Regulatory 101
What is AIQ ?
Complete DQ/IQ

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10 Steps to a "*New Instrument*"….

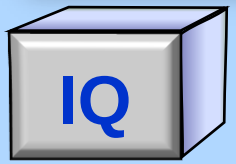
User Requirement Specification

- *What you need the instrument to do*
- *Purchasing decision*

Design Qualification

- *Why suitable*
- *Range of use*

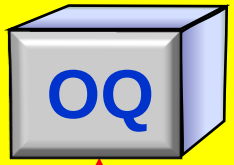
1. Analytical Need
2. Approval To Buy
3. Instrument "*Selection*"
4. Order Instrument
5. Delivery



Installation Qualification

- *Installed correctly*
- *Lab. is suitable*

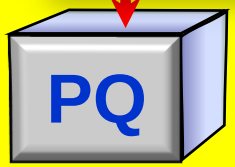
This Seminar Will Focus On These areas



Operational Qualification

- *Functional tests - works as expected – in the Lab.*
- *Test range of use*

6. Install
7. Qualification
8. Review & Approval
9. Release For Use
10. Maintenance



Performance Qualification

- *Application test – works with your applications*

September Seminar

WebEx Structure

Can't answer detailed questions about specific analytical methods, or accreditation…….

However, if you have a specific compliance question you would like an answer to - use the on-line system to ask, and we will provide reference information.

A key part of this WebEx is to highlight similarities and differences across industries for exchanging information and sharing best practice. In the future, further convergence and sharing of best practice is expected.

