Design & Implementation of a new flexible Vaccine Drug Substance production facility

Case Study by Dr. Minör (IDT Biologika) and D.Steinhäuser (Glatt Engineering) - Pharmakongress 2022

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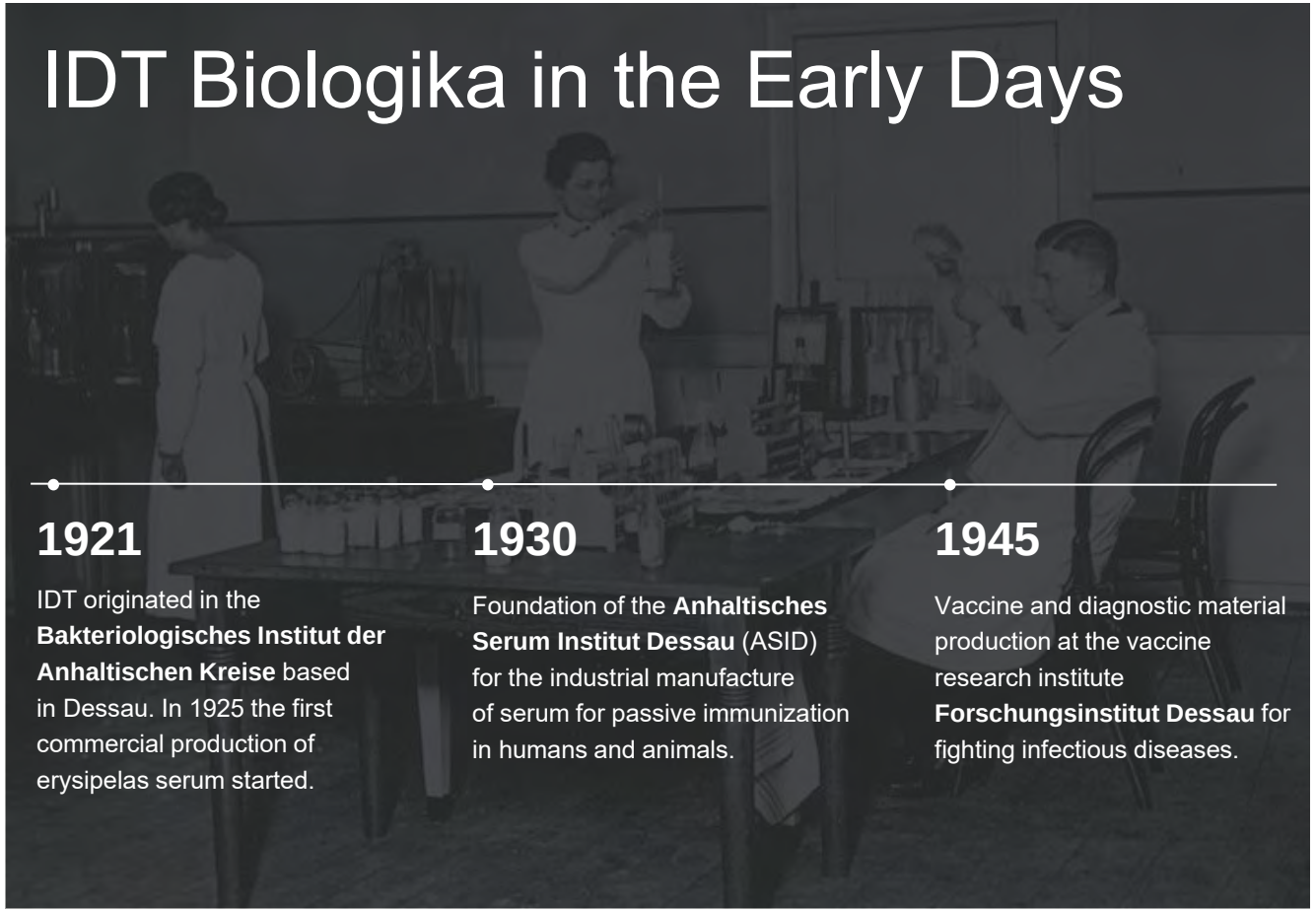
IDT Biologika
Glatt Ingenieurtechnik GmbH

Case Study new Bio Drug Substance Facility

Agenda

1. Introduction of IDT Biologika
2. Objectives for new bio Drug Substance facility and specific Requirements
3. Overview on project 205: Multipurpose Drug Substance Manufacturing facility
4. Engineering phase and Fast track implementation
5. Commissioning and Qualification
6. Go live – Challenges and solutions
7. Lessons learnt

IDT Biologika in the Early Days



1921

IDT originated in the **Bakteriologisches Institut der Anhaltischen Kreise** based in Dessau. In 1925 the first commercial production of erysipelas serum started.

