Today’s Speakers

Mark E Newton
Heartland QA

Mark is an independent consultant in laboratory informatics and data, data integrity, validation of computer systems/spreadsheets, analytical instruments and LIMS/ELN. He has 30+ years of pharmaceutical experience in QC Labs, computer systems validation and lab informatics. Mark co-lead Eli Lilly’s data integrity remediation program for QC Labs worldwide in 2012, consulted and audited several Lilly sites preparing for data-integrity focused inspections. He is a co-leader for the GAMP Data Integrity Special Interest Group and Chair of ISPE Global Documents Committee.
Today’s Speakers

Paul A. Smith

Global Strategic Compliance Specialist
Agilent Technologies

Paul has a passion for laboratory compliance. He started his career as an Infrared Spectroscopist, recording and interpreting infrared and Raman spectra and chemometric modeling of FT-IR, Raman, and NIR data. He did his first software validation work in 1992, before moving into broader analytical chemistry and laboratory management roles. Overall, he spent 17 years in the pharmaceutical industry and has worked in laboratory consultancy roles for the last 17 years.

He has worked in Pharmaceutical R&D, New Product Introduction and Quality Assurance and has focused on compliance of laboratory instruments and harmonization of this compliance, writing articles, while papers and contributing to GAMP Good Practice Guides.

In his current Agilent role, he monitors laboratory compliance change and non-compliance trends, sharing this information with customers and colleagues.
Overview

- Speakers Introduction
- Intent of the Good Practice Guide
- Scope (In/Out)
- Differences between v1 and v2 of GPG
Intent of GPG

The GAMP Good Practice Guide for GxP Compliant Lab Computerized Systems

• Risk-based approach to managing computerized systems
• Holistic view of equipment and software
• Consistent with ASTM E-2500 and GAMP 5
• Consistent with USP<1058>
• Intended for systems in all GxP environments
• Authored and reviewed by industry and regulators

Goal: computerized lab systems that are fit for purpose using “right-sized” approach to validation, where effort is matched to risk.
Scope of GPG

The GPG applies to computerized analytical systems that generate data.

Non-data equipment is out of scope (see USP<1058>)
- Shaker baths
- Centrifuges

Multi-user software applications are out of scope (see GAMP5)
- Chromatography
- ELN/LIMS
- Lab Execution Systems
- Other multi-user systems
Differences: GPG v1 and v2

For those who remember the original GPG (2005):

• Lifecycle model was modified to ASTM E-2500, which was adopted with GAMP 5. (Concept, Project, Operate, Retire)
• Moved away from categories (seven) based on functionality (equipment type) to three levels, based on data capabilities/complexity.
• Dropped non-data equipment, as it moved to USP<1058>.
The GAMP Approach
Systems Classifications (good/bad)
Symbiosis: USP <1058>, GPG, GAMP 5
GAMP – Good Practice Guide
A Risk-Based Approach to GxP Compliant Laboratory Computerized Systems
Second Edition

Table of Contents

1. Introduction (5 pages)
2. Key Concepts (5 pages)
3. Life Cycle Approach (3 pages)
4. Life Cycle Phases (19 pages)
5. Quality Risk Management (6 pages)
6. Regulated Organization Activities (4 pages)
7. Supplier Relationships (3 pages)

Systems & Examples (49 Pages)

18. Retention, Archiving, and Migration
19. References
20. Glossary

Appendices (103 pages)

8. Categories of Software
9. System Description
10. Data Integrity
11. Simple Systems
12. Medium Systems
13. Complex Systems

Considerations (32 Pages)

Supplier (5 Pages)

General (12 Pages)

Key Strength of Guide

Concept
Project
Operation
Retirement

2012 (GPG 2)
Historical Dilemma 1

Often, software and hardware (the instrument) were considered independently!

Example of Key Principles

- Must Define User Requirements
- Risk Based
- Scalable Approach
- Implementation Life Cycle
- Define Responsibilities
- Leverage Supplier Information

These are Common Principles Between GAMP and USP <1058>
**Historical Dilemma 2**

1987 – FDA Process Validation Guide Lines

2002 – FDA Guidance For Industry
- General Principles of Software Validation

**Process Validation Guidance**

**Medical Device Focus**

**Industry Needed Guidance**

GAMP 4 *(2001)* + GAMP Good Practice Guide *(2005)*

USP <1058> *(2008)*

> 1000, Optional General Chapter

Which Approach? *(GAMP or USP <1058>)*

**Simple approach, regulatory source**

**Structured development, consensus based**

GAMP 5 *(2008)*

**Not a Regulatory Source**
Life Cycle Approach

Evolution of USP <1058> and GAMP GPG

2005
GPG 1
(Good Practice Guide)
Validation of Laboratory Computerized Systems

2008
USP <1058>
Analytical Instrument Qualification
Risk-Based Approach to GXP Compliant Laboratory Computerized Systems

2012
GPG 2
(Good Practice Guide)

2017
New USP <1058>
Analytical Instrument Qualification
Data Integrity Focus

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Stronger Alignment of GAMP and USP <1058>

