Centre for Biopharmaceutical Excellence

Validation – Principles and Practices

What will be covered

- Traditional Approach to Validation
- Lifecycle Approach to Validation Utilising CPP/CQA approach
- Validation Documentation and VMPs
- Continued Process Verification (CPV)
- Validation of Vaccines – some examples /Aseptic Processing

Some Regulatory Guidance Documents

- **WHO GMP for Biological Products - Proposed replacement of: TRS 822, Annex 1 – Section 15**
  - WHO ANNEX4-TRS992 Hold Time Studies
  - WHO_TRS961_ANNEX09 Transport Studies
  - WHO ANNEX5-TRS992 Transport Studies
- FDA: Guidance for Industry: Process Validation: General Principles and Practices (January 2011)
- ICH Q8R2 – Pharmaceutical Development
- PICs Annex 15 (Qualification and Validation) - 2014
- EMA Guideline on process validation for finished products for regulatory submissions (Dec 2013)
- EMA Guidance – Annex 15 (March 2015)

Some Key Definitions

Continuous Process Verification

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

EU Guidelines/ICH Q8

Continued Process Verification

Assuring that during routine production the process remains in a state of control.

FDA PV Guidance.

Ongoing (Continued) Process Verification

Documented evidence that the process remains in a state of control during commercial manufacture.

EU Guidelines

Process Validation (PV) Definitions

Establishing **documented** evidence which provides a **high degree of assurance** that a specific process will **consistently** produce a product meeting its **pre-determined** specifications and quality attributes.

FDA Guideline General Principles of Process Validation, 1987

The collection and evaluation of data, from the **process design stage throughout production**, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation involves a series of activities taking place over the **lifecycle** of the product and process.

FDA Guideline General Principles of Process Validation – 2011

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

EMA Annex 15 - 2015

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5

Scientific Aim of Process Validation

- To provide documented evidence of ongoing control
- To evaluate the "robustness" of the Method of Manufacture - Demonstrate the process is robust to expected changes and challenges
- To demonstrate process reliability, and acceptable variation in critical process parameters **(CPPs)**
- To demonstrate the process/product consistently meets specifications and critical quality attributes **(CQAs)**
- To demonstrate product uniformity/homogeneity
- **Within batch homogeneity and between batch consistency must be assessed.**

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6

Defining CPPs and CQAs

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. (ICH Q8)

CQA: A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality. (ICH Q8)

WPP: A critical process parameter that is robust to operating changes. Would a reasonable excursion (e.g double the operating range) likely impact a CQA ?

Validation Master Plan (EU cGMP Annex 15 - Clause 1.5)

The VMP or equivalent document should define the qualification/ validation system and include or reference information on at least the following:

i. Qualification and Validation policy;
ii. The organisational structure including roles and responsibilities for qualification and validation activities;
iii. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;
iv. Change control and deviation management for qualification and validation;
v. Guidance on developing acceptance criteria;
vi. References to existing documents;
vii. The qualification and validation strategy, including requalification, where applicable.

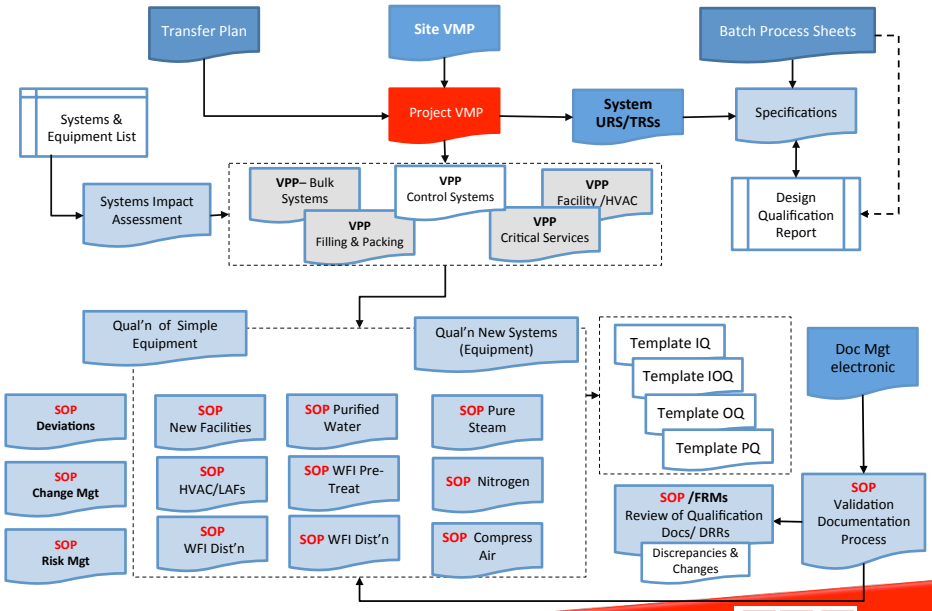
Example VMP Table of Contents

Table of Contents

EU/PICs Validation Documentation

- The inter-relationship between documents in complex validation projects should be clearly defined.
- Validation protocols should be prepared which **defines the critical systems, attributes and parameters** and the associated acceptance criteria.
- Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).
- Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.
- Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.

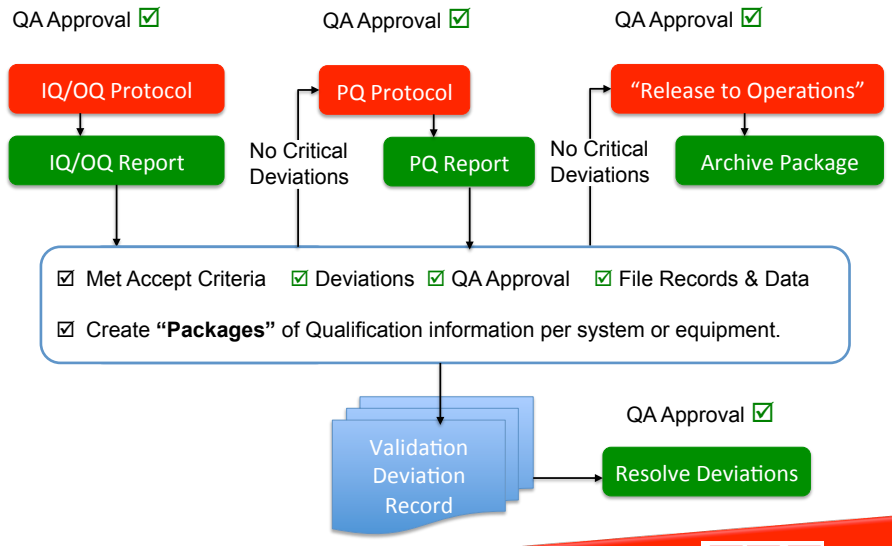
Q&V Document Tree – New Project Example



Qualification Staged Approvals – Clause 2.10

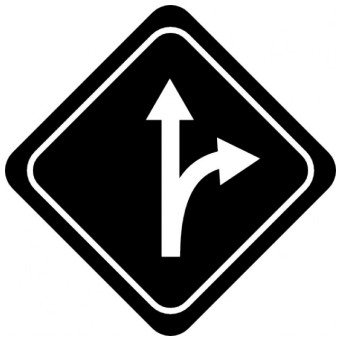
- A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document.
- Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

Staged Approvals and Release to Operations



Validation Deviations

- Investigate failed results – failures tell us a lot about the process conditions !
- If change to the protocol or sampling plan are required, justification must be documented
- All deviations, resolutions and rationales must be documented in a **deviation report**.



Validation Reports

Validation Report - Document that cross-references the qualification and/or validation protocol, summarising the results obtained, and the conclusions drawn.

