MODULE 7

HVAC AND ASEPTIC PROCESSING
All products and their supporting processes and utilities must be supported by appropriate complete validation.
A good way to start QbD for a new project for an Aseptic process is to start from scratch .......

The recipe is as follows ..... 

1) Make a group of subject matter experts.
2) List the keywords of your process.
3) For each keyword, implement :
   1) Enablers.
   2) Parameters.
   3) Attributes.
4) Make an assessment : « Direct impact VS Non direct impact »
5) Make a risk assessment.
6) Write a Validation Master Plan
Critical Parameters Process

- Action limits
- Air changes
- Alert limits
- As built
- Aseptic filling
- Aseptic process
- Air flow
- At rest

- Bio burden
- Cleanroom
- Clean zone
- Contact
- Contaminant
- Critical processing
- Dosage
- Efficiency
Critical Parameters Process

- Filter
- Gowning
- HEPA
- Isolator
- In operation
- Particle.
- Pre filter
- Core process
- RABs

- Risk based approach
- Room Monitoring system
- Sterile drug substance
- Supplier
- ULPA
- Viable particle
- Sterility
<table>
<thead>
<tr>
<th>KEYWORD</th>
<th>DEFINITION</th>
<th>CPP</th>
<th>DIRECT IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>STERILITY</td>
<td>MUST COMPLY WITH TEST FOR STERILITY. NO VIABLE PARTICLE DETECTABLE;</td>
<td>C.F.U</td>
<td>YES</td>
</tr>
<tr>
<td>CLEAN ZONE</td>
<td>FIVE DIFFERENT ZONES A TO E DEPENDING ON THE DESIGN, AIR FLOW, PRESSURE DIFFERENCE, AND FILTRATION</td>
<td>PRESSURE VELOCITY HEPA RH TEMPERATURE</td>
<td>YES FOR PREPARATION, ASEPTIC FILLING, CRIMPING, OPEN CONTAINER TRANSFERS PREPARATION OF CELL BANKS</td>
</tr>
</tbody>
</table>
Critical Parameters Zones

• Factory
  • Administration.
  • Cafeteria
  • Lockers
  • Canteen
  • Corridors

• Technical
  • Workshops
  • Utilities rooms
  • Clean steam generation
  • Water treatment
  • HVAC room
  • Corridors
Critical Parameters Zones

- Quality control
  - Sampling area
  - Raw materials
- General labs
- Microbiological labs

- Warehousing
  - Receiving
  - Dispatching
- Storage
- Cool store
- Tank farm
Production Zones

- Corridors
- Airlocks
  - To E
  - To D
  - To C
  - To B
  - Et.c
- Dispensing area
- Sterile filtration area

- Sampling area
- Preparation area
- Production of master cell bank
- Inoculum preparation area.
- Final purification steps area
- Sampling for IPC
- Cell harvesting
Production Zones

