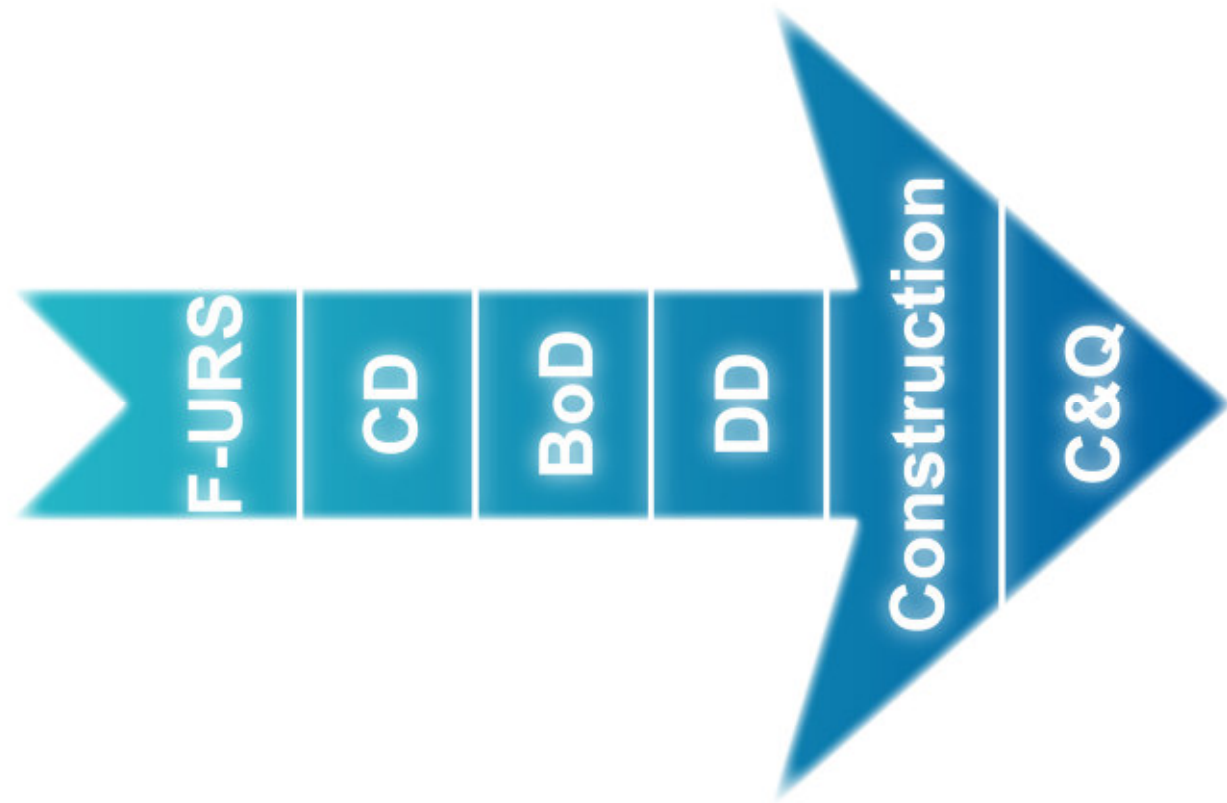




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Project Setup: From the Beginning  
until the End



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## Table of Contents

Steps, structure and organization of a facility design, planning and construction project:

- Facility URS
- Conceptual Design
- Basis of Design
- Detailed Design
- Construction
- Commissioning

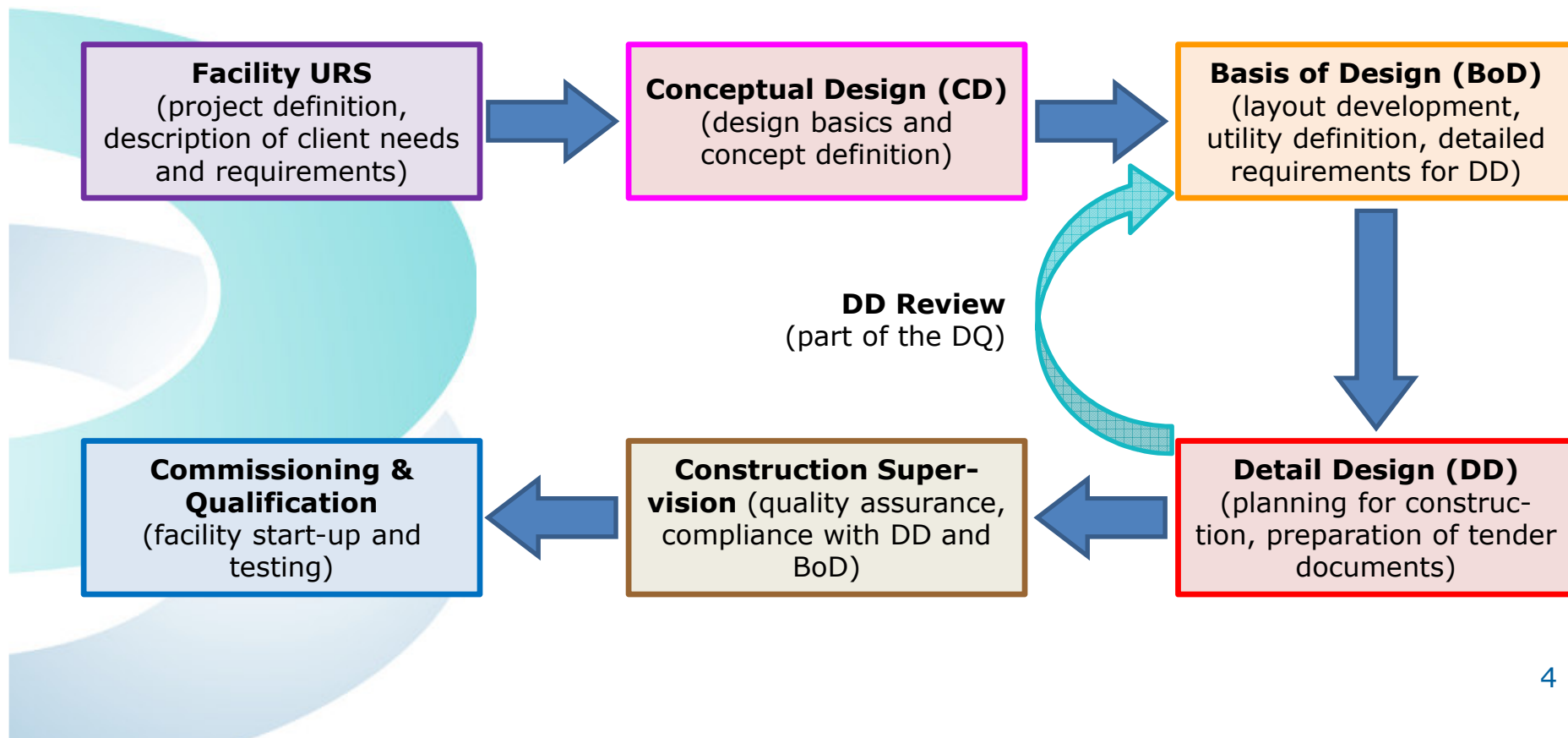


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## Relevant Guidelines

- Local Guidelines (NRA)
- Current WHO GMP guidelines (documented in technical report series, TRS)
- WHO biosafety guidelines
- Product-specific WHO guidelines (TRS containing GMP and biosafety relevant information)
- European GMP guidelines (EudraLex, Volume 4)
- ISPE good engineering practice guidelines

## Project Steps – Design & Realization





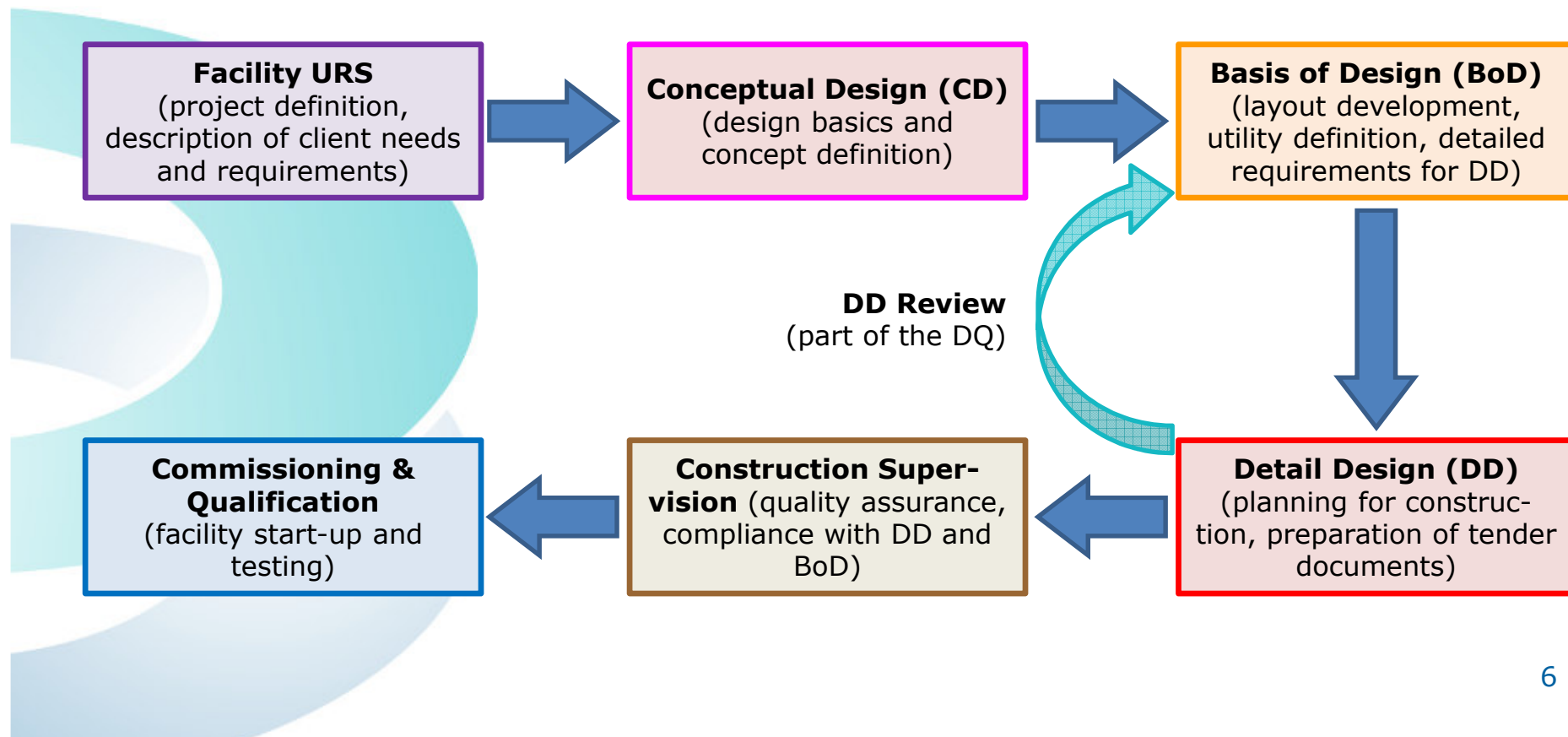
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## Basic Structure of Documents

To be described in increasing detail with the progress of a project (F-URS, CD, BoD)

<b>1</b>	<b>INTRODUCTION</b>	<b>4</b>	<b>FACILITY DESCRIPTION</b>
1.1	Project Background	4.1	Facility Design Basics
1.2	Purpose and Objectives	4.2	Process Description
1.3	Scope	4.3	Equipment Concepts
1.4	Project Organization	4.4	Media- and Buffer Preparation
1.5	Abbreviations and Definitions	<b>5</b>	<b>UTILITIES</b>
1.6	Guidelines and Regulatory Requirements	5.1	Building Utilities (Black Utilities)
<b>2</b>	<b>FACILITY DESIGN BASICS</b>	5.2	Process Utilities (Clean Utilities)
2.1	GMP Basics	<b>6</b>	<b>HVAC</b>
2.2	Biosafety Basics	6.1	Clean Room Operating Parameters
<b>3</b>	<b>BUILDING PROPERTIES</b>	6.2	UAF / LAF Operating Parameters
3.1	Site Description	6.3	Air Filtration
3.2	Building Description	6.4	Ventilation Design Concept
3.3	Architectural Layout	6.5	Biosafety Containment Features
3.4	Building Concept	<b>7</b>	<b>COMPUTERIZED SYSTEMS</b>
3.5	Requirements for Interior Finishes	7.1	Building Automation System
		7.2	GMP Monitoring System

## Project Steps – Design & Realization



## Purpose

A “Facility User Requirement Specification” should fulfill the following purposes in a construction project:

- Summary of user requirements for the project
- Definition of basic conceptual requirements to be implemented for further planning
- Definition of the project organization and schedule
- Definition of the location (building / site) for project realization

## Inputs Required from Customers (I/II)

The following basic input is required to start with the F-URS:

- Type of product and related hazards (biosafety, toxicity, virus risk, etc.)
- Manufacturing process description / flow diagram, including media / buffer demand
- Processing capacities: Batch size, batches per year, target harvest volume / yield, etc.