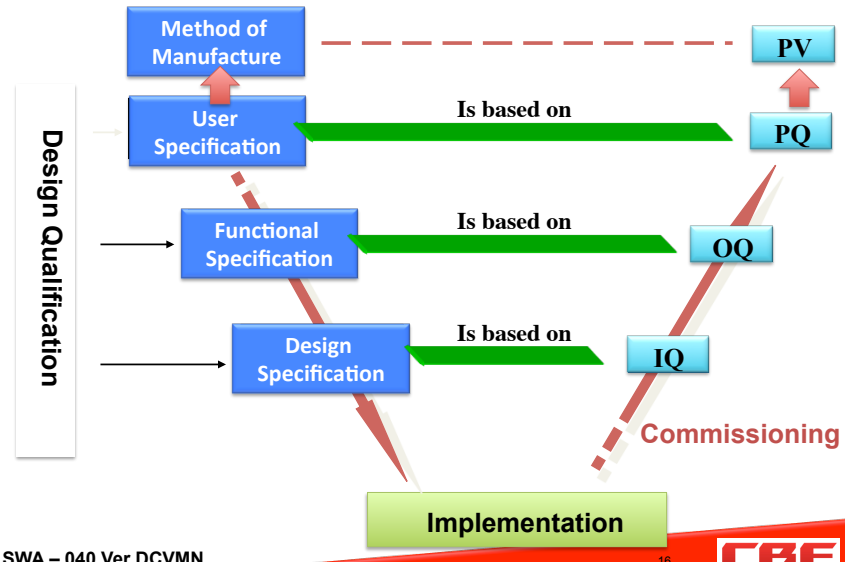
PIC/S Code of GMP - Annex 15 (part)

EMA Recommendations:

- Batch analytical data – summary tables and graphs
- Certificate of Analysis (summary of results)
- Batch production records
- Reports on unusual findings, deviations, modifications or changes
- Final conclusions
- Should list all deviations and their investigations

Traditional Validation "V Model"

(Specifications and Protocols)



Traditional View of Validation

- Perform a minimum of three validation batches at product commercialization scale;
- Do not consider worst case situation;
- If acceptance criteria meets specification then process validation is complete;
- If any batch do not pass, follow quality system (Deviation, CAPA) then repeat the validation exercise until 3 consecutive batches pass;
- Process Validation is considered complete and no ongoing monitoring / review is required;

PIC/S – Traditional Approaches to Process Validation

Prospective Validation	Concurrent Validation	Retrospective Validation
• Required by regulators • Regulator will review the protocol and report • General rule is 3 consecutive successful batches	• Generally need to request approval from the regulator • Is not the nor • Can release each batch after intensive testing • Requires final report	• Not the preferred approach • Need a protocol • Must demonstrate process control • The collection of data showing that batches always meet specification is not, in itself, validation.

Often Observed in Industry

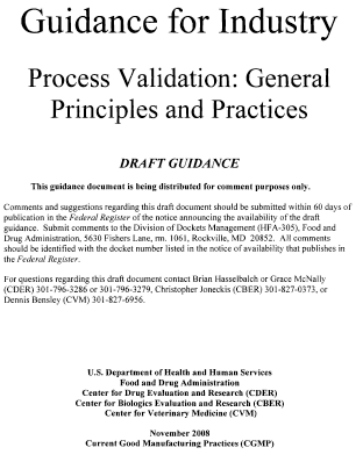
- Run 3 batches to make sure they meet specifications
- Reluctance to have tighter acceptance criteria for validation batches
- Blending operations are generally included
- Lack of focus on critical unit operations / process steps
- Lack of consideration of any challenge or worst case conditions
- No program for re-validation
- Production of paperwork seems to be a key objective

What's wrong with the traditional industry validation approach ?

Current Trends in Process Validation (FDA Lifecycle Approach)

- Overall validation is not "completed", but ongoing
- Necessitates comprehensive process design to understand sources of variability and achieve process understanding
- Incorporates risk management
- Recognizes that more knowledge will be gained during commercialization

Grace McNally, FDA



Guidance for Industry

Process Validation: General Principles and Practices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Brian Hasselbalch or Grace McNally (CDER) 301-796-3286 or 301-796-3279, Christopher Joneckis (CBER) 301-827-0373, or Dennis Bensley (CVM) 301-827-6956.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

November 2008
Current Good Manufacturing Practices (CGMP)

2015 EU GMP Annex 15

- Released 30 Mar 2015. Operational 01 Oct 2015
- Based on previous PIC/S Annex 15
- Three approaches…
  - Traditional (3 batches)
  - Continuous process verification
  - Hybrid
- Specifies approaches to:
  - **Transport qualification**
  - **Packaging qualification**
  - **Utilities qualification**
  - **Test method validation**
  - **Cleaning validation**

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Medicinal Products – Quality, Safety and Efficacy

Brussels, 30 March 2015

EudraLex

Volume 4

EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Annex 15: Qualification and Validation

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: Revision

Reasons for changes: Since Annex 15 was published in 2001 the manufacturing and regulatory environment has changed significantly and an update is required to the Annex to reflect this changed environment. This revision to Annex 15 takes into account changes to other sections of the EudraLex, Volume 4, Part I, relationship to Part II, Annex 11, ICH Q8, Q9, Q10 and Q11, QWP guidance on process validation, and changes in manufacturing technology.

Deadline for coming into operation: 1 October 2015

PIC/S is likely to adopt EU Annex 15 into PIC/S GMP

Key Principles: FDA and PICs/EU
(URS/DQ/FAT/SAT/FS/DS)

- Basis is process validation and understanding of the process.
- It is essential that activities and studies resulting in process understanding be documented.
- Documentation should reflect the basis for decisions made about the process
- This information is useful during the process qualification and continued process verification stages.

- Extensive guidance on what is required for equipment / services
- The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification.
- The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level.
- The URS should be a point of reference throughout the validation life cycle.

Key Principles: FDA and PICs/EU
(Process Control)

- Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall.
- Strategies for process control can be designed to reduce input variation, or adjust for input variation during manufacturing.
- Process controls address variability to assure quality of the product.

- It is a GMP requirement that manufacturers control the **critical aspects** of their particular operations through qualification and validation over the life cycle of the product and process.
- The frequency of sampling used to confirm process control should be justified;
- Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

Key Principles FDA and PICs/EU (Continued Process Verification – CPV)

Stage 3 — CPV

- **Ongoing program to collect and analyze product and process data that relate to product quality.**
- Data collected should include relevant process trends and quality of incoming materials, in-process material, and finished products.
- The data should be statistically trended and reviewed by trained personnel.
- The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

Ongoing Process Verification During Lifecycle

- Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.
- **Ongoing process verification** should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review (PQR)

Key Principles FDA and PICs/EU (Release of PPQ Batches)

- In most cases, the PPQ study needs to be completed successfully before commercial distribution.
- In special situations, the PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and activities, i.e., concurrent release.
- FDA expects that concurrent release will be used rarely.

- Concurrent validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches.

Key Principles FDA and PICs/EU (Number of PPQ Batches)

- The commercial manufacturing process and routine procedures must be followed during PPQ protocol execution.
- The PPQ lots should be manufactured under normal conditions by the personnel routinely expected to perform each step of each unit operation in the process.
- There is no mention if a specific number of batches **– the manufacturer must justify their decision.**

- The number of batches manufactured and the number of samples taken should be based on QRM principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation.
- Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.
- **Generally acceptable for a minimum 3 consecutive batches**.

Key Principles FDA and PICs/EU (Re-validation and Change Control)

- The CGMP - Section 211.180(e) requires that information and data about product quality and manufacturing experience be **periodically reviewed to determine whether any changes to the established process are warranted**.
- Ongoing feedback about product quality and process performance is an essential feature of process maintenance.
- **There is no specific mention of routine re-validation or re-qualification**

RE-QUALIFICATION

- **Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.**
- Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.

Key Principles FDA and PICs/EU (Worst Case Conditions)

- No mention of “worst case” conditions in FDA guidance.
- Stage 3 - CPV - should allow detection of undesired process variability.

- Worst case is applied to OQ and PQ phases. It is not specifically required for PV.
- Worst case applies to cleaning val,n
- **Worst Case.** A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

Key Principles FDA and PICs/EU (Bracketing Approach to PV)

- No mention of bracketing approach.

- Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, e.g. for a tablet range made with different compression weights of a similar basic granulation
- Different strengths, batch sizes and pack sizes/container types may also use a bracketing approach, if justified.
- Bracketing can be applied to different container sizes or different fills in the same container closure system.

