Global Bioanalysis Consortium: Analytical Instrument Qualification
Team A9

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GBC Mission

Create an all inclusive Global Bioanalysis Consortium (GBC) consisting of represented scientific associations with world wide influence to merge existing or emerging bioanalytical guidances to create one, unified consensus document that can be presented to the regulatory bodies/health authorities on various countries.
GBC Objectives

• To bring together stakeholders from the pharmaceutical industry, contract research organizations and academia to share current understanding of bioanalysis guidelines identify differences in these guidelines or differences in the interpretation or application thereof to routine Bioanalysis.

• To come forward with recommendations to Health Authorities and regulatory bodies worldwide on globally agreed best practices for Bioanalytical Method Validation (BMV) and application of such methods/technologies to the analysis of drugs of all molecular sizes in support of clinical and nonclinical studies.

• To invite relevant stakeholders, from industry, academia, Health Authorities and regulatory bodies, to jointly discuss the GBC recommendations at a global conference(s) in order to achieve globally agreed guidelines on Bioanalysis.

• Going forward, to serve as a pivot point on the continued harmonized interpretation and/or updates of globally agreed guidelines.
Organization Chart

Steering Committee (GBC-SC)

Scientific Leadership Team (GBC-SLT)

Harmonization Team # 1

Harmonization Team # 2

Harmonization Team ‘n’
Which Harmonization Teams?

Overview

GBC SC

GBC-SLT

A: Harmonization teams focusing on topics which apply for both chromatography based assays and Ligand Binding Assays (All molecules)

S: Harmonization teams focusing on topics which apply for Chromatography based assays (Small molecules)

L: Harmonization teams focusing on topics which apply for Ligand Binding Assays (Large molecules)
Which Harmonization Teams?

A1 Scope and regulations
A3 Method Transfer, partial/cross validations
A5 Sample Management
A7 Repeat analysis and ISR
A9 Analytical Instrument Qualification
A11 Biomarkers

A2 Tiered approaches for method validation
A4 Reference standards and reagents
A6 Stability
A8 Documentation
A10 New Frontiers

L1 Large molecule specific run acceptance
L2 Large molecule specific assay operation
L3 Assay formats
L4 Reagents and their stability Link with tiered approach
L5 Automation practices in LM bioanalysis
L6 Immunogenicity (effect on PK).

S1 Small molecule specific run acceptance
S2 Small molecule specific assay operation
S3 Chromatographic Run Quality Assessment
Why AIQ in GBC?

- Many regulations that are implicitly applicable
- Few regulations that are explicitly applicable
- Not clear which regulations apply, must pick and choose pieces from many sources
- Not included in most (any) guidance documents for regulated Bio (eg. FDA, EMA)
- Easy to overdo it (go GMP). Pharma needs to reduce overhead
- Easy to underdo it. Due to lack of time and/or resources
- Opinions inside companies vary as much (or more?) between different departments in the same company than between the same departments between different companies.
Some of the Regs to Consider

GLP

Engineering
• ISPE GAMP 5
• NIST Risk Mgmt Guide for IT systems

Clinical
• FDA Guidance Comp Systems in Clinical Investigations
• Japanese Guideline for Electromagnetic Records in Applications for Pharmaceuticals

GMP
• USP <621>
• USP <1058>
• FDA 21 CFR Part 11
• EMA GMP Annex 11
• FDA General Principles of Software Validation
Keep it in perspective

In Scope
• Equipment Software Validation
• Change control/Routine requalification
• Instruments/Equipment
• System Suitability (overview)
• Holistic Approach
• Regulatory/Audits
• Role of the Laboratory and IT in Lab Software Validation

Out of Scope
• IT Infrastructure Qualification
• Design Qualification
• Stand-alone/non-instrument controlling software: spreadsheets, homegrown, COTS
• LIMS, ELN where not interfacing with instruments
Current Situation

- AIQ is a globally recognized, required activity
- Most regulated labs do some form of AIQ
- Who does which activities varies greatly
- Terminology is not harmonized
- Amount of effort in companies varies greatly, often dependent on understanding and awareness of process.
- Effort should always involve: Operations, IT, QA and Vendors
Overview

• IQOQPQ
• Traditional approach still valid
• Software validation in AIQ process
• Requalification (RQ?)
• Audits – Part 11, other regs?
• Defining the roles of Operations, QA and IT in the process
Components of Data Quality

