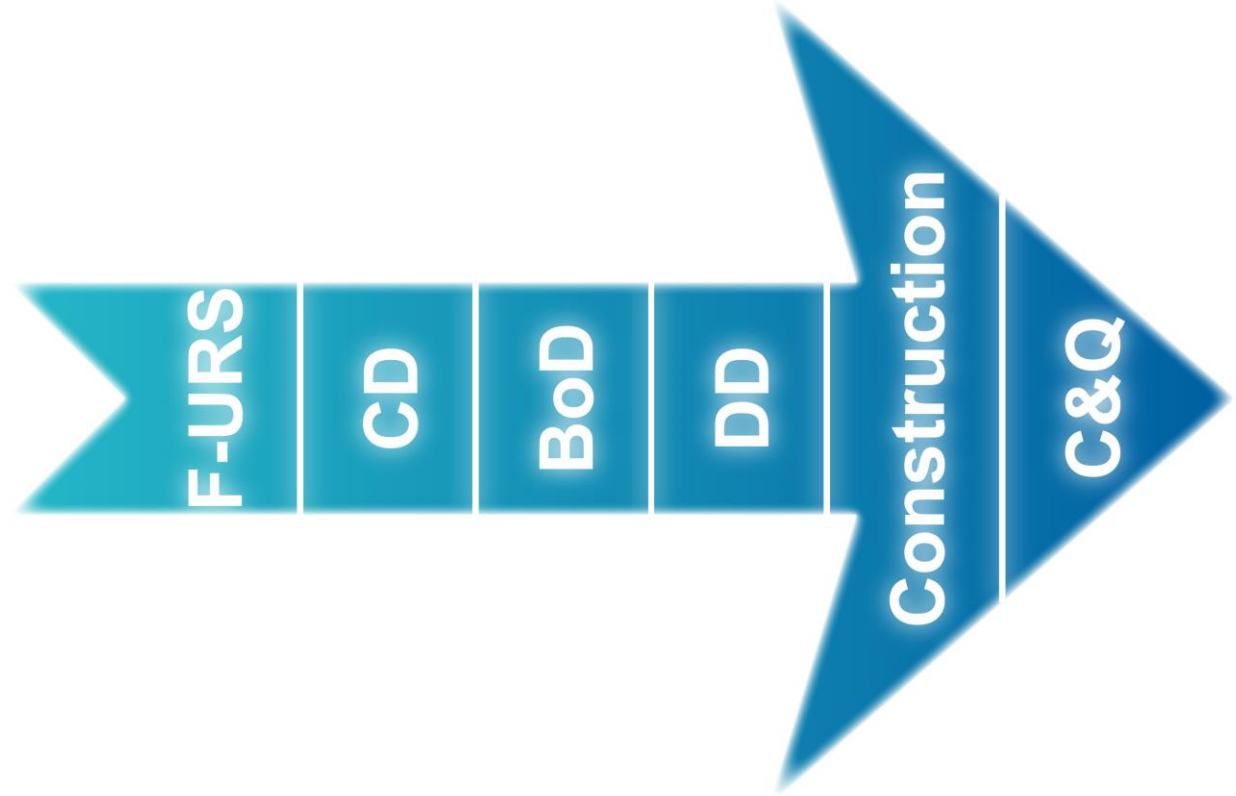




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Project Setup: From the Beginning
until the End



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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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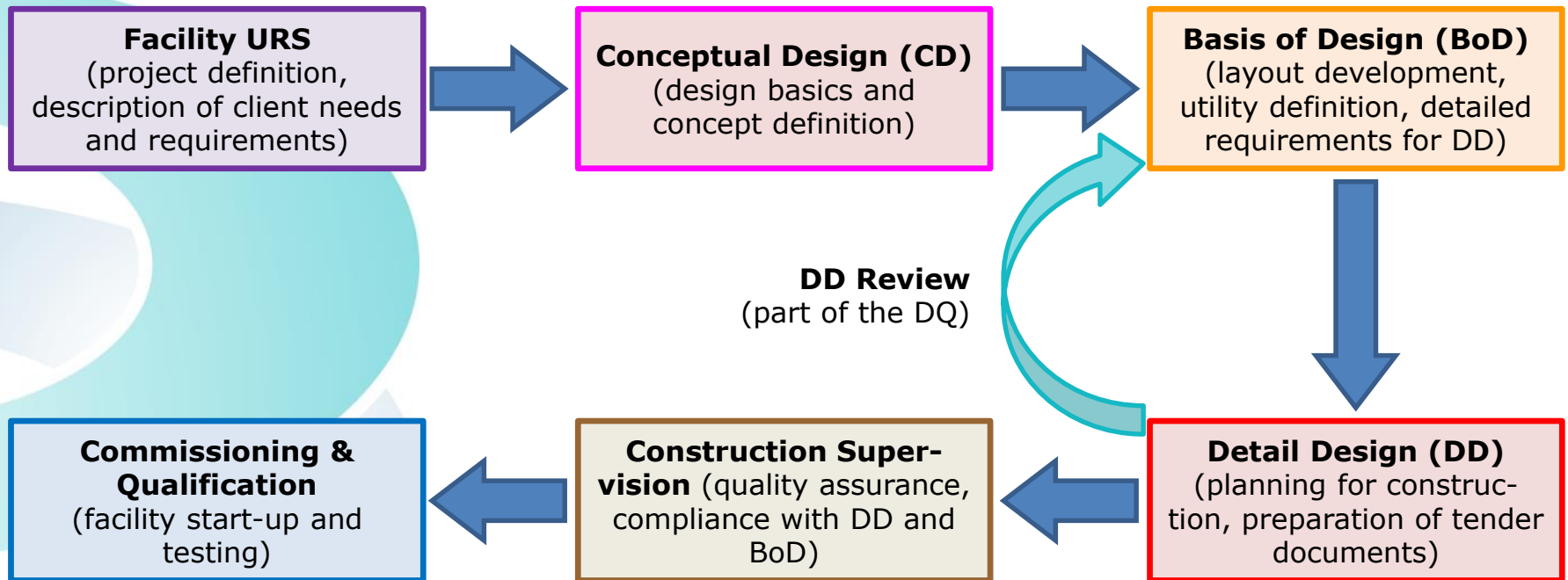
Relevant Guidelines

- Chinese GMP guideline (2011 edition)
- 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



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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)

1 INTRODUCTION

- 1.1 Project Background
- 1.2 Purpose and Objectives
- 1.3 Scope
- 1.4 Project Organization
- 1.5 Abbreviations and Definitions
- 1.6 Guidelines and Regulatory Requirements

2 FACILITY DESIGN BASICS

- 2.1 GMP Basics
- 2.2 Biosafety Basics

3 BUILDING PROPERTIES

- 3.1 Site Description
- 3.2 Building Description
- 3.3 Architectural Layout
- 3.4 Building Concept
- 3.5 Requirements for Interior Finishes

4 FACILITY DESCRIPTION

- 4.1 Facility Design Basics
- 4.2 Process Description
- 4.3 Equipment Concepts
- 4.4 Media- and Buffer Preparation

5 UTILITIES

- 5.1 Building Utilities (Black Utilities)
- 5.2 Process Utilities (Clean Utilities)

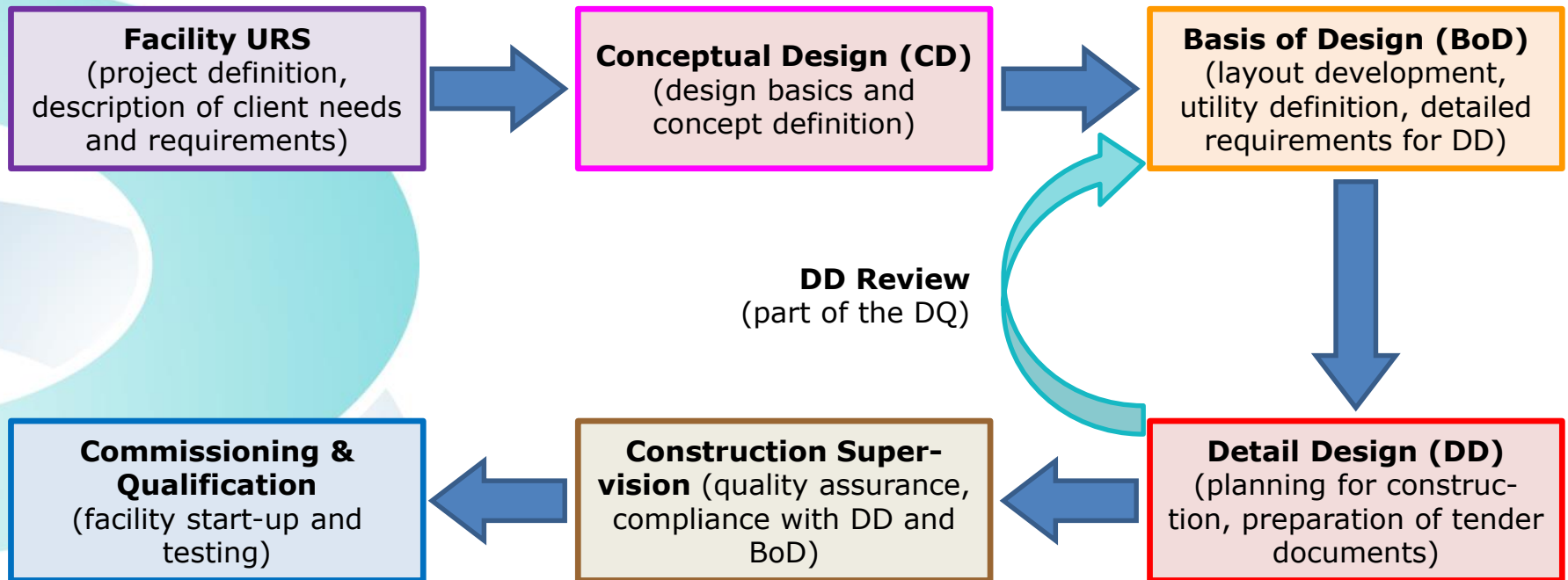
6 HVAC

- 6.1 Clean Room Operating Parameters
- 6.2 UAF / LAF Operating Parameters
- 6.3 Air Filtration
- 6.4 Ventilation Design Concept
- 6.5 Biosafety Containment Features