Contents

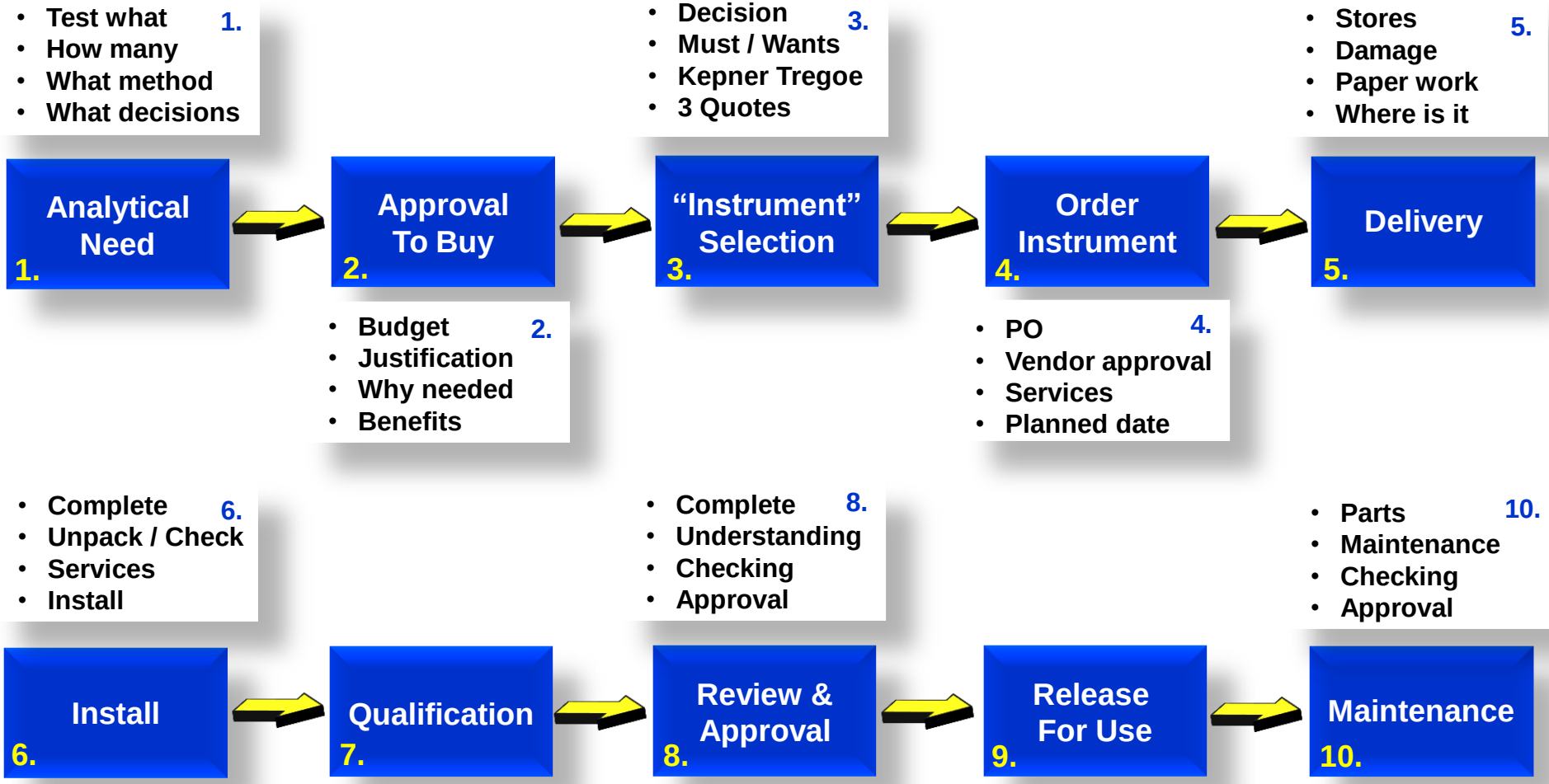
The Instrument Life Cycle

Business Aspects

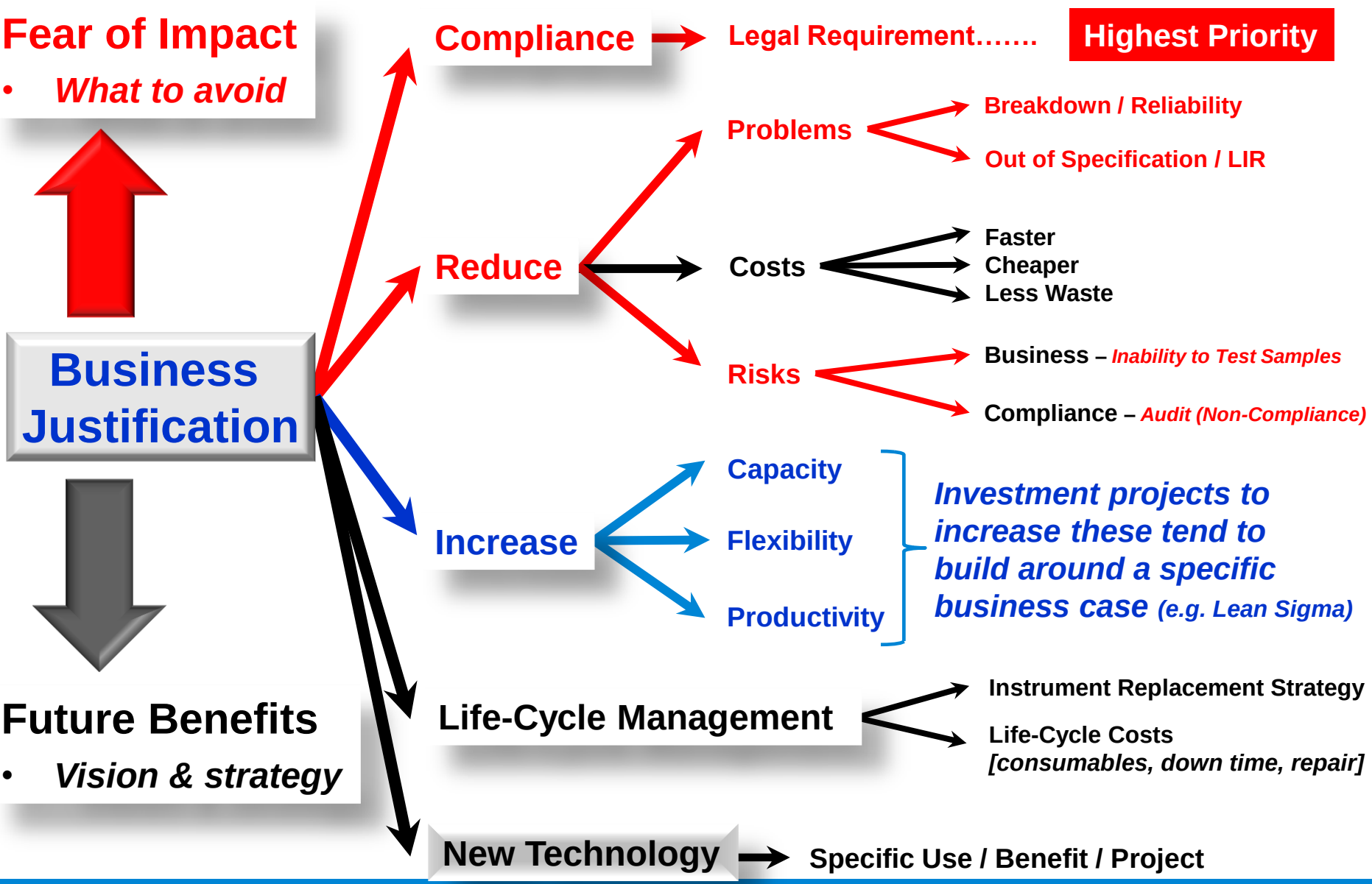
Analytical Instrument Qualification (AIQ)

USP <1058>

10 Steps to a New Instrument



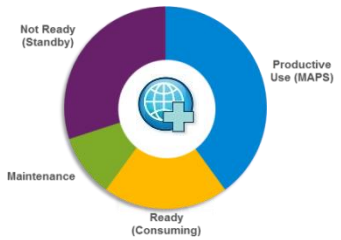
What To Do – To Purchase a New Instrument ?



