Centre for Biopharmaceutical Excellence

Change Management and Equipment Qualification

Change - Module Outcomes

On completion of this module the participant should be able to:

- Interpret cGMP requirements for change management
- Develop a Change Management SOP
- Describe the GMP rules for Prospective Equipment Qualification
- Describe the GMP rules for re-validation of Equipment
- Assess the compliance of existing “legacy” equipment

Module Topics

- GMP Rules for Change
- Change Management Systems
- Equipment Qualification
  - Prospective
  - Re-qualification
  - Assessing legacy Equipment

Is Change Management a QA Responsibility ?

- Every Department is involved in Change Management
- Production, Regulatory Affairs, Development, Engineering, Quality Control IT as well as Quality Assurance.
- Many regulatory citations and product recalls originate in poor change control practices.
- Change control is one of the hardest QS elements to manage!

Some Lessons Learnt

- Manufacturer of sterile saline changes the bottle seal (initiated by purchasing) - alters the heat penetration during autoclaving ….. Unsterile units manufactured …….. leading to deaths.
- Manufacturer used a different granulation process for sustained release tablet - particle size different and tablet fast releases - causes uncontrolled rapid release of active ….. Heart attacks result.
- Manufacturer substitutes a new software program without validation – update causes product formulation error leading to recall .

Document Change and Change Management

- **Document Change** and **Change Management** are NOT the same thing.
- A document change can be due to
  - Editorial change (Minor)
  - As a final step in Change Control – an action as a result of an implemented change
- Change control is much more than simple document update.

Why Have Change Control Procedures ?

- Maintain compliance to the Marketing Authorisation
- Assess whether regulatory approval is required
- Ensure that any changes that are made preserve product quality (ISPE)
- Co-ordinate changes across all impacted groups
- Maintain currency of procedures and instructions
- Stay in control and within compliance

Who is Involved in Change Control ?

Regulatory Affairs
- Checking the change and advising any regulatory impact
- Liaise with Regulators
- Submission of Requests and Documents

Quality Assurance
- Classifying the change request
- Assessing impact of change - level
- Forwarding requests to the Technical Committee
- Managing the change control procedure - (see co-ordinator)
- Chairing the Technical (Change Control) Committee;
- Monitoring that change actions are implemented

Technical (Change Control) Committee
- Meeting regularly to review all major change requests;
- Review and approval of all major changes;
- Liaising with regulatory authorities, where required.

Change Co-ordinator/Specialist
- Co-ordinating requests
- Organising approvals
- Reviewing change plans
- Ensuring validation is undertaken
- Post change verification of implementation

Document Administrator/Control
- Maintaining the change request register;
- Filing completed change reports.

Change control scope includes, but is not limited to

- Product Formulation
- Manufacturers of Active Pharmaceutical Ingredients (APIs)
- Batch scale up or down beyond +/-10%
- Manufacturing and packaging process steps (CPP/CQA impact)
- Cleaning and sanitising programs
- Labelling and packaging components;
- Critical starting materials;
- Direct impact equipment;
- Direct impact services or facility;
- Laboratory test methods and specifications (for both starting materials and finished products);
- Stability program, storage conditions and expiration dating;
- Sub-contract facilities or operations.

Examples of Change Control Scope

Product Changes	Process Changes	QC Changes	Equipment Engineering
Formulation and Container/Closure	Validated Steps	**Critical Quality Attributes (CQAs)**	Processing Equipment
Starting Materials API Source	**Critical Process Parameters (CPPs)**	**Critical Material Attributes (CMAs)**	Pharmaceutical Services (Water, Gas, HVAC)
Printed Matter	Batch Scale Up/ Down	Test Methods and Specification	GMP Facility
Indications Market Claims Use Directions	Cleaning Sanitation Sterilisation	Laboratory Instruments	Critical GMP Related Computers

What are CQAs, CPPs and CMAs

Critical Quality Attribute (CQA)

- A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Process Parameter (CPP)

- A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Starting Material (CSM or CMA)

- Critical Quality Attribute(s) of a Starting Material

Significance of CQAs, CPPs and CMAs

- Critical means the parameter or attribute has a potentially significant impact on product quality, safety, purity, identify or strength.
- Therefore ANY change to a CQA, CPP or CMA has a potentially significant impact
- Therefore it should be treated as a **major** change and should be validated.

