



EVOLUTION OF TECHNOLOGY

Single-Use Vs Stainless Steel – Are Hybrid Facilities the Best of Both Worlds?

- Company introduction
- Single-use systems, who and/or what do we mean?
- Current trends and thinking
- Stages of single-use system integration
- Case studies
- Conclusions

ZETA Group



- Key supplier of biopharmaceutical turnkey projects
- Established in 1989, 30 years of experience
- Headquarters in Lieboch/Graz, Austria, Europe
- Worldwide presence through branches and partners
- Approx 600 employees, of which 350 are engineers



- Lieboch, Graz
- 1.700 m² (18,300 sq ft)
- Total indoor height: 8,5 m (335")
- Crane hook height: 7 m (275")
- Crane load: 2 x 8 metric tons
- Door height: 7,5 m (295")
- Door width: 4,5 m (180")
- Connection to clean media distribution center



- Lieboch, Graz
- 430 m² (4,600 sq ft)
- Total indoor height: 14 m (550")
- Crane hook height: 12 m (475")
- Crane load: 1 x 15 metric tons
- Door height: 7 m (275")
- Door width: 4,8 m (190")
- Connection to clean media distribution center



- Lebring, Austria
- 1.300 m² (14,000 sq ft)
- Total indoor height: 12 m (475")
- Offices 250 m² (2,700 sq ft)



- Brno, Czech Republic
- 1.200 m² (12,900 sq ft)
- Total indoor height: 6 m (235")
- Offices 200 m² (2,100 sq ft)

Engineering & Services

- General Planning
- Plant Installation & Commissioning
- Engineering: Conceptual, Basic, Detail
- Process Development & Scale-Up
- Process Optimization & Retro-Fitting
- CQV
- Maintenance
- Customer Care Services
- 24/7 Service Hotline



Customized Systems

- USP Systems: Fermentation, Media/Buffer Preparation, Harvest
- DSP Systems: Filtration, Chromatography, Viral Inactivation
- Solution/Buffer Preparation Systems
- Formulation Systems
- Clean Media Systems
- CIP/SIP Systems



Automation

- Engineering: Conceptual, Basic, Detail
- Project & Quality Management
- DCS, Batch Management & SCADA System Solutions, SUB and freeze/thaw controls
- Software & Hardware Design & Engineering
- Switchgear and Cabinets
- Installation & Commissioning
- FAT/SAT
- CQV



Products & Components

- Magnetic Agitators
- Freeze & Thaw Systems
- Transfer Panels
- De-dusting Rings



Food Systems

- Pasteurizing Systems for Food Applications
- CIP/SIP Solutions
- Ingredient Adding Systems
- Aseptic Filling Systems
- Sampling Devices
- Screening Solutions
- Consulting & Engineering



EU CUSTOMER (<\$150M)

GLOBAL CUSTOMER (>\$150M)

GLOBAL CUSTOMER
(Sub-Contractor)

ZETA EPCM

Overall Control Procurement SCM Schedule CQV

Appointed EPCM

Overall Control Procurement SCM Schedule CQV

Appointed EPCM

Overall Control Procurement SCM Schedule CQV

EPCM

CONTRACTOR

	PROCESS	CIVILS	HVAC/ UTILITIES	ELECTRICAL	PROCESS	CIVILS	HVAC/ UTILITIES	ELECTRICAL	PROCESS	CIVILS	HVAC/ UTILITIES	ELECTRICAL
Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design	Conceptual Design
Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design	Basic Design
Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design	Detail Design
Fabrication	Construction	Construction	Construction	Construction	Construction	Construction	Construction	Construction	Fabrication	Construction	Construction	Construction
Automation		Automation	Automation	Automation	Automation	Automation	Automation	Automation	Automation	Automation	Automation	Automation
Commission		Commission	Commission	Commission	Commission	Commission	Commission	Commission	Commission	Commission	Commission	Commission
Qualification		Qualification	Qualification	Qualification	Qualification	Qualification	Qualification	Qualification	Qualification	Qualification	Qualification	Qualification

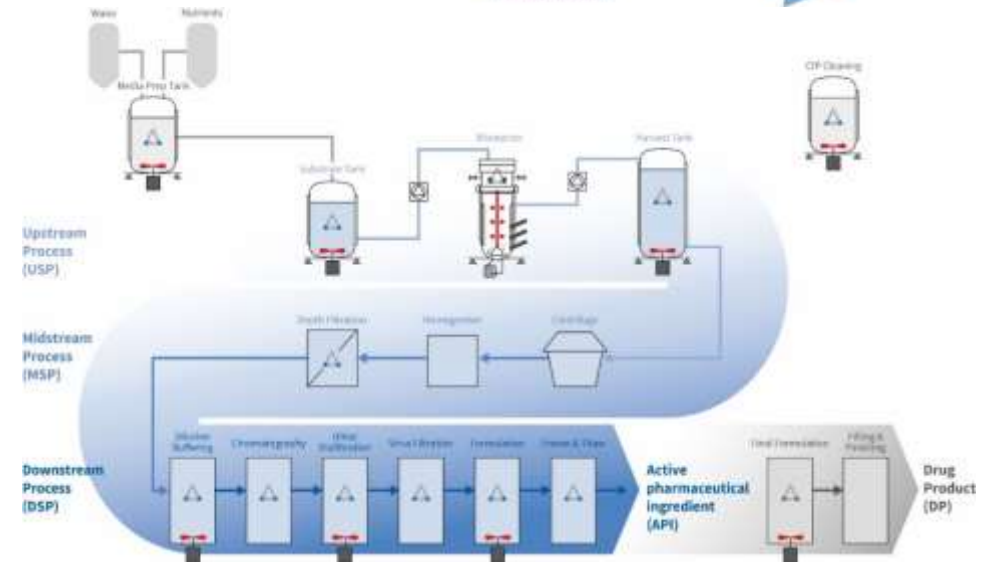
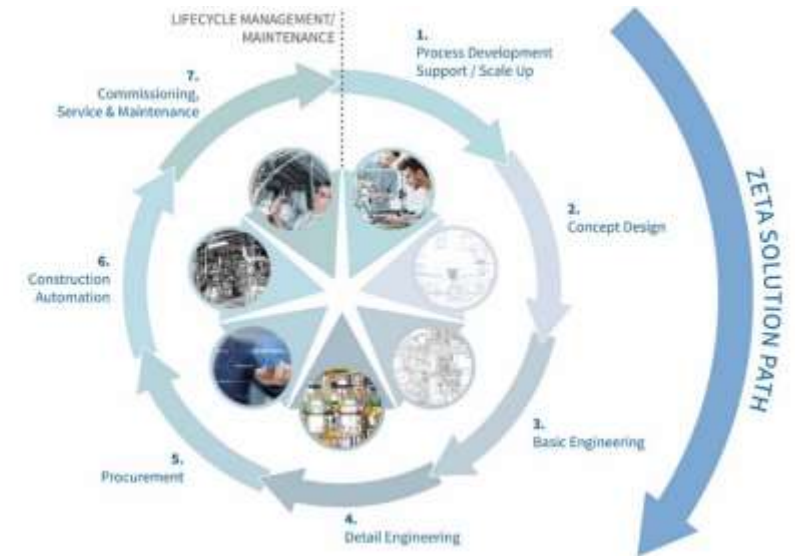
ZETA

