CONCEPTUAL DESIGN
Key to get a GMP compliant facility

Developing Countries Vaccine Manufacturers Network

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Index

- Introduction
- Facility design: Steps to follow
- Starting information needed
- Utilities, architecture and lay out
- Equipment considerations
- Example
- Last industry trends
- Conclusion
Introduction
Facilities and equipment shall be placed, designed, built and maintained according to the operations that will take place.

The design goal is minimizing mistakes, allowing for effective cleaning and maintenance, preventing cross contaminations, and dust and dirtiness accumulation as well as any adverse effect in products quality.
Several factors contribute to the quality of products:

1. Starting & packaging materials
2. Validated Processes
3. Personnel
4. Procedures
5. Equipment
6. Facility Design & Quality
7. Production Environment

If any of the named factors is not adequate, products will be under quality
Classically it is said that contamination is linked to 5 parameters that have to be controlled (5 “M’s”)

- Men
- Material
- Raw Materials
- Media
- Methods
PERSONNEL: Particles release increases with activity

PERSONNEL: Number of microorganisms in human body

<table>
<thead>
<tr>
<th>AREA</th>
<th>AMOUNT</th>
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<tbody>
<tr>
<td>Hair</td>
<td>1-2 million/cm²</td>
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<tr>
<td>Underarm</td>
<td>2-3 million/cm²</td>
</tr>
<tr>
<td>Forearm</td>
<td>100-5000 /cm²</td>
</tr>
<tr>
<td>Back</td>
<td>300 /cm²</td>
</tr>
<tr>
<td>Front</td>
<td>200,000 /cm²</td>
</tr>
<tr>
<td>Feces</td>
<td>100,000 million/g</td>
</tr>
<tr>
<td>Urine</td>
<td>1000 /ml</td>
</tr>
<tr>
<td>Nose (secretion)</td>
<td>1-10 million/ml</td>
</tr>
<tr>
<td>Ear (earwax)</td>
<td>10-100 million/g</td>
</tr>
</tbody>
</table>
When designing a new facility

- **How shall we start?**
  - Is it a green field project?
  - Are we talking of a revamping?
  - What pharmaceutical forms will be handled?
  - Which products?

- **What steps shall we cover?**
  - Getting information
  - From concept to detailed
  - What about the future?
• What are GMP and other guidelines asking for?
  - Which are the markets where the products will be sold?
  - Are changes in the regulation expected?

Let’s start designing!!!!!
Facility Design: Steps to Follow
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Facility Design: Steps to Follow

**User brief**
- Value management 1
- Shared brief taking
- Analysis & objectives
- Benchmarking
- Lateral thinking

**Enquiry stage**
- Clear understanding of project
- Value free
- Cost model

**Feasibility stage**
- Correct option selection
- Audit trail
- Single solution to concentrate on

**Concept design**
- Value management 2
- Option analysis against objectives
- Lateral thinking

**Detailed design**
- Correct component selection
- Co-ordinated project
- Co-ordinated implementation
- Reduction in cost

**Fabrication design**
- Feedback to V.M.
- Audit trail

**Construction**
- Analysis of as built cost

**Handover**
- New benchmark

**Single team**
- Value engineering
  - by design
  - by project
  - by work package
  - Lateral thinking
  - Analysis & alternatives
  - Life cycle costing
Facility Design: Steps to Follow

CONCEPTUAL ENGINEERING (Standard Documents)

• Based on a URS:
  • Description of production processes
  • Overview of facilities
  • Production capacity of the plant
  • Pharma/Industrial applicable regulations

• In collaboration with Client
  • Lay out of the plant
  • Flow of personnel, materials and waste
  • Block diagram
  • Preliminary list of production equipment/utilities
  • Budget estimated ± 30%
Facility Design: Steps to Follow

BASIC ENGINEERING (Standard Documents)

- Define production equipment, Make and Model
- Estimate capacities of utilities
- Freeze the lay out, with the technical areas
- Freeze the URS
- Distribute points of use in lay out
- Carry out P&ID basic utilities
- Execute routing facilities without dimensions
- Make architecture facilities
- Room data sheet
- Make a schedule of project implementation
- Budget estimated ± 20%

This step may be omitted and go directly to detail engineering, but it is advisable as it helps on definitions.
Facility Design: Steps to Follow

