International GMP Requirements for Quality Control Laboratories and Recomendations for Implementation

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Overview

- GMP requirements for Quality Control laboratories along the sample and data workflow
- Requirements for the entire laboratory
- 8 Essential steps for effective implementation
- Planning – documentation – organization
- Training – material, suppliers
- Analytical methods
- Equipment and computer systems
- Sampling – sample analysis
- Data review and archiving

FDA Logo means reference to FDA Warning letter. The number is a reference to www.fdawarningletter.com (190)

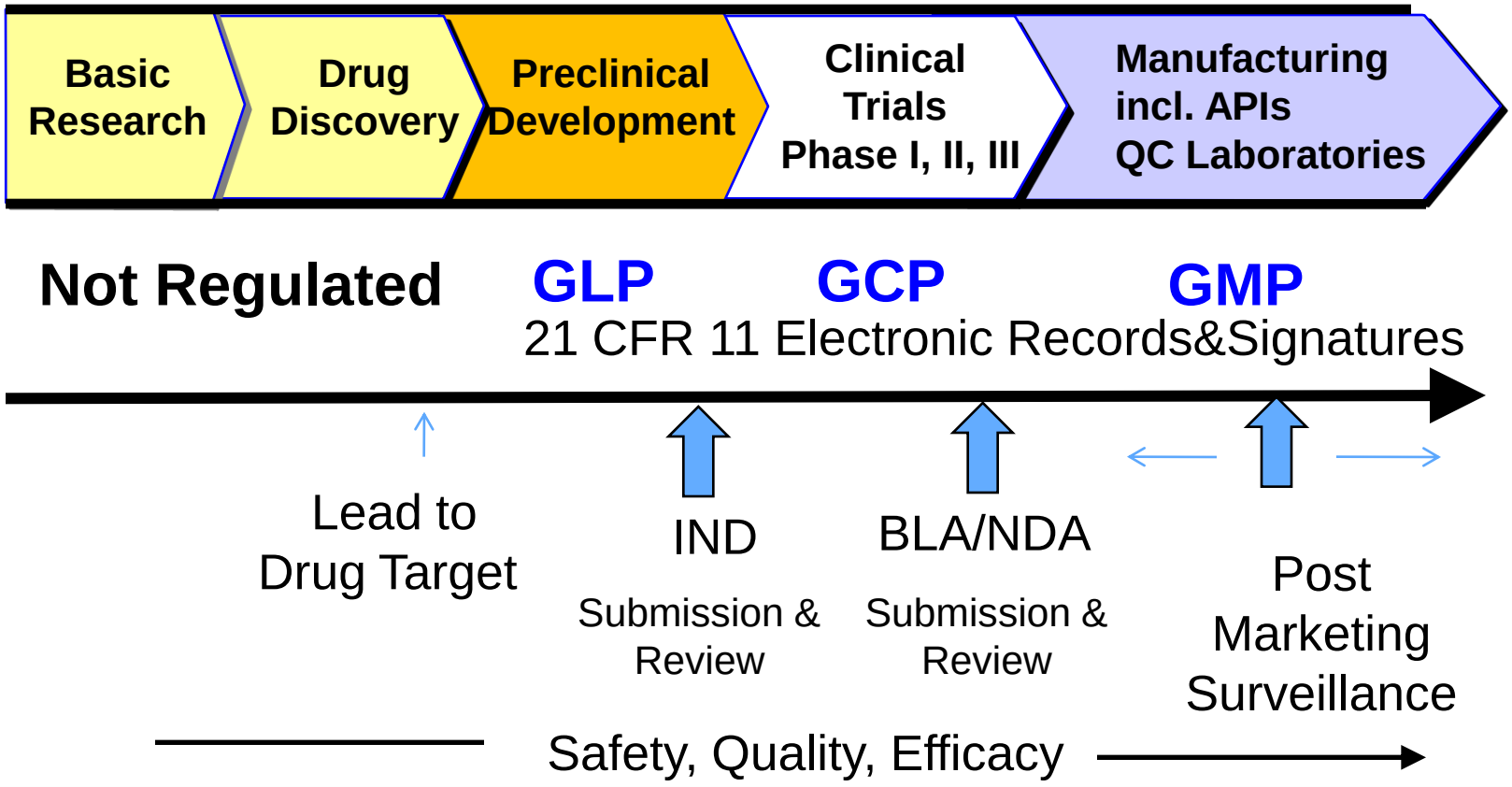
Related Regulations and Guidelines

- GMP regulations in EU and USA
- ICH
  - Guidance documents are signed into regulations of member countries: e.g., Q7, Q8, Q9, Q3D
- PIC/S (40 members)
  - Develop GMP guidelines, may be used as regulations
  - Harmonize inspections through training
- Pharmacopeias (EP, USP)
  - Develop procedures how to implement regulations e.g., USP 1058, 1224, 1226, 232/233