Partner

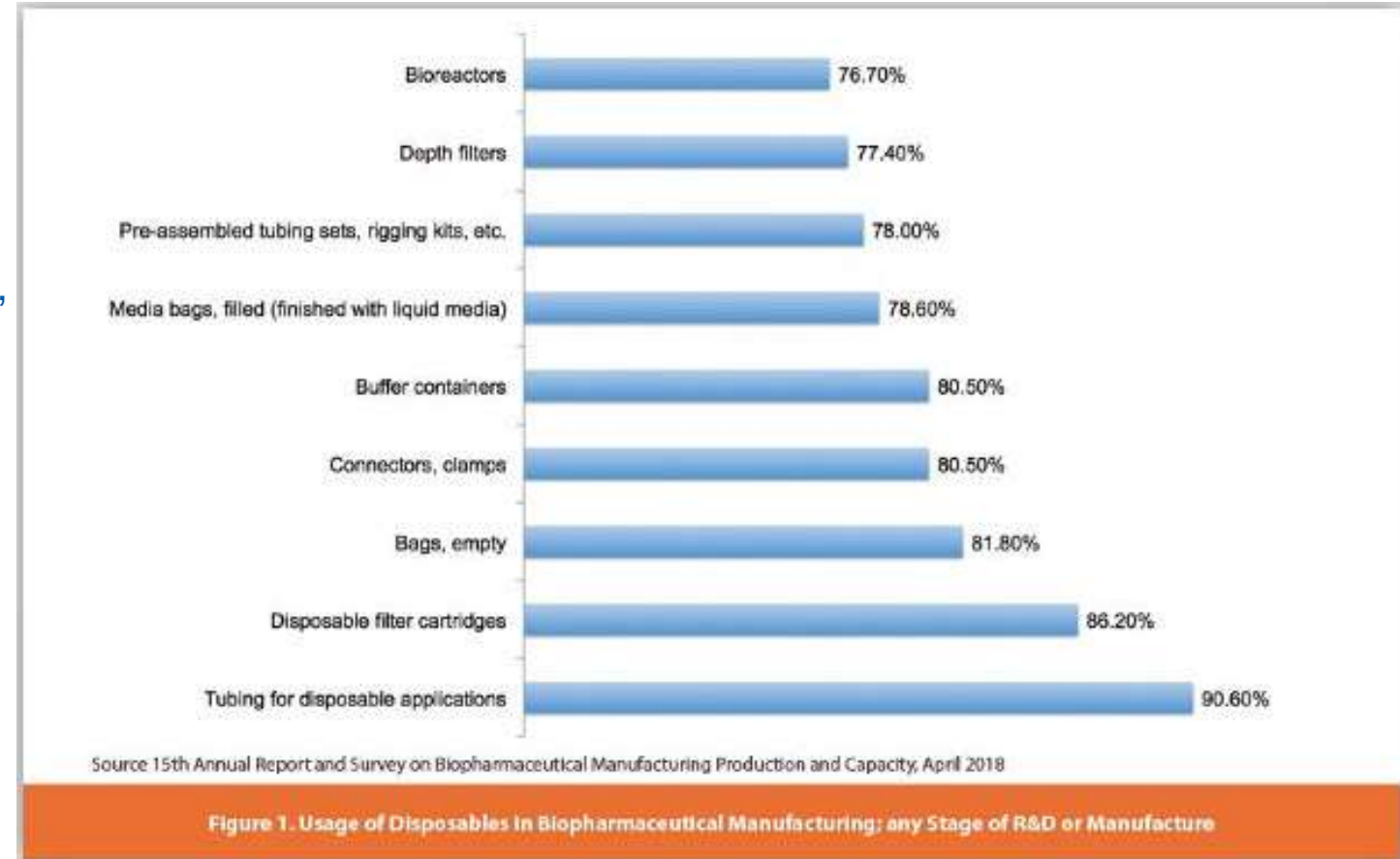
1. Delivering the project on time

2. Being on budget

3. Quality of product and delivery



- Equipment type
 - Bags – buffer, media, additives and ingredients
 - Single-use bioreactors (SUB)
 - Upstream and downstream – connectors, tubing sets, manifolds, assemblies, filters, cartridges, columns etc...
- Brands (SUBs)
 - ABEC
 - GE
 - Pall
 - Sartorius
 - Thermo Fisher
 - Merck Millipore etc...



The average responses from developer survey respondents reporting use of various SUS equipment at their facility.

Eric S. Langer & Ronald A. Rader, BioPlan Associates, Inc. in American Pharmaceutical Review, October 2018.

The leading reasons cited as “very important” resulting in adoption of single-use systems were:

- “Decrease risk of cross-product contamination” cited by 46.2%.
- “Eliminating cleaning requirements” 41.2%.
- “Reducing time to get facility up and running” 44.1%.
- “Reduce capital investment in facility & equipment” 40.4%.

The top downsides or potential problems with single-use systems, those cited by >50% of respondents, were:

- “Breakage of bags and loss of production material” cited by 75.0%
- “Leachables and extractables” cited by 73.3%.
- “High cost of disposables” 68.8%.
- “Material incompatibility with process fluids” cited 56.7%
- “We do not want to become vendor-dependent (single-source issues)” also at 56.7%.

When asked about plans for bioreactors purchases, 70.2% of developer/manufacturer respondents reported they would specify single-use bioreactors (SUB) for any new facilities at clinical scale and 51.9% for new commercial manufacturing facilities.

About half of the respondents now expect to see fully single-use facilities in five years.

Eric S. Langer & Ronald A. Rader, BioPlan Associates, Inc. in American Pharmaceutical Review, October 2018.

Trends in the Biopharma Market

- **Year-on-year growth**
- **Development of more potent drugs**
- **Trend toward personalized medicine**
 - » Reduced batch size per drug
 - » Increasing demand for smaller production capacity
- **Cost pressure**
 - » Diminished likelihood of finding new blockbuster
 - » Increased competition due to biosimilars
- **Resurgence of cell and gene therapy**
- **Quick time to market (fast track projects)**
 - » Decision on investment as late as possible
- **Biopharma industry is forced to adapt its production facilities to the evolving markets**

Production facilities: flexible and cost efficient



Large scale fermentation



**Single-use
technology:
one size
fits all?**

Single-use technology



Patient scale model

PROS

- **Investment costs are much lower**
Krämer, Müller, SANOFI: 24 - 40 %
Guldager, NNE: max. 30 %
- **Project realization is much faster**
BUT: lead times for customized bags:
up to 25 weeks
- **No CIP/SIP of single use flow path**
BUT: utilities available at commercial scale
- **Higher degree of flexibility**
BUT: also stainless steel equipment can be modular design

CONS

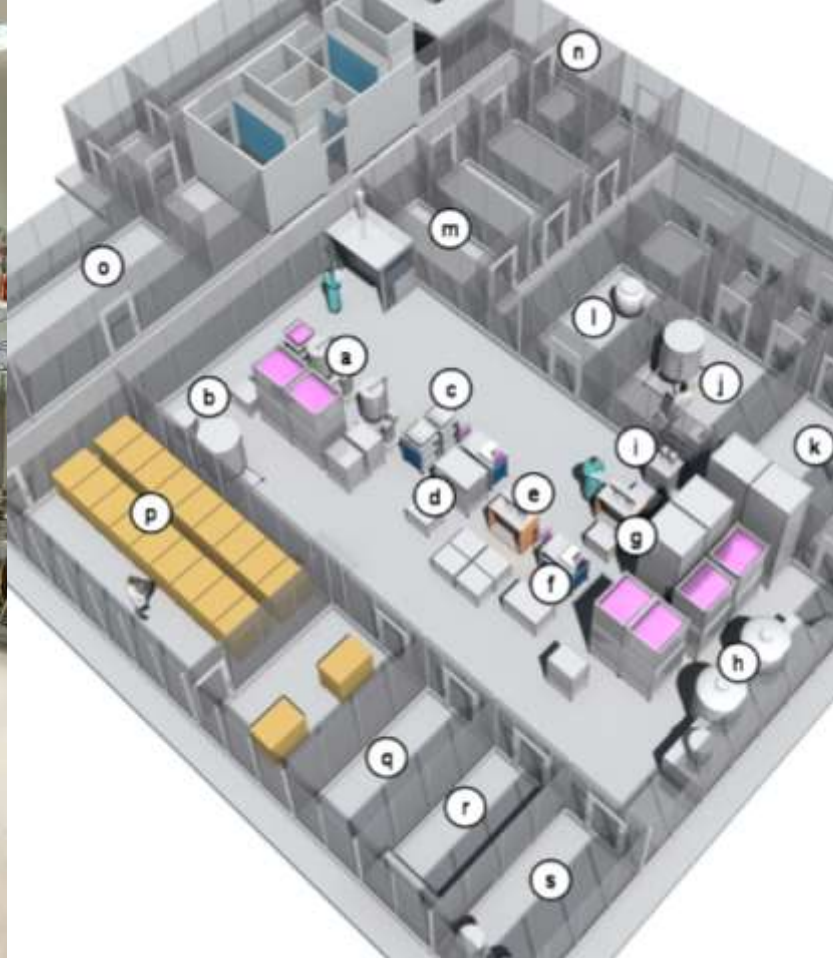
- **Limited industrial usability**
Lack of standards and specifications
- **1 design fits all**
Off-the-shelf products limit process flexibility
- **Limited customization service**
- **Limited project execution**
- **Automation islands**
- **Lack of suitable sensors**
- **Many manual operations**
- **Range of choice of SUT**

➔ Strong need to “mature“ SU systems for GMP

➔ Standards and methods similar to those recognized in Stainless Steel systems required for SUT

STAGE I – THE BALLROOM CONCEPT

Standalone Process Units & Highest Flexibility



Character	Definition
a	2 × 200l perfusion fermenter
b	1 × 200l and 1 × 1,000l media preparation tank
c	2 × depth filtration (one for each fermenter)
d	Ultrafiltration
e	Continuously operated protein A capture
f	Low pH viral inactivation
g	Flow-through intermediate purification and polishing (e.g., AEX and CEX)
h	1 × 200l and 2 × 1,000l buffer preparation tank
i	Viral filtration
j	Post viral part (formulation, bioburden reduction, filling of bulk drug substance)
k	Seed lab
l	Autoclave and Washing
m	Equipment storage
n	Cell bank
o	Frozen storage
p	Storage room (e.g., process consumables)
q	Weighing
r	In process control (IPC) lab
s	Coldroom

