

CONCEPTUAL DESIGN

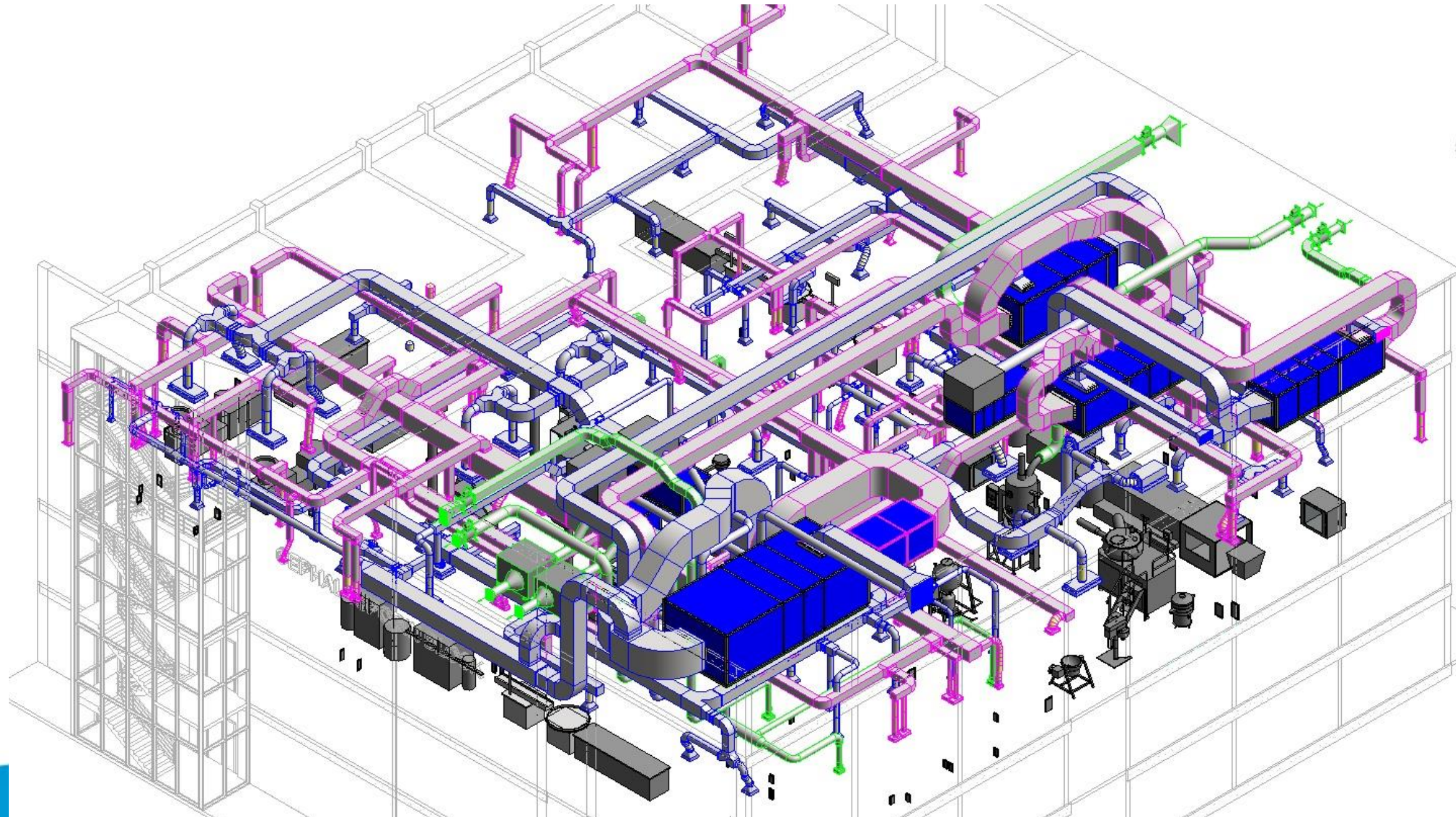
Key to get a GMP compliant facility



Developing Countries Vaccine
Manufacturers Network

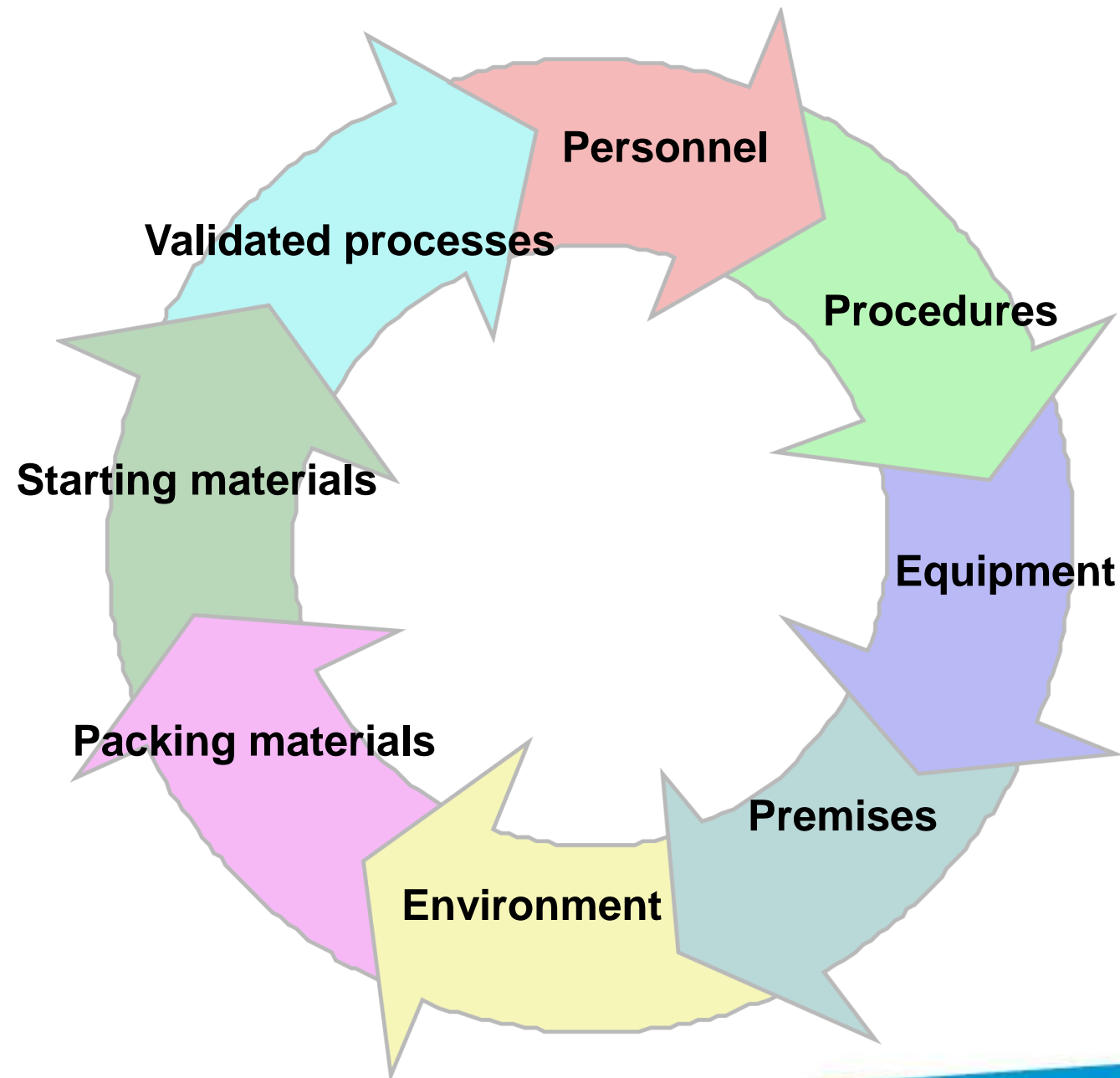
Rafael Beaus - 2022
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- Introduction
- Facility design: Steps to follow
- Starting information needed
- Utilities, architecture and lay out
- Equipment considerations
- Example
- Last industry trends
- Conclusion



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

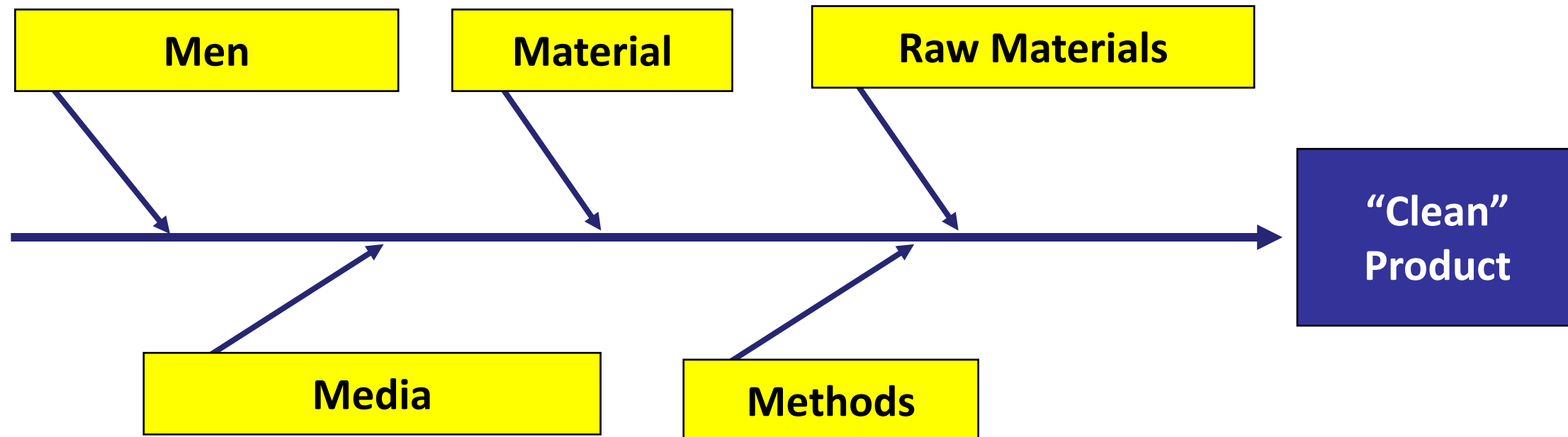


Several factors contribute to the quality of products:

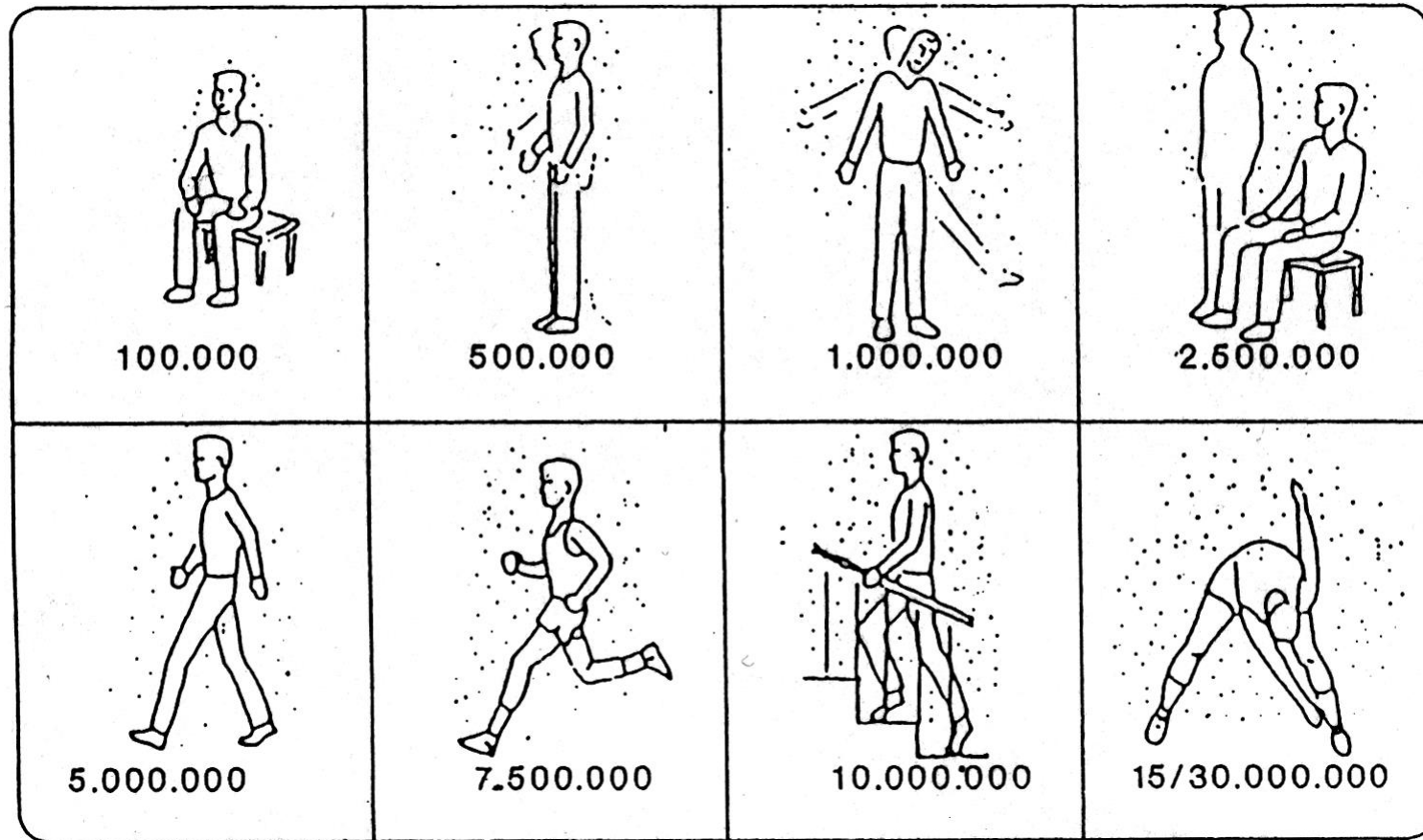
1. Starting & packaging materials
2. Validated Processes
3. Personnel
4. Procedures
5. Equipment
6. Facility Design & Quality
7. Production Environment

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”)