- **Its important to know and understand your CQAs, CPPs and CMAs**

Regulatory Agency Requirements and Rules for Change Management

- Regulator is a key stakeholder in change since they have approved the marketing of the product.
- MUST manufacture in compliance with the Marketing Authorisation, but able to supplement
- Significant penalties apply for non-compliance, including criminal sanctions in the USA

Regulatory Change Requirements

- Regulatory Agencies all have explicit requirements for either **prior approval**, **notification of intention** or **"self assessable" (annual reporting)**
- Rules are different for Rx, OTC, CM and device products
- Common requirement is that validation of change needs to be assessed per GMP rules.
- Many Regulatory Agencies have change guidance eg TGA (Appendix 12) and FDA (SUPAC)

FDA and (Post Approval) Change Control

CDER Human Drugs

Refer (FDA Regulation - 21 CFR 314.50)

Prior Approval Supplement - FDA Evaluation (Major/Significant)

- Must wait for FDA approval (3 - 18 months)
- May initiate an inspection
- May submit a "comparability protocols" for FDA approval

Notification of "Changes Being Effected" (Moderate)

- File notification of intention to change
- Company is fully responsible for control of changes/validation
- wait 30 - 60 days then change if no response

Annual Report System (Minor Change)

- Effect change without reference to FDA
- Company is fully responsible for control of changes/validation
- Record in the Annual Report

Possible Change Control Levels

Minor Change
The change is unlikely to have a detectable impact on critical attributes of the product or process. Change is procedural or editorial in nature only.

Moderate Change
The change could or may have a significant impact on critical attributes of the product or process.

Major Change
Change is likely to or will have a significant impact on critical attributes of the product or process.

Changes to	Minor	Major
Contract Service Providers		✓
Regulatory Updates eg. Pharmacopeial update	✓	✓
Contract Testing laboratories	✓	✓
Contract Manufacturers		✓
Critical Equipment or Services • "like for like" • Different	✓	 ✓
Master Engineering Diagrams / schematics etc.		✓
Change to a Critical Quality Attribute (CQA)	Tighten	Widen
Change to a Critical Process Parameter (CPP)	Tighten	Widen
Change to a Critical Starting Material Attribute (CSM)	Tighten	Widen
Master Batch Records (validated processes and Formulation)		✓
Specifications Components Primary – registered Secondary & non registered	 ✓	 ✓
Packaging Materials Primary – registered Secondary & non registered	 ✓	 ✓ ✓
Printed Matter Primary – registered Secondary & non registered	 ✓	✓ ✓
Product - Specification Tighten the Limit Widen the Limit	✓	 ✓
Product - Test Add a Test Delete a Test	✓	 ✓
Shelf Life Conditions (expiry or storage)		✓
Test Methods	✓	✓
Utilities or Services Critical Non-critical	 ✓	✓

Examples of Typical Change Levels

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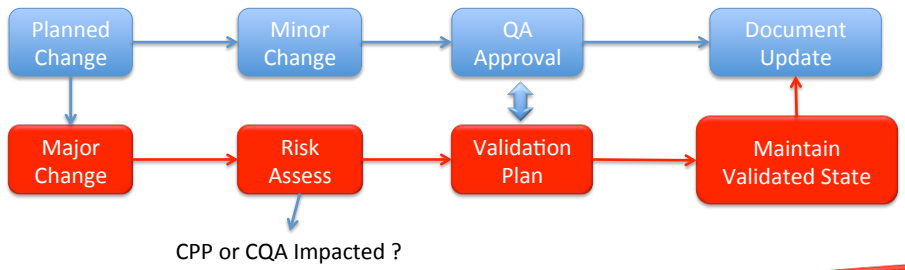
Change and Risk Assessment

- Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. (EU cGMP – Annex 15)
- The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis.
- ***The need for, and the extent of, requalification and re-validation should be determined.***