7 COMPUTERIZED SYSTEMS

- 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

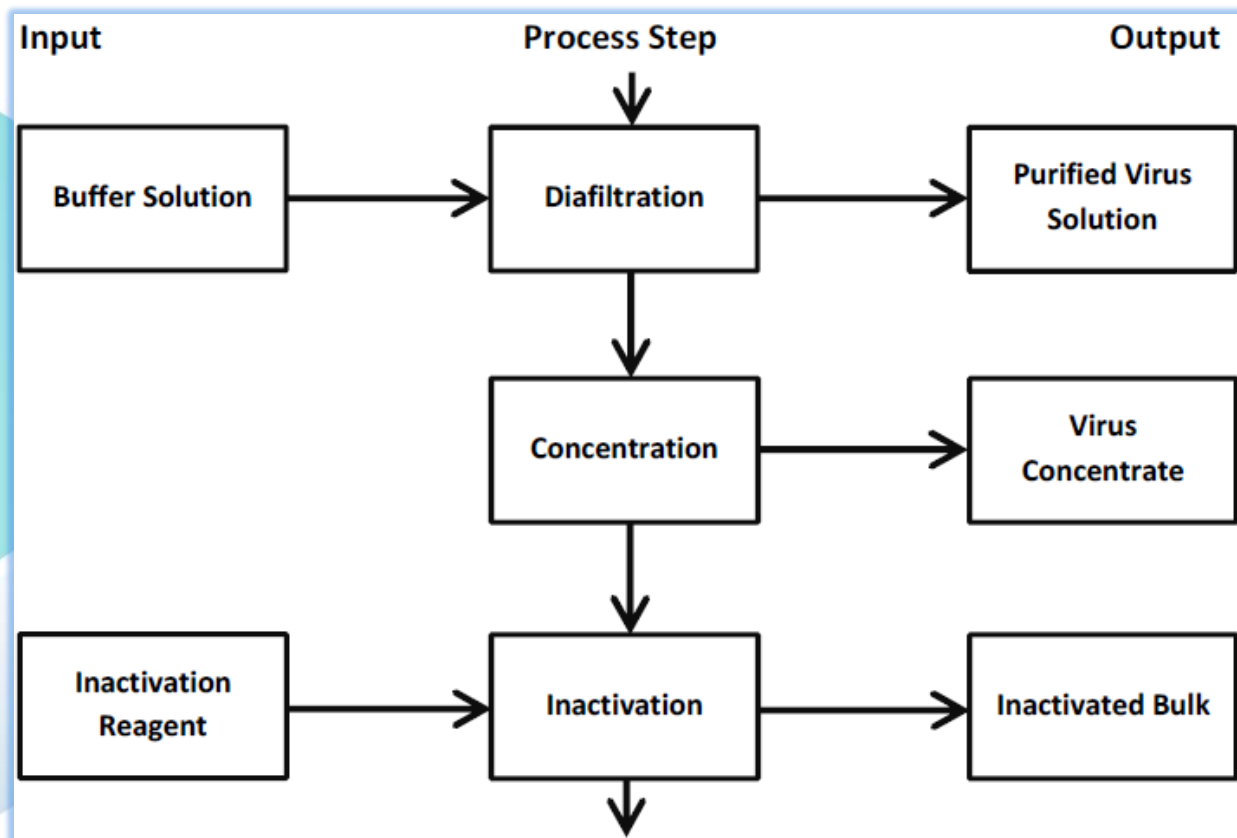
工序 Process	生产周期 production cycle	岗位定员 staff number
溶液配制 solution preparation	4 天 4 days	3 人
细胞解冻复苏 Cell thawing	1 天 1 day	2 人
摇床种子扩增 Seed proliferation with Shaker	12 天 12 days	3 人
Wave 反应器准备及接种 WAVE reactor preparation and inoculation	2 天 2 days	3 人
Wave 反应器细胞扩增 WAVE reactor cell proliferation	5 天 5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

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

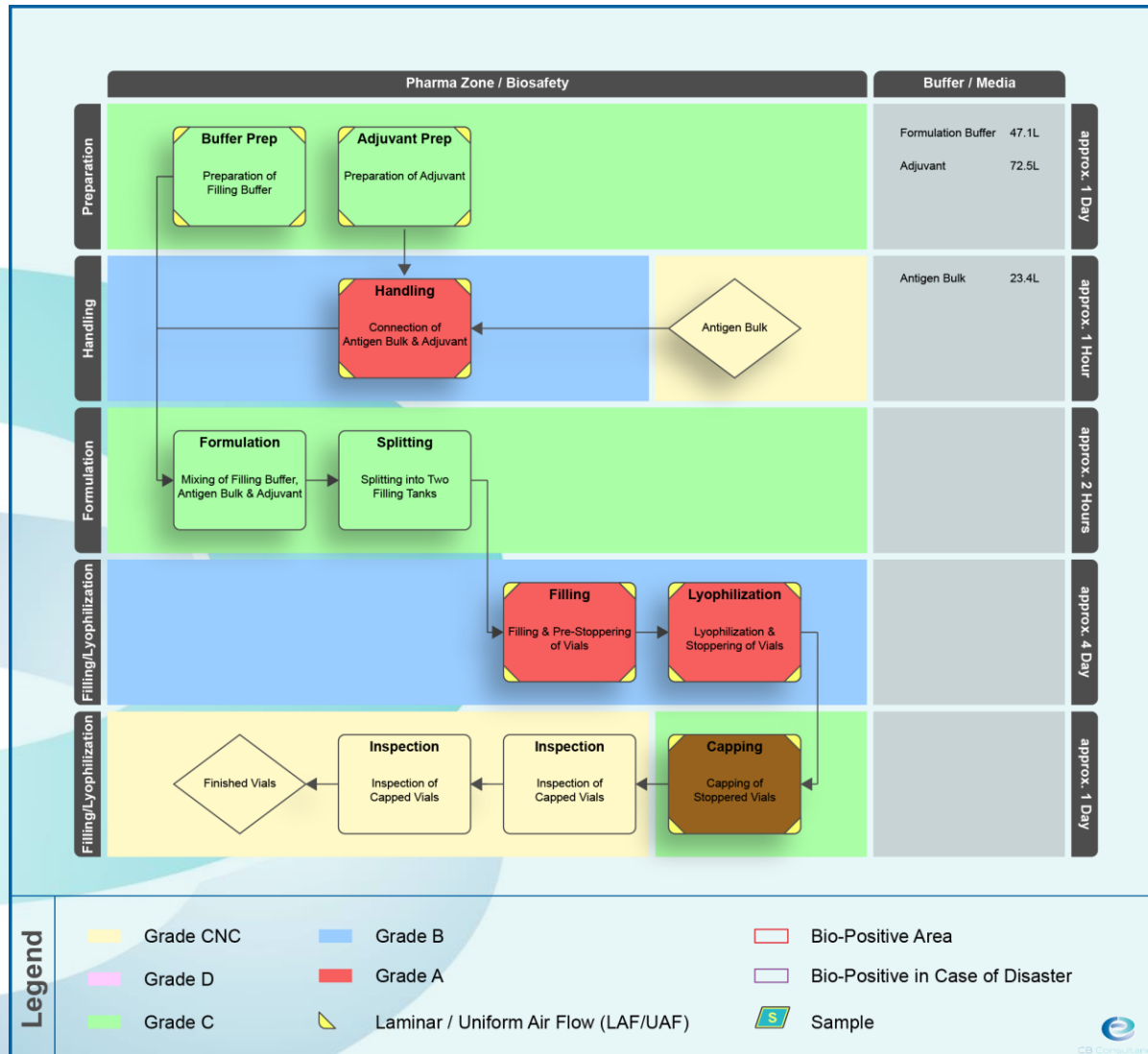
Process Flow Diagram



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)

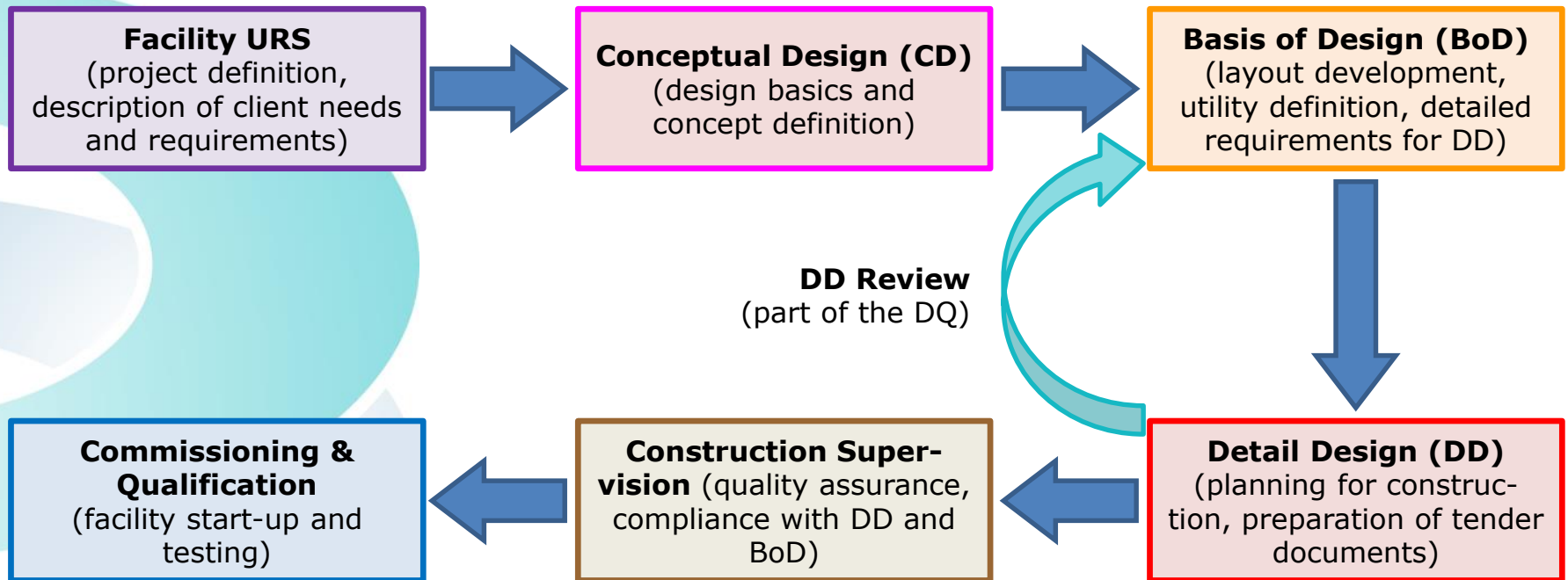
=> see e.g. the WHO guideline "environmental monitoring of clean rooms", November 2012