## Inputs Required from Customers (II/II)

The following basic input is required to start with the F-URS:

- Basic equipment information: Disposable, single-use or reusable, max. working volumes, etc.
- Required / available utilities at the site / in the building
- Existing building and space available for project realization, or new building required?

## Conceptual Requirements

With the basic input, the following conceptual requirements can be defined:

- Required clean room grades for processing
- Material and personnel flows: Unidirectional or bi-directional
- Segregation of process steps (different rooms)
- Segregation of HVAC systems
- Segregation of utility systems

## Example of Input from Customer

### Schedule

原液生产周期和岗位定员: Bulk production cycle and staff number

工序 Process	生产周期 production cycle	岗位定员 staff number
溶液配制 solution preparation	4天 4 days	3人
细胞解冻复苏 Cell thawing	1天 1 day	2人
摇床种子扩增 Seed proliferation with Shaker	12天 12 days	3人
Wave 反应器准备及接种 WAVE reactor preparation and inoculation	2天 2 days	3人
Wave 反应器细胞扩增 WAVE reactor cell proliferation	5天 5 days	2人
200L 反应器准备及接种 200L reactor preparation and inoculation	2天 2 days	4人
200L 反应器种子扩增 200L reactor seed proliferation	3-6天 3-6 days	3人
2000L 反应器准备及接种 2000L reactor preparation and inoculation	2天 2 days	4人

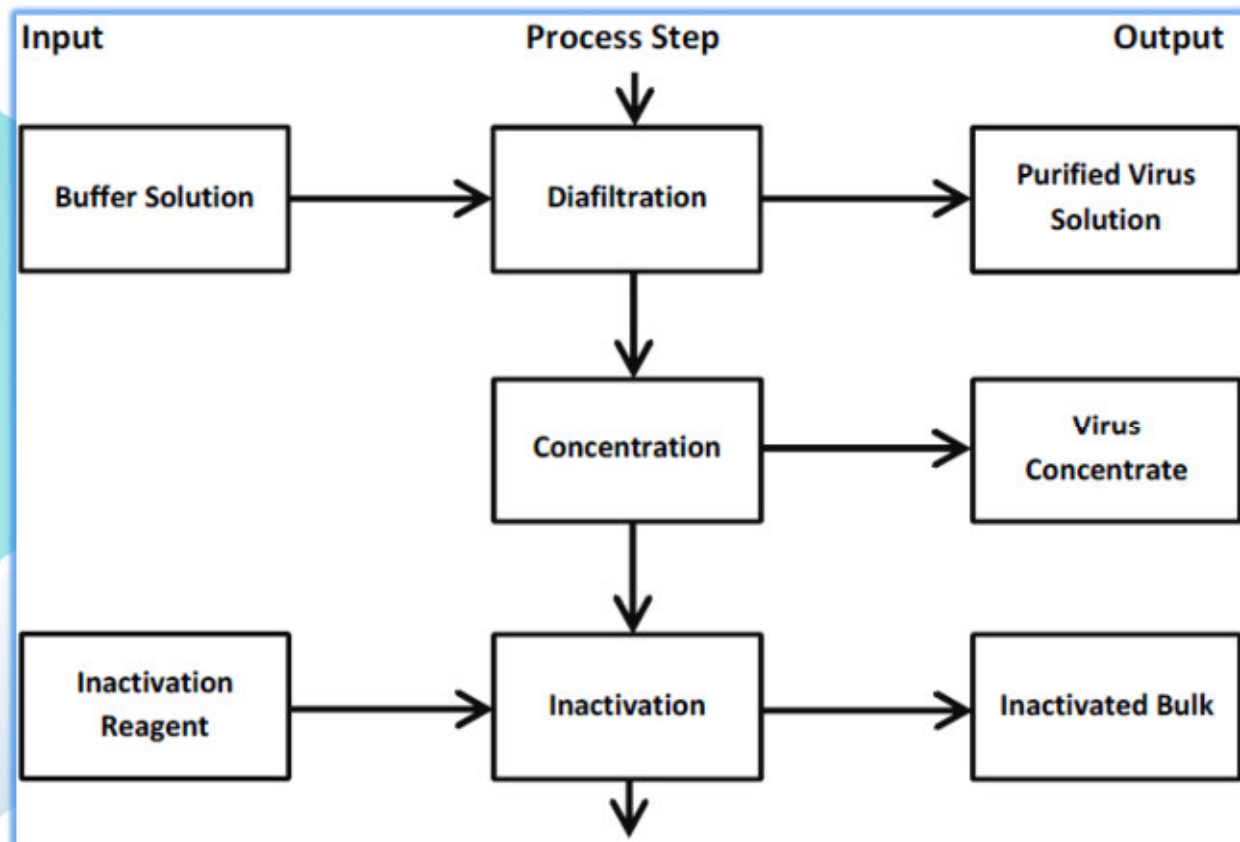
**Facility URS**  
 (project definition,  
 description of client needs  
 and requirements)

# Example of Output from CBC Schedule

Batch No	Train	Week																			
		1	2	3	4	5	6	7	8	9	10	...	40	41	42	43	44	45	46	47	48*
1	1	Flasks	Wave	2x200L	2x2000L																
2	2		Flasks	Wave	2x200L	2x2000L															
3	1			Flasks	Wave	2x200L	2x2000L														
4	2				Flasks	Wave	2x200L	2x2000L													
5	1					Flasks	Wave	2x200L	2x2000L												
6	2						Flasks	Wave	2x200L	2x2000L											
7	1							Flasks	Wave												
8	2								Flasks												
9	1									Flasks											
...	...																				
31	1																				
32	2																				
33	1																				
34	2																				
35	1																				
36	2																				
37*	1																				
38	2																				
39	1																				

## Example of Input from Customer

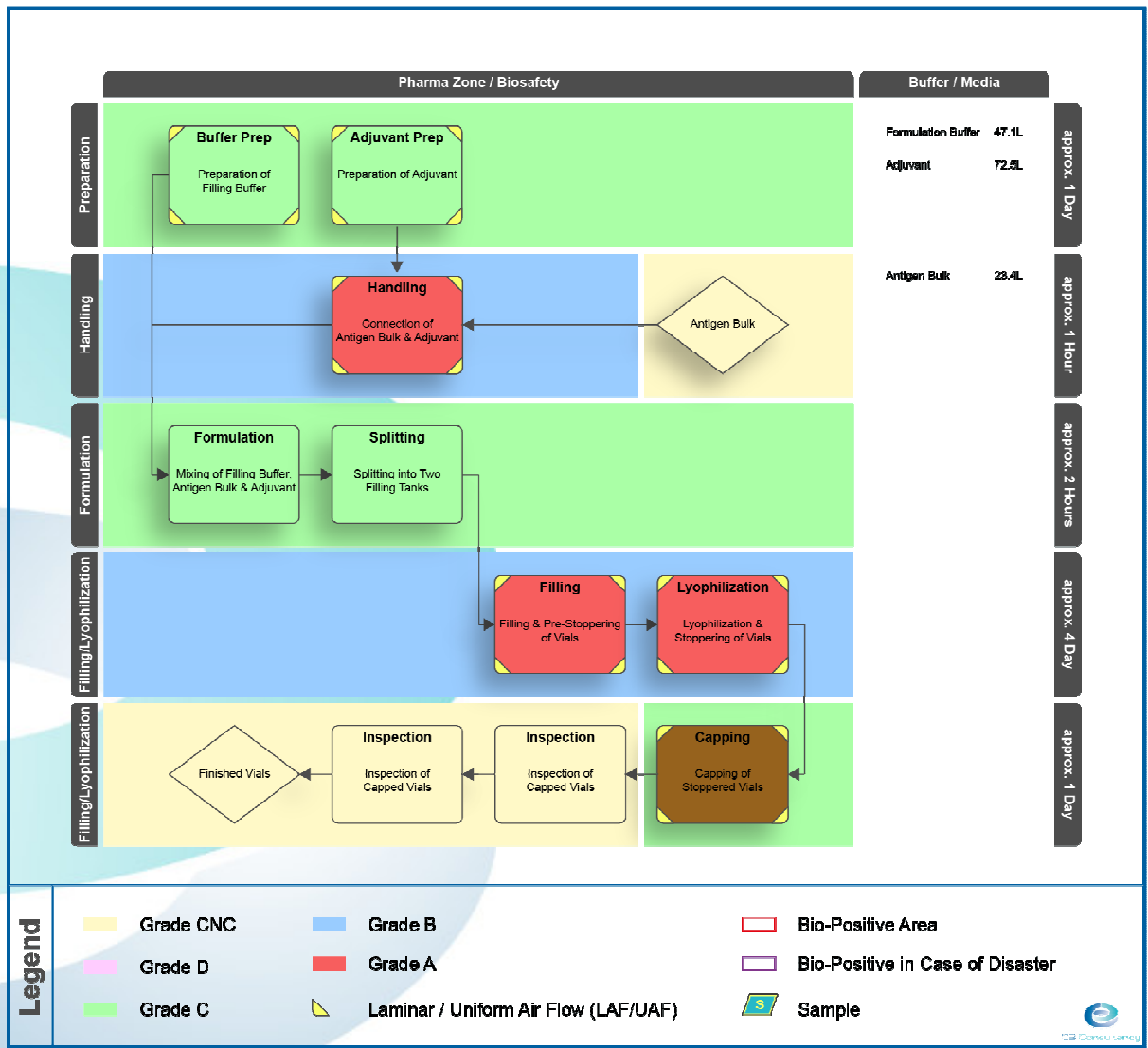
### Process Flow Diagram



# Example of Output from CBC



**Facility URS**  
(project definition, description of client needs and requirements)



## Process Flow Diagram

Process steps mapped against the required room grades defined in the GMP guidelines (A, B, C and D)

## Clean Room Grades

Required clean room grades (A, B, C, D) follow the GMP guidelines. The following concept applies:

- Grade D: For closed process steps (product not directly exposed to the clean room environment)
- Grade C: For open processing of unsterile intermediates (low bioburden)
- Grade A in B: For open processing under aseptic conditions (sterile products or max. contamination control)

=> see e.g. the WHO guideline "environmental monitoring of clean rooms", November 2012