1930

Foundation of the **Anhaltisches Serum Institut Dessau** (ASID) for the industrial manufacture of serum for passive immunization in humans and animals.

1945

Vaccine and diagnostic material production at the vaccine research institute **Forschungsinstitut Dessau** for fighting infectious diseases.

IDT Biologika Today

1993

Entrepreneur Hartmut Klocke privatizes the company under the new name **Impfstoff-werk Dessau-Tornau GmbH.**

2015

IDT acquires a **production location in Rockville, MD, USA** for the process development and production of vaccines in clinical phases I and II.

2016

IDT expands **process development capacities** for human viral vaccines **in Magdeburg, Germany.**

Today

Contract development and manufacturing of **human viral vaccines, gene and immune therapeutics and fill & finish of biologics.**

IDT Biologika Investments

2012
Setting up safety devices and autoinjector assembly lines

2016
Expanding storage capacities at - 80°C and for stability and retention samples, GMP upgrade of pharma production facility, Setting up pilot filling line and Schubert Multipacker packaging line

2019
Expanding Drug Substance Manufacturing capacities by set-up of a new building

2015
Expanding visual inspection capacities, Setting up large scale filling line

2017
Expanding large scale filling capacities with a new state-of-the-art filling line

2023
Investments:
- Large scale filling capacities with a new state-of-the-art filling line
- Additional capacities in Drug Substance production with a new building
- Visual Inspection

Company Sites in Germany and the US

BSL2 production facilities I FDA, EMA, ANVISA

Magdeburg

- Process development

Dessau

- Process development
- Clinical Trial Materials for phases I – III
- Commercial Manufacturing

Rockville, MD

- Process development
- Clinical Trial Materials for phases I – II

Production location

Process development

IDT Biologika in Dessau-Rosslau

Case Study: a new DS Facility at IDT Biologika in Dessau

Part of Task: Integration into existing environment

Situation at IDT Biologika and Requirements

- Increased demand for virus vaccines
- DS and DP capacities are well used for commercial products
- New technologies – How to transfer to large scale manufacturing ?
- Construction of new facilities takes > 4 years (at least)

(until Manufacturing permit)

➔ *Can design, implementation and qualification be speeded up?*

Objectives IDT Biologika for the new Bio project

Multipurpose manufacturing facility for the production of:

- Live recombinant viral vaccines
- Gene Therapy Medicinal Products (GTMP)

Key elements:

- High quality clean rooms
- Containment for environmental safety and prevention of cross contamination
- Waste control and inactivation
- Cleaning and room decontamination

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Objectives and Requirements for the new Bio project

Flexibility and scalability

Key elements:

- Tentative process flow scheme / design / volume flow
- Preparation for open aseptic operations (grade B environment for grade A operations)
- Large size clean rooms
- Major focus on disposable technologies
- Fast track change over systems

Objectives and Requirements for the new Bio project

Fast track and successful start of manufacturing

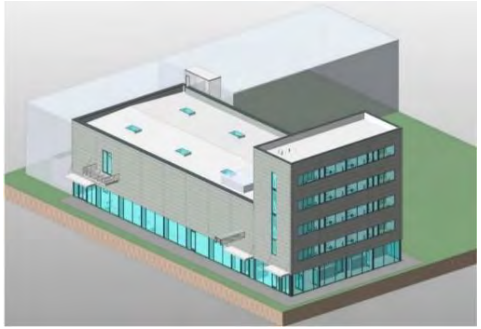
Key elements:

- Experienced management
- Knowledgeable engineering team
- Knowledgeable and well trained operators
- Experienced quality support

„People who have done that before“

Project 205 at a Glance

- New biologicals drug substance manufacturing plant for human vaccines (BSL 2)
- Time of Construction and Commissioning 20 months
- Production building with approx. 900 sqm clean rooms class B and C for multi product use; plus additional office building and social area
- Contract manufacturing for external customers
- Mainly single-use technologies in Upstream / Downstream Processing
- Facility planed for possible extension



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Key Facts IDT Biologika Project 205