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

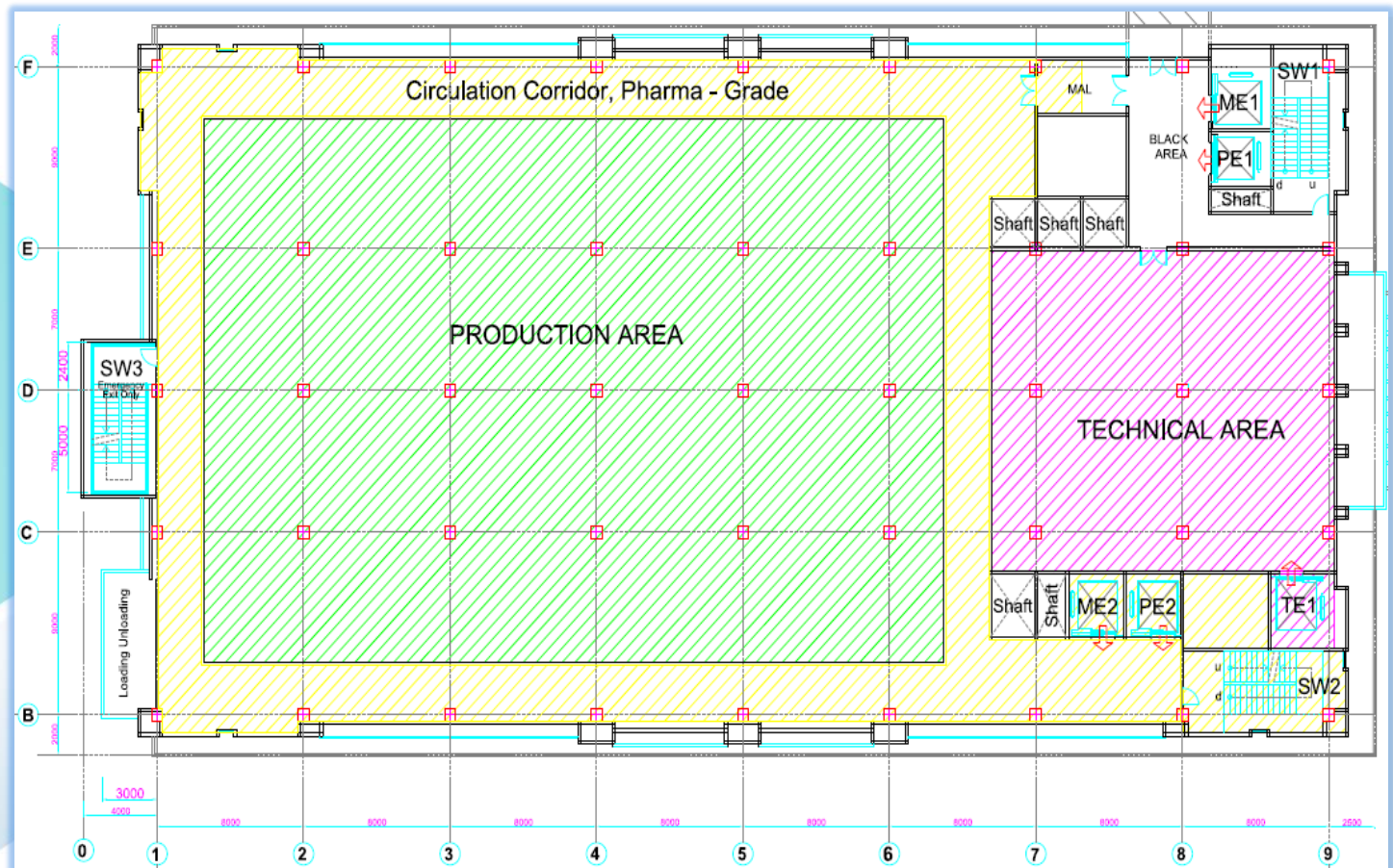


Conceptual Design (CD)
(design basics and
concept definition)

Output from CD Phase (Example)

Building footprint with layout concept

Layout Concept





Output from CD Phase (Example)

Building Concept

20



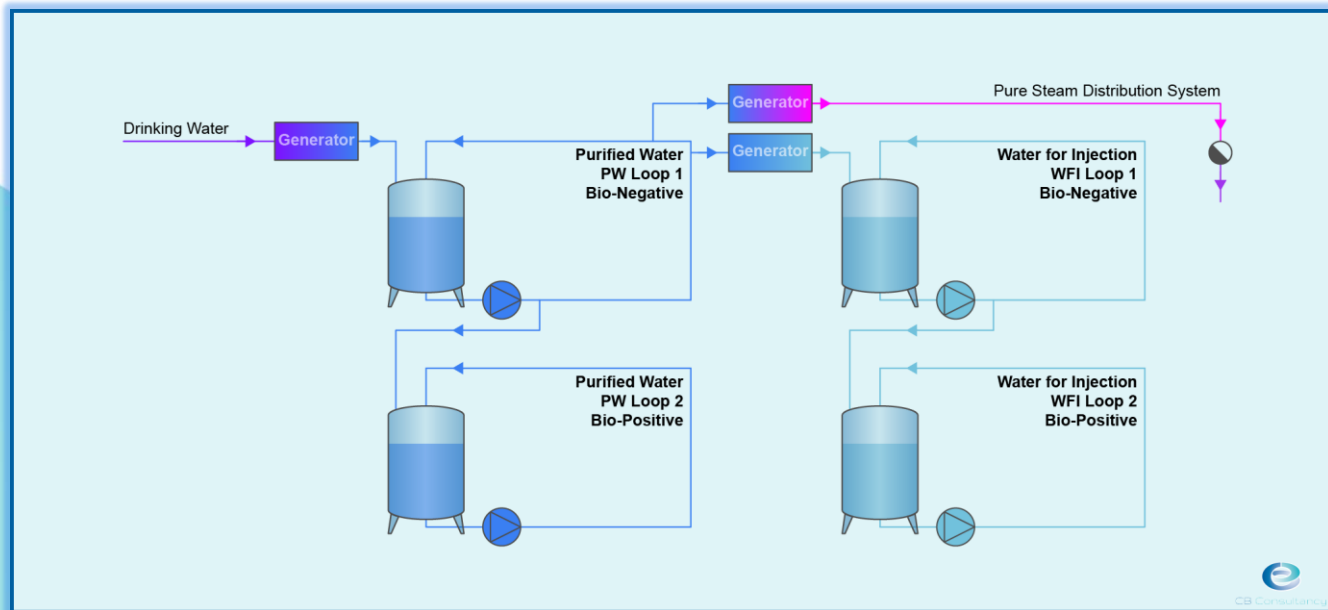
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Conceptual Design (CD)
(design basics and
concept definition)

Output from CD Phase (Example)

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

Clean Utility Concept





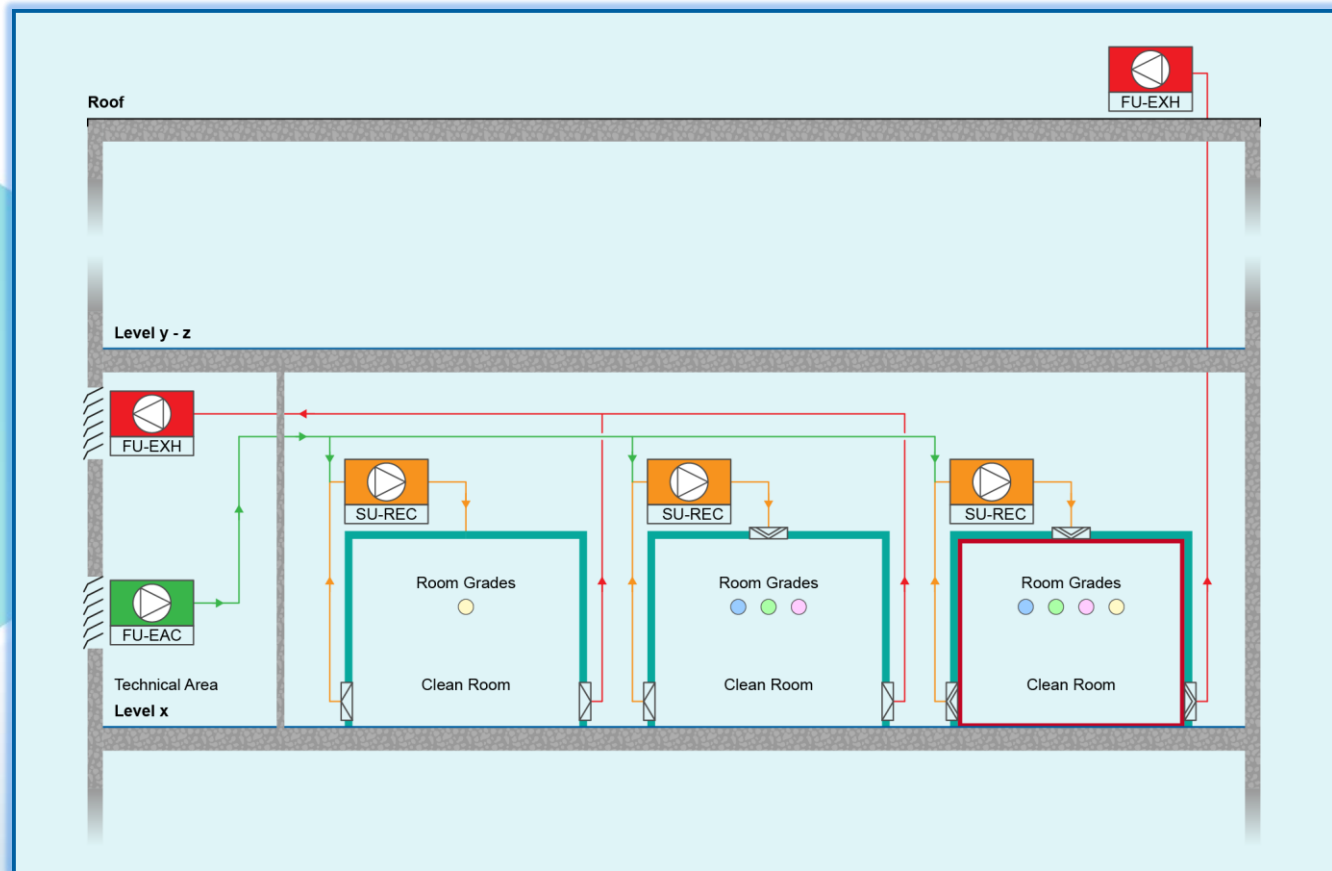
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Conceptual Design (CD)
(design basics and
concept definition)

Output from CD Phase (Example)

HVAC concept illustrating air handling units supplying different room types.

