in the instrument or in the analytic system.
 - Appropriate charts (e.g. Levy Jennings [LJ] charts or control charts) must be utilized by personnel to document quantitative QC data to allow for determination of acceptability of the QC run and to aid in detection of shifts and trends in the control data.
 - Laboratory personnel performing QC runs, recording of results, and plotting of data on graphs must record their initials, date, and time (as applicable), as testing is performed. For example, if Technologist ABC performs the QC run for HIV viral load on a given morning, Technologist ABC must document his or her initials, date, and time on all applicable QC records.
 - If QC materials are aliquoted, then they should be labeled in such a way that they are traceable to the material name and lot, preparation date, expiration date and technician.
- QC records should contain detailed information to reconstruct establishment of ranges for each QC material used for monitoring analytic performance.

Note: Please refer to Appendix 5 for L-J Chart and Appendix 6 for QC Log examples.

Corrective Action Logs

The laboratory must ensure a corrective action log is present to facilitate documentation and resolution of QC failures.

Supervisor Review of Quality Control Documentation

Appropriate laboratory supervisory personnel must regularly review, sign, and date QC records and corrective action logs according to the following guidelines:

- A laboratory manager or designee must review, sign, and date the corrective action log at least monthly.
- The laboratory director or designee must review, sign, and date QC data at least monthly.

Note: Documentation of all designees must be included in the current QC plan.

Quality Control Record Retention

The following records must be retained by the laboratory in a secured fire-proof (preferred), fire-resistant, or fire-protected (least preferred; e.g. stored in area with operational automatic sprinkler system) storage area/facility for a period of time that has been defined by the laboratory or institution:

- Instrument printouts
- All QC records including worksheets if QC is recorded manually
- Package inserts
- Certificates of Analysis

Retention time periods established by the laboratory or institution must meet or exceed the requirements set forth by the sponsor and/or any applicable regulatory bodies such as the FDA. Retention times are addressed in Section 8 of these GCLP Guidelines.

Labeling and Storage of Quality Control Materials and Reagents

All QC materials and reagents must be properly labeled, as applicable and appropriate, with the following:

- Storage requirements
 - All QC materials and reagents currently in use must be prepared and stored as required by the manufacturer.
 - If ambient storage temperature is indicated, there must be documentation that the defined ambient temperature is maintained and corrective action taken when tolerance limits are exceeded. Ambient temperature logs should be utilized to document the acceptable ambient temperature range, record daily actual temperatures, and allow for documentation of corrective action taken should the acceptable temperature ranges be exceeded.

Note: Ambient temperature tolerance limits must reflect the most stringent needs of all reagents, supplies, and specimens stored at ambient temperature; if Reagent A's acceptable storage temperature range is 20-28°C, and Reagent B's acceptable storage temperature range is 23-30°C, the tolerance limit for the room must be 23-28°C.

- Date opened, prepared, or reconstituted by the laboratory, and the initials of personnel who prepared/reconstituted the QC material and reagents.
- Expiration date

Deteriorated or outdated (expired) QC materials must not be used.

An expiration date must be assigned to QC materials that do not have a manufacturer-provided expiration date or an expiration date that changes upon reconstitution or use. The manufacturer should be consulted should this situation arise. (Exception: Microbiological organisms; storage and sub-culturing techniques will determine time of use).

Calibrators must not be used as QC materials unless the laboratory is employing some other method when a separate control product is not available.

Note: If a calibrator is used as a control, it must be from a different lot number than that which is used to calibrate the method.

Inventory Control

The laboratory must have an established documented inventory control system in operation.

- The laboratory storage area must be sufficient to maintain an appropriate amount of “working” supplies and reagents. Appropriate levels of working supplies and reagents is defined as an amount that is adequate to handle current workload demands until new orders can be placed and received for use.
- All storage areas must be temperature controlled, well organized, free of clutter, and allow for ease in determining supply levels.
- There must be evidence of a system which highlights the need to place supply orders, tracks orders, and defines alternate plans for delayed deliveries of supplies and recovery procedures for “out-of-stock” conditions (a system that details steps to ensure minimal lapse in ability to perform testing).

Parallel Testing

For each new lot of reagents, the laboratory must document that samples are tested in parallel with each current lot and that the comparable results are obtained before or concurrently with being placed in service.

- Parallel testing should include study-participant-based comparisons when possible. Use of study-participant samples should be restricted to assays that are required by the applicable clinical trial protocols and results obtained from new lot numbers retained for QA purposes only.

Note: Use of study-participants for internal QA practices, such as parallel testing, may require approval by the applicable Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

Study-participant specimens tested on an established (current) lot number of reagents should be tested on the new lot number of reagents to assess comparability of results across lots.

If study-participant specimens are not available for use, manufacturer-provided reference materials or proficiency testing materials with peer group means are acceptable.

- For quantitative tests, parallel testing should be performed by assaying the same study-participant specimens or reference materials with both the old and new lot numbers to assess comparability. QC materials must also be run when comparing old and new lots.
- For qualitative tests, minimum parallel testing must include re-testing at least one known positive (or abnormal) and one known negative (or normal) study-participant sample.

If study-participant specimens are not available for use, manufacturer-provided reference materials or proficiency testing materials are acceptable.

Note: A weakly positive sample must also be used in systems where study-participants' results may be observed as weakly positive (e.g. Western Blot).

Water Quality Testing

If specific water types are required per manufacturer for certain testing procedures, the laboratory must have a documented policy that defines the standards and frequency of water testing. Laboratory water is classified as Type 1, 2, or 3 (defined by NCCLS guideline C3-CA) and each type has different specifications for maximum microbial content, resistivity, maximum silicate contents, and particulate matter.

- The laboratory must ensure that records of water quality testing are complete and/or indicate that the required standards for water quality (e.g. pH, resistivity) are consistently met.
- The laboratory must document evidence of corrective action taken when water testing does not meet defined tolerance limits.
- When decontaminating the clinical analyzer water reservoirs and water storage containers, manufacturer's recommendations should be followed to avoid problems linked to poor water quality due to contaminants.

References:

42 CFR § 493.1256

42 CFR § 493.1282

College of American Pathologists Commission on Laboratory Accreditation, Accreditation Checklists, April 2006.

Preparation and Testing of Reagent Water in the Clinical Laboratory-third edition. NCCLS document C3-CA. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2002.

Westgard, James O. Basic QC Practices 2nd Edition. Madison, WI: Westgard QC, Inc., 2002.

7. Verification of Performance Specifications

A. Introduction to Performance Specifications

Before reporting study-participant results, each laboratory that introduces a **non-waived** (a CLIA designation) test system must demonstrate that it can obtain performance specifications comparable to those established by the manufacturer (as found in manufacturer's publications such as user manuals or package inserts). These steps ensure the assay is performing optimally within the environment the testing will be performed. Verification of performance specifications may also be referred to as **validation** of the method. Validation experiments should be performed for safety, diagnostic, and endpoint assays when implementing a new analyzer, new testing methodology, or new assay. All validation experiments should occur prior to testing study-participant specimens; documentation of experiment results and approval should be readily accessible. Methods that are defined as **waived** by CLIA do not require method validation. Endpoint assays, point-of-care testing, and "rapid" tests, if not classified as waived testing, require method validation as determined by their FDA-approval status as described above. Laboratories are not required to verify or establish performance specifications for any protocol-specific analytical test system used by the laboratory before April 24, 2003, provided the laboratories have documented acceptable Quality Control and external proficiency testing results.

For **unmodified FDA-approved** testing systems, the following experiments must be performed:

- Reportable range of test results for the test system
- Linearity (should be verified concurrently with reportable range)
- Precision
- Accuracy
- Verification that the manufacturer's or other adopted reference intervals (normal values) are appropriate for the laboratory's study-participant population
- Analytical sensitivity and analytical specificity (interfering substance) data provided by the manufacturer can be used and does not need to be verified

For **modified** FDA-approved, and/or **non-FDA-approved** testing systems, the following experiments must be performed:

- Reportable range of test results
- Analytical sensitivity
- Accuracy
- Precision
- Analytical specificity (interfering substances)
- Establishment of reference intervals (normal values) that are appropriate for the laboratory's study-participant population

Should the results of validation experiments not meet the manufacturer's specifications, the laboratory director should work with the manufacturer to determine

the source(s) of disparate results. A corrective course of action should then be taken to resolve the issue(s) that may include on-site repairs, upgrades, or method replacement.

B. Standards for Performance Specifications

Reportable range: useful analytical range of a laboratory method, i.e. the lowest and highest test results that are reliable and can be reported.

Verification and documentation of normal responses for each test system, including reportable range and normal range(s), must be established to determine the usable and reliable range of results produced by that system.

Verification and documentation of both the Analytical Measurement Range (AMR) and the Clinically Reportable Range (CRR) must be performed when establishing the reportable range.

AMR: verifies the lowest and highest test results that may be reliably reported by an assay without additional steps beyond the routine procedure, such as dilutions or concentrations.

The following guidelines must be used when selecting materials for AMR validation and when performing the validation experiment:

- If using purchased materials for AMR validation experiments, the matrix of these materials should not interfere or otherwise bias results of the method.
- The validation materials must have analyte values which span the range of the AMR (i.e. near the low, mid-point, and high values of the stated AMR).
- Each laboratory must define limits for accepting or rejecting validation tests of the AMR.

Note: Often, the manufacturer will specify the AMR and procedures in the format of “if result is greater (or less) than X, dilute (or concentrate) specimen”. If unable to discern the manufacturer’s claims for AMR from published information, contact the manufacturer.

CRR: the range of analyte values that a method can measure with additional pretreatment of the original specimen and which thereby extends the reportable range of an assay/methodology. The CRR takes into consideration the need for dilutions or changes in concentrations, combined with clinical decisions made by a medical director or principal investigator, as to the clinical significance of results obtained by such dilutions or concentrations.

- The following guidelines and considerations must be used when performing the CRR validation experiment:
 - The CRR must be determined during initial verification of a method and not revised/updated until the method changes.
 - Values lower than the CRR must be reported as “less than” the limit.
 - The upper limit of the CRR will usually not be indicated unless there is a method or analyte limitation of a dilution protocol. Otherwise, it will be considered to be good clinical laboratory practice to dilute until a value in the AMR is achieved.
 - The diluent must be specified for each analyte that can be

- The lower limit of the CRR will often be represented by the lower limit of the AMR as described previously. For example, an assay for quantitative human chorionic gonadotropin (hCG) demonstrates a lower AMR limit of 3 mIU/mL; the medical director for the laboratory decides that the lower limit of 3 mIU/mL is acceptable for diagnostic and prognostic causes and does not need to be extended to a lower value. In this case, the medical director has effectively set the lower limit of CRR equal to the lower AMR of 3 mIU/mL.
- The laboratory may perform verification of reportable range by using the following materials and methods:
 - The laboratory may assay low and high calibration materials or control materials.
 - The laboratory may evaluate known samples of abnormal high and abnormal low values.

Please refer to Appendix 7 for an example of how to determine the reportable range.

Analytical sensitivity: estimate of the lowest concentration of an analyte that can be measured.

The analytical sensitivity (lower detection limit) estimates the lowest concentration of an analyte that is reliable and reproducible. The analytical sensitivity of each assay must be verified or established and documented according to the following guidelines:

- For FDA-cleared/approved tests, documentation may consist of data from manufacturers or the published literature.
- If non-FDA approved methods are utilized, the laboratory must establish and document analytical sensitivities.
- Analytical sensitivity may be verified by the laboratory by preparing dilutions of controls, standards, or specimens and determining the lowest concentration that can be determined reliably.

Note: Analytical sensitivity values that are smaller than the applicable standard deviation of the method are typically unreliable indicators of the method's lower detection.

Please refer to Appendix 8 for an example of how to determine analytical sensitivity.

Precision: measurement of the scatter or random error between repeated measurements.

Precision of each test must be established by performing repeat measurement of samples at varying concentrations or activities (such as one would measure with enzymatic reactions) by using the following guidelines:

- The laboratory must verify the precision of each test by assessing day-to-

- day, run-to-run, and within-run variation.
- Precision verification may be accomplished by one or a combination of the following methods:
 - The laboratory may repeat testing of known study-participant samples over a period of time.

Note: Use of study-participants for internal QA practices, such as method validation, may require approval by the applicable Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
 - The laboratory may test QC material in duplicate and over time.
 - The laboratory may repeat testing of calibration materials over time.
- Precision validation for qualitative tests:
 - Validation of a test's precision should be performed if the manufacturer's package insert mentions precision testing AND if value will be gained with such testing.

Please refer to Appendix 9 for an example of precision experiment.

Analytical Specificity (Analytical Interferences): estimate of the systematic error caused by other materials that may be present in the specimen being analyzed.

The analytical specificity experiment is performed to estimate the systematic error caused by non-analyte materials (such as hemolysis, icterus, lipemia, or medications) that may be present in the specimen being analyzed.

Analytical interferences for each test must be verified or established and documented according to the following guidelines:

- For FDA-cleared/approved tests, the laboratory's documentation may consist of data from manufacturers or the published literature.
- If non-FDA approved methods are utilized, the laboratory must establish and document interfering substances.

Please refer to Appendix 10 for an example of how to determine analytical specificity.

Accuracy: measure of how close a measured value is to the true value.

Where current technology permits (i.e. comparative or reference methods exist), the laboratory must establish accuracy of the test system.

- The laboratory may use reference materials with known concentrations or activities (such as one would measure with enzymatic reactions).
- The laboratory may compare results of tests performed by the laboratory against the results of a reference method, or compare split-sample results with the results obtained from a method which is shown to provide clinically valid results.

Note: For qualitative methods, the lab must verify that a method will identify the presence or absence of the analyte.

Please refer to Appendix 11 for an example of accuracy experiment results.

Reference (Normal) Ranges: specified interval bound by two limiting values that contains 95% of the values found in healthy individuals.

If the test system to be validated is an unmodified, FDA-approved method, the manufacturer's reference range may be verified. If the test is modified, or not FDA-approved, the reference range must be established.

- The reference range must be established or verified for each analyte and specimen source/type (e.g. blood, urine, cerebrospinal fluid), when appropriate.
 - The laboratory may use the manufacturer's reference range when appropriate specimens are difficult to obtain (e.g. 24-hour urine specimens, 72-hour stool specimens, urine toxicology specimens), provided the range is appropriate for the laboratory's study-participant population.
 - In cases where the appropriate specimens are difficult to obtain and the manufacturer has not provided reference ranges appropriate for the laboratory's study-participant population, the laboratory may use published reference range(s).
- An appropriate number of specimens must be evaluated to verify the manufacturer's claims for normal values or, as applicable, the published reference ranges. Typically, the minimum number of specimens required to verify the manufacturer's or published ranges is 20 specimens. These specimens should be fresh and appropriately collected from patients that have been predetermined as "normal" by established inclusion/exclusion criteria (e.g. HIV-negative, HBsAg-negative). The specimens should be representative of the population (age, gender, etc.).
- An appropriate number of specimens must be evaluated to establish reference ranges. Typically, the minimum number of specimens required to establish reference ranges is 120 specimens per demographic group (e.g. if the laboratory wishes to establish gender-specific reference ranges, then the minimum number of specimens would be 240: 120 specimens collected from normal male patients, and 120 from normal female patients).
- Reference intervals must be evaluated at the following times:
 - Upon introduction of a new analyte to the test offerings by a laboratory (e.g. a laboratory that uses a FACSCalibur to perform CD4 testing desires to also add CD8 testing to their test menu).
 - With a change of analytic methodology (e.g. replacing CD4 testing performed on the FACSCount with testing performed using the FACSCalibur).
 - With a change in study-participant population (e.g. a method typically used for determining test results for adults is to be used for a primarily pediatric population).

Please refer to Appendix 12 for an example of how to determine reference values.

Correction Factors

Correction factors, if used, must be incorporated into the relevant test procedure and reflected in the appropriate SOPs if the laboratory has determined the need for correction factors based on the validation exercises. Correction factors represent adjustments made to compensate for constant and proportional error (or bias), and are often written in a linear regression equation format. For example, two similar assays, "A" and "B", are used interchangeably within a laboratory to perform quantitative human chorionic gonadotropin (hCG). Assay B has been found to have a proportional bias of 2% and a constant bias of 3 mIU/mL when compared with Assay A. In order to insure interchangeability of results obtained from either assay, the laboratory applies the equation, "A = 1.02 (B) + 3" to any raw result that is produced by Assay B before reporting the final, calculated result.

References:

42 CFR § 493.1253

College of American Pathologists Commission on Laboratory Accreditation, Accreditation Checklists, April 2006.

Westgard, James O. Basic Method Validation 2nd Edition. Madison, WI: Westgard QC, Inc., 2003.

Clinical and Laboratory Standards Institute. *User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline*. NCCLS document EP12-A. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2002.

Clinical and Laboratory Standards Institute. *Evaluation of Precision Performance of Quantitative Measurement Methods*. NCCLS document EP5-A2. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2004.

Clinical and Laboratory Standards Institute. *User verification of Performance for Precision and Trueness*. CLSI document EP15-A2. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2005.

Clinical and Laboratory Standards Institute. *Interference Testing in Clinical Chemistry*. CLSI document EP7-A2. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2005

Clinical and Laboratory Standards Institute. *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*. NCCLS document EP6-A. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2003.

Clinical and Laboratory Standards Institute. *Method Comparison and Bias Estimation using Patient Samples*. NCCLS document EP9-A2. Clinical and Laboratory Standards Institute, Wayne, PA USA, 2002.

Clinical and Laboratory Standards Institute. *How to Define and Determine Reference Intervals in the Clinical Laboratory*. NCCLS document C28-A2. NCCLS, Wayne, PA, USA 2000

8. Records and Reports

A. Introduction to Records and Reports

All additional information and documentation generated by the laboratory, such as specimen tracking, chain of custody, availability of normal ranges on the reports, and identity of performing laboratories are crucial to troubleshooting specimens and

attest to credibility of test results. These documents are also necessary in full study reconstruction and other similar auditing purposes. For this reason, laboratories involved in specimen testing that supports a clinical trial should maintain all applicable records and reports following the guidelines below.

B. Standards for Records and Reports

Record and report tracking

The laboratory must maintain a system for providing and maintaining clinical trial data records and reports. These records and reports may include the following:

- Specimen tracking forms/laboratory requisitions
- Chain of custody documents
- Laboratory reports
- QC data (all records pertaining to proficiency testing, quality control, corrective action, and preventive action)
- Equipment service and maintenance logs (all records pertaining to the maintenance, repair, temperature monitoring, validation, and any other pertinent documentation related to the performance of the instrumentation)
- Analyte results with reference intervals
- Raw data source documentation [laboratory worksheets, records, memoranda, notes, or exact copies thereof that are the result of original observations and activities of a non-clinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study [21 CFR §58.3(k)].
- Other operational documentation (all policies and procedures pertinent to the conduct of the study, including but not limited to standard operating procedures, safety policies, safety incident reports, specimen management, protocols/manuals, Laboratory Information System (LIS), and specimen storage documentation)

Record retention

Research documentation and final reports are transferred to archive during or at the end of the study [21 CFR §58.33(f)]. The space dedicated to archive will have limited access by authorized personnel only and allow expedient retrieval of documents. Storage conditions must ensure document preservation for the specified retention time. A commercial archive service may be contracted if required. (21 CFR §58.190)

Research documents are to be retained for a period of at least two years following the date on which an application for a research or marketing permit, in support of which the results of the non-clinical laboratory study were submitted, is approved by the Food and Drug Administration. For studies supporting investigational new drug applications (INDs) or applications for investigational device exemptions (IDEs), records will be retained for a period of at least five years following the date on which the results of the non-clinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit. If the non-clinical laboratory study does not result in the submission of the study in support

of an application for a research or marketing permit, records are retained for a period of at least two years following the date on which the study is completed, terminated, or discontinued. Records may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. (21 CFR § 58.195)

Note: Record retention is governed by multiple authorities, in both U.S. and non-U.S. settings. Local IRB/REC policies, regulations, and laws are to be followed if more stringent retention guidelines apply.

Data integrity

Adequate manual or electronic systems must be in place to ensure assay results and other study-participant-specific data (e.g. participant identifiers) are accurately and reliably sent from the point of data entry (whether entered via an analyzer interface or manually) to the final report destination in an accurate and timely manner, or according to specifications detailed within specific protocols and/or the study/analytical plan. These data include the following:

- Results reported from calculated data;
- Results and study-participant-specific data (e.g. participant identifier) electronically reported to the data management center, or via interfaced systems;
- Manually transcribed or electronically transmitted results and study-participant-specific information reported directly (or upon receipt) from outside referral laboratories, satellite, or point-of-care testing locations; and
- Test report information maintained as part of the study-participant's chart or medical record.