Area parameters

Building footprint: 1150 m²
Clean room area: 900 m²

Investment volume

23 million €

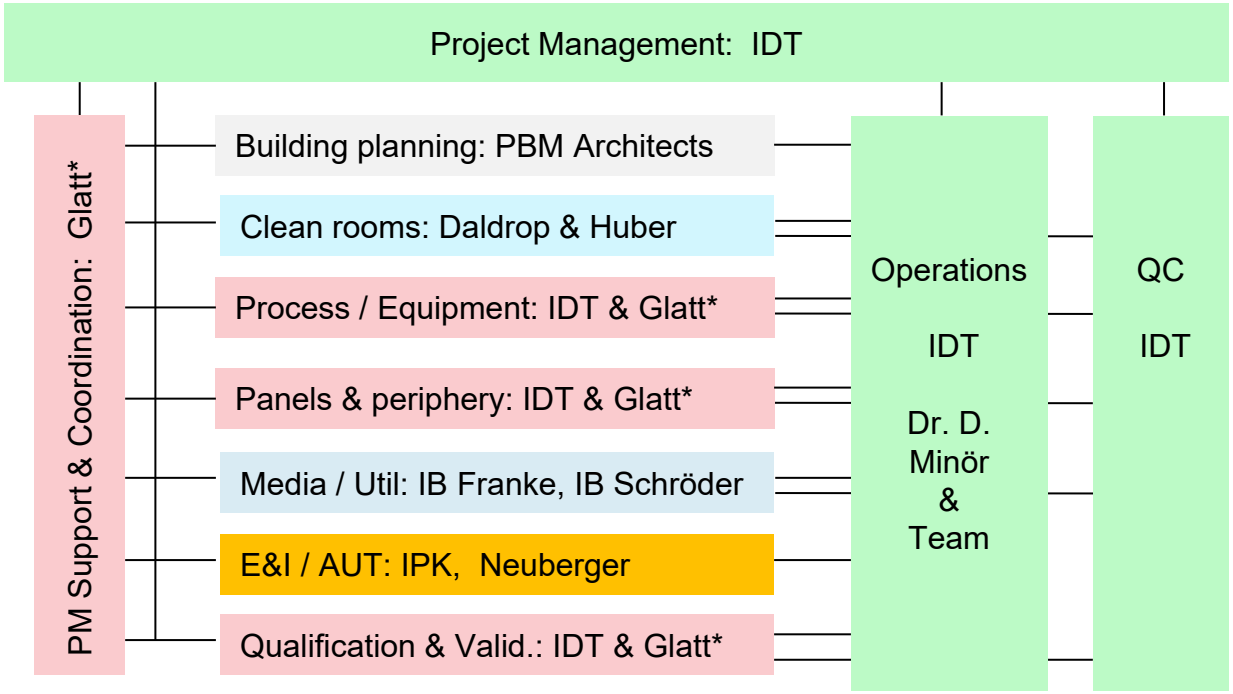
Time schedule

Start Planning (Basic Design & Permit doc.s)	Dec. 2017
Start of construction	April 2018
Topping out (“Richtfest”)	Sep. 2018
Installation, Commissioning + Qualification + Validation ➔ Permission for GMP Manufacturing	Dec. 2019
Time Construction and Commissioning	20 months
Total Time duration	24 months

Main partners

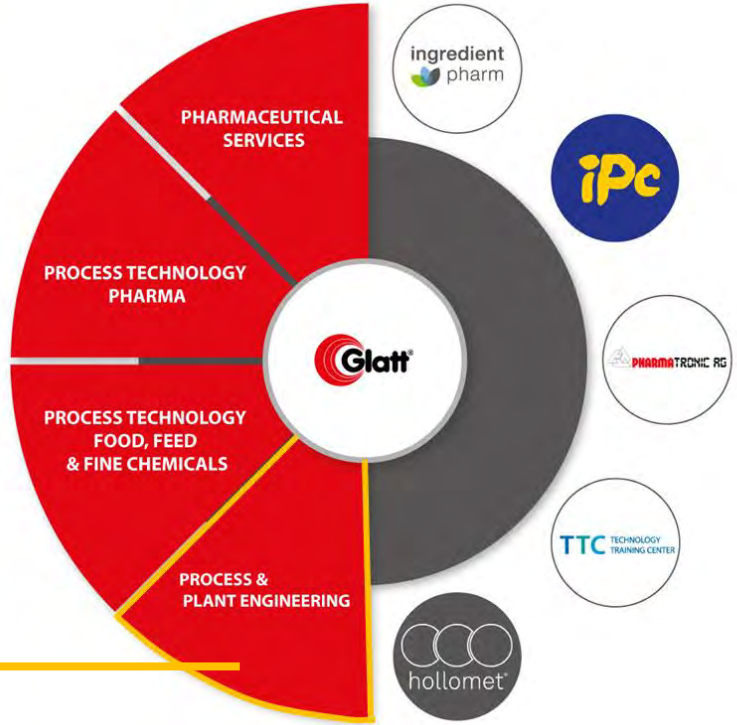
Architecture/ Building: PBM Architects GmbH Leipzig
Process Engineering: Glatt Ingenieurtechnik GmbH