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Make up of Change Control Committee

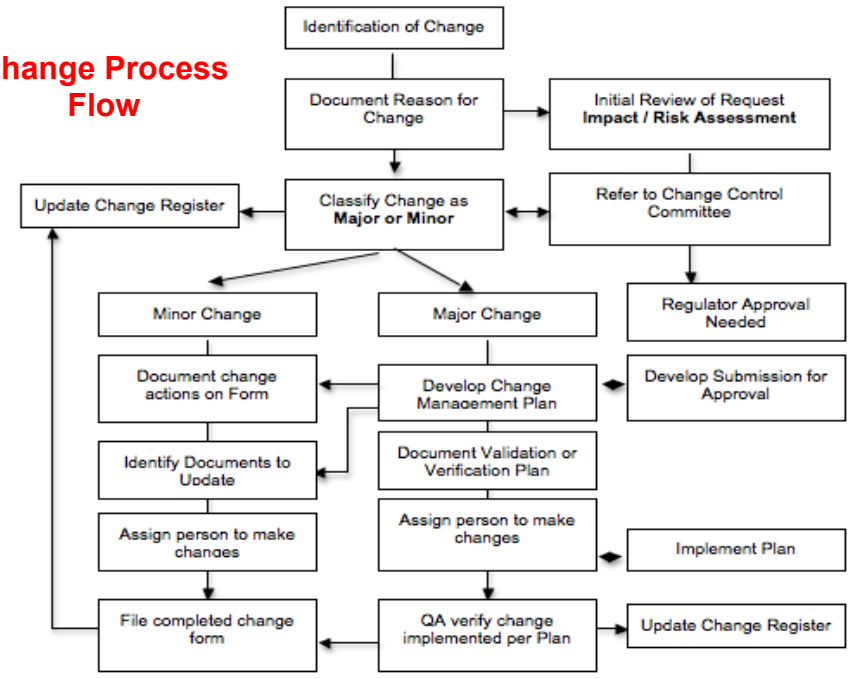
The Change Control Committee (CCC) is made up from persons representing some or all of the following:

- Regulatory Affairs
- Quality Assurance/Authorised Person
- Technical Services (Validation / Stability)
- Production
- Development*
- Engineering*
- Laboratory*
- IT*

* As needed

- CCC generally meets monthly to specifically look at major changes

Change Process Flow



Change Request Form

1. Description and reason for change - tracking #
2. Initial review of Change Request - “Impact/Risk assessment”
3. Classification of Change - Major or Minor
4. Proposed change action (if Major)
   - Plan or protocol
   - Stability programs
   - Validation
   - Verification of equivalency (for products)
5. Documents required to be updated (Major and Minor)
6. Post change Verification of Change Impact (Major)

Change Request Number:	**CR _ _ - ~~~~**	**Change Type (*circle one*):**	**Major / Minor**
Product or Group of Products affected by			
Summary of Change			

SECTION 1

Change Control Identified By:		**Date:**	
Brief Overview of Change Required:			
Details and Reasons for change:			

SECTION 2 - Describing the Change

Does the change affect *(circle all that apply)*:					
One product / **multiple** products		**Sterile / Non-Sterile** Rx Product/ **OTC** product			
What does the Change Control involve – tick ☑one or more items listed below					
Sterilisation/Sanitation process		Raw material change		Master Batch Records	
Production equipment change		Testing equipment change		Specification/Test Method	
Air handling system (HVAC)		Personnel changes		Shelf Life Conditions	
Water purification system		Change in a process step		Utilities or Services	
Packaging components change		CPP or CQA change		Other	
Areas affected by the change (tick *whichever applies*):					
Product Development		Validation		Regulatory	
Stability		Training		Document Update	

Impact Assessment and Classification

Impact / Risk Assessment (circle whether the change is major or minor	
Minor Change/Low impact	An impact or risk assessment is generally not expected
Major Change/High Impact	A impact/risk assessment may be required if the change involves a change to a CPP, CQA or CSM or is complex in nature.
Regulatory Change ? Yes / No **If Yes the rate as Major/High Impact**	Determine if the proposed change mut be approved or notified to a regulatory agency before implementation.
Impact / Risk assesment required ? Yes/No	If Yes refer to RA # .....
Approved by (QA Representative)	

Documents impacted

Documents Affected by the Change:	Document No.	Responsibility	Target Date	Date Completed

SECTION 3 – Change Management Plan

Regulatory Agency Approval required ? Yes / No –

If Yes, indicate date of approval Date: .....

