AGENDA

• Introduction Validation & Qualification

• Pre-requisites

• Process Validation (PV)

  • Analytical Methods Validation (AMV)
  • Shipping Validation / Supply Chain

• Re-validation / evaluation
REGULATIONS

• Annex 15 of Eudralex Volume 4
  — New annex in effect since the 1st of October 2015.
  — LIFE CYCLE APPROACH

• EMA Process Validation Guideline Finished Products (27 Feb 2014)

• Guidance to Process Validation (FDA, January 2011)

• WHO TRS 937 (Revision for Appendix 7 in TRS 992)

• ICH - Q 2, 8, 9, 10 & 11
Besides the Eudralex:

- PIC/S
- GAMP5
- ASTM-2500 (uses the term Verification)
- PDA / ISPE
- ...
VALIDATION (INCL. QUALIFICATION)

What is Validation / Qualification

Refer to the descriptions in the guidelines, but in general:

The documented evidence of the verification that a pharmaceutical:

• Process (production, cleaning, shipping,....)
• Machine
• Testing-method
• Procedure
• Etc.

Meets the (pre-determined) including knowledge development.
VALIDATION (INCL. QUALIFICATION)

• Requirements can be found in the guidelines.
• By knowledge development during (product/process) development or project phases.
• Multidisciplinary input is required for an holistic approach
TYPES OF VALIDATION

• Proces validation
  – Aseptic processes
  – Biotech processes

• Cleaning

• Analytical Methods

• Holding Times: store (of semi-finished products, buffers etc.)

• Pharmaceutical Gasses

• Automated Systems

• Shipping

• ……….
TYPES OF QUALIFICATION

• Paradigm:
  – URS
  – FAT/SAT
  – DQ/IQ/OQ/PQ (US-FDA; Qualification of Facilities/PPQ)

• Equipment

• Air treatment

• Utilities

• Vendors

• Personnel
  – For Example: Visual Inspection; Aseptic Production
• TYPES of Validations/Qualifications
• TYPES of PROCESSES/STUDIES
• Protocols
• Risk Assessments
• Test Scripts
• Reports
• Raw Data
• (project) Validation Master Plan
• A VMP should/could contain the following elements:
  – Validation/qualification and re-validation/re-qualification guidelines, including “Risk Assessment”
  – Annual Validation Plan:
    • Plant(s)
    • Utilities
    • Systems
    • Equipment
    • Processes, including cleaning
      – Project Validation Plan
      – Organization and responsibilities
      – Documentation norms for validation
QUALIFICATION
PREPARATION/EXECUTION
• Posessing **knowledge** of what is to be validated/re-validated is a pre-requisite.

• We have to know/control “the case”, and not just the validation procedures by itself. 
   
   *An common pitfall of many validation studies.*

• Knowledge can originate from R&D-work, peers/communities, risk assessments, guidelines, education, SME’s, professional literature, VENDROS,....
EXAMPLE TRAJECTORY

New Autoclave for penetrable loads

Activities:

• Gather a group of SME’s
• Determine loads
• Create a URS
• Vendor Selection
• DQ (Design Qualification)
• FAT / SAT

Factory Acceptance Testing / Site Acceptance Testing
EXAMPLE TRAJECTORY

New Autoclave for penetrable loads

Activities:

• IQ (Installation Qualification)
• OQ (Operational Qualification)
• Cycle / Load Development
• WCL / WCS Determinatie

Worst Case Locations / Worst Case Situations

• PQ (Performance Qualification)
New Autoclave for penetrable loads

**Most Important Characteristics:**

- Only saturated steam creates (at $t=15$ min and $T =121^\circ C \ (249,8 \ ^\circ F)$) a log-reduction of $10^6$ micro-organisms
  
  **SAL (Sterility Assurance Level)**

- Air $>>$ 1 hour at the same temperature (e.g. 120min $160^\circ C \ (320 \ ^\circ F)$)

- Initial-Situation when autoclaving = only air.....

- This Implies: removing the air and replacing it with steam (saturated, “all air” is gone).