Project structure and further partners



* Glatt = Glatt Engineering, i.e. Glatt Ingenieurtechnik GmbH

Engineering Division within Glatt group



Glatt Ingenieurtechnik GmbH
HQ in Weimar, Germany

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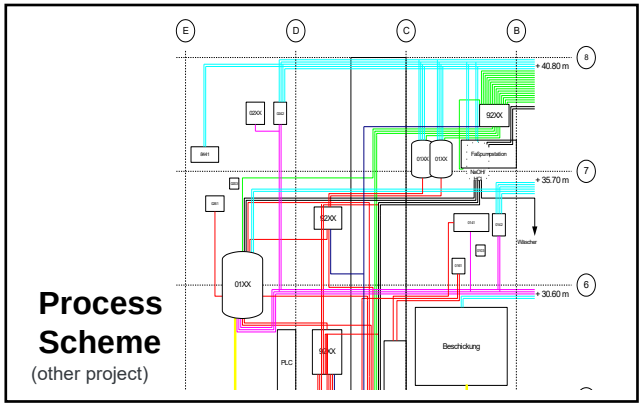
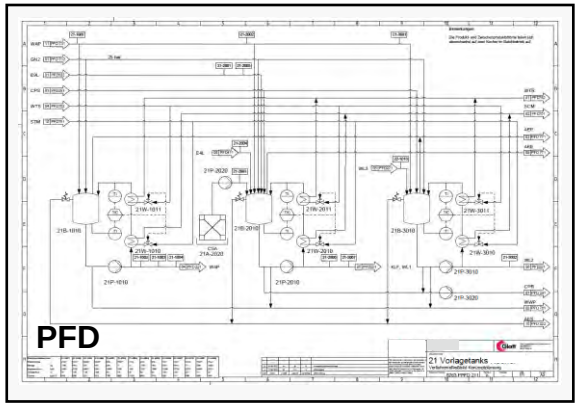
Engineering Involvement in IDT Project 205

- Engineering services for process equipment, periphery and support equipment, utilities
- Equipment arrangement and Layout planning
- Specification for process equipment, coordination with vendors / suppliers, FAT / SAT
- Technical coordination and PM support, scheduling and resource planning, controlling support
- Qualification: participation in preparation and implementation of DQ, IQ, OQ, PQ,
- Coordination of calibration

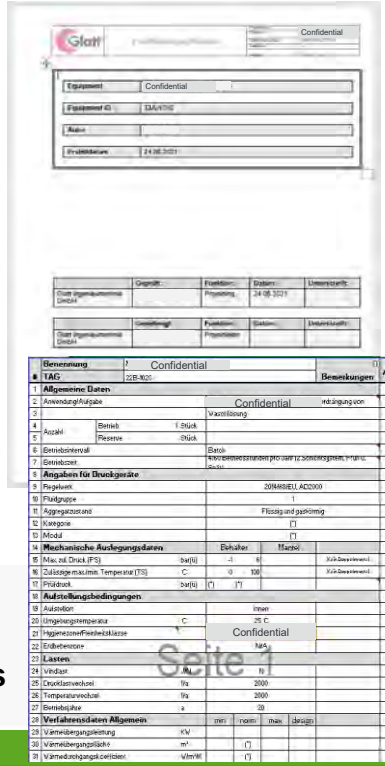
Overview on Case Study project 205 Process Engineering



Process Scheme
(other project)



PFD



Generation of Process Fundamentals

- Process strategy / schemes
- Process Flow Diagrams (PFD‘s)
- Main equipment data ➔
  Equipment list (type and number), main parameters and dimensions