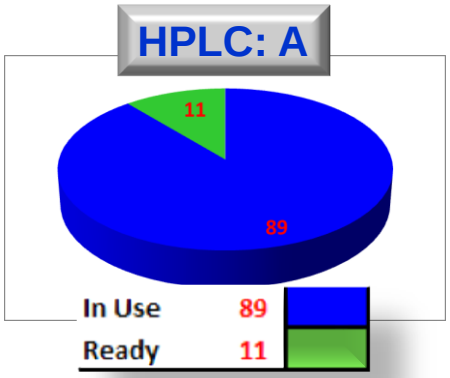
Leverage: Understanding Capacity & Business Risks

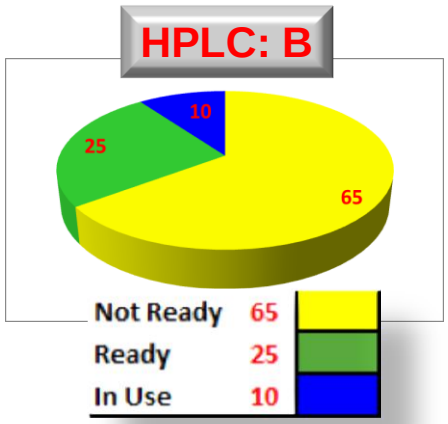
Examples of Understanding Laboratory Capacity

- Instrument Capacity
- Trained Analyst
- Project - Routine
- Reference Materials
- Work Sequence



Instrument Utilisation
[can be across whole site / lab.]





Level Load Your Instruments *[reduce risk]*
Have data to Justify New Instruments

Over Worked **Under Used**

Criticality of Analysis

Repair History

System ID	Building	Equipment		N-Level	Condition Code	Age	Utilization	
HPLC-01	Lab #32	1100 Quaternary HPLC	Green	N-4	C	11	12%	
HPLC-02	Lab #36	1100 Binary HPLC	Yellow	N-4	C	10	8%	8
HPLC-03	Lab #36	1100 Quaternary HPLC	Red	N-4	C	10	16%	17
HPLC-04	Lab #36	1100 Binary HPLC	Yellow	N-4	C	13	3%	9
HPLC-05	Lab #36	Waters Alliance	Yellow	N-4	C	11	12%	6
HPLC-06	Lab #39	Waters Alliance	Yellow	N-4	C	9	19%	14
HPLC-07	Lab #39	Waters Alliance	Green	N-4	C+	14	2%	3
HPLC-08	Lab #39	Waters Alliance	Yellow	N-4	C	13	0%	2

Technology of Instruments

Instrument Analytics

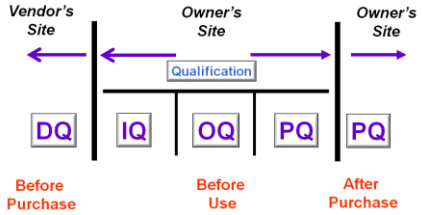
- *Criticality:* ***Business Risk***
- *Technology:* ***Replacement***
- *Repair:* ***Breakdown Risk***
- ***Replacement Strategy***

Summary of USP <1058> - Current USP

Areas of <1058>

Definitions
- Roles:
  - User
  - QA
  - Supplier
- Responsibilities
- DQ / IQ / OQ / PQ

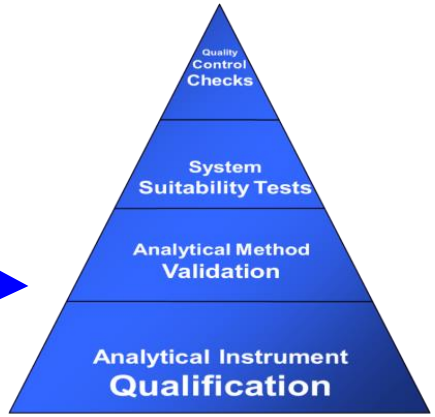
Simplification
of the Life Cycle Process:



Flexibility
- What is done in OQ / PQ

Risk Management by
- Categorisation: A / B / C

Examples…



Components of Data Quality / Integrity
- Principles Apply to All Labs.

Summary of USP <1058> - Current USP

650 ⟨1057⟩ Biotechnology-Derived Articles / General Information USP 36

gen content of the USP Reference Standard or reference material.

⟨1058⟩ ANALYTICAL INSTRUMENT QUALIFICATION

INTRODUCTION

A large variety of laboratory equipment, instruments, and computerized analytical systems, ranging from simple nitrogen evaporators to complex multiple-function technologies (see *Instrument Categories*), are used in the pharmaceutical industry to acquire data to help ensure that products are suitable for their intended use. An analyst's objective is to consistently obtain reliable and valid data suitable for the intended purpose. Depending on the applications, users validate their procedures, calibrate their instruments, and perform additional instrument checks, such as system suitability tests and analysis of in-process quality control check samples to help ensure that the acquired data are reliable. With the increasing sophistication and automation of analytical instruments, an increasing demand has been placed on users to qualify their instruments.