ICH: International Conference for Harmonization

PIC/S: Pharmaceutical Inspection Convention/Cooperation Scheme

Regulations Along the Drug Life



GLP = Good Laboratory Practices
GMP = Good Manufacturing Practices
GCP = Good Clinical Practices

GxP = GLP+GCP+GMP = Predicate Rules
IND = Investigational New Drug Application
BLA = Biologic License Application
NDA = New Drug Application

Pharmaceutical Laboratory Compliance

Sampling	Sample handling& storage	Testing	Data review and approval	Record archiving
Representative Sampling Sampling plan	Avoid cross Contamination Ensure sample integrity	Clear specifications & test protocols	Primary & secondary review Handling OOS	Ensure data Integrity @ availability

Compliance across all workflow steps

- Validation of analytical methods & procedures
- Equipment calibration testing & maintenance
- Qualification of material
- Traceability
- Control of non-conforming testing
- Qualification of personnel
- Controlled environmental conditions
- Written procedures

Incremental costs: 20-30%

#1: Plan for GMP Compliance

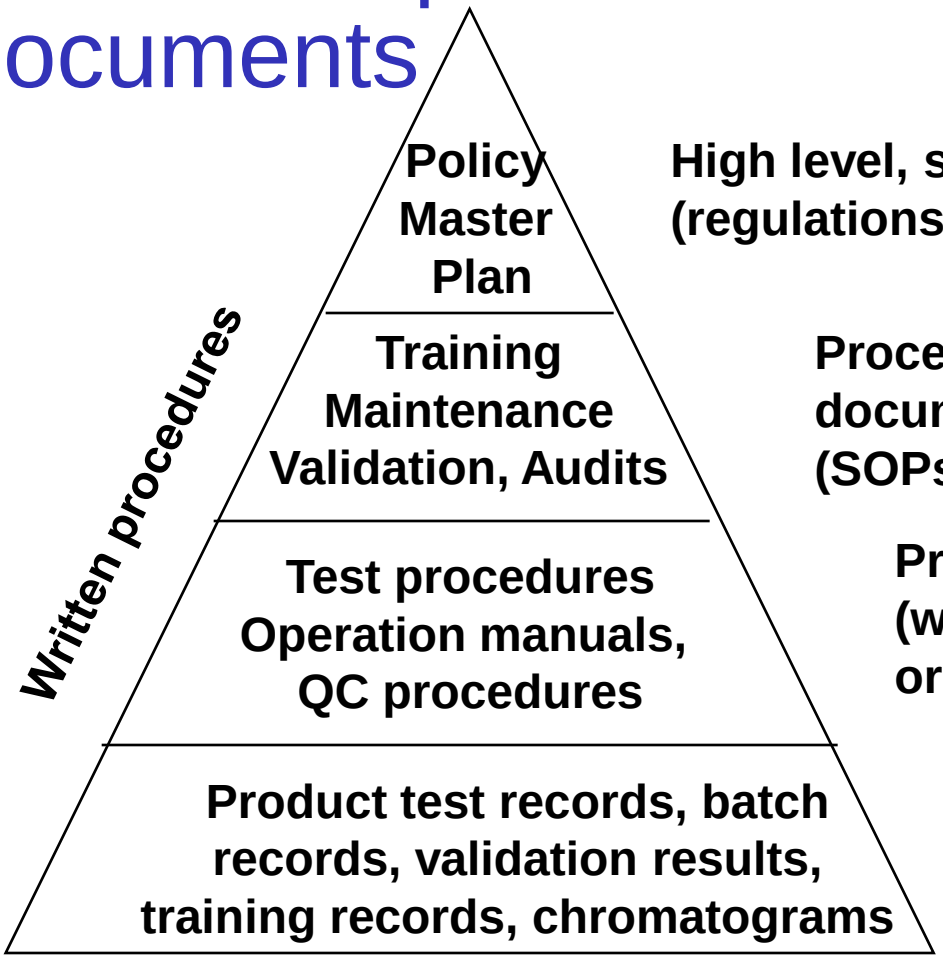
Compliance master plan

- Guideline for effective and consistent implementation of GMP regulation
- Documents the laboratory's approach for compliance
- Ensures efficiency AND consistency
- Useful for audits to explain the laboratory's approach towards compliance

Project Plan

- Outlines steps, tasks, deliverables and owners

‘#2: Develop Procedures and other Documents



High level, strategic documentation (regulations, business, quality)

Process related documentation, approaches (SOPs)

Product/event related documentation (work instructions, also called SOPs or test scripts, protocols)

Compliance Records (batch/event related documentation)