PERSONNEL: Particles release increases with activity



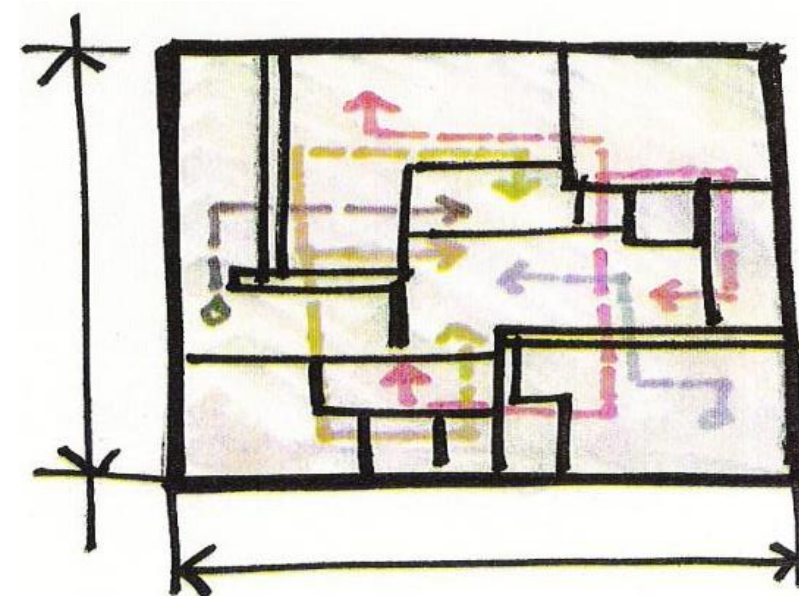
PERSONNEL: Number of microorganisms in human body

AREA	AMOUNT
Hair	1-2 million/cm ²
Underarm	2-3 million/cm ²
Forearm	100-5000 /cm ²
Back	300 /cm ²
Front	200.000 /cm ²
Feces	100.000 million/g
Urine	1000 /ml
Nose (secretion)	1-10 million/ml
Ear (earwax)	10-100 million/g



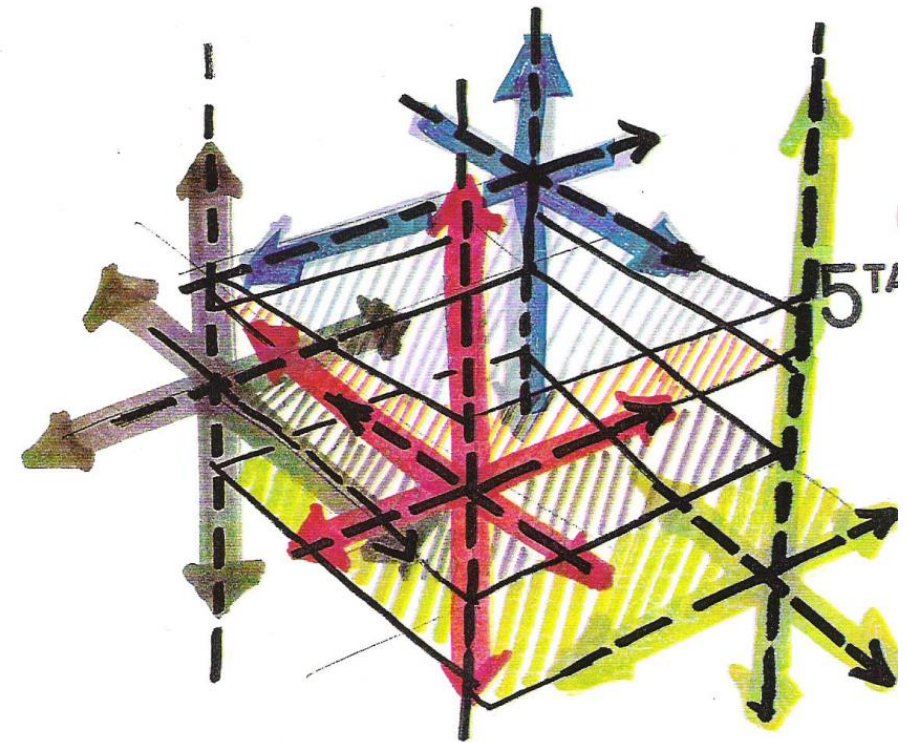
When designing a new facility

- 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?

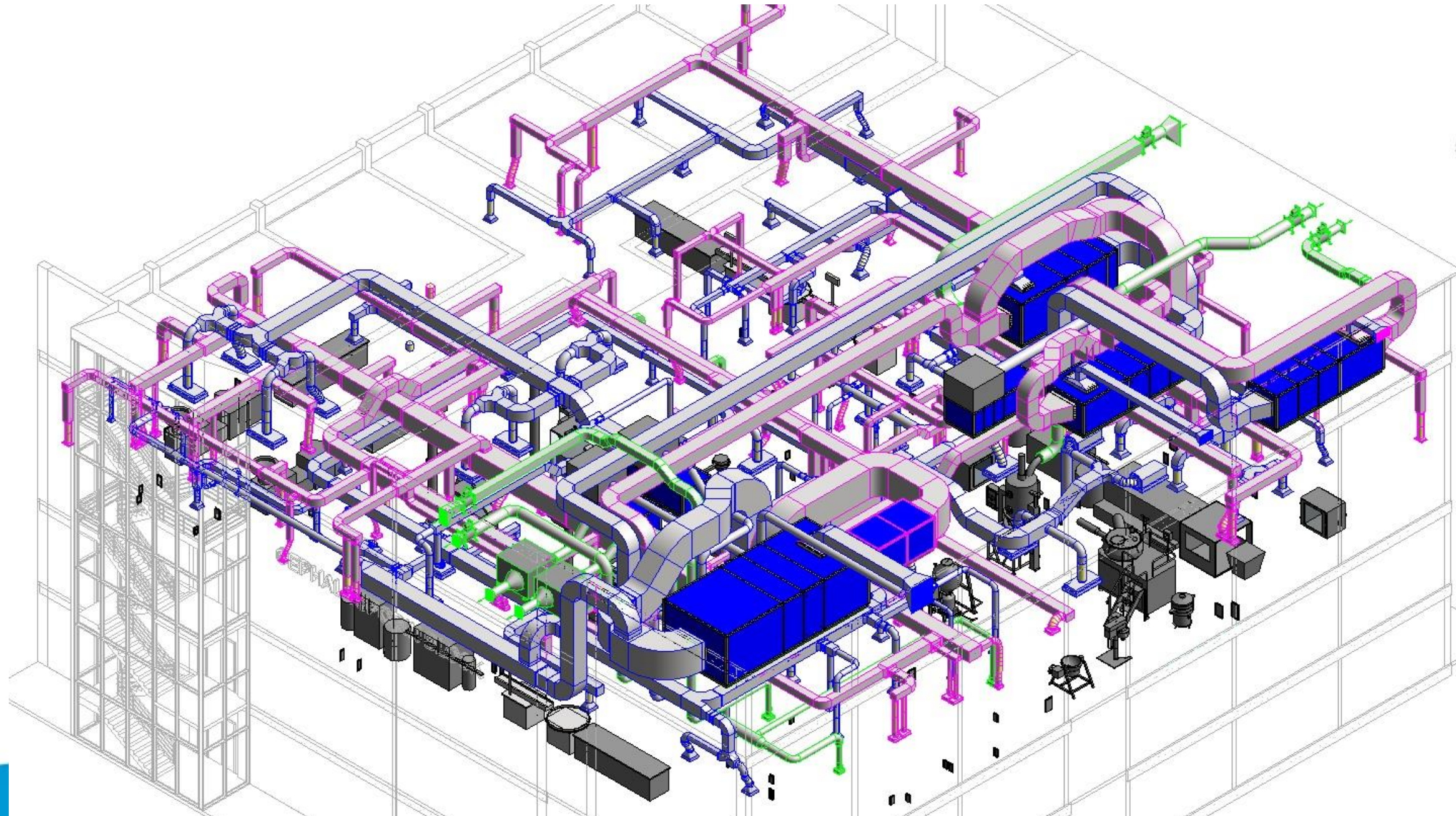


- What are GMP and other guidelines asking for?
 - Which are the markets where the products will be sold?
 - Are changes in the regulation expected?

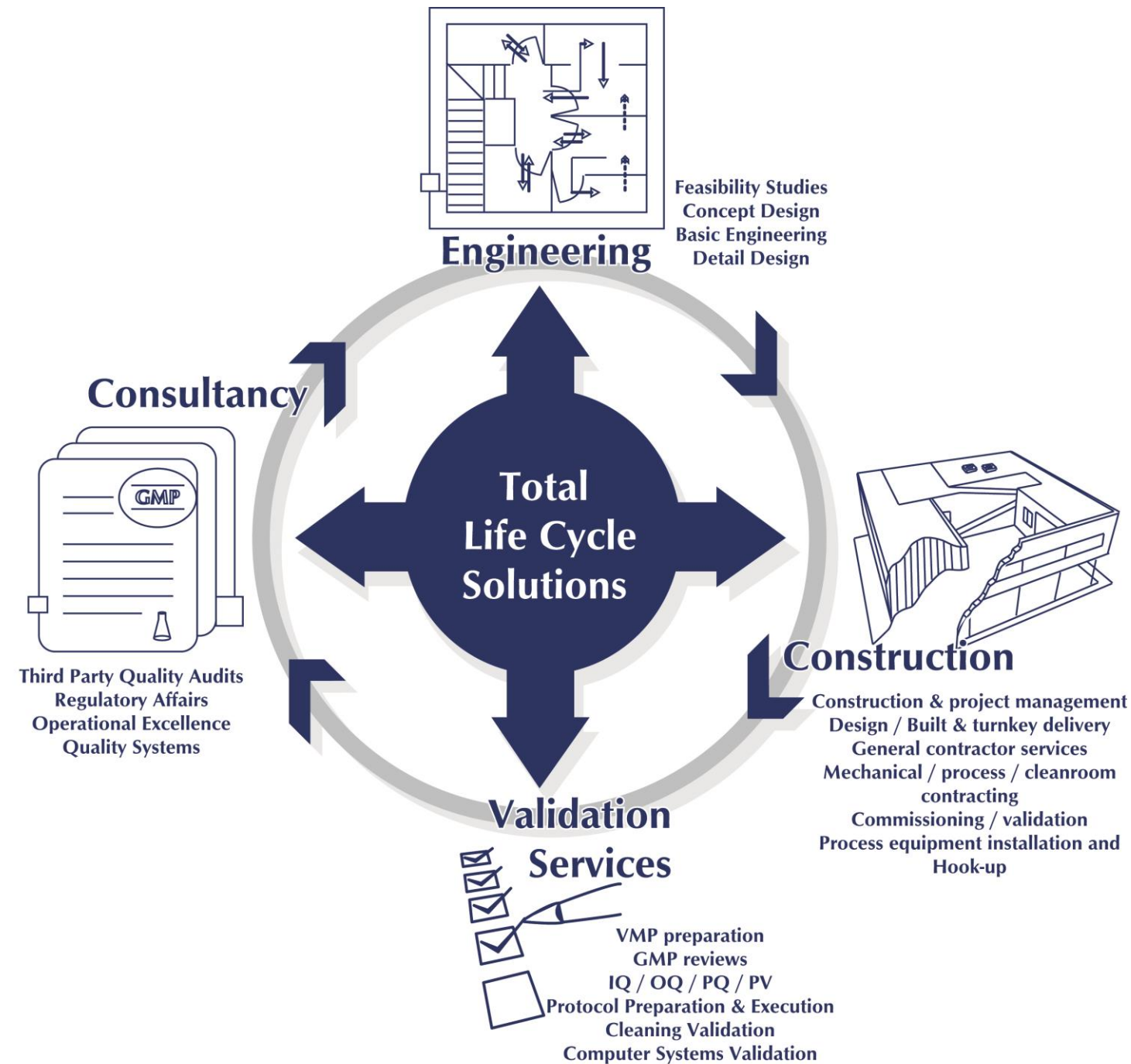
Let's start designing!!!!



