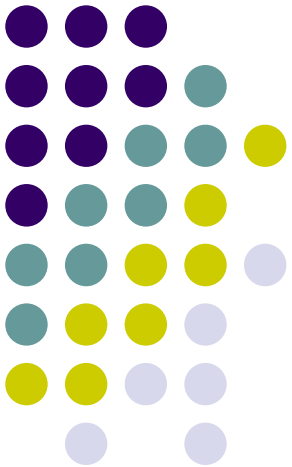
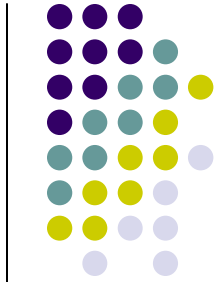
Gyrolab in a Validated Environment

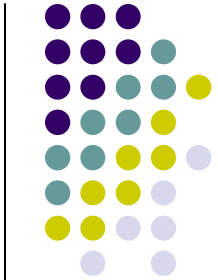


Marian Kelley
MKelley Consulting LLC



INTRODUCTION

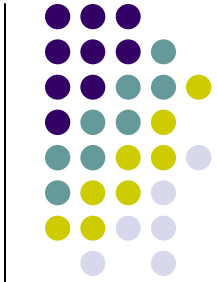
Rule 21 CFR PART 11



- Provides criteria for acceptance of electronic records by the FDA. With this regulation, electronic records are considered equivalent to paper records and handwritten signatures.

- Analytical laboratories in regulated areas who use computers for automated data acquisition and evaluation "must" comply with Part 11.

- The rule applies to all industry segments regulated by the FDA that includes Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and current Good Manufacturing Practice (cGMP).

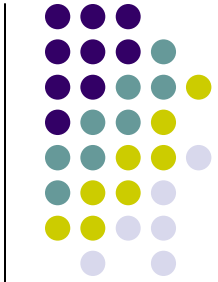


Rule 21 CFR Part 11 is an umbrella that dictates the many components that go into ensuring an electronic record is valid and acceptable when submitted to the Regulatory Authorities

Some Requirements of Part 11

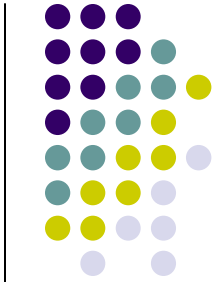
- Use of validated computerized systems.
- System and data security, data integrity and confidentiality through limited authorized access to systems and records.
- Secure retention of electronic records and instant retrieval.
- User-independent computer generated time-stamped audit trails.
- Use of secure electronic signatures for closed and open systems.
- Determination that the persons who develop, maintain or use electronic systems have the education, training and experience to perform their assigned task.

System Validation – 11.10(a)



"All computer systems used to generate, maintain and archive electronic records must be validated to ensure accuracy, reliability, consistent independent performance and the ability to discern invalid or altered records".

Computer Validation

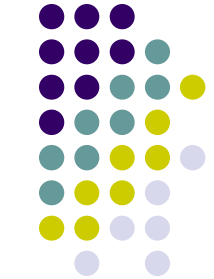


- Planning
  - Design specifications
  - Functional specifications
  - User specifications (where and how it will be used and by whom)
- Acquisition
- Risk Assessment
  - Determine if system requires validation and if so, its scope and the documentation required
- **Installation and qualification testing**
- Implementation
- Use in production
- Retirement

Qualification Phases: Installation (IQ)

- The intent of installation qualification (IQ) is to ascertain the comprehensiveness of delivered components, installed software, and required documentation
- Results should be documented and demonstrate that the acceptance criteria were met
- Summary report should document that installation procedure was followed, environmental recommendations were met and explain and justify deviations
- Signed by person conducting the testing

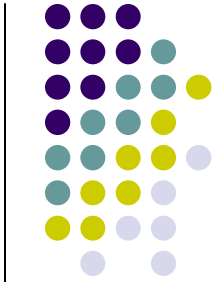
Vendor-Driven



- Typically the responsibility of the vendor to conduct the unpackaging and installation of a new system driven platform at the location it is to be used

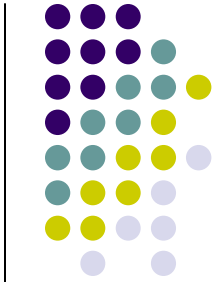
- A signed IQ document should be provided by the vendor

Operational (OQ)



- Ascertains the system's conformance to functional specifications
- Test scripts should adequately challenge all required functionality, focusing on those specifications that are pivotal to system operation
- During execution screen shots should be saved
- Discrepancies (failures) documented with resolution identified
- Summary Report should include scripts and results, deviations and their follow-up, whether acceptance criteria were met, signed

Vendor-Driven



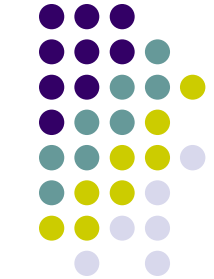
- Typically the responsibility of the vendor to conduct this qualification at the location it is to be used

