Risk-Based Validation and Requalification of Processes & Equipment

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Order of Operations

- US Predicate law always comes first
  - US Guidances
    - Other non US regulatory standard accepted by FDA
      - Industry Standards recognized by regulators follow behind
        - » Other standards can be put in place with regulatory permission.

Order of Operations

- US Predicate law always comes first
  - 21 CFR 11, 58, 210, 211, 600, 606, 820, 1270, 1271
  - Covers electronic records and signatures (CSV issues)
  - GLP related validation practices
  - Pharmaceutical GMP related validation
  - Blood and Biological related validation
  - Human tissue related validation
  - US Guidances

Order of Operations

- US Guidances
  - Guidances on Part 11
  - Guidances on Aseptic Processing
  - Guidance on Process Validation

Order of Operations

- Other non US regulatory standard accepted by FDA
  - European Union GMP Annexes
  - World Health Organization GMP and Validation Guidances
  - GHTF Documents (Except for Medical Device Process Validation, FDA Accepts GHTF as their own for device)
  - PIC/s (Pharmaceutical Inspection Co-operation Scheme)

Order of Operations

- Industry Standards Recognized by FDA Regulators
  - ISPE Baseline Guides
  - ISPE GAMP 4 or 5
  - ASTM F838 (Sterilizing filter validation)
  - Some but not all PDA Technical Reports:
    - PDA Technical Report No. 1, Revised 2007 Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control
    - PDA Technical Report No. 44, Quality Risk Management for Aseptic Processes
    - PDA Technical Report No. 3, Validation of Dry Heat Processes Used for Sterilization and Depyrogenation
  - Some but not all AAMI Standards
  - All of ISO 14644

Order of Operations

- Other standards can be put in place with regulatory permission, (pre-approval of the agency)
  - ASTM E2500
  - Non recognized PDA or AAMI Standards

What is Qualification / Verification / Commissioning / Validation?

- Validation
  - Commissioning
  - Qualification
  - Verification

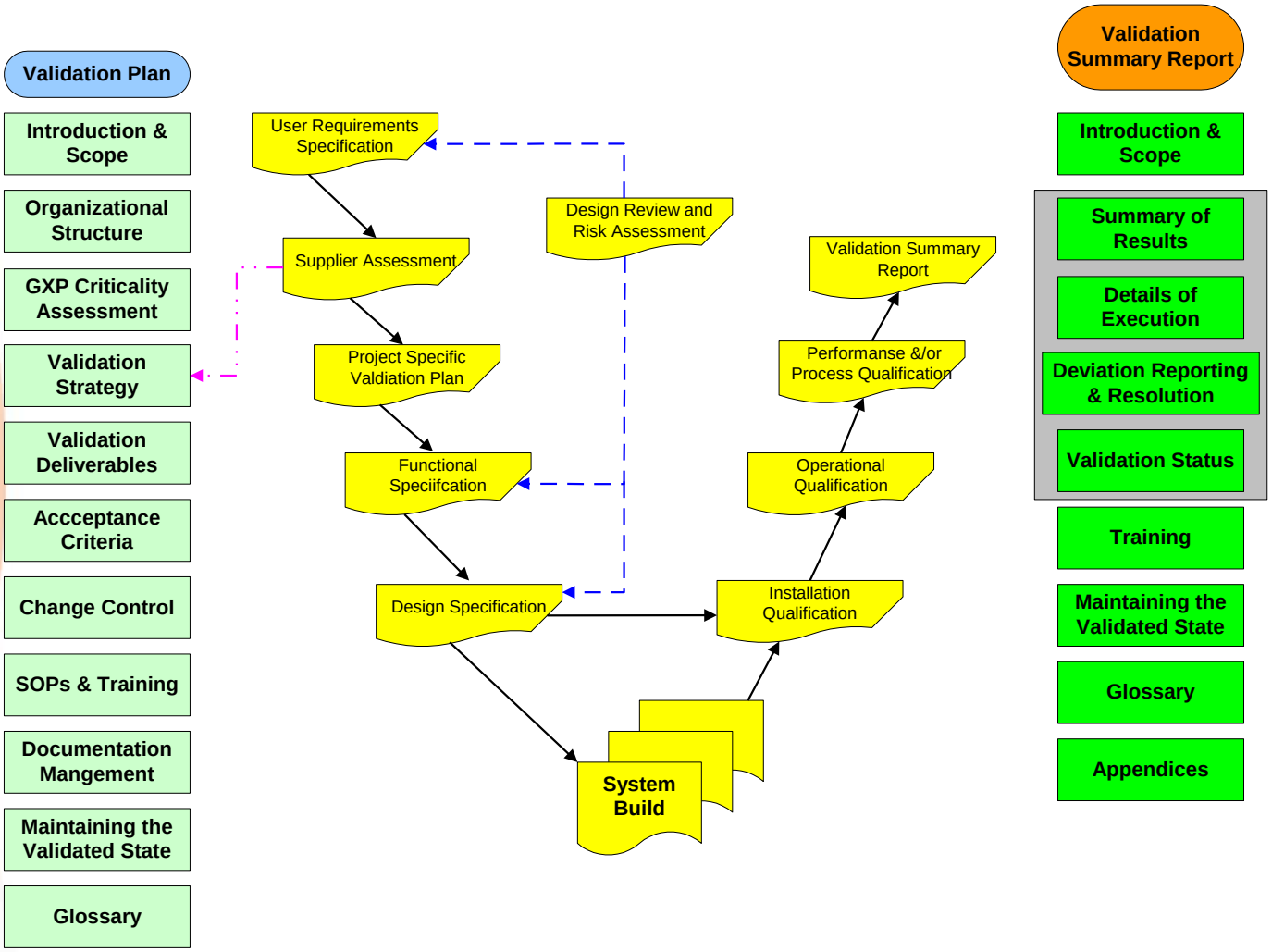
What is Qualification / Verification / Commissioning / Validation?