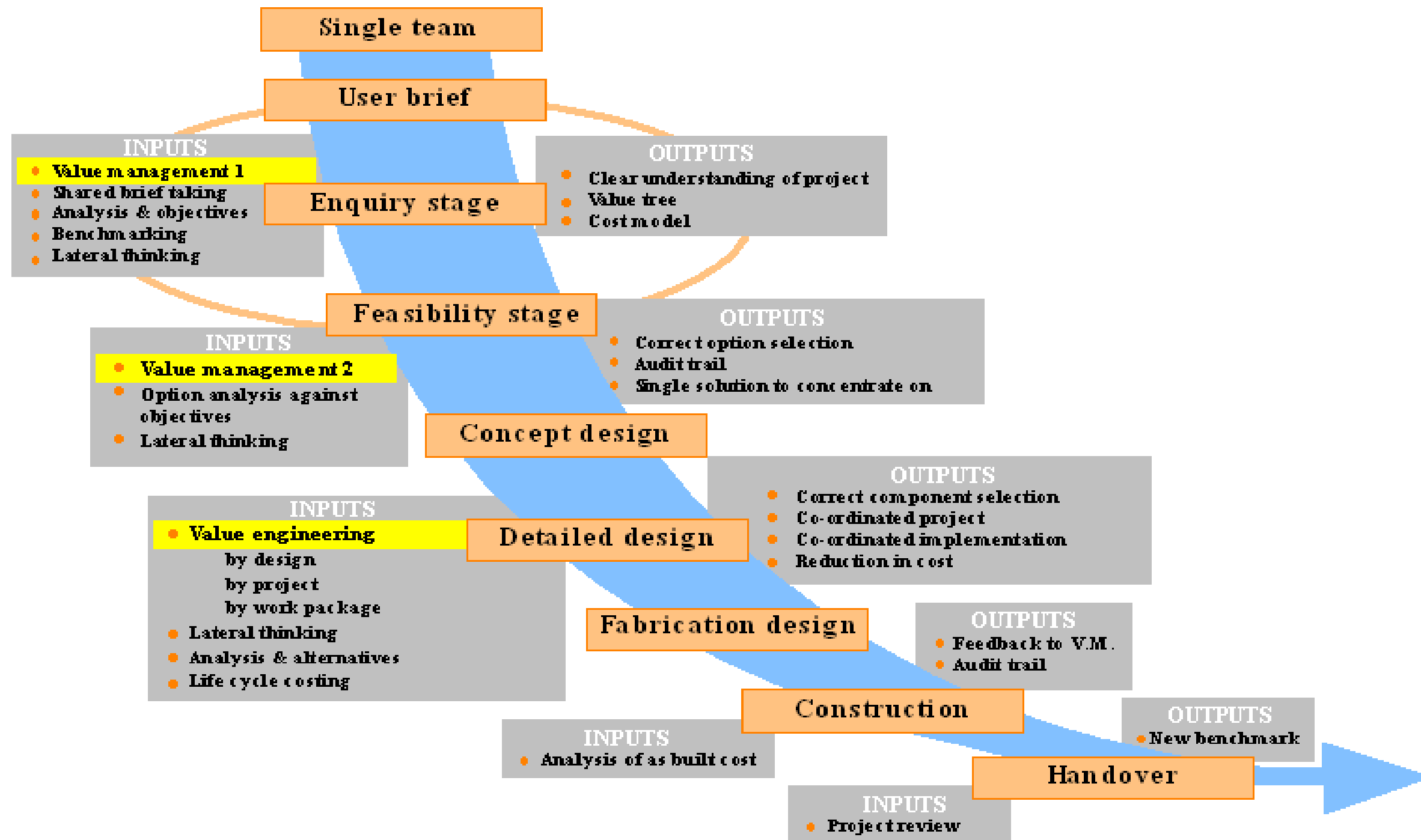
Facility Design: Steps to Follow



Facility Design: Steps to Follow



Facility Design: Steps to Follow



Conceptual Engineering

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 $\pm 30\%$

Basic Engineering

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 $\pm 20\%$

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

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

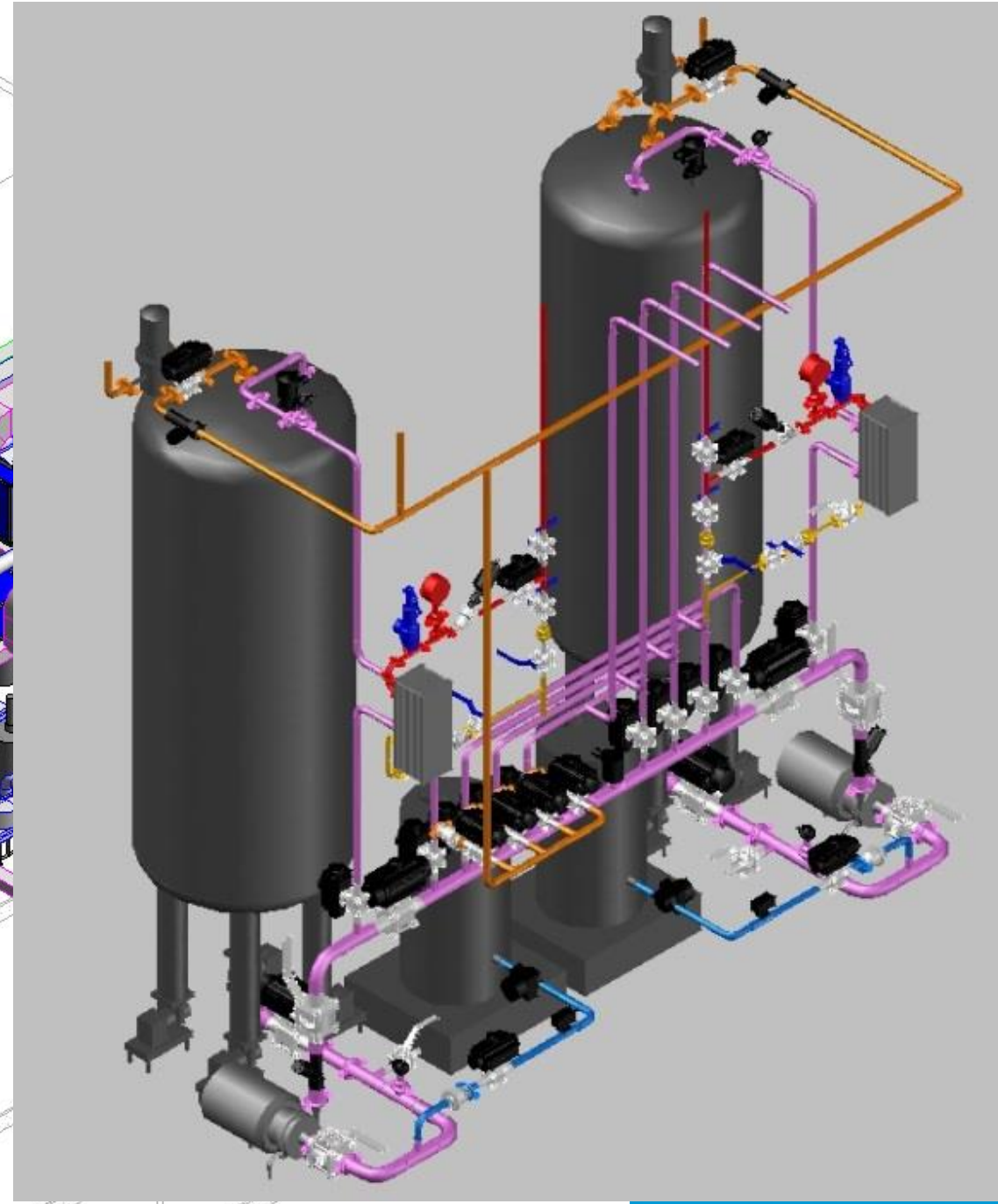
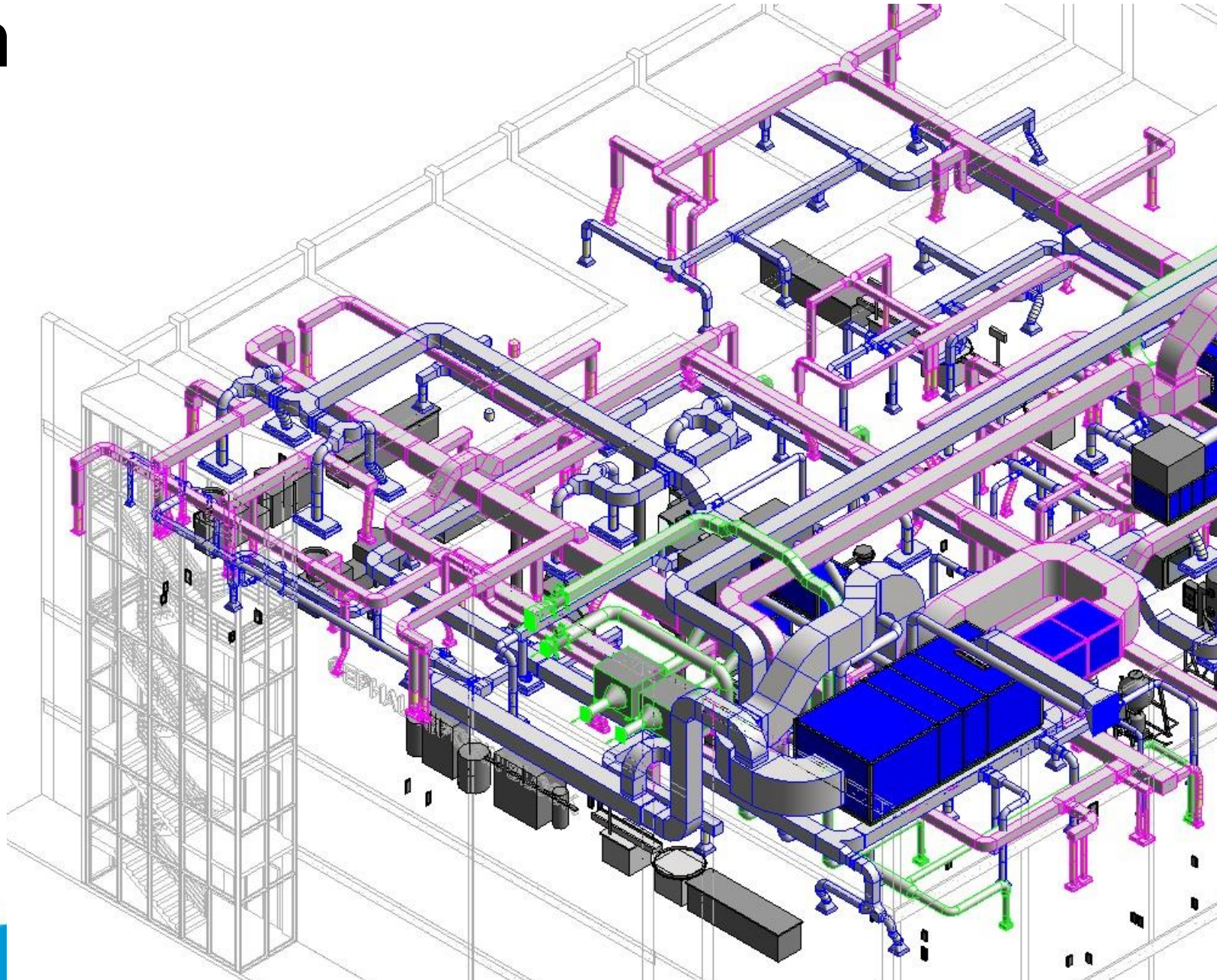
Constructive Engineering

CONSTRUCTIVE ENGINEERING

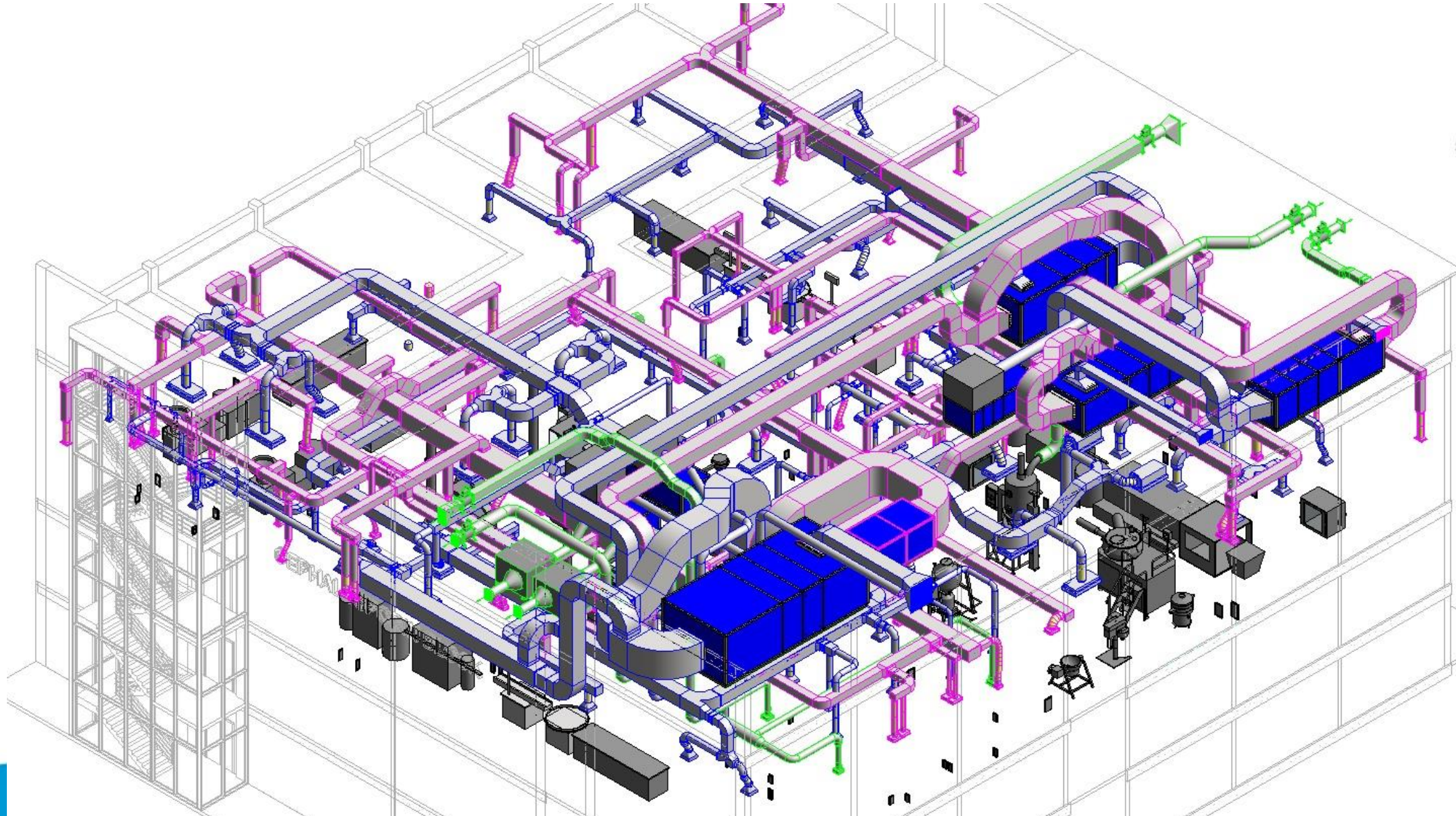
- Review Concept design documents to confirm suitability:
 - Lay out of the plant
 - Flow of personnel, materials and waste
 - Block diagram
 - Preliminary list of production equipment /utilities
- Review Detail Engineering documents to confirm suitability:
 - Technical and functional specifications with calculations
 - Design the P&ID
 - Routing facilities with dimensions
 - Isometrics of critical facilities
 - Bill of Quantities of facilities
 - 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