Report format

The laboratory's test report must indicate the following items:

- Either the study-participant's name and/or a unique study-participant identifier;
- The name and address of the laboratory location where the assay was performed;
- The date and time of specimen receipt into the laboratory;
- The assay report date;
- The name of the test performed;
- Specimen source (e.g. blood, cerebrospinal fluid, urine);
- The assay result and, if applicable, the units of measurement or interpretation or both;
- Reference ranges along with age and gender of study-participants, if these affect the reference range;
- Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability;
- The records and dates of all assays performed; and
- The identity of the personnel who performed the test(s).

Pertinent reference ranges

Pertinent reference ranges (relevant or applicable to the local or study population, as defined in Section 7. Verification of Performance Specifications), as determined by the laboratory performing the tests, must be available to the authorized person who ordered the tests and, if applicable, the individual responsible for using the test results.

Laboratory assays and performance specifications

The laboratory must, upon request, make available a list of test assays employed by the laboratory and, as applicable, the performance specifications established or verified. This list may also contain expected time-to-result (turnaround time, or TAT) for each assay.

Please see example of Laboratory Test Method List in Appendix 13.

Assay results

- Information that may affect the interpretation of assay results (i.e. test interferences) must be provided upon request.
- Study-participants must be provided with pertinent updates on assay information whenever changes occur that affect the assay results or interpretation of test results. For example, if during a study a manufacturer improves the sensitivity of an assay so that result normal ranges are reported differently, this information must be communicated to the study-participants. This communication may require the combined efforts of laboratory staff, study coordinators, and Principal Investigators.
- Assay results must be released only to authorized persons and, if applicable, the individual responsible for requesting the test(s). Laboratories should maintain a list of locations to which results are reported.
- Alert and critical values
 - The Laboratory Director must define alert or critical values in consultation with clinicians served.
Note: Alert or critical values represent those results that require prompt, rapid clinical attention to avert significant study-participant morbidity or mortality.
 - Complete procedures must be in place for immediate notification of key study personnel/responsible clinic staff when assay results fall within established alert or critical ranges.
 - Communication logs must be maintained that show prompt notification of the appropriate clinical staff after obtaining test results that fall within a critical range. Documentation on these logs must include:
 - Date and time of notification,
 - Responsible laboratory individual performing notification,
 - Name and credentials of person notified at the clinic and test results given, and
 - Any problem encountered in accomplishing this task.

- When the laboratory cannot report study-participant test results within the time frames established by the laboratory or institution, the laboratory must notify the appropriate individual(s) of the delayed testing.
- If a laboratory refers study-participant specimens for testing to another laboratory:
 - The referring laboratory must not revise results or information directly related to the interpretation of results provided by the testing laboratory.
 - The referring laboratory may permit each testing laboratory to send the test result directly to the authorized person who initially requested the test.
 - The referring laboratory must retain, or be able to produce an exact duplicate of, each testing laboratory's report for the period of time defined by the laboratory or institution.
 - The authorized person who orders a test must be notified by the referring laboratory of the name and address of each laboratory location where the test was performed. (See sponsor statement regarding laboratories listed on Form FDA 1572).
- All test reports and records must be maintained by the laboratory in a manner that permits ready identification and timely accessibility.

Result modification log and errors in test results

Clinical or trial decisions or actions are often based on the results obtained by laboratory testing. If an erroneous result is reported and then corrected, it is important to replicate all of the previous information (test results, interpretations, reference intervals) for comparison with the revised information, and to clearly indicate that the result has been corrected.

- A log or other appropriate record must be kept for result modifications.

Note: Result modification is defined as reports that contain any changes to study-participant results, accompanying reference intervals and interpretations or study-participant identifiers, but not minor typographical errors that are not of any clinical consequence.
- The laboratory must ensure that all forms of study-participant reports (paper, computer displays, etc.) that display revised results must clearly indicate that the new result is a change from a previously reported result.
- The laboratory must have a system that will always provide identification of the analyst performing and completing the test result modification, along with the date and time.
 - When there are multiple sequential corrections of a single test result, all corrections must be referenced in sequential order on subsequent reports.
 - All corrections must be referenced in the study-participant report.

- A supervisor or designee must review, sign, and date the Result Modifications/Corrective Action Logs at least monthly.
- The laboratory director or designee must review the Result Modifications/Corrective Action Logs at least monthly.

Note: A laboratory may perform more frequent review at intervals that it determines appropriate.

- When errors in the reported study-participant test results are detected, the laboratory must do the following:
 - The laboratory must promptly notify the appropriate clinician and/or clinic staff member.
 - The laboratory must issue corrected reports promptly to the authorized person ordering the test and, if applicable, the individual using the test results.
 - The laboratory must maintain copies of the original report as well as the corrected report.

Archiving reports or records

- The laboratory may archive test reports or records, but these documents must remain readily available (able to be produced for review within 24 hours) for the duration defined by the laboratory or institution. These documents may be archived either on- or off-site, based on the laboratory's discretion. These records must be safely and securely kept for confidentiality purposes, and to ensure the ability to fully reconstruct the study if necessary.
- Access to archived records must be limited to authorized personnel.
- The use of correction fluids, tapes, or other methods of obliterating results must be prohibited for all research-related and clinical laboratory documents. Proper error correction techniques (e.g. single line through error, signature, and date) must be utilized at all times by the laboratory.
- Sole copies of research documents, defined as documents not having any back-up copy, must be stored by the laboratory in such a manner to protect them from damage due to the elements (fire, water, wind, humidity, etc.).

References:

42 CFR § 493.1291

42 CFR § 493.1251

9. Physical Facilities

A. Introduction to Physical Facilities

The laboratory facility must be designed in such a manner that the safety of the employees and the quality of the work is not compromised. Proper space for instrument placement, ventilation, temperature control, and operation must be available. The laboratory design must ensure the safety of the personnel when they

are moving through the work area, working with the equipment, and performing laboratory testing. Specimen movement and workflow through the laboratory must be such that opportunities for specimen loss, specimen mix-up, and exposure of laboratory personnel to biohazards are minimized.

B. Standards for Physical Facilities

General Space

- Laboratory work areas must have sufficient space so that there is no hindrance to the laboratory work.
- Laboratory walkways must be unobstructed.

Temperature and Humidity Controls

Laboratory room (ambient) temperature and humidity must be controlled so that equipment and testing is maintained within the tolerance limits set forth by the manufacturer.

Cleanliness of Facilities

All floors, walls, ceilings, and bench tops of the laboratory must be clean and well maintained.

Archiving and Storage Spaces

- Space must be allocated to the archiving of data in a secured fire-proof (preferred), fire-resistant, or fire-protected (least preferred; e.g. stored in area with operational automatic sprinkler system) environment which is accessible only to authorized personnel. These documents may be archived either on- or offsite, based on the laboratory's discretion.
Note: Retention time periods established by the laboratory or institution must meet or exceed the requirements set forth by the sponsor and/or any applicable regulatory bodies such as the FDA. Retention times are addressed in Section 8 of these GCLP Guidelines.
- Laboratory storage areas must be allocated to adequately preserve the identity, purity, and stability of laboratory reagents, control materials, calibrators, and other laboratory materials.

Molecular Amplification Work Areas

Molecular amplification procedures within the laboratory that are not contained in closed systems must have a uni-directional workflow. This must include separate areas for specimen preparation, amplification, detection, and as applicable, reagent preparation.

References:

Clinical and Laboratory Standards Institute. *Laboratory design; approved guideline*. NCCLS document GP18-A. Clinical and Laboratory Standards Institute, Wayne, PA USA, 1998.

10. Specimen Transport and Management

A. Introduction to Specimen Transport and Management

The accuracy of all laboratory test results depends on the quality of the specimen submitted. The laboratory can ensure specimen integrity when following appropriate specimen management and transportation procedures. The establishment of a sound specimen chain of custody is paramount in ensuring the aforementioned procedures are carried out properly.

B. Standards for Specimen Transport and Management

Standard Operating Procedure

The laboratory must have a documented procedure describing methods for the following tasks associated with specimens:

- Specimen collection,
- Tracking,
- Labeling,
- Preservation,
- Conditions for transportation, and
- Storage.

Specimen Labeling

The laboratory must have documented standard labeling practices in place and demonstrate evidence of adherence.

- All specimen containers must be properly identified with the unique participant identifiers.

Laboratory Testing Request Form (Requisition)

A properly completed request form/log sheet must accompany each study-participant sample to the laboratory; this documentation serves as the integral link between a specimen, the study participant from which it was collected, and the testing requested.

- The request form must document unique study-participant identifiers, specimen collection date and time, study-participant demographics, specimen type, and the collector's (phlebotomist's) identity.
- Any discrepant or missing information must be verified promptly, before specimens are processed or stored by laboratory personnel.

Specimen Acceptance/Rejection Criteria

The laboratory must have in place documented instructions for receipt and inspection of samples (including rejection criteria) and demonstrate evidence of adherence in order to ensure positive study-participant/specimen identification, adequacy, and

integrity of the specimen.

- The specimen inspection process must involve verification of the specimen container label information with the request form or log sheet.
- Specimen evaluation must also involve checking for the volume and quality of the samples (as influenced by such factors as hemolysis, lipemia, and icterus).

Audit Trails and Chain-of-Custody

The laboratory must maintain a complete audit trail for every specimen from collection to disposal or storage. Audit trails must verify the date and time an activity was performed and the personnel responsible for that activity. Procedures must be available to document the chain of custody for all specimens. Chain-of-Custody forms and/or internal laboratory tracking documents must be maintained and include the following information:

- Collection site, date, and time of specimen collection and shipping;
- Name, date, and signature of phlebotomist or person who collected the specimen from the trial volunteer;
- Name, date, time, and signature of driver (if specimen transported);
- Type of sample;
- Types of testing requested by clinician or as per study visit requirements, as defined by the protocol and study/analytical plan;
- Project, site, and collection site names;
- Identity of the receiver and inspector of the specimens (upon arrival at the testing or storage facility);
- Date and time of sample receipt;
- Laboratory sample receiver name and signature;
- Observed sample condition and documentation of other factors that may effect specimen integrity noted at time of receipt;
- Sample and/or cooler temperatures at time of receipt; and
- Transporter name and signature, if applicable.

Specimen Transportation and Shipment

- Transportation of samples must be monitored to maintain specimen integrity. This ensures that they were shipped :
 - Within the timeframe appropriate for the nature of the requested specimen and test to be performed;
 - Within the temperature interval specified;
 - Within the designated preservatives (e.g. anticoagulants) to ensure specimen integrity; and
 - In a manner that ensures safety for the laboratory, carrier, and public.
- A shipping procedure must be documented that addresses safety and logistical issues when transporting samples. This procedure must be readily available and detail the following items:
 - Proper organization, labeling (i.e. biohazard), packaging, shipping, and handling of specimens to ensure specimen integrity, while maintaining

- timely and safe shipment of specimens.
- Shipments must be prepared by following all federal and local transportation of dangerous goods regulations (e.g. IATA).
- Laboratory personnel who ship specimens must be trained and certified in hazardous materials/dangerous goods transportation safety regulations.
 - The regulation training must be renewed every two years.
 - Certification of regulation training must be on file and readily available.

Specimen Preparation, Analysis and Retention

- Documented protocol-specific procedures for specimen preparation and analysis must be available and must address (if applicable) the following:
 - Any specimens which must be retained for potential reanalysis; and/or
 - The length of time the specimens must be retained, appropriate for the type of specimen and test.

For example, EDTA specimens might be stored up to seven days at 4°C for CBC testing; however, if the EDTA was for CD4/CD8 testing, the specimen should be kept at room temperature and only for 24 hours.

- Twenty-four-hour monitoring of storage conditions (using personnel and/or electronic monitoring with alert systems) and SOPs for response to alerts must be in place to ensure the integrity of samples is maintained.
- A documented disaster recovery procedure must be available to ensure the continued integrity of specimens.

References:

49 CFR § 172

42 CFR § 493.1241

42 CFR § 493.1251

Clinical and Laboratory Standards Institute. *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture-Fourth Edition*. NCCLS document H3-A4. Clinical and Laboratory Standards Institute, Wayne, PA USA, 1998.

11. Personnel Safety

A. Introduction to Personnel Safety

Safety of laboratory employees must be a top priority for any laboratory facility. Engineering controls (e.g. shields and biosafety hoods), PPE (e.g. gloves, laboratory coats) and adequate training on the use of these tools is paramount in ensuring a safe working environment for all laboratory personnel. The laboratory safety program and training should address topics such as blood-borne pathogens, chemical hygiene, and fire safety, especially as these topics relate to site-specific characteristics such as testing of blood products or potential exposure to a specific pathogen. It should also address availability of prophylaxis measures, such as Hepatitis B vaccinations and post-pathogen exposure options.

B. Standards for Personnel Safety

Safety Equipment

- The following safety equipment must be in the laboratory to ensure the continued safety of laboratory staff and any authorized individual who may enter the laboratory:
 - Eye wash that may be plumbed (attached to sink or as “stand-alone”) or portable (sealed or refillable bottles),
 - Emergency shower/drench hose,
 - Fire extinguishers, and
 - Sharps containers.
- The laboratory must test and/or inspect equipment on the following schedule:
 - Plumbed eye wash (attached to sink or as “stand-alone”) must be flushed weekly.
 - Portable (sealed bottles) eye wash must be inspected monthly for signs of contamination and replaced prior to expiration or as required by manufacturer.
 - Portable (refillable bottles) eye wash must be cleaned and refilled weekly or as required by manufacturer.
 - Emergency shower/drench hose must be flushed weekly (preferred) but no less often than once per month.
 - Fire extinguishers must be inspected monthly to ensure proper charge and recharged as required by local standards or the manufacturer’s requirements, if applicable.
 - Sharps containers must be inspected daily and replaced when three-fourths full.

Documentation

- The laboratory must document the testing and/or inspection of safety equipment (the laboratory may forego the documentation of the sharps container inspection and replacement).
- Documents recording the testing and/or inspection of safety equipment must be signed and dated by the personnel performing the task.
- Records of inspection must be readily available.

Personal Protective Equipment (PPE)

- The laboratory employer must assess the workplace to determine if hazards are present or are likely to be present which necessitate the use of PPE. PPE must be provided to all laboratory staff. PPE includes but is not limited to:
 - Gloves (both latex and non-latex);
 - Gowns or laboratory coats (must be fluid resistant);
 - Eye protection (goggles, face shield, engineering controls such as laminar flow hoods and splash shields); and
 - Masks (required when using goggles).

- All laboratory employees must use PPE if there is a potential for exposure to blood or other potentially infectious material through any route (e.g. skin, eyes, other mucous membranes).

Material Safety Data Sheets

- To ensure proper handling and storage, the laboratory must have Material Safety Data Sheets (MSDS) or equivalent in the workplace for each hazardous chemical that they use.
 - MSDS must include chemicals that are used for testing (e.g. Ficol-Hypaque).
 - MSDS must include chemicals that are for general use (bleach, disinfectants, etc.).
 - The laboratory must maintain each MSDS in the local language, although the laboratory may maintain copies in other languages as well.
 - Laboratory personnel must be trained on reading the MSDS. There is no standard format or order of information presented within MSDS; this training is necessary to ensure they can identify and locate the different types of information contained within an MSDS, such as Hazards Identification, First Aid Measures, Handling and Storage.
 - MSDS must be readily available to employees during each work shift and to employees when they are in their work area(s).
 - MSDS may be maintained electronically as long as no barriers to immediate employee access in each workplace are created by such options.

Note: It is recommended that an index of MSDS be maintained and that all MSDS should be updated periodically, within a two-year period, to ensure staff is equipped with the most current hazard and first aid information.

Safety Policies

Safety policies defined according to regulatory organizations such as the Occupational Safety and Health Administration (OSHA) or the International Organization for Standardization (ISO) must be present in the laboratory. The following safety policies must be in place to ensure the continued safety of laboratory staff and any authorized individual who may enter the laboratory:

- Standard Precautions/Universal Precautions Policy. This policy or group of policies defines all human biologic specimens as potentially infectious and addresses topics of consideration when dealing with potentially infectious specimens, such as hand care, PPE, working with open lesions, handling contaminated needles and other sharp objects, autoclaving, and disposal of materials.
- Chemical Hygiene/Hazard Communication Plan. This policy or group of policies addresses aspects of safe chemical handling. Chemical Hygiene policies typically address storage and utilization and disposal of chemicals, with the goal of minimizing exposures and risks associated with those chemicals. Hazardous Communication policies typically provide information

- about the identities and hazards of chemicals, required appropriate labeling, MSDS, exposure first aid, etc.
- Waste Management Policy. This policy details appropriate measures to take when disposing of waste materials to ensure continued human and environmental health.
 - General Safety Policies. These policies address less specific topics as they relate to laboratory safety, such as fire and back safety.
 - Safety Equipment. These policies typically detail all available safety equipment, their purposes, and proper utilization.

Safety Training

- All laboratory staff must receive safety training. At a minimum, the safety training must include:
 - Blood-borne pathogens, (includes information on standard precautions, risks and types of infectious diseases contracted through exposure, proper safeguards, and methods of handling potential contaminants);
 - PPE. All laboratory employees must be trained on the proper use of PPE prior to starting work in the laboratory (i.e. at employment), and periodically thereafter. Such training must include/describe:
 - When PPE is necessary;
 - What PPE is necessary;
 - How to properly wear PPE;
 - What are the limitations of PPE; and
 - The proper care, maintenance, useful life, and disposal of PPE.
 - Chemical Hygiene/Hazard Communications (how to properly handle chemicals and what to do to avoid exposure and in the event of an exposure);
 - Use of safety equipment in the laboratory (eyewash, emergency shower, fire extinguisher, etc.);
 - Use of cryogenic chemicals-dry ice and liquid nitrogen (if handled by laboratory for shipping, receiving and/or storage of specimens, supplies, and reagents);
 - Transportation of potentially infectious material-IATA (proper packaging and labeling of shipped materials);
 - Waste management/biohazard containment (appropriate disposal of biohazards); and
 - General safety/local laws related to safety.
- Documentation of completion of safety training must be maintained.
 - Documentation of safety training must note the presenter, a brief description of the topics covered, and the date of the training.
 - Safety training, at a minimum addressing the above topics, must be completed before any employee begins working in the laboratory and on a regular basis thereafter. Ongoing safety training must take place each calendar year. Documentation of this training must be signed and dated by the employee.

Safety Incident Reporting

- Safety-related incidents must be documented and submitted to the Laboratory Manager or designee. Examples of safety-related incidents include, but are not limited to:
 - Injuries (needlestick, sharps injury, falls, burns, etc.);
 - Chemical Exposure;
 - Malfunctioning equipment posing a safety risk (e.g. potential for electrical shock); or
 - General accidents.
 - Submitted safety incident reports must be reviewed and signed by the Laboratory Manager or designee on a regular basis, but this review must not exceed one month from time of submission. Timeliness of incident reports will allow for rapid correction of a problem to prevent recurrence.
 - Safety reports must be incorporated into the Quality Management (QM) program. This would allow the laboratory to note trends and correct problems to prevent recurrence.

Note: To maintain employee confidentiality, all personal identifiers must be removed prior to submission to the Quality Management team.

References:

29 CFR § 1910.1200

ANSI Z358.1-2004. Emergency Eyewash and Shower Equipment. American National Standards Institute, 01-Jan-2004

Clinical and Laboratory Standards Institute. *Clinical Laboratory Safety*. CLSI document GP-17A. Clinical and Laboratory Standards Institute, Wayne, PA USA, 1996.

Refer to manufacturer's websites for downloadable MSDS. Other websites for downloading MSDS are also available on the internet (i.e. <http://www.msds.com>, <http://www.msdssearch.com>).

12. Laboratory Information Systems

A. Introduction to Laboratory Information Systems

Clinical laboratories perform the laboratory tests, endpoint assays, and point-of-care testing as requested by physicians or as directed by clinical trial protocols. These laboratories must often generate the correct data (often in the form of a report) on the appropriate study participant and deliver or transmit the report to a predetermined location or individual, such as a Principal Investigator within a clinically useful period of time.