Check Regulations

Use the same set throughout the organization

Use Consistent Documentation Across the Company

- Validation master plan
- Supplier qualification
- Risk assessment
- Validation procedures
- Templates for records

→ Improves efficiency
→ Improves consistency

Req. ID	Requirement	Critical	Test Priority	Test ID

Items	Requirem	Results	Passed
Recognition in the market place			◻ yes ◻ no
Experience with the vendor			◻ yes ◻ no
Quality assurance			
ISO Certification			◻ yes ◻ no
Efficient compliant handling.			◻ yes ◻ no
Support			
Provide certificate of analysis			◻ yes ◻ no
Provide expiration date			◻ yes ◻ no
Provide test method			◻ yes ◻ no
Phone and onsite support			◻ yes ◻ no
Product offering			
Certified reference materal			◻ yes ◻ no

Test ID _____ Test System ID: _____
Test Objective: _____
Specification: _____

Step	Test Procedure	Expected Result	Actual Result	Required documents	Pass/fail
1					
2					

Tester: I confirm that I have all tests executed as described
Name: _____ Signature_____ Date_____
Tests passed: yes no Comment: _____

Reviewer: I confirm that I have reviewed test documentation
Name: _____ Signature Date

Template for Testing

Example

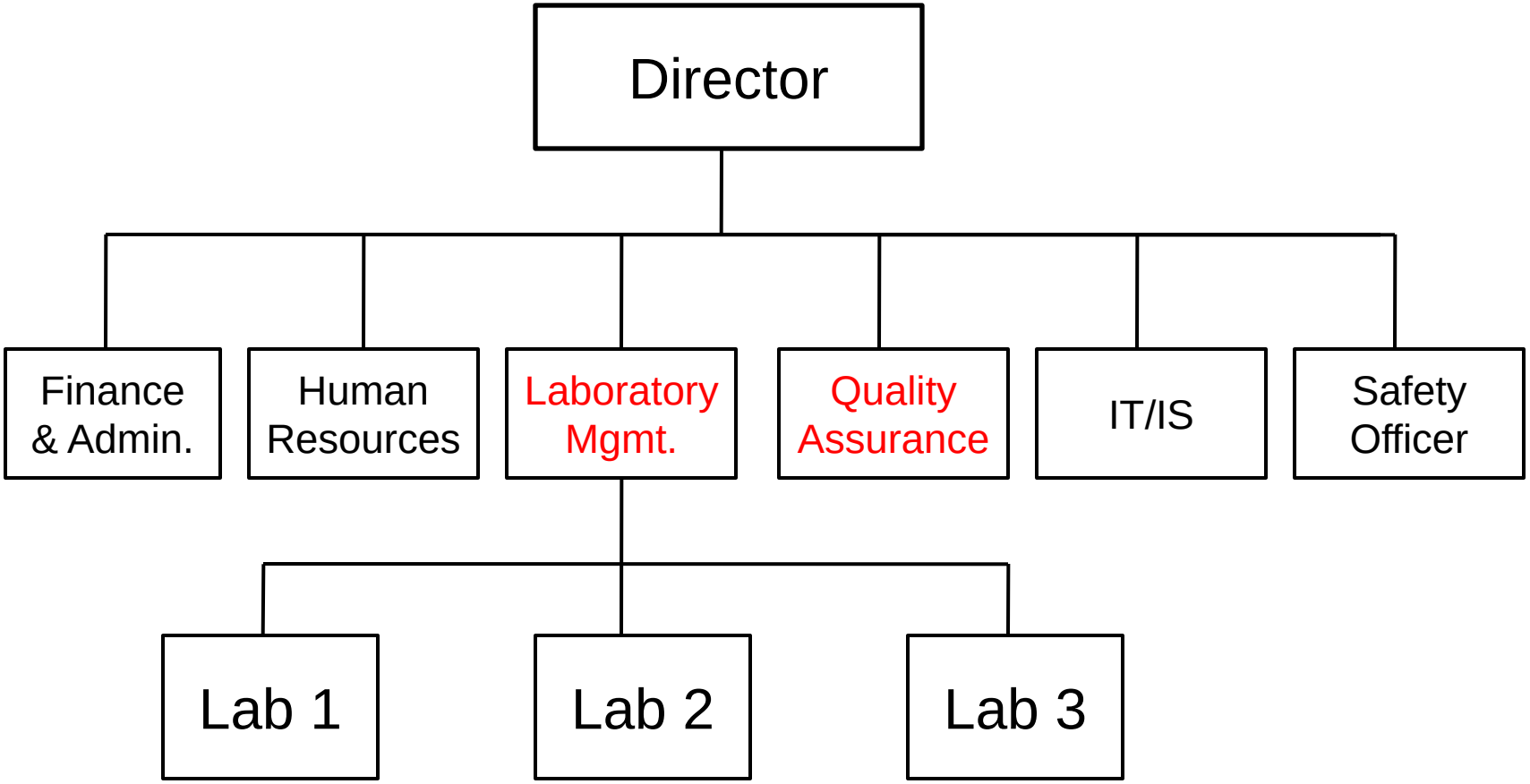
Test ID T10 _____ Test System ID: _____
Test Objective: _____
Specification: _____