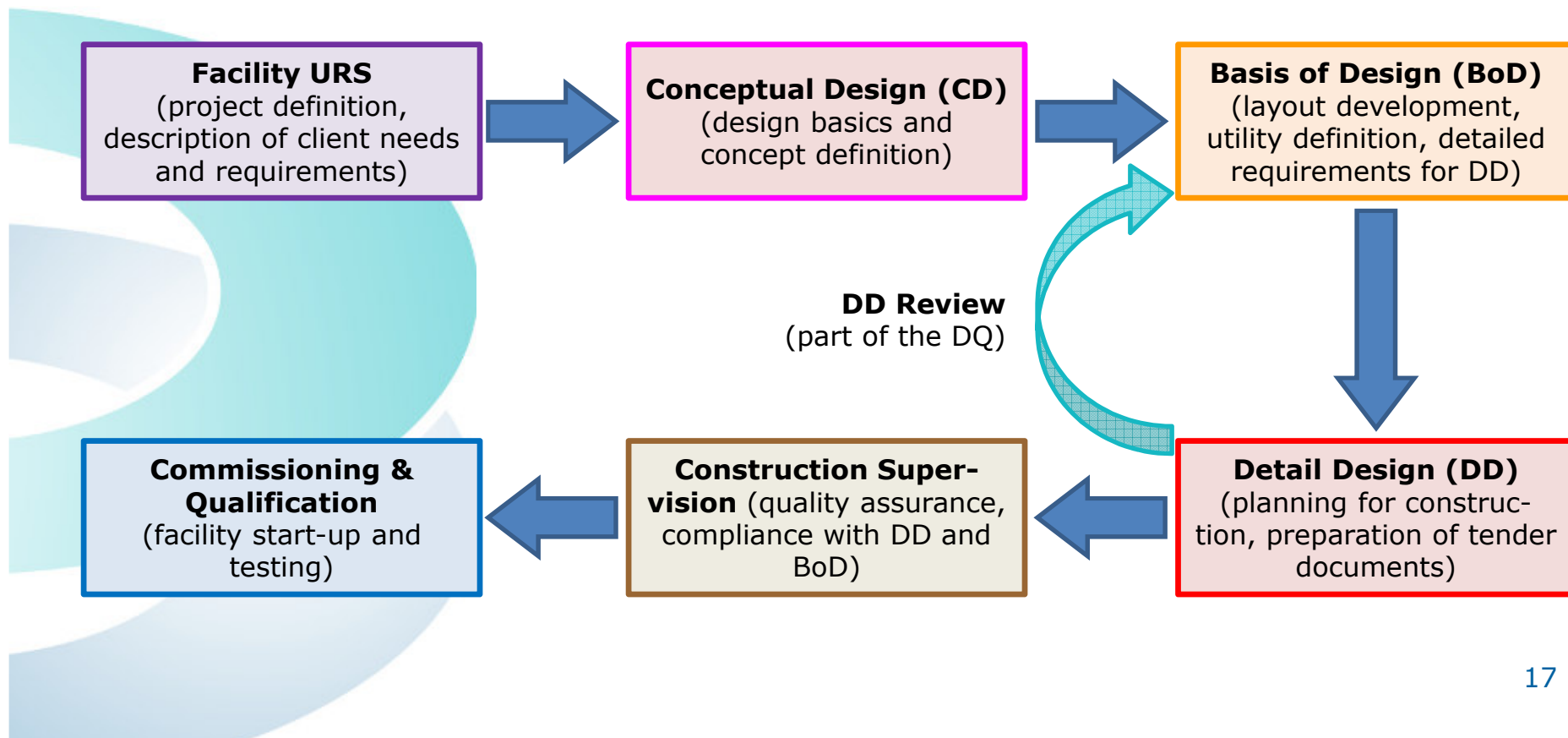
## Associated / Supportive Area

Definition of associated / supportive areas to be included in the project:

- Cleaning and sterilization area for equipment, small lab ware, garments, etc.?
- Buffer, solution and media preparation rooms?
- Area for production of master / working seed virus or bacteria (or master / working cell bench)?
- QC labs?
- Storage capacities for product in quarantine and released product?
- Etc.



## Project Steps – Design & Realization



## Purpose

A “Conceptual Design” document should fulfill the following purposes in a construction project:

- Definition of the building concept
- Definition of the basic facility properties and concepts (e.g. GMP, biosafety, utilities, HVAC, automation, etc.)
- Provides all concepts for further planning in basis of design (BoD) phase
- Development of basic layout



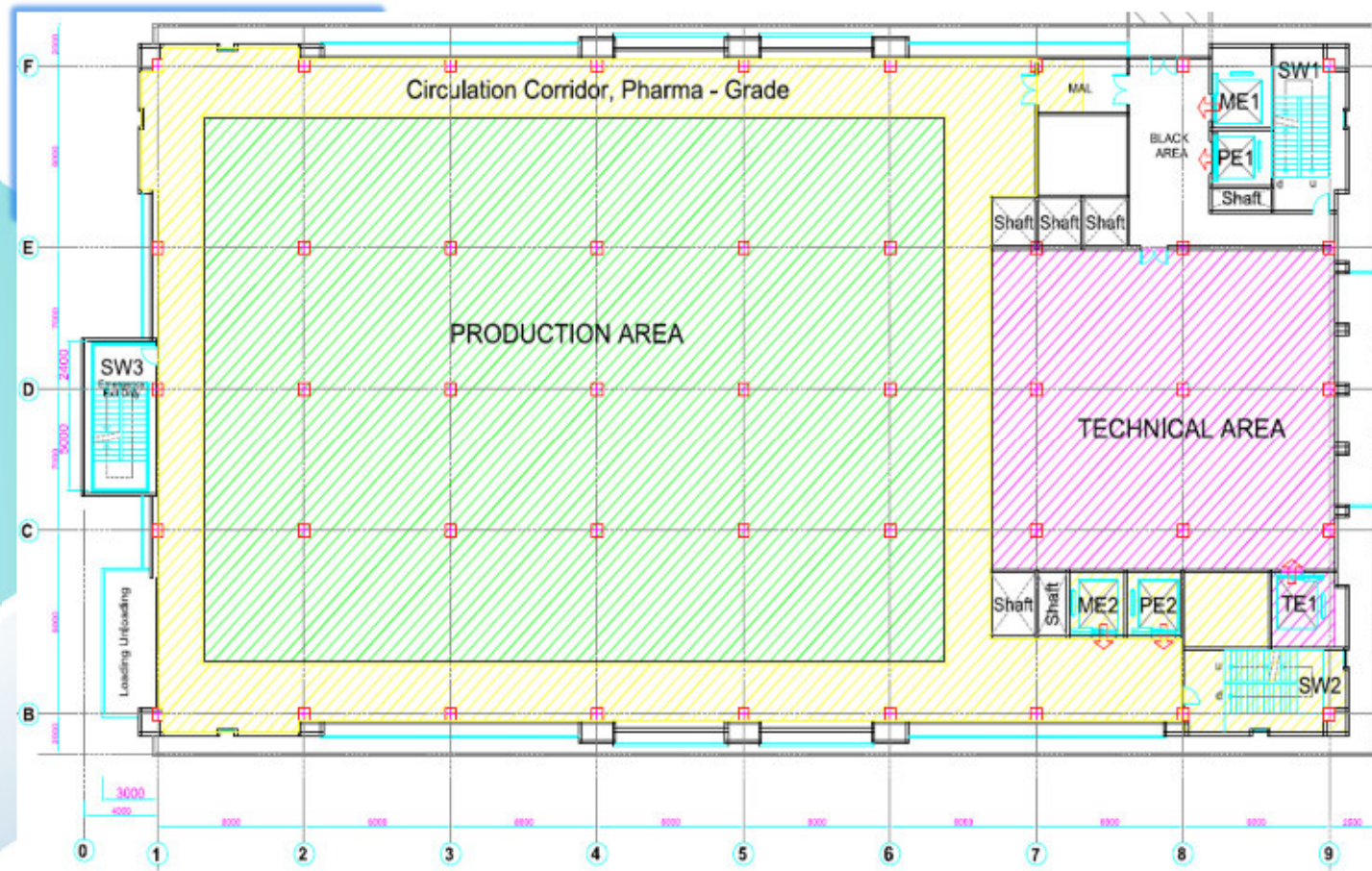
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**Conceptual Design (CD)**  
(design basics and  
concept definition)

# Output from CD Phase (Example)

Building footprint with layout concept

Layout Concept





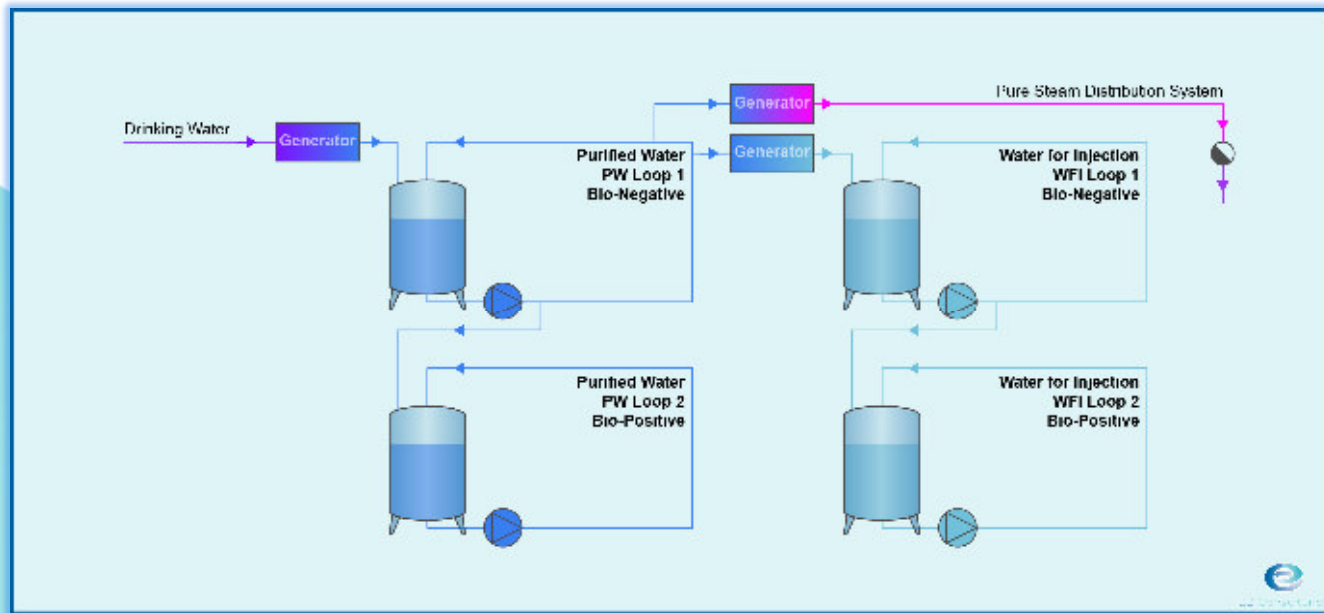
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**Conceptual Design (CD)**  
(design basics and concept definition)

## Output from CD Phase (Example)

Clean utility concept showing generation and distribution of purified water, water for injection and pure steam