BIM Building Information Modeling Plan



Starting information needed



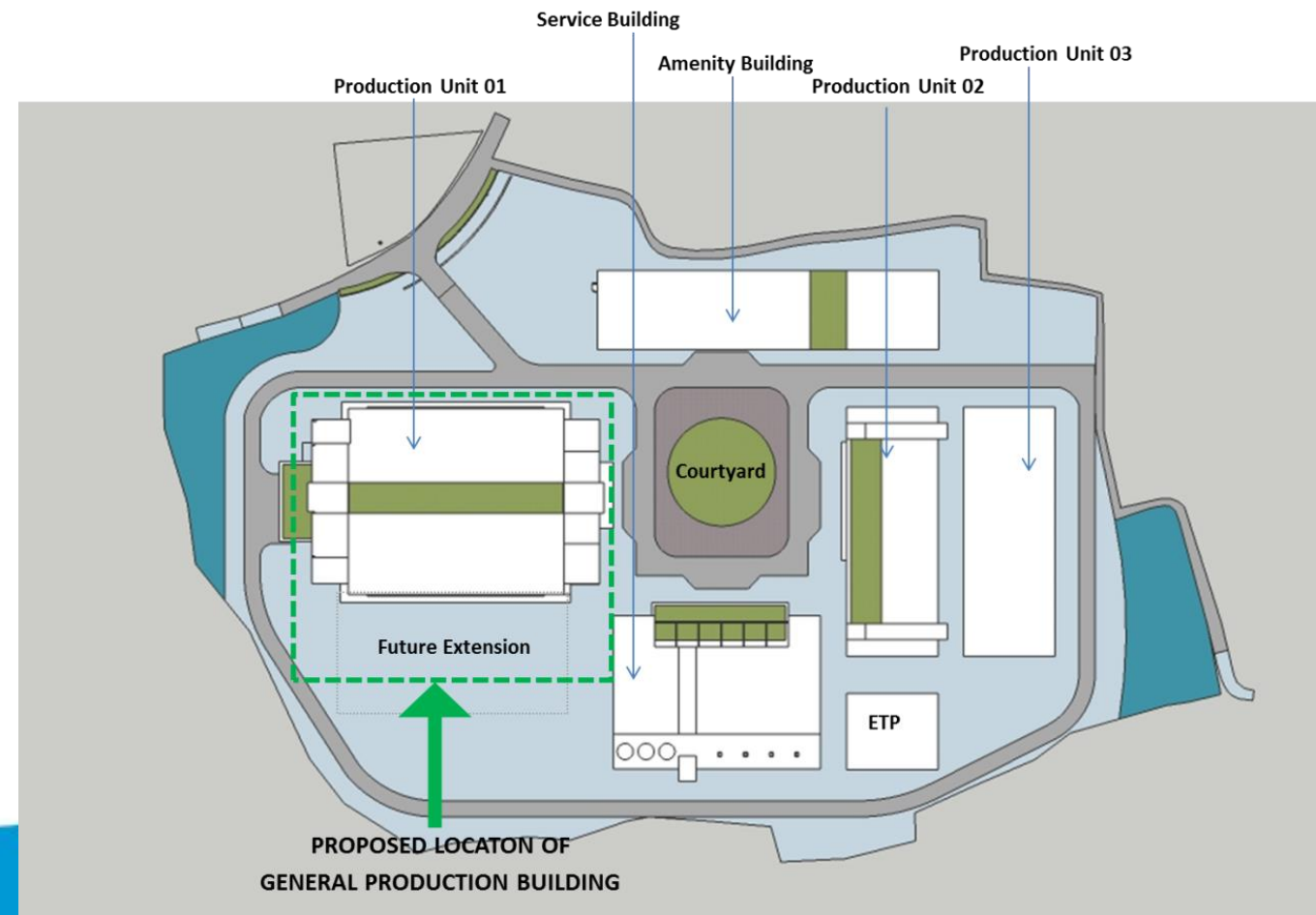
Starting information needed

- 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



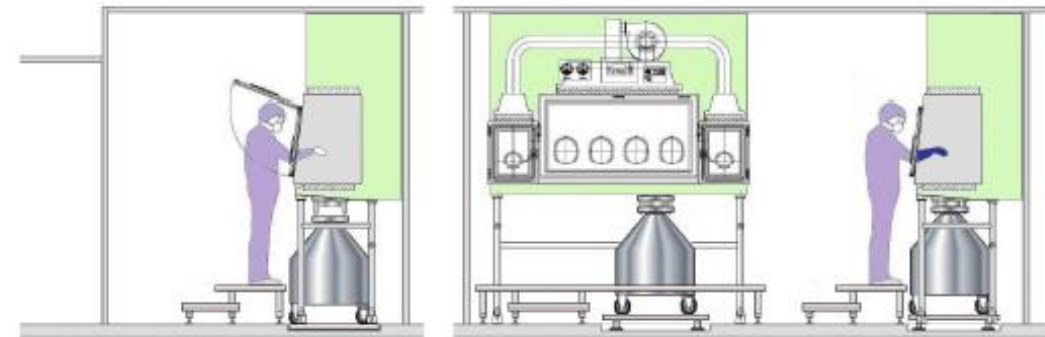
Basis of design

- 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

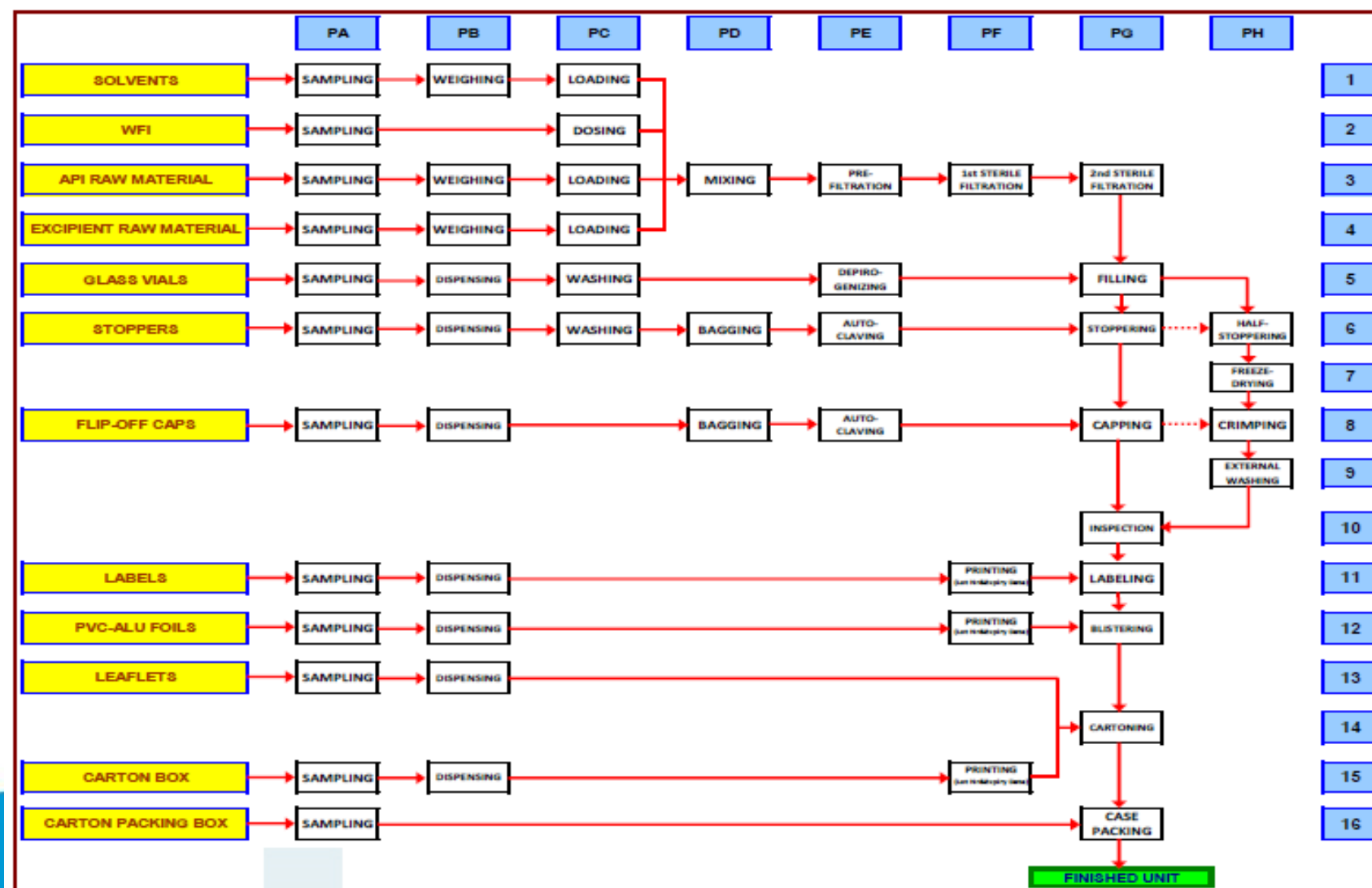
Volume requirement and Assumption: Analysis of x-year sales forecasts in order to determine the required installed and future capacities. → Capacity Study if needed

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

Basis of design

- Product list

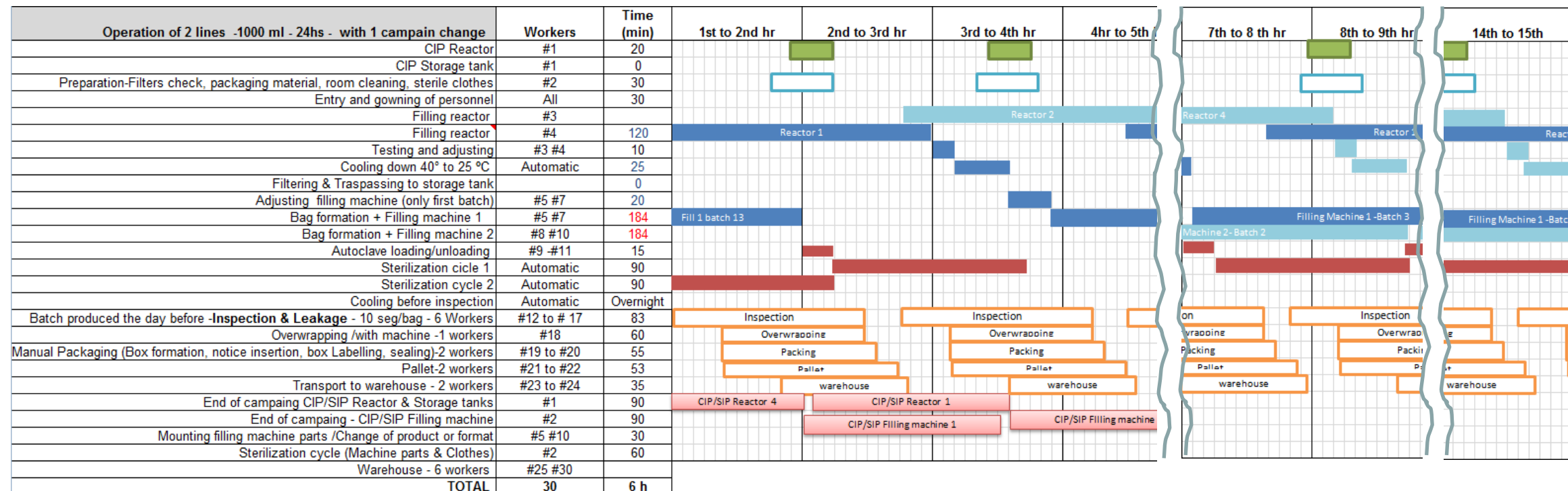
Process Description → Process flow diagram depicting the production process in schematic form



Starting information needed

Basis of design

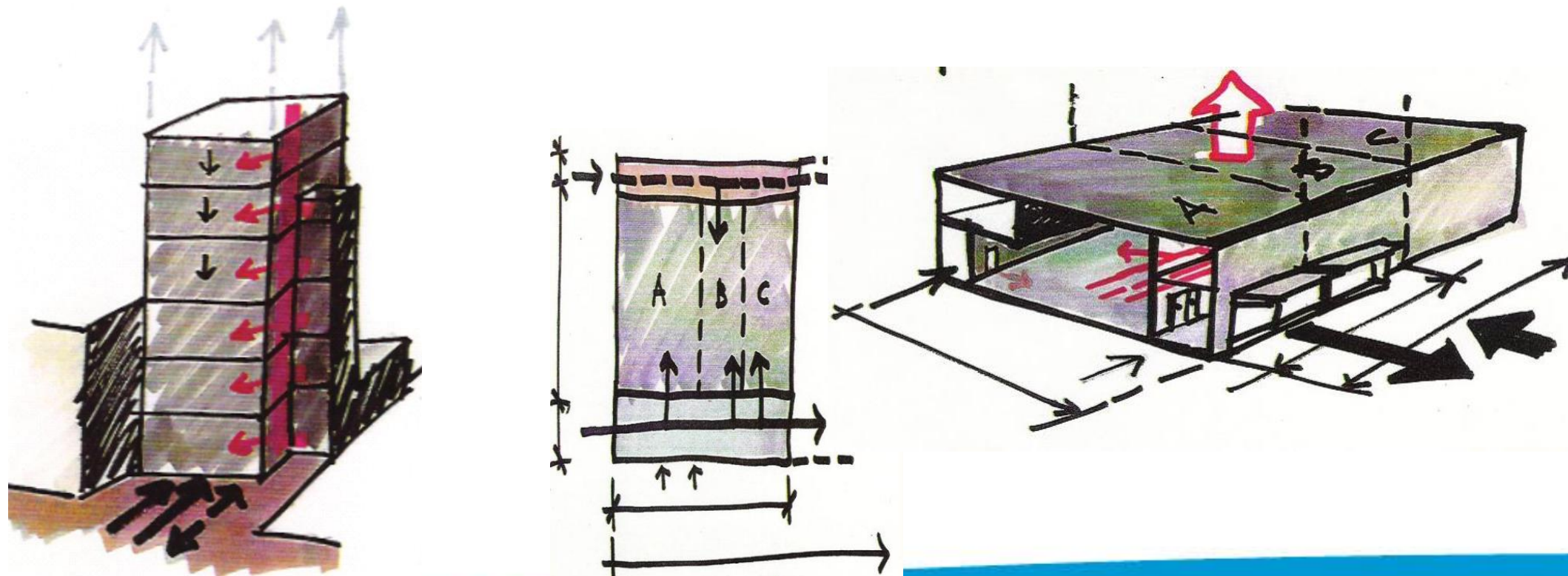
- Product list
- Capacity Study if needed