Unlike method validation and system suitability activities, analytical instrument qualification (AIQ) currently has no specific guidance or procedures. Competing opinions exist regarding instrument qualification and validation procedures and the roles and responsibilities of those who perform them. Consequently, various approaches have been used for instrument qualification; approaches that require varying amounts of resources and generate widely differing amounts of documentation. This chapter provides a scientific approach to AIQ and considers AIQ as one of the major components required for generating reliable and consistent data. Note that the amount or rigor applied to the qualification process will depend on the complexity and intended use of the instrumentation. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments.

Validation versus Qualification

In this chapter, the term validation is used for manufacturing processes, analytical procedures, and software procedures and the term qualification is used for instruments. Thus, the phrase "analytical instrument qualification" (AIQ) is used for the process of ensuring that an instrument is suitable for its intended application.

COMPONENTS OF DATA QUALITY

There are four critical components involved in the generation of reliable and consistent data (quality data). *Figure 1* shows these components as layered activities within a quality triangle. Each layer adds to the overall quality. Analytical instrument qualification forms the base for generating quality data. The other components essential for generating quality data are analytical method validation, system suitability tests, and quality control check samples. These quality components are described below.

Figure 1. Components of data quality.

Analytical Instrument Qualification

AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose. Use of a qualified instrument in analyses contributes to confidence in the validity of generated data.

Analytical Method Validation

Analytical method validation is the collection of documented evidence that an analytical procedure is suitable for its intended use. Use of a validated procedure with qualified analytical instruments provides confidence that the procedure will generate test data of acceptable quality. Additional guidance on validation of compendial procedures may be found in the general information chapter *Validation of Compendial Procedures* ⟨1225⟩.

System Suitability Tests

System suitability tests verify that the system will perform in accordance with the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test. USP general chapter *Chromatography* ⟨621⟩ presents a more detailed discussion of system suitability tests as related to chromatographic systems.

Quality Control Check Samples

Many analysts carry out their tests on instruments standardized using reference materials and/or calibration standards. Some analyses also require the inclusion of quality control check samples to provide an in-process or ongoing assurance of the test's suitable performance. In this manner, AIQ and analytical method validation contribute to the quality of analysis before analysts conduct the tests. System suitability tests and quality control checks help ensure the quality of analytical results *immediately before or during* sample analysis.

ANALYTICAL INSTRUMENT QUALIFICATION PROCESS

The following sections address in detail the AIQ process. The other three components of building quality into analytical data—analytical method validation, system suitability

Risk Based Categorisation:
A, B, C:

Strength of <1058>

A – Verify by Observation
(e.g. Stirrer)
- **No calibration or Measurement Capability**

B – Verify by Calibration
- Calibrate by SOP / Document
(e.g. pH Meter)

C – Qualify
(e.g. HPLC)
- **Complex Systems**
- **Verify by Full Qualification**

GAMP Good Practice Guide (GPG)

A Risk-Based Approach to GxP Compliant Laboratory Computerized Systems

GPG *Edition 1*

Contents:
19 Sections
- Process Based Approach
(Table of Contents Available on Line)

Contents:
7 Sections
- Risk Based Model
(Table of Contents Available on Line)

GPG *Edition 2*

Aligned With GAMP 4

Risk Management by Instrument Categorisation.

7 Categories Examples:

- A - *Sonicator*
- B - *pH Meter*
- C - *Key Pad HPLC*
- D - *PC HPLC*
- E - *NMR*
- F - *Spread sheet*
- G - *Bespoke*

Aligned With GAMP 5

Risk Assessment.....
No Formal Categorisation !

(Fixed Categories VS. Risk Based Thinking)

Appendices:
1. Determining System Impact
2. Testing Priorities
3. Supplier Assessment Scheme

Glossary
References

Appendices:
1. Categories of Software
2. System Description
3. Data Integrity
4. Simple Systems
5. Medium Systems
6. Complex Systems
7. System Interface Considerations
8. Robotic Systems
9. Defining Electronic Records and Raw Data
10. Security Management for Laboratory Computerized Systems
11. Supplier Documentation and Services

Expansion and Examples....

The Hardware & Software *"Catch 22"*

All instruments contain some level of software (unless only electro-mechanical / mechanical)

All instruments and Software must be suitable for intended use – in GXP work

Qualify the Instrument

Validate the Software

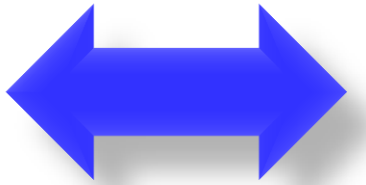
- **For Simple Instruments** – ***these are combined***
- **For Complex Systems** – ***these are independent***

- For Simple Instruments – calibrate (e.g. pH Meter)
- For Complex Instruments– qualify (e.g. HPLC)
- For Complex Systems – validate (e.g. CDS)

Qualify the Instrument

Can't qualify without software control.