Clean Utility Concept



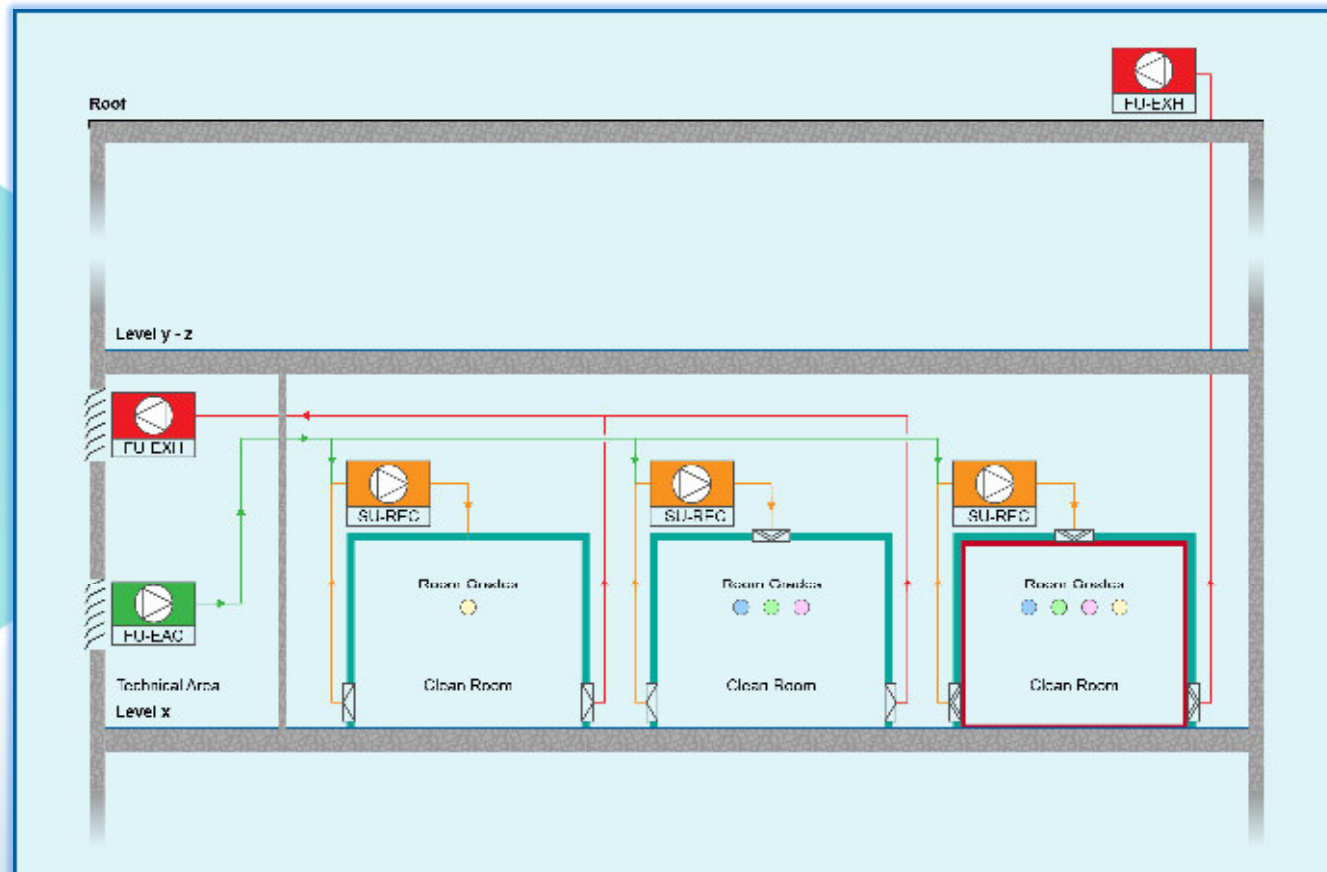


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**Conceptual Design (CD)**  
(design basics and  
concept definition)

## Output from CD Phase (Example)

HVAC concept illustrating air handling units supplying different room types.



HVAC Concept



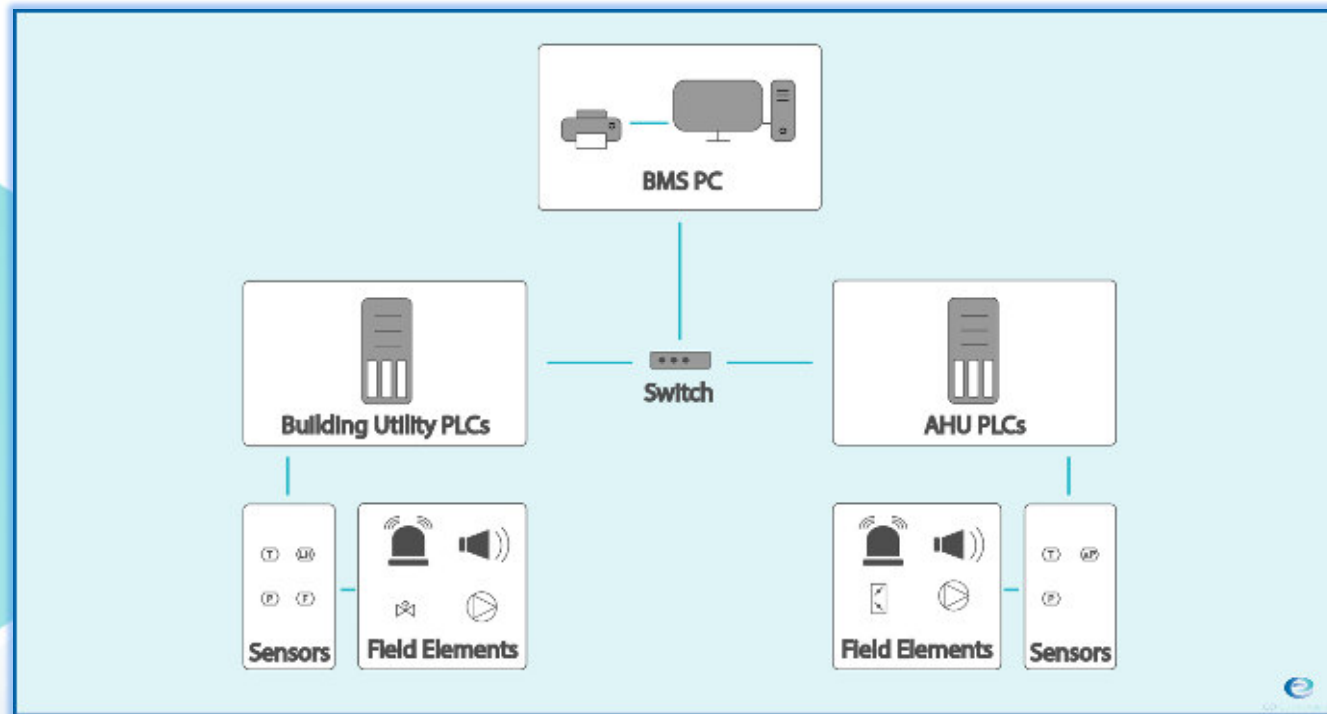
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**Conceptual Design (CD)**  
(design basics and  
concept definition)

## Output from CD Phase (Example)

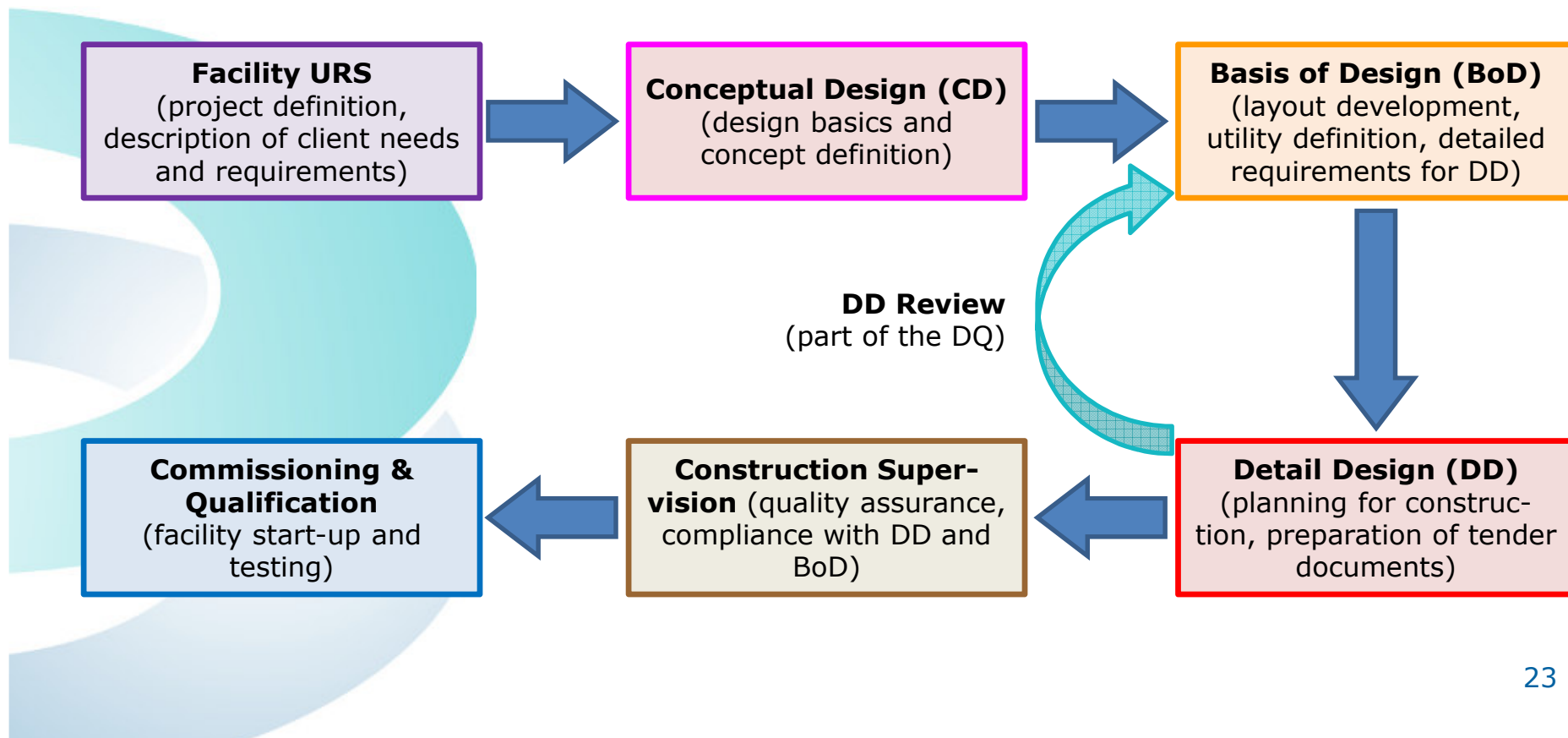
Automation concept showing the setup of the building management system.

Automation Concept





## Project Steps – Design & Realization



## Purpose

A “Basis of Design” document should fulfill the following purposes in a construction project:



- Definition of general technical solutions incl. approximate dimensioning (e.g. utilities, HVAC, automation, etc.)
- Definition of pressure cascades & AHU areas
- Detailed material, product and personnel flow incl. gowning concept
- Detailed layouts
- Provides the basis for detail design activities





## Output from BoD Phase (Example)

Gowning concept showing appropriate gowning for the different room grades.

Room Grade	Garment	Illustration / Example
CNC / D / C / B (Layer 1, underwear for all areas)	Socks Long underpants Sweatshirt / t-shirt	
Room Grade	Garment	Illustration / Example
B (Layer 2)	Socks Long underpants Sweatshirt Safety shoes Grade B (see picture) Full-body protective overall for Grade B (see picture) Gloves (see picture) Head cover (see picture) Safety goggles (see picture) Face mask (see picture)	