Step	Test Procedure	Expected Result	Actual Result	Required documents	Pass/fail
1					
2					

Tester: I confirm that I have all tests executed as described
Name: _____ Signature_____ Date_____
Tests passed: yes no Comment: _____

Reviewer: I confirm that I have reviewed test documentation
Name: _____ Signature Date

#3: Build the Right Organizational Structure and Assign Tasks (Example)



Avoid Conflicts of Interest

Responsibilities

Should be defined for

- Management
- Quality Assurance
- Department managers
- Supervisors
- Analysts
- IT

Failure to maintain written procedures that describe the responsibilities and procedures applicable to the quality control unit (173)

#4: Qualify Personnel

Job description

1. Define requirements
   - what is the assigned task?
2. Identify knowledge
3. Determine gaps
4. Make a plan to fill the gaps
5. Train
6. Evaluate training
7. Document

ongoing

Maintain qualification

1/2 year or yearly reviews

Training Records

- Policy
- SOP
- Job descriptions, requirements
- Employees qualifications
- Training plan
- Training records of event
  - Certificate of attendance, date, contents, duration
  - Evidence of competence

Failure to adequately establish procedures for identifying training needs and ensure all personnel are trained to adequately perform their assigned responsibilities and the training is documented (228)

#5: Qualify Suppliers and Materials

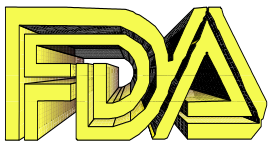
1. Documenting internal and external experience
2. Mail audit with follow up
3. Direct audit
   (for high risk suppliers)

Criteria

- Product risk
- Supplier risk

Items	Requirem	Results	Passed
Recognition in the market place			▫ yes ▫ no
Experience with the vendor			▫ yes ▫ no
Quality assurance			
ISO Certification			▫ yes ▫ no
Efficient compliant handling.			▫ yes ▫ no
Support			
Provide certificate of analysis			▫ yes ▫ no
Provide expiration date			▫ yes ▫ no
Provide test method			▫ yes ▫ no
Phone and onsite support			▫ yes ▫ no
Product offering			
Certified reference materal			▫ yes ▫ no

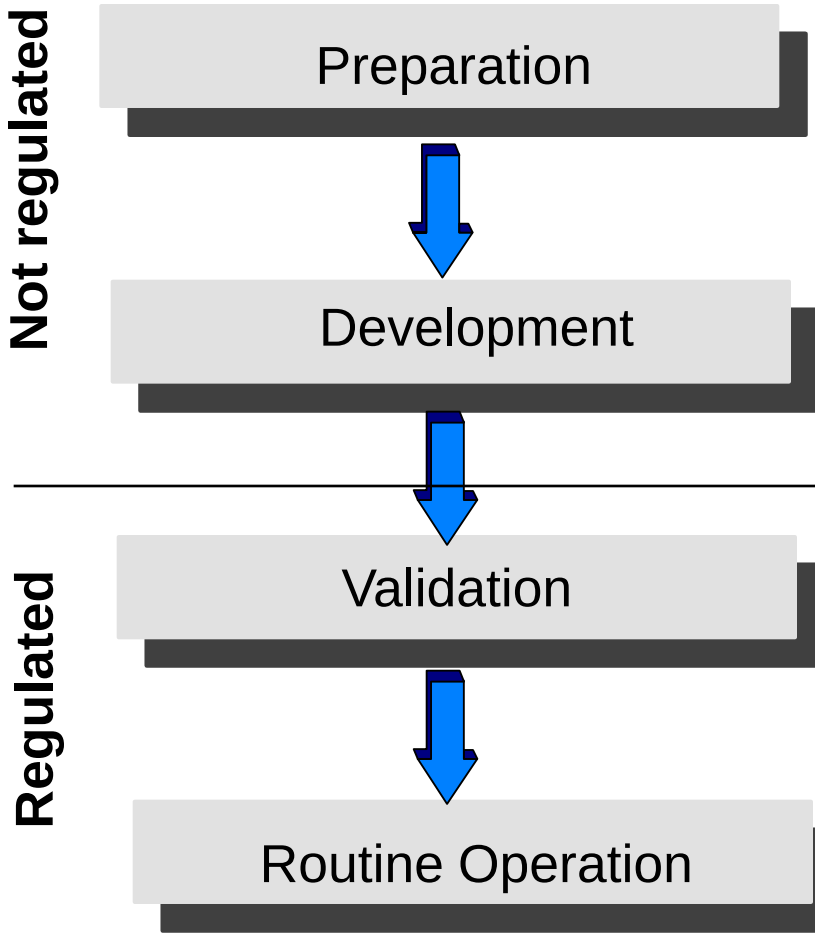
There is no assurance that your firm establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (W-245)