HVAC Concept





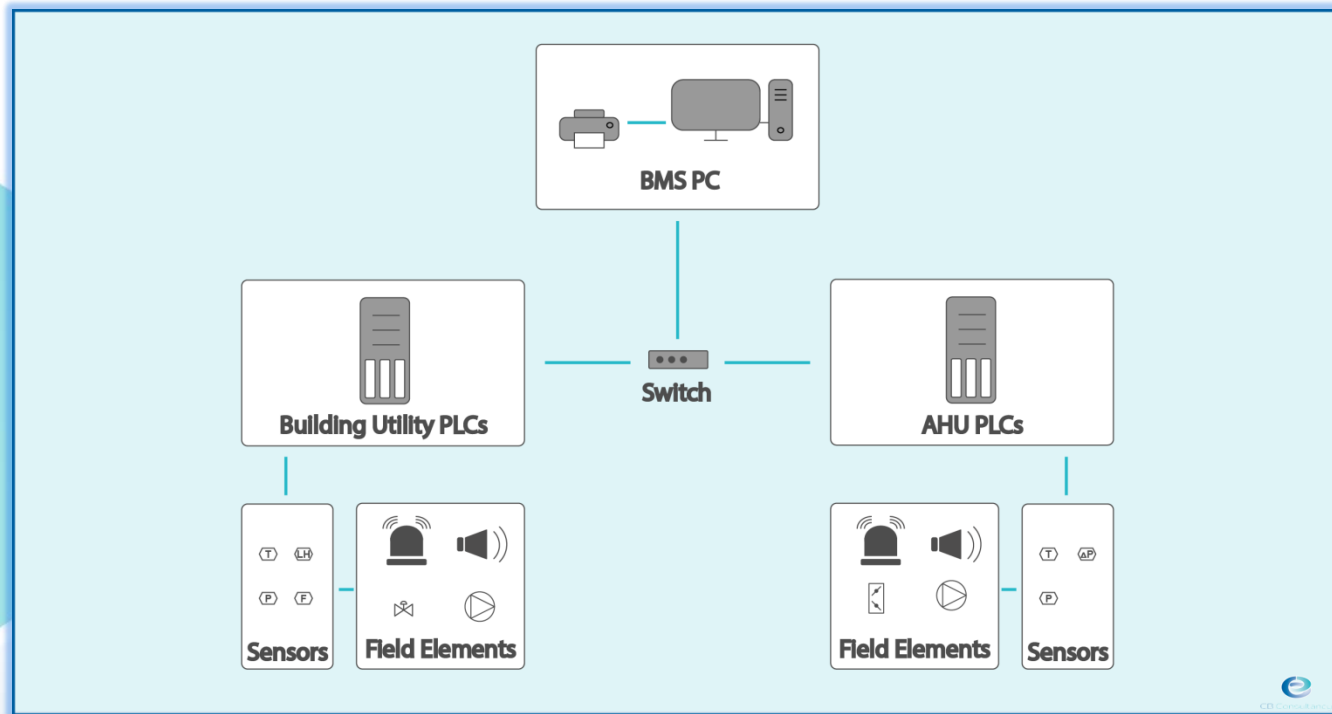
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Conceptual Design (CD)
(design basics and
concept definition)

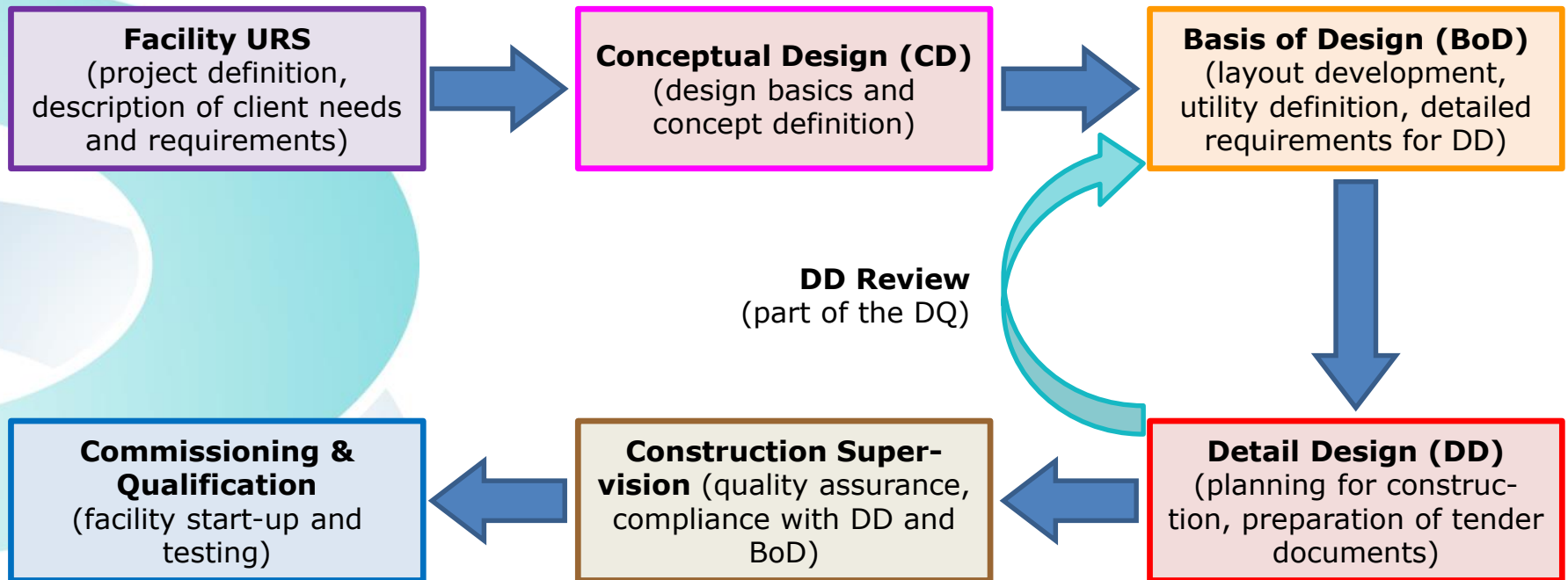
Output from CD Phase (Example)

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



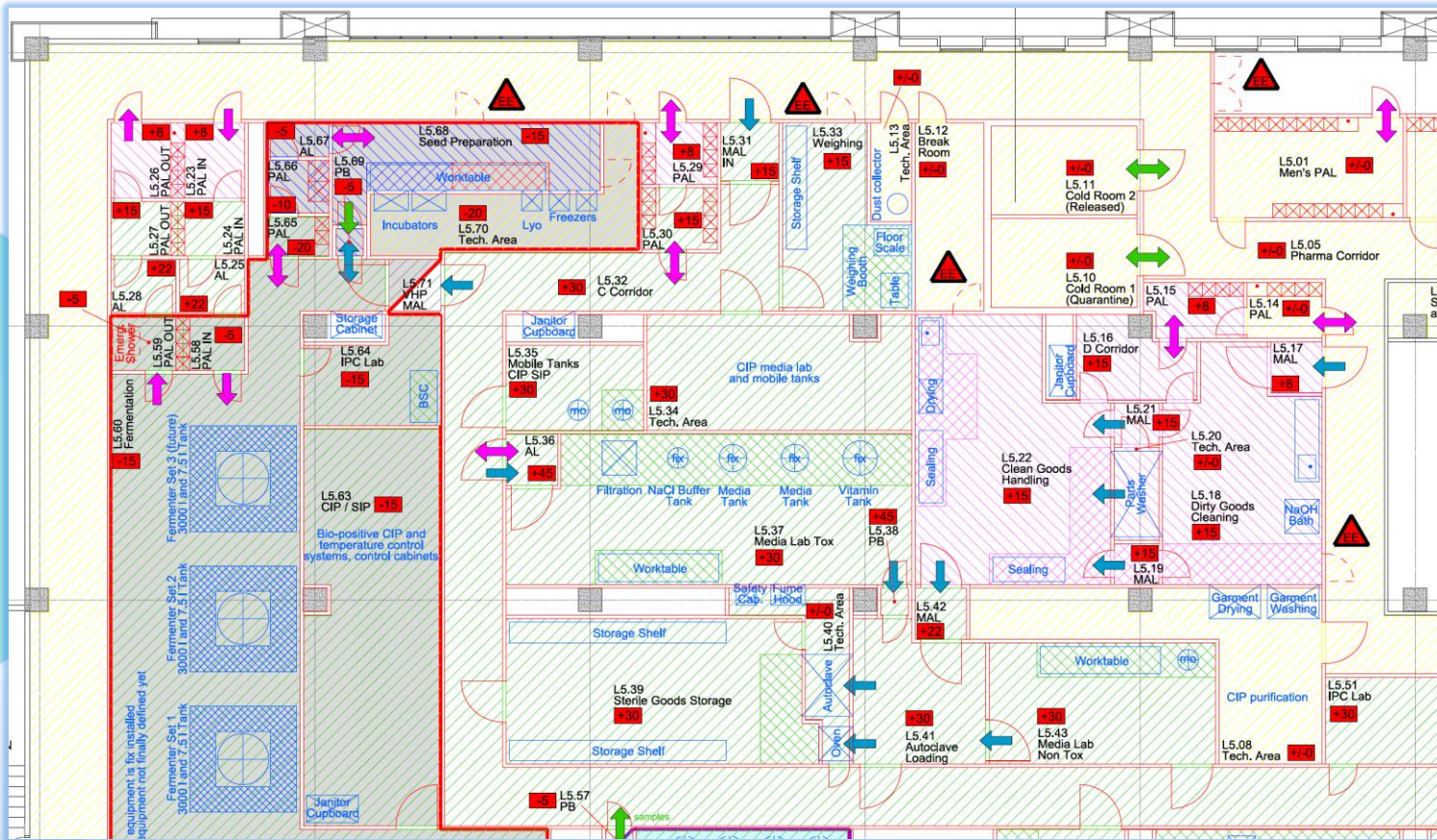
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Basis of Design (BoD)
(layout development,
utility definition, detailed
requirements for DD)

Output from BoD Phase (Example)

Detailed layout showing room grades, pressure, flow & BSL border

Detailed Layout







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

Output from BoD Phase (Example)

Gowning concept showing appropriate gowning for the different room grades.