DETAILED ENGINEERING

• Develop technical and functional specifications
• Design the P&ID
• Develop routing facilities with dimensions
• Make isometrics of critical facilities
• Make Bill of Quantities of facilities
• Develop instrumentation lists
• Project schedule more reliable
• Final quotation of the execution
Facility Design: Steps to Follow

CONSTRUCTIVE ENGINEERING

• Review Concept design documents to confirm suitability:
  o Lay out of the plant
  o Flow of personnel, materials and waste
  o Block diagram
  o Preliminary list of production equipment/utilities

• Review Detail Engineering documents to confirm suitability:
  o Technical and functional specifications with calculations
  o Design the P&ID
  o Routing facilities with dimensions
  o Isometrics of critical facilities
  o Bill of Quantities of facilities
  o Instrumentation lists

• Develop missing documents or modify any change

• Project schedule updated

• Last quotation of the execution

This step is not always done; it is advisable if team in charge of construction is different or if a long period of time has passed from the detail engineering development to the construction
Facility Design: Steps to Follow

BIM Building Information Modeling Plan
Starting information needed
Remembering many of the questions we made

- Is it a green field project?
- Are we talking of a revamping?
- What pharmaceutical forms will be handled?
- What about the future?
- Which are the markets where the products will be sold?

We need to develop the Basis of Design
Basis of design

- Site layout
  
  In case of green field project, drawing showing the site layout with roads, perimeter walls and all ancillary buildings requested → SMP
Starting information needed

Basis of design

- Product list
  
  Type of product (sterile/non sterile), activity (Potent products), production process applicable
  
The list of the products to be manufactured in the facility → information provided by the client → dedicated/multipurpose
  
  Process Description → Process flow diagram depicting the production process in schematic form

Batch sizes

Volume requirement and Assumption: Analysis of x-year sales forecasts in order to determine the required installed and future capacities. → Capacity Study if needed

The required capacity of the facility is analyzed so that the type and quantity of equipment can be determined.
Basis of design

- Product list

Process Description → Process flow diagram depicting the production process in schematic form
Starting information needed

Basis of design
- Product list
- Capacity Study if needed
Starting information needed

Basis of design
  • Design Philosophy

  The approach taken by designer to conceptual design (vertical vs horizontal).
Basis of design
- Design Philosophy
  Mixed model

Starting information needed
Starting information needed

Basis of design

- Area requirements
  - Production, warehouse, QC lab, R&D area
  - Special room needs: Offices, praying area, toilets, canteen, areas to rest, laundry, ...

- Manpower requirements
  - Estimate of manpower required for the production process differentiating men & women
  - Operating times and shifts

- Utilities availability
  - Type and distance
Basis of design
- GMP requirements
  - Countries where products will be sold
    - The list of the relevant regulatory standards and reference documents to which the design must comply
- Machinery requirements
  - Existing/New
  - Capacities
- Utilities requirements
- Containment strategy
- Any other requirement from client: Type of clean room material, HVAC, brand names, Corporate policies to comply with,.....
Utilities, architecture and lay out
Utilities, architecture and lay out

GMP MANUFACTURING ENVIRONMENT

PRODUCT PROTECTION
- Contamination (Control)
- Cross-contamination Control
- Correct temperature & humidity

PERSONNEL PROTECTION
- Prevent contact with dust
- Prevent contact with fumes
- Acceptable comfort conditions

ENVIRONMENT PROTECTION
- Avoid dust discharge
- Avoid fume discharge
- Avoid effluent discharge

SYSTEMS

SYSTEM VALIDATION

Shell-like containment control concept
Utilities, architecture and lay out

Segregation

- It is the first step to reach a good design:
  - GMP vs non GMP areas
  - Differentiated areas for certain products
  - Each product in its lowest requested cleanliness level
  - Flows crossing prevention
Utilities, architecture and lay out

Architecture

- It is defined:
  - Structure
  - Inner Partitions
  - Sanitation
  - Coverings
  - Flooring
  - Carpentry
Critical Systems

- It is defined:
  - HVAC
  - Electricity and Lighting
  - Clean Steam (CS) / Pure Steam (PS)
  - Sterile Compressed Air (SCA)
  - Purify Water (PW) & Water For Injection (WFI)
  - Waste Treatment/BIWASTE
  - CIP/SIP
  - Special Gases
  - Vacuum
  - SAS
  - Other Installations
Environment control (HVAC)

The control of the “environment” surrounding the product can be achieved with different techniques:

- By “classical” clean rooms that protect the product with the cleanest possible environment
- By using ISOLATORS, that set a physical barrier between the product and the environment
- By using techniques in between like RABS
Manufacture of pharmaceutical products

• Carried out in clean areas with airlocks for personnel and/or for equipment and materials.

• Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

• Clean areas are classified according to the environment: Each operation requires a cleanliness level (minimise particulate or microbial contamination risks).
Utilities, architecture and lay out

Environment classification

- **as built**
- **at rest**
- **In operation**
Environment classification (EU GMP Annex 1)

- **Grade A**: The local zone for high risk operations. Normally such conditions are provided by a laminar air flow work station, that should provide a homogeneous air speed at the working position in a range of: 0.36 – 0.54 m/s. The maintenance of laminarity should be demonstrated and validated.

- **Grade B**: For aseptic preparation and filling, this is the background environment for the grade A zone.

- **Grade C and D**: Clean areas for carrying out less critical stages in the manufacture of sterile products.
Utilities, architecture and lay out

Sterile Operations

Grade Examples of operations for terminally sterilized products
A Filling of products, when unusually at risk
C Preparation of solutions, when unusually at risk. Filling of products
D Preparation of solutions and components for subsequent filling

Grade Examples of operations for aseptic preparations
A Aseptic preparation and filling
C Preparation of solutions to be filtered
D Handling of components after washing
Non Critical Systems

- It is defined:
  - Electricity and Lighting
  - Industrial Steam
  - Compressed Air
  - Cooling Water
  - Sanitary Cold-Hot water
  - Waste Handling
  - Fire Protection System
  - Data and Voice network
  - Access Control
  - Industrial Gases
  - Vacuum Network
  - Other Installations
Utilities, architecture and lay out
Utilities, architecture and lay out

Drawings
The following ones are developed:

- **Civil and Architecture Drawings**
  - Plot Plan
  - Building layouts
  - Lateral Views
  - Sections Views
**Drawings**

The following ones are developed:

- **Process Drawings**
  - Process Flow Diagrams (PFD’S).
  - Production area layout
  - Room Classification and Pressure Distribution Layouts
  - Personnel (all type) and Material (any material) Flows
  - Basic Equipment Layouts

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**Granulation & Blending-1 for Capsules**

- **Dispensing of API and Raw Materials** (Dispensing booth with weighing balances)
- **Sifting of API and Raw Materials** (Vibratory Sifter)
- **Dry Mixing** (API + Excipients) (Rapid Mixer Granulator)
- **Granulation-Wet Mixing** (Rapid Mixer, Granulator and Paste Kettle)
- **Granulation-Drying** (Fluid Bed Processor)
- **Granulation-Sizing** (Sieve and Multi Mill)
- **Blending** (Bin Blender)
Utilities, architecture and lay out

Drawings
The following ones are developed:

• PFD

• Utilities drawings
  – HVAC Diagrams
  – Electrical Diagrams
  – Steam Diagrams
  – Purify Water and Water for Injections Diagrams
  – Compressed Air Diagrams
  – Fire Protection Diagrams
  – CIP/SIP, BIOWASTE, etc.
Equipment considerations
Equipment considerations

**Equipment**

- Choice of equipment & technology
  Fit for purpose equipment & technology are determined based on level of technology, budget and quality requirements
- Machinery requirements
  - Existing/New Capacities
- List of major equipment complete with proposed equipment quantity, capacity, description, sizing and example of make
- Delivery dates constraint
- Any other special features
Last industry trends
Last industry trends
Last industry trends

AUTOMATIC LOADING SYSTEMS
MODULAR FACILITIES

Last industry trends

Source KP
Conclusion
Facilities and equipment shall be placed, designed, built and maintained according to the operations that will take place.

To design we need to develop the Basis of Design: Knowing what will be done in the factory and for whom

Make it simple, agree on a concept design, freeze it and develop the other engineering steps by using the new available tools

Think about future needs, but don’t forget that it has to be used before reaching this future: step by step
Questions

Thanks a lot

To get more information read: https://b2bcentral.co.za/issues/2022/pcr/july/ (p. 37).
Part I: https://ispe.org/pharmaceutical-engineering/conceptual-design-key-challenge-production-efficiency-part-i
Part II: https://ispe.org/pharmaceutical-engineering/conceptual-design-key-challenge-production-efficiency-part-ii