Documenting Supplier Selection

Items	Requirem	Results	Passed
Recognition in the market place			yes no
Experience with the vendor			yes no
Quality assurance			
ISO Certification			yes no
Efficient complaint handling			yes no
Support			
Provide Certificates of Analysis			yes no
Provide expiration dates			yes no
Provides test methods			yes no
Phone and onsite support			yes no
Product offering			
Certified Reference Material			yes no

#6: Develop & Validate of Analytical Methods



- Select preliminary method, scope & specifications
- Assure performance of equipment
- Assure that operators are qualified

- Select and optimize method & parameters
- Robustness testing ⟵ Hot Topic
- Define operational limits and SST
- Preliminary validation experiments

- Document final acceptance criteria
- Document final scope
- Perform validation tests, incl. robustness

- Controlled transfer
- Regular review
- Controlled changes & Revalidation

Method Validation Parameters for different Method Tasks (ICH Q2)

Analytical Task	Identifi-cation	Impurity Quantitative	Impurity Qualitative	Assay
Accuracy	No	yes	No	Yes
Precision				
Repeatability	No	Yes	No	Yes
Intermediate	No	Yes	No	Yes
Reproducibility	No	Yes	No	Yes
Specificity	Yes	Yes	Yes	Yes
Limit of detection	No	No	Yes	No
Limit of quantitation	No	Yes	No	No
Linearity	No	Yes	No	Yes
Range	No	Yes	No	Yes
Robustness	Expected to be done during Method Development			

Parameters and Tests (ICH Q2)

Parameter	Tests (examples)
Accuracy	Minimum at 3 concentrations, 3 replicates
Precision	
Repeatability	Minimum of 9 determinations over the specified range
Intermediate	Over 3 days, 2 operators, 2 instruments,
Reproducibility	Only required if testing is done in different laboratories
Specificity	Prove with specific methods: HPLC, DAD, MS, dif. columns
Limit of detection	Visual approach, S/N >= 3
Limit of Quantitation	S/N >= 10, Standard deviation of response
Linearity	Min 5 concentrations: visual, correlation coefficient (r)
Range	80 to 120% of test concentration, from linearity tests

Intermediate Precision Example

Sample	Day	Operator	Instrument
100% conc. (3x)	1	1	1
100% conc. (3x)	1	2	2
100% conc. (3x)	1	3	3
100% conc. (3x)	2	1	2
100% conc. (3x)	2	2	3
100% conc. (3x)	2	3	1

- Minimum: 2 days, 2 operators, 2 instruments,
- Calculate overall RSD

18 runs

Examples for HPLC Robustness Testing

- Deliberately change critical operational limits and evaluate impact on performance: precision, accuracy
- Include sample preparation and testing parameters

Sample preparation (accuracy)

- Extraction time (-20% of target)
- Extraction temperature (± 5 ºC)

HPLC

- Col Temperature (± 3 ºC)
- Mobile phase composition (± 2%)
- Buffer concentration (± 2%)
- Flow rate (± 0.3 mL/min)
- Detection wavelength (± 1 nm)
- Column Lot (quality, selectivity)

Ambient temperature/humidity

Stability of samples, standards

For reliability in routine
- Avoid OOS -
For revalidation criteria

Define operational limits in method SOP !

Examples for Acceptance Criteria

Quantitative **Impurities** in Finished Drugs

Parameter	Test
Accuracy	90 – 110%, 80 – 120% at specifications limit
Precision	
Repeatability	<4 % RSD (up to 15% at LOQ)
Intermediate	<5.0 % RSD (higher at LOQ)
Reproducibility	< 6% RSD (higher at LOQ)
Specificity	Peak resolution >1.5 (related substances) or >2 (main peak) Peak purity check with UV DAD or MS
Limit of Detection	N/A
Limit of Quantitation	0.05%
Linearity	visual inspection of linearity curve, r>0.9900
Range	o.k. if accuracy, precision, linearity criteria are met