<table>
<thead>
<tr>
<th>Instrument or Method?</th>
<th>When Performed?</th>
<th>Controls What</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>• During an analytical run</td>
<td>• System drift over the time of the analytical run and over time of all runs</td>
</tr>
<tr>
<td></td>
<td>• On the day of analysis</td>
<td>• Confirmation that the system (instrument and method combination) functions</td>
</tr>
<tr>
<td></td>
<td>• Before committing samples for analysis</td>
<td>within predefined limits</td>
</tr>
<tr>
<td>Instrument</td>
<td>• At initial instrument set up</td>
<td>• Confirmation of method operating parameters</td>
</tr>
<tr>
<td></td>
<td>• At regular intervals thereafter</td>
<td>• Sample preparation</td>
</tr>
<tr>
<td></td>
<td>• Following major maintenance</td>
<td>• Operator-to operator bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Instrument-to-instrument bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Method transfer between laboratories</td>
</tr>
</tbody>
</table>

IQ OQ PQ

At least we’re not validating that!
IQ OQ PQ in one slide!

User Requirement Specifications → Functional Specifications → Design Specification → Design Qualification → Installation Qualification → Operational Qualification → Performance Qualification

Process Flow → Reference
**IQ and OQ**

**Installation Qualification (IQ)** - The IQ is comprised of documentation that demonstrates that the system is installed properly.

**Operational Qualification (OQ)** - The OQ is comprised of documentation that demonstrates that the system is operational in its installed environment.

Performed by manufacturer (sometimes 3rd party)
Oversight and sign-off by system owner
Performance Qualification

• The PQ is comprised of documentation that demonstrates that the system performs the functions that the users need it to.

• Testing is adjusted to the intended use. Some suggestions follow.

• PQ phase verifies integrity of installation at site, including network access, security, configuration tests; PQ also includes customer-specified tests that may be more relevant to the site, such as the execution of a trusted method.

• Aspects of PQ can be holistic. eg. you might need the MS to test the HPLC acquisition.

• Design/customize scripts specific to the environment you are working in.

• Core validation run with curve, QCs.
  • To verify carryover, sensitivity, device communication, other instrument performance parameters.
Multiple Instruments?

First Instrument
• Full IQ/OQ/PQ
• Software validation
• IT Environment set up and check
  • Functionality with anti-virus, etc.
  • Network, folder security
• Write SOPs
• Establish maintenance schedules

Replicate Instrument (2nd, 3rd, etc) of same type.
• Level of qualification can be determined based on history, use and environment the equipment has been used in.
• Same IQ/OQ
• Replicate IT settings
• Minimal or no PQ (just SST may be enough)
• Review SOP
• Implement same PM
Categorization

- For each item of incoming equipment, user/lab manager to select equipment category and document selection rationale according to local regs, then qualify according to category.

- Which categorization approach?
  - GAMP 5
  - USP 1058 (adapted from Bansal, et al white paper)
  - Very simple
    - Tools, instruments
    - Metrology tools – reference weights, check plates (binding assays)

- Categories are based on complexity, configurability, and criticality.
Random thoughts…

• Owner should review draft OQ carefully, remove those test scripts that simply generate busywork for vendor or CRO, and add scripts that test holistic performance.

• A well designed OQ specific to the user’s workflow will reduce the effort for the end user and the vendor.

• Requirements not for what you buy but what you must test.
• Use requirements to build traceability matrix

• Consider qualification of metrology tools
  • Vendor should provide the specifications and any expiration dating for these materials. From time to time, these standards will need to be re-verified.
  • Calibration standards provide traceable “standard of truth” to verify or recalibrate instruments to acceptable performance.
Procurement Process

Vendor Risk Analysis
- 3rd party installer’s qualified
- Safety Procedures
- ISO Certificate
- Reputation

Approaches
- Teleconference
- Questionnaire
- May audit on-site for major equipment

If vendor process is good, it can minimize your work.
Comments on Equipment Control Software Validation

- For most complex instruments, software can’t be validated separately from the instrument qualification.
  - Complete computerized system validation.

- What reg’s apply to electronic data?
  - FDA’s 21 CFR Part 11 recognized as a global “standard” for electronic data but can’t forget other regs that are emerging
  - EMA Annex 11, GAMP5, many others?

- Is there value in executing standard test scripts? Probably not. Only tests aspects that can change in your installation.

- It is more value added to focus on how the instrument works in your operation with the software.

- Validation of configured portions of the software only.