- Virus inoculation.
- Virus deactivation.
- Formulation of buffers
- Final purification
- Final filling
- Container docking
- Washing rooms
- Sterilization tunnel
- Autoclave.
- Crimping
- Inspection
<table>
<thead>
<tr>
<th>KEYWORD</th>
<th>DEFINITION</th>
<th>CPP</th>
<th>DIRECT IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARVEST ZONE</td>
<td>MUST BE IN ZONE 2</td>
<td>CLOSED CONTAINERS. GRADE X TEMPERATURE RH ....</td>
<td>YES</td>
</tr>
<tr>
<td>SAMPLING</td>
<td>MUST BE PERFORMED IN AREAS WHICH MINIMIZE THE RISK OF CONTAMINATION</td>
<td>CLOSED GRADE B TEMPERATURE RH ....</td>
<td>YES</td>
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</table>
HOW DO WE MAKE THE LINK BETWEEN CPP AND URS?
<table>
<thead>
<tr>
<th>KEYWORD</th>
<th>DEFINITION</th>
<th>URS</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAMPLING</td>
<td>MUST BE PERFORMED IN AREAS WHICH MINIMIZE THE RISK OF CONTAMINATION</td>
<td>PROVIDE:</td>
<td>CONTAMINATION FALSE POSITIVES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PROTECTION AGAINST CONTAMINATION</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LOGICAL AND DIRECT FLOW</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GOOD STAGING</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GOOD ACCESS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NO POSSIBLE CONFUSIONS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NO MIX UPS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MINIMIZE DISTANCES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MINIMIZE HANDLING STEPS</td>
<td></td>
</tr>
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</table>
AND FOR THE PERSONNEL?
<table>
<thead>
<tr>
<th>KEYWORD</th>
<th>DEFINITION</th>
<th>URS</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERSONNEL</td>
<td>MUST BE DESIGNED TO PROTECT THE PRODUCT FROM CONTAMINATION</td>
<td>SEGREGATION GOWNING DEGAOWNING PROTECTION SECURITY</td>
<td>CONTAMINATION FALSE POSITIVES</td>
</tr>
<tr>
<td>PROCESS CRITERIA</td>
<td>EXAMPLE</td>
<td>URS</td>
<td>RISK</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>CRITICAL ROOM PARAMETERS</td>
<td>TEMPERATURE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONTAMINATION</td>
<td>POLLUTED FLOOR</td>
<td>LIST SOURCES OF CONTAMINATION:</td>
<td>EVALUATE CONDITIONS IN CASE OF EQUIPMENT FAILURE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EXTERNAL AIR</td>
<td>RECOVERING TIME INTERLOCKS FAL SAFE MODES.….</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BAD FILTRATION</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DAMAGED FILTERS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BAD AIR FLOW</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HVAC FAILURE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PERSONNEL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CONSTRUCTION MATERIALS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DRAINS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SPRINKLERS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MIX UP</td>
<td></td>
</tr>
<tr>
<td>NOT AFFECTED</td>
<td>CLOSED SYSTEMS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ARE YOUR FAMILIAR WITH FAIL SAFE?
A camera inspection station detects bad vials and sends a signal to an ejection station.
THE BAD VIAL IS SENT TO A REJECTED CONTAINER
SO HOW CAN I BE FAIL SAFE FOR HVAC?
IT IS SOMETIMES POSSIBLE:

1. LOCKERS: SIGNAL TO HVAC
2. COOLING BATTERIES
3. ETC
IT IS SOMETIMES NOT POSSIBLE:

1. OPERATOR ACTION IN CASE OF FAILURE
IN DESIGNING THE CRITERIA AND THE CPP CONSIDERATION MUST FOCUS ON RISK AND OPERATING RANGE.

THIS WILL LEAD THE TIGHTNESS OF CONTROL RANGE OF THESE PARAMETERS
H.V.A.C

IS TEMPERATURE A CRITICAL PARAMETER?

YES IF THE CRITICAL QUALITY ATTRIBUTES LIKE

• QUALITY
• STABILITY
• EFFICIENCY

ARE AFFECTED

CRITICAL PARAMETER ➔ QUALIFICATION
H.V.A.C

Is temperature a critical parameter?

No if the critical quality attributes like

• Quality
• Stability
• Efficiency

are not affected

General parameter ➔ Commissioning
## H.V.A.C – TEMPERATURE

<table>
<thead>
<tr>
<th>GRADE</th>
<th>GENERAL PARAMETER</th>
<th>CRITICAL PARAMETER</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - ISO 5</td>
<td>18 – 26 °c</td>
<td>MORE RESTRICTIVE</td>
</tr>
<tr>
<td>B - ISO 7</td>
<td>IDEM</td>
<td>MORE RESTRICTIVE</td>
</tr>
<tr>
<td>C - ISO 8</td>
<td>IDEM</td>
<td>MORE RESTRICTIVE</td>
</tr>
<tr>
<td>D - ISO 8</td>
<td>17 – 27</td>
<td>MORE RESTRICTIVE</td>
</tr>
<tr>
<td>E - NA</td>
<td>12 - 28</td>
<td>MORE RESTRICTIVE</td>
</tr>
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</table>

**COMMISSIONING**

**QUALIFICATION**
SO WE CAN DO THE SAME FOR ALL THE CPP
# H.V.A.C – Relative Humidity

<table>
<thead>
<tr>
<th>RH</th>
<th>General Parameter</th>
<th>Critical Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact with Product</td>
<td>No</td>
<td>Yes – Humidifier must have the same CPP as water used in the process</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>Yes – Desiccant must be evaluated as CPP</td>
</tr>
</tbody>
</table>