Application of Risk Management to Qualification and Validation

Risk and Impact Assessment in Validation – cGMP Requirements

The PICs cGMP Annex 15 specifically states the following:

- *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.

EU cGMP Annex 15: A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and **documented risk assessment of the facilities, equipment, utilities** and **processes.**

Risk and Impact Assessment in Validation – cGMP Requirements

- *"A quality risk management approach should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the project phase or during commercial production,* ***the risk assessments should be repeated****, as required."*
- *"The way in which risk assessments are used to support qualification and validation activities should be clearly documented."* **(in a VMP)**
- ***PICs – Re-Qualification:*** *"Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed."*

Equipment Impact Assessment

Direct Impact	Indirect Impact	No Impact
• Direct contact with the product. • Provides an excipient, ingredient or solvent used in cleaning or sterilisation • Preserves product status. • Produces data used to accept / reject product • Is a process control system • **If yes to any one of these then the equipment is considered direct impact**	• Equipment used in processes that do not meet the criteria for direct impact, but are a supporting system e.g instrument compressed air.	• Equipment that has no impact at all on product quality

Equipment Complexity Assessment

Complex	Novel	Simple
• **Complex** equates to novel or multi-module equipment where there is a need for integrated components to work synchronously e.g. a freeze dryer or filling machine	• A novel item is one that is custom built for the process step – it may be either complex or simple, but is generally classified as complex.	• Equates to equipment that has only one module or unit e.g. a filter press, a mixing tank or an incubation room. • These items are often purchased "off the shelf" are stand alone and not integrated

Item Name: **Liquid Mixing Tank**	Equipment #: 123
Part of Process Line: **Liquids Bulk Manufacture**	Location/Room:
GxPs taken into account; X GMP ☐ GDP ☐ G(QC)LP X GAMP ☐ Other	
Description of the main functions: Bulk Mixing of non- sterile liquids. There is a HMI controller for the tank which provides readout/printout of critical process conditions (time and temperature)	

Example

	Complete the checklist questions below by ticking each line. If the answer is Yes but only related to a component of the item tick Yes and the Component box.	Component	Yes	No
1	Is the item, or components in direct contact with the product or auxiliary solutions during production or during monitoring ?	☐	✔	☐
2	Item provides an excipient or process ingredient ?	☐	☐	✔
3	Does the item (or a component) produce data which impacts in process or final product release ?	☐	✔	☐
4	Does the item wholly or partly independently decide on the further processing of products ?	☐	☐	✔
5	Does the item (or a component) monitor a CPP or WPP control system with no independent verification ?	☐	✔	☐
6	Item preserves product quality e.g. vent filter, HVAC, Gas etc ?	✔	✔	☐
7	Failure or alarm has direct effect on product quality or impacts a CPP/WPP ?	☐	✔	☐
8	Does the item directly or indirectly control/monitor prescribed environmental conditions of products ?	☐	☐	✔

DIRECT IMPACT	**If the answer to any <u>one</u> of the above is Yes then the item is Direct Impact.**
INDIRECT IMPACT	If the answer to any <u>one</u> of the above is Yes but relates to a component only then the item is **Indirect Impact.**
NO IMPACT	If the answer to all of the above is **No** then the item has no (GxP) impact. This conclusion does not imply that it does not have GEP significance.
Complexity Assessment	
COMPLEX	**Complex** equates to novel or multi-module equipment where there is a need for integrated components to work synchronously e.g. a freeze dryer or filling machine.
NOVEL	A **Novel** item is one that is custom built for the process step – it may be either complex or simple, but is generally classified as complex.
SIMPLE	**Simple** equates to equipment that has only one module or unit e.g. a filter press, a mixing tank or an incubation room. These items are often purchased "off the shelf" are stand alone and not integrated

Risk and Impact Assessment in Equipment Qualification

Criticality of System	Complexity of System	URS/ FAT / SAT Required	IQ/OQ Required	PQ Required
Direct Impact	**Simple**	URS Only	IQ and OQ required (or combined IQ/OQ)	Yes
	Complex or Novel	Yes	IQ and OQ required	Yes
Indirect Impact	**Simple**	No	Commissioning plus Calibration	No
	Complex	Maybe	Commission + IOQ for critical components	No
No Impact	**Simple**	No	Commission Only	No
	Complex	No	Commission Only	No

EXAMPLE ONLY

Impact Assessment Example

Unit Op #	Process Line	Equipment Description	Equip Impact	Complexity	Risk Class	Controller
EC	Capsule 1	Capsule filling machine	Direct	Complex	High	Yes / HMI
EC	Capsule 1	Capsule Polisher/ metal detector	Indirect	Simple	Medium	Yes/HMI
Compress Air	Instrument air	Air compressor	Indirect	Simple	Low	No
DRY	Dryer	Rotary vacuum drier	Direct	Simple	Medium	No
DRY	Dryer	Mill cum sifter (Sieve)	Direct	Simple	Medium	No
TAB	Micronization equipment	Micronization equipment line	Direct	Simple	Medium	Yes/HMI

Flash Quiz
Impact Assessment Example

Process Line	Equipment Description	Equip Impact	Complexity	Risk Class	Qualification Activity ?
EMS	EMS	Direct	Simple / HMI		combined IQ/OQ + PQ
General	Movable lifter	No Impact	Simple		Commission
Film coating	Film Coat Machine	Direct	Simple		combined IQ/OQ + PQ
Fluid bed dryer	Mill & Sieve	Direct	Simple		combined IQ/OQ
Fluid Bed Dryer	Fluid bed dryer	Direct	Complex		URS/DQ/FAT/SAT IQ + OQ + PQ
Powder Mill (Coarse)	Powder mill machine	Direct	Simple		combined IQ/OQ + PQ
Plant Steam	Boiler	No Impact	Simple		Commission

FDA Process Validation Guidance
Three Stages of Validation Described

Stage 1 Process Design

- 1.a. Building and capturing process knowledge and understanding
- 1.b. Establishing a Strategy for Process Control **(the Control Plan)**

Stage 2 Process Qualification

- 2.a. Design of a Facility and Qualification of Utilities and Equipment
- 2.b. Performance Qualification Approach
- 2.c. Performance Qualification Protocol
- 2.d. Protocol Execution and Report

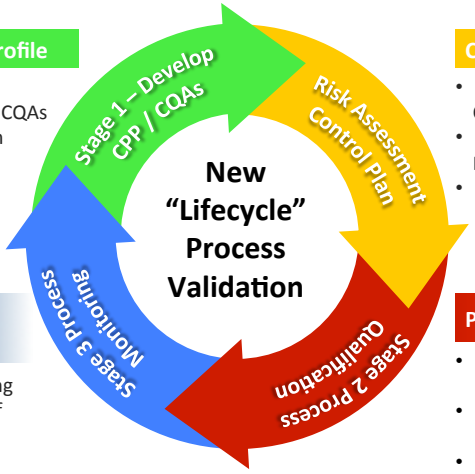
Stage 3 Process Verification

- Continually assure that the process remains in a state of control (the validated state) during commercial manufacture
- **Product Quality Review**

Lifecycle Approach to Validation

Develop CPP/CQA Profile

- R&D – ICH Q8
- Define likely CPPs and CQAs
- Develop a Control Plan



Control Plan

- Risk Assessment on CPPs and CQAs
- Finalise the Control Plan
- Finalise batch record

Continued Process Verification (CPV)

- Post Stage 2 monitoring
- Ongoing monitoring of some CPPs / CQAs
- PQRs

Process Qualification

- Equipment/Utility/Facility Qualification
- Process Performance Qualification
- Transfer to Operations

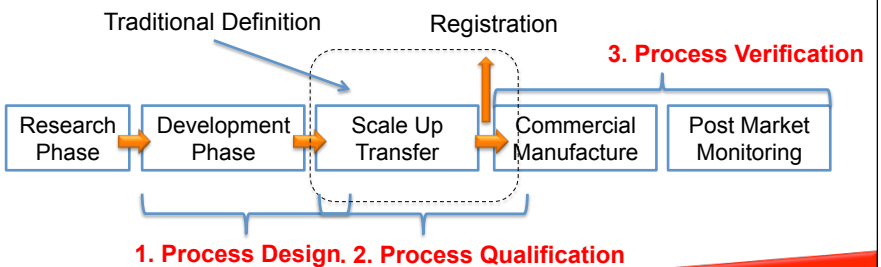
Three Times Proves It ?