Basis of design

- Design Philosophy

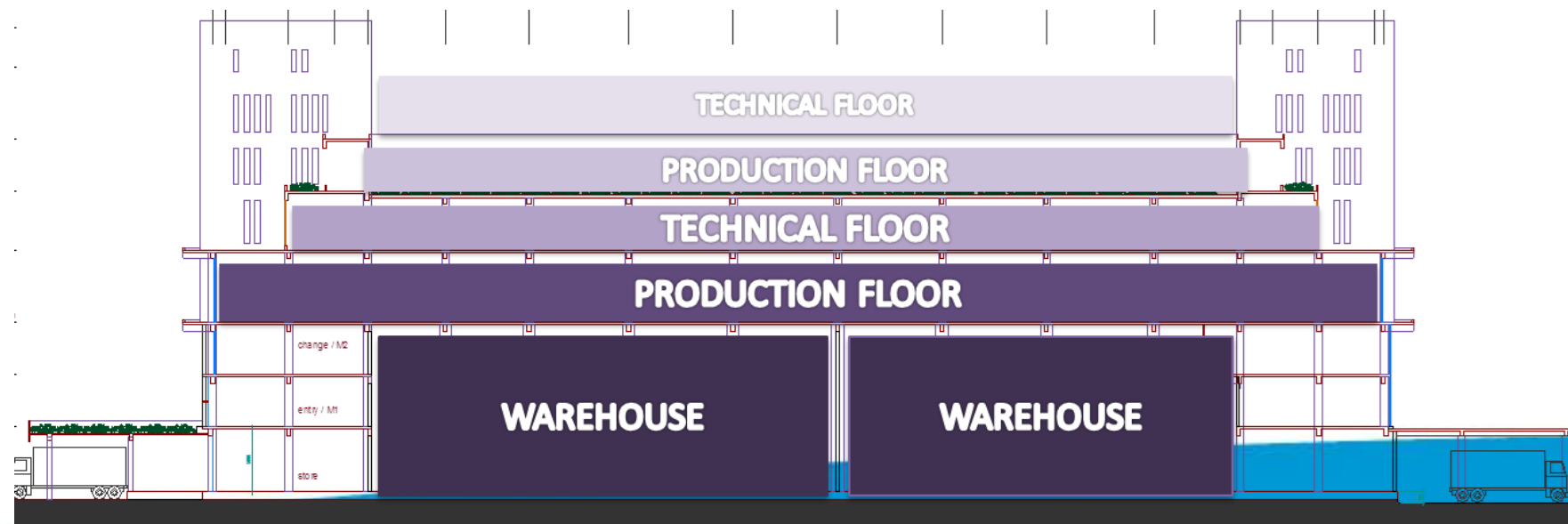
The approach taken by designer to conceptual design (vertical vs horizontal).



Starting information needed

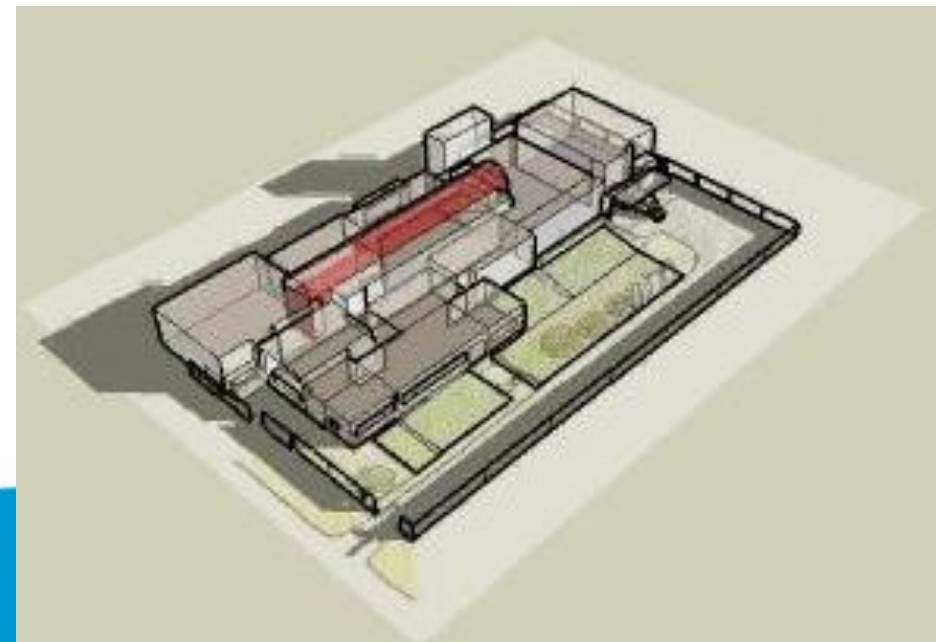
Basis of design

- Design Philosophy
Mixed model



Basis of design

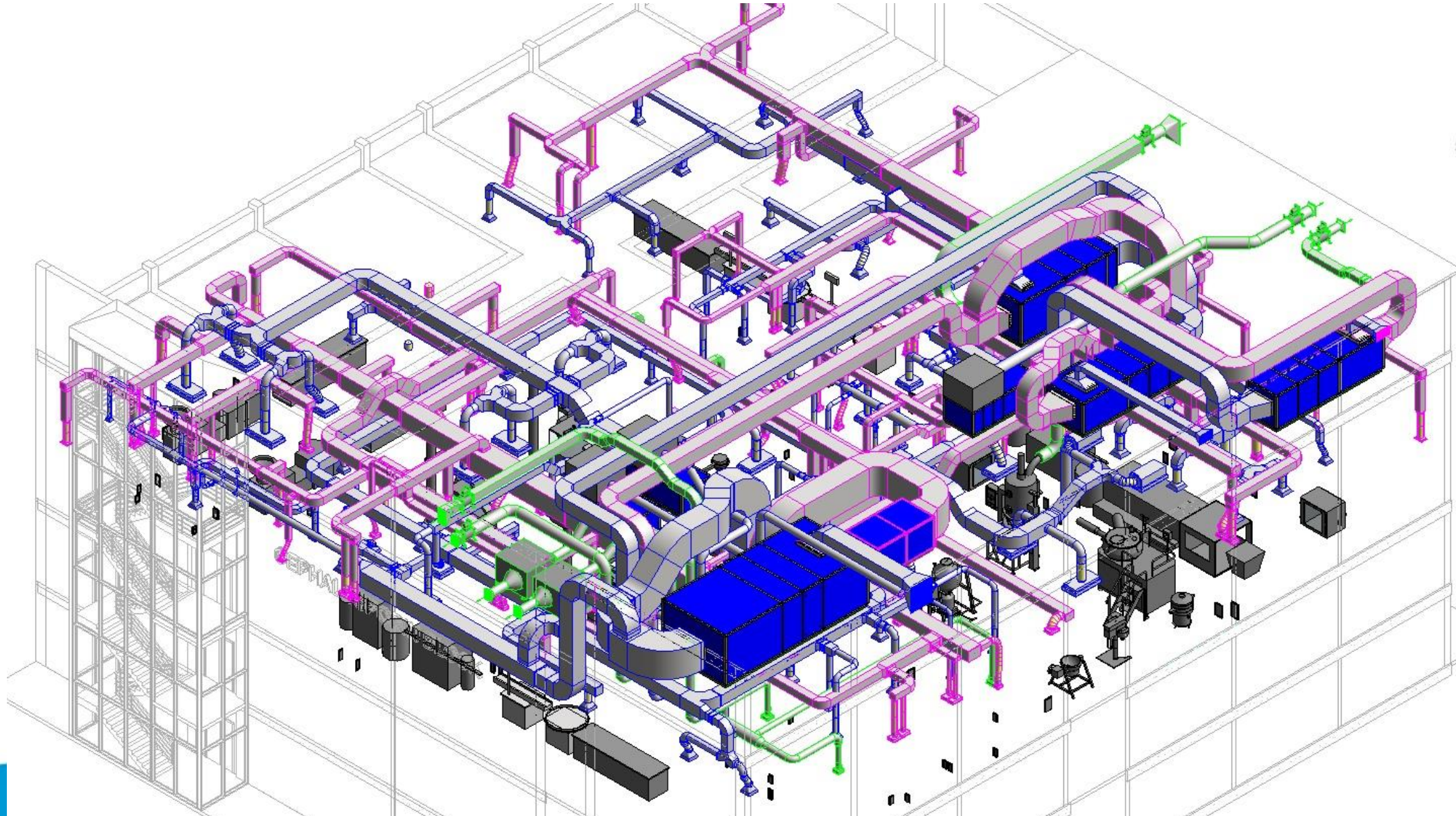
- Area requirements
Production, warehouse, QC lab, R&D area
Special room needs: Offices, praying area, toilettes, canteen, areas to rest, laundry, ...
- Manpower requirements
Estimate of manpower required for the production process differentiating men & women
Operating times and shifts
- Utilities availability
Type and distance

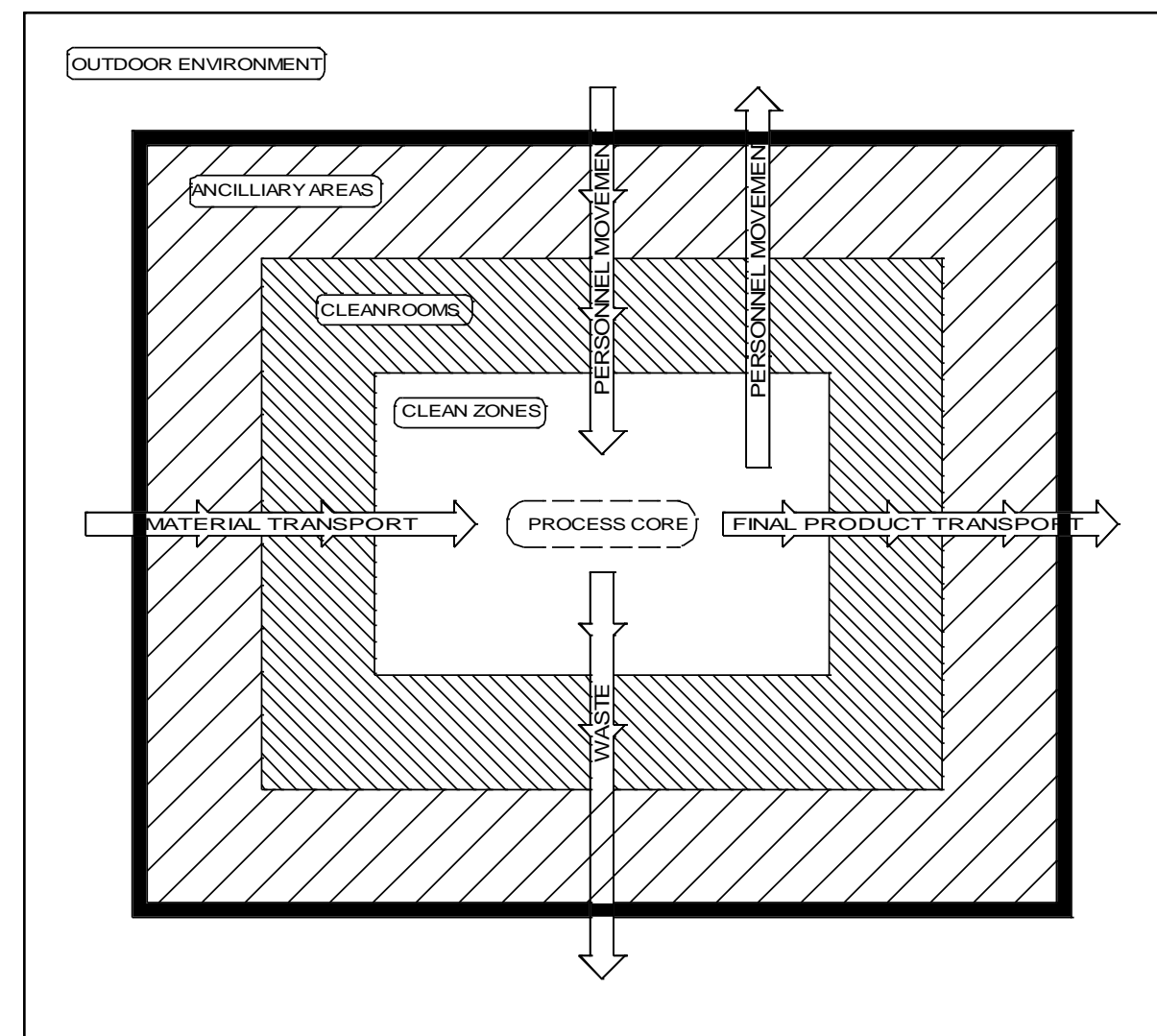
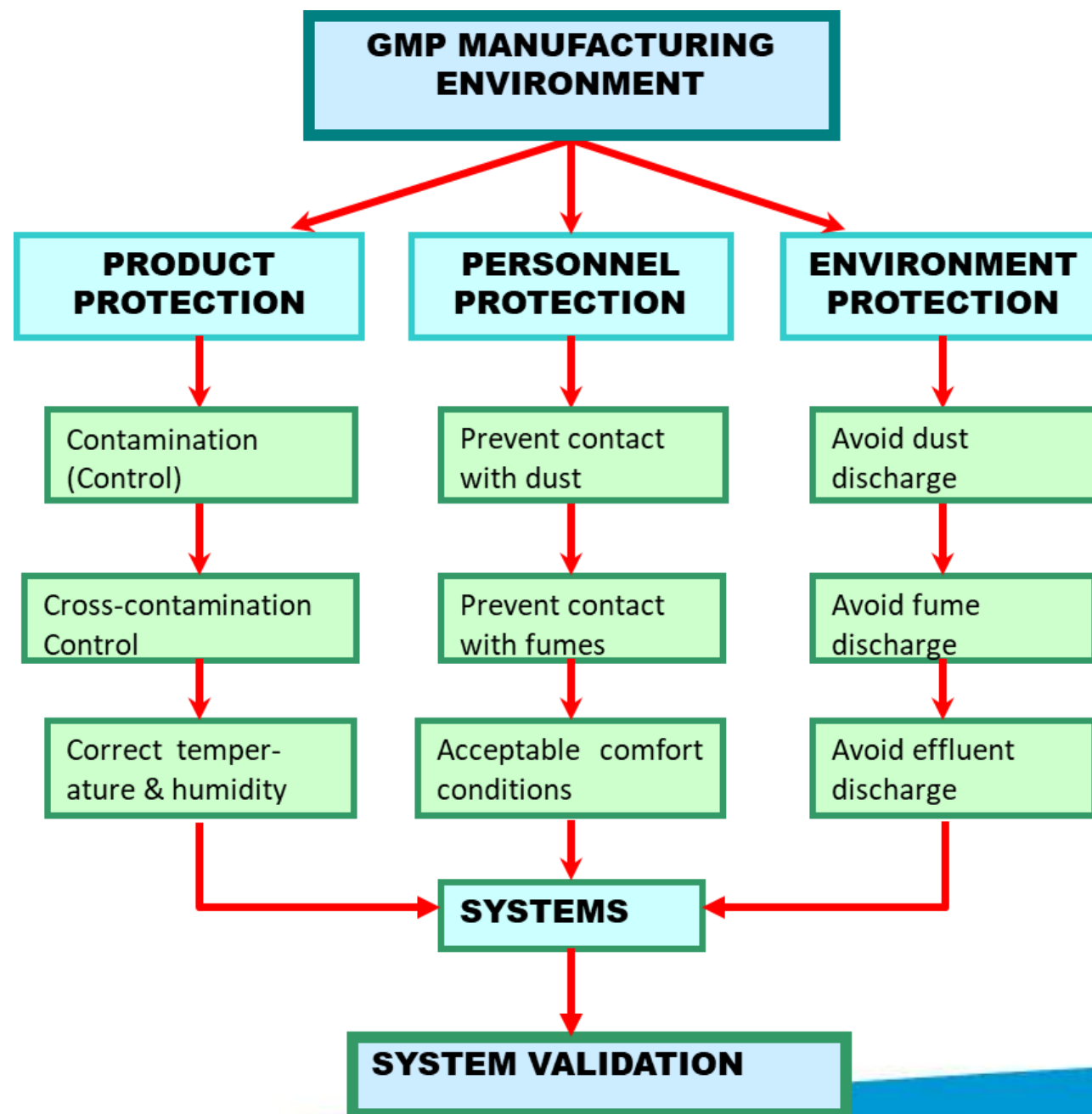