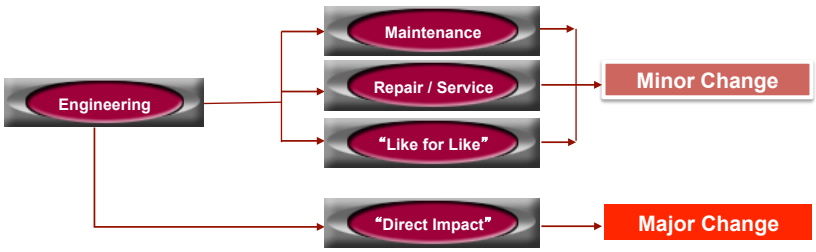
Proposed Action: Mandatory for Major changes and optional for Minor changes	Responsibility	Target Date	Date Complete
1.			
2.			
3.			
4.			
Is verification of the effectiveness of the implemented change required ?	**Yes / No**	By:	

Actual Action Implemented (if different from above):	Responsibility	Target Date	Date Complete
Change Implementation Checked and Closed out by:		**Date:**	

Documents Impacted by Change

- Product Documents;
  - Registration Dossier / Regulatory Filing
  - Master Manufacture /Packaging Instructions;
  - Protocols or Methods;
  - Specifications;
- Records, Work Instructions, Standard Operating Procedures;
- Engineering Drawings & P&IDs;
- Contract Agreements;
- Validation Documentation

Different Change Systems - Engineering Changes



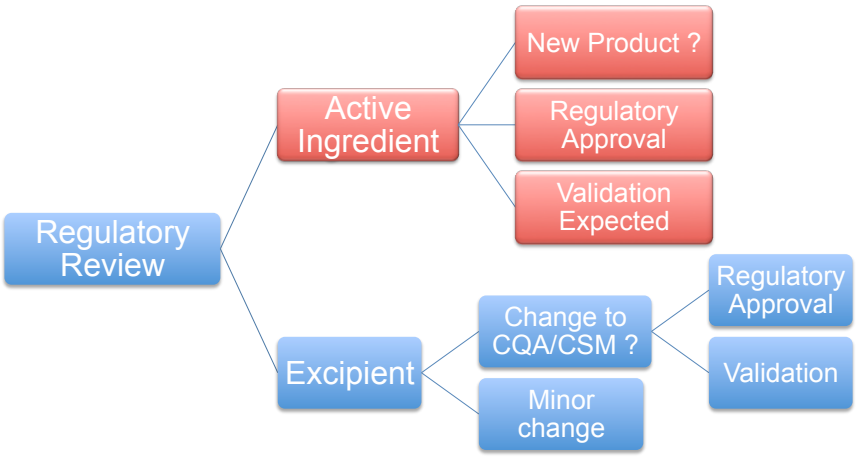
Document Control as a Result of Engineering Change

- Update Drawings and P&IDs
- Update Manuals
- Update Operator Instructions
- Review Safety
- Review Maintenance and Calibration programs
- Review IQ/ OQ programs for major changes

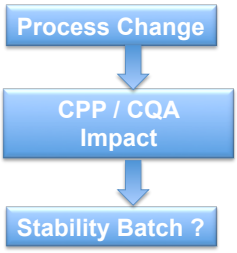
Equipment Changes - Impact Assessment Strategy

- Product Contact Equipment ?
- Controls a CPP or a CQA ?
- Used in CIP/SIP or Sterilization ?
- Failure or alarm has direct effect on product quality ?
- Preserves product quality ?
- Etc…….