STAGE I – Off-the-Shelf Single-Use Process Units



Allegro™ Single-Use Tangential Flow Filtration Systems Allegro CS4500

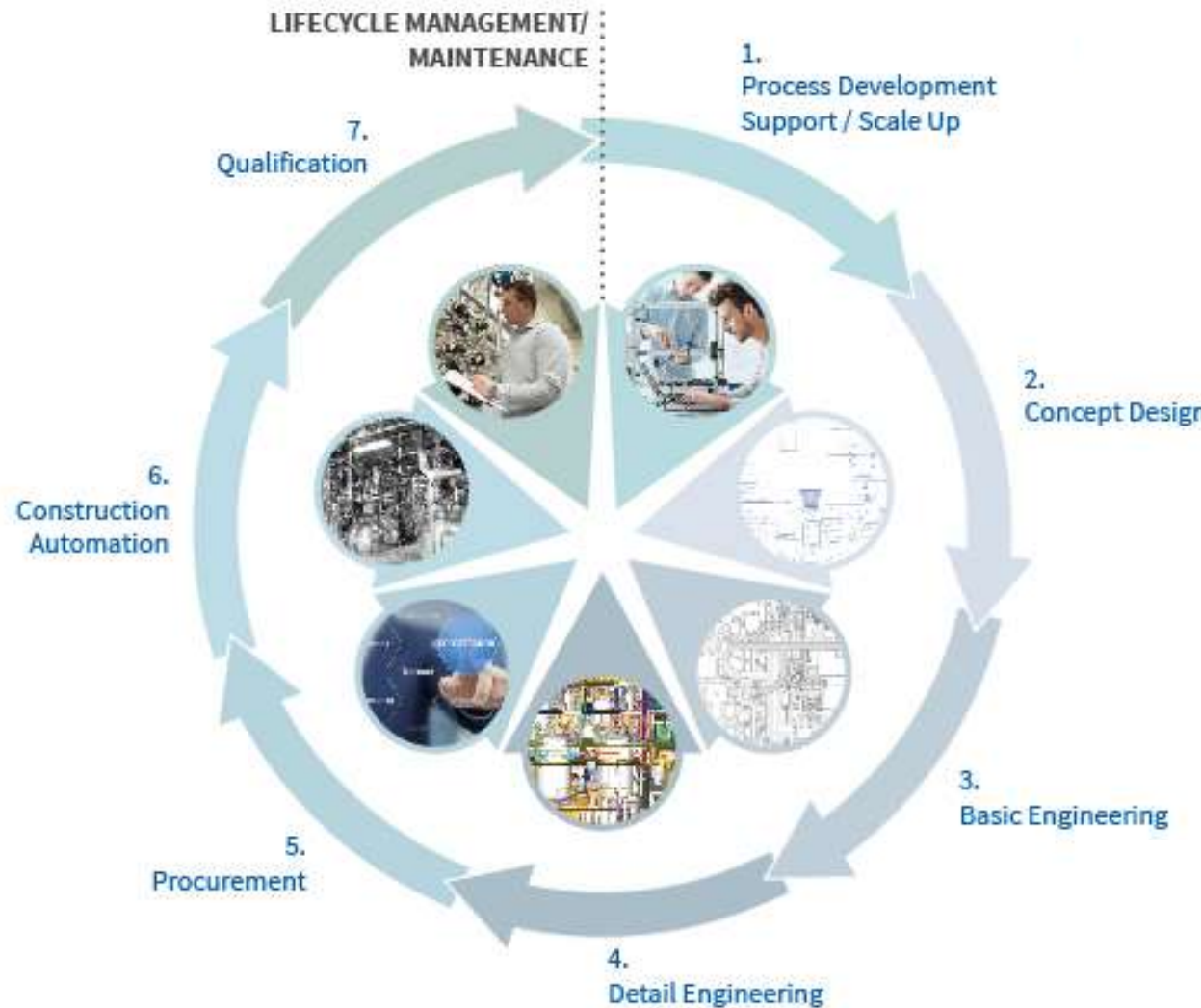


Äkta™ Ready System



- Standardized, dedicated SU system
- Stand-alone package solutions
- Limited customization service
- Rigid project execution

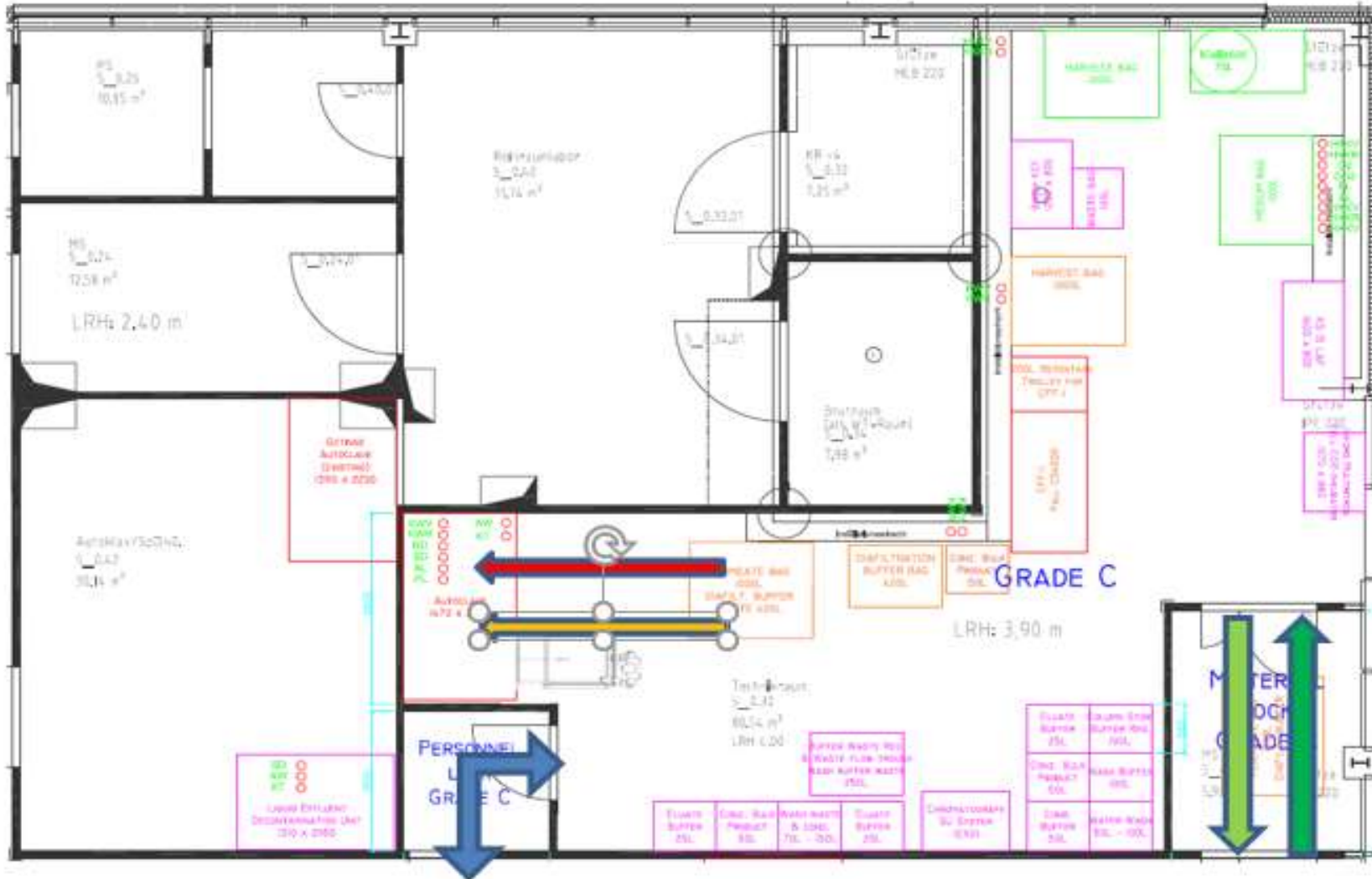
STAGE I - Process for GMP Compliant Facilities



- Process flow
- Facility layout
- **Interfaces**
- **Automation**
- **Validation**
- Operability
- Safety
- Maintenance
- **Project Management**

Case Study 1 - STAGE I – THE BALLROOM CONCEPT

Engineering for Intelligent Clustering of Mobile SU Process Units

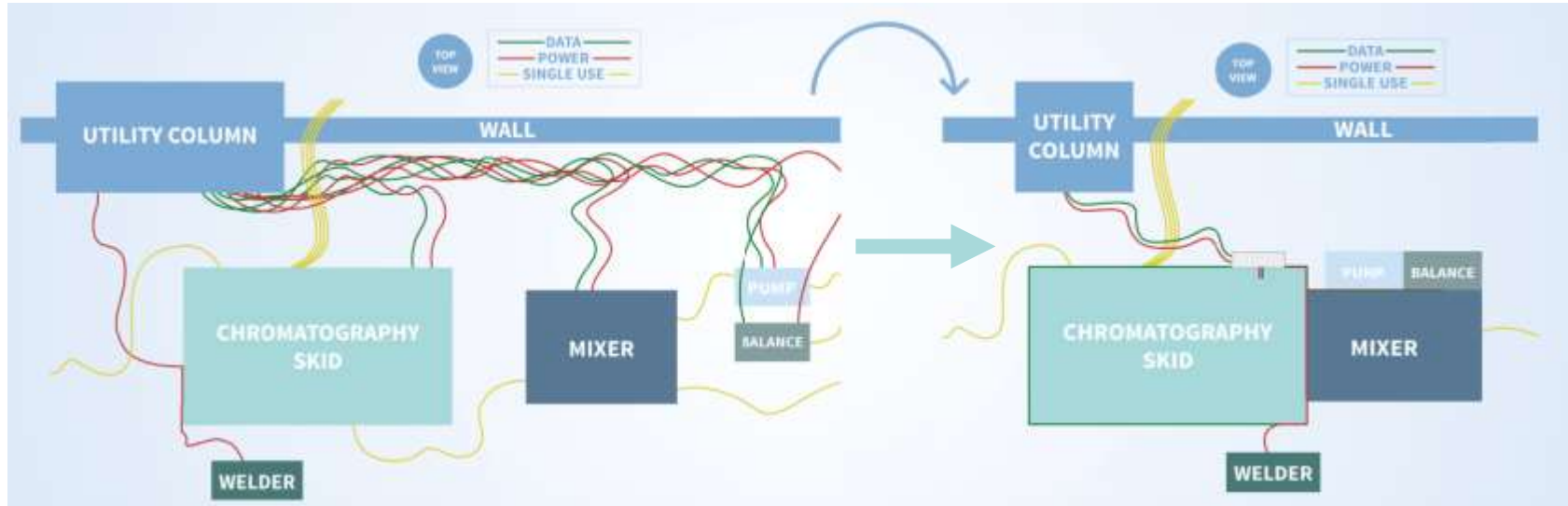


Layout optimisation studies

- Personnel & material flow
- HVAC & pressure zone specification
- Provision of
 - structures,
 - platforms
 - media supply points
 - user interfaces