Starting information needed

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,.....

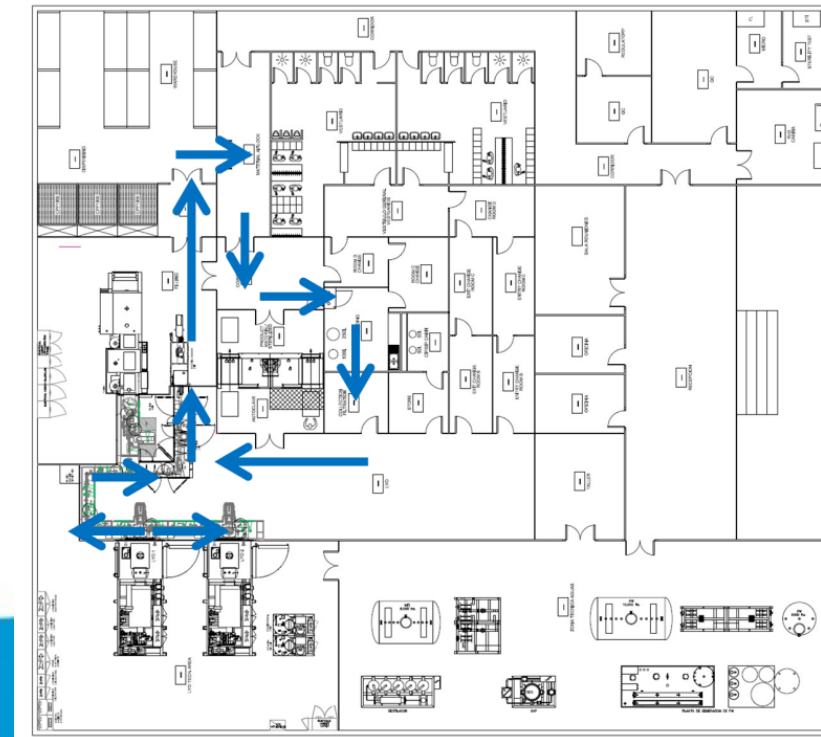
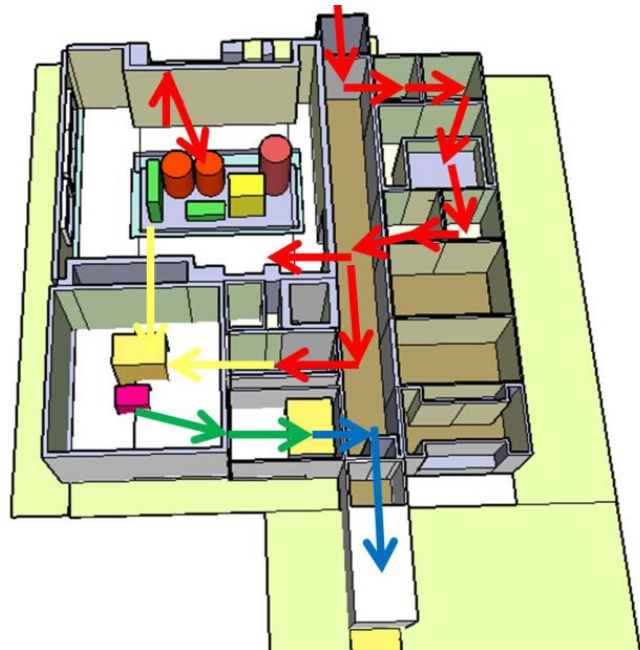




Shell-like containment control concept

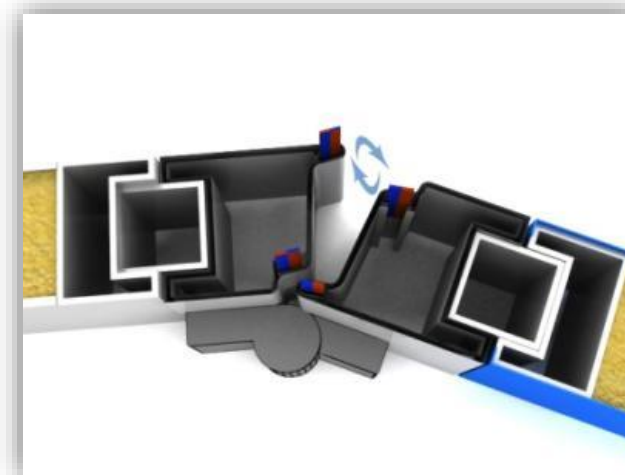
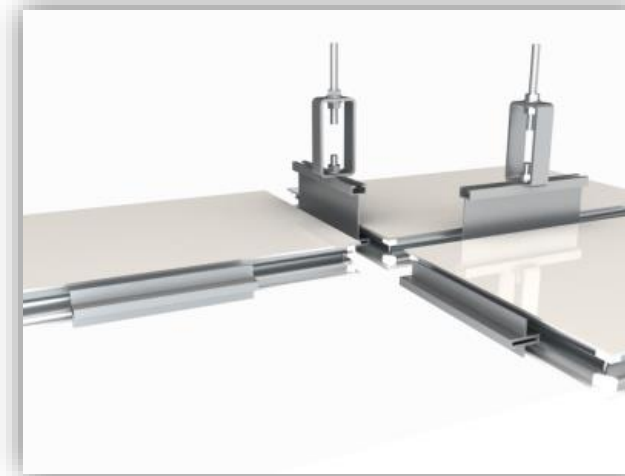
Segregation

- 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



Architecture

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



Critical Systems

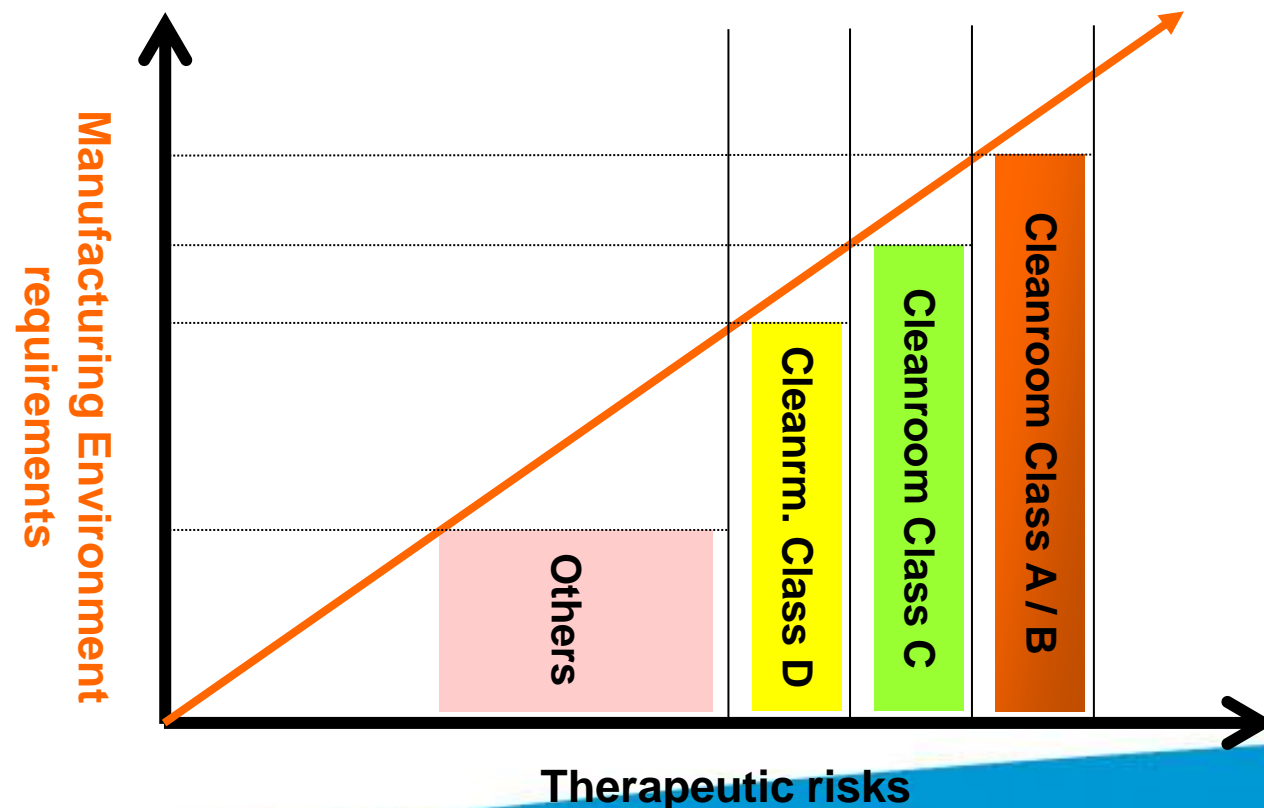
- It is defined:
 - HVAC
 - Electricity and Lighting
 - Clean Steam (CS) / Pure Steam (PS)
 - Sterile Compressed Air (SCA)
 - Purify Water (PW) & Water For Injection (WFI)
 - Waste Treatment/BIOWASTE
 - CIP/SIP
 - Special Gases
 - Vacuum
 - SAS
 - Other Installations



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



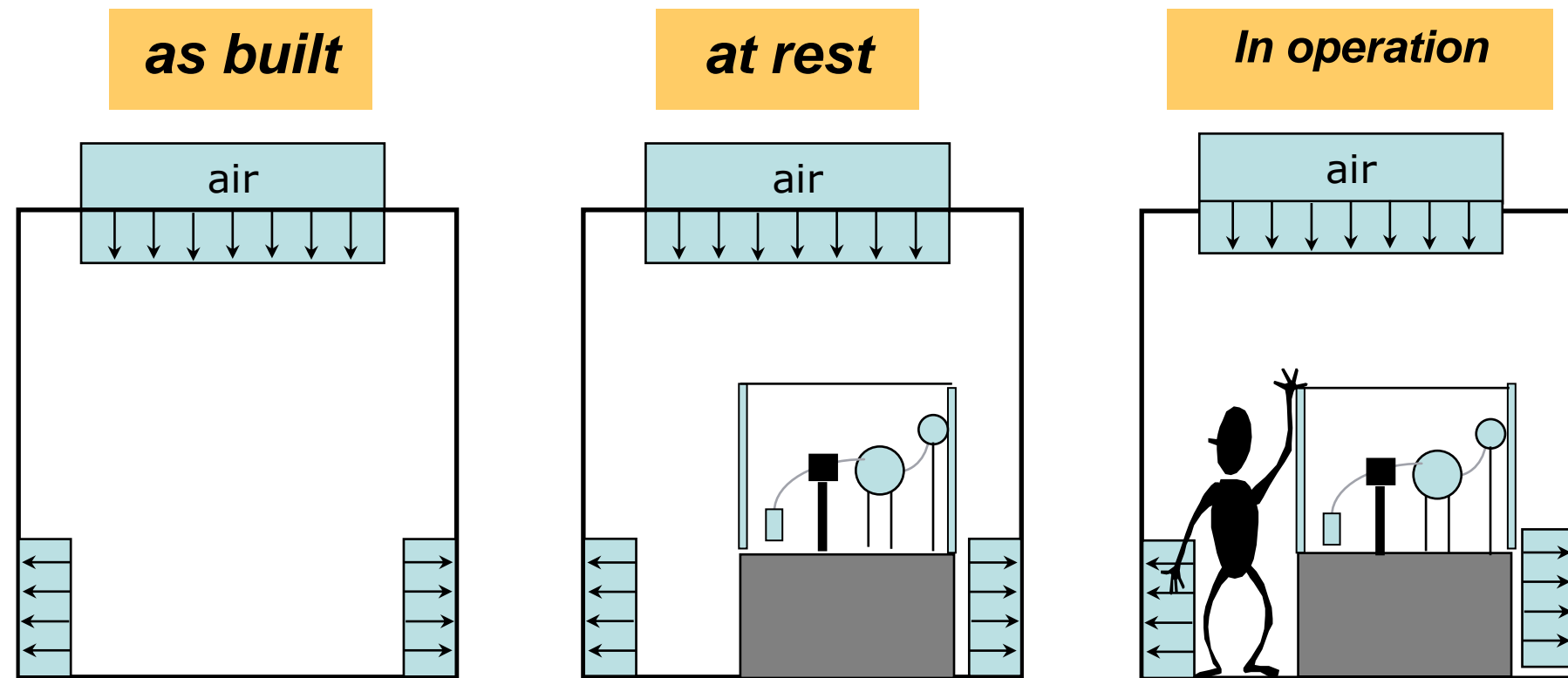
☐ By using ISOLATORS, that set a physical barrier between the product and the environment

☐ 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).