Formulation Change



Changes to Process Conditions (From FDA SUPAC - Immediate Release Solid Oral Dose)



Significance	Approval Level	Validation
Level 3	Prior Approval	Expected
Level 2	Regulatory Affairs	QA Decides per GMP
Level 1	QA Decision	Not expected

Level 1 Changes

This category includes process changes including changes such as mixing times and operating speeds within marketing application and validation ranges.

Level 2 Changes

This category includes process changes including changes such as mixing times and operating speeds outside of application or validation ranges.

Level 3 Changes

This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

Changes in Batch Size - (Scale Up / Scale Down)

- Post-approval changes in the size of a batch from the registered details requires assessment of change impact.
- All scale-up changes should be properly validated and where required submissions to regulatory agencies
- The dose form has a large input to the impact eg.
  - Biological products **(are at highest risk of impact)**
  - Sterile products
  - Topicals Suspensions
  - Tablets and capsules (microdose/narrow therapeutic range)
  - Other oral dry products
  - Liquids solutions **(are at lowest risk of impact)**

Comparability Protocols - FDA Initiative

- A comparability protocol is a detailed, written plan for assessing the effect of specific CMC (Chemistry and Manufacturing Control) changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product.
- Describes the changes that are covered under the protocol and specifies:
  - the tests and studies that will be performed
  - including the analytical procedures that will be used
  - and acceptance criteria that will be achieved
- To demonstrate that specified CMC changes do not adversely affect the product.
- Protocols are to be submitted to FDA prior to commencing the change.

Changes to Pharmacopeias

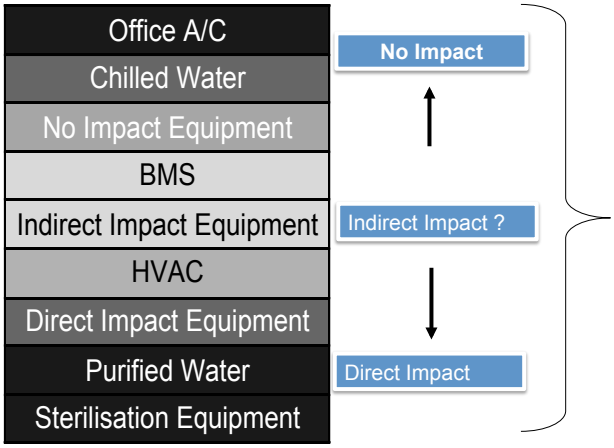
- Expected to keep current with monographs
- Generally Reg. Affairs or QA take this responsibility
- Considered a minor change, except if
  - A RM is a critical material
  - Change in testing technology – new instrumentation
  - Change to a Finished Product Specification
- Generally involves document only change:
  - Specifications
  - Test Methods

In Summary
Change Control (CC) Systems

- Change Control is a cross - functional responsibility
- Must have a change control program (SOP/Change Request) and technical review system
- Identify & document what are **Major** and **Minor** changes in the SOP
- Assess “Risk /Impact” and verify implementation post change
- Focus on CPPs and CQA impacted changes
- Must ensures practices match drug application commitment per Marketing Authorisation

Qualification, Re-qualification and Assessment of Legacy Equipment

The Impact "Spectrum"



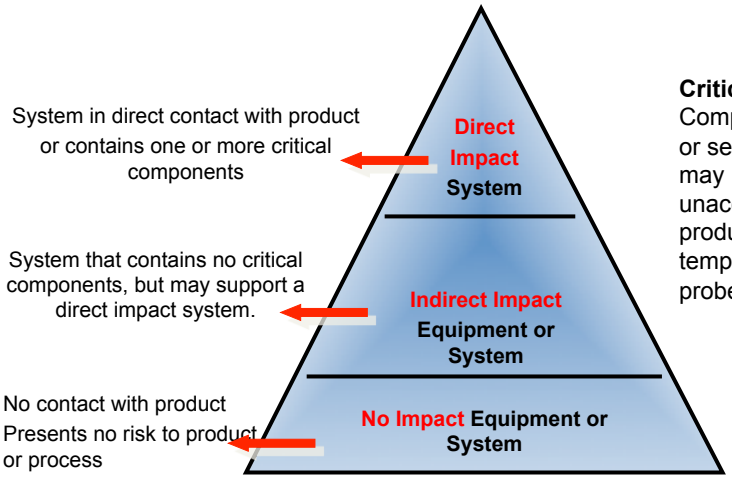
How we design and choose to use these systems can affect their impact !