Case Study 1 - STAGE I – THE BALLROOM CONCEPT

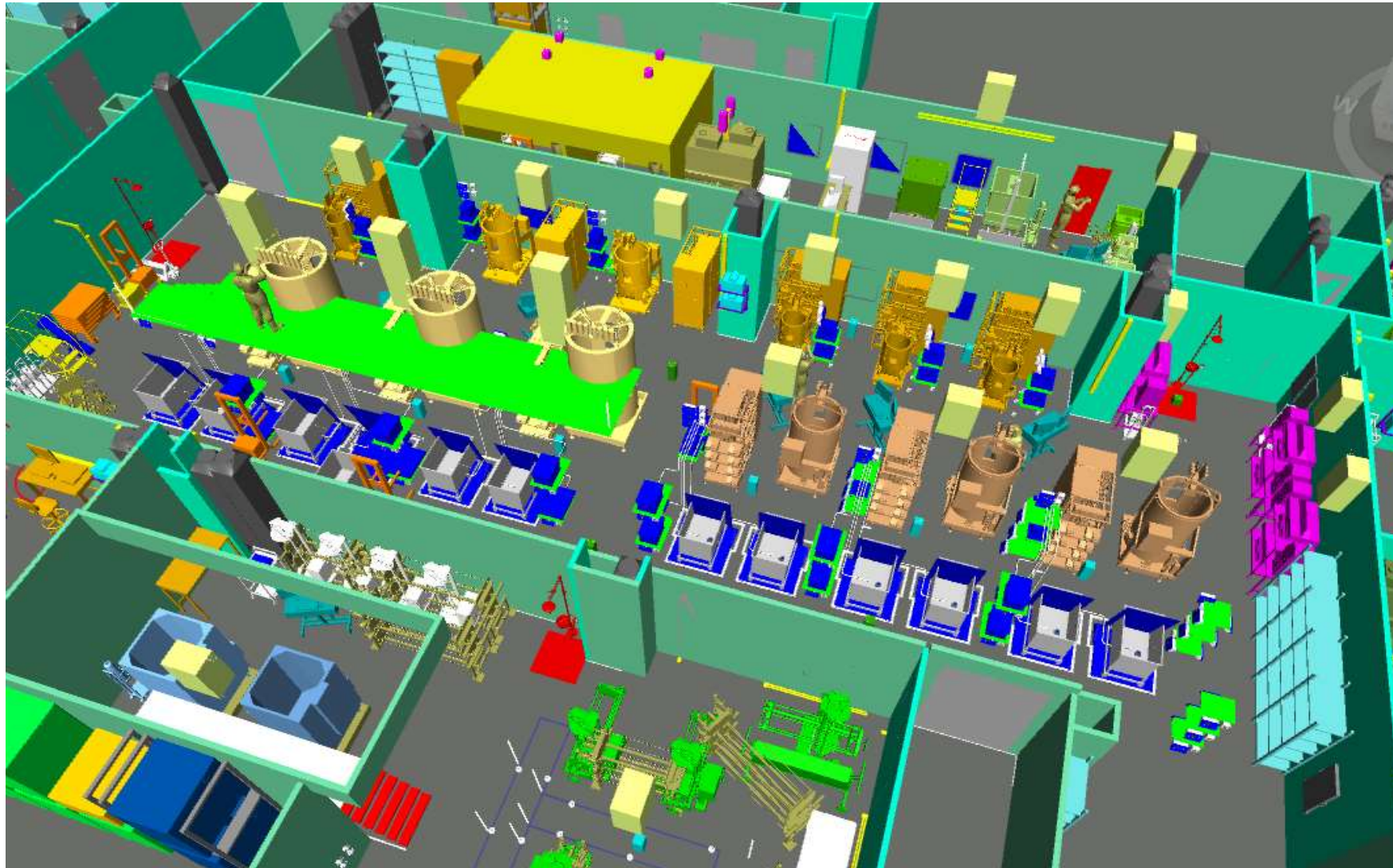
Engineering for Intelligent Clustering of Mobile SU Process Units



Benefits:

- Professional set-up for industrial scale production
- Reduces operator errors
- Increases operability & operator safety
- Increases process safety
- Improves routing & tubing management

Case Study 2 - Stage II – Stainless Steel Support for Intelligent Clustering of SU Process Units