Example: Report Summary Table

Validation Parameter	Measure	Acceptance criteria	Results
Accuracy	Recovery – Conc1 Recovery – Conc2 Recovery – Conc3	97 – 103 % 97 – 103 % 97 – 103 %	99% 100% 100%
Method Precision	RSD	≤ 1.5 %	0.4%
Intermediate Precision	RSD	≤ 2.0 %	0.8%
Specificity	Peak Resolution Factor R	R for all peaks >1.5	All peaks >2.0
Linearity	Correlation Coefficient Visual inspection of plot	≥ 0.9900 Linear response plot	0.9900 Shows linearity
Range	Correlation Coefficient Precision at 3 concentrations Recovery at 3 Conc.	≥ 0.9900 ≤ 1.5 % 97 – 103%	0.9900 <1% 99.6%
Robustness	Column Temp. ±2 C Mobile Phase ±2 % Sample extraction time -20 % Compound stability 6 days	R for all peaks >1.5 R for all peaks >1.5 Recovery in spec. <3% degradation	R for all peaks >2.0 R for all l peaks >2.0 Recovery in spec <2% degradation

Transfer of Analytical Methods

- Follow USP <1224> for Validation of analytical procedures
- Use comparative testing
- Representative samples are tested in the transferring and receiving laboratories
- Acceptance criteria to be defined before testing
- Number and type of tests based on risk

Hot Topic

USP 1224

Method transfers were not completed on test methods prior to using them. The firm failed to perform finished product test method transfers for 34 products (187)

Transfer of Analytical Methods Considerations for Comparative Testing

- Number of samples, lots, batches (1-3)
- One or more concentrations (1-3)
- Number of repetitive analysis / sample (4-6)
- One or more analysts? (1-2)
- One or more days? (2-5)
- Equipment from one or more manufacturers? (1 - all)

USP 1224
May 2012

Verification of Compendial Methods

- Check USP <1226>
- Run system suitability test runs
- Conduct 1-3 validation runs, depends on
  - complexity
  - impact on (drug) product quality and patient safety
  - experience of the lab
  - specifications of the product, and
  - the procedure

Method verifications for compendial tests are not performed. Any method, including compendial methods, must be verified as suitable under actual conditions of use. (247)

Change vs. Adjustment of Methods

- Laboratory can not get performance with ‘Standard Method’

1. **Check USP <621>** and EP 5, Section 2.2.4 for allowed variables, e.g., flow rate, col. Temperature, column i.d.
2. If modifications are in the allowed range, perform system suitability testing.
3. If SST pass, continue with analyses. If not make further modifications. If total modifications are in allowed ranges, go back to 2. Otherwise revalidate

Hot Topic

USP 621

Question: What if the performance of home made method drifts out of acceptance criteria, e.g., resolution in chromatography

Allowed Variations USP/EP

USP 621

HPLC Column

	USP	EP
Length	70%	70%
Internal diameter	25%	25%
Particle size	Reduction of 50%, no increase	Reduction of 50%, no increase

#7: Maintain, Calibrate and Qualify Equipment and Computer Systems

- Develop procedures for equipment purchasing, qualification, calibration and maintenance
- Qualify the equipment
- Identify defect or non-qualified equipment
- Develop and implement maintenance and qualification schedule
- Keep equipment under change control and re-qualify, if necessary
- Record changes

Qualification/Validation Phases 4Q Model

USP 1058

+ Design specifications for development

Validation Plan

Design Qualification

- User requirement specifications
- Functional specifications
- Operational specifications
- Vendor qualification

Installation Qualification

- Check arrival as purchased
- Check proper installation of hardware and software

Operational Qualification

- Test of operational functions
- Performance testing
- Test of security functions

Performance Qualification

- Test for specified application
- Preventive maintenance
- On-going performance tests

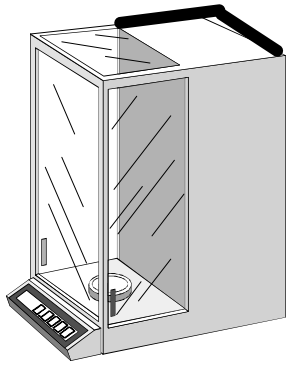
Validation Report

DQ – Selected Functional Specs

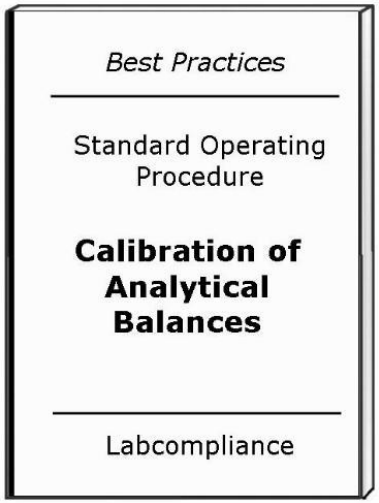
Functions and performance	User Requirements	Supplier Specification	Requirement met
Autosampler sample capacity	>90 x 2 ml vials	100 x 2 ml vials	yes
Injection volume range	0.1 – 100 ul	0.1 – 100 ul	yes
Injection volume precision	<1% with 10 ul injection volume	<0.05% with 10 ul	yes
Sample carry over	<0.1%	<0.05%	yes
Flow rate range	0.1 – 10 ml/min	0.1 – 10 ml/min	yes
Flow rate precision	<0.5% RSD at 1 ml/min	<0.3% RSD at 1 ml/min	yes
Flow rate accuracy	<5%	<5%	yes
Column heater temperature range	Ambient to <70 deg C	Ambient to <70 deg C	yes
Column heater temperature precision	<+-1 deg C at 40 deg C	<+-1 deg C at 40 deg C	yes
Column heater temperature accuracy	<+-3 deg C at 40 deg C	<+-3 deg C at 40 deg C	yes
Baseline noise	± 2 x 10^{-5} AU	± 2 x 10^{-5} AU	yes
Baseline Drift	3 x 10^{-4}AU/hr	3 x 10^{-4}AU/hr	yes