USP <1058>
[Hardware Focus]



Validate the Software

Can't validate the software without the instrument.

GAMP
[Software Focus]

Polling Question 1

Qualification Life Cycle – Beyond the 4Q Model

Laboratory Instruments: Compliance Requirements

Laboratory instrument compliance requirements are influenced by:

Quality System

- What samples you test
- What analysis you do
- What decisions the results are used for

Laws & Regulations Supply
[Products & Services]

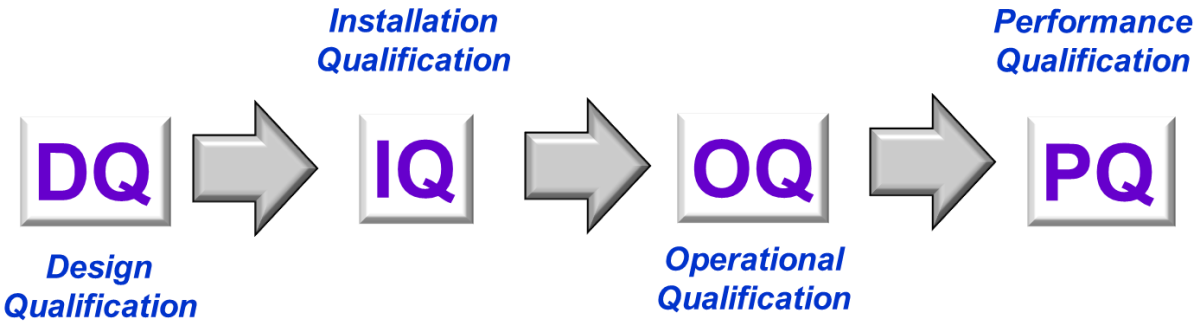
- **ISO 9001:** Update Q4 2015 – to include Risk assessment
- **ISO 17025:** New ALACC Guide Lines Available August 2015

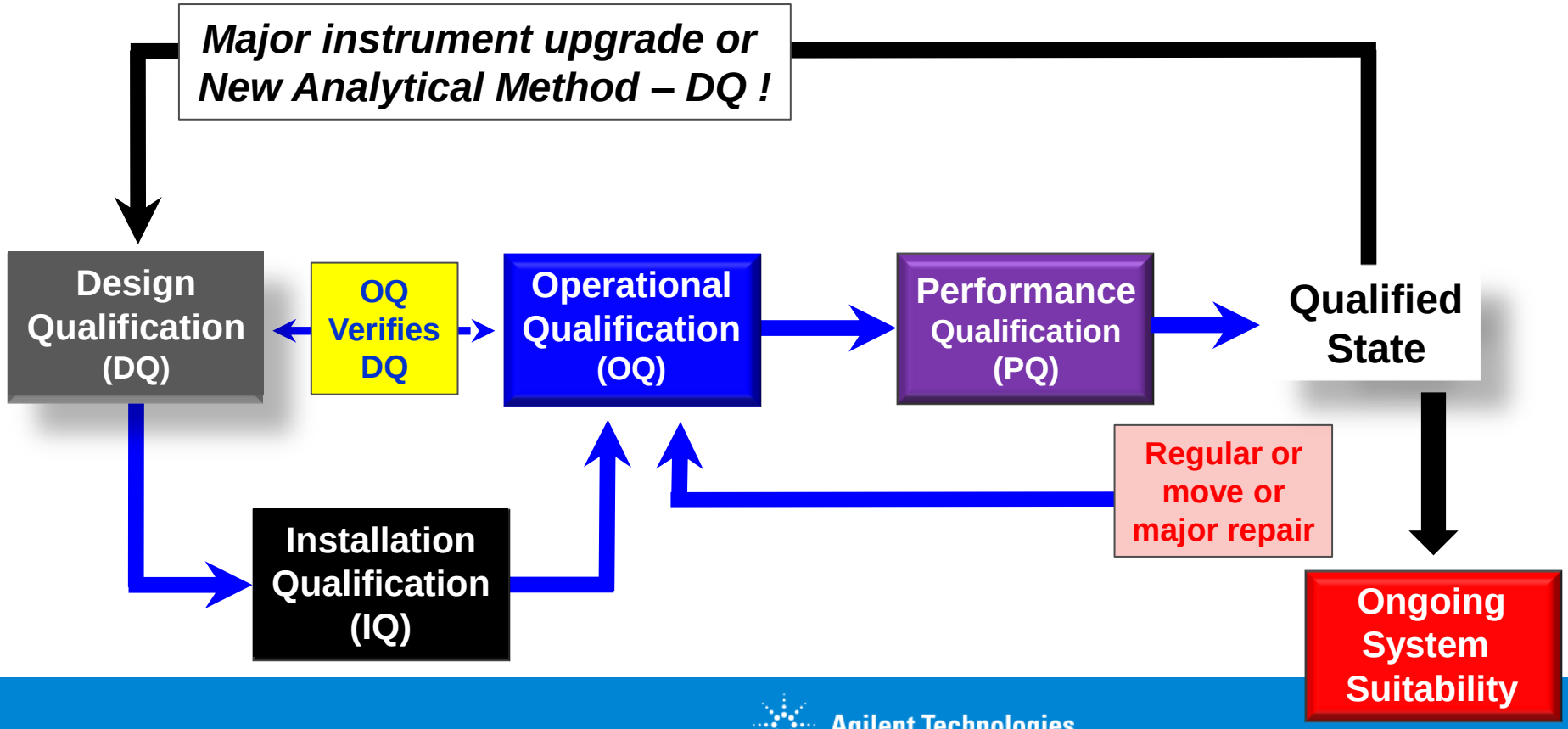
Laboratory instrumentation: *"must be suitable for its intended use"*