“Fixed” Categories (A to G - EXAMPLES)

Common Evolution

“FIXED” EXAMPLES

An Integrated Approach to
Computer Software Validation (CSV)
And
Analytical Instrument Qualification (AIQ)

Risk-Based Approach to GXP Compliant Laboratory Computerized Systems

GPG 1
(Good Practice Guide)

2005
Validation of Laboratory Computerized Systems

2008
USP <1058>
Analytical Instrument Qualification

2012
GPG 2
(Good Practice Guide)

2017
New USP <1058>
Analytical Instrument Qualification

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Continuum Between <1058> and GAMP

Risk-Based Approach to GXP Compliant Laboratory Computerized Systems
GPG 2

RDI
Key Concepts
Regulatory Guidance

2017 New USP <1058>
Analytical Instrument Qualification
USP <1058> Instrument Categories: A, B and C

Have to determine which category (A, B or C)

By:
Risk Assessment & Intended Use

“…..the same type of instrument can fit into one or more categories, depending on its Intended use”
GAMP Good Practice Guide – *Instrument Complexity*

**Key Strength of GPG, 2nd Edition**

**Original Instrument “Fixed” Categories**
- A - Sonicator
- B - pH Meter
- C - Key Pad HPLC
- D - PC HPLC
- E - NMR
- F - Spread sheet
- G - Bespoke

- Based on features of the “system”

**Based on Lifecycle & how The system Is used**

- **Concept**
  - Simple
- **Project**
  - Medium
- **Operation**
  - Complex
- **Retirement**

- **Good Project Management**

**In Appendix**
- pH Meter
- Pipette
- Balance
- PCR cyclers
- HPLC/GC
- FT-IR
- CDS/HPLC

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Poll Question #1

What guidance do you use for your laboratory computerized systems?
A. USP <1058>
B. GAMP GPG for Lab Systems
C. GAMP 5
D. Other
Vendor Evaluation
Importance to Data Integrity
Deciding the Best Approach
Responding to What is Discovered
Total Cost of Ownership
Vendor Evaluation

• The type of evaluation should reflect the risk (and/or cost) to the organization
  • Onsite evaluation
  • Teleconference
  • Questionnaire/survey
  • None at all

• As systems move up the complexity curve, the type of evaluation can move up as well.

• Good evaluations (regardless of type) usually require multiple specialties
  • Business
  • QA
  • IT
Vendor Evaluation

Assess the vendor’s development process and quality practices

• Is there a development methodology?
• Do they have a QA function?
• Do they conduct formal, written tests?
• Do they have a complaint management process?
• How large is installed user base for this item?
Vendor and Data Integrity

• Appendix 11, *Supplier Documentation and Services*, describes services and information that vendors can supply.

• Vendor designs can eliminate – or create – data integrity gaps in computerized systems. It is imperative to evaluate data integrity gaps prior to purchase:
  • Assessing enables an estimate of the mitigations and their cost to the organization (total cost of ownership)
  • Assessing permits a cost/benefit comparison of competing models on a like vs like basis
  • Assessing provides a tool for price negotiations, esp. if gaps are found.
Responding to Discoveries

• Why perform Vendor Evaluation if it does not lead to action?
• Some possible outcomes:
  • If vendor has tested some of requirements, then accept vendor testing on those requirements
  • If vendor has no evidence of testing, test all requirements (or all high/medium requirements)

• Software risks are usually higher than hardware risks, because software has low detection
• When vendors outsource software development, must go to software firm as well

(Insert experiences here)
Total Cost of Ownership

Total Cost = purchase + project + 10 year use + retirement

Better data integrity compliance = lower project and use costs
Mitigating gaps adds to project cost and use costs—more SOPs/training required
Buy based on total cost, not purchase price
Special Considerations: Project (Development)
Requirements
Design/Configuration
Testing
Traceability Matrix
Requirements (Specifications)

• Requirements (or specifications) describe the characteristics or attributes that the equipment must possess to be fit for its intended use
• Requirements form the basis for all subsequent design and testing activities
• Requirements have an important role in the selection of computerized systems, and configuring it for use
• For computerized lab systems, not necessary to write separate user/functional requirements – a combined set is sufficient
• Give emphasis to security, data integrity and audit trails

NOTE: Vendor specs from manuals, etc are not business specifications!!!!!!!
Design/Configuration

- Configuration (and configuration control) can impact the complete record of testing; therefore, it must be well-documented
  - Time clock, audit trails, calculation types, etc.
- For complex systems, configuration can be a challenge, as it requires both business and IT expertise. Often need to work with vendor to understand options
- CRITICAL: document WHY (rationale) each setting is chosen, so future change proposals can be evaluated.
Instruments and Software......