A computer alone does not constitute a Laboratory Information System (LIS). An LIS consists of computer hardware, software, and data; it performs or assists with functions of test ordering, delivery of necessary specimens to laboratory, clerical duties of specimen receipt, as well as unique identifier generation, aliquoting, worksheet generation, order information transmission to analyzers, translation of

instrument output into usable results, storage of data, report generation, and QC functions (e.g., Laboratory Data Management System, or LDMS). Reports generated by the LIS must be concise, readable, standardized in format, and chronological.

B. Standards for Laboratory Information Systems

Laboratory Information System (LIS) Validation

The laboratory must maintain documented validation data for the LIS. All steps and results of validation must be documented and available for review.

- Document the installation of new computer programs when first installed. Any changes or modifications to the system must also be documented, and the laboratory director or designee must approve all changes before they are released for use.
- Document testing of all possible anticipated permutations of processes (for example, entry of normal, abnormal low, abnormal high, critical and absurd results).
- Document testing and validation of all calculations that are performed by an LIS.
- Document the validation of all data transmitted from the LIS to other computer systems and their output devices.
- Document the verification of reference ranges and comments as well as actual testing results.
- Document a validated emergency preparedness system.

Generation of Reports

- The LIS must be capable of generating accurate and complete copies of study-participant results.
- The laboratory must be capable of reprinting a complete copy of archived study-participant test results.
 - Results must include original reference ranges and interpretive comments.
 - Results must include any flags or footnotes that were present in the original report.
 - Results must include the date of the original report.
- Stored study-participant result data and archival information must be easily and readily retrievable within a time frame consistent with study/trial needs (e.g. within 24 hours).

Audit Trails

- Computer time-stamped audit trails must be used by the LIS.
- The laboratory must ensure that, when individual tests from a single test order (e.g. multiple tests with same accession number) are performed by separate individuals and the test result is entered into the LIS, the system

- If auto-verification is used, then the audit trail must reflect that the result was verified automatically at a given time and date.

Access and Security

- The laboratory must ensure that LIS access is limited to authorized individuals.
- Documentation must be maintained indicating that all users of the computer system receive adequate training both initially and after system modification.
- The laboratory's LIS policies must define those who may only access study-participant data and users who are authorized to enter study-participant results or modify results.
- The laboratory must establish user codes to permit only specifically authorized individuals to access study-participant data or alter programs.
 - A user code is typically assigned to each employee upon employment or at the point of completion of training.
 - All employees who will use the system should have a user code that is linked to an appropriate level of access, as determined by his/her job requirements.
 - The system typically maintains active employees' access codes as a database from which hard-copy reports may be created.
 - User access codes should be inactivated upon termination of an employee. The user code, once inactivated, should not be used for another employee.
 - User codes must not be shared with coworkers.
- The security of the system must be sufficient to prevent unauthorized personnel from installing software. Unauthorized installation of software may expose the system to a security breach, virus, worm, or spyware.

Documentation

The laboratory must maintain a written SOP for the operation of the LIS and should follow these guidelines:

- Procedures must be appropriate and specific to the day-to-day activities of the laboratory staff as well as the daily operations of the Information Technology staff. Current use of LIS must match policy and procedure documents.
- The purpose of the computer program, the way it functions, and its interaction with other programs must be clearly stated.

Technical Support and Preparedness

The laboratory must have a documented back-up system and accompanying procedure for the LIS based on the following guidelines in an effort to maintain integrity of data and reduce impact and severity of unscheduled downtimes and

destructive events:

- The laboratory must have a procedure outlining the technical support staff and/or vendor for the system including emergency contact information.
- Documented procedures and disaster-preparedness plan must exist for the preservation of data and equipment in case of an unexpected destructive event (e.g., fire, flood) or software failure and/or hardware failure, allowing for the timely restoration of service.
- Documented procedures must exist to ensure reporting of study-participant results in a prompt and useful fashion during partial or complete LIS downtime, to include:
 - Steps to prevent the corruption and/or loss of active data,
 - Procedures for periodic backing up and storing of information,
 - Procedures for off-site storage of back-up data, and
 - Procedures for restoring information from backed-up media.

Note: The procedures must specifically address the recoverability of study-participant information, the physical environment, and equipment.
- The LIS should be run in a closed environment, as much as is practical, to protect participant confidentiality.

References:

21 CFR § Part 11

College of American Pathologists Commission on Laboratory Accreditation, Accreditation Checklists, April 2006.

Clinical and Laboratory Standards Institute. Protocols to Validate laboratory Information Systems. CLSI Document AUTO8-P. Clinical and Laboratory Standards Institute. Wayne, PA USA, 2005.

13. Quality Management

A. Introduction to Quality Management

Quality Management (QM) is composed of the coordinated activities to direct and control an organization with regard to quality; it is a systematic approach to achieving quality objectives. A QM plan (or program) identifies the specific steps that a laboratory will take to ensure that quality and study-participant safety is being maintained.

External Quality Assurance (EQA) is an integral component of a total QM Program. EQA specimens must be analyzed, quality assured and reported just as study-participant specimens are tested in the laboratory. EQA provides the opportunity for a laboratory to compare results and/or interpretations obtained on a set of specimens, photographic slides, and/or case studies with those of a peer group (a group of laboratories performing the same analyses with similar methodologies). If available, this external evaluation of the laboratory's analytical performance is paramount to a complete quality assessment of laboratory operations.

B. Standards for Quality Management

Quality Management Plan

- The laboratory must have a documented Quality Assurance Plan/Quality Management Program. This program must:
 - Be developed and maintained by an individual or a group of individuals that is (are) separate and distinct from the testing personnel of the laboratory, if practical and possible;
 - Be integrated with the institutional Quality Assurance/Quality Management program, if applicable;
 - Detail an operational plan that describes the goals and objectives of the QM program;
 - Be accessible to all staff;
 - Be designed to monitor, assess, and (when indicated) correct problems identified in pre-analytic, analytic, and post-analytic systems as well as general systems;
 - Address monitoring to include complaints and incidents;
 - Include all aspects of the laboratory's scope of care;
 - Address any problem that could potentially interfere with study-participant care or safety while addressing risk assessment;
 - Include information on how the quality and safety information is to be collected and communicated;
 - Include control activities (e.g. QC and EQA);
 - Include any measurable key indicators of quality that are related to the lab operations that are explicitly targeted for improvement:
 - Key indicators must reflect activities that are critical to and/or have a significant impact on study-participants or study outcomes.
 - *Examples of key indicators:* Test turnaround time, specimen acceptability, test order accuracy, safety events.
 - The number of key indicators monitored by a laboratory should be proportional to the scope of the laboratory's services.
 - The laboratory must record investigation of key indicators and record corrective and/or preventive actions taken.
 - There must be evidence of appropriate follow-up action taken as a result of monitoring, as well as an evaluation of the effectiveness of corrective action undertaken with these key indicators.
- Include results of ongoing measurement activities of these key indicators compared with internal or external benchmarks and trended over time (e.g. quality indicators should be measured and compared against defined quality goals).

Please see example of Quality Management Plan in Appendix 14.

- The laboratory must be able to use this QM document for guidance when conducting annual appraisals of effectiveness. The QM program documentation must demonstrate regular (at least annual) review by the laboratory director or designee(s). This review must ensure that recurrent problems have been addressed and that new or redesigned activities have been evaluated. The laboratory must be able to provide evidence of

appraisal of its QM plan, to include:

- Annual written QM report, and
 - Revisions to laboratory policies and procedures and to the QM plan.
- The laboratory must provide evidence of implementation of this QM plan including:
 - Minutes of committee meetings,
 - Results of ongoing measurement, and
 - Documentation-related complaint investigation.

Internal Audits

The laboratory's monitoring of the QM program must include an internal auditing program. Internal audits involve an individual or a group of laboratory personnel performing a self-assessment comprised of a comprehensive comparison of the actual practices within the laboratory against the laboratory's policies and procedures (e.g. personnel files, training documentation, QC performance, review of SOPs). These audits may also compare the laboratory's practices against a standard set of guidelines or standards. All findings (of both compliance and noncompliance, or deficiencies) that result from the internal audit should be documented in an organized format to allow for appropriate corrective actions and follow-up through resolutions.

Testing Turnaround Times

The laboratory must have a list of assay turnaround times readily available to all laboratory staff as well as to customers of the laboratory.

Laboratory Communication Plan

The laboratory must have a non-retaliatory policy for employees to communicate concerns regarding testing quality or laboratory safety to laboratory management.

C. Standards for External Quality Assurance

For all laboratories participating in an EQA Program, the following standards apply:

- Laboratories should enroll in EQA programs that cover all study protocol analytes.
 - EQA programs for study protocol analytes must be approved by DAIDS.
 - Laboratory performance in DAIDS-approved proficiency-testing programs will be monitored for successful performance by DAIDS or its designee.
- EQA specimen testing should be rotated among staff members.
- The laboratory director (or equivalent) or designee must review all external quality assurance data.
Note: Documentation of the designee must be included in the current QC or QM program.
- Regular supervisory review of EQA Program results must be evidenced by:
 - Signature and date of review of *all* results, and

- Documentation of corrective action taken and appropriate preventive action in response to any unacceptable results.

References:

42 CFR § 493.1233

42 CFR § 493.1701

College of American Pathologists Commission on Laboratory Accreditation, Accreditation Checklists, April 2006.

NCCLS. *Application of a Quality Management System Model for Laboratory Services; Approved Guideline-Third Edition*. NCCLS document GP26-A3. NCCLS, Wayne, PA USA, 2004.

NCCLS. *A Quality Management System Model for Health Care; Approved Guideline-Second Edition*. NCCLS document HS1-A2. NCCLS, Wayne, PA USA, 2004.

Version History

Modifications are made to the DAIDS Guidelines for Good Clinical Laboratory Practice (GCLP) Standards via letters of amendment.

The table below describes the version history of, and modifications to, the DAIDS Guidelines for Good Clinical Laboratory Practice (GCLP) Standards.

Document History and Modifications Date	Version	Modification	Comment	
21 July 2011	2.0	Letter of Amendment 1 (10 June 2011)	Item 1	Cover Page: author list revised
			Item 2	Section 1., Sponsor Statement – Introduction section, Food and Drug Administration’s Form 1572: revised language, clarification of specific requirements in Section 4
			Item 3	Section 4., Equipment - Subsection B., Standards for Equipment, Documentation Guidelines: language added, clarification that all laboratory equipment should be listed on an inventory document
			Item 4	Section 4., Equipment – Subsection B., Standards for Equipment, General Guidelines: added language, clarification of policy/procedure for temperature monitoring in absence of staff
			Item 5	Section 4., Equipment - Subsection B., Adjustable and Fixed-volume Automatic Pipettors: revised language, clarification of volumetric accuracy and reproducibility check requirements, as well as recalibration
			Item 6	Section 4., Equipment - Subsection B., Thermometers: added language to indicate NIST-certified (or equivalent) thermometers follow manufacturer’s recommendations for calibration and expiration date
			Item 7	Section 6., Test and Control - Subsection B., Frequency of Quality Control Testing and Types of Control Materials: language added, clarification of frequency for FDA-approved, CLIA-waived tests, as well as non-FDA approved tests

Document History and Modifications Date	Version	Modification	Comment	
21 July 2011	2.0	Letter of Amendment 1 (10 June 2011)	Item 8	Section 7., Verification of Performance Specifications - Subsection B. Standards for Performance Specifications: language added, clarification regarding precision validation for qualitative tests
			Item 9	Section 8., Records and Reports - Subsection B., Standards for Records and Reports, Assay Results: language added, clarification of process to indicate the laboratories maintain a list of locations to which results are reported
			Item 10	Section 13., Quality Management - Subsection C., Standards for External Quality Assurance: language added, clarification of EQA specimen testing rotation among staff members in laboratories

Glossary

accession: The process of identifying a specimen and entering a unique specimen identifier into laboratory records

accuracy: A measure of how close a measured value is to the true value

alert values: See critical values

aliquot: A portion of a specimen or product used for testing

aliquotting: The action of dispensing a product or specimen into smaller quantities. A portion of this product or specimen (aliquot) is typically used for testing or placed into long term storage.

American National Standards Institute: Organization that oversees the creation, proliferation, and use of thousands of rules and guidelines that effect a broad range of businesses; also engaged in accrediting programs that assess conformance to standards, such as ISO 9000 management systems (<http://www.ansi.org>)

American Society for Testing and Materials: Organization that develops and generates voluntary standards that are used worldwide (<http://www.astm.org>)

AMR: Abbreviation for Analytical Measurement Range

analyte: The substance being measured in an analytical procedure

Analytical Measurement Range: The range of analyte values that a method can directly measure on the specimen (without any pre-treatment not included as a procedural step of the assay)

analytical run: An interval, period of time, or number of specimen for which the precision and accuracy of the method is expected to remain stable

analytical sensitivity: The estimate of the lowest concentration of an analyte that can be measured

analytical specificity (Analytical interferences): The estimate of the systematic error caused by other materials that may be present in the specimen being analyzed (e.g. lipemia, drugs)

ANSI: Abbreviation for American National Standards Institute

ASTM: Abbreviation for American Society for Testing and Materials

audit: An activity to determine through investigation the adequacy of, and adherence to, established procedures, instructions, specifications, codes, and standards or other applicable contractual and licensing requirements, and the effectiveness of implementation

audit trail: Documentation that allows reconstruction of the course of events

authorized persons/personnel: The staff designated by an authorizing organization that is responsible for a work activity's technical and administrative objectives

back-up copy: A magnetic copy of data, software, user-developed application, or operating parameters associated with an automated system and not considered the original

benchmark: A specific standard against which some aspect of performance can be compared

blood-borne pathogens: Microorganisms that are present in human blood and cause diseases in humans; while HBV, HCV and HIV are specifically identified in the standard, the term includes any pathogenic microorganism that is present in human blood or other potentially infectious material that infects and causes diseases in persons who are exposed to blood containing the pathogen.

calibrator: A material of known composition or properties used for calibration of an analytical instrument or procedure.

calibration: The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements

central laboratory: Laboratory (or a group of laboratories) utilized by all sites participating in a given clinical trial for performance of certain assays, typically as a result of desired standardization of results and/or assay complexity.

certification: Documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are acceptable. Personnel certification is proof that a person has achieved a certain level of qualification.

CFR: Abbreviation for Code of Federal Regulations

chain of custody: Procedures to account for the integrity of each specimen by tracking its handling and storage from point of specimen collection to final disposition of the specimen

Chemical Hygiene/Hazard Communications: A written program developed and implemented that sets forth procedures, equipment, personal protective equipment (PPE) and work practices that are capable of protecting employees from the health hazards presented by hazardous chemicals used in that particular work place

CLIA: Clinical Laboratory Improvement Act/Amendments, 1988: Clinical Laboratory Improvement Act of 1967 (and amendments of 1988) which sets the guidelines for any clinical laboratory which tests material obtained from human clients, i.e. blood, tissue, swabs, etc. CLIA is administered through the U.S. Health Care Financing Administration (HCFA).

Clinically Reportable Range: The range of analyte values that a method can measure with additional pre-treatment of the original specimen and which thereby extends the reportable range of an assay/ methodology

Closed Information System: A laboratory information system that requires no input from sources outside of the facility or its realm of control (i.e. all entries are made by the site's laboratory staff; opposite of an Open Information System.)

Code of Federal Regulations: The general body of regulatory laws governing practices and procedures performed by federal administrative groups

Coefficient of Variation (CV): A statistical representation of the precision of a test. The CV is often expressed as a percentage of the ratio of the standard deviation to the mean, (standard deviation/mean) X 100.

competence: Demonstrated ability to apply knowledge and skills

compliance: The act or process of fulfilling requirements

confidentiality: Prevention of disclosure, to other than authorized individuals, of information which is considered private

contract laboratory: Laboratory used on contractual basis to perform limited list of assays associated with a clinical trial.

control chart: A graphic representation of a measured variable showing process generated control limits and data values as plotted points (See also Levy-Jennings Chart)

control material: A control solution that is available whose concentration is already known

corrective action: Steps that are taken to remove the cause(s) of a detected nonconformity or other undesirable situation in order to prevent recurrence or to achieve quality improvement at any stage of the process

critical values: Results that require prompt, rapid clinical attention to avert significant study-participant morbidity or mortality

CRR: Abbreviation for Clinically Reportable Range

Curriculum Vitae: A summary of academic and professional history and achievement.

deficiency: A situation in which a prescribed action was not carried out or an applicable requirement was not met

designee: One who has been indicated as responsible for a particular responsibility

detection limit: Lowest concentration of an analyte that can be reliably detected

diagnostic assay: Testing performed to aid in medical diagnosis (e.g., Hepatitis B Surface Antigen)

Document Control Plan: Description of steps to manage individual documents throughout their progression of development, including creation, organization, versioning, access control, and archiving

documentation: Written material that provides proof of work performed and/or and event that occurred

endpoint assay: Testing performed to aid in monitoring of a trial's effectiveness for treatments and prophylaxis/prevention

engineering controls: Well designed work areas and equipment that minimize or eliminate exposure to hazards

EQA: An abbreviation for External Quality Assurance

External Quality Assurance: An external evaluation and comparative assessment of a laboratory's analytical performance or proficiency in conducting laboratory assays. See also proficiency testing.

FDA: Abbreviation for Food and Drug Administration

GLP: Abbreviation for Good Laboratory Practice

Good Laboratory Practice: A world-wide quality management system for the design, conduct and reporting of studies in support of licensing/ product registration of drugs/food/chemicals for human or veterinary use

guidelines: A statement or other indication of policy or procedure by which to determine a course of action

IATA: Abbreviation for International Air Transportation Association.

IND: Abbreviation for Investigational New Drug.

Investigational New Drug: A drug that is under study but does not yet have permission from the U.S. Food and Drug Administration (FDA) to be legally marketed and sold in the United States.

inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources

Key Indicators: A significant and descriptive factor that reflects activities critical to patient outcome, affect a large proportion of the laboratory's patients, or that have been problematic in the past

Laboratory Data Management System: An information system that manages the collection, storage, and transportation of samples from clinical research units to either the researching laboratory or the specimen repository; the system is capable of recording the tracking steps of the specimen from the point of collection to the final disposition as consumed, discarded, or long-term storage

Laboratory Information System: consists of computer hardware, software, and data; it performs or assists with functions of test ordering, delivery of necessary specimens to laboratory, clerical duties of specimen receipt, as well as unique identifier generation, aliquoting, worksheet generation, order information transmission to analyzers, translation of instrument output into usable results, storage of data, report generation, and QC functions

LDMS: Abbreviation for Laboratory Data Management System

Levy Jennings Chart: A commonly used control chart in which individual control measurements are plotted directly on a chart with limit lines drawn either as mean \pm 2s or mean \pm 3s. Time is displayed on the x-axis usually in terms of days or runs. This chart is used to assess precision as it reflects on the stability for a specific assay.

licensure (certification): The granting of legal permission to provide a specific service by a regulatory body to an organization that meets certain expectations

LIS: Abbreviation for Laboratory Information Systems

lot: A quantity of homogeneous material assembled from uniform components under similar conditions that function in a uniform manner

Material Safety Data Sheets: Information provided by manufacturers describing the chemical and physical properties of a substance as related to its safe handling and storage

matrix: All the physical and chemical constituents of the material or specimen, except the analyte

mean: the simplest statistic, an average, is calculated by adding all related data points, then dividing the resulting sum by the number of data points that were added together

method validation: The process of testing a measurement procedure to assess its performance and to validate that performance is acceptable

modified FDA-approved test: Assay, procedure or system that does not follow the manufacturer's procedure without deviation, or is used for clinical indication(s) that is (are) not approved by the manufacturer.

morbidity: The state of carrying a disease or the relative incidence of a disease

mortality: The number of deaths in a given time or place, within a population

MSDS: Abbreviation for Material Safety Data Sheet

NIST: Abbreviation for National Institute of Standard and Technology

noncompliance: A situation in which a requirement is not met

non-waived test: Laboratory tests that are not classified as waived; often referred to as tests of moderate- or high-complexity (e.g. a complete blood count with a manual differential is considered to be test of high-complexity)

normal range: By convention, the normal range is set to cover 95% of values from a normal population. Normal range has been replaced by the more neutral term, reference values. See reference range.