Gowning Concept

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)	



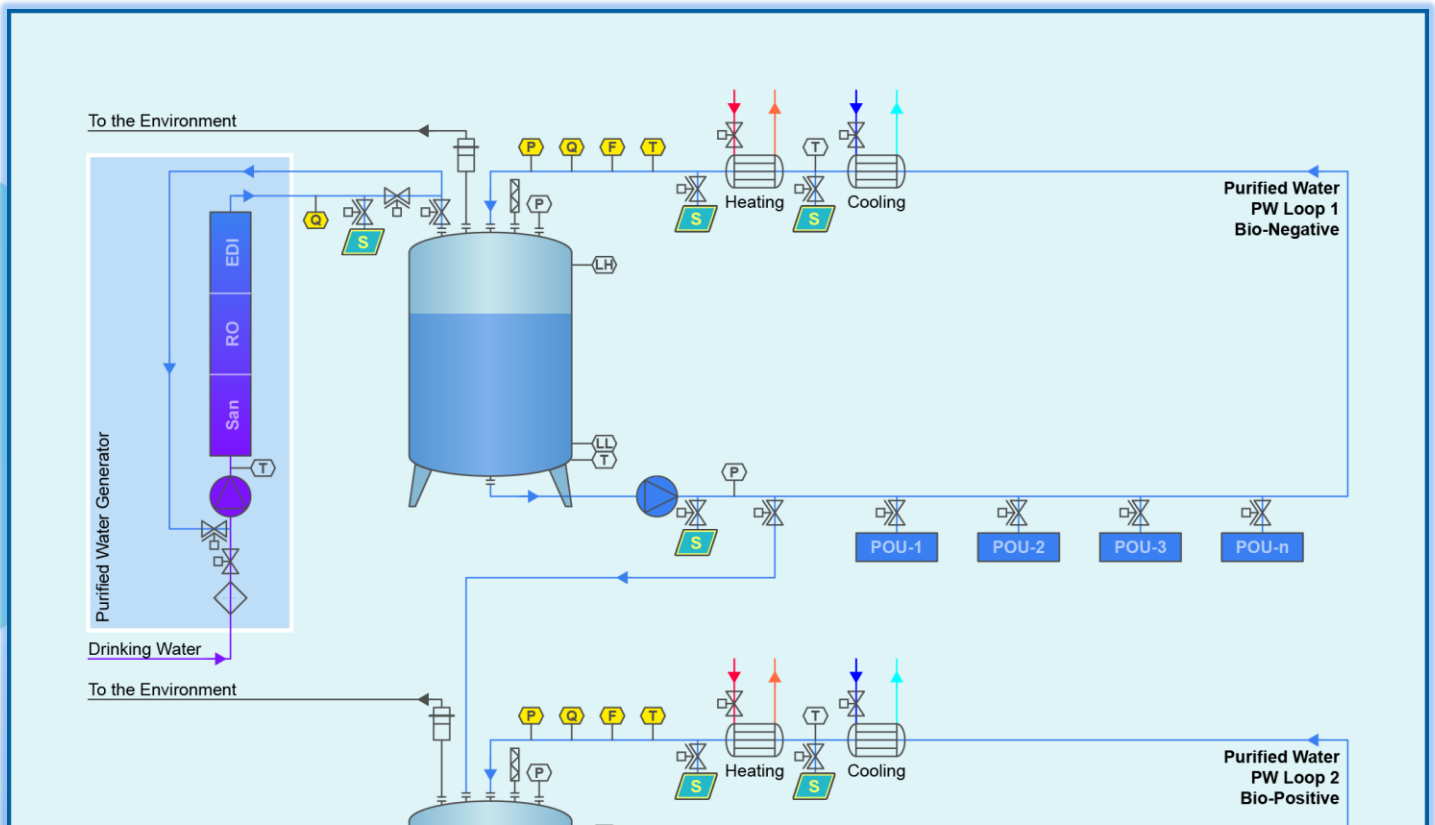
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Basis of Design (BoD)
(layout development,
utility definition, detailed
requirements for DD)

Output from BoD Phase (Example)

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

Schematic for Purified Water





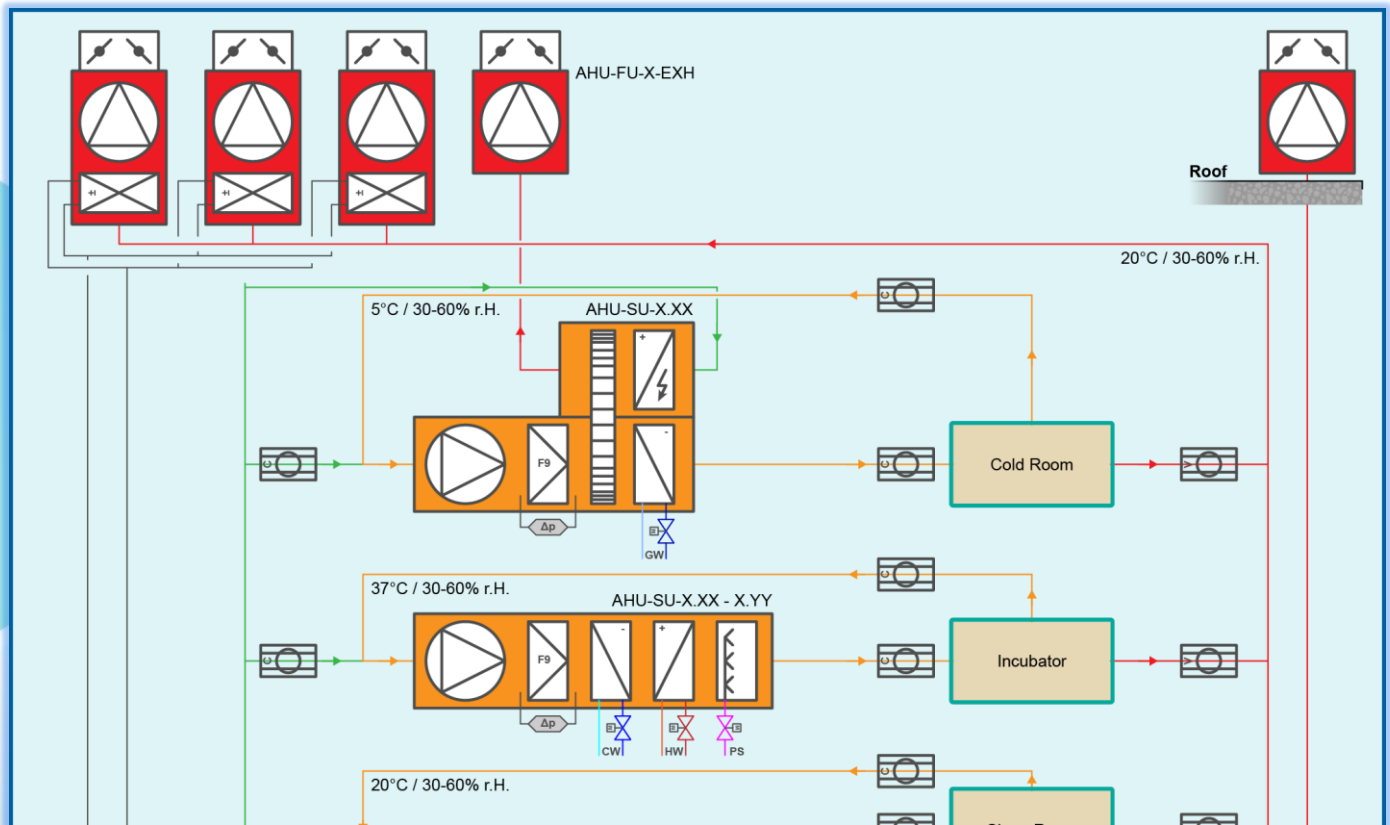
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Basis of Design (BoD)
(layout development,
utility definition, detailed
requirements for DD)

Output from BoD Phase (Example)

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

Schematic for HVAC





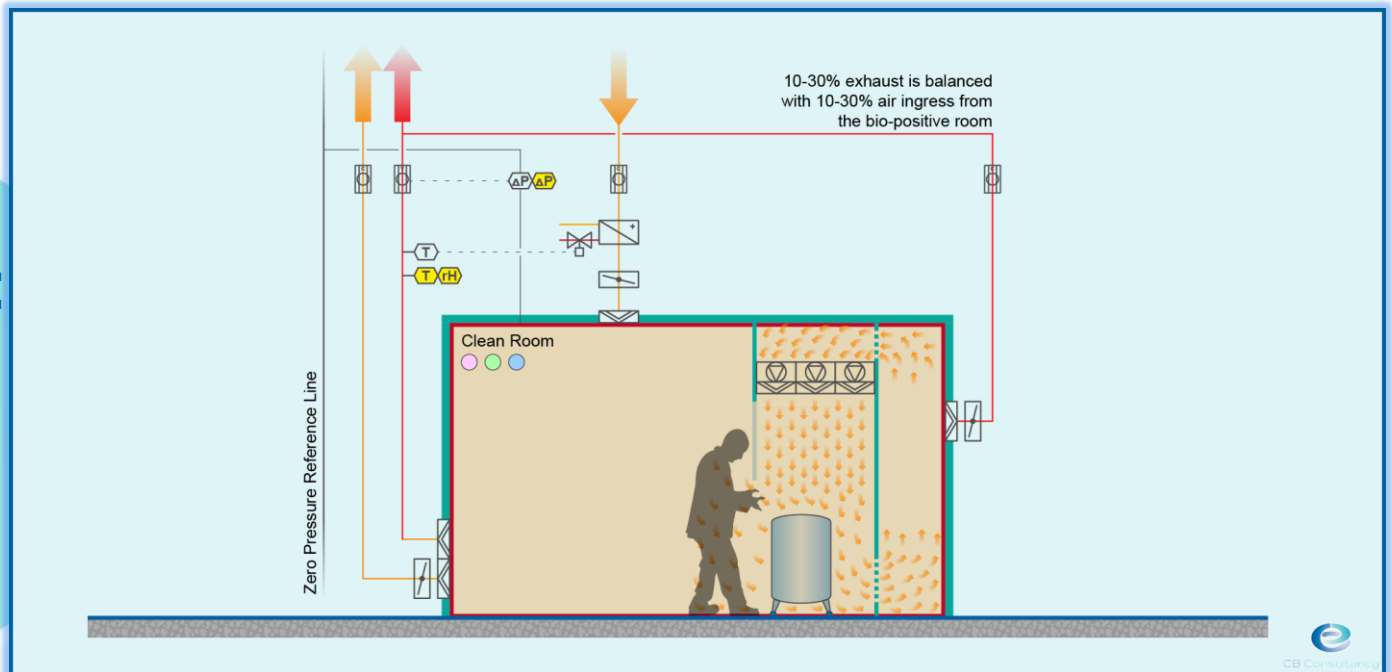
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Basis of Design (BoD)
(layout development,
utility definition, detailed
requirements for DD)