- Instrument parameters established by the software are not validatable by end user. Example: MS source temperature, MS voltages, robotic movement details.

- COTS code review is not necessary
After the IQOQPQ Process

Routine Maintenance
System Suitability
Requalification (RQ)
Audits
Routine Maintenance

• Establish during or following qualification
• Define the process
  • SOP, Work Instruction, refer to Manual
• Calibration Process
• Who to call for repair?
• Understand your service contract and ensure it is filed for future reference along with all other documentation of maintenance.
• Build a schedule and document it somewhere so its not forgotten
  • Give it to QA, they’ll make sure you do it.
Requalification (RQ)

- Establish process BEFORE release
- Must have predefined process
- Defined: Simple test that confirms the system is operating correctly after a minor change
- Repair and Change Categories (may perform through change control process)
  - Move of instrument (not reinstallation)
  - Upgrade
  - Broken
    - Minor
    - Major
- Requalification is what you must do before restarting the batch
- Often includes some elements of IQ/OQ/PQ and routine maintenance tests.
Holistic Qualification

• Qualification of all components of an entire system at once.
• Useful approach in many occasions
  • Repaired systems can be re-qualified holistically using a reference method.
  • Often part of PQ and RQ
  • System Suitability is a common example of holistic qualification.
• Performance checks using a small number of specific samples (blank, LLOQ, etc.)
Where Does System Suitability Fit In?

Why?
• Ensure instruments and equipment are prepared for run.
• In regulated bioanalysis system suitability is the assay specific part of the qualification process.
• Performed at regular intervals but not always for every batch

Chromatographic Assays
• In GLP is usually assay specific.
• A few injections before, during and/or after a run

Binding Assays, Plate Format
• More instrument specific
• Qualification plate specific to your assay type
• Standard controls for counters

Details
• Specific details within other teams
Regulations and Audit Preparation

- **Lack of consistency**
  - Regulators often don’t have consistent audit practices, some better than others.
  - May get very little notice of FDA audits so must be prepared on the IT side. Other agencies generally give more notice.
  - Companies in transition

- **Expectation for GMP testing and documentation**
  - GMP is often not necessary or appropriate but should be looked at for a guide particularly with failures, investigations and CAPA.

- **Audits often focus more on process and documentation, not details of tests**
  - Spend extra time on documentation and ensure thorough review.
  - Keep complete and reproducible audit trails including security levels/access rights.
  - Written procedures in place. Follow your procedures.

- **Printed versus electronic records:**
  - What is the definition of the raw data? Sometimes more important is what is your companies definition.
  - All of the data throughout the process is the raw data, not just the finalized data.
  - Are printed versions of electronic records required?
Roles and Responsibilities 1 of 3

IT – LAB specialist and QA
- Develop Requirements
- Manage Documentation
- Maintain Validated State throughout Lifecycle
  - Change control
  - Archival and retirement
- Software IQ/OQ and configuration
- Help Users in Acceptance testing, manage issue resolution
- Interpret and communicate regulations
- Perform Periodic Reviews

Vendor
- Provide system/software installation.
- Some vendor will conduct IQ and OQ to release the equipment to business unit.
- Ensure they follow their processes and use qualified 3rd parties.
- Obtain approval from system owner before conducting their testing.
Roles and Responsibilities 2 of 3

Lab
• Identify System Owner / Validation Leader
• System/operational requirements
• Ensure proper level of validation and deliverables based risk-based assessment.
• Work with IT to generate user acceptance tests scripts.
• Conduct user acceptance tests.
• Prepare related SOP before system release to production.
• Ensure that the validation status is maintained throughout the lifecycle of the computerized system.
• Conduct instrument PQ
• Ensure proper training for users.
• Document calibration, maintenance, upgrades and services.
• Manage change control.

General Consensus
• Business unit is the leader to ensure proper validation activities and right functions are tested.
• QA and business project owner / validation leader will sign off for software validation package
• Both IT or business unit may own the software validation/instrument qualification.
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• IT and Operations should be aligned. Do IT’s Software Validation SOPs contradict or overlap Operations AIQ SOPs?
Summary

• Instrument Qualification is not optional
• Many good sources for an approach
• Categorization is essential
• It is not necessary to over-test
  • Risk-based approach
  • Test what you will use
• AIQ is more than just IQ/OQ/PQ.
  • Very difficult to separate software from hardware testing with complex systems
  • Maintenance, system suit, requalification, etc. are part of the lifecycle management.