OECD: Abbreviation for Organization for Economic Cooperation and Development

Open Information System: A laboratory system that allows entry of information, such as orders or test results, from a remote location and by a third party; requires access to the onsite information system via internet, networking, or interfacing. Opposite of Closed Information System.

Organization for Economic Cooperation and Development: The OECD groups 30 member countries sharing a commitment to democratic government and the market economy. Best known for its publications and its statistics, its work covers economic and social issues from macroeconomics, to trade, education, development and science and innovation. In regards to GLP, "The primary objective of the OECD Principles of GLP is to ensure the generation of high quality and reliable test data related to the safety of industrial chemical substances and preparations in the framework of harmonising testing procedures for the Mutual Acceptance of Data (MAD)". (<http://www.oecd.org>)

package insert: The written pamphlet in every diagnostic test kit which includes instructions for proper use of the kit. In addition, the package insert contains some or all of the following: information on intended use; summary and explanation of the test; principles of the procedure; reagents provided; special precautions; specimen collection, storage and transport; materials provided/not provided with kit; procedural limitations; performance characteristics; results; and QC.

parallel testing: Side-by-side comparison of existing and new product lots to demonstrate the reproducibility of the new product lot within defined acceptance criteria

Personal Protective Equipment: Specialized clothing or equipment worn by an employee to protect against health and safety hazard

point-of-care testing: A test conducted by a health professional during a patient encounter. Test results are typically available a few minutes after the specimen is collected.

post-analytic variables: Steps in the overall laboratory process between completion of the analytic phase of testing and results receipt by the requesting physician

PPE: Abbreviation for Personal Protective Equipment

pre-analytic variables: Steps in the process prior to the analytic phase of testing, starting with the physician's order

precision: A measurement of the scatter or random error between repeated measurements expressed statistically as the standard deviation

preventive (or preventative) actions: Steps taken to eliminate the causes of a potential nonconformity or other undesirable situation in order to prevent occurrence

preventive (or preventative) maintenance: A time or cycle-based program with planned maintenance activities to prevent equipment malfunctions

primary laboratory: Laboratory determined to be the main site of performing specimen assays for a given protocol; this laboratory is typically a local laboratory, often physically located on the site of the clinical trial facility

processing laboratory: Laboratory that serves to perform primarily the pre-analytical tasks associated with study-participant specimens, such as collection, centrifugation, aliquoting, and storage

proficiency testing: The determination of laboratory performance by comparing and evaluating calibrations or tests on the same or similar items or materials by two or more laboratories in accordance with predetermined conditions

QA: Abbreviation for Quality Assurance

QAU: Abbreviation for Quality Assurance Unit

QC: Abbreviation for Quality Control

QM: Abbreviation for Quality Management

qualitative tests: Determining the presence or absence of analytes in the specimen without assigning numerical values

Quality Assurance: All the planned and organized activities implemented within the laboratory system to provide adequate confidence that the test results provided are as accurate and reliable as possible

Quality Assurance Plan: The document that provides guidance for the operation of a laboratory. This document generally contains, but is not limited to, information pertaining to: laboratory personnel, sampling procedures and sample rejection criteria, sample handling and chain of custody routines, the equipment employed by the laboratory, analytical methods, validation and reporting, calibration and QC procedures, equipment

maintenance, routine procedure for precision and accuracy, method validation, verification and corrective actions, and health and safety policy and training.

Quality Assurance Unit: Any person or organizational element, except the study director, designated by testing facility management to perform the duties relating to quality assurance of non-clinical laboratory studies (21CFR58.3)

Quality Control: The part of quality management focused on operational techniques and activities to determine whether the process exhibits nonrandom variation

Quality Management: Coordinated activities to direct and control an organization with regard to quality.

Quality Management program: Any management system that addresses all areas of an organization, emphasizes customer satisfaction, and uses continuous improvement methods and tools

quantitative tests: The accurate numerical determination of the quantity of an analyte present in a specimen

Reagent Grade Water: Water suitable for use in making up critical reagents or for use in sensitive analytical procedures

reference intervals: See reference range

reference materials: A material or substance in which one or more properties are sufficiently well established to be used for the calibration of an apparatus, for the assessment of a measurement method, or for assigning values to materials

reference range: The specified interval bound by two limiting values that contains 95% of the values found in healthy individuals. See Normal range.

referral laboratories: A laboratory that conducts tests for other laboratories; reference laboratories are usually large and may be independent or hospital based

regulation: A requirement having the force of law

requirement: Any rule, order, regulation, law, policy, or contractual agreement that directs or compels a specific action

reportable range: The useful analytical range of a laboratory method, i.e., the lowest and highest test results that are reliable and can be reported

result modification: Reports that contain any changes to study-participant results, accompanying reference intervals and interpretations, or study-participant identifiers, but not minor typographical errors that are not of any clinical consequence

risk assessment: The establishment of a relationship between the risks and benefits of potential hazards to which people may be exposed by identifying potential failure modes, determining severity of consequences, identifying existing controls, determining probabilities of occurrence and detection, and evaluating risks to identify essential control points

safety assay: Test that is performed to both monitor potential adverse events and to verify the study-participant's continued satisfaction of study inclusion/exclusion criteria, as appropriate, for each protocol.

self-assessment: An assessment performed by the responsible organization to determine how well it is performing its job and meeting its responsibilities

sensitivity: The probability that a test will detect an analyte when it is present in a specimen

sharps: Any object that can penetrate the skin, including, but not limited to, needles, scalpels, and broken capillary tubes

SOP: Abbreviation for Standard Operating Procedure

source documentation: Original documents, data, and records in electronic and hard copy formats

specificity: The probability that a test will be negative when an analyte is absent from a specimen

sponsor: The company, institution, government agency, group or individuals who assumes financial and legal responsibility for a clinical trial; the sponsor is also responsible for supervising and overseeing the trial

stability: The extent to which a product retains the same properties and characteristics that it possessed at the time of manufacture, throughout storage, and use

standard: A material of reference of known purity whose concentration is already known to a high degree of accuracy

standard deviation: A statistical measure of variation used to describe a frequency distribution; the square root of the average of the squared deviations from the mean; to calculate a standard deviation, the data points are first averaged, then this mean value is subtracted from each data point, giving the “difference score”; these difference scores are then each squared, and the squared difference scores are added together; the sum of the squared difference scores is then divided by the number of original data points less one, or “n-1”; a square root of the resulting quotient is the standard deviation

Standard Operating Procedure: Detailed, written instructions to achieve uniformity of the performance of a specific function

standard precautions: An approach of infection control in which all specimens containing or contaminated with human blood and body fluids are treated as if infectious; formerly known as Universal Precautions

tolerance limits: Specified interval giving upper and lower boundaries of permissible values

traceability: The ability to relate an identifiable measurement or value to a known standard, through an unbroken chain of comparisons all having stated uncertainties

turnaround time: Length of time from when a sample arrives in the laboratory and when the final result is issued to the ordering physician. .

validation: See verification

verification: The formal process of confirming and documenting that specified requirements have been met

unmodified FDA-approved test: Assay, procedure or system that follows the manufacturer's procedure without deviation, and is used only for the clinical indication(s) approved by the manufacturer.

waived test: Test that can be performed by technical personnel as well as non-technical personnel, and either in a clinical or non-clinical setting; the test is simple, relatively error-proof, and if error should occur, the test would cause little or no harm. The tests that are listed in the original regulation are: (1) Dipstick or tablet reagent urinalysis (non-automated) for bilirubin, glucose, hemoglobin, ketone, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen; (2) Fecal occult blood; (3) Ovulation tests--visual color comparison tests for human luteinizing hormone; (4) Urine pregnancy tests--visual color comparison tests; (5) Erythrocyte sedimentation rate--non-automated; (6) Hemoglobin--copper sulfate--non-automated; (7) Blood glucose by glucose monitoring devices cleared by the FDA specifically for home use; (8) Spun microhematocrit; and (9) Hemoglobin by single analyte instruments with self-contained or component features to perform specimen/reagent interaction, providing direct measurement and readout. Since that time, new tests and methods are regularly gaining the designation of waived status; the manufacturers should provide documentation regarding the status of methods. The website for the Centers for Disease Control and Prevention (<http://www.cdc.gov/index.htm>) also contains up-to-date information regarding additions and revisions of testing complexity statuses.

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Appendix Descriptions

Appendix 1: Study or Analytical Plan

Quality First Laboratory officials have determined that a recently received study protocol is not adequate in addressing all tasks and processes that must be carried out by its laboratory personnel when working with clinical trial specimens. For this case, they have decided to create a formal laboratory-specific supplement in the form of an analytical or study plan. In order to ensure the plan describes all laboratory-specific components of the trial, defining study objectives and design for the conduct of the study within the laboratory setting, they will use a template to develop the study plan.

Appendix 2: Training Attendance Log

Velma Young, fictitious manager of Quality First Laboratory, wishes to train the key operators on the ChemSmart 2000, by Ingenious. In an effort to capture full documentation of the training, she creates a training attendance log (TAL). This sample training attendance log provides an appropriate level of documentation for the training given to employees of the laboratory. This training log captures important details of the training such as topics, trainer information, and appropriate signatures verifying that the training was given/received. This log may be kept with personnel files for easy retrieval.

Appendix 3: Signature Sheet

Within Quality First Laboratory, personnel often use their initials to document performance of a task; the laboratory information system employs “tech codes” to log identities of personnel who execute functions, such as result entry, within the system. Velma Young, Laboratory Manager, must be able to quickly identify personnel by their printed initials or tech codes. This sample key is useful in linking signatures, initials, and tech codes (if applicable) as these identifiers are used throughout the laboratory’s documentation, to a legible printed name. This key ensures complete audit-ability of laboratory records.

Appendix 4: Standard Operation Procedure in CLSI Format

As a component of implementing a new assay within Quality First Laboratory, a stepwise procedure must be created for this assay to ensure consistently correct performance of the testing and to provide a reference to personnel for additional assay information. This SOP for *HDL Cholesterol* demonstrates an example of a standard format that is compliant with CLSI recommendations for SOP creation. Note the components of the procedure as they relate to the SOP format guidelines given in Section 5: *Testing Facility Operations*. Use of this or a similar format will also ensure ease of use of the SOP and consistency throughout a laboratory’s entire collection of SOPs.

Appendix 5: Levy-Jennings Control Chart

Quality First Laboratory must document the results of all Quality Control runs. This Levy-Jennings (LJ) control chart is an example of an appropriate chart that may be utilized by personnel to document QC data. This chart allows for plotting of results by date of the month (on the horizontal or X-axis) according to these results’ relationships to pre-established value means, \pm one standard deviations (the calculated standard

deviation multiplied by positive one and negative one), \pm two standard deviations (standard deviation multiplied by positive two and negative two), and \pm three standard deviations (standard deviation multiplied by positive three and negative three). One chart is created for each QC material used. The calculated mean and standard deviation results are manually entered for the corresponding fields on the vertical or Y-axis.

This chart may also be created to record results by run number if multiple runs are performed on a given date. When completed appropriately, this record will also capture other vital QC documentation such as the control material description/lot number and routine managerial review.

These charts are used to document QC data to allow for determination of acceptability of QC run, and to aid in detection of shifts and trends in control data. The charts are a quick visual representation that assists with the evaluation of rule failures (e.g. if Westgard rules are employed by a laboratory, the graphing of data supports identification of 1-2S, 2-2S, and etc. failures). Often, the type of rule failure will assist with determining appropriate troubleshooting steps to effectively resolve the contributing instability within the testing system.

Appendix 6: Quality Control Log

The QC log, as represented in this appendix sample, is a very close companion to the LJ Control Chart above. This sample QC log allows for Quality First Laboratory's recording of the control material run information (date, time, technologist, and result) and links the data to the accompanying LJ chart. This document also allows for recording interpretation of the acceptability for the QC run and provides for complete documentation of appropriate corrective action.

The documented corrective action then becomes a tracking mechanism to help in discovery of larger testing system trends and issues with stability, and also allows users to review corrective action steps taken in the past to resolve similar issues they may be currently facing.

Like the LJ chart, this record will also capture the other vital QC documentation such as lot numbers, acceptable range, SD, and routine managerial review.

Method Validation

In the event a laboratory adopts a new method or assay, method validation must be performed. Typically, the experiments are performed in the following order:

- Reportable Range
- Analytical Sensitivity (if applicable)
- Precision, within-run
- Analytical Specificity (if applicable)
- Precision, across-runs
- Accuracy
- Reference Interval

The following example follows one course of actions that could be taken by a fictitious laboratory, named Quality First Laboratory, and its manager, Velma Young, to validate a

cholesterol assay performed on a new analyzer acquired by the laboratory, the ChemSmart 2000, manufactured by Ingenious.

- **Appendix 7: Reportable Range Experiment Results**

This linearity evaluation example represents a set of tables that allows entry of an experiment's results from analysis of five samples (CLSI recommends a minimum of four) that have assigned concentrations.

Quality First's Laboratory Manager, Velma Young, wishes to validate the manufacturer's data regarding the useful analytical range (lower and upper limits of test results that are reliable for reporting purposes) of the new cholesterol method as it is performed on the ChemSmart 2000.

- Initially for this experiment, Ms. Young obtains a standard kit that contains five samples with known (or assigned) concentrations of cholesterol that span the range documented by the manufacturer.
- Next, Ms. Young performs four replicate tests (also recommended by CLSI) for cholesterol on each sample.
- Ms. Young then enters any descriptive information for the assay into the set of tables (e.g. analyte, method, units of measurement). Ms. Young also inputs the definition (name or description) of the materials used and their assigned concentrations. Finally, she inputs the four replicate results obtained for each known sample.
 - Note:* Grey fields within the table indicate input cells (information or result entry fields).
- The set of tables calculates the mean, percent recovery (ratio of result obtained to assigned concentration), a linearity forecast (given the other data points for the curve, the expected result at a given concentration), and % bias (the relative difference between the forecast and the result obtained) for each of the five samples. These calculated values may assist Ms. Young in discovering deviations from linearity (e.g. percent recovery for one set of replicates is very different from those of the rest of the sets, the forecast is dramatically dissimilar from the mean obtained, or the percent bias varies greatly for a set of data points). The table also creates a Linearity Scatter Plot and Percent Recovery Plot for user review.
- Upon review of the data and the plots, Ms. Young may then enter her assessment of the linearity of each of the five samples and her overall evaluation of the assay's linearity.
- Conclusion: In this experiment, Ms. Young determines from a visual review of the graph of her experiment's results, given the known concentrations available, which have verified linearity of the cholesterol to 995 mg/dL. The calculated values support her determination in that there are no outliers among the percent recoveries, the linearity forecast, and % bias. Ms. Young and the laboratory director must then determine if this is comparable to the manufacturer's data and sufficient for Quality First's requirements.

- **Appendix 8: Analytical Sensitivity Experiment Results**

If the lower detection limit must be verified for the cholesterol assay, this example of the analytical sensitivity experiment results represents a table that allows the user to document verification of the manufacturer's published sensitivity. This experiment will approximate the lowest concentration of cholesterol that Quality First Laboratory can expect to be able to measure with the ChemSmart 2000.

- Initially, Quality First's Laboratory Manager, Velma Young, determines from the package insert that the manufacturer's (Ingenious) published sensitivity for cholesterol on the ChemSmart 2000 is 10 mg/dL, and that Ingenious determined this sensitivity employing Lower Limit of Detection (LLD) methods based on 2 standard deviations. She enters this information into the table.

Note: Grey fields within the table indicate input cells (information or result entry fields).

- Next, Ms. Young determines that the "blank" sample she will use for this experiment is the cholesterol diluent provided by the manufacturer; the blank sample contains no cholesterol. She also creates a "spiked" sample (using a material with a known standard concentration of cholesterol), creating a known concentration of 10 mg/dL cholesterol, to reflect the manufacturer's published detection limit. She enters this information into the appropriate cells of the table.
- Ms. Young then performs twenty replicates (minimum of 10 replicates recommended for statistical validity) of cholesterol for both the "blank" and "spiked" samples.
- Finally, Ms. Young records the measurement response (raw data) generated by the method for the "blank" and "spiked" samples, and enters them appropriately into the table.
- The table then calculates the uncertainty in estimate of blank and spiked sample by multiplying the number of standard deviation(s) used by the manufacturer by the calculated standard deviations of the measured responses of the blank and spiked samples, respectively.
- The table then calculates the Calibration Factors by subtracting the mean of the blank measurements from the mean of the spiked sample measurement, then multiplying the resulting difference by the concentration of the spiked sample.
- The minimum detection limits are then calculated using the uncertainty and the calibration factors.
- In the case of Ms. Young's calculated results, the Lower Limit of Detection that has been calculated must now be compared with the manufacturer's published LLD.
- Conclusion: In her experiment, Ms. Young produced an LLD of 2.02 mg/dL (a value that is well below that of the manufacturer's published LLD). Ms. Young has therefore verified the manufacturer's LLD.

Note: The table will also allow for comparison to Biological Limit of Detection (BLD), or Functional Sensitivity, if these methods were used by the manufacturer to determine analytical sensitivity.

- **Appendix 9: Precision Experiment Results**

This example of Precision Validation represents a sample set of tables that evaluates both short-term (within run) and long-term (across runs) precision for two specimens.

Velma Young, Laboratory Manager, wishes to estimate the random error associated with performing the cholesterol assay on the ChemSmart 2000. She wants to determine the variability of repeat measurements and compare her laboratory's analyzer with the performance guidelines (or data) published by the manufacturer, Ingenious.

- First, Ms. Young decides to analyze control materials QualityTrol I and QualityTrol II for both short- and long-term components of this experiment. She based her choice for the number of materials on the levels of concentrations that are critical for the medical use of cholesterol. She chose controls over study-participant samples as specimens for precision testing based on the convenience and the quantity of materials.
- Next, Ms. Young enters the assay descriptive information (e.g. the analyte, unit of measure, method), and the sample information (e.g. name/description).
 - Note:* Grey fields within the table indicate input cells (information or result entry fields).
- She then performs the 20 *within-run* replicates (widely accepted as sufficient statistically, while maintaining costs); then she enters the results on the appropriate pages of the set of tables for each of the two specimens.
- Ms. Young then assigns to team members the continued performance of the 20 *across-run* replicates for each of the two samples over a longer period of time (minimum of five days, introducing as much variation with environmental and operator conditions as is reasonable to represent a realistic working environment for the testing system). She enters these results on the appropriate pages of the set of tables for the two specimens.
- Finally, Ms. Young enters the Ingenious's data of precision (found in the package insert or in published method specifications) and the CLIA-defined Allowance for Total Error (this information may be found at <http://www.westgard.com/clia.htm>; 10% for cholesterol).
- The set of tables calculates the mean, standard deviation, and coefficient of variation for each set of results. It calculates outliers for each set of results based on an internal comparison of result with a running Standard Deviation "Index", and displays a precision plot for each set. The set of tables also creates a report that includes the within-run and across-run statistics for each specimen; in addition this report compares the data to the manufacturer's data and CLIA's Allowance for Total Error.
- Conclusion: In the case of the sample data, the standard deviations and coefficients of variation would appear to be comparable to the manufacturer's data for both within-run and across-run components. Likewise, the experiment passes on all counts for total error allowance. Ms. Young and the laboratory director must evaluate the report data to determine if this performance is acceptable by comparison with the manufacturer's data and sufficient for Quality First's requirements.

- **Appendix 10: Analytical Specificity Experiment Results**

If the analytical interferences (or analytical specificity) for an assay must be verified, this example represents a table that allows documentation of the results of these analytical specificity experiment(s).

Results of these experiments will assist Ms. Young, Laboratory Manager, in approximating the systematic error caused by non-analyte (non-cholesterol, in this example) components/characteristics of specimens, such as icterus when performing the new cholesterol assay on these specimens. These experiments may also give Ms. Young additional information regarding systematic error issues she may encounter when performing the accuracy experiments.

- Initially, Ms. Young decides to verify that there is no interference from hemolysis, lipemia, and icterus for the cholesterol. She creates a table for each of these potential interferents, and enters the assay descriptive information as before (e.g. assay name, method, units of measure). The example reflects the studies she performed for lipemia effects on the cholesterol.

Note: Grey fields within the table indicate input cells (information or result entry fields).

