Strategies for Risk Based Validation of Laboratory Systems

Video Web Seminar
September 23, 2004

Ludwig Huber
E-mail: ludwig_huber@agilent.com

Agilent Technologies
Today’s Agenda

• Background information: why risk assessment, FDA directions, industry recommendations

• Approach for risk assessment of laboratory systems with examples for high and low risk systems

• Approach for risk based validation (how much validation is enough?)

• Vendor contributions for validation
Reference material

SOP’s with templates
- Risk Assessment for laboratory systems
- Risk-based validation of laboratory computer systems
- Part 11 scope and controls

Gap analysis Part 11

FDA/EU guides on validation of software and computer systems

http://www.labcompliance.com/conferences/laboratory-risk.htm
(available until May 31, 2005)
FDA Warning Letters/483’s - Examples

• Failure to have a complete calibration program for the HPLCs in that the gradient accuracy and detector linearity is not being verified (w-110)

• Data transfer of a (chromatographic) client-server system not validated (w-029)

• QA/QC Spreadsheet Validation, is deficient in that only a small range of values are being used to challenge computerized spreadsheet mathematical calculations (w-063)

Reference: www.fdawarningletter.com
FDA Warning Letters/483’s - Examples

• No documented evidence to demonstrate the WAN was capable of properly performing backup and recovery of data on the QC server (w-029)

• No validation after hardware and software upgrades and configuration changes (w-029)

Reference: www.fdawarningletter.com
Risk Assessment and the FDA

- 21 CFR Part 820: Quality system regulation and lots of experience with medical device industry
- Part of FDA’s drug cGMP initiative for the 21st century: Merging science and risk”
- Risk-based Part 11 implementation
We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety and record integrity.

Validation – audit trail – record maintenance, archiving – electronic copies

Link on reference website
FDA: Risk Assessment and Validation

FDA Guidance –
General Principles of Software Validation; (2002):

The selection of validation activities, tasks, and work items should be commensurate with the complexity of the software design and the risk associated with the use of the software for the specified intended use.

For lower risk devices, only baseline validation activities may be conducted. As the risk increases additional validation activities should be added to cover the additional risk.
Recommendations from the Industry

• GAMP 4 - Appendix M3 on risk assessment

• Pharmaceutical Research and Manufacturing Association
  - High risk:
    - manufacturing batch records,
    - LIMS and QA systems

• International Society for Pharmaceutical Engineering (ISPE)
  - High risk: batch records, laboratory test results
  - Low risk: environmental monitoring records not affecting product quality, training records, setup and configuration parameters
Risk Management

- Risk Analysis: Identify hazards and possible harms
- Risk Evaluation: Define risk level (probability/severity)
- Risk Mitigation/Control: Cost/benefit analysis, Mitigation steps
- On-going Evaluation: Monitor for new harms, Monitor risk levels, Update plan

ISO 14971-1:1998: Medical devices

Key criteria: product quality (public health), business continuity

Agilent Technologies
Start With a Risk Management Master Plan

- Approach for risk management
- Steps for risk analysis/evaluation
- Steps for risk mitigation/control
- Inputs for risk assessment
- Risk categories and examples
- Appropriate controls for different risk levels
- SOP with Templates
- Responsibilities

Improves
- efficiency
- consistency

<table>
<thead>
<tr>
<th>Risk descript.</th>
<th>Severity</th>
<th>Probability</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Matrix

www.labcompliance.com/books/risk
Step 1. Risk Analysis

- Collect information on possible hazards and harms
- Inputs come from user experience with the same or similar equipment, validation reports, service records, internal audit records, previous FDA inspections

<table>
<thead>
<tr>
<th>Risk Description</th>
<th>Impact - possible harm-</th>
<th>Probability of occurrence</th>
<th>Suggestion for mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Step 2. Risk Evaluation

• Categorize and prioritize risks in business (continuity) and compliance/health risks

• Define criteria for classifications and classify as high (3), medium(2) and low(1)

• Estimate and classify probability of occurrence

• Calculate risk factor
  (Business impact + compliance impact) x Occurrence

<table>
<thead>
<tr>
<th>Risk Description</th>
<th>Business impact</th>
<th>Compliance impact</th>
<th>Probability of occurrence</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Examples - Risk categories

<table>
<thead>
<tr>
<th></th>
<th>Business Continuity</th>
<th>Compliance/health</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Failure has significant impact to deliver products for several days</td>
<td>Failure of the system may cause harm to patients, and there is no correction possible</td>
</tr>
<tr>
<td>Medium</td>
<td>Failure has potential impact to deliver products for 1 to 2 days</td>
<td>Failure of the system can cause harm to patients, but there is a good potential to correct the failure</td>
</tr>
<tr>
<td>Low</td>
<td>Failure has negligible to deliver products</td>
<td>Failure of the system will not cause harm to patients</td>
</tr>
</tbody>
</table>

Develop and follow SOP (included on the reference website)
Documenting Risk Assessment for Part 11

- Use tables with description of risks, severity, probability and the rational behind
- Calculate overall risk factor
- Classify factors in high, medium and low