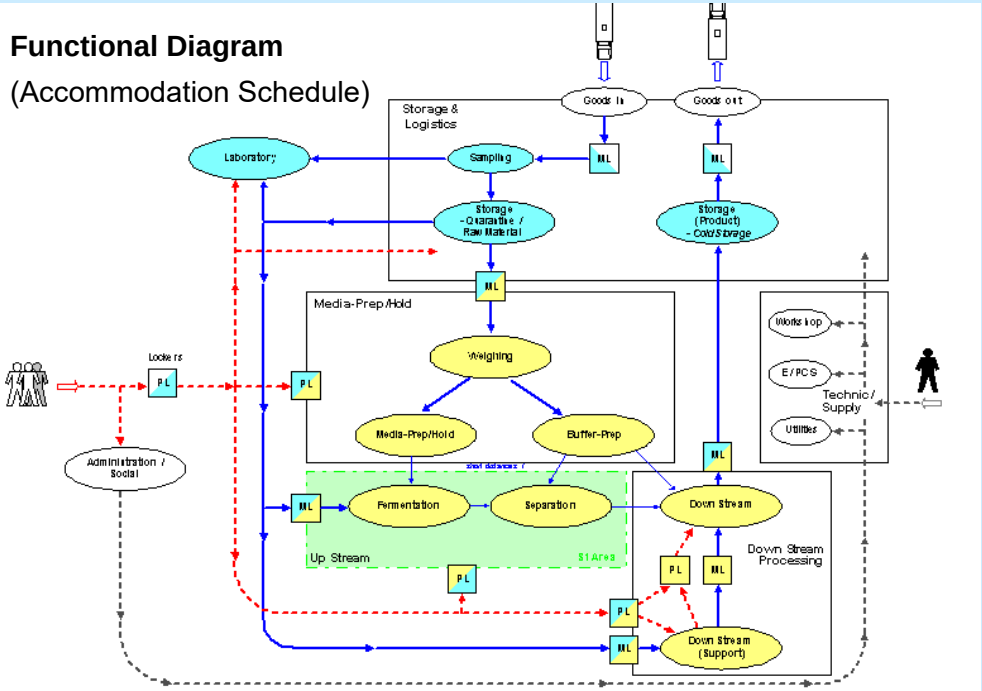
URS and specifications

Approach for Case Study project
Design Principles and Layout Concept

- Programming
- Functional Diagram
- Layout Typicals
- Block Layout
- Functional Layout

Functional Diagram

(Accommodation Schedule)

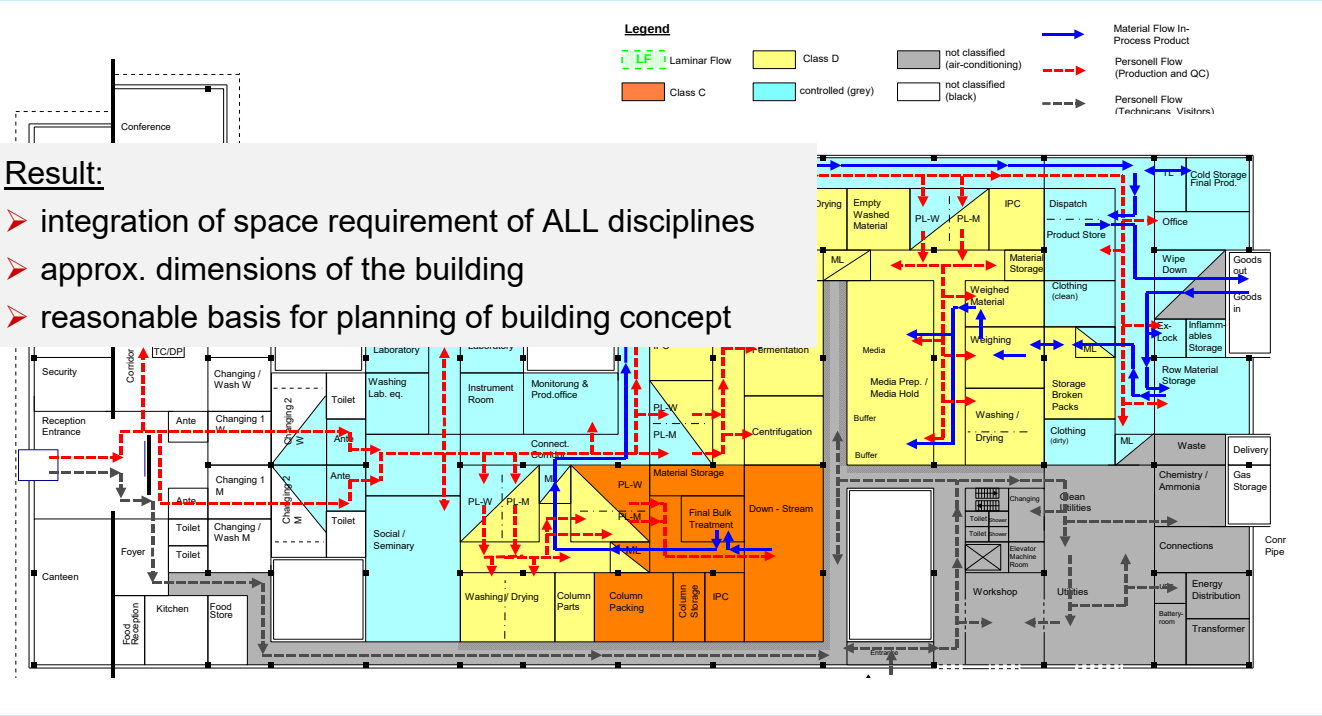


Method bases on:

- **ISPE Baseline Guides** for
  a) Biopharmaceuticals &
  b) Sterile Manufacturing Facilities chapter 4.3.2.
- relating GMP cleanliness classification to functions
- optimized structuring of GMP zoning concept, personnel and material flow

Approach for Case Study project
Design Principles and Layout Concept

- Programming
- Functional Diagram
- Layout Typicals
- **Block Layout**
- Functional Layout



Result:

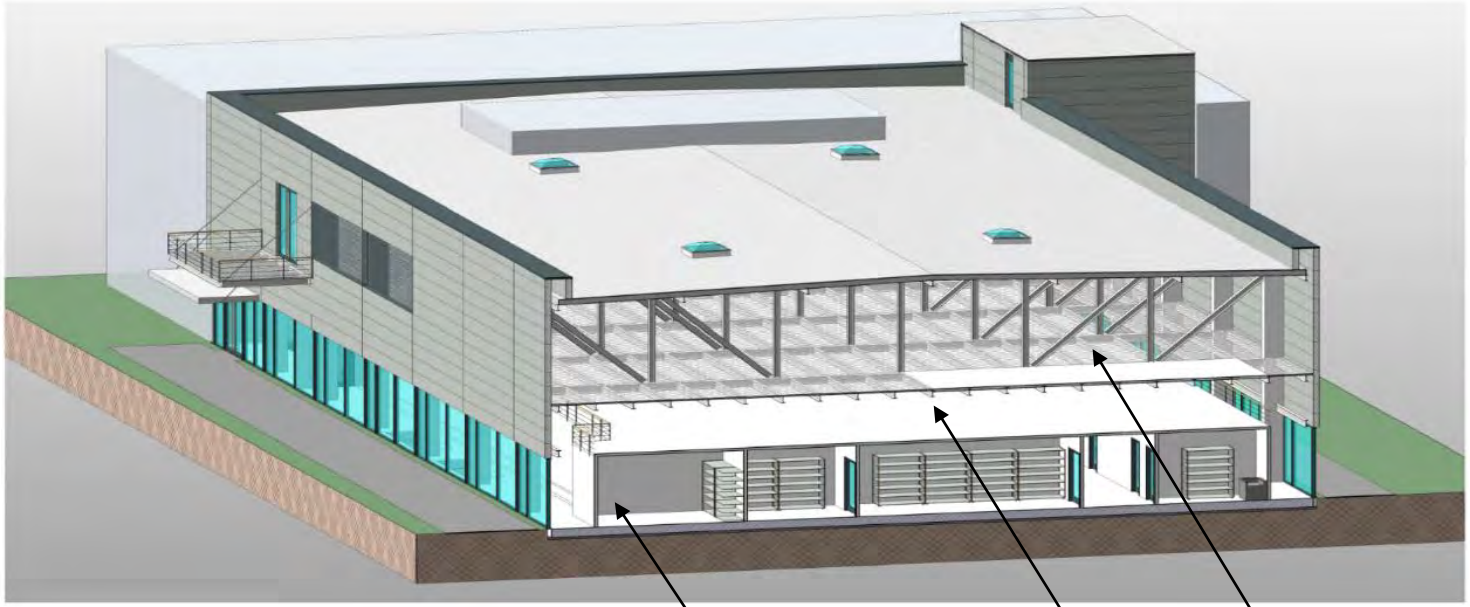
- integration of space requirement of ALL disciplines
- approx. dimensions of the building
- reasonable basis for planning of building concept

Overview on Case Study project 205
Flexibility by prepared compartments

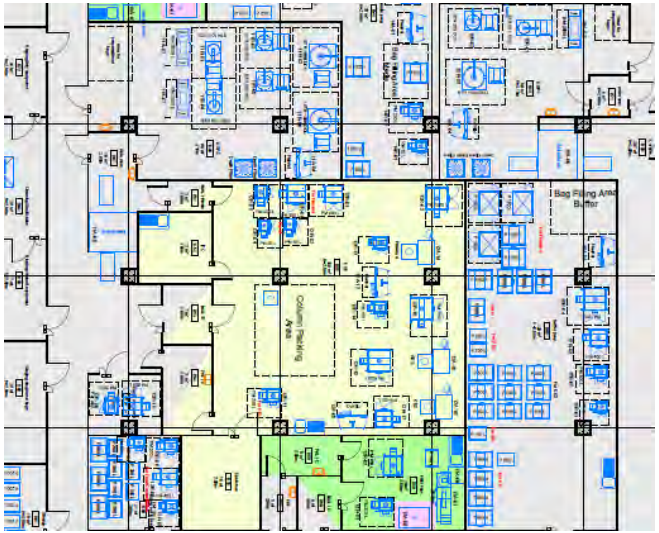
4 flexible class B / C
production compartments