- Next, Ms. Young decides to use normal saline as a diluent (it contains no hemoglobin) for the purposes of this experiment. She also uses a known concentration of 1000 mg/dL Liposyn[®] standard to perform the experiment. She inputs this information into the table.
- Ms. Young then decides to create two sets of 1:2 dilutions of 10 samples: one set with the diluent and the other set with the interferent. The resulting concentration of Liposyn[®] is then 500 mg/dL. She enters this information into the table.
- Next, the cholesterol assay is performed on the resulting total of 20 samples in duplicate, and all of the results are entered by Ms. Young.
- Ms. Young also enters the upper limit of the reference range and the allowable systematic error (from CLIA) for the assay into the appropriate cells.
- The table calculates the differences between the specimen/diluent mixtures and the specimen/interferent mixtures; it then calculates the average interference of the ten sets of data.
- Conclusion: The table calculates the allowable error at the upper limit of the reference range and evaluates the performance of the assay's experimental results. In Quality First's case, the lipemia at concentrations of 500 mg/dL is verified to not be an interferent at patient results of 130 mg/dL. This "Pass" evaluation is based on the fact that the calculated average interference is less than the allowable error at the upper reference range limit.

- **Appendix 11: Accuracy Experiment Results**

This example of Accuracy Validation represents a sample set of tables that allows comparison of the new cholesterol assay as performed on the ChemSmart 2000 with that of the analyzer currently in place within Quality First Laboratory. The comparison of methods will allow Velma Young, Laboratory Manager, to approximate the systematic error (reflecting both proportional and constant error)

that is inherent in the new assay. This comparison will also assist Ms. Young in determining if the two assays will produce clinically comparable results.

- First, Ms. Young enters the assay’s descriptive information (e.g. the analyte under investigation, reporting units, and the methods being compared for this experiment) into the set of tables.

Note: Grey fields within the table indicate input cells (information or result entry fields).

- Ms. Young then proceeds to analyze 40 samples (as recommended by Clinical and Laboratory Standards Institute) in duplicate (provides a check for validity of results) on both the comparative (reference) method and the test method over a period of days (five minimum per Clinical and Laboratory Standards Institute). These 40 samples should span the reportable range of the testing system, including abnormally low, normal, and abnormally high results, if applicable. She enters these samples’ results into the appropriate cells within the set of tables, along with specimen and run information (e.g. identification, date, time).
- The set of tables calculates the means associated with each result pair, calculates the accompanying linear regression statistics, and creates comparison and bias plots.
- Conclusion: Ms. Young then reviews the statistics and plots, and enters her visual check of the comparison graph. In this case, she determines that the plot is linear. Ms. Young and the laboratory director must now determine if the regression statistics and comparisons between the two methods are acceptable for Quality First’s requirements, or if additional steps must be taken.

- **Appendix 12: Reference Range Experiment Results**

This reference interval (normal range) verification example represents a set of tables that will assist Velma Young, laboratory manager, in determining if the manufacturer’s reference intervals may be transferred to Quality First Laboratory during this final step of the performance specification verification. The verification of reference intervals is an important conclusion to the validation process in that it supports the interpretation of patient test results.

- Ms. Young enters the assay information (analyte name, method, units of measure) and the specimen identifiers from 20 pre-defined normal patients using inclusion/exclusion criteria (the minimum for transference per Clinical and Laboratory Standards Institute).

Note: Grey fields within the table indicate input cells (information or result entry fields).

- Cholesterol assays are performed on all 20 samples, and Ms. Young inputs the results into the appropriate cells of the set of tables. Ms. Young must also input the proposed (manufacturer’s) reference interval.
- Conclusion: The set of tables calculates the statistical analysis of the data, determines the number of results obtained that fell outside the proposed range, and evaluates the experiment’s results (Pass/Fail). In Quality First’s experiment, the data is evaluated as a “Pass” because no more than 10% of results fell outside of the proposed range, indicating that the reference ranges may be transferred. Velma Young, Laboratory Manager, along with the

Director of the Laboratory, must then assess the appropriateness of the ranges.

- A similar set of tables that requires entry of 40 or 80 specimen results may also be necessary to use in the event this experiment fails (i.e. more than 10% of results fall outside of the proposed reference range). An additional set of tables that requires entry of 120 specimen results is necessary to use if reference ranges must be established.

References:

Westgard, James O. Basic Method Validation 2nd Edition. Madison, WI: Westgard QC, Inc., 2003.

Appendix 13: Laboratory Test Method List

This sample Laboratory Test Method List represents a catalog of available assays. This list is created so that, if requested, clients of the Quality First Laboratory may obtain a directory of assay-specific information that includes the test methods employed by the laboratory, accompanying reference intervals, and other performance specifications.

Appendix 14: Quality Management Plan

This Quality Management Plan represents a comprehensively documented Quality Assurance/Quality Management program for Quality First Laboratory. The plan is written so that the context of the master document may change little from year to year, but the recorded attachment, "Quality Management Monitors," will change as frequently as necessary to meet the quality requirements of the laboratory.

Appendix 1: Template of a Study Plan Used for a Specific Laboratory Endpoint Assay

Name of Institution
 Study Plan
 Protocol # Name of Lab Endpoint Assay

Version: 1.0

Author(s): Name, degree, role in the protocol, affiliation

Approval: Approved By

 Name, degree, Head of Endpoint Assays Date

 Name, degree, Head Central QAU Date

 Name, degree, Principal Investigator and Study Director Date

Revision History:

<i>Version</i>	<i>Description</i>	<i>Date</i>
----------------	--------------------	-------------

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Appendix 1: Template of a Study Plan Used for a Specific Laboratory Endpoint Assay, *continued*

Protocol #, Name of Lab Endpoint Assay

PURPOSE/GOALS

This document describes the overall plan for the detection of _____ by name of the assay for Protocol #.

CONTENTS

1.0	Authority and Responsibility.....	pg
2.0	Distribution and Document Control.....	pg
3.0	Key Contacts/Agreements.....	pg
4.0	Introduction and Background.....	pg
5.0	Definitions.....	pg
6.0	Reagents and Materials.....	pg
7.0	Specimens and Shipping.....	pg
8.0	Instrumentation.....	pg
9.0	Assay Protocol.....	pg
10.0	Analytical Plan (Statistical Analysis).....	pg
11.0	Timeline.....	pg
12.0	Record Keeping Specifics.....	pg
13.0	References.....	pg

1.0 Authority and Responsibility

The Head of Endpoint Assays, the Head of the Central QAU for the Endpoint Assay Laboratory, and the Principal Investigator of the provide name of the laboratory here have the authority to establish this procedure and are responsible for its implementation.

The Study Plan must be reviewed by the Central QAU.

The Central and Local QAUs are responsible for the distribution of this document (as described below).

Appendix 1: Template of a Study Plan Used for a Specific Laboratory Endpoint Assay, *continued*

Name of Institution

Study Plan

Protocol XX Name of Lab Endpoint Assay

2.0 Distribution and Document Control

This Study Plan may be distributed only by the name of Institution Laboratory Program QAU. It will be distributed to authorized personnel as described in the SOP for Writing and Implementing Study Plans. This Study Plan **MUST NOT** be copied and re-distributed by any of the primary recipients without prior authorization from the name of the Institution Laboratory Program Manager or the Director of the Laboratory Program

3.0 Key Contacts/Agreements

Name(s), degree, affiliation

4.0 Introduction and Background

Protocol # is a phase _____ to evaluate _____.
The name of the assay proposed in this study plan will help assess _____.
This assay is composed of provide a brief description of the assay here.

5.0 Definitions

Provide key definitions (e.g., vaccine product being tested in the protocol)

6.0 Reagents and Materials

Reagents and materials specific to the name of the assay for Protocol # are listed here. For more detailed information refer to institution SOP for this assay.

7.0 Specimens and Shipping

7.1 Specimen collection and processing

Indicate here:

Type of specimens collected

Type of containers used to collect samples

Labs/sites where specimens will be collected

Processing of specimens by labs/sites if applicable

Shipping from where to where (explain if shipping will include sending specimens to a central lab or facility for repository/re-distribution)

Other specific information pertaining to specimens and shipping

Appendix 1: Template of a Study Plan Used for a Specific Laboratory Endpoint Assay, *continued*

Name of Institution
Study Plan
Protocol XX Name of Lab Endpoint Assay

7.2 Specimen Assay Schedule

Name of the assay will be performed on all/subgroup/#/etc participants during the following schedule: indicate hours, days, months when assay will be conducted and their corresponding visit #. Indicate if special testing requirements are needed (e.g., positive signal during the first time point will determine further testing).

8.0 Instrumentation

List equipment needed for name of the assay.
Reference SOP for name of the assay for further details.

9.0 Assay Protocol

Provide information of validation conducted for name of the assay as described in the name of the institution SOP.

Provide any specific/relevant information regarding a special reagent or step needed for name of the assay.

Provide information on the controls used in name of the assay (reference SOP for name of the assay for details)

10.0 Analytical Plan (Statistical Analysis)

Describe in detail the statistical analysis to be performed on the data set.

11.0 Timeline

Describe in detail the schedule of events (testing, obtaining results, statistical analysis, report of results) to be followed from the beginning to the end of the Study Plan.

12.0 Record Keeping Specifics

Include information on:

12.1 Checklist

Each assay will have a corresponding checklist. The checklist identifies the reagents' lots used and confirms that each procedure's step is done correctly. Each checklist is signed by the technician performing the procedure as well as a witness.

Appendix 1: Template of a Study Plan Used for a Specific Laboratory Endpoint Assay, *continued*

Name of Institution

Study Plan

Protocol XX Name of Lab Endpoint Assay

Storage: The checklist is kept in the technician's notebook (located in the laboratory) with the readout for each assay.

12.2 Raw Data

Indicate if raw data will be kept electronically (describe the system) and if it will also be stored as signed hard copies that will be kept in a protocol-specific notebook in the laboratory for each technician.

12.3 Data calculation and transfer

Indicate if data calculation is needed and if transfer of electronic and/or hard copies) will occur to authorized personnel (describe this staff).

13.0 References

Provide a list of SOPs and other documents cited in the Study Plan.

Appendix 2: Training Attendance Log

Quality First Laboratory
123 Sunny Hospital Street
Johannesburg
South Africa

Training Attendance Log

Subject:

ChemSmart 2000: Key Operator Training

Description:

This classroom program is a comprehensive operational training course for the key operator of the Ingenious ChemSmart 2000. All aspects of operation and system maintenance are demonstrated and practiced during this 4-day course.

Topics/objectives include:

- Communication with the System through the Control Unit
- Interpretation of the error messages and appropriate actions
- How to load reagents through Reagent Management and Configuration
- Configuration features of the System through Options
- Basic understanding of Diagnostics
- Set up and review of quality control files through Quality Control
- Use of stored patient data once samples have been run through Review Results
- Calibration

Trainer: Velma Jones, MT

Date(s): 05, 06 May 2006

Trainer Signature: _____

Length of Training Session: 16 hours

Continuing Education Units (if applicable): N/A

Attendee Name	Attendee Signature*	Date Attended:

* By signing this Training Attendance Log, I confirm my attendance to the session(s) as detailed above. I understand that this training session will, if applicable, be followed by required demonstration of competencies I obtained during this training. These competency assessments will be recorded on a separate document.

Appendix 3: Example of Signature Sheet

Quality First Laboratory
 123 Sunny Hospital Street
 Johannesburg
 South Africa

Signatures and Initials Key

Name	Tech Code	Signature	Initials	Date of Signature
Frank Lee	111	Frank Lee	FAL	01Jan05
Janice Wall	112	Janice Wall	JMW	02Jan05
Elizabeth Collins	114	Beth Collins	BKC	12Dec04
Bradley Johns	115	Brad Johns	BCJ	15Dec04
Dawn Evers	116	Dawn Evers	DJE	11Nov04
Velma Jones	117	Velma Jones	VJ	24Nov04
Clyde Moore	118	Clyde Moore	CLM	22Nov04
	119			
	120			

Form Approved By: Laboratory Director

Date:

Review Date	Revision Date	Signature

Appendix 4: Example of SOP in CLSI Format

Quality First Laboratory
123 Sunny Hospital Street
Johannesburg
South Africa

Title:	Serum/Plasma HDL Cholesterol, ChemSmart 2000® Chemistry System		
Total Pages:	9		
Origination Date:	03 December 2001	Section:	Chem
Effective Date:	08 August 2004	Policy No.:	CH.4500v.2
Prepared By:	Velma Jones, MT	Supersedes Procedure Dated:	03 Dec 2001
Approved By:	Frank Lee, Laboratory Director	Date:	08 August 2004
Approved By:	Daphne Lane, M.D., Medical Director	Date:	08 August 2004
Distributed To	# of Copies	Distributed to	# of Copies
Quality First Chemistry	1		
Quality First Phlebotomy	1		

PURPOSE:

The HDL method used on the ChemSmart 2000® clinical chemistry system is an *in vitro* diagnostic test intended for the quantitative determination of high density lipoprotein cholesterol in **serum** and **plasma**.

PRINCIPLE:

The HDL Cholesterol assay is a homogeneous method for directly measuring HDL levels without the need for off-line pretreatment or centrifugation steps. The method is in a two-reagent format and depends on the properties of a unique detergent, which solubilizes only the HDL cholesterol lipoprotein particles, thus releasing HDL cholesterol to react with cholesterol esterase to produce color.

HDL measurements are used as an aid in the diagnosis of lipid disorders.

SCOPE:

Quality First Laboratories

Appendix 4: Example of SOP in CLSI Format, *continued*

SPECIMEN:

Type: Serum or Heparinized plasma

Source: Venous blood collected by peripheral venipuncture

Amount to be collected: 2 mL whole blood preferred, 1 mL minimum

Collection Container: Red-top or green top tubes

Sample Size: 28 μ L

Patient Preparation:

Blood should be collected after a 12-hour period of fasting by normal procedures. Normal procedures for collecting serum and plasma may be used for samples to be analyzed by this method.⁵ Please refer to *Specimen Collection Standard Operating Procedure* located in the *Phlebotomy Procedures Manual*.

Specimen Handling Conditions:

Serum or plasma should be removed from cells within three hours of venipuncture. Serum or plasma may be refrigerated at 2-8°C for up to three days if not tested within 24 hours. For longer pre- or post-analytical storage, samples may be frozen at -20°C for up to one month or at -70°C for up to two years.

EQUIPMENT AND MATERIALS:

Analyzer or Test Kit:

ChemSmart 2000® Chemistry Analyzer

Reagents and Media:

Required Reagents and Media:

HDL reagent cartridges, Cat. No. ABC may be obtained by ordering directly from Ingenious.

Special Safety Requirements:

Used cuvettes contain human body fluids; handle with appropriate care to avoid skin contact and ingestion.⁶ For *in vitro* diagnostic use only.

Reagents and Media Preparation:

Reagent cartridges are ready for use. Any reagent preparation is performed on board the clinical chemistry analyzer.

Storage Requirements

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

Refer to the carton for the expiration date of individual unopened reagent cartridges. Sealed or unhydrated cartridge wells on the instrument are stable for 30 days. Once wells 1 through 3 have been entered by the instrument, they are stable for 3 days. Once well 4 has been entered by the instrument, it is stable for 10 days. Once wells 5 and 6 have been entered by the instrument, they are stable for 15 days.

Appendix 4: Example of SOP in CLSI Format, *continued*

Supplies:

The HDL Cholesterol test also requires the following supplies:
Disposable pipettes, analyzer pipette tips, sample cups, gauze, and cuvettes.

EQUIPMENT CALIBRATION:

Calibration Details

<i>Assay Range:</i>	10 – 150 mg/dL
<i>Reference Material:</i>	HDL Calibrator, Cat. No. DEF
<i>Suggested Calibration Levels:</i>	0, 50, 165 mg/dL
<i>Calibration Scheme:</i>	Three levels in triplicate
<i>Calibration Frequency:</i>	Every new reagent cartridge lot. Every 3 months for any one lot
<i>Assigned Coefficients:</i>	C0 0.000 C1 2.000

Performing a Calibration:

1. To access the calibration software, from the Main Operating menu on the analyzer monitor,
 - a. Press **Process Control**.
 - b. Press **Calibration**.
 - c. Press **SETUP and RUN**.
2. Select the test method to be calibrated.
3. Enter all information on the screen.
 - a. Press **QC yes/no** to change to yes.
 - b. Press **Assign cups**.
 - c. Press **Load/run**.
4. Load samples as indicated on the load list.
5. Press **RUN**.

Reviewing a Calibration:

1. To access the calibration software, from the Main Operating menu on the analyzer monitor,
 - Press **Process Control**.
 - Press **Calibration**.
 - Press **Enter**.
 - Press **Review Data**.
2. Select the test to be reviewed.

Appendix 4: Example of SOP in CLSI Format, *continued*

3. Press **Calculate**.
4. Evaluate m (slope) and b (intercept) using the following guidelines:
Acceptance Criteria for Use in Review of Calibration:
 - Precision: No obvious outliers
 - Slope (m): Calibrated: Linear: 0.97-1.03
Logit: 0.95-1.05
 - Intercept (b): Close to zero or clinically insignificant
 - Correlation Coefficient (r): 0.990-1.000
 - Quality Control (QC): within acceptable range
5. Press **Accept Data** or **Reject Data**.
6. Enter QC into the laboratory computer system if run along with the calibrators.

Troubleshooting Calibrations:

1. Ensure you are using the correct calibrator insert sheet for the lot you are calibrating.
2. Review calibrator preparation, storage conditions, and the expiration date on the calibrator product's package insert sheet. For the lyophilized products, the preparation steps must be followed precisely.
3. Check that the sample cups were loaded into the segments in the correct order. If not, press **Reject Data** and rerun the calibration.
4. Review instrument maintenance logs and the system counters screen for overdue maintenance. Check the cycle count for the sample probe tip, especially if the problem is on a method with low sample volume.
5. Check that all temperatures are within range on the Daily Maintenance screen. Check the temperatures with a calibrated thermometer using the temperature calibration procedures in *Module 3: Maintaining* in the *ChemSmart 2000® Operator's Guide*.
6. Compare the C4 term on the calibration Review Data screen to the C4 value on the method insert sheet. If it is not the same, contact the Technical Assistance Center. Only logit methods have a C4 term.
7. If calibration problem remains unresolved, contact the Chemistry Resource Technologist or the site Manager.

QUALITY CONTROL:

Frequency:

Perform QC runs at least once daily

Number of Control Materials

Solutions at two levels of a QC material with known concentrations

Appendix 4: Example of SOP in CLSI Format, *continued*

Description of Control Materials

QualityTrol Unassayed Chemistry Control (Human), Levels 1 and 2 supplied by Ingenious, catalog # 601 and 602.

Storage of Control Materials

QualityTrol Unassayed Chemistry Controls are stable until the expiration date when stored unopened at -10° to -20° C. Once thawed and opened, all analytes will be stable for 6 days when the control is stored tightly capped at $2-8^{\circ}$ C.

Preparation and Handling of Control Materials

QualityTrol Unassayed Chemistry Controls should be treated the same as patient specimens. Before sampling, allow the control to thaw completely at room temperature for 15-20 minutes. Once thawed, gently invert the vial 4-5 times to ensure homogeneity and use immediately. Do not use a mechanical mixer.

Control Criteria

QC ranges are established using the laboratory's cumulative mean as well as the peer group reported standard deviation. QC is reviewed weekly by the key operator and submitted monthly for manager and peer review.

If control values are unacceptable, do not report patient results; instead:

1. Determine whether the QC failure(s) is/are the result of systematic or random error, and troubleshoot based on this determination.
2. Implement corrective action based on investigation results.
3. Rerun QC materials to evaluate effectiveness of corrective action. If issue resolution is successful, perform patient testing and determine accuracy of patient results released since the last successful QC run. If repeat of the QC run is unsuccessful, repeat steps 1–3 as necessary to resolve issue(s).
4. Document all steps taken, both successful and unsuccessful attempts at resolution.

HDL CHOLESTEROL TESTING PROCEDURE:

Instructions for Processing Samples

Bar-Coded Tubes

1. Place bar code labels on tubes. 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.
2. Short bar-coded tube samples can be transferred into the clear plastic small sample containers (SSC). The SSC is then put in the corresponding bar-coded sample tube. Place tubes in segments with the bar codes facing the bar code reader.

Sample Cups

3. Samples without bar codes can be put in plastic sample cups and placed in either brown or green adaptors. Enter patient information manually.
4. Urine and CSF specimens can be processed in sample cups. Patient information must be entered manually. Place in either brown or green adaptors.
5. Manually entering patient information:

Appendix 4: Example of SOP in CLSI Format, *continued*

- a. From the main operating menu, press **Enter Data**.