Gowning Concept



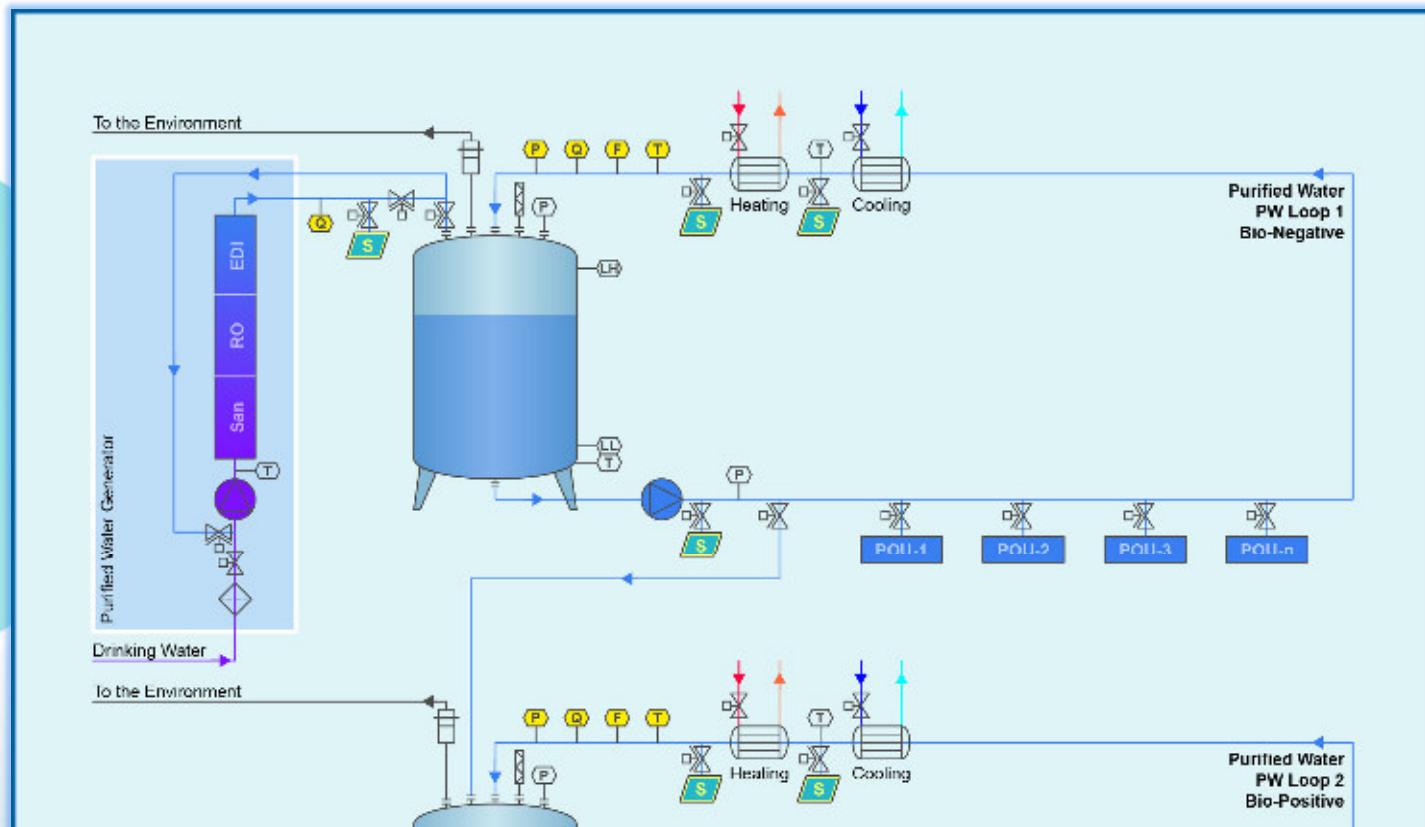
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**Basis of Design (BoD)**  
(layout development,  
utility definition, detailed  
requirements for DD)

## Output from BoD Phase (Example)

Detailed schematic for clean utilities showing POUs, sampling points & monitored parameters

Schematic for Purified Water





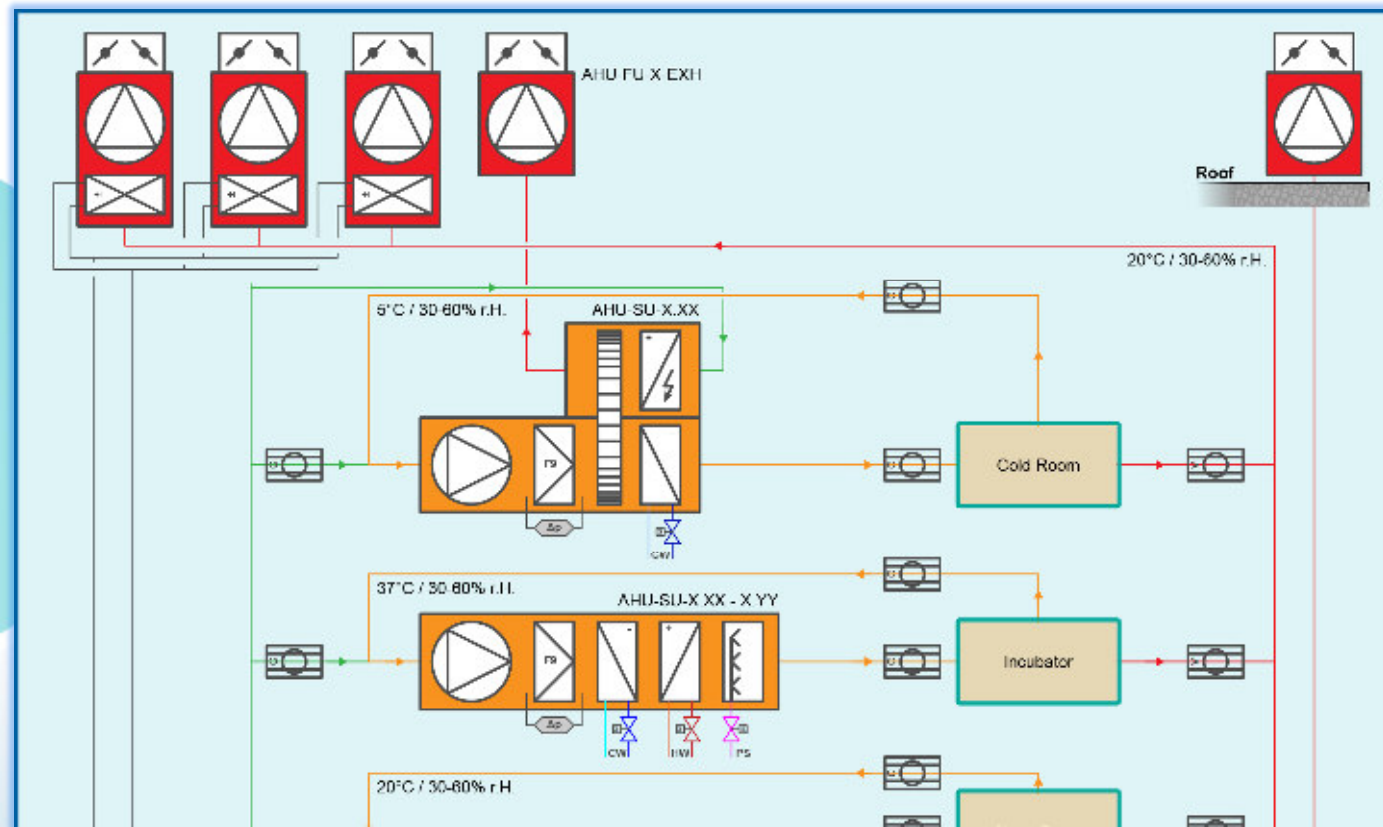


**Basis of Design (BoD)**  
(layout development,  
utility definition, detailed  
requirements for DD)

## Output from BoD Phase (Example)

Detailed schematic of AHUs showing the individual components and required utilities.

Schematic for HVAC





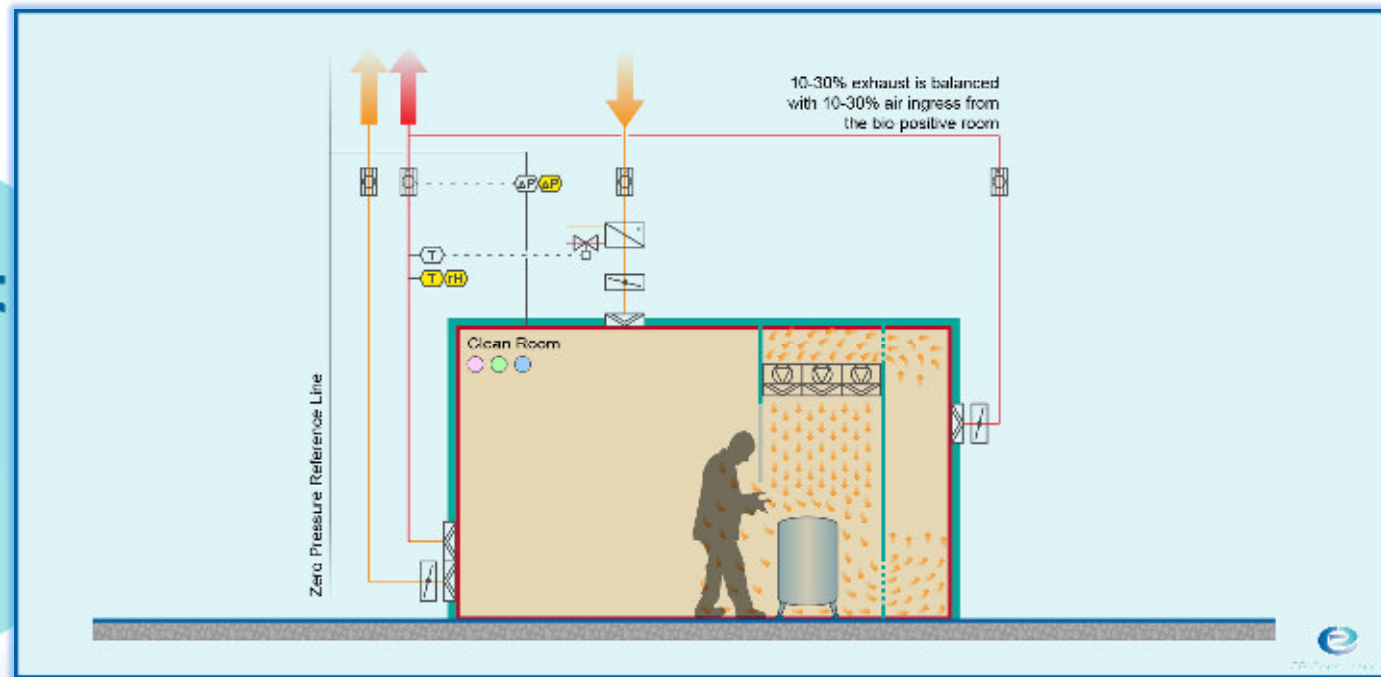
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**Basis of Design (BoD)**  
(layout development,  
utility definition, detailed  
requirements for DD)

## Output from BoD Phase (Example)

HVAC room typical for a bio-positive clean room with UAF providing inward air flow.

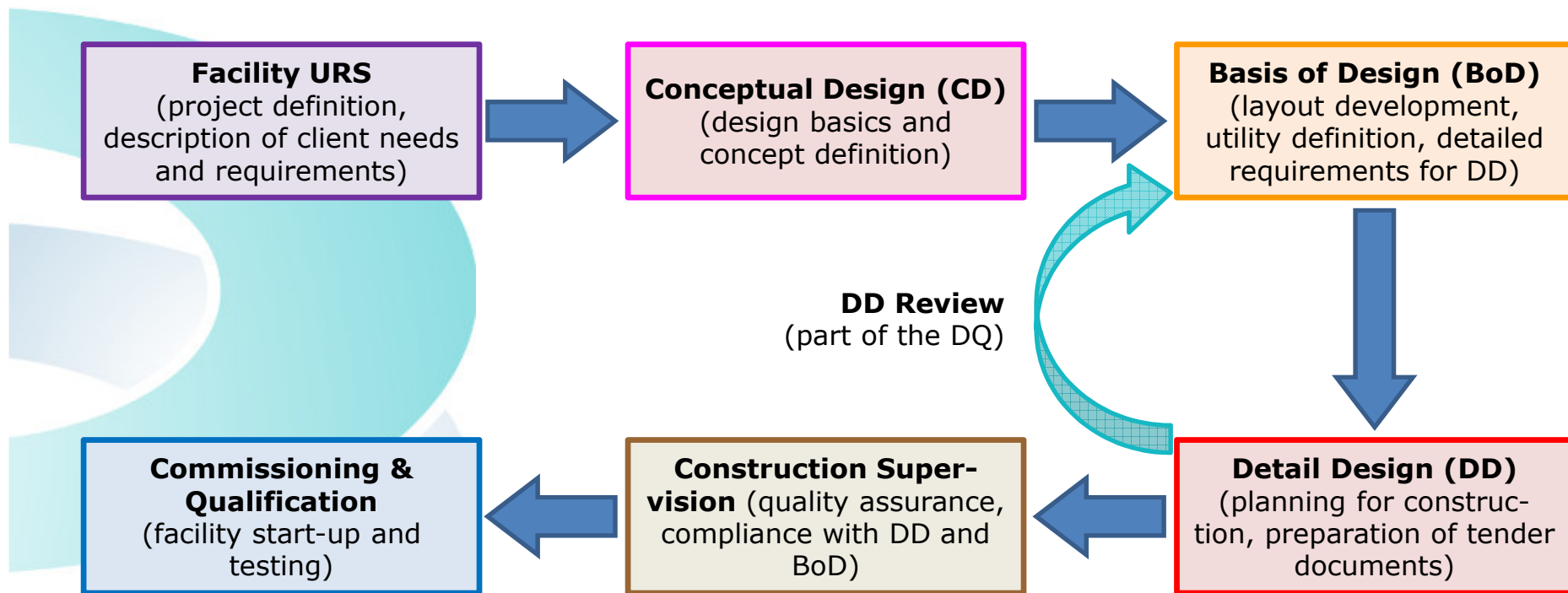
HVAC Room Typical

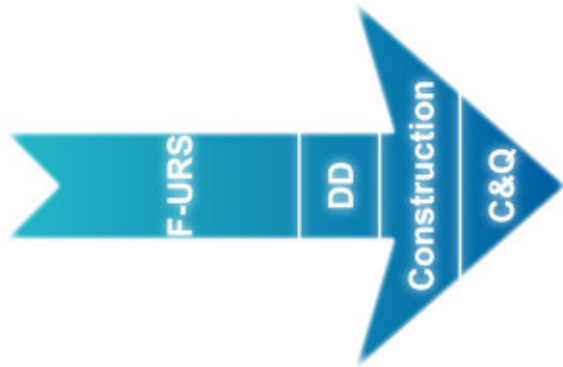




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## Project Consolidation & Acceleration