CNC
Class C, AER 10-20 / h
Class B, AER 40 / h

Overview on Case Study project 205
Flexibility by “House-in-house” concept

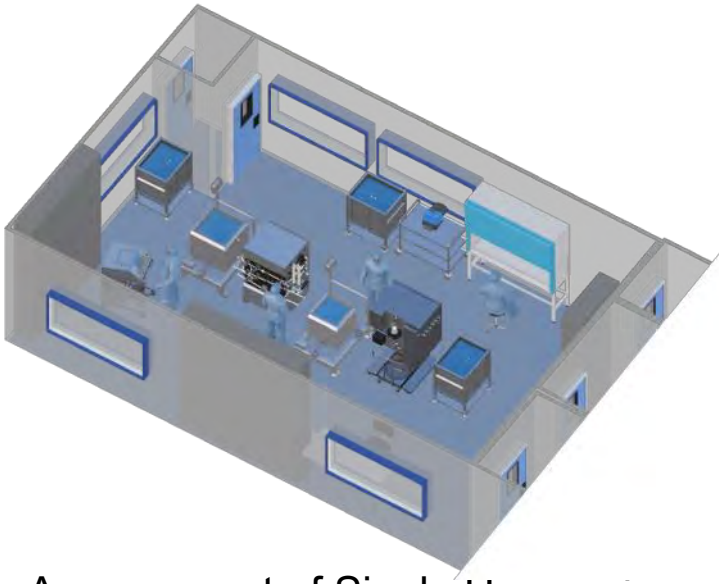


Overview on Case Study project 205
Layout Concept and Equipment arrangement



Layout concept

(image from other example)



Arrangement of Single Use equipment
in 3D CAD conceptual model
using typicals from supplier

Overview on Case Study project 205
Layout Concept and Flows

Personal Flow

Material Flow

Waste Flow

Multipurpose Drug Substance Plant 205
Fast track building construction

Fast track building construction with prefabricated concrete elements

Multipurpose Drug Substance Plant 205
Fast track building construction

Combined building construction: concrete and steel

Fast track building construction with prefabricated concrete elements

Multipurpose Drug Substance Plant 205
Fast track building construction

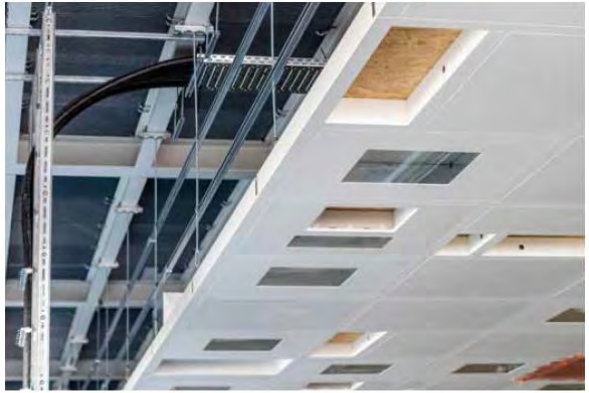
Elements fitted

Floor prep work

Multipurpose Drug Substance Plant 205
Internal finishing and cleanroom construction

Cleanroom floor installation work

Multipurpose Drug Substance Plant 205
Internal finishing and cleanroom construction



Cleanroom ceiling installation work

Cleanroom floor installation work

Case Study IDT Biologika Project 205
Overview on periphery and systems

Technical level

Clean room ceiling, walkable

Case Study IDT Biologika Project 205
Overview on support and service systems

WFI use point / Media panel

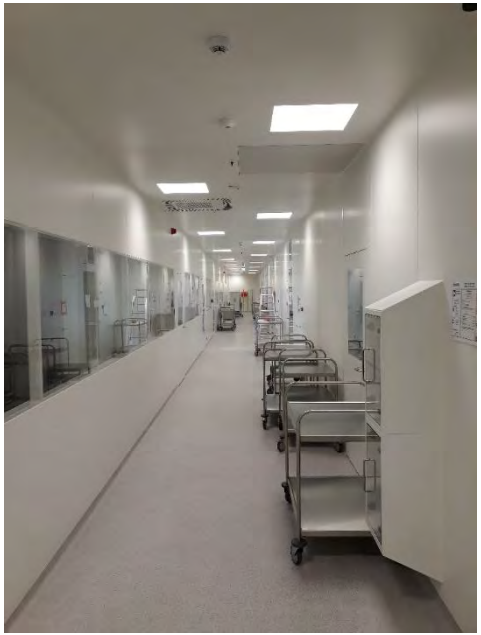
Connect panel from cleanroom ceiling (keeps flexibility on floor)

Clean steam sampling and media panel

Decontamination autoclave

Case Study IDT Biologika Project 205 Impressions

Production area (during installation / IQ)



Clean corridor for service

Multipurpose Drug Substance Plant 205
Commissioning and Qualification

C & Q of the Clean rooms

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Multipurpose Drug Substance Plant 205 Commissioning and Qualification

C & Q Strategy

- …integrated…
- …parallel….