Direct Impact equipment associated with a CPP or CQA is higher risk

Impact Assessment - Definitions

Definition: **If the equipment or component fails or is incorrectly specified product quality …….**	**Examples**
Direct Impact …… is "likely" to be affected, OR the component is in direct contact with product.	Water purification systems, product pumps and vessels, product sieves, product temperature control systems, product mixing systems.
In-direct Impact - ……. may possibly be affected, through the failure of a related system.	coating pan drive motors, temperature monitoring probes, instrument air
No Impact ……. is not likely to be affected, through the failure of a related system.	Plant cooling water

System Impact Categories



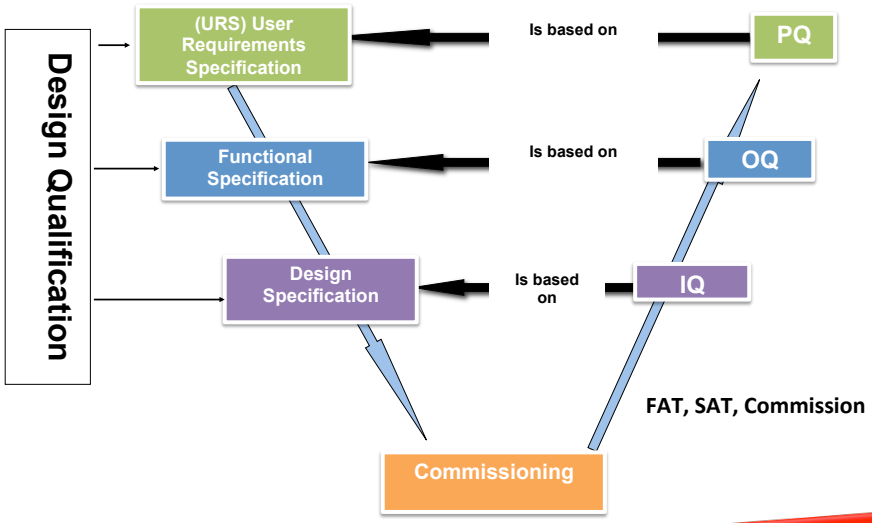
Critical Component: Component of equipment or service whose failure may pose an unacceptable risk to product quality. e.g temperature controlling probe in an autoclave.

Decision Matrix

Based on Risk (Impact / Complexity)

Criticality of System	Complexity of System	Initial Qualification Required ?	Re - Qualification Required ?
Direct Impact	Simple / Off the shelf	Yes IQ/OQ/PQ	Assess the need for re-qualification
	Complex/Novel	Yes DQ/IQ/OQ/PQ	Periodic Re-Qualification Expected
Indirect Impact	Simple / Off the shelf	Commission Only	Not expected M & C Only
	Complex/Novel	Maybe IQ/OQ	Assess Reliability Only
No Impact	Simple / Off the shelf	Commission Only	Not expected Maintenance Only
	Complex/Novel	Commission Only	Not expected Maintenance Only

Traditional V Model
(Applied to Direct Impact Systems)



Risk Based Qualification - 21st Century

- The PQ is a true test of acceptability ... the URS is therefore the most important document
- If PQ is the most important (replicate the tests to provide consistency) the IQ/OQ are sub-ordinate (conduct test only once)
- Activities that are a paperwork exercise should be eliminated/ Only data which serves a useful purpose should be collected.
- Different types of equipment and systems (custom, COTS, simple, complex etc...) require different levels of attention
- Supplier standard inspection and test documents can be used and not replicated by the company

ISPE A White Paper on Risk-Based Qualification for the 21st Century 2005

Qualification and Validation Principles

- It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations.
- Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated.
- ***"A risk assessment approach should be used to determine the scope and extent of validation."***

PIC/S Code of GMP- Annex 15 Clause 1

What the PICs Rules Say – Re - Validation – Annex 15

- 45. Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid.
- Where **no significant changes** have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfills the need for revalidation.