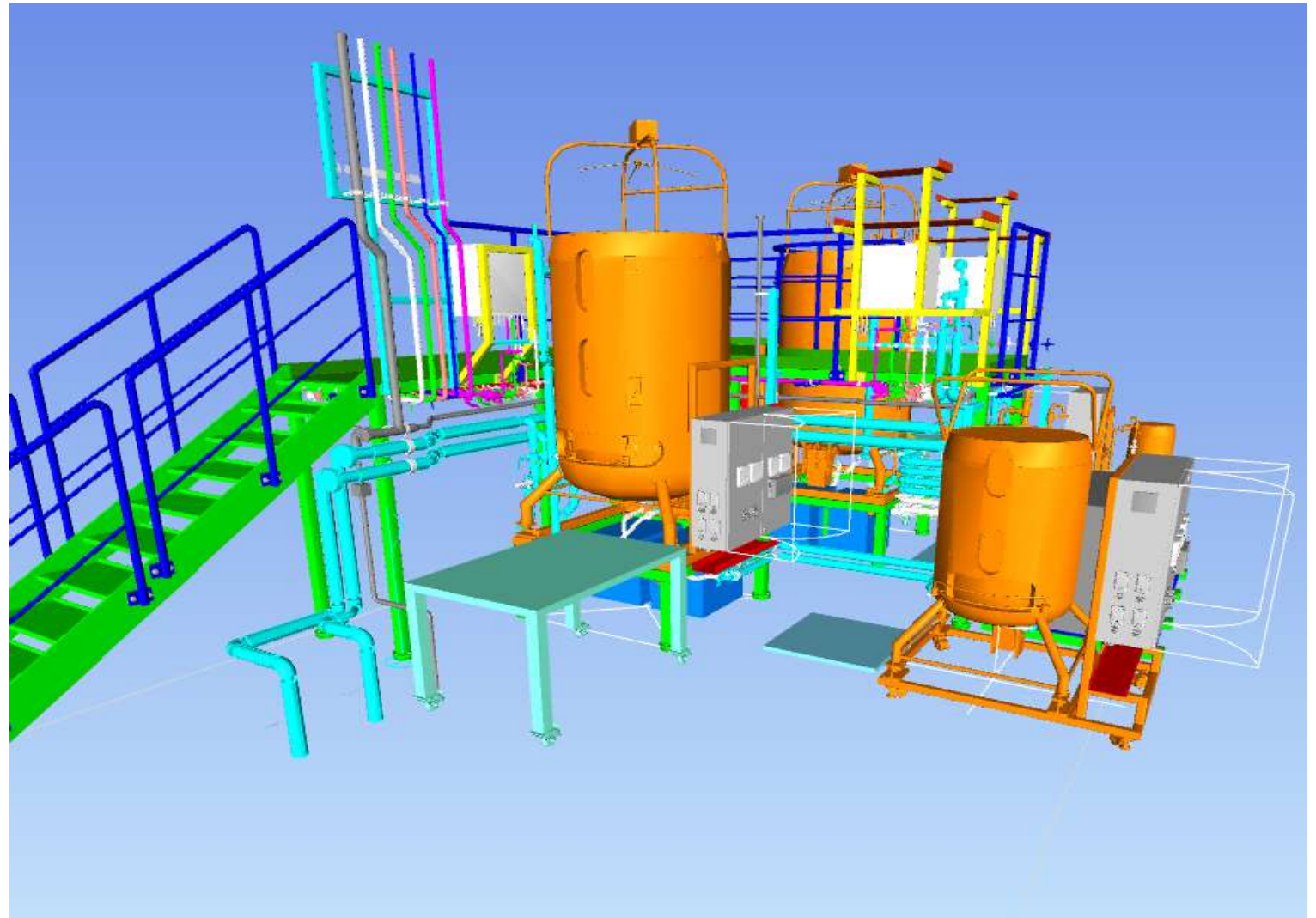


Case Study 3 – Stage II - Hybrid Plant 50, 500 & 2000L SUB

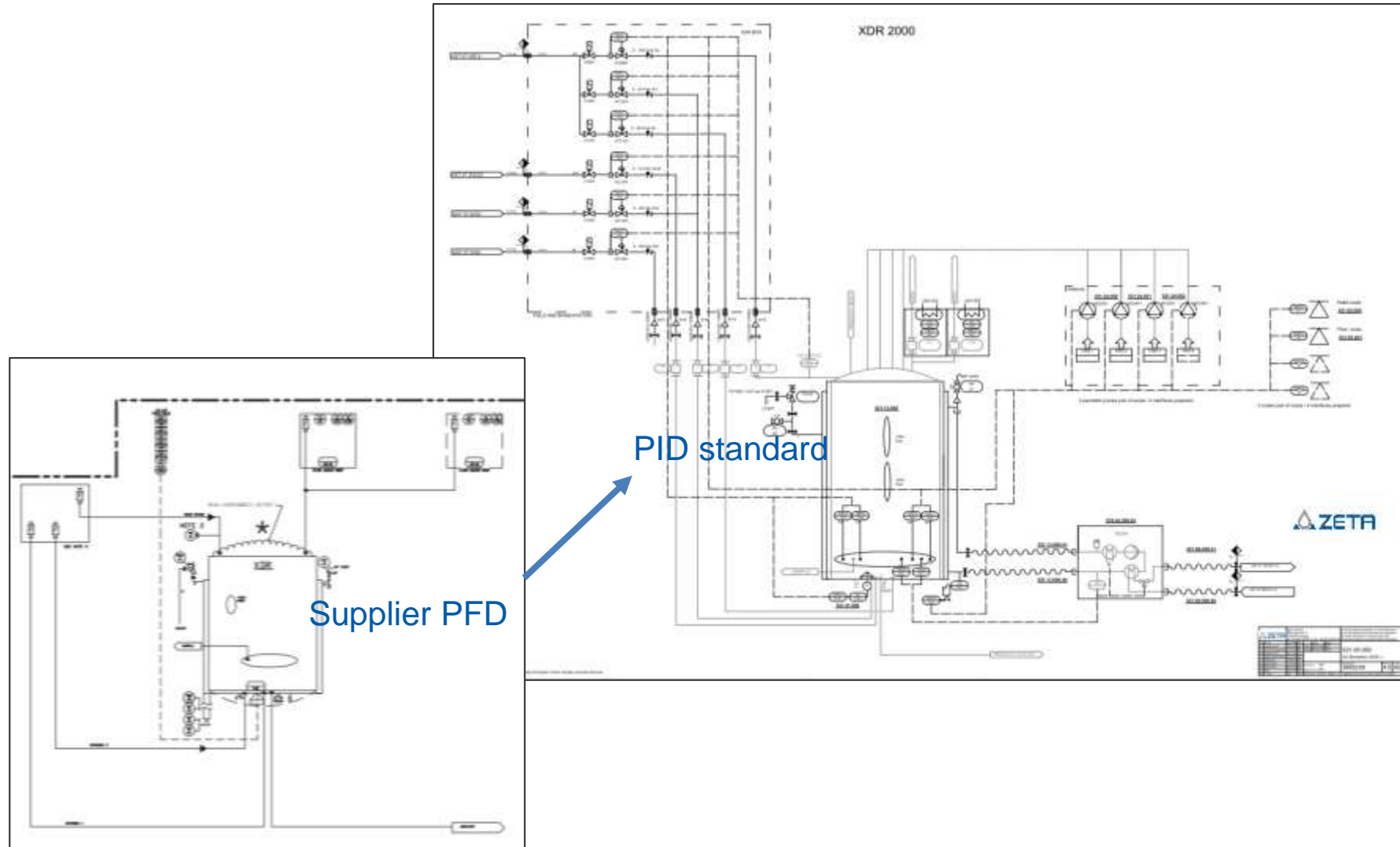
LOCATION:	Switzerland
PROJECT NAME:	Work platform & automation of single-use bioreactors (SUBs)
SYSTEM CATEGORY:	Single-use technology integration
PRODUCT:	Engineering, manufacturing and installation of stainless steel work platform incl. media supply piping in clean rooms & automation/EMSR of SUB
DURATION:	10 months in total, mechanical engineering, automation & SUB
DESCRIPTION:	Integration of single use process equipment into a stainless steel plant

Case Study 3 - Stage II - Hybrid Plant 50, 500 & 2000L SUB

- Basic Design
- Detail Design
- Assembly of all components into a functional system
- Static & Dynamic FAT
- Delivery
- Electrical and mechanical Installation
- Programming
- Commissioning
- Qualification

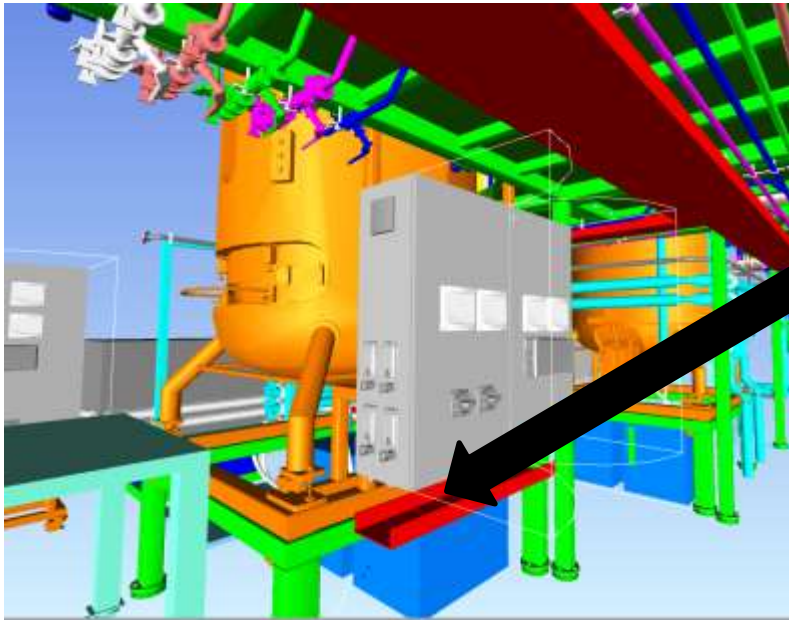


Case Study 3 - Stage II – Engineering Documentation

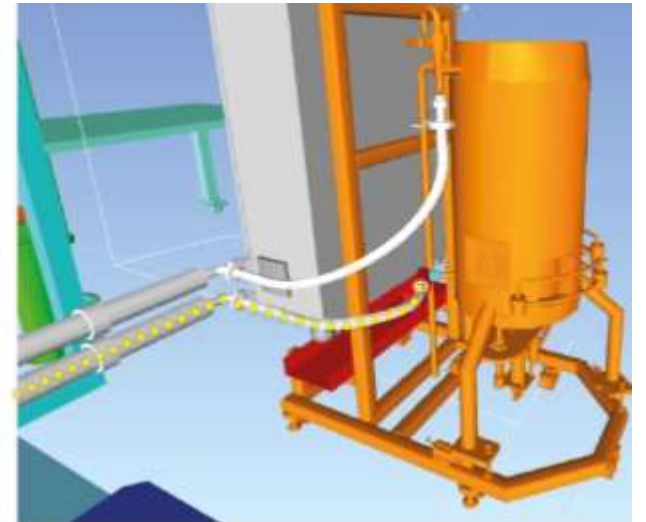
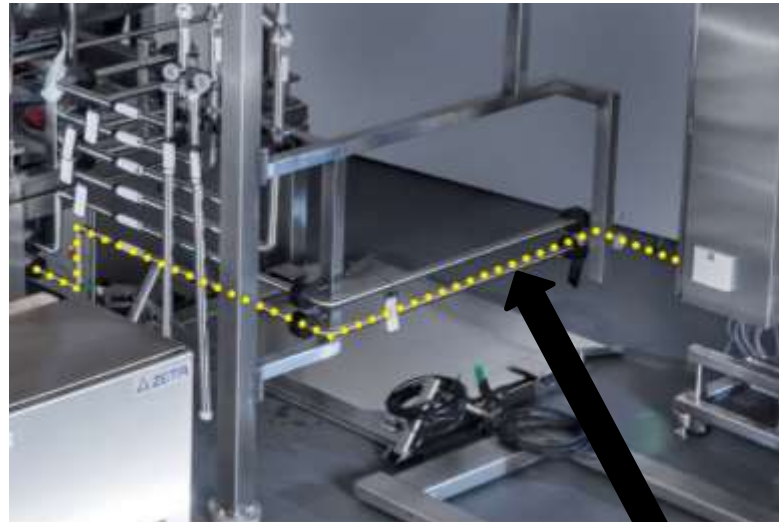


PID creation for the SUB

- Pipes, tubes, signals, balances, probes
- Stainless steel standard
- Scope of supply
- Interfaces