- A signed OQ document should be provided by the vendor

Performance (PQ)
User Acceptance Testing (UAT)

- PQ verifies that the computerized system meets the predetermined business, security, and regulatory needs detailed in the user requirements document
- PQ should challenge the adequacy of user training and operational SOPs. For this reason, a member of the user group (other than the protocol's author) should execute the testing using company specific pre-defined datasets or actual live data
- Scripts are executed, signed and dated
- Failures are logged and resolution documented
- Summary Report written to include scripts and results, deviations and their follow-up, whether acceptance criteria were met, signed

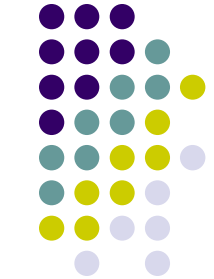
Performance Qualification vs Routine Maintenance



- PQ (UAT) is a component of Part 11 CSV that must be completed to consider the instrument ready for use in a GLP study

- Routine Maintenance occurs once a validated system is implemented to produce data. Routine maintenance may include a ”performance test”, (e.g., a pre-packaged assay) that helps monitor the instrument peformance on a routine basis (e.g., monthly or some period cited in the user manual/SOP)

PQ Testing



- Consists of scripts that test and sometimes challenge the instrument under conditions likely to be encountered during normal use.

- Clients' SOPs contain different interpretations of how to accomplish UAT

- Possible PQ scripts that Gyros can contribute to:
  - Discrete steps that reflect different aspects of the control software
  - Conduct of the Assay
    - Use of 96 well plate,
    - Generate assay run using robust method
    - Acceptable CD performance
  - Analysis Software: review all available regressions
  - Generation of Reports
  - Data storage and retrieval

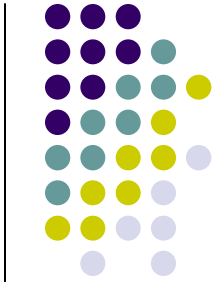
Validation Component		Gyros	Client
Planning	Design	✓	
	Functional	✓	
	User Requirements and traceability matrix	✓	
Acquisition	Vendor Audit		✓
Risk Assessment	Business Regulatory		✓
Qualifications	IQ	✓	
	OQ	✓	
Performance testing	aka User Acceptance Testing	✓	✓
Production	Periodic Requalification Problem reporting Change Control		✓
Retirement	Maintain or migrate data		✓

Documenting Technical Architecture

Captures the configuration of the CLI at the time of validation. Include text and screen shots, as appropriate, to describe the following:

Physical inventory
Manual and software titles
Detailed system diagrams
System workflows
Physical and logical access
User groups and permissions
Application software settings
Macros and custom calculations
Reports and templates
Default file locations and accessibility
Audit trail configuration
Troubleshooting

Computer System Validation Package



Compilation of all the documents that contributed to the final decision that a computer system is valid for its intended use.

Planning: User requirements, functional spec etc.

Traceability Matrix

Risk Assessment

IQ/OQ/PQ & summary reports

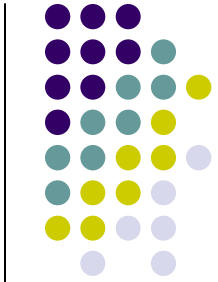
Testing protocols and scripts

Error reports and resolutions

Technical Architecture

Change Control Process

Software Requirements for Security Controls

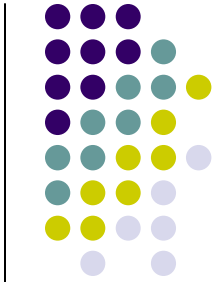


- Limited Access
  - Individual Accounts that are secured
  - Forced to change password on first log-in and at regular intervals
  - Log in/log out (automatic when idle)
  - Inactive periods revert to password protected screen saver
  - Failed log-in results in automatic lock outs
  - Create password convention rules

Password Conventions

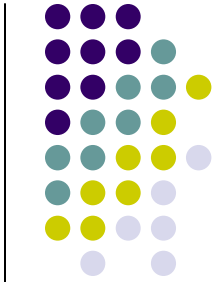
- Examples of password requirements
  - Miniumum length of characters
  - Multiple types of characters (up, lc, letters, numbers, special characters etc.)
  - Forced expiration (typícally 90 days)
  - Change password after first log-in
  - Lock-out after 3 unsuccesful attempts and cannot be automatically unlocked
  - Re-use of the last few passwords not permitted

Security



- Audit Trails
  - Changes trigger computer generated time stamp and identify responsible person
  - Ensures only authorized additions, deletions, alterations of information
  - Permits reconstruction of original entries
  - Documents by whom, when and reason for the change

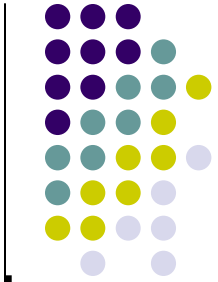
Security



- Date/Time Stamps
  - Changes made to the date and time are under authorized personnel control
  - Year, month, day, hour, minute and time zone