Qualification of Equipment & Systems (Planning and Execution)

- Risk analysis (FMEA)
- DQ/IQ/OQ/PQ Qualification plans / reports
- Test protocols
- TRM (Traceability Matrix)
- CSV (Computer Software Validation) according to GAMP 5 / 21 CFR Part11

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Fast Track implementation

Fast track implementation of new facility ✓

Expectations

- Minimum of process implementation time
- Flexible processes
- Short Change over times

Key Elements

- Process equipment available
- Single use materials
- Effective room decontamination
- Well trained & experienced personal

Case Study IDT Biologika Project 205
Overview on equipment and systems

Equipment

- Autoclaves (sterile /decontamin.)
- CO_2 Incubators
- Block thermostates
- Safety workbenches
- Roller racks
- Moebius mixing systems
- Pallet tanks
- Tangential Flow Filtration (TFF)
- Chromatography systems (Äkta Ready)
- LN2 storage tanks / system

Small units

- Bio sealer, Bio welder
- Fridges and freezer cabinets
- Filter integrity measurement
- Peristaltic pump skids
- Scales / balances
- etc.

Further systems

- HVAC units (AHUs and special systems)
- Clean rooms / Air locks (grade D, C, B)
- WFI distribution / loops / use points
- Clean steam distribution / use points
- Cold stores, cooling capacity
- Incubation rooms
- H_2O_2 room decontamination systems
- Wastewater inactivation plant (thermal)
- Mixed gas supply
- Clean gases supply (N_2, CO_2, O2)
- Media panels

Case Study IDT Biologika Project 205
Impression Upstream Bioprocessing area

Roller racks RC 40 with single-use bottles for cell cultivation

Case Study IDT Biologika Project 205
Impression Upstream Bioprocessing area

Cell stack manipulator

Mobile rack of cell factories

Case Study IDT Biologika Project 205
Impressions Downstream Bioprocessing area

- Flow through centrifuges
- TFF
- Filtration
- Sonication
- Chromatography

Case Study IDT Biologika Project 205
Process flexibility via single use systems

Case Study IDT Biologika Project 205
Pros and Cons of single use equipment

Pros Single Use Equipment

- Short supply time (less engineering effort, shorter manufacturing / delivery time)
- Lower cost of investment
- No CIP/SIP and no cleaning validation
- Sterile (gamma irradiation)
- Mobile availability (not fixed to specific processes or locations)
- Moderate qualification effort (DQ,IQ,OQ)
- In summary short process until use

Case Study IDT Biologika Project 205
Pros and Cons of single use equipment

Cons Single Use Equipment

- Higher manual effort due to less automation (intense training)
- Complex disposal
- Comparable high operating costs (procurement, incoming goods inspection, documentation and logistic)
- Risk of confusion / necessity of clear identification (Leachables & Extractables)
- Higher space requirement due to manual handling
- Potentially open processes caused by tube connections
- Complex supply chain
- Sensitive plastic materials (difficult detection of leakages)

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Multipurpose Drug Substance Plant 205
Lessons learnt

- Mechanical defects (defect weld on bags, defect connectors)
  ➔ check at delivery / before use, apply scrutiny
- Handling errors (f.e. connecting of wrong tubes, filigree sterile connectors)
  ➔ train, implement checking routine, document
- In time material supply
  ➔ long lead times, order on stock
- Air bubbles in tube systems, esp. critical for chromatography systems
  ➔ check, if prone to occur: implement bubble trap

Case Study IDT Biologika Project 205 Conclusions

Recommendation of single use application:

- Small scale to medium batch size
- Frequently change over
- Fast track implementation / time to market
- Difficult cleaning validation

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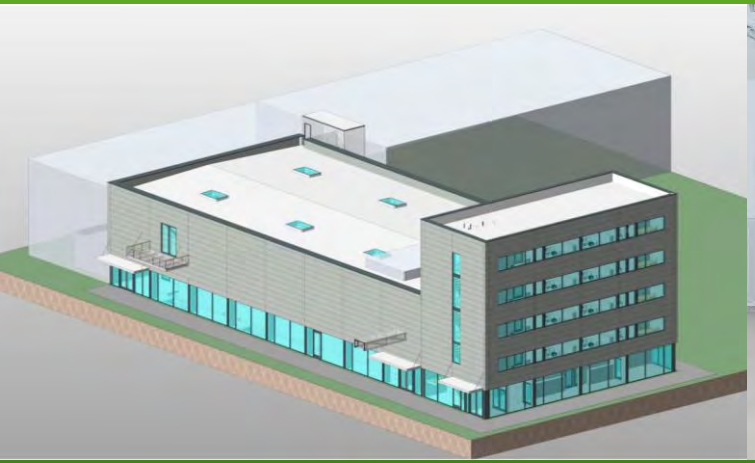

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Thank you !

Time for your Questions

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