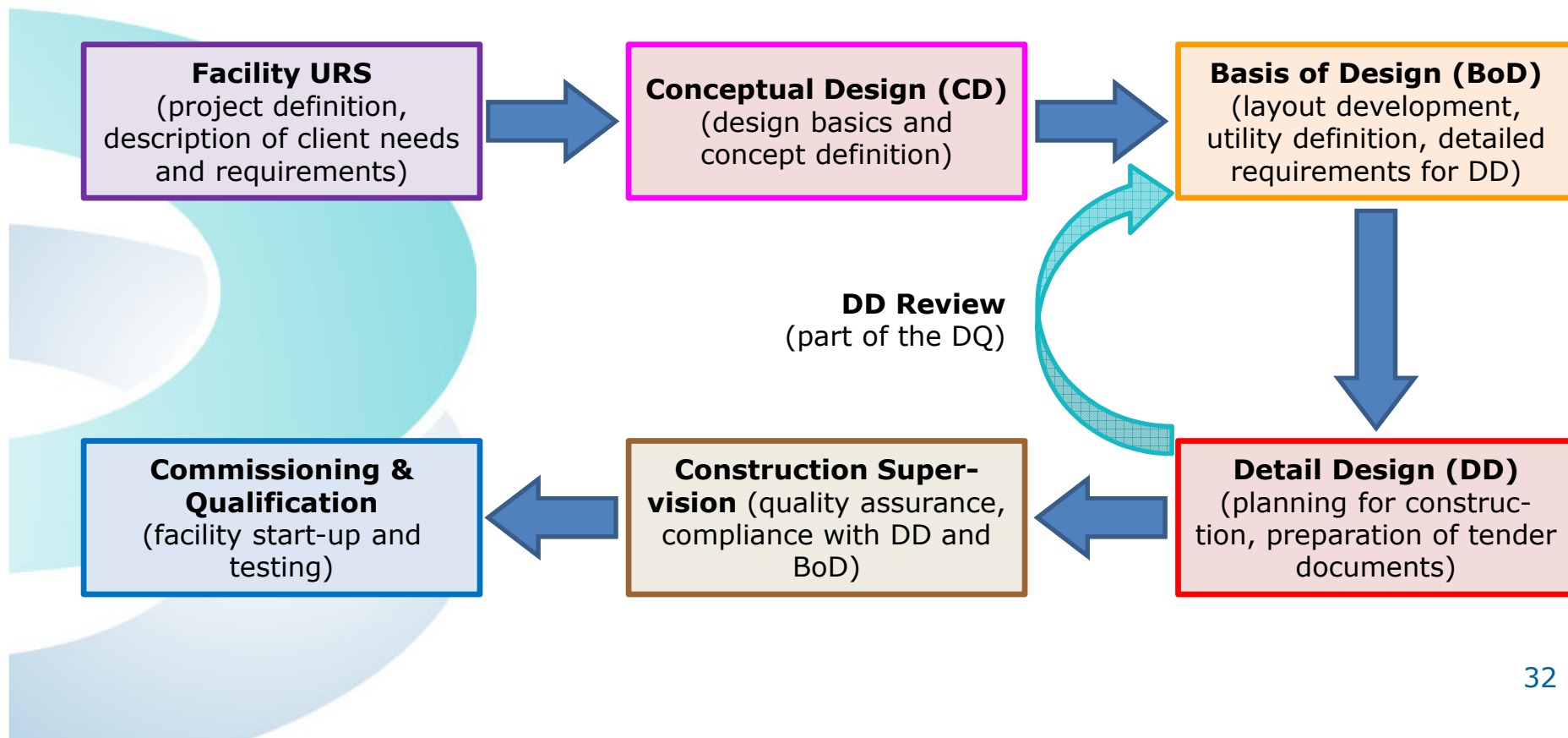


## Project Consolidation & Acceleration

Information from CD and BoD might be compiled in the F-URS document, providing the following advantages:

- 👍 Consideration of approved conceptual solutions in the early stage of a project (avoid re-inventing the wheel)
- 👍 Promotion of early (cheap) decisions
- 👍 Elimination of redundant information in different documents (F-URS, CD, BoD)
- 👍 Consolidation of any important information into one document (information is easy accessible)
- 👍 Acceleration of the project
- 👍 Cost effectiveness

## Project Steps – Design & Realization





## Purpose

A “Detail Design” phase should fulfill the following purposes in a construction project:

- Elaboration of tender documentation
- Distribution of bid packages to different supplier
- Evaluation of offers
- Selection of suitable suppliers
- Detailed planning for construction

## Output from DD Phase (I/III)

### Tender Documentation:

- Is issued by the planner
- Contains the following information:
  - General project and discipline description
  - Project organization & -schedule
  - Organization of the construction site
  - General terms and conditions
  - Detailed scope of work to be offered
  - Detailed list of deliverables
- Shall be reviewed by the customer
- Is distributed to suitable suppliers (at least three per discipline)

## Output from DD Phase (II/III)

### Selection of most suitable supplier:

- Typical process of supplier selection
  - Evaluation of offers (Planner)
  - Awarding & negotiation meetings (Planner/Customer/Supplier)
  - Revision of initial offer (Supplier)
  - Evaluation of revised offers (Planner)
  - Final negotiations (Customer)
  - Contract (Customer/Supplier)
- For GMP-relevant systems: Supplier Audit may be required

## Output from DD Phase (III/III)

### Detail Design Documents:

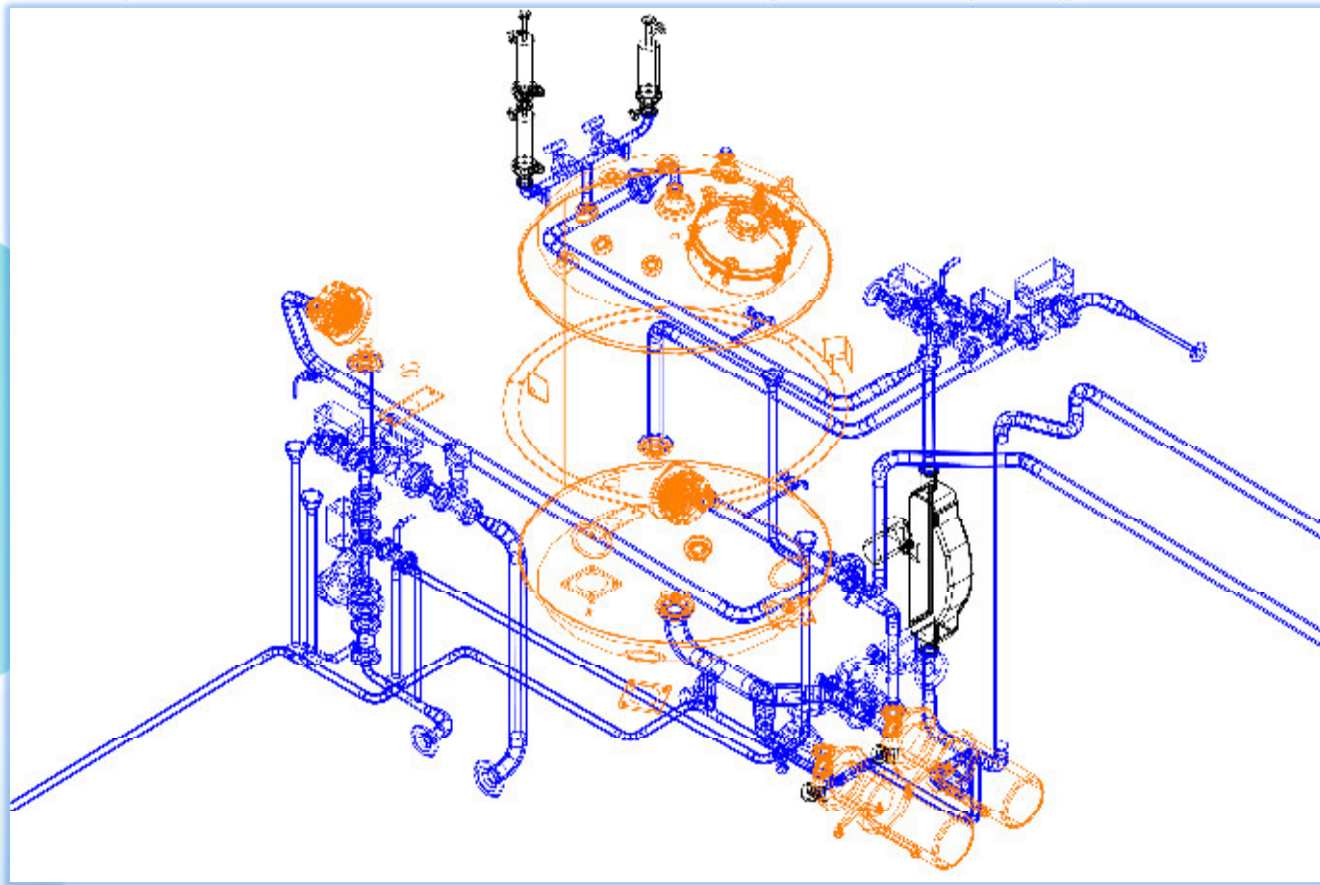
- Elaboration of detailed design
- Selection of most suitable materials & components
- Spatial coordination
- Interfaces to other disciplines
- Implementation plans for review by customer
- “Good for Construction” (GFC)



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**Detail Design (DD)**  
(planning for construction,  
preparation of tender  
documents)