- Validation
  - A process that provides an appropriate amount of assurance through testing that critical processes in producing a drug substance or drug product can be shown to be operating in the correct sequence and effective over time
- Commissioning
  - A process that will ensure installed equipment or systems perform in conformity with their intended design.

What is Qualification / Verification / Commissioning / Validation?

- Qualification
  - The process of insuring equipment or system are properly installed or properly operating or properly performing a process.
- Verification
  - Evidence that establishes or confirms the accuracy or truth of something at a single point in time.

Validation Lifecycle



Categories of GXP Systems/Processes

- Computerized Systems, non equipment
- Computerized Systems, manufacturing equipment
- Computerized Systems, instruments
- Non computerized equipment
- Non computerized instruments
- Defined processes, batch workflows, cleaning, sterilization &/or sanitization

Categories of GXP Systems/Processes

- Computerized Systems, non equipment
  - IOQ and Performance Verification where indicated
    - GXP Software Applications
- Computerized Systems, manufacturing equipment
  - IOQ and Performance Verification where indicated
    - Covers most manufacturing equipment with automation
- Computerized Systems, instruments
  - IOQ and Performance Verification where indicated of the application controlling the instrument
    - Ex BMS reporting instruments
    - PAT systems

Categories of GXP Systems/Processes

- Non computerized equipment
  - IOQ and Performance Verification where indicated
- Non computerized instruments
  - IOQ
- Defined processes, batch workflows, cleaning, sterilization &/or sanitization
  - Process Validation

How Do I Determine Risk

- What is the process/equipment?
- What functions will I use?
- What functions will I not use?
- Are there any critical parameters the manufacturer requires t be met?
  - Can I use a vendor commissioning document to support this parameters?