POSITION	Enter the segment letter (if applicable) position that you want to use.
PATIENT NAME	Enter the name (if applicable).
SAMPLE NO	Enter the patient accession number (if applicable).
LOCATION	Entry optional.
TEST	Select test by pressing method keys on keyboard.
MODE	Select the sample container you are using. Sample cup primary tube, SSC, etc.
PRIORITY	Routine, stat, etc.
DILUTION	Enter the dilution factor (if applicable).
FLUID	Serum, urine, plasma, or csf.
 - b. To run a single specimen, enter the patient information. Place the specimen in the segment position you have selected and press **Process Single**.
 - c. If you have more than one sample to enter manually, press **New Sample** after each entry. After entering all samples, press **Load List**. Place samples in the designated segment positions and press **Run**.
 - d. Segments that are in use are highlighted in red at the top of the screen. Any segments in red should not be taken off the instrument.
 - e. To initiate processing of down-loaded samples:
 - From the Sample Status screen, move the cursor to the double-asterisked sample.
6. The cursor will change to a box.
 - Enter the segment position for the sample.
 - Press **Enter**.
 - Load barcoded samples.
 - Press **Run**.
 7. Sampling, reagent delivery, mixing, processing, and printing of results are automatically performed by the ChemSmart 2000[®] system. For details of this processing, refer to your ChemSmart 2000[®] system manual.

METHOD PERFORMANCE SPECIFICATIONS

Analytic Sensitivity

The sensitivity of the HDL method is 10 mg/dL, and is defined as the concentration at two standard deviations above the mean of the Level 1 Chem1 Calibrator (0 mg/dL). See package insert for detailed information regarding the analytic sensitivity.

Analytic Specificity

Interference from icterus (bilirubin 60 mg/dL), hemolysis (hemoglobin 1000mg/dL), and lipemia (1000mg/dL) was less than 10 %. See package insert for detailed listing of substances having no measurable effect on the HDL method.

Reportable Range

10 – 150 mg/dL

Dilution Protocols

Maximum dilution for samples: 1:10

Diluent: Normal Saline

Appendix 4: Example of SOP in CLSI Format, *continued*

CALCULATIONS

Formulas:

cLDL is a reported chemistry test that is calculated and not directly measured by the analyzer.

Calculate the cLDL by the following formula:

$$\text{cLDL} = \text{Chol} - \text{HDL} - \text{vLDL}$$

$$\text{vLDL} = \text{Trig} \div 5$$

Examples:

Chol = 185 mg/dl

LDL = 185 – 45 - (300 ÷ 5)

Trig = 300mg/dl

LDL = 185 – 45 - 60

HDL = 45mg/dl

LDL = 80 mg/dl

Calculation Notes:

Calculation is inaccurate with triglyceride > 400mg/dl. In such cases, ultracentrifugation at a specialized lab may be desired.

EXPECTED RESULTS

The instrument automatically calculates and prints the concentration of HDL in mg/dL using the calculation scheme illustrated in your ChemSmart 2000® system manual. Reportable ranges as determined by Quality First and Quality First Satellite laboratories: Results are reported in mg/dL and rounded to the nearest whole number.

Normal range: HDL = >35 mg/Dl

INTERPRETATION OF RESULTS

cLDL cholesterol normal range: < 130 mg/dl is desirable

Borderline High Risk 130 – 159 mg/dl

High Risk >159 mg/dl

The National Cholesterol Education Program recommends against use of combined risk factor indices. Each risk factor should be evaluated separately

PROCEDURE NOTES, REFERENCES, AND ATTACHMENTS

Procedure Notes:

Fibrin in the sample may cause sampling problems. Rim the sample with a wooden applicator to remove the fibrin. Re-spin the sample and re-analyze.

Routine test orders should be completed within four hours from collection.

Stat test orders should be completed within one hour from collection. If testing will be delayed beyond these limits, the attending physician or nurse must be notified and the specimen stored appropriately.

Appendix 4: Example of SOP in CLSI Format, *continued*

References:

1. Tietz NW. Textbook of Clinical Chemistry, Philadelphia: WB Saunders Co., 1986:52–53 (techniques and procedures to minimize laboratory infections), 478–497 (specimen collection and storage recommendations), 1829 (reference interval).
2. Gotto Am. Lipoprotein metabolism and the etiology of hyperlipidemia, Hospital Practice 1988; 23: Suppl.1, 4.
3. Rifai N, Warnick GR, Dominiczak MH. Handbook of lipoprotein testing, Washington: AACC Press, 1997.
4. NIH Consensus Conference, Triglyceride, high-density lipoprotein, and coronary heart disease, JAMA 1993; 4:505-510.
5. Castelli WP, et al. HDL Cholesterol and other lipids in coronary heart disease, Circulation 1977;55:767.
6. Badimon JJ, Badimon L, Fuester V. Regression of atherosclerotic lesions by high-density lipoprotein plasma fraction in the cholesterol fed rabbit, Journal of Clinical Investigation 1990;85:1234-41.
7. Kannel WB, Castelli WP, Gordan T. Cholesterol in the presence of atherosclerotic disease; New perspectives based on the Framington study, Am J Med 1979; 90:85.
8. Warnick GR, Wood PD. National Cholesterol Education Program recommendations for measurement of high-density lipoprotein cholesterol: Executive summary, Clin. Chem. 1995;41:1427-1433.
9. Collins, Elizabeth. HDL Cholesterol Procedure, New Hanover Regional Medical Center, Wilmington, NC, 2004.

Attachments:

1. ChemSmart 2000 ® Maintenance Log
2. ChemSmart 2000 ® Calibration Worksheet
3. ChemSmart 2000 ® Reagent Log

DOCUMENT RETENTION

ChemSmart 2000® Maintenance log is kept in the QC/Maintenance notebook at the analyzer. This is to be stored for the life of the instrument plus seven years.

ChemSmart 2000® Calibration Worksheet is kept in the Calibration notebook. This is to be stored for seven years.

Review Date	Revision Date	Signature
07 August 2005		Frank Lee

END

Appendix 4: Example of SOP in CLSI Format, *continued*
Quality First Laboratory
ChemSmart 2000® Maintenance Log

Month: _____ Year: _____

Daily Maintenance Task					
Date	System Check	Sample Probe Wash	Reagent Probe Wash	Reagent Inventory	Initials
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					

Weekly Maintenance Tasks				
Week #	Replace Electrolyte Sensor	Flush Waste Lines	Date	Initials
1				
2				
3				
4				
5				

As Needed Maintenance			
Wash Cuvettes	Replace Lamp	Date	Initials

Reviewed: _____ Date: _____

Appendix 4: Example of SOP in CLSI Format, *continued*

Quality First Laboratory
ChemSmart 2000[®] Calibration Worksheet
Analyte: _____

Acceptable Ranges:	Lot #	Slope (m)	Intercept (b)	Correlation Coefficient (r)	QC Acceptable? (Y/N)	Initials
		Linear: 0.97 – 1.03 Logit: 0.95 – 1.05	Approx. 0 -Or- Clinically Insignificant	0.990 – 1.000		
Date						

Reviewed: _____ Date: _____

Reviewed: _____ Date: _____

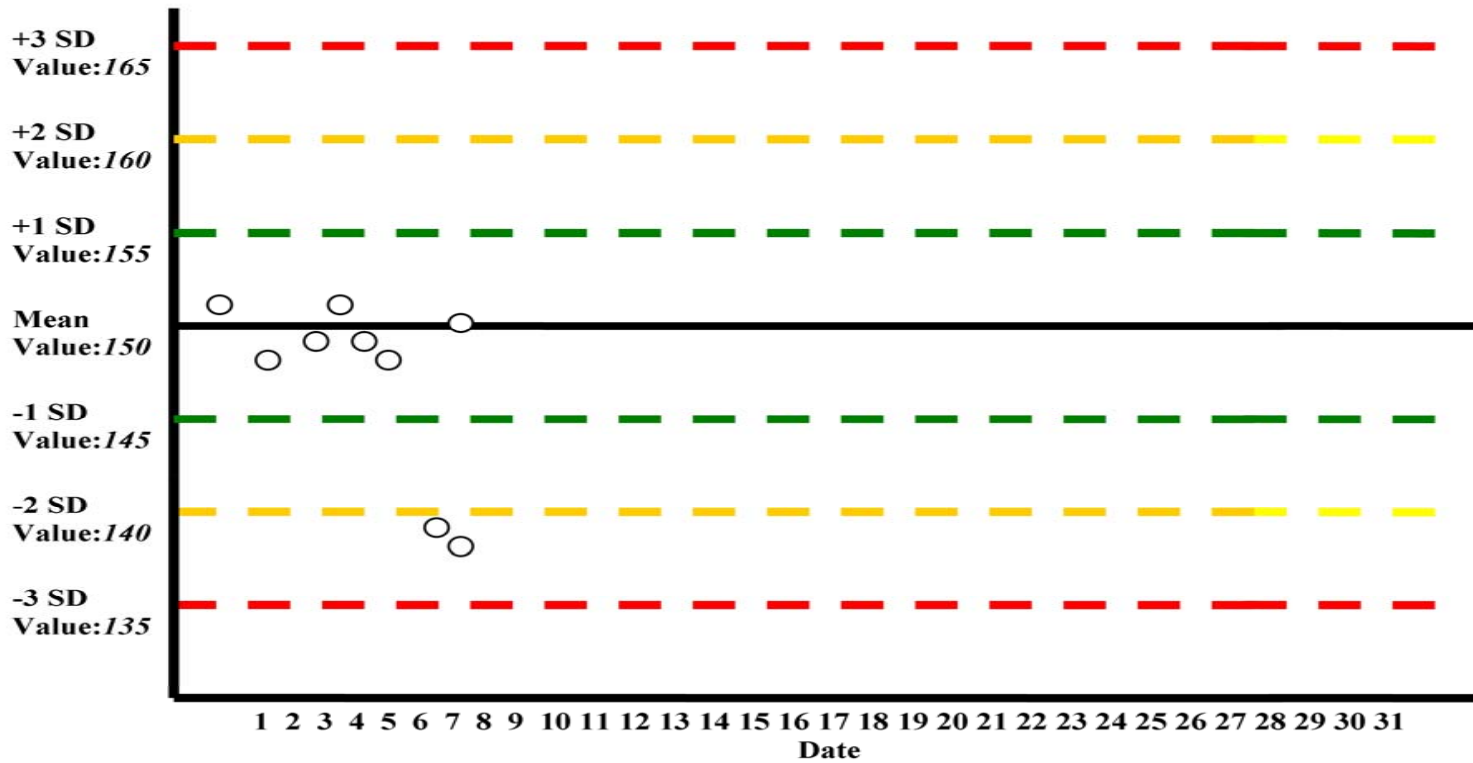
Appendix 5: L-J Chart Example

Quality First Laboratory
123 Sunny Hospital Street
Johannesburg South Africa

Levy Jennings Quality Control Chart
Analyzer: *ChemSmart 2000* Month/Year: *July 2006*
QC Material/Level: *QualityTrol Level 1* Lot Number: *ABX-128*

Reviewed:

Date:



Appendix 6: Quality Control Log Example

Quality First Laboratory
 123 Sunny Hospital Street
 Johannesburg
 South Africa

Levy Jennings Quality Control Log

Analyzer: ChemSmart 2000 Month/Year: July 2006

QC Material/Level: QualityTrol Level 1 Lot Number: ABX-128

Mean Value: 150 SD Value: 5.0 Units: mg/dL Acceptable range: 140 to 160

Date	Time (HHMM)	Tech Initials	Result	Plotted on LJ Chart? (Y/N)	Acceptable? (Y/N)	Corrective Action Log/Comments
1	0815	FAL	151	Y	Y	
2	0900	BKC	148	Y	Y	
3	0823	VJ	149	Y	Y	
4	0910	FAL	151	Y	Y	
5	0825	BKC	149	Y	Y	
6	0812	VJ	148	Y	Y	
7	0805	VJ	139	Y	Y	1-2S rule failure; warning only, will observe closely
8	0810	FAL	138	Y	N	2-2S failure; shift possible, lamp damaged; replaced lamp, next run of 150 acceptable
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						

Reviewed by: _____ Date of Review: _____
 Reviewed by: _____ Date of Review: _____

Appendix 7: Example of Reportable Range Experiment Results

Linearity Evaluation

Assay:	Cholesterol
Method:	ChemSmart 2000
Units:	mg/dL

	<i>Linearity Material</i>	<i>Assigned Concentration</i>	<i>Accuracy/Recovery Mean</i>	<i>Accuracy/Recovery % Recovery</i>	<i>Linearity Forecast</i>	<i>Linearity % Bias</i>	<i>Visually Linear?</i>
Level 1	Standard 1	25	23.0	92.0	15.8	-31.4	Yes
Level 2	Standard 2	100	95.0	95.0	91.0	-4.3	Yes
Level 3	Standard 3	250	225.0	90.0	241.3	7.2	Yes
Level 4	Standard 4	500	495.0	99.0	491.9	-0.6	Yes
Level 5	Standard 5	1000	995.0	99.5	993.1	-0.2	Yes

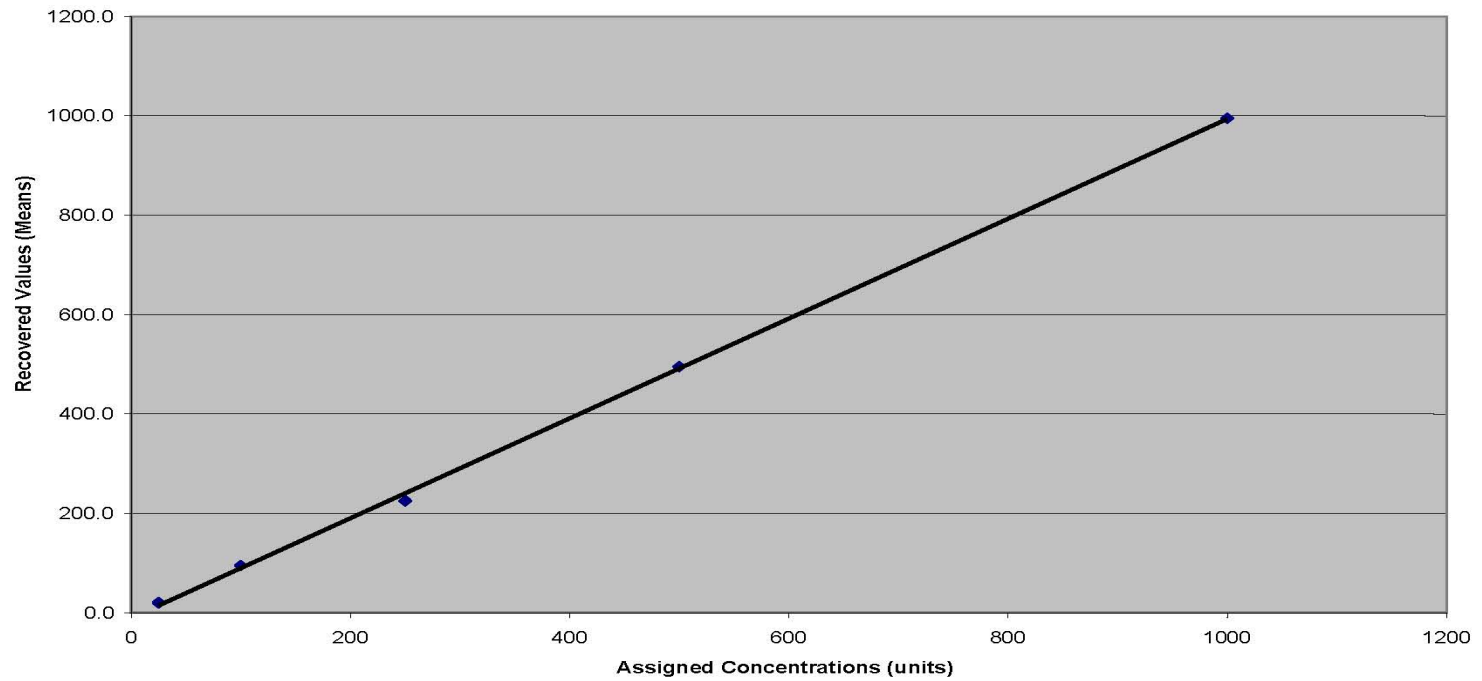
Experiment Results				
	<i>Rep 1 Result</i>	<i>Rep 2 Result</i>	<i>Rep 3 Result</i>	<i>Rep 4 Result</i>
Level 1	22	24	22	24
Level 2	95	97	93	95
Level 3	225	227	223	225
Level 4	495	497	493	495
Level 5	995	997	993	995

Regression Analysis			
Slope	Intercept	Standard Error	Correlation Coefficient
1.00233871	-9.277016129	10.77	1.000

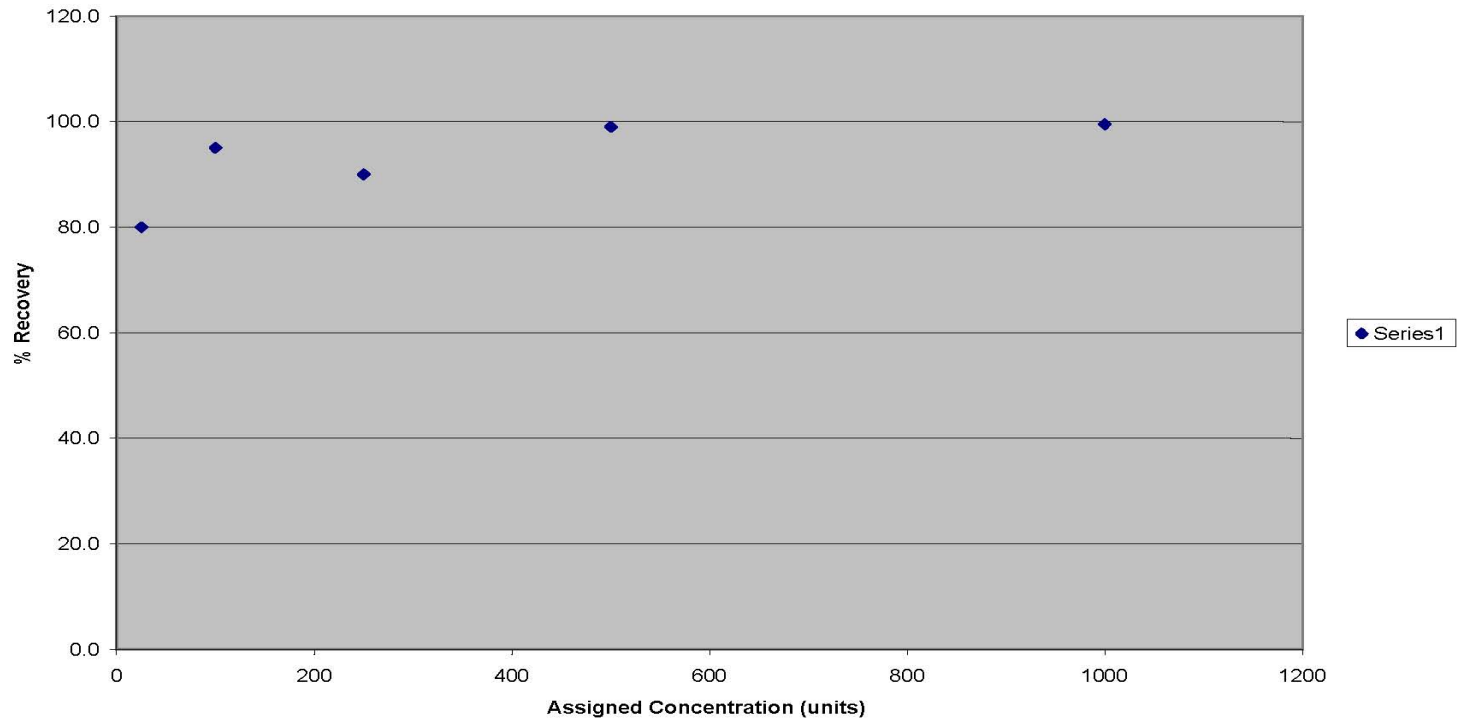
Visual Check for Linearity:	Yes
Analyst:	Velma Jones
Date:	4-Apr-06

Approval:
Date:

Appendix 7, *continued*
Linearity Scatter Plot



Appendix 7, continued
Linearity Percent Recovery



Appendix 8: Example of Analytical Sensitivity Experiment Results

Sensitivity Experiments

	Concentration	Units
"Blank" Material Used:	0	mg/dL
Spiked Sample 1:	10	mg/dL (Note: should represent manufacturer's detection concentration)
Spiked Sample 2 (if applicable):		mg/dL

Experiment Results

<i>Measurement Response</i>			
Replicate #	Blank	Spiked Sample 1	Spiked Sample 2
1	910	1800	
2	1090	2200	
3	900	1800	
4	1100	2200	
5	910	1800	
6	1090	2200	
7	900	1800	
8	1100	2200	
9	910	1800	
10	1098	2200	
11	900	1800	
12	1098	2200	
13	900	1800	
14	1101	2200	
15	899	1800	
16	1100	2200	
17	900	1800	
18	1100	2200	
19	900	1800	
20	1100	2025	
Mean	1000.3	1991.25	
Standard Deviation	100.03	199.88	

Lower Limit of Detection

Manufacturer's Multiple of SD used in determination of LLD: 2

Uncertainty in Estimate of Blank: 200.1 measurement response

Calibration Factor: 1 mg/dL per 99.095 measurement units

Minimum Detection Limit (LLD): 2.02 mg/dL

Biological Limit of Detection

Manufacturer's Multiple of SD used in determination of BLD: 2

Uncertainty in Spiked Sample: 399.8 measurement response

Calibration Factor: 1 mg/dL per 99.095 measurement units

Minimum Detection Limit (BLD): 6.05 mg/dL

Functional Sensitivity

SD in Concentration Units, Spiked Sample 1: 2.02 mg/dL

CV Spiked Sample 1: 20.2 %

Note: Target for CV is 20% to determine Functional Sensitivity.