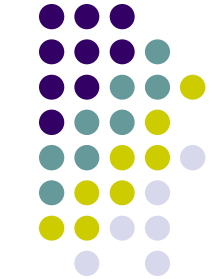
- External Security
  - Limited access to facility
  - Control over use of external applications (e.g., e-mail)
  - Documentation of controls to limit viruses etc
  - Ensure against catastrophic loss by back-up and secure storage

Electronic Signature



- Contains printed name, date and time, and the meaning (author, review, approval)
- Linked to the respective document so that it cannot be excised or associated with another document
- Unique ID and never re-assigned
- Requires two distinct components (ID and password)
- Owners of electronic signatures must ensure its security and intergrity

Change Control Process



- Ensures the integrity of the system
- Changes should be authorized
- Effects of changes should be evaluated
- Changes may require validation

Software upgrades

Security and performance patches

Equipment and component replacement

New Instrumentation

Traceability Matrix

Directly links the User Requirements to the test scripts executed during validation

Indicates where each user requirement will be tested, met procedurally, or verified through supplier audits

Within the matrix, specifies the exact test in which an individual requirement is tested

A trace matrix helps plan test activities that will prove all requirements are met through either system functionality or procedural means

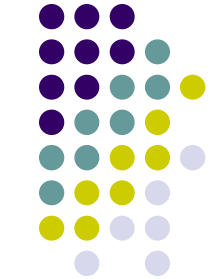
Secure Retention of Electronic Records and Instant Retrieval – 11.10(b) and 11.10(c)

"Procedures should be in place to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Records must be protected to enable their accurate and **ready retrieval** throughout the records retention period".

What is required to initiate bioanalysis for a GLP study?

- Instrument used to generate, analyze, report or store data for a GLP study must meet 21 CFR Part 11 compliance
- Instrument has an approved Maintenance and Use SOP
- Training on SOP is documented, including certifications

What is required to initiate bioanalysis for a GLP study?



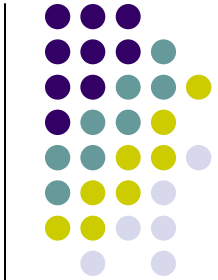
- Instrument has:
  - owner,
  - log book,
  - unique indentity,
  - been added to inventory,
  - been mapped to a location in the lab
- Assay method to be used to analyze the samples must be validated ”for the intended purpose”.
- Training on the method is documented

Use and Maintenance SOP

- Use typical SOP format (title, date, version scope, purpose, definitions, roles and responsibilities, training, deviations, approval signature, history etc.)

- Procedure:
  - Account set-up, maintenance and inactivation (forms)
  - Change Control
  - Security
  - Software and hardware maintenance
  - Back-up, Archiving and Retrieving
  - Periodic review and evaluation
  - System unavailability
  - Decommissioning

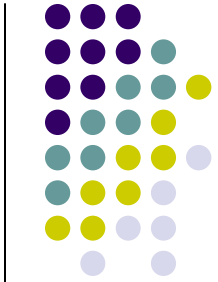
What is required to be included in an NDA when submitting data from a new platform?



- FDA is generally very accepting of new platforms for analysis of protein biotherapeutics

- Technology must be:
  - clearly discussed (including pros and cons) in the bioanalytical introduction section of the NDA
  - cross-validated with standard platforms to establish validity (esp, if other platforms are employed during the conduct of the studies included in the NDA)
  - provide data equal to or better than present technologies when supporting PK

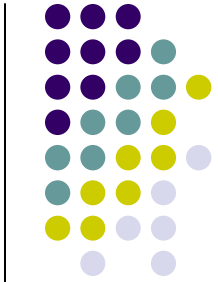
Conclusion



- Client
  - Signed system validation “package”
  - Completed and implemented SOP
  - Manage Change Control throughout life cycle
  - Validate method using validated platform

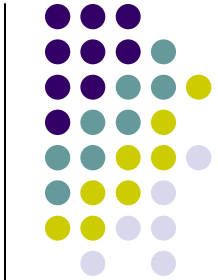
- Vendor
  - Signed IQ/OQ
  - Support PQ (UAT)
  - Training
  - Support method development
  - Understand how software updates impact validated state of system (Change Control)

Conclusion



- Gyros understands what system validation entails and is ready to support the client
  - Provide complete signed IQ/OQ documentation
  - Propose User Acceptance Testing formats
  - Training on the Gyrolab software
  - Basic training on method development
- New functional capabilities in method design and set-up will permit flexible and rapid method validation
- Updated manual
- Investigating the benefits of a “performance test” for routine maintenance

Computer Validation References



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The Auditing Group Inc, Validations .com

John F Cuspilich, Senior Editor, GMP Publications, Inc.

GAMP - "Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture" Produced by the GAMP Forum

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures Scope and Application http://www.fda.gov/cder/guidance/5667fnl.pdf

http://www.labcompliance.com/tutorial/csv/default.aspx

http://www.lsit.org/news/articles/dia_ramp.pdf