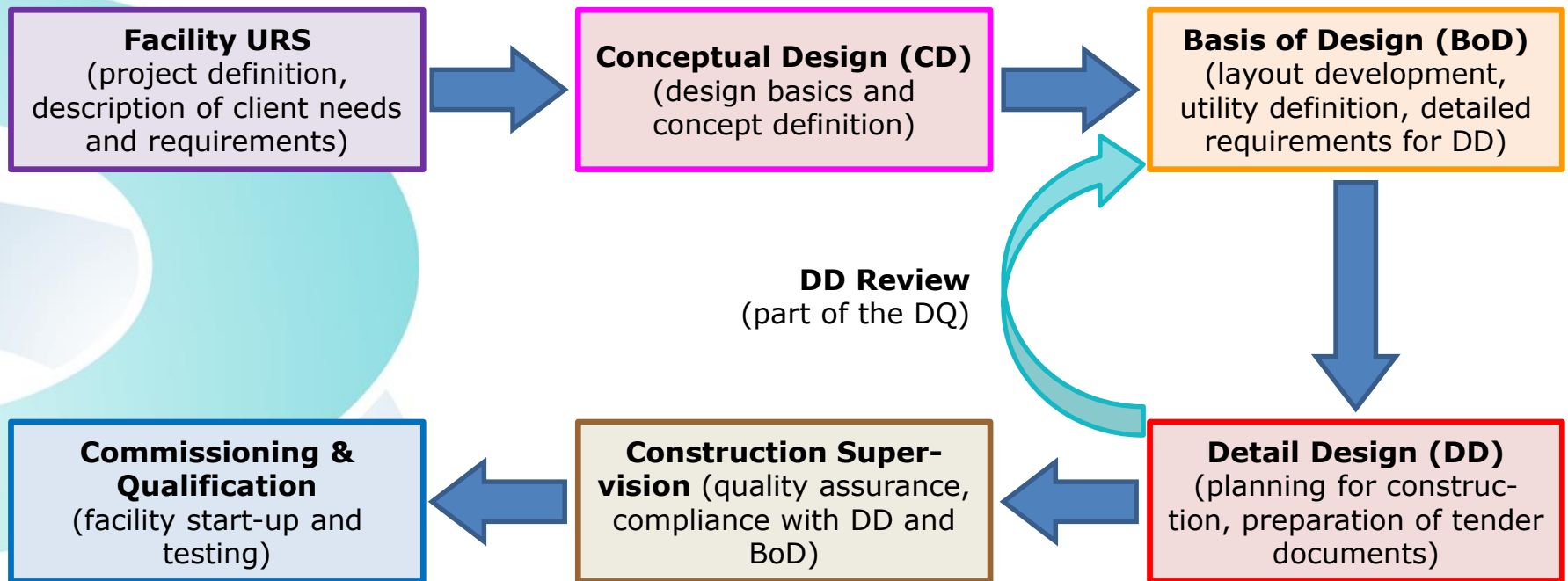
Output from BoD Phase (Example)

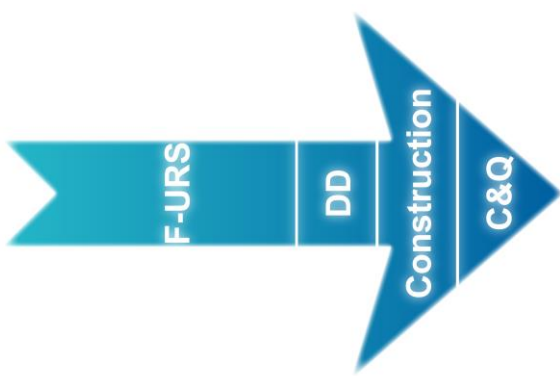
HVAC room typical for a bio-positive clean room with UAF providing inward air flow.

HVAC Room Typical



Project Consolidation & Acceleration



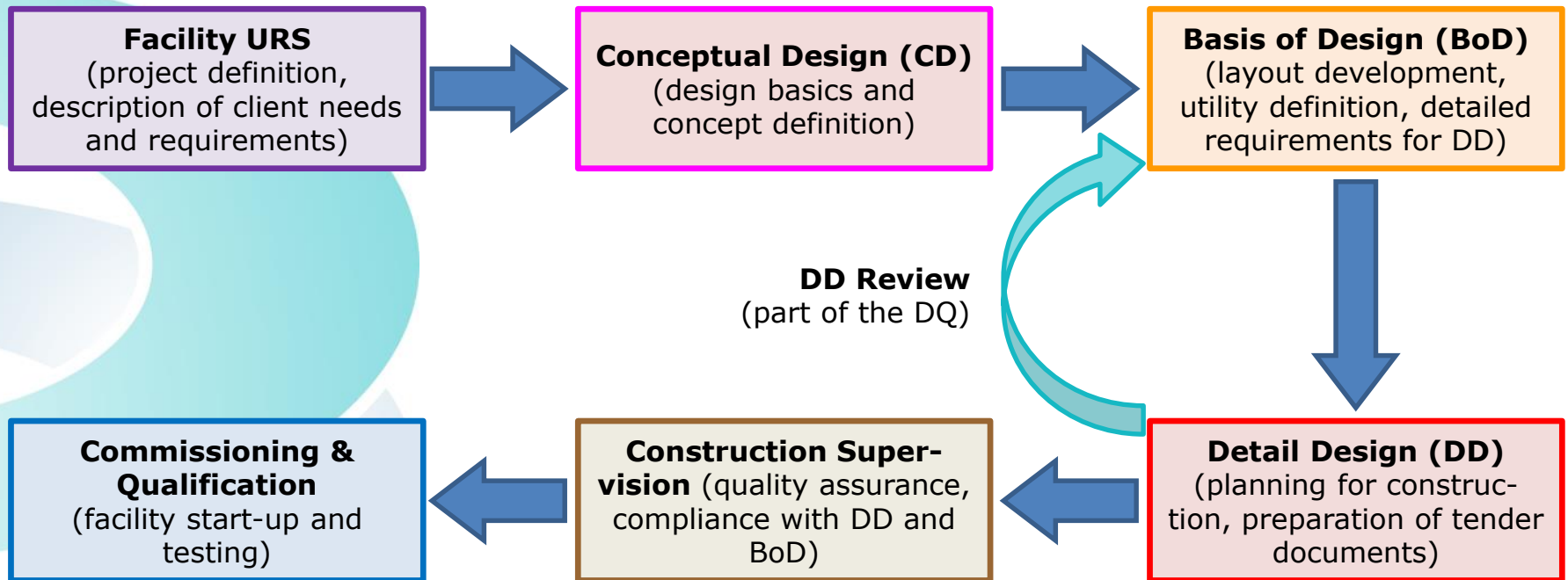


Project Consolidation & Acceleration

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

- 👍 Consideration of approved conceptional 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)

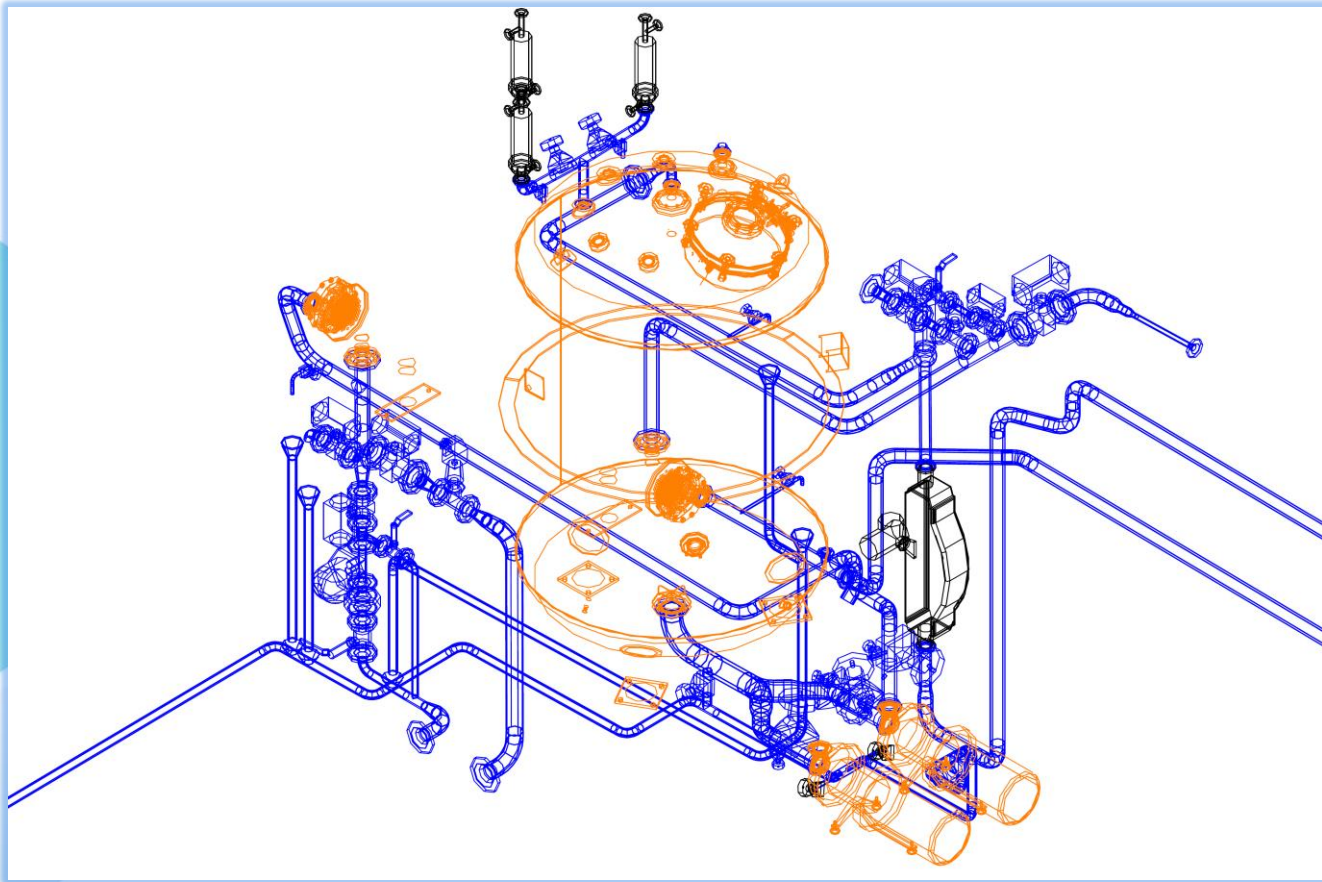


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Detail Design (DD)
(planning for construction, preparation of tender documents)

