Project Setup: From the Beginning until the End
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Steps, structure and organization of a facility design, planning and construction project:

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

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

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

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

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

- **Construction Supervision**
  (quality assurance, compliance with DD and BoD)

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

- **DD Review**
  (part of the DQ)
Basic Structure of Documents
To be described in increasing detail with the progress of a project (F-URS, CD, BoD)

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<td>UTILITIES</td>
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<td>HVAC</td>
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<td>Site Description</td>
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<td>3.2</td>
<td>Building Description</td>
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<td>Architectural Layout</td>
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<td>COMPUTERIZED SYSTEMS</td>
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<td>Building Automation System</td>
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1.2 Purpose and Objectives
1.3 Scope
1.4 Project Organization
1.5 Abbreviations and Definitions
1.6 Guidelines and Regulatory Requirements
2.1 GMP Basics
2.2 Biosafety Basics
3.1 Site Description
3.2 Building Description
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4.4 Media- and Buffer Preparation
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6.2 UAF / LAF Operating Parameters
6.3 Air Filtration
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7.1 Building Automation System
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Project Steps – Design & Realization

- **Facility URS** (project definition, description of client needs and requirements)
- **Conceptual Design (CD)** (design basics and concept definition)
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- **DD Review** (part of the DQ)
- **Detail Design (DD)** (planning for construction, preparation of tender documents)
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

<table>
<thead>
<tr>
<th>工序 Process</th>
<th>生产周期 production cycle</th>
<th>岗位定员 staff number</th>
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<tbody>
<tr>
<td>溶液配制 solution preparation</td>
<td>4天 4 days</td>
<td>3人</td>
</tr>
<tr>
<td>细胞解冻复苏 Cell thawing</td>
<td>1天 1 day</td>
<td>2人</td>
</tr>
<tr>
<td>插床种子扩增 Seed proliferation with Shaker</td>
<td>12天 12 days</td>
<td>3人</td>
</tr>
<tr>
<td>WAVE 反应器准备及接种 WAVE reactor preparation and inoculation</td>
<td>2天 2 days</td>
<td>3人</td>
</tr>
<tr>
<td>WAVE 反应器细胞扩增 WAVE reactor cell proliferation</td>
<td>5天 5 days</td>
<td>2人</td>
</tr>
<tr>
<td>200L 反应器准备及接种 200L reactor preparation and inoculation</td>
<td>2天 2 days</td>
<td>4人</td>
</tr>
<tr>
<td>200L 反应器种子扩增 200L reactor seed proliferation</td>
<td>3-6天 3-6 days</td>
<td>3人</td>
</tr>
<tr>
<td>2000L 反应器准备及接种 2000L reactor preparation and inoculation</td>
<td>2天 2 days</td>
<td>4人</td>
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Facility URS
(project definition, description of client needs and requirements)
## Example of Output from CBC

### Schedule

<table>
<thead>
<tr>
<th>Batch No</th>
<th>Train</th>
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<th>Week 2</th>
<th>Week 3</th>
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<th>Week 5</th>
<th>Week 6</th>
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</table>

### Facility URS

- (project definition, description of client needs and requirements)
Example of Input from Customer

Process Flow Diagram

[Diagram showing process flow from Input: Buffer Solution, Diafiltration, Concentration, Inactivation, to Output: Purified Virus Solution, Virus Concentrate, Inactivated Bulk]
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

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  (facility start-up and testing)

- **DD Review**
  (part of the DQ)
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
Output from CD Phase (Example)
Building footprint with layout concept
Output from CD Phase (Example)

Clean utility concept showing generation and distribution of purified water, water for injection and pure steam
Output from CD Phase (Example)

HVAC concept illustrating air handling units supplying different room types.
Output from CD Phase (Example)
Automation concept showing the setup of the building management system.
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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)
Detailed layout showing room grades, pressure, flow & BSL border
Output from BoD Phase (Example)
Gowning concept showing appropriate gowning for the different room grades.

<table>
<thead>
<tr>
<th>Room Grade</th>
<th>Garment</th>
<th>Illustration / Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNC / D / C / B (Layer 1, underwear for all areas)</td>
<td>Socks&lt;br&gt;Long underpants&lt;br&gt;Sweatshirt / t-shirt</td>
<td><img src="image1.png" alt="Illustration" /></td>
</tr>
<tr>
<td>B (Layer 2)</td>
<td>Socks&lt;br&gt;Long underpants&lt;br&gt;Sweatshirt&lt;br&gt;Safety shoes Grade B (see picture)&lt;br&gt;Full-body protective overall for Grade B (see picture)&lt;br&gt;Gloves (see picture)&lt;br&gt;Head cover (see picture)&lt;br&gt;Safety goggles (see picture)&lt;br&gt;Face mask (see picture)</td>
<td><img src="image2.png" alt="Illustration" /></td>
</tr>
</tbody>
</table>
Output from BoD Phase (Example)
Detailed schematic for clean utilities showing POUs, sampling points & monitored parameters
Output from BoD Phase (Example)
Detailed schematic of AHUs showing the individual components and required utilities.
Output from BoD Phase (Example)

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

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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
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(planning for construction, preparation of tender documents)

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(facility start-up and testing)

**DD Review**
(part of the DQ)
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)
Output from DD Phase (Example)

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

P&ID Makeup- & Exhaust Air Unit

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

3D Model HVAC Installation

Detail Design (DD)
(planning for construction, preparation of tender documents)
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design basics and concept definition

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(facility start-up and testing)

Construction Supervision
(quality assurance, compliance with DD and BoD)

Detail Design (DD)
(planning for construction, preparation of tender documents)
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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(part of the DQ)
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
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)
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
Further Questions?