Additional Spiked Samples may have to be analyzed until desired 20% CV reached.

Functional Sensitivity: 10 mg/dL

SD in Concentration Units, Spiked Sample 2:

CV Spiked Sample 2: %

Analyst: Velma Jones

Date: 4-Apr-06

Approved:

Date:

Appendix 9: Example of Precision Experiment Results

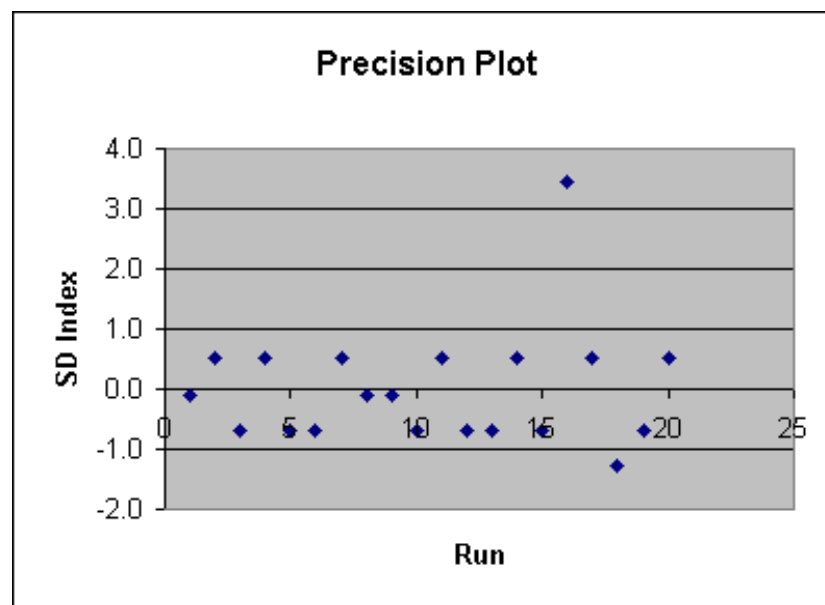
Short-Term Precision

Method:	Selectra XL
Manufacturer:	Biosmart
Analyte:	Cholesterol
Units of Measure:	mg/dL

Sample Name / Description:	Monitrol I
Date:	21-Apr-06
Analyst Name:	Velma Jones

Experiment Results

Run #	Result	SDI	Outlier?
1	210	-0.1	No
2	209	0.5	No
3	211	-0.7	No
4	209	0.5	No
5	211	-0.7	No
6	211	-0.7	No
7	209	0.5	No
8	210	-0.1	No
9	210	-0.1	No
10	211	-0.7	No
11	209	0.5	No
12	211	-0.7	No
13	211	-0.7	No
14	209	0.5	No
15	211	-0.7	No
16	204	3.5	Outlier
17	209	0.5	No
18	212	-1.3	No
19	211	-0.7	No
20	209	0.5	No



Preliminary Estimate of Precision, Short Term

User's:	Mean	209.9	Manufacturer's Claims:	Mean	210.0
	Standard Deviation	1.7		Standard Deviation	2.0
	CV%	0.81		CV%	0.95

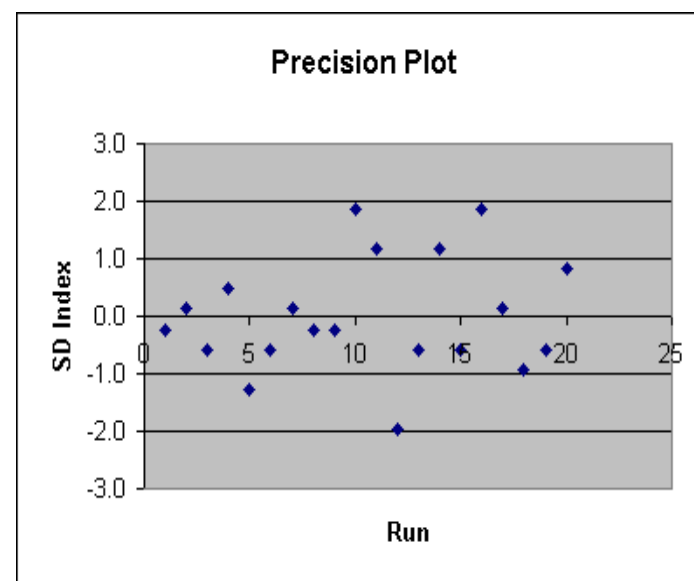
Appendix 9: Example of Precision Experiment Results, *continued*

Long Term Precision

Method:	Selectra XL
Manufacturer:	Biosmart
Analyte:	Cholesterol
Units of Measure:	mg/dL
Sample Name/Description:	Monitrol I

Experiment Results

Run #	Date of Run	Tech Init	Result	SDI	Outlier?
1	4-Mar-06	SS	210	-0.2	No
2	5-Mar-06	SD	209	0.1	No
3	6-Mar-06	VD	211	-0.6	No
4	7-Mar-06	MEM	208	0.5	No
5	8-Mar-06	DES	213	-1.3	No
6	9-Mar-06	KEL	211	-0.6	No
7	10-Mar-06	WLM	209	0.1	No
8	11-Mar-06	DES	210	-0.2	No
9	12-Mar-06	WLM	210	-0.2	No
10	13-Mar-06	DES	204	1.9	No
11	14-Mar-06	KEL	206	1.2	No
12	15-Mar-06	SS	215	-2.0	No
13	16-Mar-06	DES	211	-0.6	No
14	17-Mar-06	WLM	206	1.2	No
15	18-Mar-06	KEL	211	-0.6	No
16	19-Mar-06	VD	204	1.9	No
17	20-Mar-06	SS	209	0.1	No
18	21-Mar-06	WLM	212	-0.9	No
19	22-Mar-06	KEL	211	-0.6	No
20	23-Mar-06	KEL	207	0.8	No



Preliminary Estimate of Precision, Long Term

User's:	Mean	209.4	Manufacturer's Claims:	Mean	210.0
	Standard Deviation	2.9		Standard Deviation	3.0
	CV%	1.36		CV%	1.43

Appendix 9: Example of Precision Experiment Results, *continued*
Precision Evaluation

Method: ChemSmart 2000
Manufacturer: Ingenious
Analyte: Cholesterol
Units of Measure: mg/dL

Name/Description of Samples	Sample 1	Sample 2
	QualityTrol I	QualityTrol II
Short-Term (within run)		
Mean	209.9	125.0
Standard Deviation	1.7	0.8
%CV	0.81	0.66
Manufacturer's Data (within run)		
Mean	210.0	125.0
Standard Deviation	2.0	1.0
%CV	0.95	0.80
CLIA Allowance		
Total Error (%)	10.0	
Total Error (calc)	21.0	12.5
Imprecision Allowance	5.2	3.1
Pass/Fail	Pass	Pass

Name/Description of Samples	Sample 1	Sample 2
	QualityTrol I	QualityTrol II
Long-Term (across runs)		
Mean	209.4	124.8
Standard Deviation	2.9	1.2
%CV	1.36	0.96
Manufacturer's Data (across runs)		
Mean	210.0	125.0
Standard Deviation	3.0	1.2
%CV	1.43	0.96
CLIA Allowance		
Total Error (%)	10.0	
Total Error (calc)	20.9	12.5
Imprecision Allowance	6.9	4.1
Pass/Fail	Pass	Pass

Approval: _____

Date: _____

Appendix 10: Example of Analytical Specificity Experiment Results

Analytical Specificity

Assay:	Glucose
Method:	ChemSmart 2000
Diluent:	
Interferent:	

Units of Measurement:	mg/dL
Undiluted Concentration:	1000 mg/dL
Resulting Concentration:	500 mg/dL

Experimental Results

<i>Specimen</i>	<i>Specimen PID</i>	<i>Volume</i>	<i>Volume</i>	<i>Result</i>	<i>Result</i>	<i>Average</i>	<i>Specimen</i>	<i>Volume</i>	<i>Volume</i>	<i>Result</i>	<i>Result</i>	<i>Average</i>
1	PID 1	50 uL	50 uL	98	102	100	PID 1	50 uL	50 uL	110	112	111
2	PID 2	50 uL	50 uL	93	95	94	PID 2	50 uL	50 uL	106	108	107
3	PID 3	50 uL	50 uL	80	84	82	PID 3	50 uL	50 uL	94	98	96
4	PID 4	50 uL	50 uL	98	102	100	PID 4	50 uL	50 uL	110	112	111
5	PID 5	50 uL	50 uL	93	95	94	PID 5	50 uL	50 uL	106	108	107
6	PID 6	50 uL	50 uL	80	84	82	PID 6	50 uL	50 uL	94	98	96
7	PID 7	50 uL	50 uL	98	102	100	PID 7	50 uL	50 uL	110	112	111
8	PID 8	50 uL	50 uL	93	95	94	PID 8	50 uL	50 uL	106	108	107
9	PID 9	50 uL	50 uL	80	84	82	PID 9	50 uL	50 uL	94	98	96
10	PID 10	50 uL	50 uL	98	102	100	PID 10	50 uL	50 uL	110	112	111

Differences Between Diluent and Interferent

<i>Specimen</i>	<i>Specimen PID</i>	<i>Difference</i>
1	PID 1	11
2	PID 2	13
3	PID 3	14
4	PID 4	11
5	PID 5	13
6	PID 6	14
7	PID 7	11
8	PID 8	13
9	PID 9	14
10	PID 10	11
Analyst:	Velma Jones	
Date:	4-Apr-06	

Average Interference:	12.5 mg/dL
Upper Reference Limit:	130
Allowable Systematic Error (%):	10
Allowable Error at Upper Reference	13
Pass / Fail:	Pass
Approval:	
Date:	

Appendix 11: Example of Accuracy Experiment Results

Accuracy (Method Comparison)

Analyte: Cholesterol
Units of Measure: mg/dL

Experiment Results

Test Method: ChemSmart 2000 **Comparative Method:** Vitros 950
Manufacturer: Ingenious **Manufacturer:** Ortho

Run #	Date	Tech Init	Time	1st Replicate	2nd Replicate	Mean
1				10	10	10
2				15	17	16
3				20	21	20.5
4				25	24	24.5
5				30	32	31
6				35	36	35.5
7				40	42	41
8				45	47	46
9				50	51	50.5
10				55	54	54.5
11				60	60	60
12				65	63	64
13				70	71	70.5
14				75	74	74.5
15				80	80	80
16				85	84	84.5
17				90	93	91.5
18				100	101	100.5
19				105	106	105.5
20				110	108	109

Time	1st Replicate	2nd Replicate	Mean
	20	20	20
	32	32	32
	42	42	42
	50	50	50
	60	60	60
	70	70	70
	80	80	80
	90	90	90
	100	100	100
	110	110	110
	120	120	120
	130	130	130
	140	140	140
	150	150	150
	160	160	160
	170	170	170
	180	180	180
	190	190	190
	200	200	200
	220	220	220

Appendix 11: Example of Accuracy Experiment Results, *continued*

Run #	Date	Tech Init	Time	1st Replicate	2nd Replicate	Mean
21				115	114	114.5
22				120	120	120
23				125	123	124
24				130	130	130
25				135	134	134.5
26				140	138	139
27				145	144	144.5
28				150	151	150.5
29				155	154	154.5
30				160	162	161
31				165	165	165
32				170	170	170
33				175	175	175
34				180	181	180.5
35				185	184	184.5
36				190	191	190.5
37				195	194	194.5
38				200	199	199.5
39				205	204	204.5
40				208	209	208.5

Time	1st Replicate	2nd Replicate	Mean
	230	230	230
	240	240	240
	250	250	250
	260	260	260
	270	270	270
	280	280	280
	290	290	290
	300	300	300
	310	310	310
	320	320	320
	330	330	330
	340	340	340
	350	350	350
	360	360	360
	370	370	370
	380	380	380
	390	390	390
	400	400	400
	410	410	410
	420	420	420

Regression Analysis

Slope

0.498

Intercept

0.618

Standard Error

1.397

Correlation Coefficient

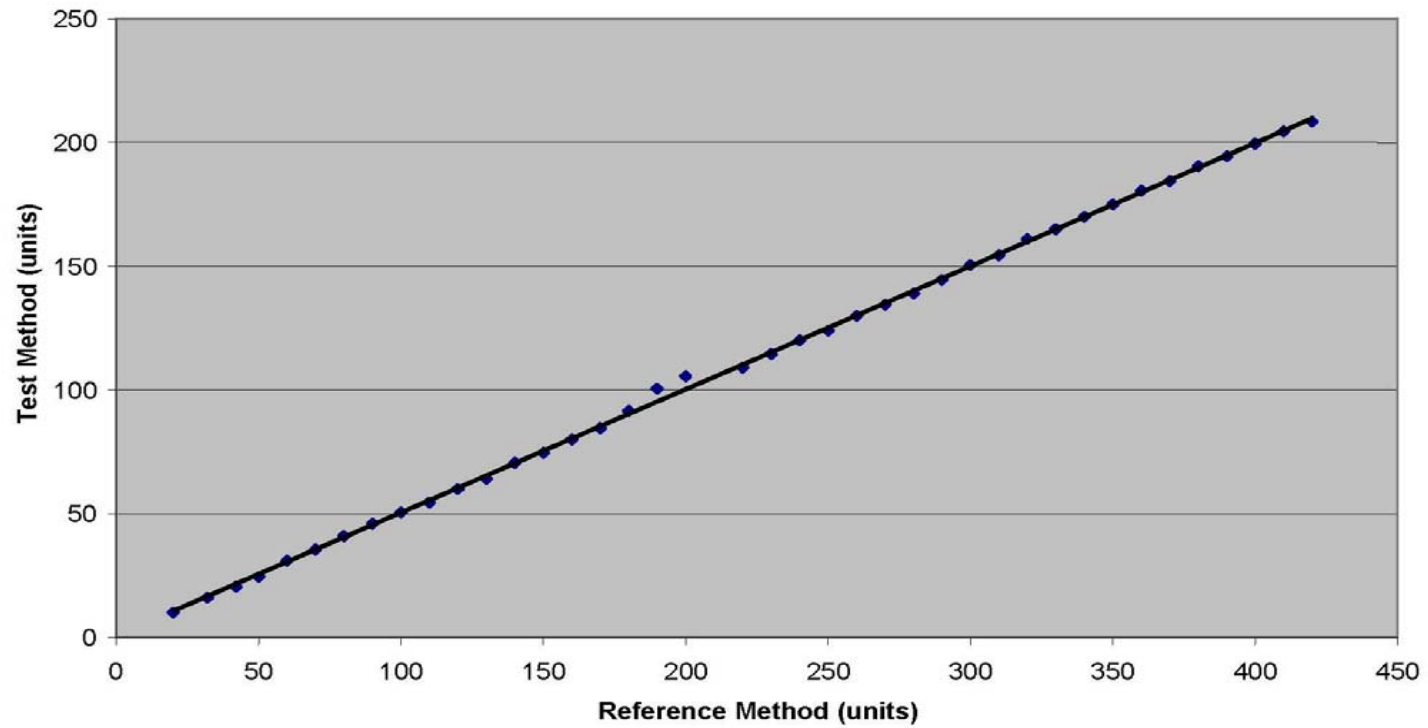
1.000

Visual Check for Comparison: YES

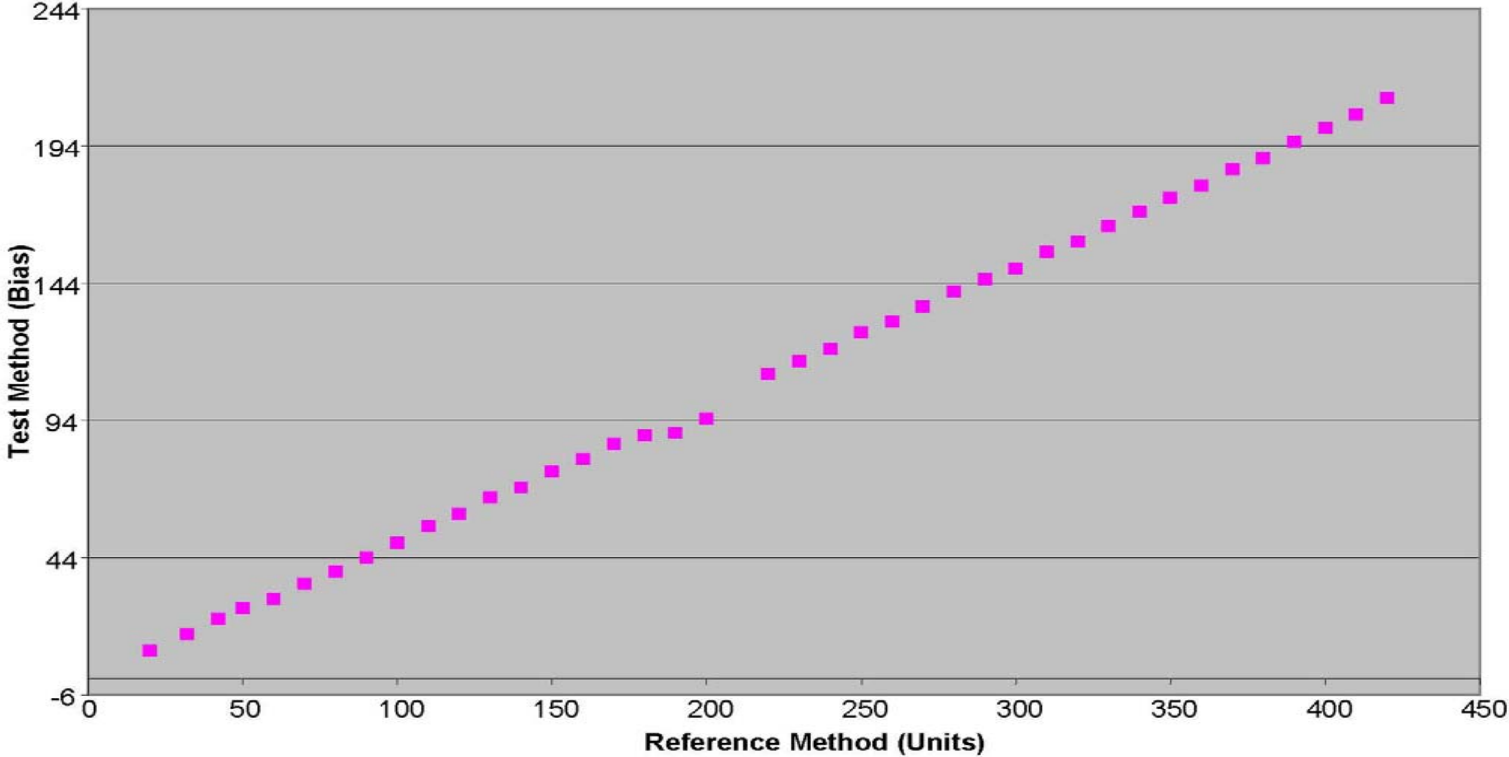
Approval: _____

Date: _____

Appendix 11, continued
Comparison Graph (Scatter Plot, Means of Replicate Results)