## 3D Model WFI Distribution System Output from DD Phase (Example)



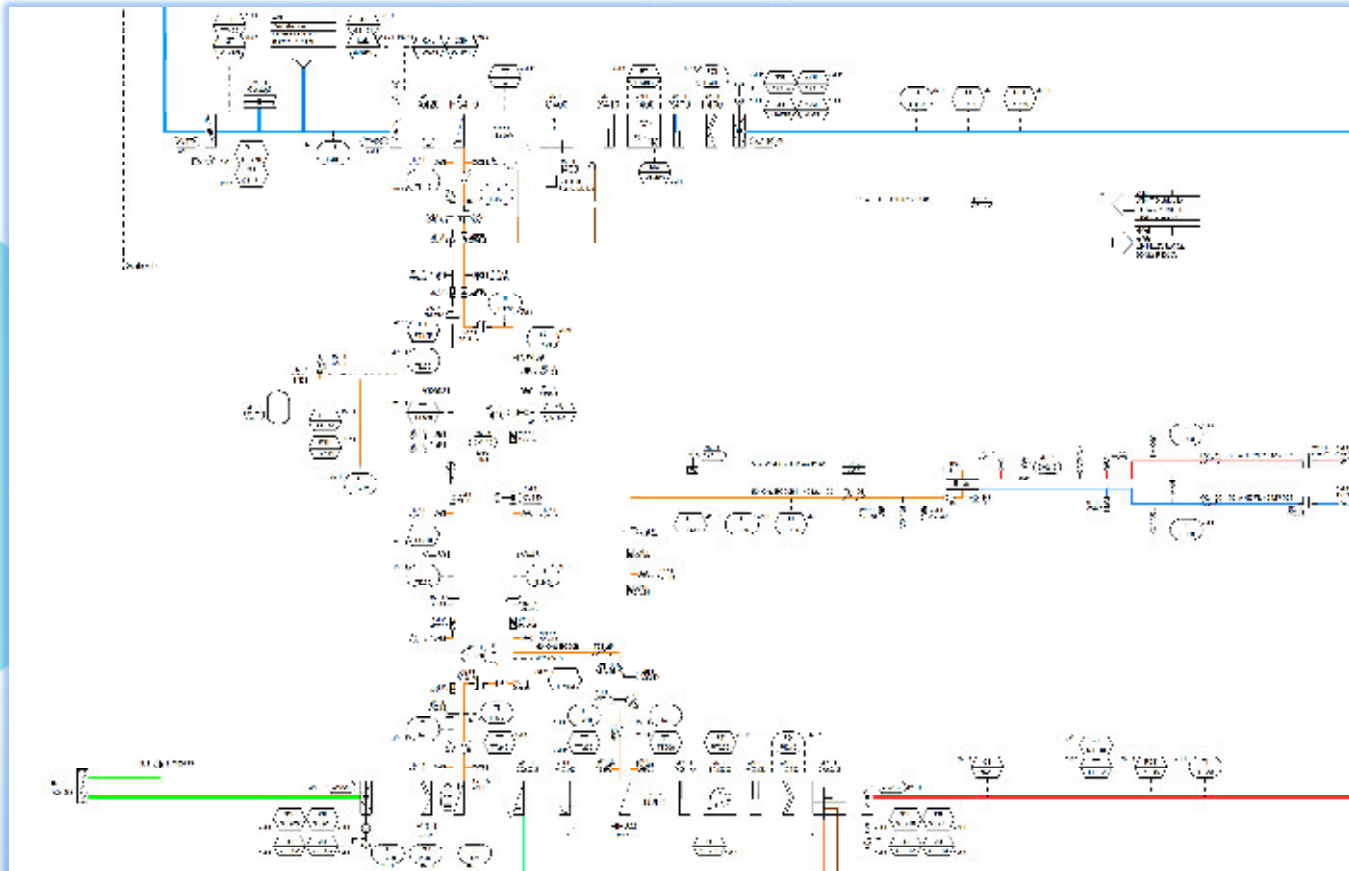


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**Detail Design (DD)**  
(planning for construction,  
preparation of tender  
documents)

**P&ID Makeup- & Exhaust Air Unit**

**Basic Output (Examples)**



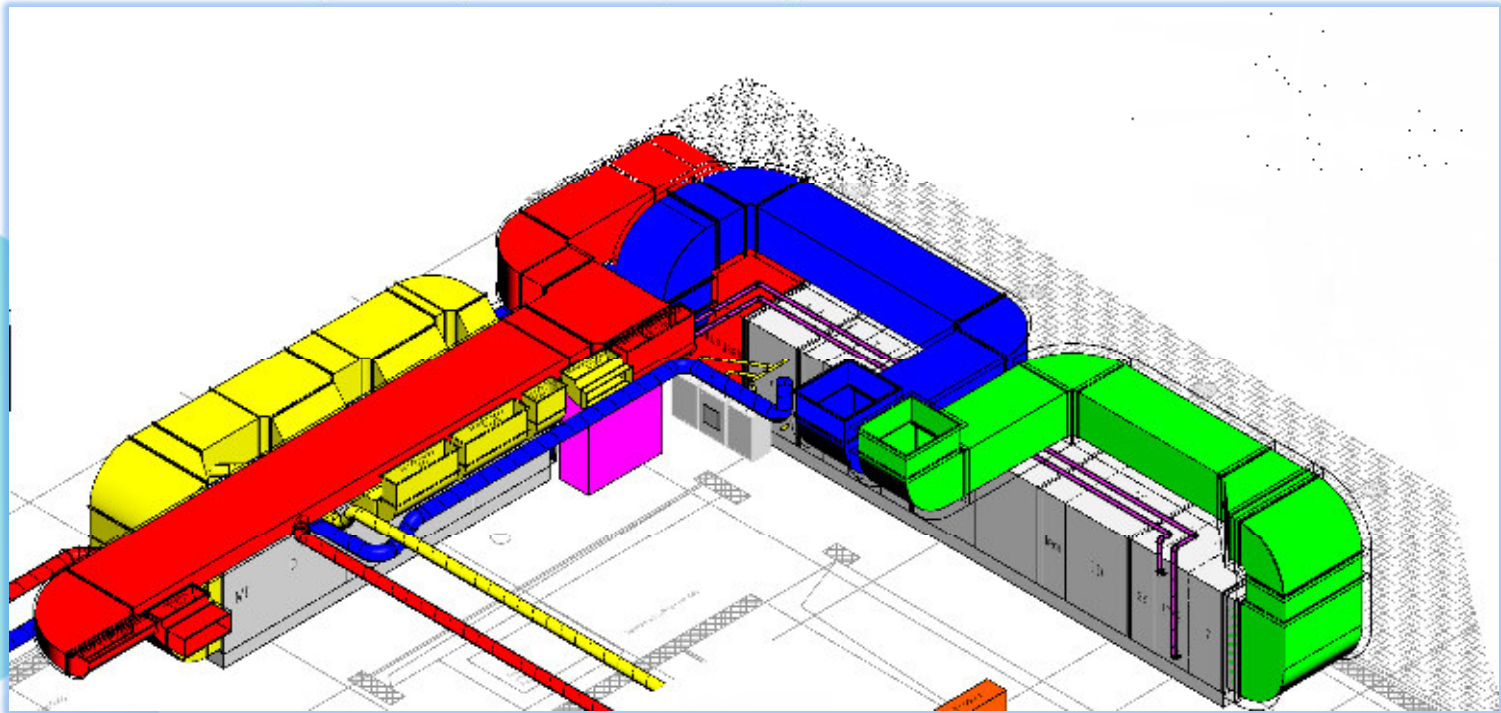


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**Detail Design (DD)**  
(planning for construction,  
preparation of tender  
documents)

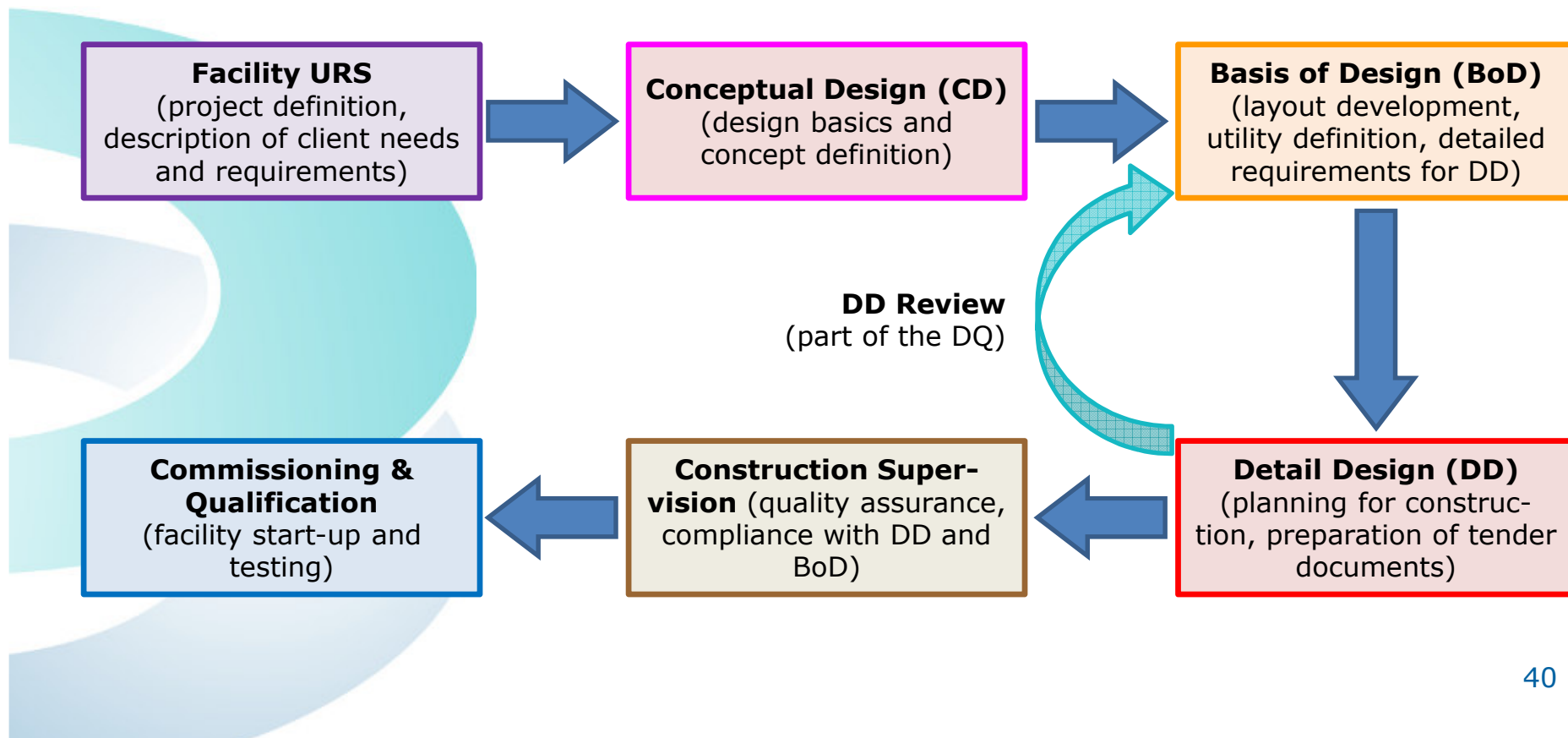
## Basic Output (Examples)