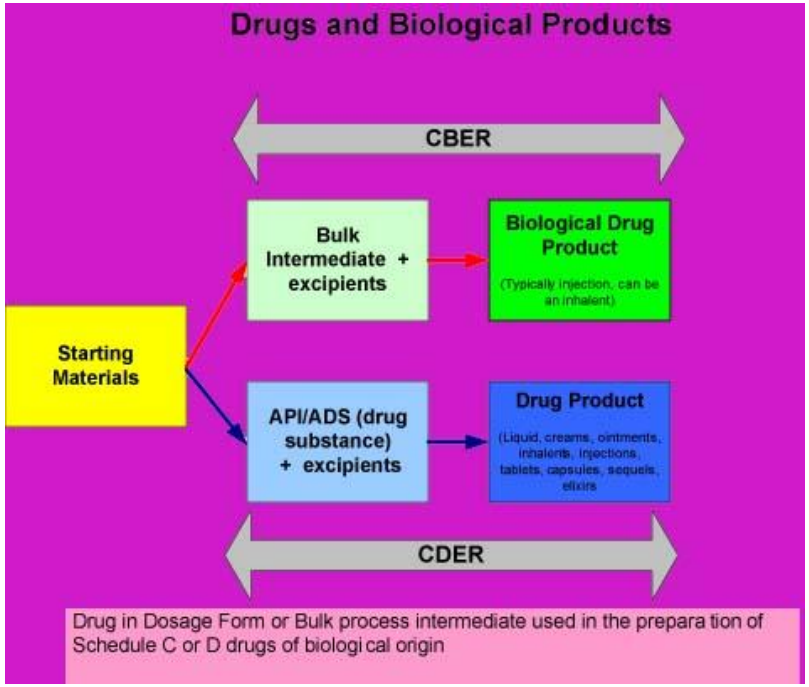
Equipment Qualification Example

- Typical Lab System With Chromatography Software:
  - Establish Validation Process by the Users Requirements
    - Software may have additional functions, but if the user is not intending to apply them to the system why test them?
  - 21CFR Part 11 Controls, most software today is Part 11 complaint
  - Tools on Menus that you will use
    - Save
    - Print
    - Create a method
    - Modify a method
    - Create a report
    - Modify a report
- Don’t test what you don’t plan on using.

Categories of GXP Systems/Processes

Process Validation

- Defined processes, batch workflows, cleaning, sterilization &/or sanitization
  - Process validation



Categories of GXP Systems/Processes

Process Validation

- Process Validation Scale
  - Process Validation is always done at the commercial scale
- Process Types
  - Cleaning
  - Sanitization
  - Fumigation
  - Depyrogenation
  - Sterilization
  - Sterile filling
  - Fermentation
  - Bulk production
  - Purification
  - Filling, capping, sealing
  - Lyophilization

Process Validation Risk Assessment

- What are your CCPs (critical control parameters)
  - You do want to show that you can control your process over it's range of operations.
    - Minimum and maximum ranges
  - Time
  - Temperature
  - Agitation
  - Contact Time
  - Drying Time
  - Clean Hold Time
  - Dirty Hold Time
  - Defined Loads (Patterns)
  - Order of Ingredient Addition
  - Torque
  - Line Speed
  - Temperature Hold Time
  - Cycle points (pH, TOC, Conductivity)
  - Critical Biomass
  - Vacuum Hold

Process Validation Example 1

- The bulk is manufactured in multiple steps by introducing raw ingredients during each step into a clean polypropylene vessel containing a clean stirbar and mixing on a magnaplate stirrer of appropriate size for that volume. Sampling and testing for conformance occurs after each step in which raw ingredients are introduced to the bulk.
- After bulking, and receipt of in-specification bulk testing results, the bulk is filtered using a filter train consisting of the following capsule filters: 1.2 micron Sartorius P/C 5571303P700B, SeraCare P/C 100064; 0.45 micron Sartorius P/C 5571306D700B, SeraCare P/C 100057; and 0.2 micron Sartorius P/C 5571307H700B, SeraCare P/C 100049.
- The filtered bulk is tested for bioburden.
- The filtered bulk is stored refrigerated at 2-8oC until filling occurs.
- Filling occurs semi-automated using a calibrated automatic dispensing systems.
- The bulk is filled into sized containers consisting of 4.0 mL tubes of Polypropylene P/C 100094 and capped with 12.5 mm/Insert FG Blue Polypropylene closures P/C 100331.

Process Validation Example 1

- CPPs
  - Vessel MOC – polypropylene
  - Concentration of Raw Ingredients after bulking
  - Types of filters
  - Post Filtration Bioburden
  - Fill Volume
  - MOC of components, vials and closures for filling.

Process Validation Example 2

- The bulk is manufactured in multiple steps by introducing raw ingredients during each step into a bioreacter at 35C with 10 RPM agitation.
- After all raw materials are added, and the reactor fluid is steadt between pH 6.4 and 6.5; 100mL of an *Escherichia coli* cell suspension between 9.1 and 9.5 OD at 420 nm is added. The agitation is reduced to 5 RPM.
- Agitation continues for 14-22 hours until the Optical Density of the reactor mass is between 72 and 76 OD at 420nm.