Elevation of bioreactor to improve access for operation and to gain space TCU

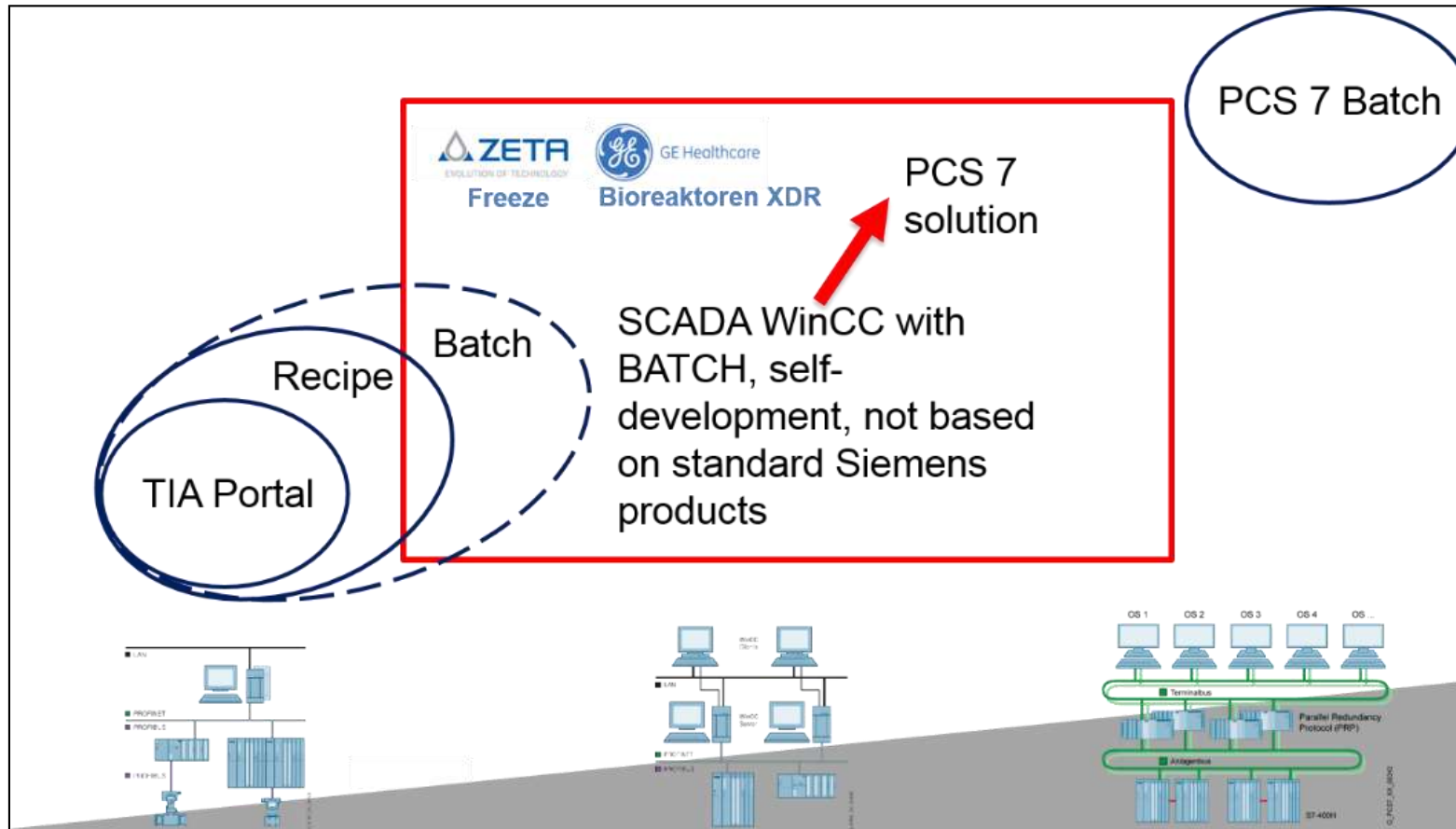


Minimize tubing length using SS piping



Avoid “kinking” and trip hazards with intelligent tube routing and management

Case Study 3 - Stage II - Automation: Modular Software Concept



- Creation of a PCS7 standard XDR software for GE in 2017
 - Use of only Siemens standard functions from the PCS7 internal library
- This standard software and its modular concept is already programmed and qualified according to GAMP 5
- PCS7 is fully compatible to CFR part 11

Case Study 3 - Stage II - Built Facility

Full integration of standalone single-use and auxiliary systems



Ensure functionality through static and dynamic FAT at ZETA workshop



GOOD PRACTICE GUIDE:
**Single-Use
Technology**



Published Nov. 2018

STAGE III – CUSTOMIZED SUPPLIER AGNOSTIC CONCEPT

Stainless Steel “Backbone” to Handle Different SU Equipment

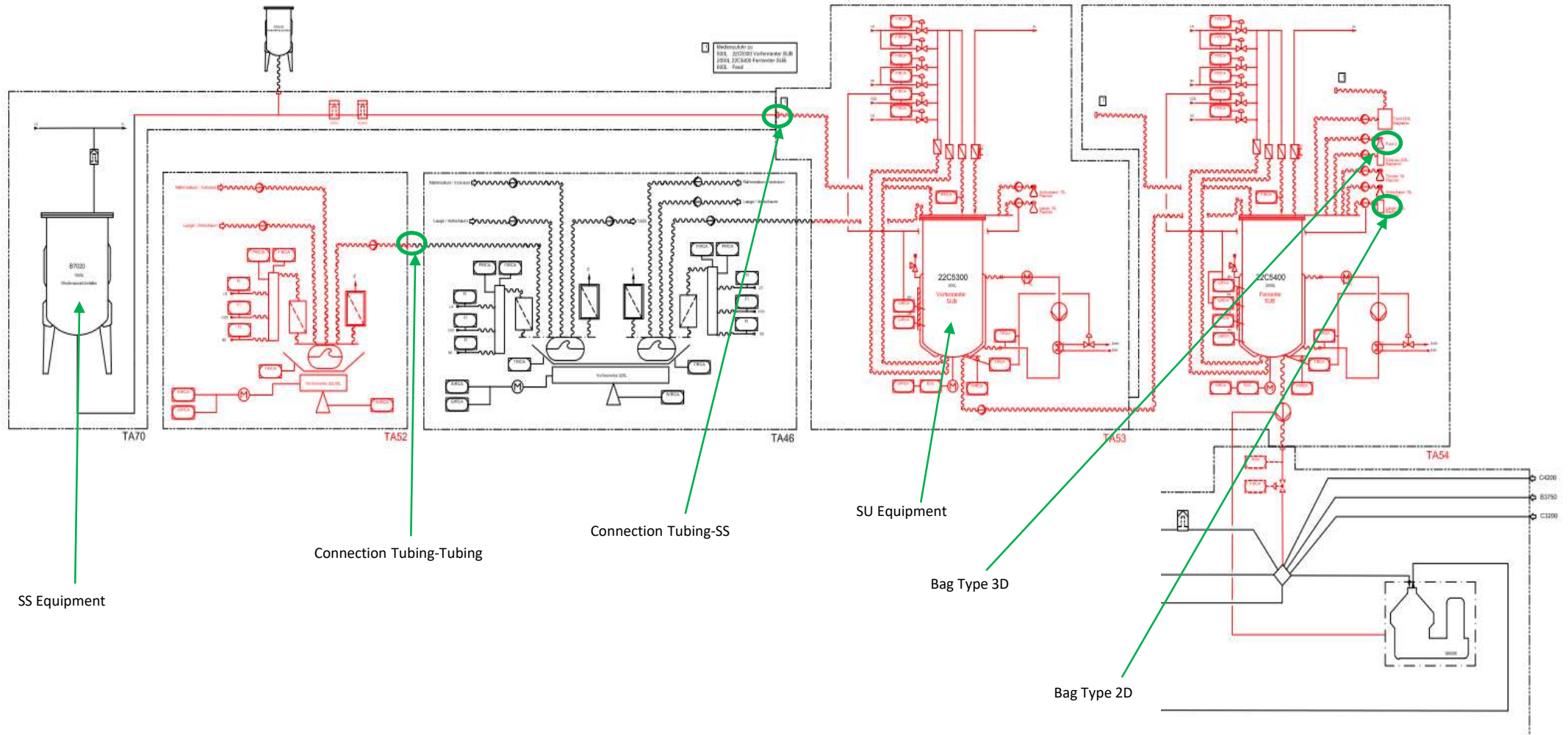


- **SS backbone** can serve equipment from different suppliers
- **SS components** (gassing units, TCU, pump stations) compatible to different SUB sizes
- **SUT/SUB supplier** is interchangeable between campaigns

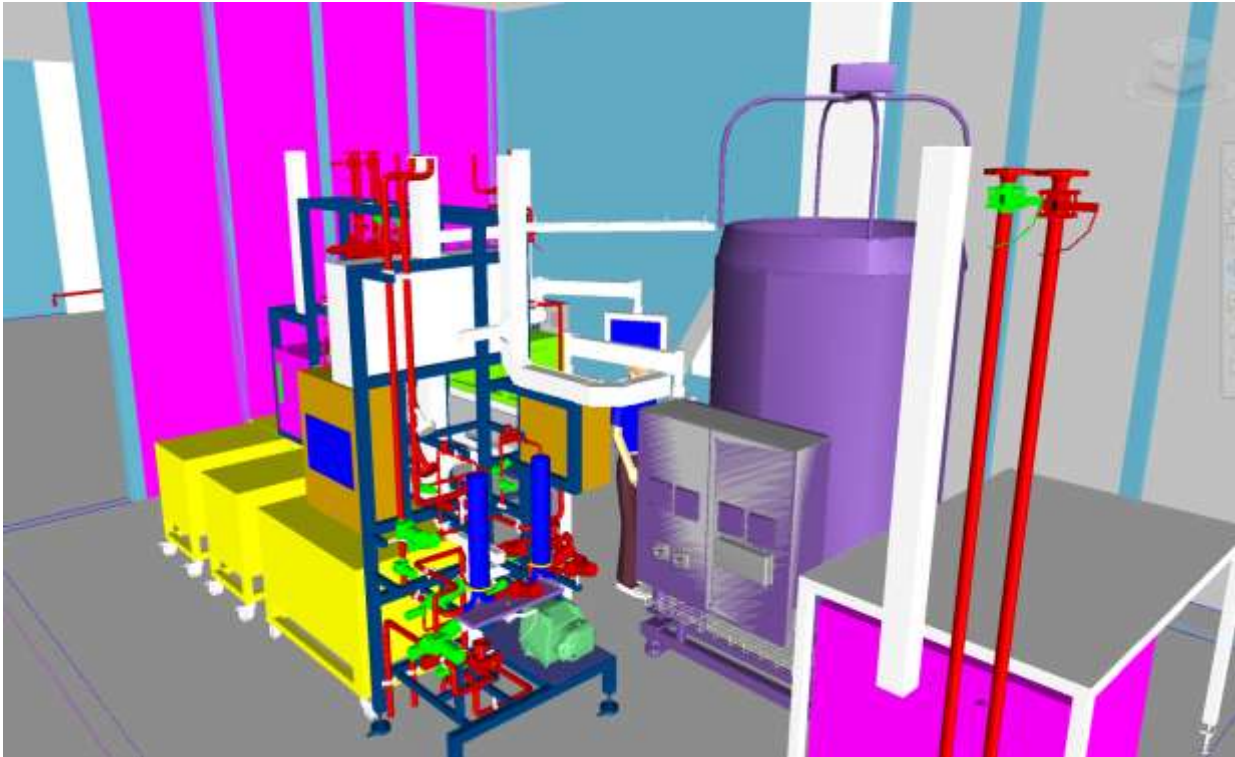
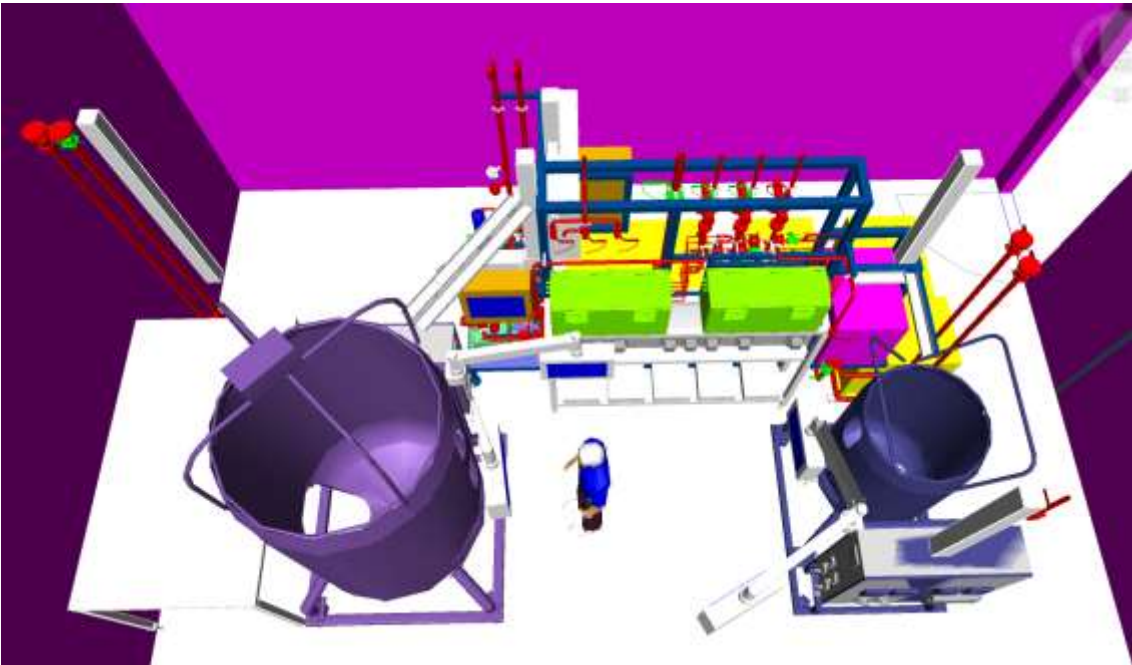
Case Study 4 – Stage III - Hybrid Plant B