3D Model HVAC Installation





## Project Steps – Design & Realization



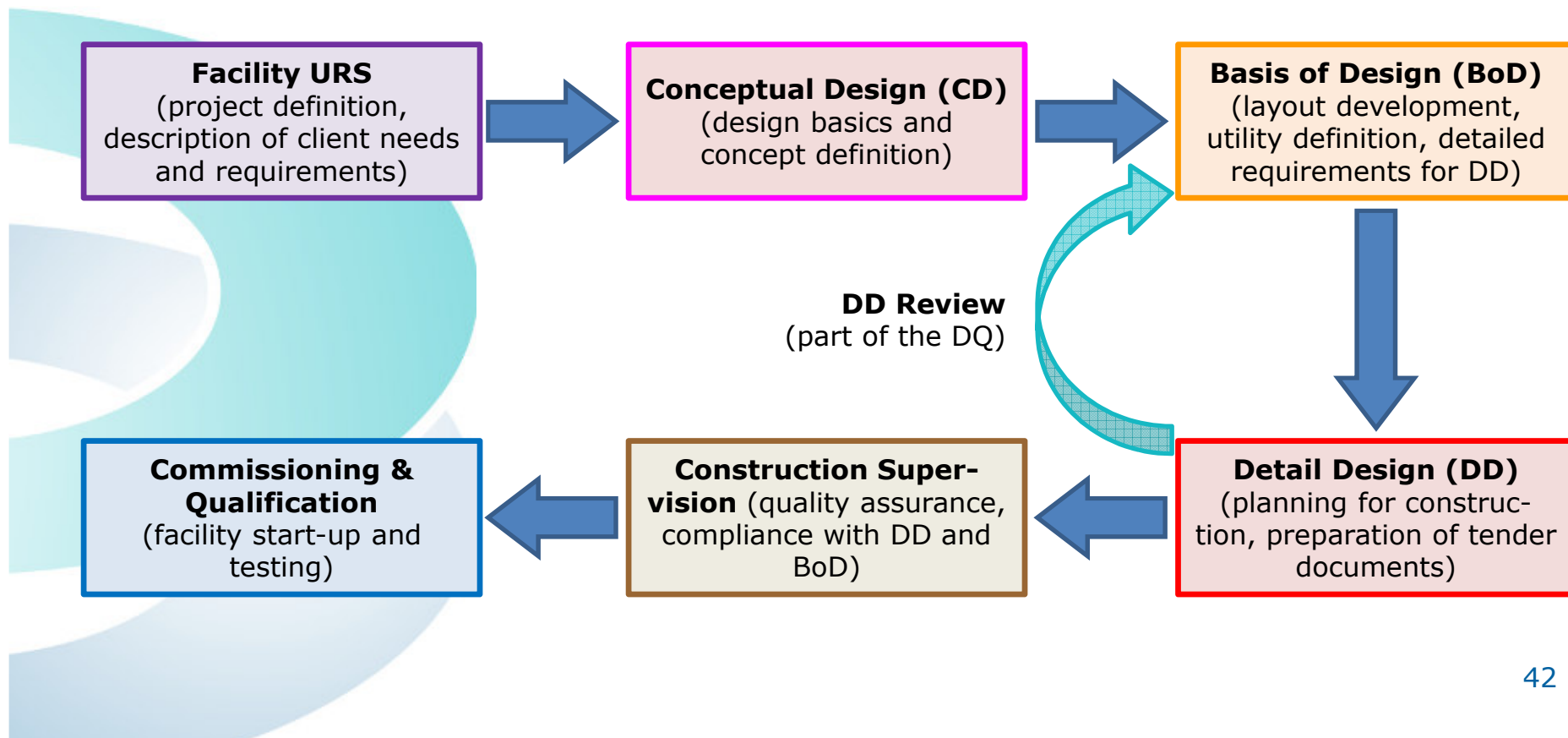


## Purpose

A “Construction Supervision” should fulfill the following purposes in a construction project:

- Coordination of different suppliers
- Compliance with the time schedule
- Quality assurance on the construction site
- Compliance with “GFC” (Good For Construction) planning
- Management of changes

## Project Steps – Design & Realization



## Definitions (I/II)

### **Commissioning**

Documented activities for start-up and testing of NON-GMP and GMP systems.

Within commissioning it will be verified, that all user requirements are met and that the system has been built, installed, and is functioning correctly.

→ All systems need commissioning

### **Qualification**

Action of proving and documenting that any premises, systems and equipment are properly installed, work correctly and lead to the expected results.

→ GMP systems need qualification

## Definitions (II/II)

### **Leveraging**

If commissioning tests executed for GMP-systems have been documented according to Good Documentation Practice (GDP), appropriate tests do NOT have to be repeated for qualification, but can be referenced (leveraged)

→ Minimizing qualification effort by leveraging commissioning tests

## Qualification

Qualification is divided into four different phases:

- DQ (Design Qualification)
  - Verification of design against user requirements (URS/RA)
- IQ (Installation Qualification)
  - Verification of installation against design (e.g. P&ID, parts list)
- OQ (Operational Qualification)
  - Verification of functionality against specification (e.g. FS)
- PQ (Performance Qualification)
  - Verification of overall performance

## Purpose

A “Commissioning & Qualification” phase should fulfill the following purposes in a construction project:

- Lead to a well-working facility which complies with...
  - Initial user requirements
  - Regulatory requirements
- Well-documented NON-GMP systems
- GMP systems qualified according to a risk-based approach

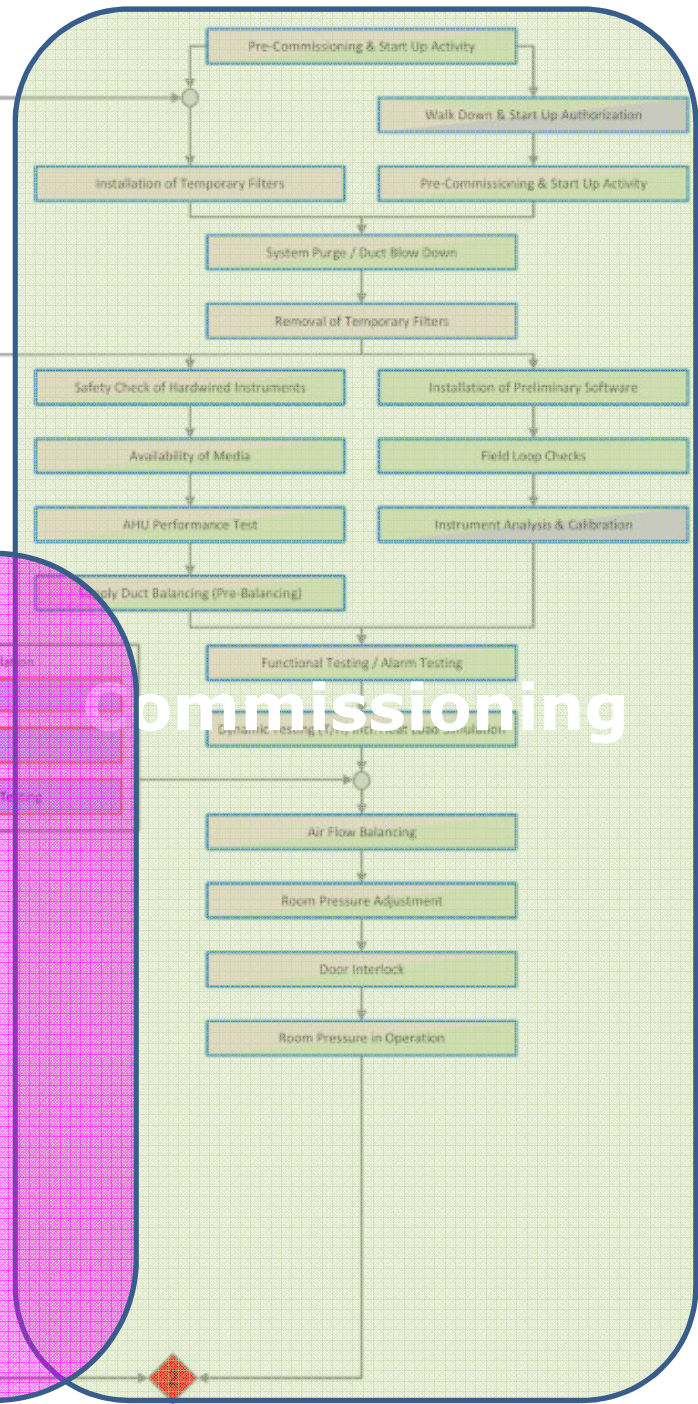
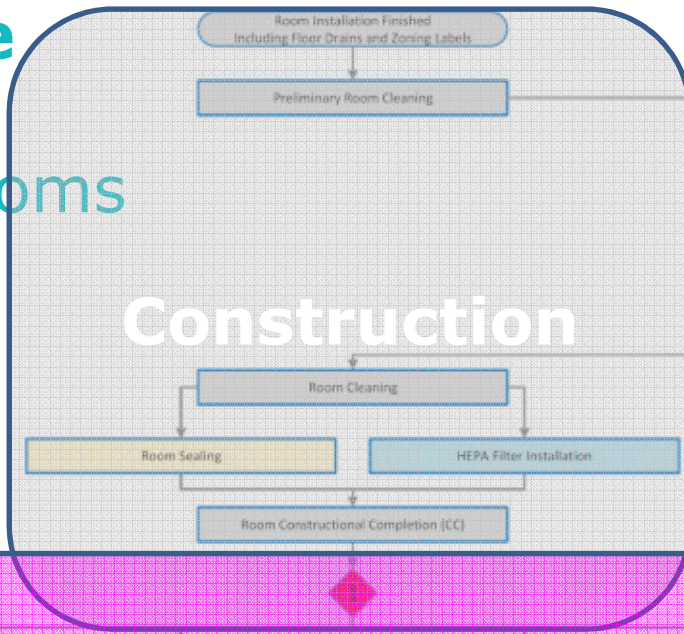
## Goal

The goals of a well-structured and well-organized Q&C:

- Minimize administrative efforts for C&Q
  - Qualification only for GMP systems
  - Employment of a risk-based qualification approach
- Coordination of C&Q activities
  - Only start with qualification after thorough commissioning
- Benefit from synergies of C&Q activities
  - Leverage as many tests as possible (avoid repeating tests)



# Example C&Q of Clean Rooms (I/II)

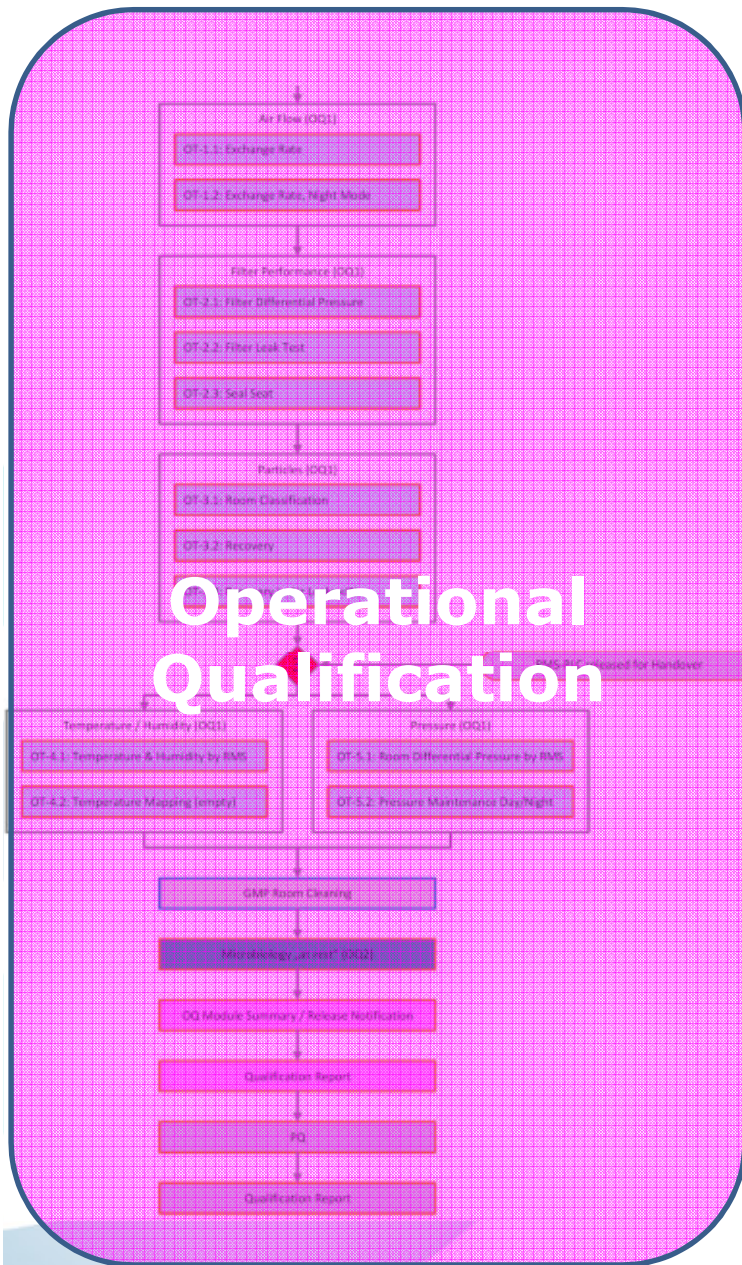




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**Commissioning & Qualification**  
(facility start-up and testing)

# Example C&Q of Clean Rooms (II/II)



- Interdisciplinary System
  - HVAC
  - Clean Rooms
  - Automation (GMS & BMS)
  - Equipment

- Major Dependencies  
Construction <-> Commissioning <-> Qualification

→ **Thorough planning of C&Q activities required**



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Further Questions?