- Air and steam cannot be mixed, steam is heavier than air.
POINTS TO CONSIDER

Load/Cycle development
WCL/WCS discussion
POINTS TO CONSIDER

Load/Cycle development
WCL/WCS discussion

Thermocouple (temperature sensor)

Liquid Flow (in process)

Steam Sterilization Cycle
POINTS TO CONSIDER

TC
Load sensor

Autoclave sensor
POINTS TO CONSIDER

- TC Load sensor
- Autoclave sensor
POINTS TO CONSIDER

Autoclave sensor

TC
Load sensor
POINTS TO CONSIDER

TC Load sensor

Autoclave sensor
POINTS TO CONSIDER

TC Load sensor

Autoclave sensor
POINTS TO CONSIDER
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POINTS TO CONSIDER

TEMPERATURE CHARACTERISTICS AS SHOWN: NOT AT SCALE

DRAWING ONLY FOR EDUCATIONAL PURPOSES, NOT MEANT TO BE TRUE / REALISTIC
POINTS TO CONSIDER

• Validation/Qualification should be weigh-In at the start of the project/R&D-phase.

  *It is often stated that validation is a status, and –to a lesser extent- function-testing*

• Information from third-parties (if qualified) may be used during validation/qualification activities

  *Note that the Inspection will examine your qualification, not the qualification of (any) third parties.*
PROCESS VALIDATION (PV)
LIFE-CYCLE AND PROCESS VALIDATION

Stage 1, Process Design

Stage 2, Process Performance Qualification (PPQ)

Stage 3, Continued Process Verification (CPV)

Gaining Knowledge

Documentation

Risk Management

QA Involvement
VALIDATION OF ANALYTICAL METHODS
Analytical Methods Validation (AMV)

- Analytical methods have to be validated unless the used method is mentioned in the related Pharmacopoeia or in any other recognized, common source.

- The suitability of all used testing methods has to be verified one way or the other:
  - Under actual testing circumstances
  - As well as being documented
Methods have to be validated taking into account the ICH Q2 guidelines.

ICH Q2: Validation of Analytical Methods

- Identification tests
- Quantitative tests for impurity values
- Limit testing for impurities
- Quantitative tests for the level of the active component in samples of the product
CHARACTERISTICS (1)

Typical validation characteristics:

• Range – lowest & highest
• Linearity – calibration line
• Accuracy – compared to the standard
• Precision – the same value, **always**
  – Reproducability (circle investigation)
  – Intermediate Precision (different labs, analysts etc.)
  – Repeatability (same sample, one after another)

• Specificity – Am I (accidentally) measuring other ingredients as well?
Typical validation characteristics:

- Detection Limit – observable, not quantifiable
- Limit for quantifiable ability – to what amount can I attribute a number?
- Robustness – pre-validation, what does and what does not matter for the end result (e.g. temperature, oxidation, matrix-effects).
SHIPPING VALIDATION (& HOLDING)
New Guideline (GDP)

• Know the Supply Chain, and Holding Conditions
• Holding Containers: Leachables/Extractables
• Cold Chain
• Counterfeits
RE-VALIDATION / EVALUATION
Evaluate at:

- Environmental Monitoring Data
- System Review (automation!)
- Annual/rolling Product Review
- Change Control with (most probably) no impact
- Continuous Monitoring / Trending (processes, cleaning, shipping,……) , OOT’s
RE-VALIDATION

Laminair Air Flow “cabinets” and HVAC – according Annex I / ISO 14644

• HEPA-Filter integrity
• Flow patterns
• Recovery time
• Debiet
• Particles (in operation and during idling)
RE-VALIDATION

• Sterilisation-processes (e.g. autoclave)
  – Steam quality
  – Vacuum leak test
  – Air filter
  – Loads (not all over again)

• Aseptic Handling
  – Gowning
  – Operator / Team Qualification
  – Media Fill
RE-VALIDATION

• Temperature-Controlled Environments

• After Changes
  — After a big change
  — After many small changes (that accumulate to a big change)

• After deviations / OOS’s

• At alterations of (common) insights
QUESTIONS ?
THANK YOU FOR YOUR ATTENTION