Rationale for Qualification Review

- undertaken where it is expected/assumed that there has been little or no change in the system, which would affect the validated state.
- Above assumption is verified by a historical, retrospective review of key data sources, combined with a physical inspection of the system.
- the review would identify any changes relative to the IQ/OQ/PQ documentation and report these with recommendation to management.

Aim of Equipment Reviews

- original documentation is formally reviewed in light of the changes in regulatory and industry expectation;
- the aging process has not adversely affected the system's "fitness for purpose" as defined in the original validation documentation;
- minor gaps in the original documentation or in the system identified as part of the review of the system are addressed as part of the review process;
- significant changes to systems or components, which have been initiated outside of the change control process, are brought to the attention of Quality Assurance and are addressed as part of the change control procedure.

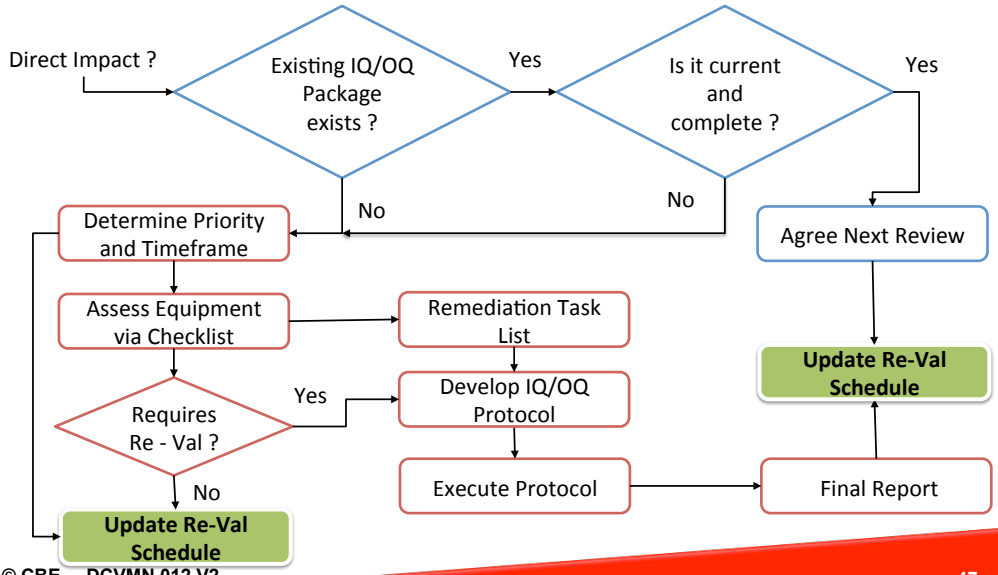
Recommended Approach

- Identify candidate process lines/unit operations on a priority basis
- Identify within the selected process line the critical equipment.
- Identify which items are used for in-process testing only and ensure they are calibrated.
- Conduct a retrospective audit using modification of checklist "*Audit Checklist for Equipment Retrospective Review",* for each item of equipment commencing with the highest priority unit operation.
- Ensure all specific CPPs are reviewed – modify the checklist accordingly.
- The need for IQ and OQ re-qualification is based on the outcome of the assessment.
- Obtain QA Approval of report and decision

Priority Considerations

- Product/Process Line higher Risk to Consumer Health
- GMP criticality of the equipment or service – level of control required
- Historical performance of the equipment (control, reliability, breakdowns etc.)
- Production utilisation importance (high use etc.)