Regulatory SOP	GMP (*Guidance*)	Pharmacopeia	Other
N/A With the exception of the FDA, who released an internal SOP on Dissolution MQ……	CFR, EU GMP…. All GMP guidance requires interpretation…… Especially for laboratory instrument compliance	USP contains general chapter <1058> on Analytical Instrument Qualification (AIQ) 2008	Many pharmaceutical companies have applied GAMP guidance and principles. GAMP 5: 2008
Industry would welcome more specific guidance ?	Industry need forum to "*engage*" with regulators ?	Draft new chapter available in Pharmacopeial Forum. 31st July – Deadline	GAMP GPG (V2 Lab. Guide) issued in 2012. Harmonisation: (GAMP & <1058>)

Qualification Overview: 4Q Model *(from <1058>)*

Typically Shown as a *Linear Flow*:…..





Examples of Laboratory Instrument Risk……

- ☑ Instrument is *not Suitable* for intended use
- ☑ Instrument *not installed correctly*
- ☑ Qualification passes, but methods *fail*

Qualification Life Cycle !

- ☑ Component *parts failure* — *Quality of parts / testing / approval*
- ☑ People don't "*know" the instrument* — *Quality of training*
- ☑ Instrument *will break down* — *Maintenance, lab. analytics*
- ☑ Problems with *method problems - OOS* results — *QbD*
- ☑ Poor *data integrity* — *Move towards electronic, away from "DIY"*

Draft USP: <1058> - Changes

Draft USP <1058> is an Evolution. However, it encompasses approximately 85 % of the changes proposed by: Bob McDowall and Chris Burgess.

Bob McDowall and Chris Burgess:

- **Issued the <1058> Stimulus Paper**
- **Drafted a proposed change to <1058>**

- **Range Classified: Simple Apparatus to Computerised**
- **Risk Assessment Required** ***(to categorise A, B or C, but not defined)***
- **Categories A, B and C are Retained** ***(but Examples are Gone)***
- **Covers Lifetime of Instrument**
- **Link Major Upgrade – to DQ Review**
- **Document Supplier, Model, Serial Numbers**
- **Link OQ Testing to DQ**
- **User Defines PQ – Which Verifies Performance Under Conditions of Use**
- **Change Management Required**
- **Significant Expansion of Firmware – Sub-Classification** ***(3 sub-classes)***
- **Reference to GAMP – Under Software Validation** ***(Harmonisation)***
- **Glossary of terms added**

Variation in Qualification Approach 1

Some companies write documents Before the 4Q Model

Some companies write documents After the 4Q Model

Before

URS

User Requirement Specification

4Q Model

Some Companies Rely on This

Installation Qualification

Performance Qualification

DQ → **IQ** → **OQ** → **PQ**

Design Qualification

Operational Qualification

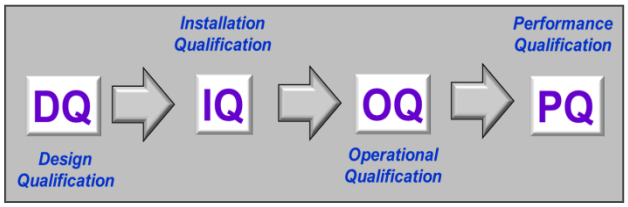
After

Validation Master Plan → **4Q Model** → **Validation Summary Report**

The BREADTH of the qualification life cycle followed is influenced by company policy / strategy ……

Common Life Cycle Options

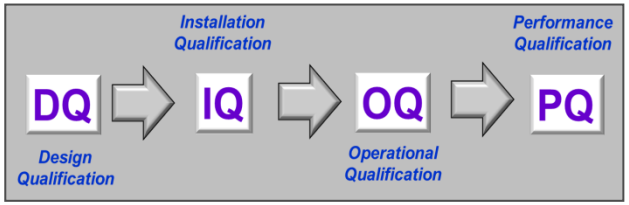
4Q Model Only



Which is "Best" ?