- FDA/EMA do not specify the number of batches needed for PPQ. The manufacturer must justify.
- EMA recognises that 3 batches as a minimum may be a practical decision.
- The manufacturer needs to assess, justify and clearly state those requirements during the preparation of the PPQ protocol

FDA Process Validation Guidance Approach

The collection and **evaluation** of data, from the **process design stage throughout production**, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Process validation involves a series of activities taking place over the **lifecycle of the product and process**.



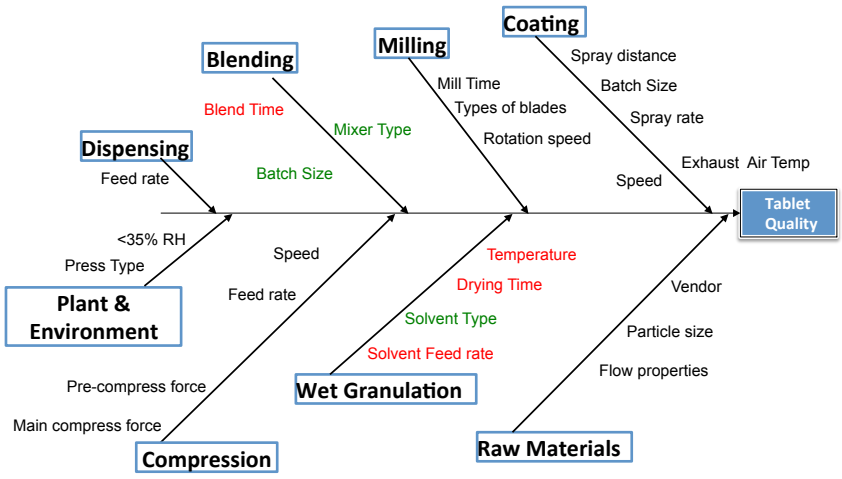
Stage #1 Process Understanding

- Evaluate the "contribution of factors" **to process variability**
  - Process settings, component Lots, operators, equipment…
  - Compare inputs and outputs at unit operations
- Variability can occur within unit operations or across unit operations;
- Particular combinations of conditions may pose higher risks of process failure. **Use risk assessment**.
- Justify the settings of process parameters (CPPs) that may impact the outcome of the process step;
- Understanding of process variability can originate from:
  - Use DoE, screening experiments and assess interactions
  - Prior knowledge of the process or equivalent processes
  - Statistical analysis of historical process

Defining Critical Process Parameters (CPPs)

- Determined by sound scientific judgment and based on prior knowledge, R&D experiments, scale-up or manufacturing experience
- Usually physical parameters (**time, temperature, speed, load** etc.) most likely to affect the CQAs of a product or intermediate
- CPPs are validated, then controlled and monitored;
- Example quality attributes derived from CPPs include:
  - Biochemical purity
  - Chemical purity / degradation profiles
  - Qualitative and quantitative impurities
  - Physical characteristics
  - Microbial quality

Defining Unit Operation and CPPs Example C&E Diagram



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47

Process Map Summary

Inputs Critical Process Parameters (Factors)	Process Step	Outputs - Critical Quality Attributes (Variables)
▸ Raw Materials Grade ▸ Sieve Diameter ▸ Crystal dispersion	**Dispensing / Sieving**	▸ Particle size distribution ▸ Bulk Density
▸ Blend speed ▸ Feed rate ▸ Volume fluid	**Granulation**	▸ LOD ▸ Granule uniformity
▸ Air Temperature ▸ Product temperature	**Fluidized Bed Dryer**	▸ Particle size ▸ LOD
▸ Blender Dimension ▸ Speed, load, time	**Blending**	▸ Blend uniformity ▸ Flow properties
▸ Press speed ▸ Compression force	**Tabletting**	▸ Weight control ▸ Disintegration/ Hardness etc.
▸ Exhaust Air Humidity ▸ Spray rate	**Coating**	▸ Dissolution rate ▸ Thickness
▸ Line speed ▸ Printed matter	**Packaging**	▸ Seal integrity ▸ Identity

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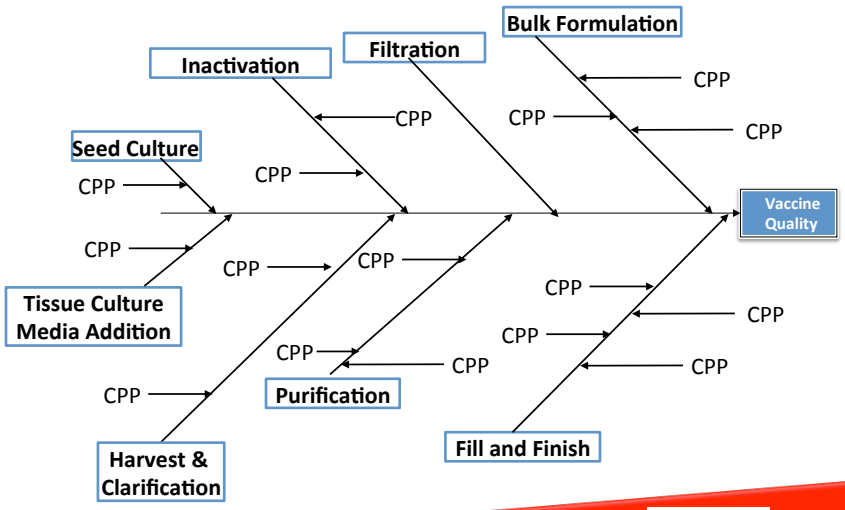
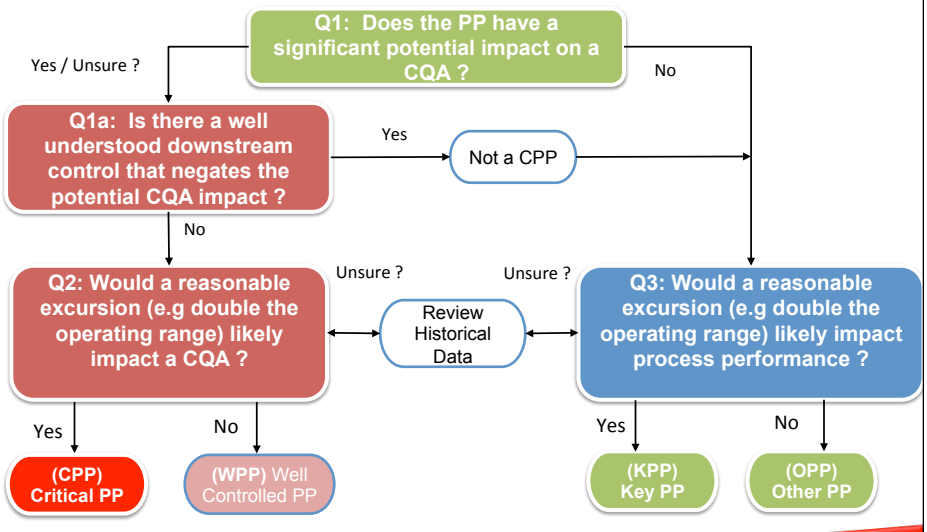
48

Defining Unit Operation and CPPs Biological



SWA – 040 Ver DCVMN 49

Assessing Unit Operation Process Parameter Criticality Using a Decision Tree



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End Stage 1 Document a "Control Plan" Example Process Step: Ultra - Centrifugation