LOCATION:	Germany
PROJECT NAME:	Basic design, detailed design, construction and integration of SUB into existing plant
SYSTEM CATEGORY:	Single-use technology integration
PRODUCT:	Engineering, manufacturing and installation of stainless steel filtration unit, inc. piping, media supply & automation/EMSR of SUB
DURATION:	6 months
DESCRIPTION	Integration of single use process equipment into a stainless steel plant

Case Study 4 – Stage III - PFD Development



Case Study 4 – Stage III – 3-D Model

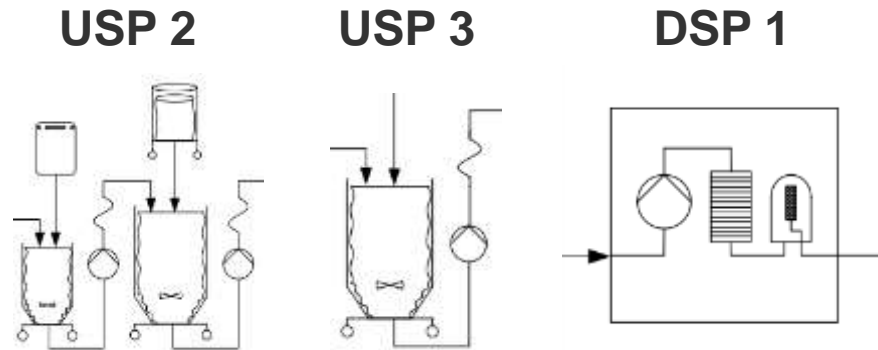


STAGE III – CUSTOMIZED SUPPLIER AGNOSTIC CONCEPT

Automation: Modular Software Concept

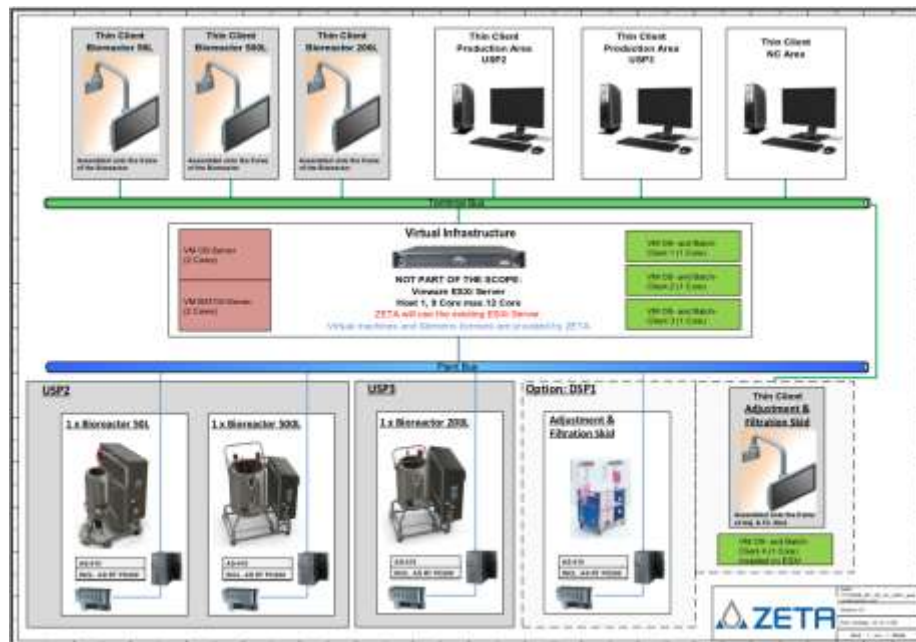


Excerpt from PFD



- Process will be structured into unit operations acc. to PFD/P&ID
- Units are the main element in the S88 physical model for batch automation
- SU equipment must also be units in the automation architecture for hybrid systems
- S88 compliant DCS with batch is able to handle automated and manual operating modes:
 - Automated for stainless steel
 - Mainly manual/semi automated for single use units
 - Manual phases will guide the operator and will track human interventions
 - Recipe operation will either call an equipment phase or a manual phase

Excerpt from Automation Architecture

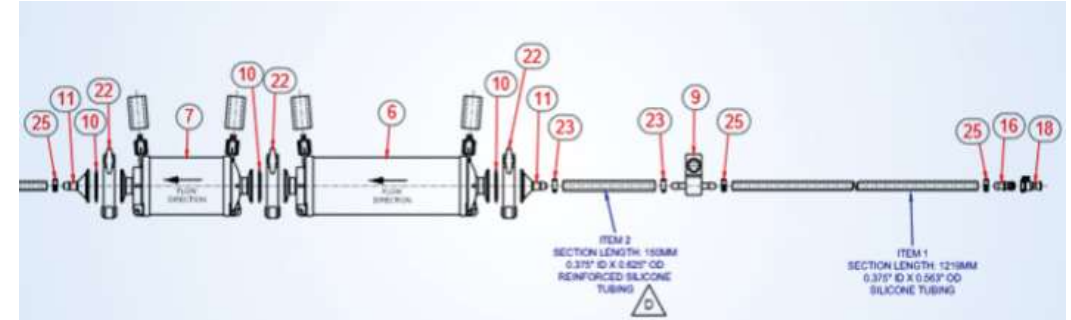


STAGE IV – CUSTOMIZED SU PROCESS UNITS

SU Components & SS Standards & Integrated Automation



- Application of SS system standards and methods for SUS solutions
- Customized design for single use units
- Supplier agnostic design (hard & software)
- Free choice of components
- Reduced dependency on SU suppliers