OQ Test - Example

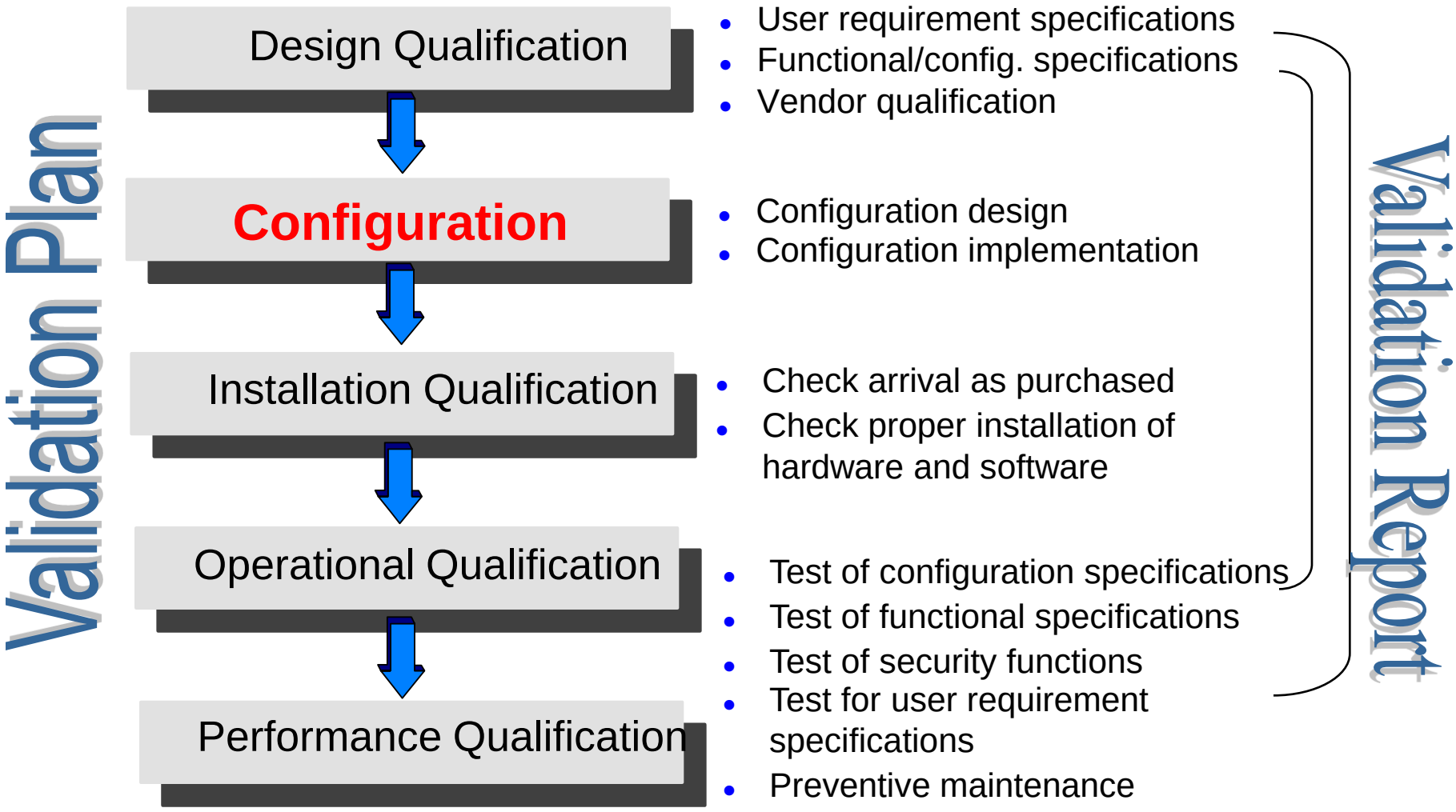
Instrument	BestBalance	
Serial number	55236A	
Maximal weight	11 g	
Control weight 1	10,000 mg	Limit +-10 mg
Control weight 2	1,000 mg	Limit: +-1 mg
Control weight 3	100 mg	Limit: +- 0.1 mg