Step #	Sub-process	Material Attributes of Input Materials	Process Control (PCP) Factor	PCP Class	CQA	CQA Class	Spec Ref.	Trending / Monitoring	Procedure Control	Process Validation
6	**Zonal Ultracentrifugation / Zonal Pool**									
6.3	**Product Processing in Centrifuge**		Zonal Flow rate 300-350 mL/min	C	RI (1.12 -1.25)	IPQC		Yes	**SOP - xxx** *Operation of Continuous Flow Ultracentrifuges* **MBR- xxx** *Zonal Centrifugation*	PVP – xxxx PV R - xxxx
			Volume processed per centrifuge ≤ 148L	C	Fraction pH (6.8 – 7.2)	C	QC 013	Yes		
			Top product temperature 5 - 27°C	K	Protein Content 1.0 – 2.5mg/mL	C	QC 104	Yes		
			Bottom product (waste) temperature 0 - 27°C	O	Fraction Purity < 0.5% impurity	C	QC 105			
			Rapid Acceleration at 3,000 rpm, then set to 39.5 - 40.5K rpm	C						
			Maximum run time 10 hours from gradient loading	K						
6.4	**Fraction Collection**		15 x ~100mL Fractions collected (taken first) 1 x ~1500mL (waste)	O					**MBR- xxx** *Fraction Collection* **SOP- xxx** *Fraction Collection*	PVP – xxxX PV R - xxxx
			Flow rate controlled during fraction collection at 150mL /min	C						

Stage # 2 - Process Qualification (Previously Traditional PV)

- In this stage the process design is confirmed as being capable of **reproducible**** commercial manufacture
- The cumulative data from all relevant studies should be used to establish PQ related manufacturing conditions
  - Understanding of the impact of CPPs and what the CQAs are
- PQ stage will have higher levels of sampling, additional testing etc. This approach should continue into Stage #3
- Must successfully complete before commercial release
- Acceptable product may be sold provided it is manufactured under cGMPs

** Replaces the old 3 batches proves it rule.

Legacy Products
The 2011 FDA guidance states:

- *"Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes.*
- *Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3."*

Process Validation Protocols

- **Validation Protocol** - A written plan that specified how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify **critical steps** and acceptance criteria.

PIC/S Code of GMP - Annex 15

- A **protocol** should be the end result of scientific input from Engineering, Production and Quality Control.

FDA Process Validation Guide 1987

Content of Process Validation Protocols

- Short description of process e.g. flowchart Master Batch record
- Responsibilities for execution and review
- Summary of the critical processing steps (Unit Operations) to be validated
- Details of the equipment/facilities and their calibration status
- Parameters to be monitored (the CPPs)
- CQAs to be tested (with sampling plans)
- Reference to the specific test methods
- Proposed in-process controls and acceptance criteria
- Method for recording and evaluating results including statistical analysis, where applicable
- Proposed timetable for the replicate batches

CPP/ CQA Process Map Example

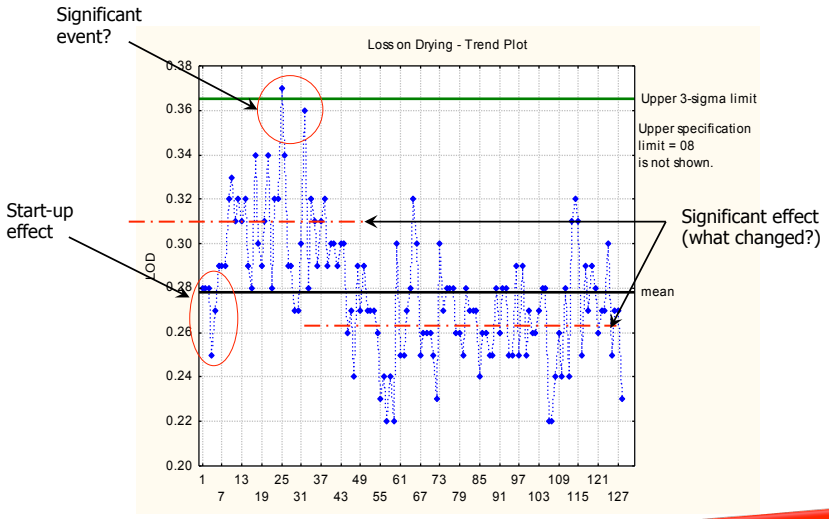
Process Step	Process Parameters (CPPs bolded)	Parameter Range	CQA	CQA Range
4. Final Bulk Mixing				
WPP	Temperature °C	<40oC	Uniformity (T/M/B)	<3.0%rsd
WPP	Stir Time (min)	10 - 15min	S.G @20oC (TMB)	All within limits
	Stir Rate (rpm)	50 - 60rpm	Appearance	All within limits
WPP	Mixing Volume (Tank	500 - 2000L	Bioburden	<10cfu/10mL
5. Wash and Dry Bottles				
WPP	Wash Speed (bottles/min	70 – 120 bottles / min	Bottles clean / dry	AQL < 1.0%
	Tunnel Pre-Heat Zone Temp	60 - 120 °C		
CPP	Tunnel Heat Zone Temp °C	100 - 150°C	Particle free	AQL < 1.0%
	Tunnel Cooling Zone Temp	30 - 40 °C		
WPP	Tunnel belt speed	Fixed speed	No defects, chips, cracks etc.	AQL < 0.5%
6. Hold Bulk Mix (Worst Case Condition)				
WPP	Hold time	Max 24 hours	Bioburden @24 hr	<10cfu/10mL
CPP	Re-stir Time	**As per step 4**	Uniformity (T/M/B)	<3.0%rsd
			S.G @20oC (TMB)	All within limits
			Appearance	All within limits

EU - Annex 15 Validation

- 4. 7 Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified. e.g. for a continuous manufacturing process.

- Note: FDA may allow reduced scale for process validation. (Check with National Regulator)
  - 1st batch >10% of the full scale – send to stability
  - 2nd batch 50% - 100% of full scale – send to stability
  - 3rd batch 100% of full scale - send to stability + sell

Look out for non-normal data



What is an Appropriate Sample ?

Consider

- Location & Frequency
- Sample size (n)
- Sampling Method
- Whether Attribute or Variable data
- Who is sampling ?

For Attributes Sampling

n = log (1- c) / log (1 - p)

n = sample size
c = confidence level (90,**95**,99%)
p = tolerable defect level (AQL%)

Process Unit Operation	Failure Mode(s)	Numerical Ranking			RPN	Risk (Reliability) (1- p)
		Frequency	Detection	Severity		
	CQA Defect	1	5	5	25	High 0.1 – 1.0%
		2	3	3	18	Medium (1.0 -2.5%)
		1	3	2	6	Low 2.5% - 4%

Stage # 3 – Continued Process Verification (CPV) Program

Continued process verification is the ongoing monitoring of the validated state of a process, usually through tools such as:

- Statistical analysis of batch data (CPPs and CQAs)
- Deviations;
- Confirmed OOS;
- Customer complaint profiles;
- Yields

- It is a cumulative process across multiple batches, which can extend into the PQR.

Ongoing Process Monitoring

- An ongoing program to collect and analyze product and process data that relate to product quality is established.
- The data collected should include:
  - relevant process parameter trends (CPPs)
  - quality of incoming materials or components (CQAs)
  - quality of in-process material, and finished products. (CQAs)
- The data should be statistically trended and reviewed by trained personnel.
- The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

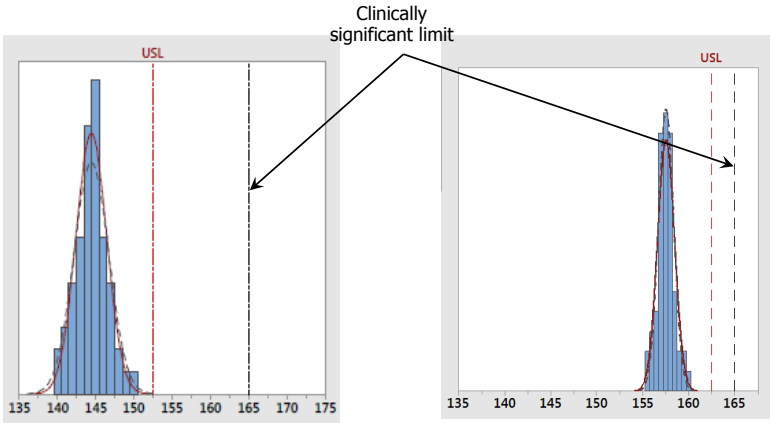
Process Capability (Cp) in CPV

- Process Capability (Cp, Cpk) = how process **could** perform in the absence of special cause;
- Process Performance (Pp, Ppk) = how process **has** performed. Does not require statistical control;
- Use Cpk for inferences, Ppk to describe outcomes;