Environment classification



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.

Sterile Operations

Grade Examples of operations for terminally sterilized products

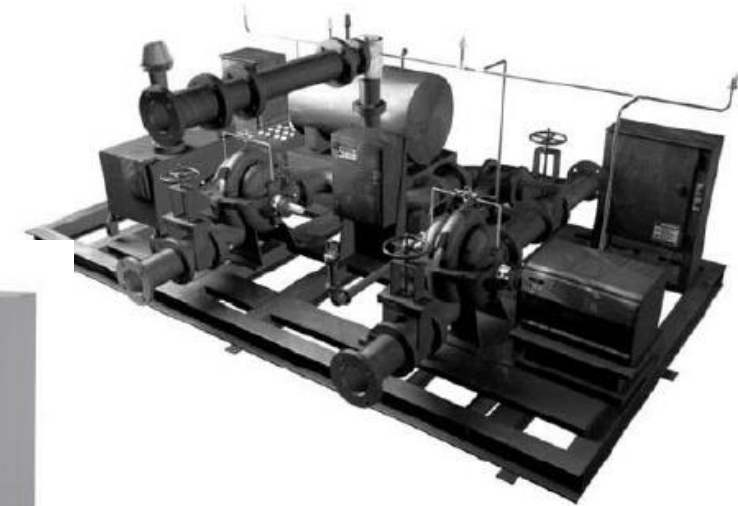
- A Filling of products, when unusually at risk
- C Preparation of solutions, when unusually at risk. Filling of products
- D Preparation of solutions and components for subsequent filling

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



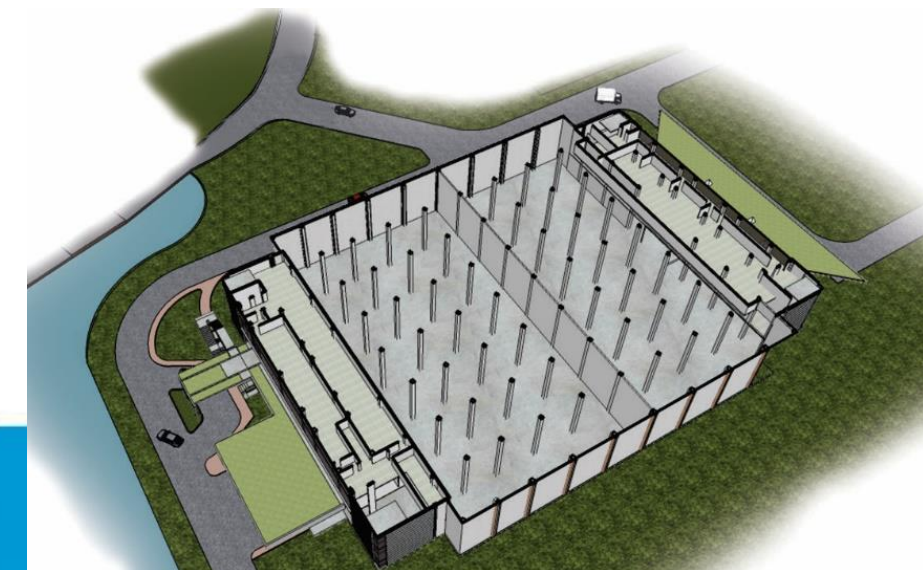
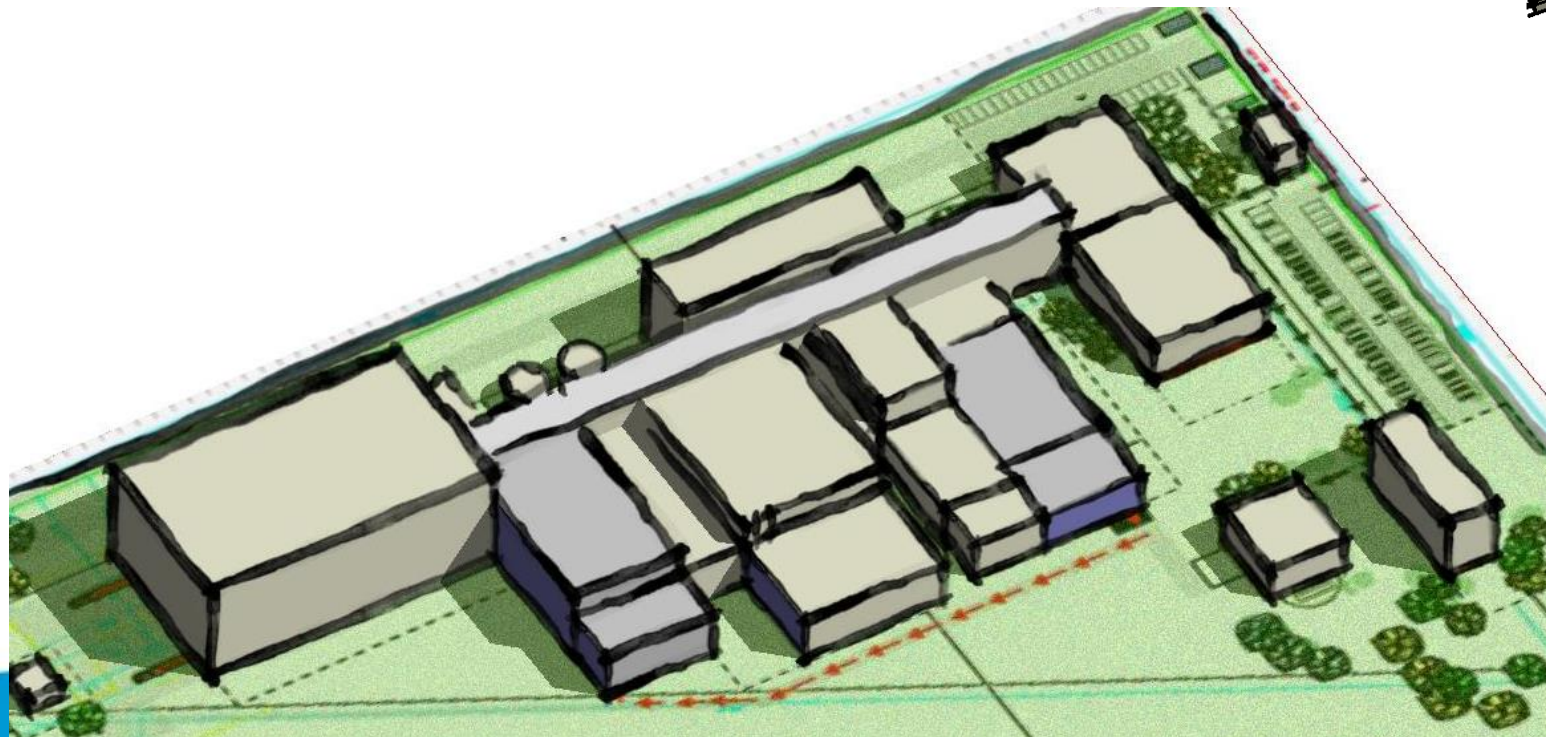
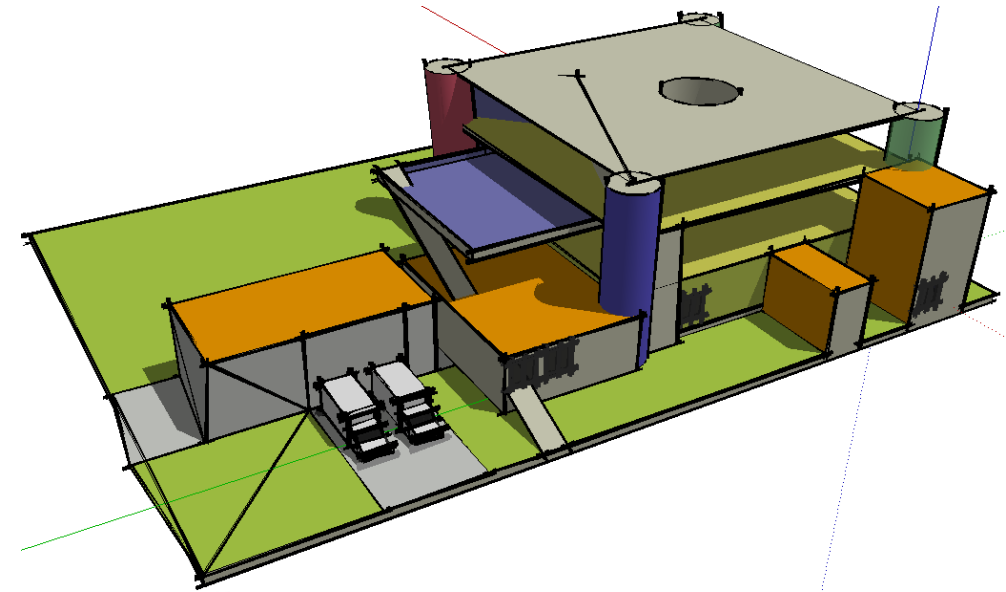
Utilities, architecture and lay out



Drawings

The following ones are developed:

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

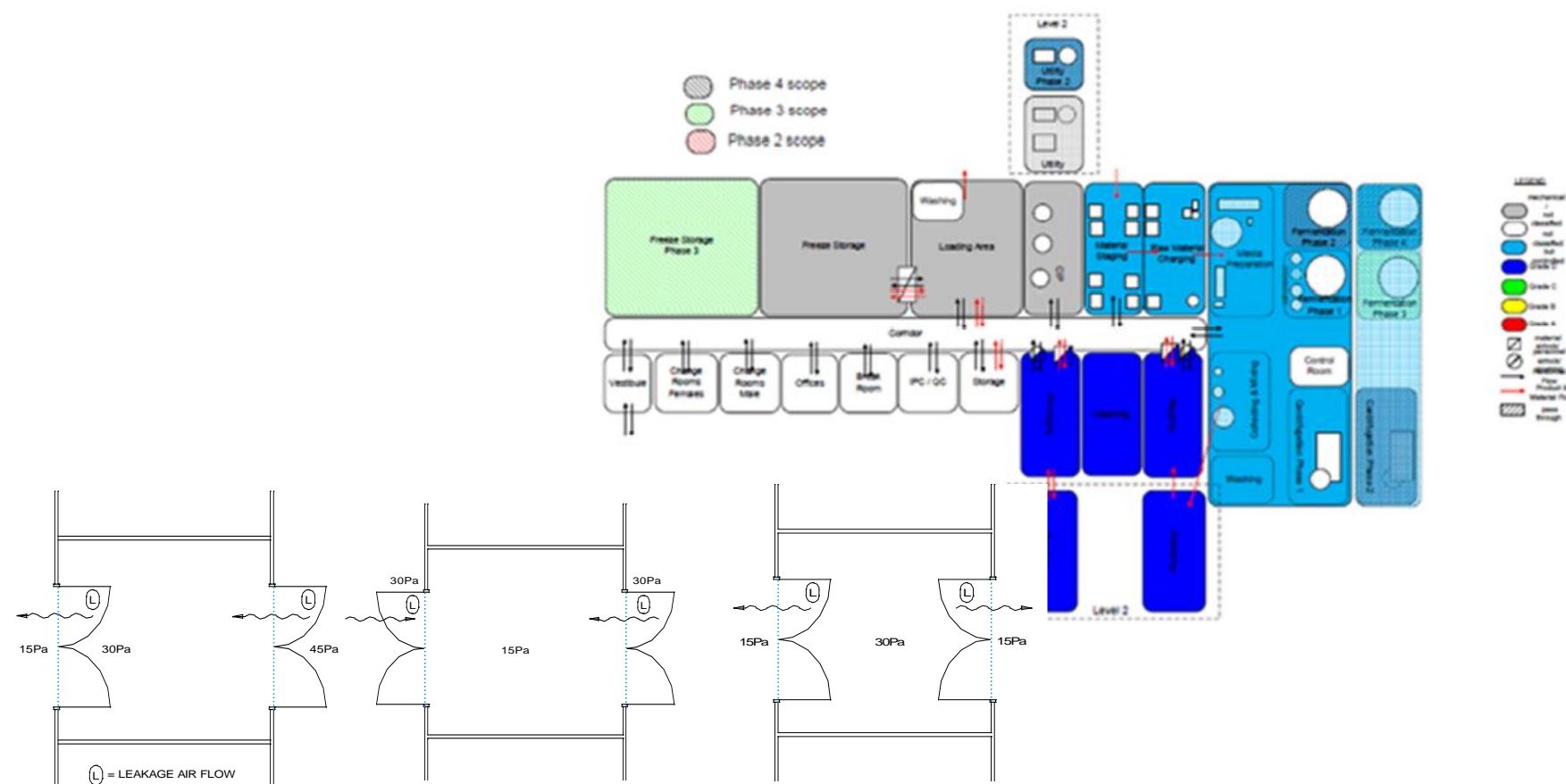


Drawings

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



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)