There are many other ways to do this

<table>
<thead>
<tr>
<th>Risk descript.</th>
<th>Severity</th>
<th>Justification</th>
<th>Probability</th>
<th>Justification</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example: QC Laboratory Data System

- Sample from plant
- Sample receipt and log in
- Sample analysis
- Review and approval
- Release Packaging Labeling

**High Risk**

- Direct impact on product quality
- Computer performs regulated action
- No subsequent verification of test results

Agilent Technologies
Example: Word Processing System for Validation Reports

- Users
- Archive

Inputs:
- Draft
- Review
- Approval Release

Low Risk:
- No direct impact on product quality
- Computer = type writer
- Indirect testing by proofreading
Consequences for High Risk Systems

- Extent of validation
e.g., vendor assessment, type and range of functional testing, frequency of revalidation
- Part 11 functionality (e.g., retention of e-records)
- Frequency of back-up
- Contingency/disaster recovery planning (e.g., availability of redundant systems)
- Level of security, e.g., physical lock vs. password protection

Should be defined in master plans (validation, risk, part11)
Lifecycle Phases - 4Q Model

- Design Qualification
  - Specification
    - Vendor assessment
  - Installation
    - Installation Documentation
  - Operational
    - Equipment testing
  - Performance
    - Application testing

All validation phases
Planning Validation Activities According to Risk Levels

<table>
<thead>
<tr>
<th>Activity</th>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specifications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vendor assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Installation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gamp = Good Automated Manufacturing Practice Forum

Increasing controls
Risk Based Tasks

• Planning
• Specifications
• Installation
• Testing
• On-going control
• Security/Access control
• Change control
• Back-up
• Contingency planning
• Part 11 controls

Develop and follow SOPs
Included on the reference website
**Example: Vendor Assessment**

<table>
<thead>
<tr>
<th>System</th>
<th>GAMP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Vendor audit</td>
</tr>
<tr>
<td>Medium risk</td>
<td>Assess through vendor checklists (mail audit)</td>
</tr>
<tr>
<td>Low risk</td>
<td>Document vendor and reputation</td>
</tr>
</tbody>
</table>
### Example: Networks

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Baseline Documentation</th>
<th>File Transfer Verification</th>
<th>Connectivity Testing</th>
<th>Baseline Documentation (inventory, diagrams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium risk</td>
<td>Baseline documentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>Baseline documentation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The most critical application supported by the network will determine criticality of the network.
Example: On-going Network Monitoring
- for networks supporting high risk records -

- Monitoring Alerts
- Monitoring Bandwidth
- Mapping Topology
Vendor Contributions
Example: Agilent’s Offers for Compliance in the Laboratory

• Products with built-in functionality for Part 11 and GxP compliance
• Documented evidence for development validation on CD with excellent track records from >100 vendor audits
• Qualification services for the entire laboratory
• Sharing compliance expertise with users

Work with FDA's and industry task forces
Agilent Analytical Products Designed for Compliance

• Leading analytical instruments with built-in functionality for Part 11 and GxP compliance
  HPLC – GC – GC/MS – LC/MS – UV/Vis – CE – Lab-on-a-Chip (LoaC)

• Scaleable client-server based data systems for multi-vendor instrument control, data acquisition, and evaluation

• Enterprise Content Management (ECM) system to collect, manage, and archive all types of data from multiple instruments and office applications

Reduce costs and compliance risks

Agilent Technologies
Agilent Compliance Services

• Instrument qualification and requalification from DQ to OQ for the entire laboratory
  – multi-vendor (Agilent and non-Agilent)
  – multi-technique (e.g., HPLC, pH-meter, balances)
  – global (same protocol world wide)

• Computer system validation with focus on environment specific performance

• Network qualification services for existing and new networks

Focus on critical characteristics

Increase uptime – efficiency - compliance
Example: From Analysis to Corporate Network

Company Intranet

Internet

Interface

Agilent Cerity ECM

Interface

Drawings

PDF

MS Office

LIMS & e-Notebook

Images

Scientific Research

GC

LC

UV

CE

LoaC

GC/MS

LC/MS

ICP-MS

The following are observed results from Project LY121:

- The efficacy of compound 344 met targets.
- There were no adverse effects noted in any rat or Monkey study.
Thank You

I would like to thank:

• Advanstar communication for organizing this video web seminar
• Agilent Technologies for sponsorship
• All attendees for your attention
• David Markovitz for moderation

Ludwig Huber

For more information on the Agilent compliance program visit
www.agilent.com/chem/regulated

For more information on Agilent products visit
www.agilent.com/chem
Institute for Effective Innovation

**serving the FDA regulated industries**

Call us for help with process innovation

- *World-class training on process innovation*
- *World-class training on GMP and QSR*
- *Consulting and Coaching on the innovation process*
- *Proven tools to equip your work groups and teams*

**New**

714-289-1233

David@DavidMarkovitz.com

Innovation Boot Camp

*A Hands-on workout designed to pump up your Innovation Instinct™ - customized for your team*

www.InnovationBootCamp.com