Caution:

- Are specifications based on performance or clinical criteria?
- **Cpk is not a failure acceptance criteria – a Cpk > 1 with limited data provides a good level of confidence.**
- Confidence in Cpk is very sample size dependent

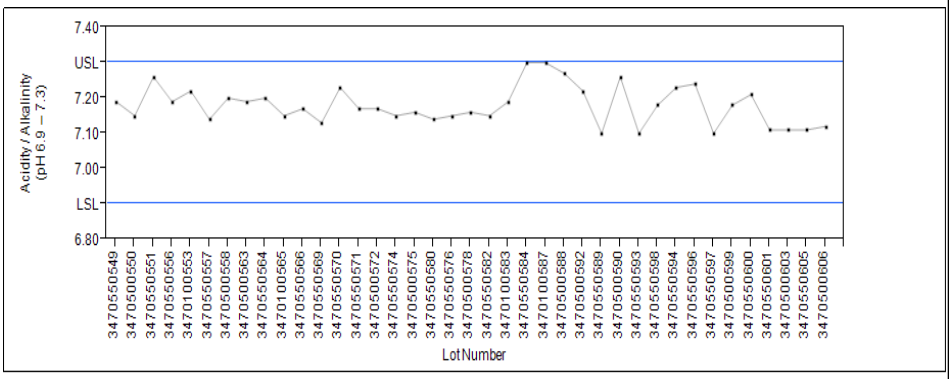
Process Capability in CPV



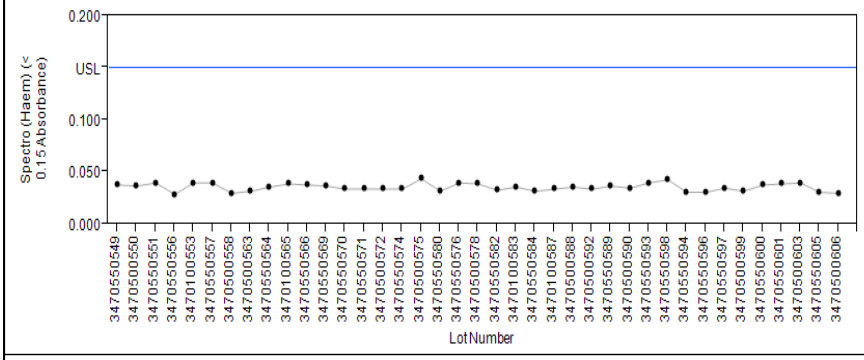
Cp = 1.18
Upper Specification = 152.5mg
Clinical specification = 165mg

Cp = 2.00
Upper Specification = 162.5mg
Clinical specification = 165mg

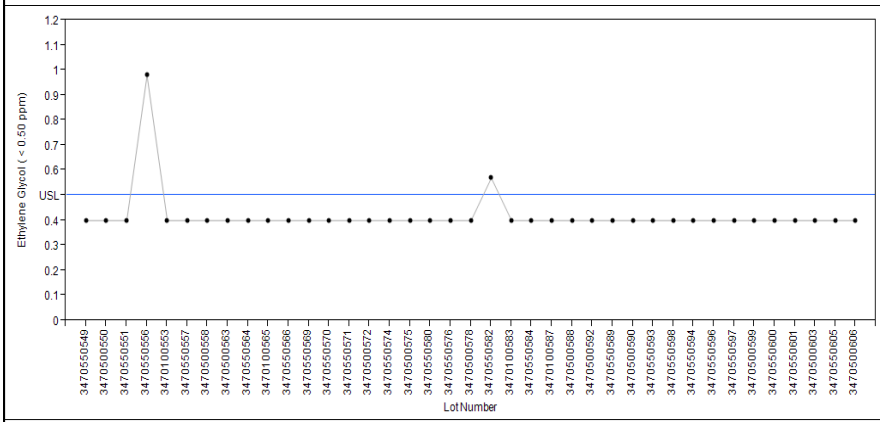
PH of Bulk Solution
Limits: 6.9 – 7.3 Target = 7.1



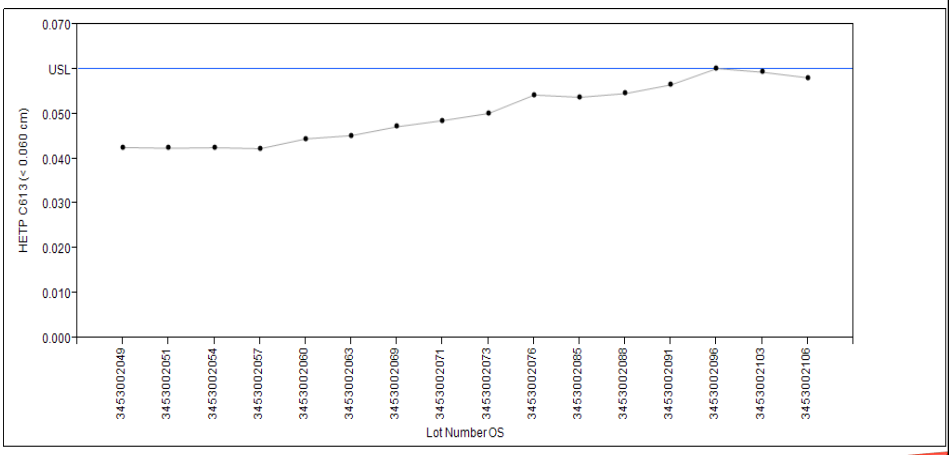
Absorbance Finished Product Limit: <0.15 Abs@403nm



Ethylene Glycol Residue Limit < 0.5ppm



Absorbance Active Bulk Limit <0.06

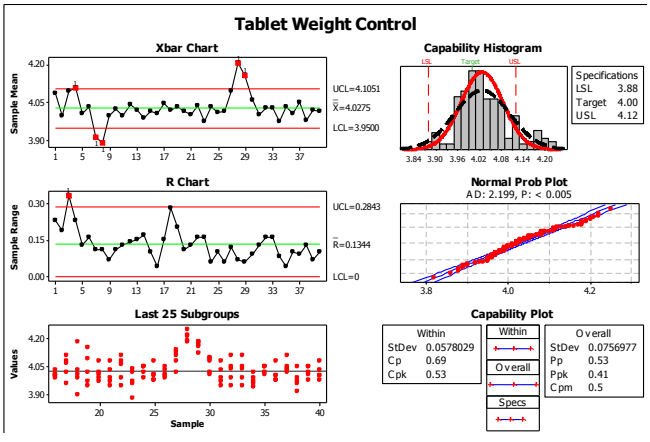


Continued Process Verification
SPC Analysis - Weight Control

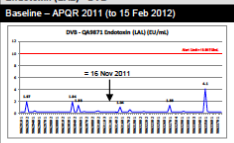
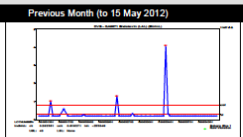
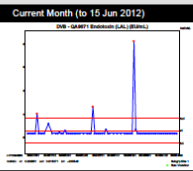
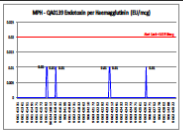
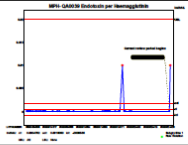
Target = 4.0g (3.88 - 4.12g)
n = 5

Data normal process is unstable.