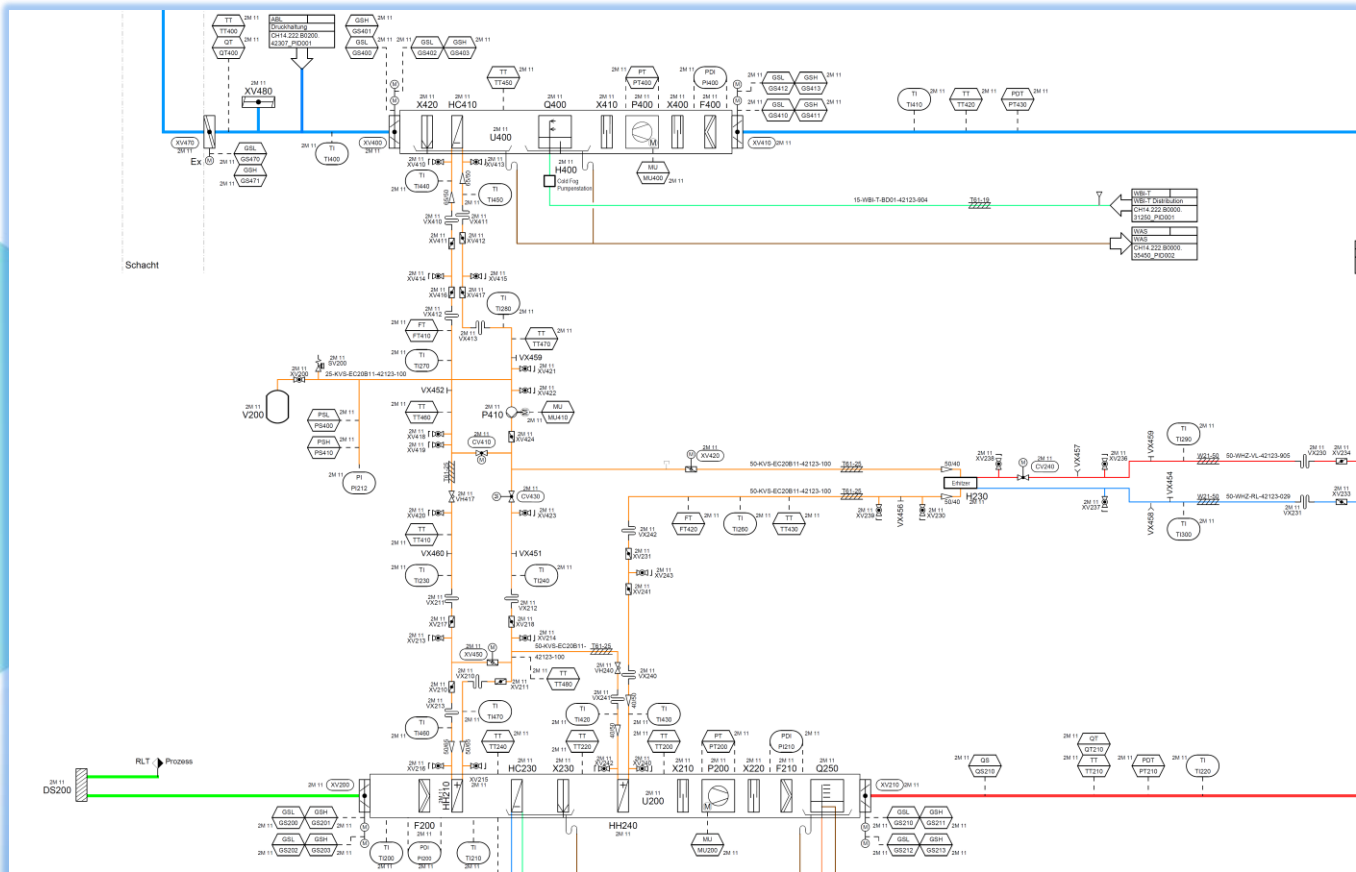
3D Model WFI Distribution System

Output from DD Phase (Example)



P&ID Makeup- & Exhaust Air Unit

Basic Output (Examples)



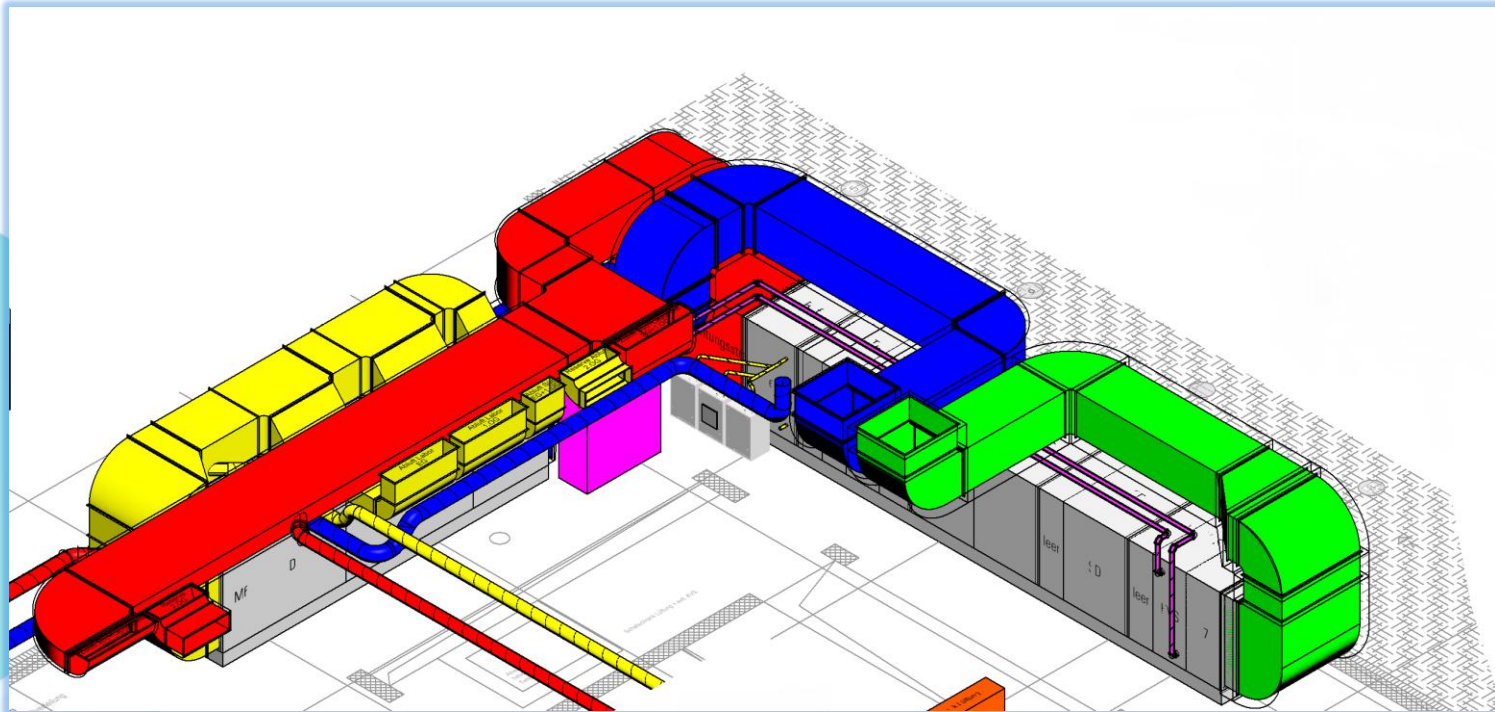


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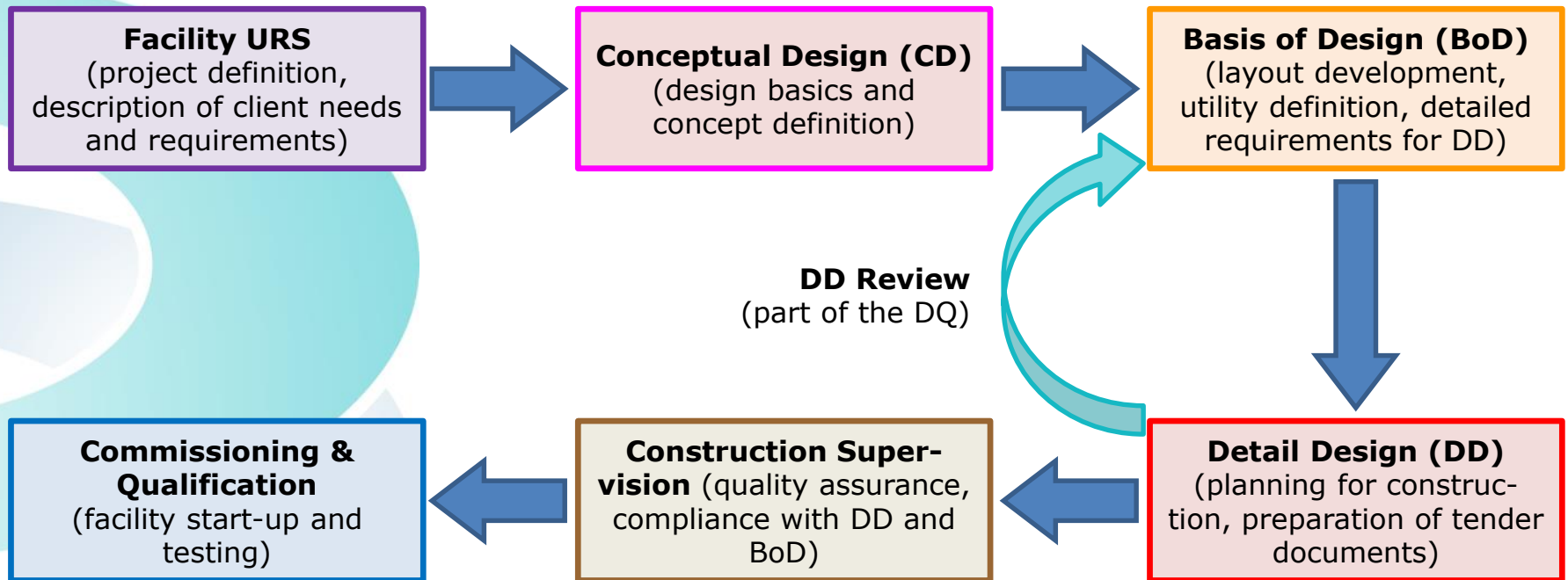
Detail Design (DD)
(planning for construction,
preparation of tender
documents)