Process Validation Example 2

- CPPs
  - Raw Ingredients charge
  - Agitation
  - Temperatures
  - pH
  - Organism spike OD & mL
  - Agitation
  - Time
  - OD of biomass

Change Control

- Evaluation of changes in assigning risk; what really is a like for like change.
  - Same make and model
  - Different manufacturer but same performance
- Maybe a like for like Change but needs evaluation
  - Different raw material and/or component sources
    - Remember Baxter's Heparin!
- Not a like for like change
  - Upgrading from ChemStation/TuboChrome to Millennium or Empower
  - Scaling up batch sizes from the validated batch sizes
  - Changing any CPPs in any process.

Key Players

- Quality Assurance
  - Despite popular rumor, the FDA does expect Quality Assurance to approve and review the validation process. This includes pre-approval review and post approval review. This is a requirement of predicate law.
  - QA should approve all validation derivations as well as all deviations related to execution.
- Manufacturer/Facilities
  - Typically the owner of most validated processes. Should be responsible for the authoring of validation deliverables, technical review of protocols and reports, and authoring protocols deviations.
- Laboratory Management
  - Unless the play the owner role, they are typically involved by testing in process related validations.

Required Quality Documents

- Validation Plan
- User Requirements
- Functional Requirements
- IQ
- OQ
- PQ where required
- Validation Summary Report

Where is validation defined to assess revalidation

- The re-qualification process – Validation Summary Report (VSR)
  - Trigger Assessment of changes
- The VSR should contain references to those documents that supported the validation:
  - *Validation Master Plans*
    - 00006VP, *Validation Plan for ACCURUN Controls*, Initial Release
    - 08-001, *Validation Master Plan for Transfer of ACCURUN Product Manufacture from West Bridgewater to Milford*, MA, Revision 2
    - 08-018, *Validation Master Plan for Qualification of Filters Used in ACCURUN Products*, Initial Release
  - *Stability Protocol*
    - #08-003, *Stability Protocol for ACCURUN Validation Lots Manufactured in Milford*, 01 May 2008

Where is validation defined to assess revalidation

- ***ATBs***
  - ATB-A001-S5100, *ACCURUN 1 Multi-Marker Positive Control*, Series 5100 Revision C, Date Approved: 13 Aug 2008
- ***Manufacturing Procedures***
  - 00572MC, *Aseptic Filtrations of ACCURUN Multi-Marker Bulks and ACCURUN A80X Negative Bulk Control*, Revision F, Date Approved: 05 Jan 2007
  - 00586MC, *OEM Bottling/Labeling,* Revision D, Date Approved: 15 Jan 2008
  - 00170SO, *Thawing Procedure for Blood Products*, Initial Release, Date Approved: 25 Nov 2003
  - 00572MC, *Aseptic Filtrations of ACCURUN Multi-Marker Bulks and ACCURUN A80X Negative Bulk Control*, Revision F, Date Approved: 05 Jan 2007
  - 500011MC, *ACCURUN 1 , Series 5100 Bottling/Labeling 3.5 mL Part Code 500011* revision C
  - 00170SO, *Thawing Procedure for Blood Products*, Initial Release, Date Approved: 25 Nov 2003

Where is validation defined to assess revalidation

- ***SOPs/POPs***
  - SOP 751.01, *Preparation of Formulation Instructions for Manufacturing*, Revision C, Date Approved: 05 Feb 2008
  - POP300379, *Bulk Formulation of Controls*, Revision B, Date Approved: 18 March 2008
  - POP300380, *Bulk Adjustment of Controls*, Revision B, Date Approved: 18 March 2008
- ***Other Procedures and Forms***
  - Form # 751.01-01, *Instructions for Product Formulation*
  - Form # 300379, *Bulk Formulation Sheet*
  - Form # 300380, *Bulk Adjustment Sheet*
- ***Test Specifications***
  - A5100TS, *ACCURUN 1 Multi-Marker Positive Control, Series 5100 Test Specification,* Revision K, Date Approved: 05 Feb 2008