URS + **4Q Model Only**

User Requirement Specification



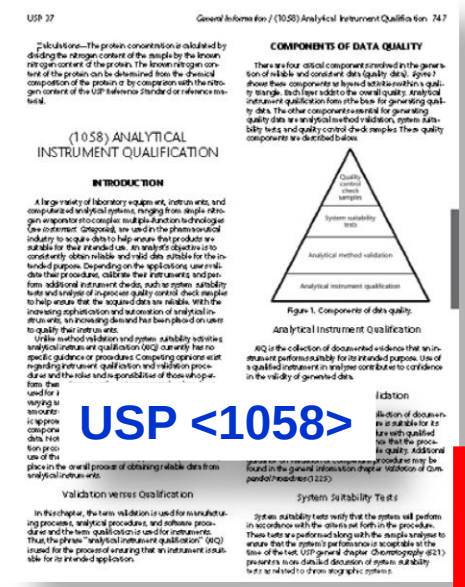
Combine: **URS** + **DQ** **Into a Single "*Design*" Document**

Some companies Follow a Complex Extended Life Cycle……..

Some companies Use a Validation Master Plan and Validation Summary Report

HPLC Risk Assessment – by Categorisation

HPLC



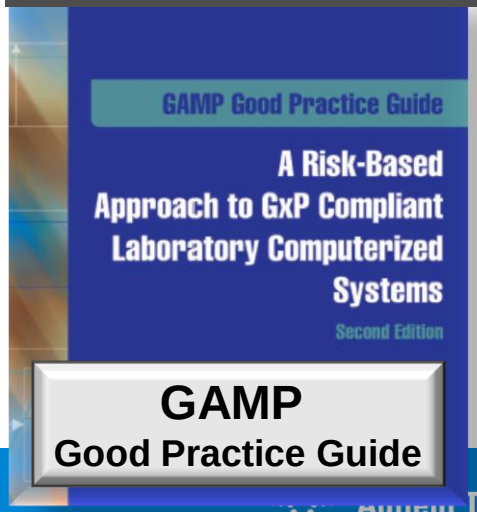
USP <1058>

USP <1058>
Analytical Instrument Qualification
Category C

Scale the Qualification Work, by Categorisation…. [but risk]

Categorisation

Edition 1 [7 fixed categories]
HPLC = Category D



GAMP
Good Practice Guide

Edition 2
HPLC = "Medium"
[Complexity]

- *Concept Phase*
- *Project Phase*
- *Operational Phase*
- *Retirement Phase*

User Requirement Specification 1

URS

User Requirement Specification

The URS is where you document what you want the instrument to do.

This must be in sufficient detail – to support the decision to purchase.

The URS should specify:

- **Where the instrument will be used *(geography)***
- **What testing the instrument will be used for**
- **What configuration *(e.g. HPLC Detector)***
- **What instrument specifications the instrument must satisfy *(care with instrument specifications)***
- **Quality requirements of the vendor**
- **Reference approval requirements of Vendor**
- **Support requirements for the instrument**
- **Include a glossary of terms**

Does this seems too simple ?

It is suggested that the URS is not used to document specific Pharmacopeial requirements:
- these should be specified in a separate document (reduces work when pharmacopeia's change).

Polling Question 2

DQ & IQ

Laboratory Instrument: Compliance Framework

Who can Perform Installation, Qualification, Maintenance and Repair ?

There are no regulatory barriers about who "*Should*" perform qualification:

- **Nothing in the Pharmacopeia's**
- **Nothing in GMP (CFR, EU or other)**
- **No FDA Warning Letters**

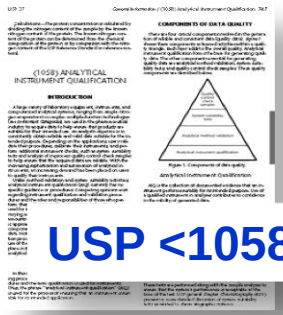
But….. you need to consider….

 # [and other Regulators]

- **Has the *Qualification* been Validated ?**
  [How do you know ?]
- **Is there a training syllabus / Hierarchy ?**
  [How do you know the quality of the training ?]
- **Is it 21 CFR Part 11 Compliant ?**
  [Where is the "Part 11 certificate" ?]
- **Does it Support Data Integrity ?**
  [Electronic data traceability ?]
  [Is repeat work "tracked" and visible ?]
- **Is it Scientifically Valid ?**
  [Can you explain / "defend" it ?]
- **Does it Meet Your Requirements ?**
  [Configured to your analytical range of use ?]
- **Is it Performed in Regulators Labs. ?**
  [Are you doing something different to the regulator do ?]

Complexity and Risk

Many companies over complicate the URS & DQ Documents….



USP <1058>

Opportunity to Simplify !