Appendix 11, continued
Bias Plot for Means of Replicate Results



Appendix 12: Example of Reference Range Experiment Results

Verification of Reference Interval

Analyte:	Sodium
Method:	ChemSmart 2000

Experiment Results

<i>Specimen Number</i>	<i>Specimen ID</i>	<i>Result</i>
1	PID 1	135
2	PID 2	160
3	PID 3	150
4	PID 4	145
5	PID 5	158
6	PID 6	136
7	PID 7	138
8	PID 8	140
9	PID 9	148
10	PID 10	150

<i>Specimen Number</i>	<i>Specimen ID</i>	<i>Result</i>
11	PID 11	148
12	PID 12	140
13	PID 13	138
14	PID 14	147
15	PID 15	140
16	PID 16	151
17	PID 17	139
18	PID 18	146
19	PID 19	142
20	PID 20	153

Analyst: Velma Jones
Date: 4-Apr-06

Statistical Analysis

Mean 145.2
Standard Deviation 7.13
Median 145.5
Range 135 to 160

Reference Interval

Proposed 125 to 155
Number of Results *Less Than* 125 0
Number of Results *Greater Than* 155 2
Total Results Outside Proposed Range: 2
Percentage Results Outside Proposed Range: 10
Pass/Fail Pass

Approval: _____

Date: _____

Appendix 12: Example of Reference Range Experiment Results, *continued*

Verification of Reference Interval

Analyte: Sodium

Method: ChemSmart 2000

Experiment Results

<i>Specimen Number</i>	<i>Specimen ID</i>	<i>Result</i>
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		

<i>Specimen Number</i>	<i>Specimen ID</i>	<i>Result</i>
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
31		
32		
33		
34		
35		
36		
37		
38		
39		
40		

Analyst:

Date:

Statistical Analysis

Mean 142.725

Standard Deviation 11.35

Median 143.5

Range 121 to 160

Reference Interval

Proposed 125 to 155

Number of Results *Less Than* 125 6

Number of Results *Greater Than* 155 6

Total Results Outside Proposed Range: 12

Percentage Results Outside Proposed Range: 60

Pass/Fail: Fail

Approval: _____

Date: _____

Appendix 13: Example of Laboratory Test Method List

Quality First Laboratory
123 Sunny Hospital Street
Johannesburg
South Africa

<i>Test</i>	<i>Methodology</i>	<i>Reference Ranges</i>	<i>Reportable Ranges</i>	<i>Interferences</i>	<i>Turnaround Times</i>	<i>Specimen Requirements</i>
Chemistry						
Albumin	Endpoint Colorimetric	3.5 - 4.8 g/dL	1.0 – 20.0 g/dL		Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL
Alkaline Phosphatase	Rate	50 - 136 U/L	15 – 500 U/L		Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL
ALT (SGOT)	Rate	19 - 55 U/L	5 – 500 U/L		Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL
AST (SGPT)	Rate	15 - 37 U/L	5 – 500 U/L		Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL
Bilirubin, Total	Endpoint Colorimetric	0.2 - 1.3 mg/dL Critical Values: >15.0 mg/dL	0.05 – 40.0 mg/dL	Hemolysis, any degree	Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL

Appendix 13: Example of Laboratory Test Method List, *continued*

Test	Methodology	Reference Ranges	Reportable Ranges	Interferences	Turnaround Times	Specimen Requirements
Chemistry						
Blood Urea Nitrogen (BUN)	Colorimetric	7 - 18 mg/dL	1.5 – 50.0 mg/dL		Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Calcium	Colorimetric	8.5 - 10.5 mg/dL Critical Values: <7.0 or >13.5 mg/dL	2.5 – 35.0 mg/dL		Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Chloride	Integrated Multisensor Technology	98 - 108 mmol/L Critical Values: > 149 mmol/L	50.0 – 155 mmol/L		Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Carbon Dioxide	Enzymatic Endpoint	21 - 32 mEq/L	9 – 40 mEq/L		Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Cholesterol, High Density Lipoprotein	Colorimetric	29 - 83 mg/dL	5 – 400 mg/dL	Lipemia, moderate to gross	Routine: 4 hours	Serum, or Lithium Heparin Plasma, 0.5 mL
Cholesterol, Total	Colorimetric	<200 mg/dL	5 – 400 mg/dL		Routine: 4 hours	Serum, or Lithium Heparin Plasma, 0.5 mL
Creatinine	Rate	0.5 - 1.2 mg/dL Critical Values: >9.9 mg/dL	0.1 – 10.0 mg/dL		Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL

Appendix 13: Example of Laboratory Test Method List, *continued*

Test	Methodology	Reference Ranges	Reportable Ranges	Interferences	Turnaround Times	Specimen Requirements
Chemistry						
Glucose	Colorimetric	72 - 112 mg/dL Critical Values: <50 mg/dL or >350 mg/dL	10 – 1000 mg/dL		Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Magnesium	Endpoint	1.6 - 2.4 mg/dL Critical Values: <1.3 mg/dL or >5.0 mg/dL	0.1 - 8.0 mg/dL	Hemolysis, any degree	Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Sodium	Potentiometric	136-146 mmol/L Critical Values: <125 mmol/L or >155 mmol/L	115 – 165 mmol/L		Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Phosphorus	Colorimetric	2.2 - 4.6 mg/dL Critical Values: <1.5 mg/dL	0.5 – 20 mg/dL		Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL

Appendix 13: Example of Laboratory Test Method List, *continued*

Test	Methodology	Reference Ranges	Reportable Ranges	Interferences	Turnaround Times	Specimen Requirements
Chemistry						
Potassium	Integrated Multisensor Technology	3.7 - 5.2 mmol/L Critical Values: <3.0 mmol/L or >6.0 mmol/L	1.0 – 9.0 mmol/L	Hemolysis, any degree	Routine: 4 hours; STAT: 30 minutes	Serum, or Lithium Heparin Plasma, 0.5 mL
Protein, Total	Endpoint Colorimetric	6.1 - 8.0 g/dL Critical Values: >12.9 g/dL	1.5 – 30 g/dL		Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL
Uric Acid	Colorimetric	female: 1.9 - 8.2 mg/dL male: 2.5-9.2 mg/dL	0.5 – 20 mg/dL		Routine: 4 hours; STAT: 1 hour	Serum, or Lithium Heparin Plasma, 0.5 mL
Hematology						
Hematocrit (HCT)	Calculated by Analyzer	female: 36.0 - 47.0 % male: 40.0 - 52.0 %	N/A	Hemolysis, any degree	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml
Hemoglobin (HGB)	Absorption Spectrophotometry	female: 12.0 - 16.0 g/dL male: 14.0 - 18.0 g/dL Critical Values: <5 g/dL	3.0 – 30 g/dL	Hemolysis, any degree	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml

Appendix 13: Example of Laboratory Test Method List, *continued*

Test	Methodology	Reference Ranges	Reportable Ranges	Interferences	Turnaround Times	Specimen Requirements
Hematology						
Mean Corpuscular Hemoglobin (MCH)	Calculated by Analyzer	27.5 - 33.0 pg	N/A	Hemolysis, any degree	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml
Mean Corpuscular Hemoglobin Concentration (MCHC)	Calculated by Analyzer	32 -36 g/dL	N/A	Hemolysis, any degree	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml
Mean Corpuscular Volume (MCV)	Calculated by Analyzer	female: 81.0 - 99.0 fl; male: 80.0- 98.0 fl	N/A	Hemolysis, any degree	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml
Platelet (PLT)	Optical Scatter	145 - 400 K/ml Critical Values: <50,000 - >800,000 K/ml	15 – 1000 K/ml	Lipemia, gross	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml
Red Blood Cell (RBC)	Electrical resistance	female: 4.00 - 5.40 M /mL male: 4.60 - 6.10 M /mL	1.50 – 15.0 M/mL	Lipemia, gross	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml

Appendix 13: Example of Laboratory Test Method List, *continued*

Test	Methodology	Reference Ranges	Reportable Ranges	Interferences	Turnaround Times	Specimen Requirements
Hematology						
White Blood Cell (WBC)	Optical Scatter	4.8 - 10.8 K/mL Critical Values: <1.0 or >25.0 K/mL	0.5 – 25.0 K/mL	Lipemia, gross	Routine: 4 hours; STAT: 30 minutes	EDTA Whole Blood, 1 ml
Clarity	Manual	Clear	N/A		Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL
Color	Manual	Yellow, Straw, Amber	N/A		Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL
Specific Gravity	Refractometer, mass gravity meter, or reagent strip	1.001 - 1.035	1.000 – 1.055		Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL
pH	Reagent strip	4.5 - 8.0	3.5 – 9.0		Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL
Ketones	Reagent strip	Negative	N/A	Bloody specimen, sulfamethoxazole	Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL
Glucose	Reagent strip	Negative	N/A	Bloody specimen, sulfamethoxazole	Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL
Protein	Reagent strip	Negative, Trace	N/A	Bloody specimen, sulfamethoxazole	Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL

Appendix 13: Example of Laboratory Test Method List, *continued*

<i>Test</i>	<i>Methodology</i>	<i>Reference Ranges</i>	<i>Reportable Ranges</i>	<i>Interferences</i>	<i>Turnaround Times</i>	<i>Specimen Requirements</i>
Hematology						
Bilirubin	Reagent strip	Negative	N/A	Bloody specimen, sulfamethoxazole	Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL
Microscopic Examination	Manual	WBC: 0-3 HPF RBC: 0-3 HPF	N/A		Routine: 4 hours; STAT: 1 hour	Urine, no preservatives, 1 mL
Urine Pregnancy	Immunoassay		N/A		Routine: 4 hours; STAT: 30 minutes	Urine, no preservatives, 1 mL

Appendix 13: Example of Laboratory Test Method List, *continued*

<i>Test</i>	<i>Methodology</i>	<i>Reference Ranges</i>	<i>Reportable Ranges</i>	<i>Interferences</i>	<i>Turnaround Times</i>	<i>Specimen Requirements</i>
Molecular Pathology						
CD3+/CD4+	Flow Cytometry	<p>Absolute Lymphocyte: 1,000 - 4,800/uL</p> <p>CD3+ T-Lymphs: 55% - 84%</p> <p>Absolute CD3+ T-Lymphs: 690 - 2,540/uL</p> <p>CD3+/CD4+ T-Helper: 31% - 60%</p> <p>Absolute CD3+/CD4+ T-Helper: 410 - 1,590/uL</p>	<p>Absolute Lymphocyte: 100 – 7,000/uL</p> <p>Absolute CD3+ T-Lymphs: 50 – 5,000/uL</p> <p>Absolute CD3+/CD4+ T-Helper: 25 – 4,000/uL</p>		<p>If specimen received by laboratory before 12H00, verbal report within 4 hours, final report in 3 days. If received after 12H00, verbal report by 09H00 following business day.</p>	<p>Whole Blood EDTA, 5-7 mL.</p> <p>Note: If specimen is collected on Friday, Saturday or Sunday collect an ACD tube (5ml - 7ml) in addition to the EDTA tube.</p>

Appendix 14: Example of Quality Management Plan

Quality First Laboratory
123 Sunny Hospital Street
Johannesburg
South Africa

Title:	Quality Management Plan – Quality First Laboratory		
Origination Date:	January 1996	Total Pages:	5
Effective Date:	04 January 2004	Policy No.:	GL 05v2
Written By:	Velma Jones, MT (ASCP)	Supersedes Policy/Procedure Dated:	26 Sept 2001
Approved By:	Frank Lee, Network Laboratory Director	Date:	04 January 2004
Approved By:	Daphne Lane, M.D.	Date:	04 January 2004

Distributed To	# of Copies	Distributed to	# of Copies
Quality First Laboratory Central Laboratory	1	Quality First Satellite Central Laboratory	1

Purpose:

The Quality Management Program is established to fulfill the department's responsibility to have a planned and systematic program for the monitoring and evaluation of the quality and appropriateness of the laboratory's contribution to support clinical trials and study participant care. Each section of the laboratory is responsible for identifying important issues in study participant care and safety and for ensuring the integrity of clinical trial data generated within the laboratory.

Responsibilities:

Each member of the Laboratory Staff is responsible for:

- Assuring the quality of work they perform, correcting errors when observed, and suggesting methods to prevent reoccurrence of any observed issues; and
- Assisting in the implementation of the Quality Management Plan.

Each Lead Technologist is responsible for:

- Assisting the Manager in the development and implementation of Quality Management plans,
- Identifying important or potential problems in their sections or shifts of responsibility, and
- Monitoring implemented plans for desired outcomes and reporting follow up activities to the Laboratory Manager.

The Quality Assurance/Quality Control Officer is responsible for:

- Overseeing all areas of Quality Management and facilitating data collection activities conducted within each department section;

Appendix 14: Example of Quality Management Plan, *continued*

- Documenting activities and reporting these to the Laboratory Management Team, Laboratory Medical Director and Quality Management department; and
- Monitoring follow up activities, assuring that the desired results have been achieved and sustained.

Each Manager is responsible for:

- Identifying important or potential problems in their assigned lab areas;
- Objectively assessing the cause and scope of problems and prioritizing investigations and resolution activities, giving highest priority to those problems with the greatest impact on study-participant care and study trial data;
- Evaluating trends to further identify problem areas;
- Implementing decisions or actions that are clinically useful to address and correct identified problems;
- Monitoring follow up activities, assuring that the desired results have been achieved and sustained; and
- Enhancing communication among co-workers, departments, and physicians in order that interrelated issues receive appropriate and expedited solutions.

The Laboratory Medical Director is responsible for:

- Overseeing ongoing departmental Quality Management activities,
- Ensuring that the program is implemented throughout the laboratory,
- Representing the Medical Staff in clinical issues that impact patient care, and
- Reporting Quality Management activities to appropriate Medical Staff committees.

Scope of Services:

The scope of services of the Clinical Laboratory is defined by the task or analytical workload presented to the Laboratory, and by the needs of the study-participant, sponsors, and those identified by the study protocol.

Laboratory evaluation of specimens is necessary to enable physicians and principal investigators involved in caring for study-participants and conducting clinical trials to monitor study-participants' progress while under therapy. Routine testing is performed in the Clinical Laboratory, while testing requiring technology not available within the hospital institution is forwarded to accredited Reference Laboratories approved by the Medical staff. A full range of testing is thus available, either in the Laboratory sections of Hematology, Chemistry, Molecular Pathology or at approved reference laboratories.

Important Aspects of Services:

Laboratory testing is dependent upon appropriately collected and positively identified specimens which are either analyzed immediately upon collection, or appropriately transported and preserved for later analysis. To assist the medical staff and hospital personnel who collect specimens, a *Laboratory Services Manual* is available via electronic format locally and off campus at outreach sites via the internet. Study-participant identification is assured by only collecting specimens on study-participants who are appropriately identified by the policy on identification of study-participants. The study-participant's name and unique identification number is recorded on each LIS (Laboratory Information System)-generated specimen label. The initials of the individual collecting the specimen, the time of collection, and the date are required for each specimen. Specimens are accessioned into the LIS by manual entry. The progress of each specimen/test is available through the Care Manager system for order entry. Before results are released, pre-processing Quality Assurance ranges are used to evaluate results, such as delta checks, critical values, and technical ranges. Depending on the method/analyzer used for testing, results that pass the established QA checks may be auto-verified or manually released by staff technologists.

Appendix 14: Example of Quality Management Plan, *continued*

The integrity of the analytical system is crucial to the testing service. This is assured by an appropriate preventive maintenance schedule and the utilization of an extensive QC program to establish the accuracy of the testing as it is performed. Clearly written, legible policy/procedure manuals, which include procedures for maintaining and appraising the function of all department testing modalities concurrent with their use, are available for every process in the department and are located at the site of the testing process. Furthermore, the department participates in interlaboratory comparison programs to promote uniformity across the field and in proficiency testing programs that assay both the analytical systems and the quality of the individuals operating them.

The credentials and qualifications of both the department and its staff are established in order to underwrite appropriate testing quality. The network laboratories are approved by the College of American Pathologists (CAP). Interim CAP self-inspections are conducted by the laboratory staff in an effort to document and correct deficiencies noted using current CAP guidelines. The interim self inspection is an important aspect of education and laboratory process improvement. Department personnel have clearly written position descriptions which define credential requirements for each position and establish the credentials of employees in those positions. Continuing education experiences and communication through departmental e-mail are used to keep staff current with the field.

Adequate reporting mechanisms are required to bring department testing to bear on study-participant care. Certain analytical procedures are identified for which abnormal values are defined as critical values and reported immediately to physicians or clinic staff when prompt intervention on the trial volunteer's behalf may be indicated by an aberrant laboratory value. More routine reporting mechanisms include computer-generated reports printed at the clinics and at outreach sites.

The adequacy of the facility is critical to quality testing. The Quality First Network laboratories maintain technological competence through the utilization of technologically current, well-maintained instrumentation throughout the department, and selected by hospital personnel for its compatibility with the demands of testing in the facility. The Biomedical Engineering department provides maintenance and service by utilizing qualified technical engineers.

Method:

Each department of the Laboratory participates in Quality Management using the following reporting methods:

1. Specific *departmental indicators* are monitored on a monthly or quarterly basis and are reported at the Department of Laboratory meetings. Each specific indicator is categorized by type, which includes the following:

-Efficacy	-Continuity	-Effectiveness	-Availability
-Appropriateness	-Safety	-Efficiency	-Timeliness
-Respect and Caring			
2. The *Risk Management Variance Report* is used for all laboratory employees to report variations from standard operating procedures and physician concerns relating to all phases of testing (pre-analytical, analytical, and post-analytical). This is completed online utilizing Inciport, a risk management software program, and provides immediate notification to all coordinators, managers, and directors of departments involved. The actions taken are documented within the Inciport system.

Tracking of Variances: Monthly variance reports are given to the Management Team for review and development of action plans if indicated, then forwarded to the Laboratory Director and the Principal Investigator for review. Specific queries are generated by Risk Management as needed to identify potential problems related to processes or procedures that are identified as High Risk, High Volume, or High Dollar.

Appendix 14: Example of Quality Management Plan, *continued*

The PDSA Process

After a specific quality issue has been identified by Risk Management Variance Reports or the departmental indicators, a team consisting of individuals directly related to the issue will be formed. Members of the team will meet as necessary to examine the entire process around the particular issue. Members may consist of laboratory personnel and/or personnel from other areas of the hospital. Each team has a facilitator who directs the activities and keeps the team focused on the issue. The clinical laboratory will have Quality Management teams throughout the year as need is identified. All departmental staff members participate in the process as determined by management.

The Laboratory Department's Quality management plan is based on the Plan/Do/Study/Act (PDSA) method of problem identification and resolution. The plan will:

1. **Plan** the improvement.
 - a. Determine benchmarks and best practices.
 - b. Describe current practices.
 - c. Measure and Analyze.
 - d. Generate and choose solutions; use Root Cause Analysis as a tool.
2. **Do** the improvement.
 - a. Map out trial run.
 - b. Implement trial run.
3. **Study** the results of the improvement.
 - a. Evaluate the results.
 - b. Draw conclusions.
4. **Act** to consistently achieve any improvements gained and continue to improve the process.
 - a. Standardize the change in practice.
 - b. Monitor and consistently achieve any improvements gained.

Communication of findings

1. Graphical tools are used to communicate quality findings and simplify comparisons across time.
2. Activities, progress, and resolutions are reported to Clinical Outcomes as needed.
3. Monthly variance reports are collated for each department manager.
4. Bulletin boards are utilized to display monthly departmental indicators and other quality management activity information.

Annual Evaluation

A summary of the previous years' activities is performed with recommendation for changes and continuation of activities as indicated by the effectiveness of the overall institutional plan. The summary is forwarded to the Principal Investigator for signed review and a copy is sent to the Quality Management Department.

Attachments or Appendices

- Attachment GL 05.1 Quality management Monitors
- Attachment GL 05.3 Risk Management Variance Report

Reference:

1. Brant, Alecia and Sweetman, Donna. Quality Management Plan, New Hanover Regional Medical Center, Wilmington, NC, 2004.

Review Date	Signature	Review Date	Signature
03 Jan 2005	Frank Lee		
02 Jan 2006	Frank Lee		

END