Process not centered
Cpk = 0.53



TRF Meeting #9 - 12 July 2012 Review Period: 16 November 2011 to 15 June 2012

Table 1	Purity (PU)					
PU_04_02	Endotoxin (LAL) - DVB					
Green Flag	Baseline – APQR 2011 (to 15 Feb 2012)		Previous Month (to 15 May 2012)		Current Month (to 15 Jun 2012)	TRF Actions/Outcomes
						
	# Data Points	Statistically In-control	# Data Points	Statistically In-control	# Data Points	Statistically In-control
	n = 102	Not relevant	n = 72	Not relevant	n = 72	Not relevant
	No points outside the specification limits. Complies with the DVB endotoxin (LAL) alert requirement of ≤ 10.00 EU/mL and specification requirement of ≤ 45.00 EU/mL. Data is not normally distributed and not amenable to SPC analysis. No action warranted on identified batches. The data was assessed across NH 2011, SH 2011 and NH 2012 (current). No between or within season trends were identified.		No new test results since last review period. Trend and commentary noted.		No new test results since last review period.	
PU_05	Endotoxin per Haemagglutinin					
PU_05_01	MPH					
Amber Flag	Baseline – APQR 2011 (to 15 Feb 2012)		Previous Month (to 15 May 2012)		Current Month (to 15 Jun 2012)	TRF Actions/Outcomes
			Not trended			
	# Data Points	Statistically In-control	# Data Points	Statistically In-control	# Data Points	Statistically In-control
	n = 202	Not relevant	N/A	N/A	n = 42	Not relevant
	No points outside the specification limits. Complies with the MPH endotoxin per haemagglutinin alert requirement of > 0.02 EU/mcg		No results since 15 Feb 2012 Trend and commentary noted.		No points outside the specification limits. Complies with the MPH endotoxin per haemagglutinin alert requirement of > 0.02 EU/mcg	

Edition: 1.00 Page 13 of 62

69

Technical Review Forums (Vaccine Quality Review Meetings)

- TRF provides expert oversight on trends and events relevant to manufacturing control and any emerging trends;
- Attendees: experts from Production, R&D, QA and QC + others.
- Agenda:
  - Assess any significant events or issues
  - Review critical process parameters (CPPs)
  - Review critical quality attributes (CQAs)
  - Put in train any corrective actions needed at either a process or batch level based on assessment
  - Provide auditable evidence of this oversight

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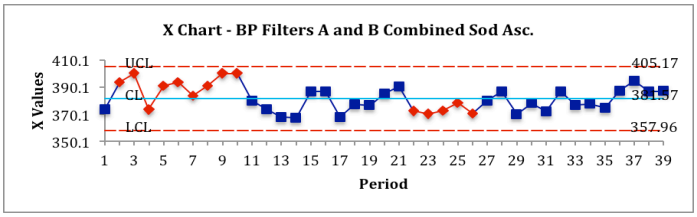
70

(Annual) Product Quality Review (PQR) and Verification



- Annual PQR is opportunity to summarise the process control status per product group or product.
- **Only trend some variables CPPs**
- **Trend or summarise CQAs**
- Verify process direct impact equipment remains in a "validated state"

Examples of Biological Unit Operations and their Validation based on CPPs and CQAs

Example
Validation of Viral Vaccine Inactivation

When is inactivation done?

- Inactivation is initiated as soon as possible after harvesting of cells. (EP)
- Immediately after clarification or purification
- Must be done for each virus strain and any change of strain

Substances are used as inactivating agents?

- if formaldehyde solution is used, the concentration does not exceed 0.2 g/l of CH_2O at any time during inactivation;
- if beta-Propiolactone (BPL) is used, the concentration does not exceed 0.1% V/V at any time during inactivation

Inactivation conditions:

- Mixing rate and duration, inactivation temperature and storage conditions.

Example
Validation of Viral Vaccine Inactivation

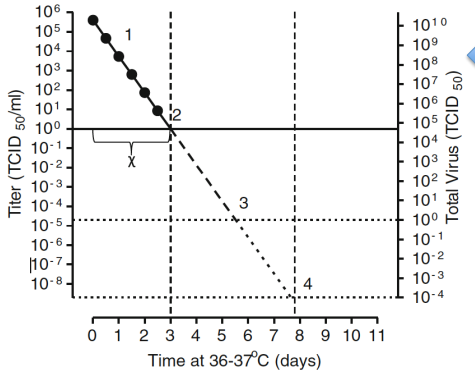
Replication

- Three times at full batch scale
- Repeat when there is any change to the unit operation

Acceptance Criteria and Safety Margin

- The inactivation process shall have been shown to be capable of inactivating the virus without destroying its antigenicity.
- no residual infectious virus
- ALV (attenuated living virus) and mycoplasmas are inactivated
- Antigens are present and active
- Bioburden is inactivated and product is sterile
- Duration of inactivation must be > 1.5 times the endpoint time. **(Refer to specific pharmacopeias and regulatory guidance for requirements)**

Example Viral Inactivation - Rabies



Must be able to draw a death rate kinetics curve.

Must validate the recovery of the virus in the presence of the inactivating agent – requires neutralisation method development and positive controls in the tests

The rate of destruction of infectivity in the bulk is followed by determining, for example, viral titers (Tissue Culture Infectious Dose 50 %, TCID50) (1). A straight line is drawn through these experimentally attained data points and extrapolated to the point indicating complete absence of infectivity at the intercept of x-axis. Followed by taking into account the total volume (i.e., 50 L) to be inactivated (3) and a safety margin to allow for imperfections in the sensitivity of the tissue culture system used for detection of residual replication competent virus the total inactivation time is defined as a total period equal to three times the interval required for interception of the baseline (χ) which would, in this example, correspond to an incubation time of 9 days: source - www.springer.com/cda/content/document/cda.../9783662450239-c2.pdf?SGWID...

Tangential Flow Filtration (TFF)

TFF has multiple uses including:

- Harvesting or removing cells
- Elimination of viruses
- Protein concentration and buffer exchange

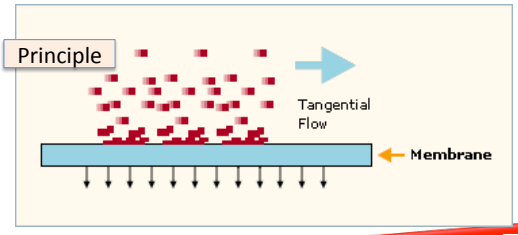
TFF – Example CQAs

- Yield
- Quality – protein functionality
- Purity – process residues
- Bioburden/endotoxin

	Microfiltration	Virus Filtration	High-Performance Filtration	Ultrafiltration TFF	Nanofiltration/ Reverse Osmosis
Components retained by membrane	Intact cells Cell debris	Viruses	Proteins	Proteins	Antibiotics Sugars Salts
membrane membrane membrane membrane membrane membrane membrane membrane membrane membrane membrane membrane membrane membrane					
Components passed through membrane	Colloidal material Viruses Proteins Salts	Proteins Salts	Proteins Salts	Small Peptides Salts	(Salts) Water
Approximate membrane cutoff range	0.05 µm – 1 µm	100 kD – 0.05 µm	10 kD – 300 kD	1 kD – 1000 kD	<1 kD

TFF systems all operate on the same principle

- The fluid (feed) stream runs tangential to the membrane, establishing a pressure differential across the membrane.
- This causes some of the particles to pass through the membrane. Remaining particles continue to flow across the membrane, "cleaning it".
- The use of a tangential flow will prevent thicker particles from building up a "filter cake".



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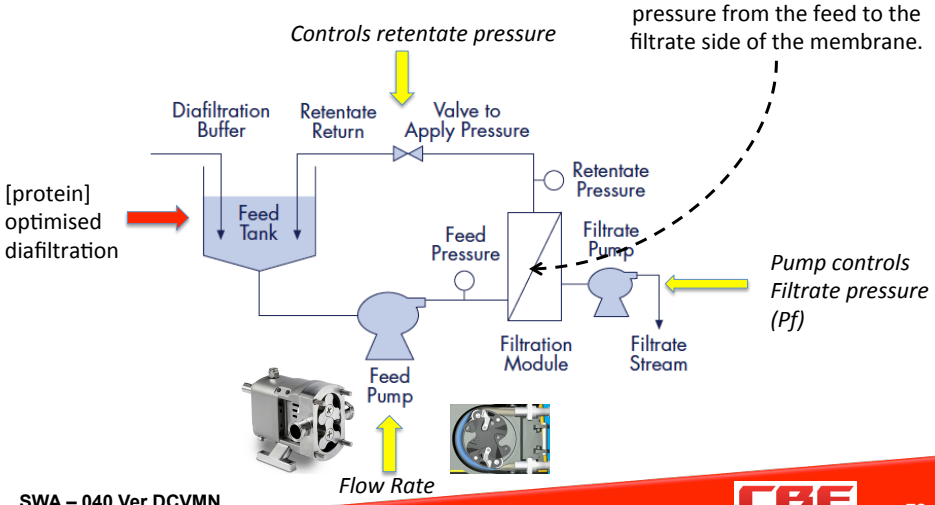
Key Parameters to Control/ Optimise TFF

Transmembrane Pressure (TMP) is the average applied pressure from the feed to the filtrate side of the membrane.