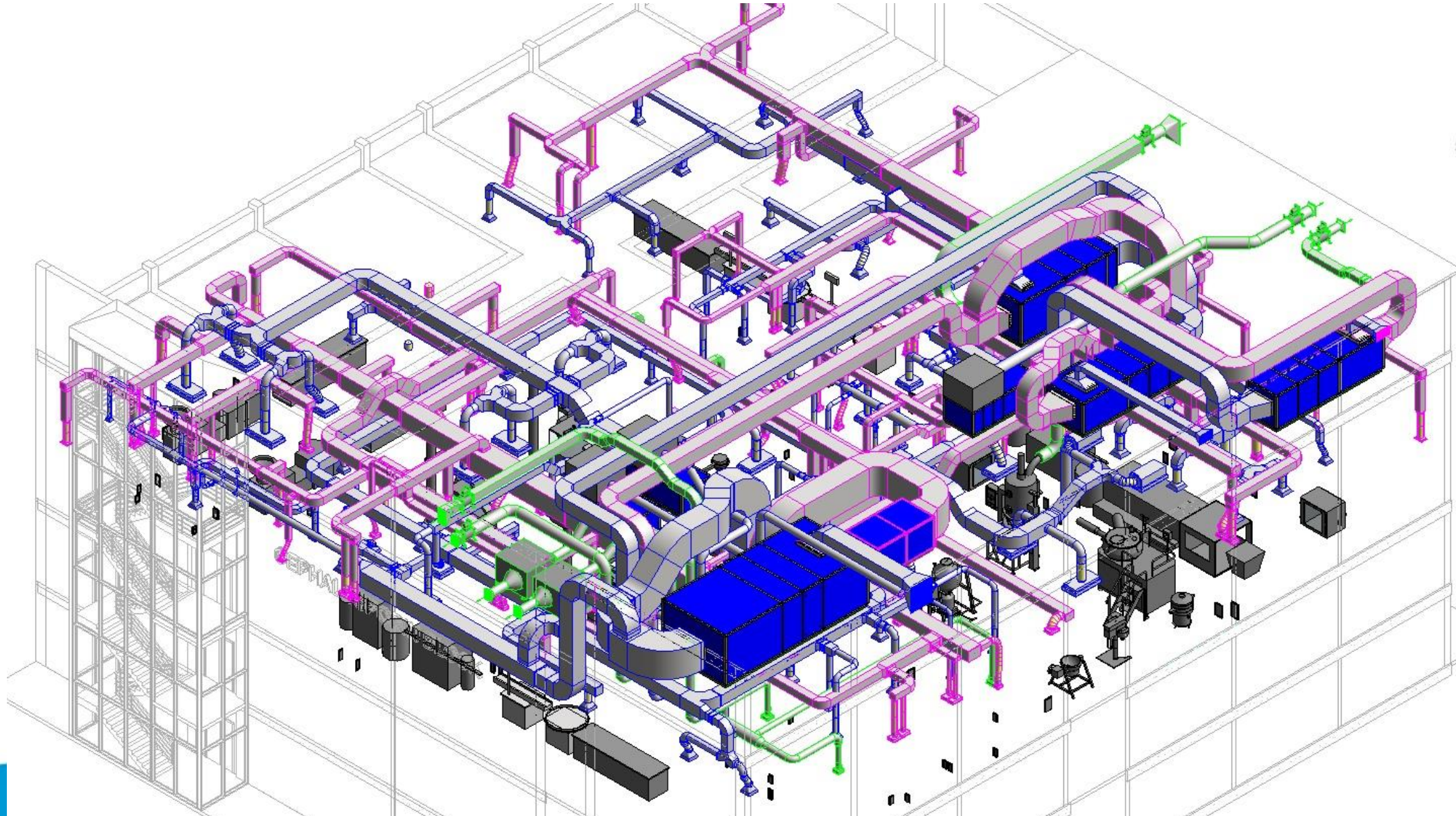
Blending
(Bin Blender)

Drawings

The following ones are developed:

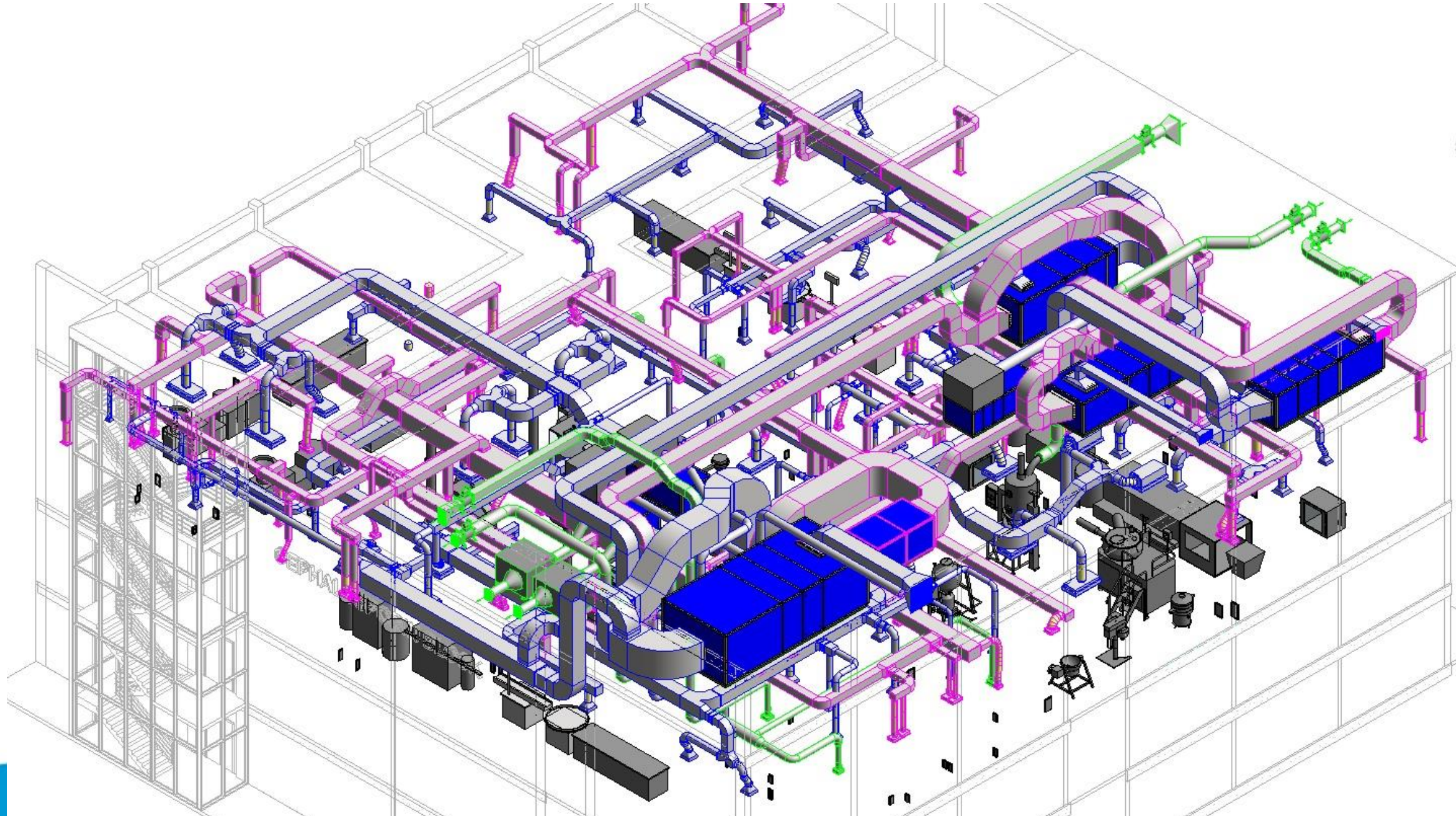
- **PFD**
- **Utilities drawings**
 - HVAC Diagrams
 - Electrical Diagrams
 - Steam Diagrams
 - Purify Water and Water for Injections Diagrams
 - Compressed Air Diagrams
 - Fire Protection Diagrams
 - CIP/SIP, BIOWASTE, etc.

Equipment considerations



Equipment

- 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



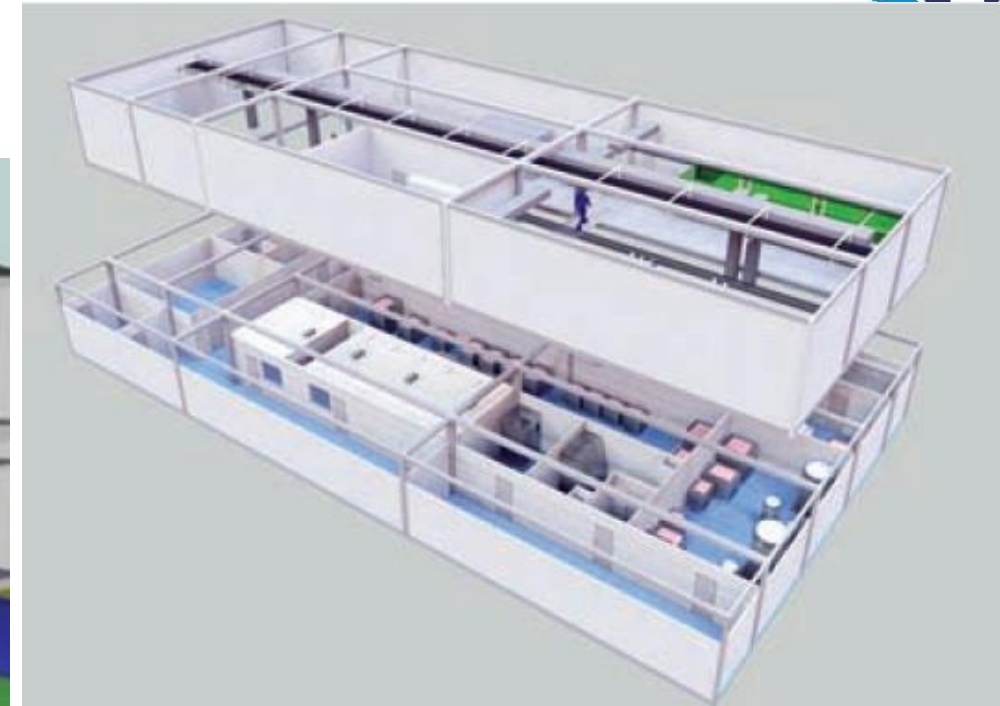
Last industry trends



AUTOMATIC LOADING SYSTEMS



MODULAR FACILITIES



Source KP



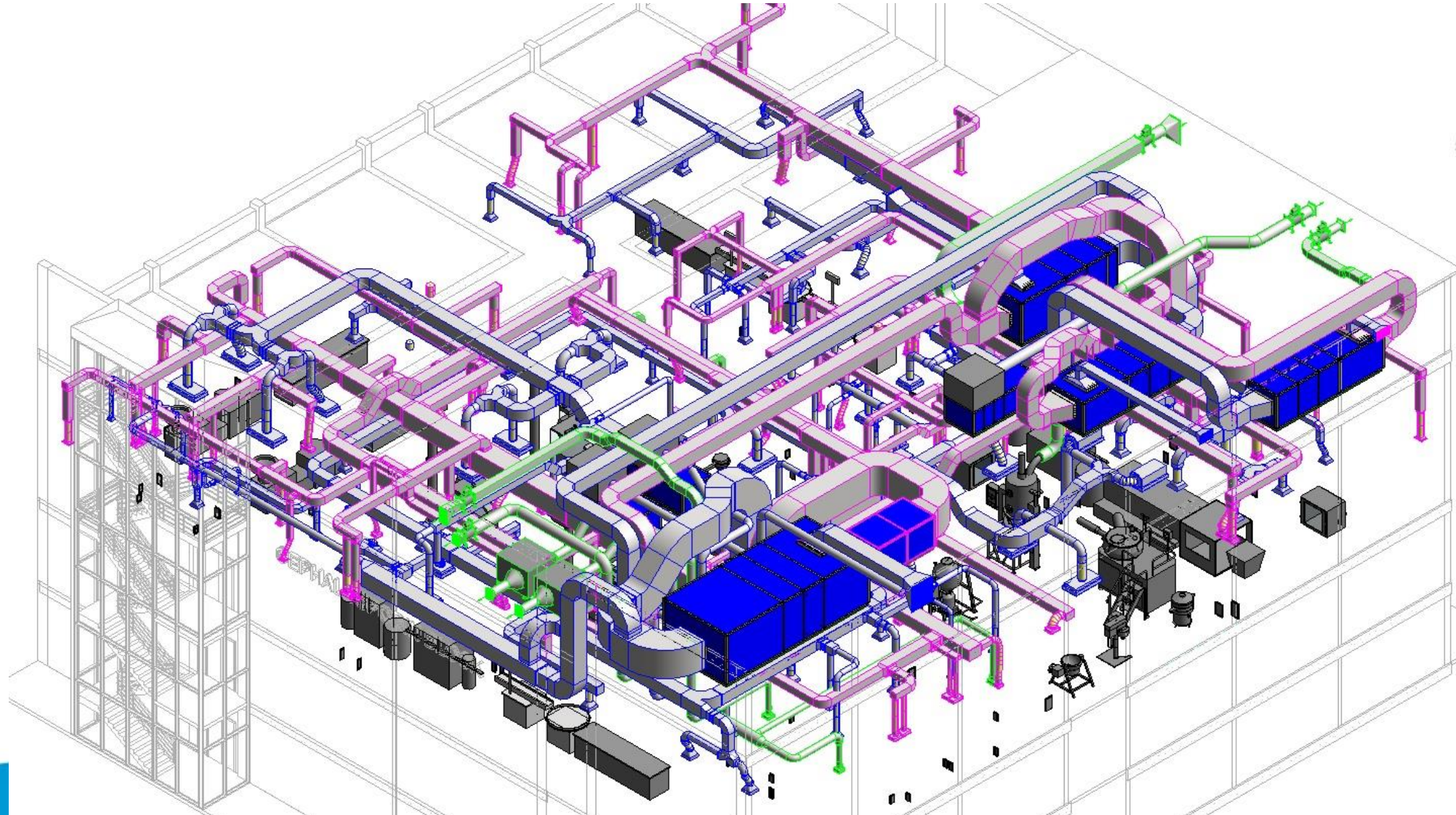
SINGLE USE FACILITIES



	Stainless Steel Facility	Single-Use Facility
Construction Time	16 months	14 months
Total Facility Area	12,153 ft ²	745 ft ²
Total Process Area	6,372 ft ²	6,781 ft ²
<i>Class C area</i>	1,109 ft ²	667 ft ²
<i>Class D area</i>	5,231 ft ²	3,315 ft ²
<i>CNC area</i>	0 ft ²	2,745 ft ²
Piping Length	2,854 ft ²	886 ft ²
Total Equipment Cost	€17.3 million	€15.0 million
Process Equipment Cost	€4 million	€3 million

Source GE





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>