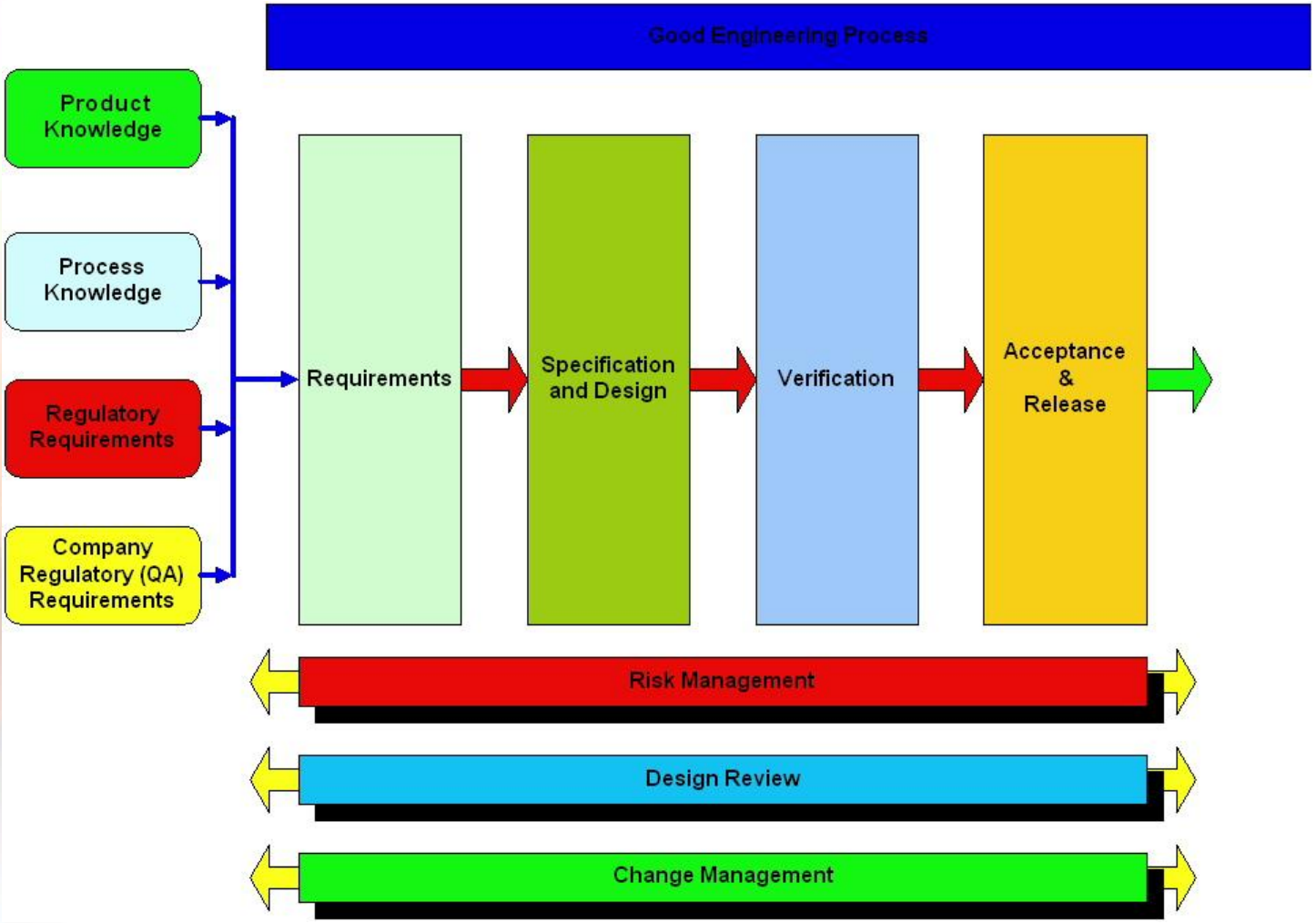
Determining Re-Validation

- Review the VSR Referenced Documents and make sure that changes to those documents are within the validated process.
- Changes outside of the validated process require revalidation

ASTM E2500

- Is not a consensus standard it is a policy statement produced by ASTM that required FDA pre-approval to utilized.

ASTM E2500


Good Engineering Process
Product Knowledge
Process Knowledge
Regulatory Requirements
Company Regulatory (QA) Requirements
Requirements
Specification and Design
Verification
Acceptance & Release
Risk Management
Design Review
Change Management

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