**Commissioning**

**Qualification**
### H.V.A.C – PARTICLES

<table>
<thead>
<tr>
<th>PARTICLES</th>
<th>GENERAL PARAMETER</th>
<th>CRITICAL PARAMETER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTACT WITH PRODUCT</td>
<td>NA</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>YES</td>
</tr>
</tbody>
</table>

- **COMMISSIONING**
- **QUALIFICATION**
## H.V.A.C – MICRO ORGANISM

<table>
<thead>
<tr>
<th>MICRO ORGANISM</th>
<th>GENERAL PARAMETER</th>
<th>CRITICAL PARAMETER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTACT WITH PRODUCT</td>
<td>NA</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>YES</td>
</tr>
</tbody>
</table>

COMMISSIONING  
QUALIFICATION
H.V.A.C – ROOM AIR CHANGE RATES

<table>
<thead>
<tr>
<th>ACH/HR</th>
<th>GENERAL PARAMETER</th>
<th>CRITICAL PARAMETER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTACT WITH PRODUCT</td>
<td>NA</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>YES</td>
</tr>
</tbody>
</table>

IMPACT ON COSTS:
- BATTERIES SIZES
- AIR HANDLING UNITS SIZES
- ENERGY CONSUMPTION
- NUMBER OF FILTERS
-......
H.V.A.C – RECIRCULATION

<table>
<thead>
<tr>
<th>ACH/HR</th>
<th>GENERAL PARAMETER</th>
<th>CRITICAL PARAMETER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTACT WITH PRODUCT</td>
<td>RISK ASSESSMENT</td>
<td>RISK ASSESSMENT</td>
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</tbody>
</table>

COMMISSIONING
QUALIFICATION

RISK OF CROSS CONTAMINATION

POTENT PRODUCTS
MULTI PRODUCTS
H.V.A.C – RELATIVE PRESSURE DIFFERENCE - CASCADERS

<table>
<thead>
<tr>
<th>DELTA P</th>
<th>GENERAL PARAMETER</th>
<th>CRITICAL PARAMETER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTACT WITH PRODUCT</td>
<td>RISK ASSESSMENT</td>
<td>RISK ASSESSMENT</td>
</tr>
</tbody>
</table>

EVALUATE:
1. OPEN OR CLOSED SYSTEMS
2. LOCAL EXHAUSTE: HOODS, DEDUSTERS
3. AIRFLOWS
4. POWDERS
5. REVERSAL FLOWS
# MONITORING

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CRITICAL</th>
<th>MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTICLES</td>
<td>YES</td>
<td>ON LINE CONTINUOUS MONITORING RECORDING DATA INTEGRITY</td>
</tr>
<tr>
<td>ROOM AIR SUPPLY</td>
<td>YES</td>
<td>DEFINE WHICH ROOMS CAN BE SUPPLIED WITH FROM THE SAME AHU DEFINE RECIRCULATION AND % OF RECIRCULATION</td>
</tr>
<tr>
<td>GEOMETRY</td>
<td>YES</td>
<td>ESTIMATE USER LOCATIONS ESTIMATE WORST LOCATION IN TERM OF AIRFLOW AND PARTICLES ....</td>
</tr>
</tbody>
</table>

...
Start with the end in mind: start with the corrective actions

User requirements: HVAC:

1. Perform investigation for possible source of contamination.
2. Perform air flow patterns.
3. Perform smoke tests.
4. Review aseptic technics of personnel.
5. Review gowning requirements.
6. Inspect incoming airfilters for leaks in filter.
7. Review air pressure differential across filter.
Start with the end in mind: start with the corrective actions

User requirements: H V A C:

1. Review room disinfection/sanitation SOPs
2. Review sanitation intervals.
3. Review sanitation efficiency.
4. Check area pressure differential.
5. Evaluate equipment as source of contamination.
6. Evaluate integrity of the room (peeling paints, cracks ..)
7. Review risk to product.
8. Review maintenance and access
ONCE YOU HAVE DONE ALL THAT.

ENGINEERS WILL WRITE THE SPECIFICATIONS

THEIR DESIGN WILL BE BASED ON YOUR URS AND WILL FEED THE QdB AND THE RISK ASSESSMENT

YOU WILL BE INVOLVED IN THESE Activités

THEN QUALIFICATION WILL START
YOU CAN GET THAT

DEPENDING ON HOW GOOD THE COMMUNICATION IS
OR THAT !!!!!!!