V Model is a **Good fit for Software**

V Model is a **Poor fit for Standard Instruments** ("COTS")

Instrument Life Cycle is a **Poor fit for Software**

Instrument Life Cycle is a **Good fit for Instruments** ("COTS")
Instrument Complexity and Traceability

Traceability: of User Requirements
(Previous on Use and Complexity of User Requirements)

- New Software - Trace Matrix
- Must be Maintained
- Periodic Testing
  (e.g. HPLC OQ ~ Annual, PQ ?)
- Traceability - Complexity of URS
  - URS/OQ Alignment
  - Formal Trace Matrix
  (as part of software or Complex URS QTOF)

- Software Validation
- Requirements Trace Matrix
- Change Control
- Risk Assessment / Re-Validation
- Periodic Review
- Re-Validation ?
Instrument Testing Considerations

See USP <1058>

**URS**: User Requirement Specifications
**DQ**: Design Qualification
**RA**: Risk Assessment
**IQ**: Installation Qualification
**OQ**: Operational Qualification
**PQ**: Performance Qualification

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**Traceability**

- Traceability from requirements to code is not possible for COTS.
- Instead, trace requirements to testing scripts.
- Consider advantages of tracing requirements to configuration decisions.
- For most systems, a spreadsheet-style approach works well.

<table>
<thead>
<tr>
<th>#</th>
<th>Critical?</th>
<th>Requirement</th>
<th>Vendor</th>
<th>DV Met?</th>
<th>Tested</th>
<th>Test Met?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>No</td>
<td>Must be able to inject 2 samples/minute</td>
<td>pg 19: capable of 4 samples/minute</td>
<td>Yes</td>
<td>PQ: 10.0 Test Volume</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Design Verification (DV)**
Special Considerations: Operation
Firmware Upgrades
Backup/Restore (Disaster/Continuity)
Archiving
System Retirement
Firmware Upgrades / Considerations

Updating Firmware is not a “like for like” change – Change Control

- Firmware is Tested by the Supplier
- Supplier Testing – may not be not always be available
- CDA Option - Confidential Disclosure Agreement
- Firmware - release notes
- Compatibility – especially between vendors
- Communication – needs to be tested
- Impact Assessment – depends on release notes
- Standardise – where possible
- Coordinate – instrument / software testing
Backup/Restore (Disaster/Continuity)

- Backup (and Restore) are critical to preservation of electronic records
- Loss of data due to no backup is a common Data Integrity finding
- If software install can be rebuilt from external media, then focus is on data.
- Need to periodically challenge restore process to verify it,

- Continuity planning is best done at the laboratory level, rather than single installs.
Archiving

• Secure, long-term storage of data/metadata until destruction
• Often required for small computerized systems
  • Storage limits
  • File vulnerabilities on local system (old systems/bad design)
• Often adds protection (few have write access)
• Not the same thing as backup files!
• Like retirement: assure that complete record is archived
System Retirement

- Retirement will focus on data retention, and system removal.
- Often results in “boneyards”: old systems for “read only”
- Better choice is data migration, if feasible
- Acknowledge that value of audit trails will decrease over time

- Move audit trails and metadata together to preserve complete record!
Efficiencies in Compliance
Multiple Installs of Identical Units
Common SOPs
Hardware and Software Re-Qualification
Common Processes

• Once software has been tested, only IQ is needed for additional installs
  • IQ/OQ always required for hardware
• Create single system administration, system maintenance, backup/restore
  SOPs for all systems at a lab level (not individual applications)
• Plan business continuity at lab (or even entire plantsite) level
**Instrument Performance Qualification – No Black/White**

**Key PQ Thought** – “How Different is your use of the instrument from how the instrument performance is “routinely” evaluated”

**OQ**: Test

**User Requirements**

**PQ**: Evaluates

**Your Use / Applications**

**SST**: Does it Work on the Day

**SST is not a PQ!**

### Justification and Implementation

<table>
<thead>
<tr>
<th>Justification</th>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>More Work to Justify (Holistic PQ is Representative of Use)</td>
<td>Simple</td>
</tr>
<tr>
<td>Easy to Justify (Method / Application based PQ)</td>
<td>Complex</td>
</tr>
</tbody>
</table>

- **OQ + Holistic PQ + SST**
- **OQ + Use - Specific PQ + SST**

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Poll Question #2

How do you manage Performance Qualification (PQ) testing for lab computerized systems?

A. Do nothing (no PQ)
B. Have vendor perform PQ
C. Annually perform PQ
D. PQ only when needed (e.g. major repair, upgrade)
Q&A

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Upcoming Webinars

• 21 August 2019 – Polishing an Old Gem: Commissioning & Qualification Baseline Guide Update

• 24 September 2019 – Qualification of PAT Systems

Topic Ideas or Feedback?
Send to ispeak@ispe.org