3D Model HVAC Installation

Basic Output (Examples)



Project Steps – Design & Realization



Purpose

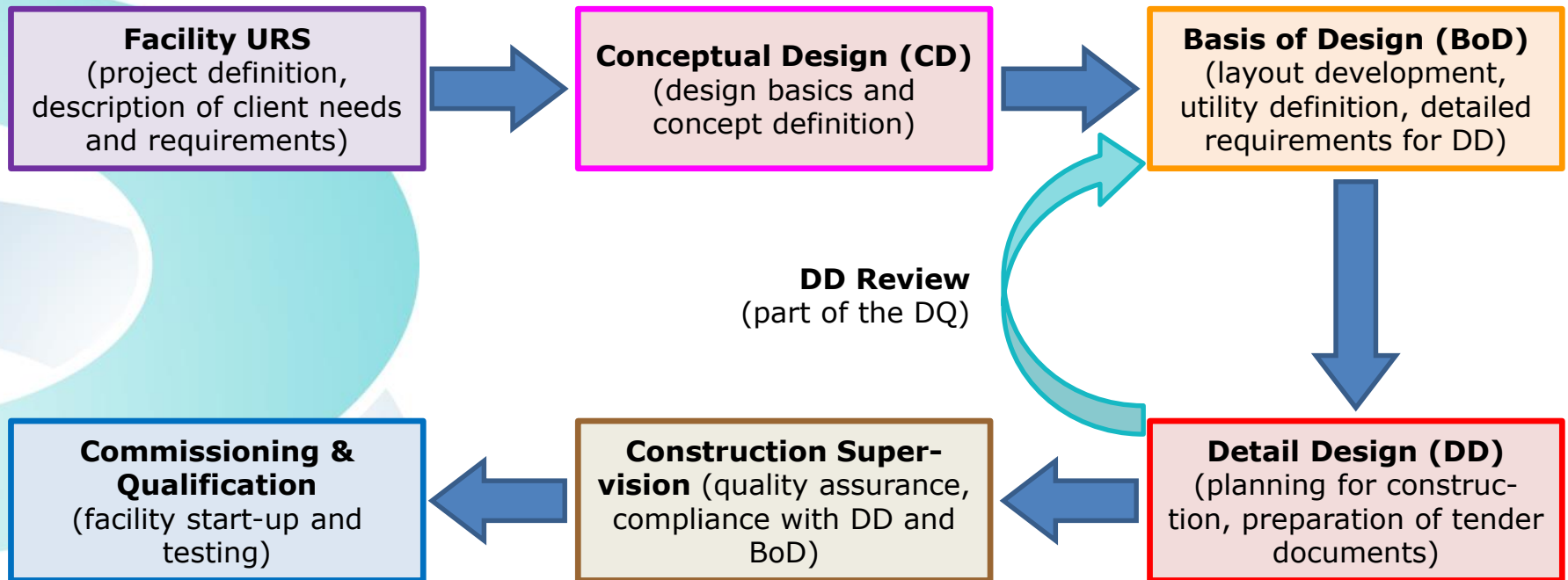
A “Construction Supervision” should fulfill the following purposes in a construction project:

- 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



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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

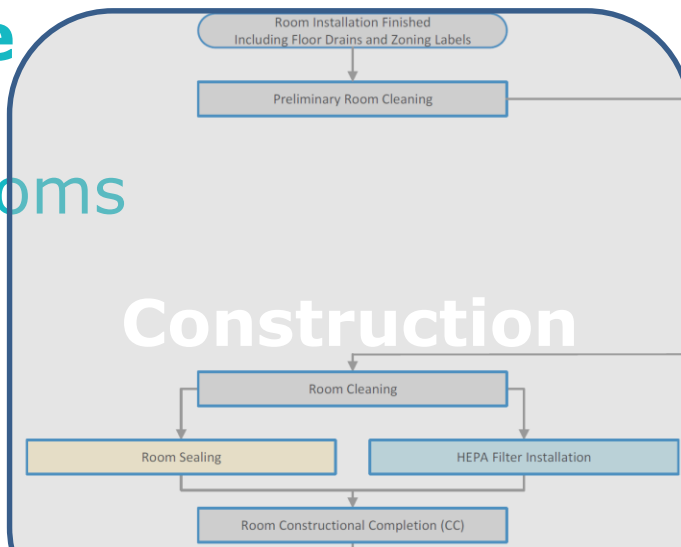
Goal

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

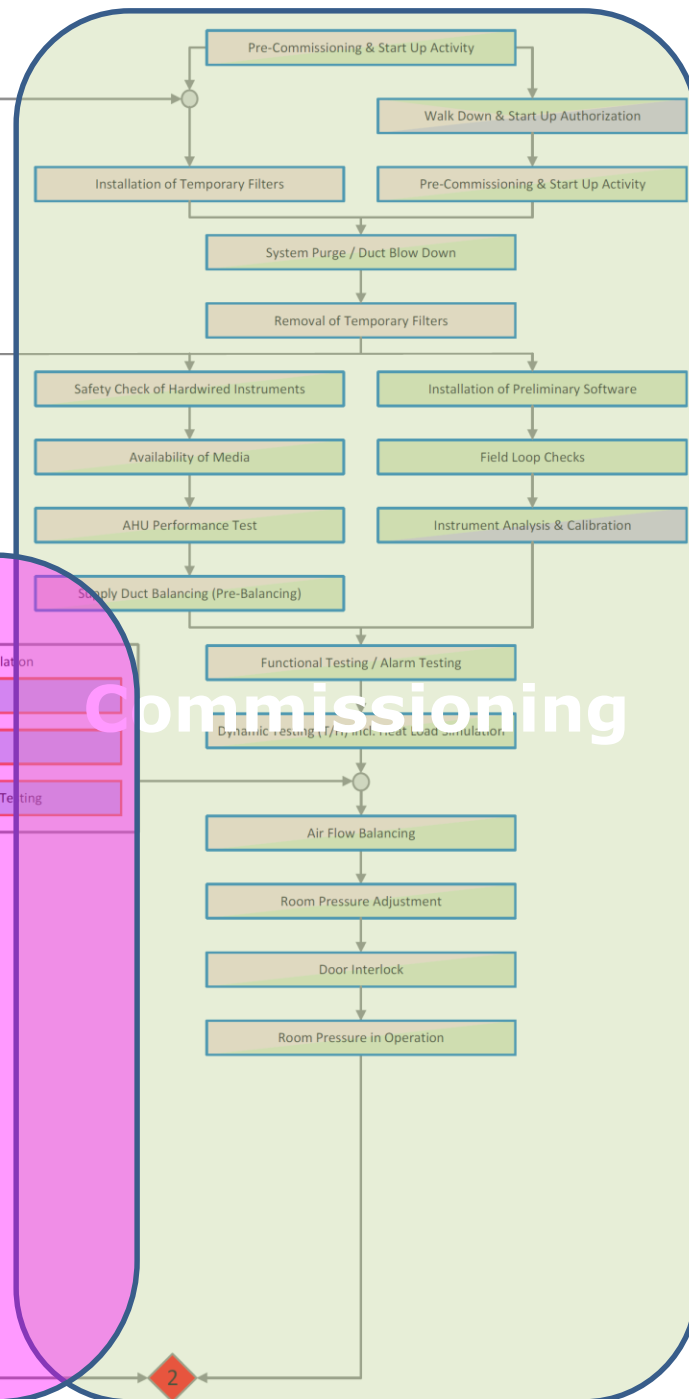
- Minimize administrative efforts for C&Q
 - Qualification only for GMP systems
 - Employment of a risk-based qualification approach
- Coordination of C&Q activities
 - Only start with qualification after thorough commissioning
- Benefit from synergies of C&Q activities
 - Leverage as many tests as possible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

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

Construction



Commissioning



Installation Qualification





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Commissioning & Qualification
(facility start-up and testing)

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

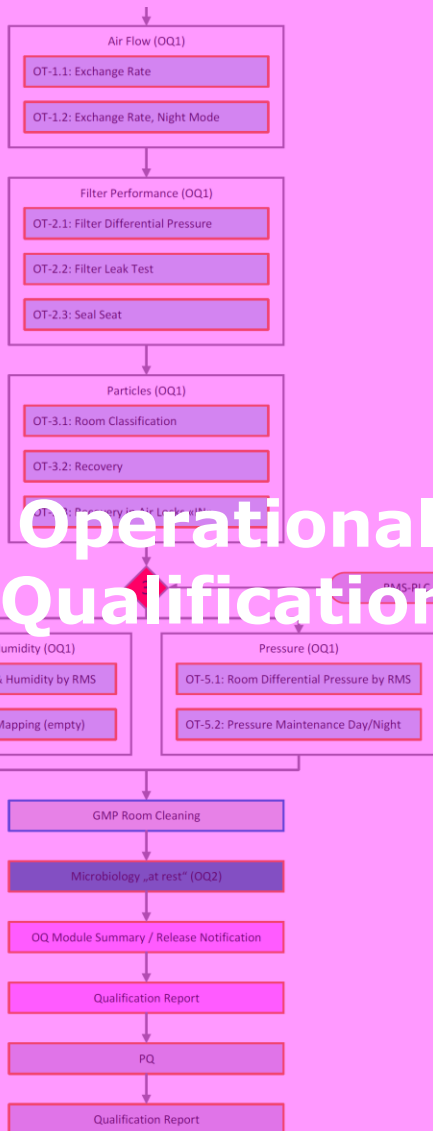
- Interdisciplinary System
 - HVAC
 - Clean Rooms
 - Automation (GMS & BMS)
 - Equipment

- Major Dependencies

Construction <-> Commissioning <-> Qualification

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

Operational Qualification





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Further Questions?