Decision Tree on What to Do



General Acceptance Criteria for Assessment

- meets the audit checklist criteria including specific critical variables control
- P&IDs & Schematics are current and reflect the system as built
- calibrated and maintained to written programs
- operated to written procedures
- sequences for PLC and other control mechanisms are verified
- generally meets current GMPs for construction, cleanability and surface finishes
- **Critical process parameters defined and in control**

Assessment Checklist

#	Item and Attribute	OK ?
1	**Item Drawings, Procedures and Manuals Review**	
	P&IDs & schematics all present, current-match as built condition ?	✔
	SOP for operation published ?	✔
	SOP for cleaning and sanitation published ?	✔
	SOPs for maintenance and calibration published ?	✔
2	**Automated (Control) Systems Review**	
	All PLC controllers verified as functional ?	✔
	PLC controller sequence verified/documented ?	✔
	SCADA or equivalent interfaces in place ?	✔
	SCADA or equivalent interfaces verified ?	✔
	Automated instructions secured and retrievable ?	✔

Assessment Checklist

#	Item and Attribute	OK ?
	Additional Areas for Assessments	
3	**Physical Inspection / Construction**	✔
4	**Monitoring Instruments**	✔
5	**Operation & Records**	✔
6	**Preventative Maintenance and Safety Programs**	✔
7	**Assessment of any Critical Process Parameter(s)**	
	Summary of Conditions and Recommendation	✔
		✔
	Remediations / Corrective Action List	✔
#	**Remediation without IQ/OQ**	**By/ when**
	Remediation with IQ/OQ	✔

What historical data to look at

- Engineering data:
- Preventative maintenance program / records in place and actioned
- Repair maintenance history is logged
- drawings generally and specifically registered P&IDs & Schematics,
- Calibration data for CPPs
- statutory documentation / certificates / safety etc,

Quality Assurance data such as audit and non – conformance reports

- change control records,
- Physical inspection:

Physical Inspection Includes

- "fit for purpose" against in-house and statutory regulations,
- review registered P&IDs & Schematics against actual installation,
- Product contact surfaces are inert – no pitting rust discolouration, staining etc
- Connected services are integral – no leaks, drips etc.
- Product contact components are in good repair eg. dyes and punches, pumps etc.
- Equipment seals are in good order and are being maintained
- Filters are on a change program and integral
- Measuring instruments are working and calibrated
- Piping is labeled correctly
- Lubricants are documented and used
- Spare parts are available

Outcomes from Reviews

No changes noted, with the equipment in good operational and validated condition:

- report to be approved and filed with the original validation documentation,
- the review date is reset to the date of approval of the completion report,

Minor changes or shortfalls in equipment or documentation which do not affect the operation or validated state of the equipment [eg minor non-critical modification not captured on P&IDs]:

- provide a deficiencies list as part of the report,
- carry out rectification works identified in the deficiency list via the appropriate quality systems [ie change control] where applicable,
- report and closed out deficiencies list to be approved and filed with the original validation documentation, and
- reset the review date to the approval date of the completion report,

Outcomes from Reviews

Significant changes in equipment or documentation which potentially affect the validated status, where these have not been captured by a validation exercise as part of the change control procedure:

- complete the report with the actions agreed by Quality Assurance and the system owner and file with the original validation documentation.
- provide a deficiency list as part of the report, which is to be actioned before sign-off of the review.
- raise the issue with the relevant validation group and with Quality Assurance to determine the steps to meet the relevant compliance requirements,
- The review date must not be reset where the review has triggered a revalidation exercise. This will occur out of the qualification exercise.

- **The decision to formally re-qualify equipment is based on the outcomes**

Re-Validation Timeframes

- No hard and fast GMP rule – risk assessment decision
- Some examples that industry use:
  - **Critical Sterile Products Equipment** – mandated **annual** PQ/PV but no mandated IQ/OQ
  - **Direct Impact Equipment**
    - Higher risk equipment with CPP attached – **3 years**
    - Medium risk – **5 years**
  - **Indirect Impact Equipment** - **> 5 years maybe 10**
  - **No Impact Equipment** – **not relevant**

Suggested Risk Based Review Periods

3 years for:
- sterilisation equipment used for process equipment and components, and for terminal sterilisation of products,
- lyophilization equipment used for the preparation of raw materials and completion of finished product, and

5 years for:
- equipment and services rated as quality critical with direct product contact,
- non-critical systems which may be subjected to more frequent change, or,
- system with a short operating life, and

10 years for:
- quality critical systems with indirect product exposure,
- systems which are historically stable, with minimal exposure to change.

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