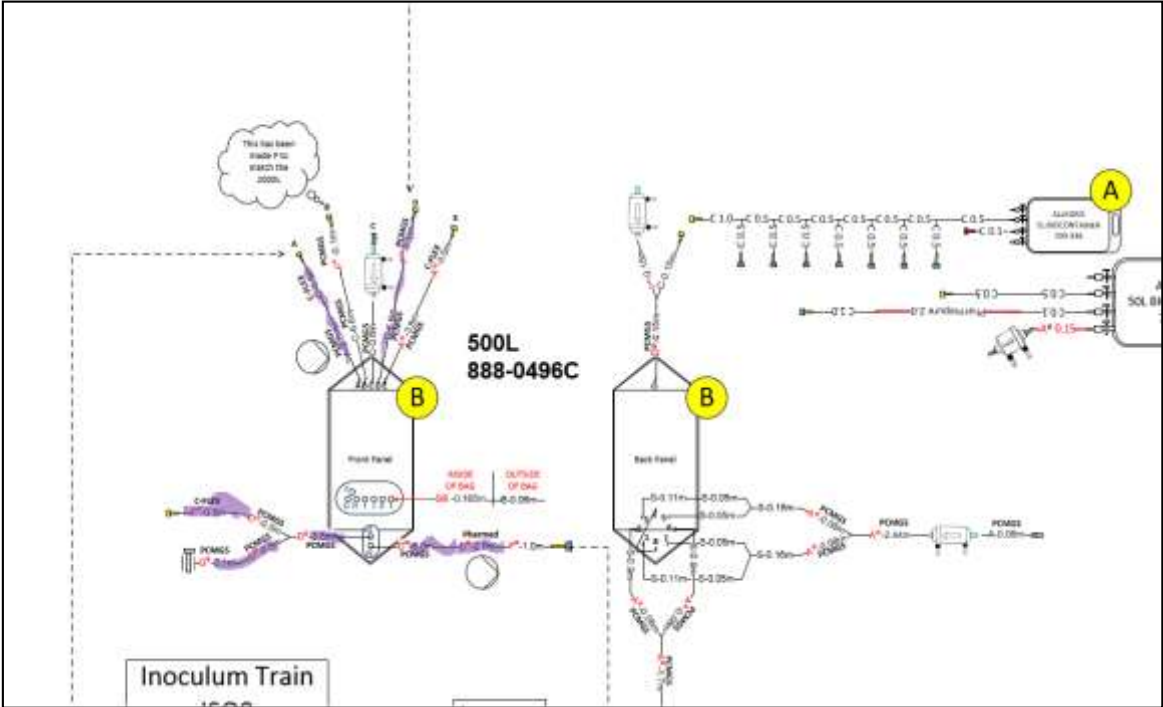
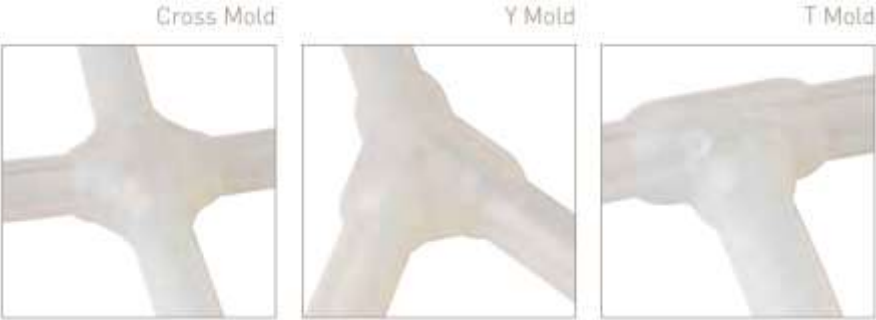
STAGE IV – CUSTOMIZED SU PROCESS UNITS

SU Components & SS Standards & Integrated Automation



Bag & manifold details

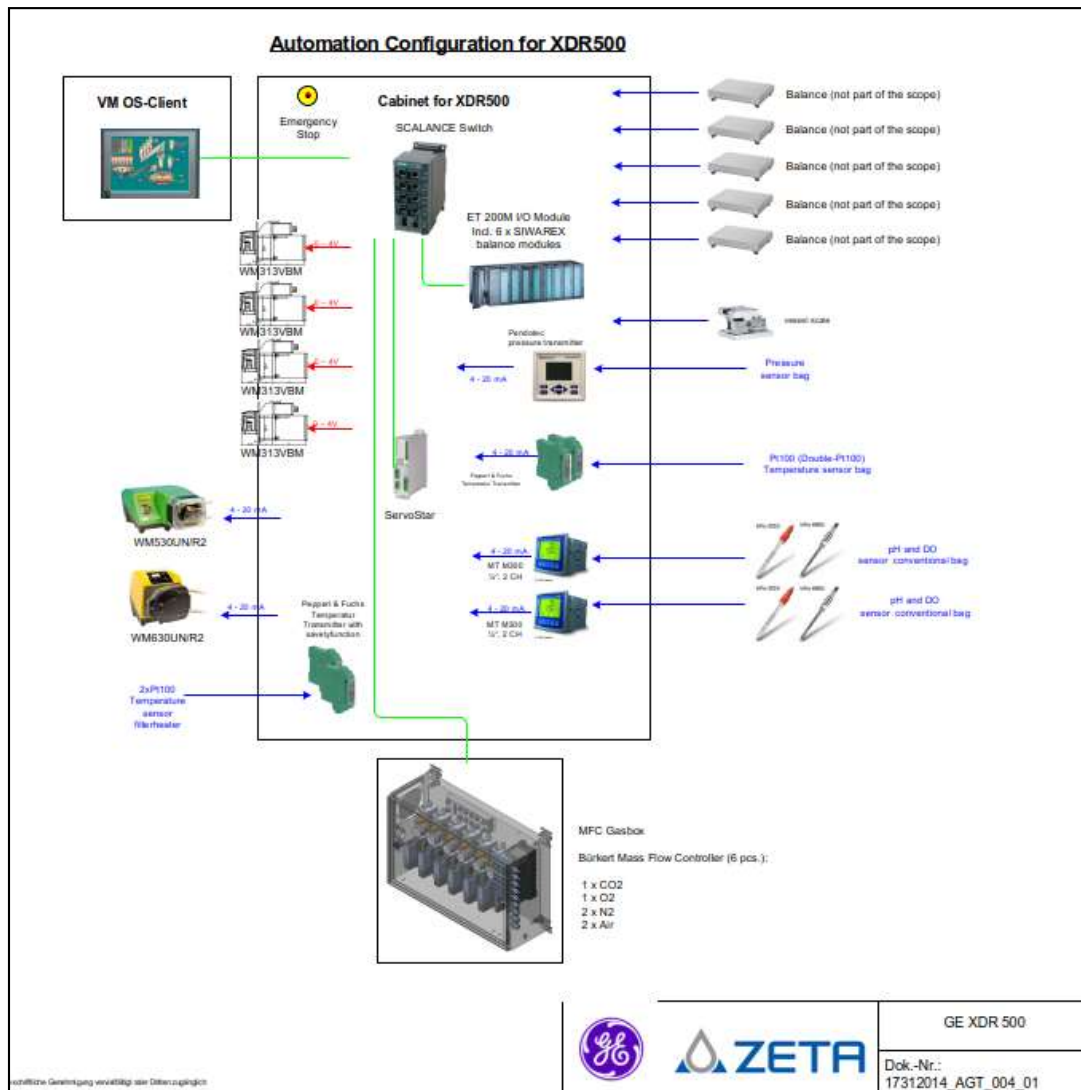
- Type of connection
- Drawing & SU specification



STAGE IV – CUSTOMIZED SU PROCESS UNITS



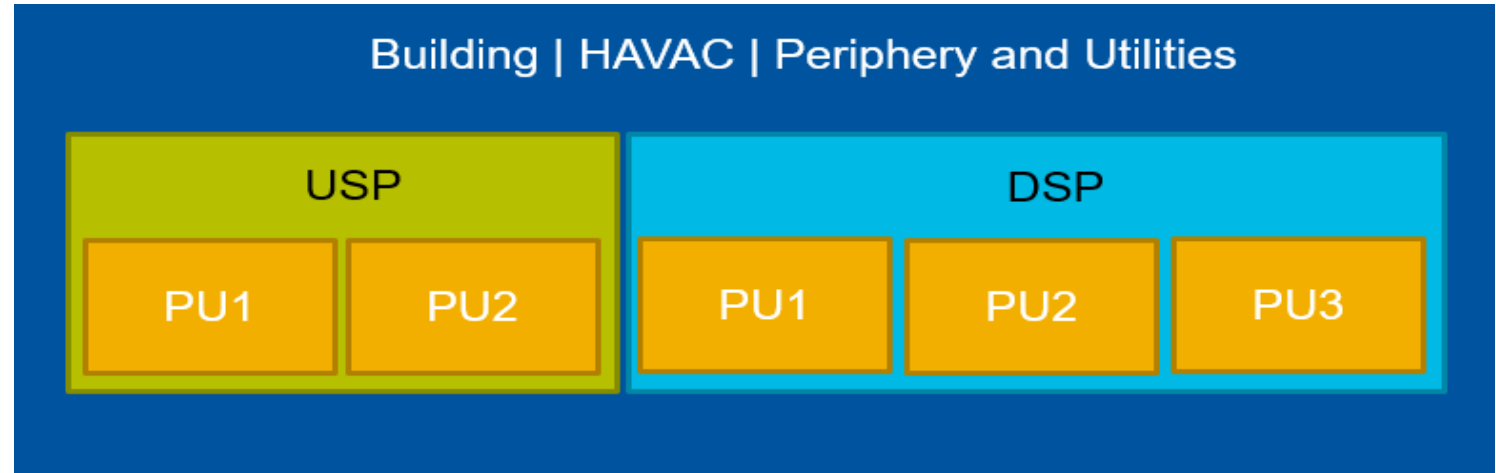
Automation – Customized Software Structure



Customized Software Engineering

- Software engineering according to customer library
- Integration into existing batch environment
- Testing software FAT & dynamic FAT
- Commissioning
- Project management

- **Process improvement**
Equipment selection “doing more with less”
(independent of “material”)
- **Holistic planning approach**
(Process / building / HAVAC / utilities & periphery)
- **Evaluation of SU vs SS technology**
Allows for mix-and-match strategy
- **Qualitative**
Facility layout, ergonomics, flexibility, turn down ratios, vendor support, material quality and variations
- **Quantitative**
Unit sizes, transfer rates, heat transfer, mixing time, yield, production schedule



- Stainless steel facilities are not becoming extinct, but are reducing in numbers:
 - “Classic, large scale, fixed, stainless steel equipment-based facilities will continue to dominate biopharmaceutical manufacturing, particularly at commercial scales and in terms of manufacturing volume.”
- Single-use will continue to grow, particularly at pre- and sub-commercial manufacturing scales.
- Process design and engineering are still heavily relied upon.
- A lot of stainless steel is required in single-use plants.
- One person’s SU facility is another person’s hybrid facility.

THANK YOU FOR YOUR ATTENTION!