Date	Weight 1	Weight 2	Weight 3	o.k.	Test engineer Name	Test engineer Signature
2/3/06	9999.8	999.9	100.0	yes	Hughes	

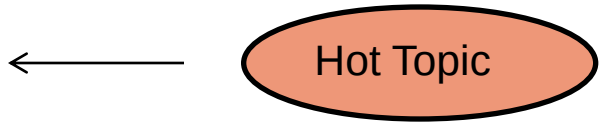


Computer System Validation



What to Test

- Functions that can be impacted by the user's environment
  - User configurations
  - User customizations
  - Hardware configurations, cabling (communication between computer and equipment)
- Real critical system functions
- Complete system test



The validation results do not meet the pre-determined acceptance criteria, and there was no documentation why the results were acceptable (WL 204)

#8: Implement Procedures for Sample Analysis

- Sampling
- Sample handling
- Testing
- Data review and approval

Sampling	Sample handling& storage	Testing	Data review and approval

Sample Testing

Hot Topic

- Develop test program for APIs, finished drugs,raw material
- **Develop clear specifications**
- **Document acceptance criteria and actual result**
- Document test procedures and test equipment
- Formally review and approve test results
  - Analysts
  - Second person (technical & independent reviewer)
- Document test conditions with test results

Sampling	Sample handling& storage	**Testing**	Data review and approval

Review and Approval of Test Results

- Develop and follow procedure for review of test results
- Review by the analyst: what to look at, how to document
- Review and approval by a second person
- Release of test results

Sampling	Sample handling& storage	Testing	**Data review and approval**

Laboratory records fail to include the initials or signature of the person who performs each laboratory test (WL 172)

Checks by QA (independent)

- Compliance with Internal procedure?
  - Handwritten entries recorded in ink
  - Correct change of data
- All checks completed by analyst?
- All checks completed by technical reviewer?
- Electronic audit trail table
- Signature not a must, if technical reviewer has reviewed QA items and signed (add QA related checklist items in technical reviewers checklist)

Hot Topic

Your firm's review of laboratory data does not include a **review of an audit trail** to determine if unapproved changes have been made.. (W-229)

Handling Failure Investigations / Out-of-Specification Test Results

- Investigation required if a test result is out of specification
- Required to identify the root cause of a problem
- Should follow documented procedure
- Failure can be caused by individual testing, process error, or product problem
- Maintain a list of all OOS test results
- Corrective and Preventive Action Plans, Root Cause Analysis
- Follow FDA Guide: *Investigating out of Specifications Test Results for Pharmaceutical Production*

Hot Topic

Missing written records of failure investigations
You have failed to extend investigations to all batches of products potentially affected by a problem (W-263)

(e)-Records Maintenance and Archiving

- Study regulations: which records are required, for how long should they be archived?
- Define raw data
- Ensure track-ability of final results to raw data
- Maintain integrity of data
- When using electronic records, follow Part 11

Hot Topic

- Ensure that electronic audit trail is available, activated and reviewed
- Develop a strategy and procedures for backup, archiving and retrieval of data

Sampling	Sample handling& storage	Testing	Data review and approval	**Record archiving**

There are no procedures for backing-up data files and no levels of security access established“ (W-138)

FDA Statement about Deleting HPLC e-Raw Data after Printing

Hot Topic

- The **printed paper copy of the chromatogram would not be considered a "true copy**" of the entire electronic raw data used to create that chromatogram, as required by 21 CFR 211.180(d).
- The chromatogram does not generally include, for example, the **injection sequence, instrument method, integration method, or the audit trail**, of which all were used to create the chromatogram or are associated with its validity
- Therefore, the **printed chromatograms** used in drug manufacturing and testing **do not satisfy** the predicate rule requirements in 21 CFR Part 211.
- The **electronic records created by the computerized laboratory systems must be maintained under these requirements**

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm

Resources

- **Agilent Primers**
  - Analytical Instrument Qualification and System Validation)
  - Validation of Analytical Methods
  - Good Laboratory Practice and Good Manufacturing Practice
  - Understanding and Implementing ISO/IEC 17025
  - Compliance for BioPharmaceutical Laboratories
  - Elemental Impurity Analysis in Regulated Pharmaceutical laboratories
  - Qualification and validation for Supercritical Fluid Chromatography
- Free tutorials (method validation, computer validation, GLP)
- Laboratory Compliance Master Plan (55 pages)
- Laboratory Compliance: Step-by-Step
- Links to FDA Warning Letters (www.fdawarningletter.com)

www.labcompliance.com/agilent
(available until July 10, 2012