Increasing complexity & risk requires greater "proof" of operation

Commercial Off The Shelf *(COTS)*

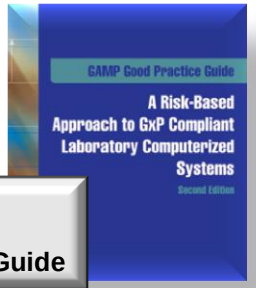
What kind of Analytical Instrument ?

Instrument

URS/DQ

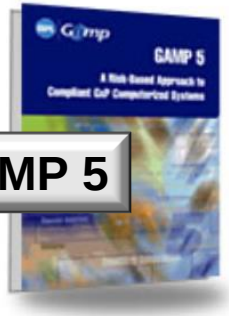
Software

More Complex System



GAMP
Good Practice Guide

Bespoke "*Integrated*" System
Unique Software….. Etc.



GAMP 5

Compliance terms can have different meanings for software and instruments

Simplification: Reduce the Compliance Burden

Do you require a separate URS and DQ ?

Draft of <1058> States:

"It is expected that the Design Qualification (DQ) requirements will be minimal for a commercial, off-the-shelf (COTS) instrument"

The URS and DQ perform different functions in the life cycle……..

URS — *User Requirement Specification*

Not mentioned in <1058>

DQ — *Design Qualification*

IQ — *Installation Qualification*

Most labs. have an existing, approved Qualification "process"

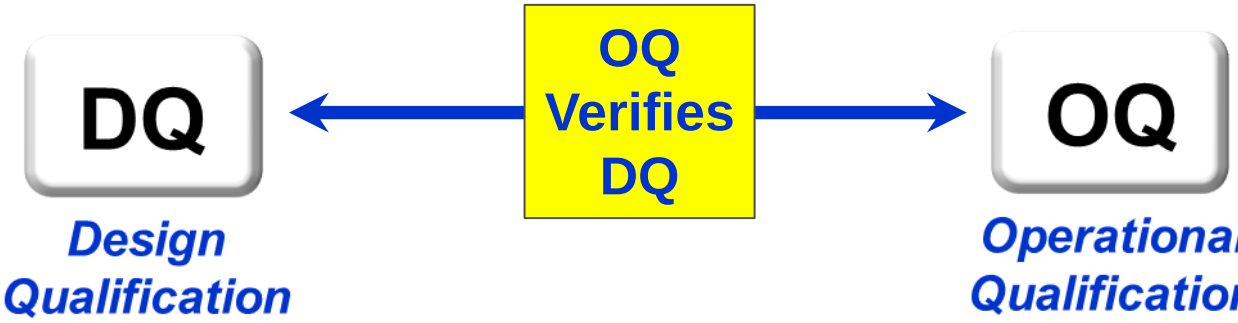
Some labs. Struggle with

Change

Change Management

Qualification developed by different organisations with equivalent quality systems, develop different, but scientifically equivalent, qualification process……

What is the Relationship Between the DQ & OQ



Associate the DQ documents to the analytical testing…….

Review Analytical Methods To List:

Maximum and Minimum Range of Use ***(in the Methods).***

This ties the DQ into the expected use and therefore, supports documenting that the instrument is suitable.

Configure the OQ testing to COVER the RANGE of USE.

Feedback Loop:
Update DQ & OQ – NEW METHODS

Ensures Range of Use Tested

Design Qualification 1

Design Qualification

Reference the URS related to the Instrument Type.

Create a table in the DQ that lists the range of Use – for HPLC:

DQ Parameter	Min.	Max.
Column Temp.	25	55
Wavelength	205 nm	273 nm
Pump Flow	1 mL/Min.	2.5 mL/Min.
Autosampler Temp.	4 °C	8 °C
Gradient Step.	10 %	85 %
% RSD (Inj. Precision)	1.00 % (UV-Vis)	
% Carry Over	0.20 % (UV-Vis)	

Note:

This can mean One URS and DQ for each Analytical Technique.

Only include Limits that are Tested in the OQ……
[URS if not tested]

Installation Qualification 1

Installation qualification (IQ) is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, and is properly installed in the selected environment, and that this environment is suitable for the instrument.

IQ applies to an instrument that is new or was pre-owned.

Relevant parts of IQ would also apply to a qualified instrument that has been transported to another location or is being reinstalled for other reasons, such as prolonged storage.

Installation Qualification 2

IQ documentation packages purchased from a supplier should be reviewed to ensure that they are acceptable by the user before and after execution.

The IQ satisfies Multiple Requirements:

- **Check delivery Vs Order** (Damage / completeness)
- **Check instrument services Vs Requirements**
- **Check Environment Vs Installation Needs**
- **Document Software Installation**
- **Perform Diagnostic Tests** (Error Messages)

2 Approaches:

- **Manually Document Temperature, Humidity, Size, Etc.**
- **Document Environment Meets Site Installation Needs**

Polling Question 3

Questions