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78

WHO GMPs for Biologicals Section 15 Validation

- A QRM approach should be used to determine the scope and extent of validation.
- All critical biological processes (e.g. inoculation, multiplication, fermentation, cell disruption, inactivation, purification, virus removal, removal of toxic and harmful additives, filtration, formulation, aseptic filling, etc.), as applicable, are subject to process validation.
- Manufacturing control parameters to be validated may include specific addition sequences, mixing speeds, time and temperature controls, limits of light exposure, and containment.

WHO GMPs for Biologicals Section 15 Validation

- After initial process validation studies have been finalized and routine production has begun, critical processes should be subject to monitoring and trending with the objective of assuring consistency and detecting any unexpected variability.
- The monitoring strategy should be defined.
- Critical processes for inactivation or elimination of potentially harmful microorganisms ……. are subject to validation.
- The integrity and specified hold times of containers used to store intermediate products should be validated.

WHO GMPs for Biologicals Section 15 Re - Validation

- Process revalidation may be triggered by a process change, as part of the change control system. In addition, because of the variability of processes, products and methods, process revalidation may be conducted at predetermined regular intervals according to risk considerations.
- A detailed review of all changes, trends and deviations occurring within a defined time period (e.g. 1 year, based on the regular Product Quality Review) may require process revalidation.

Aseptic Processing Important References

- **FDA Guideline on Sterile Drug Products Produced by Aseptic Processing Sept 2004**
- PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 1 Manufacture of Sterile Medicinal Products
- PIC/S Recommendation on the Validation of Aseptic Processes January 2011
- PDA - Points to Consider for Aseptic Processing
- ISO 13408-1:2008 Aseptic processing of health care products – Part 1: General requirements (parts 2-8 also deal with aseptic processing)
- PDA Technical Report No. 28 Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals

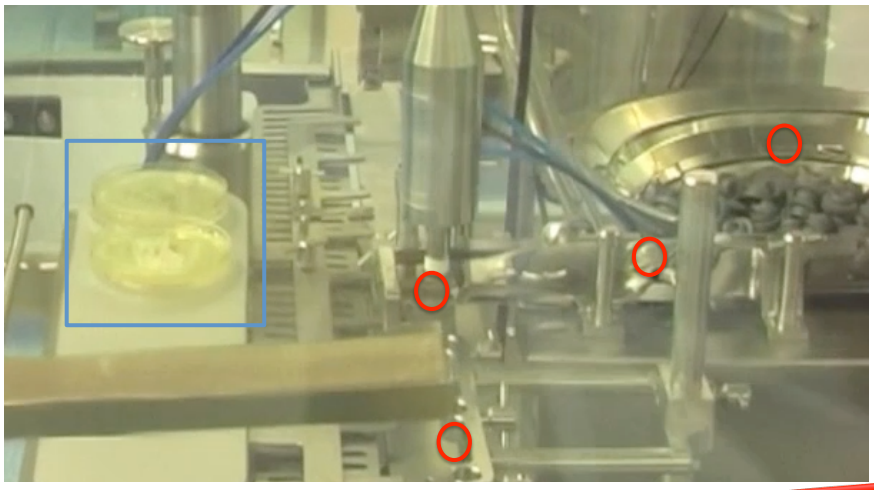
Sterility Assurance

- Sterility Test is limited – does not provide sufficient sterility assurance – PNSU < 14% (95% confidence)
- Media Fills are far more relevant PNSU < 0.1%(99% confidence)
- Only as good as critical parts & control of bio-burden:
  - Aseptic operators technique
  - Sterilization Systems
  - HVAC systems
  - Product filtration programs
  - Cleanroom / Facility / Pressure etc.
  - Cleaning and sanitation program
  - Movement of materials into Grade Band Grade A

Some Basic GMP Rules – cGMP Annex 1

- Low to no reliance on the sterility test
- Only sterilized or sanitized items in Grade B, then A
- Aseptic technique is critical - must be challenged
- Aseptic operators must be qualified, re-qualified or dis-qualified
- EM programs must include set up as well as operation
- **Intervention = Risk.** Keep people remote from product
- Cannot be any air entrainment from B to A space
- Intensive monitoring program
- All incidents/events must be reviewed

Critical Space and Critical Surfaces



Personnel: Aseptic Personnel Qualification Program

- Demonstrate an understanding of applicable Standard Operating Procedures (SOPs)
- Demonstrate an understanding of Basic Microbiology
- Demonstrate an understanding of Aseptic Practice Theory and Cleanroom behavior
- Demonstrate gowning proficiency by actually completing three consecutively successful gownings.
- Successfully complete a "Media Transfer Evaluation" within a Grade A hood in a laboratory environment demonstrating successful aseptic technique simulating interventions.
- Successfully participate in a process simulation (media fills) annually – covering interventions

Elements of Aseptic Process Validation
(FDA Guidance – 2004)

- Media Fill Conditions / worst case situation / What are the risk factors ?
- Frequency and Number of Runs
- Duration of Run
- Size of Run
- Line Speed
- Environmental Conditions
- Media
- Incubation and Examination of Media-Filled Units
- Interpretation of Results

Risk Rating Interventions - Considerations

Risk Rating	Intervention Activity	Potential Contamination Risk	Frequency of inclusion in Media Fill	Glove monitoring required post any intervention
5	Critical surface	Very High	Every fill	Yes
4	Proximal to an open container	High	Every fill	Yes
3	Remote to open container	Medium	Once per year	No
2	Outside Inner Grade A area	Low	Once per year	No
1	Grade B Area Activity	Very Low	Once per two years	No

Media Fill Validation

- Evaluates the entire process
- Must occur every 6 months per process line per shift
- Must include all aseptic operators over time eg. annually
- Must include “ancillary” staff who have to enter the room
- Must be “worst case” challenge to the process:
  - Routine and non-routine interventions by each operator
  - Different container – closure combinations
  - Maximum # personnel in the room
  - Changeovers and sterile hold times for equipment
  - 100% inspection process
- Run size: 5000 or maximum # processed on lien for the container closure combination. Pass = NIL positives

Maintaining the “Validated State”

- Three important systems:
  - Change Control and Re-validation
  - Routine Re-validation (based on risk)
  - Periodic (Annual) Product Reviews

Change Control

A formal system by which qualified representatives of appropriate disciplines** review proposed or actual changes that might affect the ***validated status*** of facilities, systems, equipment or processes.

The intent is to determine the need for action that would ensure and document that the system is maintained in a ***validated state***.

PIC/S Code of GMP– Annex 15 Glossary

** Includes Quality Assurance representative

Change Control and Revalidation

- GMPs requires proposed changes to processes to be assessed for potential GMP impact
- Change system should include an impact assessment
- **"Like for like"** changes do not require validation UNLESS they have the potential to impact GMP or change the state of validation (IQ, OQ, calibration or PQ).
- Must have a rational for justifying "like for like"

Process Re-validation may be required under the following circumstances:

- Significant change to Master Processing Instructions
- Change in raw material suppliers or components
- Change to Bill of Materials, formulation or batch proportions (Scale Up)
- Significant alteration to processing equipment
- Introduction of new equipment or utilities
- If in-process or quality control results are outside pre-set limits – the process lacks control
- If Product Review (in-process or quality control data) indicates a significant process shift or change in process capability