奥星

Hybrid Systems linking Stainless Steel with Single Use for Antibody Process
Hybrid系统在生物单抗工艺的应用

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本课程目的
The content of this course

1.什么是Hybrid系统？

What’s Hybrid System?

2.生物单抗设计周期中Hybrid系统的应用

The application of Hybrid system for Bio-antibody design.

3.培养基添加、原液分装的风险控制

Risk control of media transport and bulk filling？

4.Hybrid系统如何实现自动化控制

Automation control design for Hybrid system

5.生物流体工艺系统新技术简介

New technologies introduction of Bio. Liquid Process Systems

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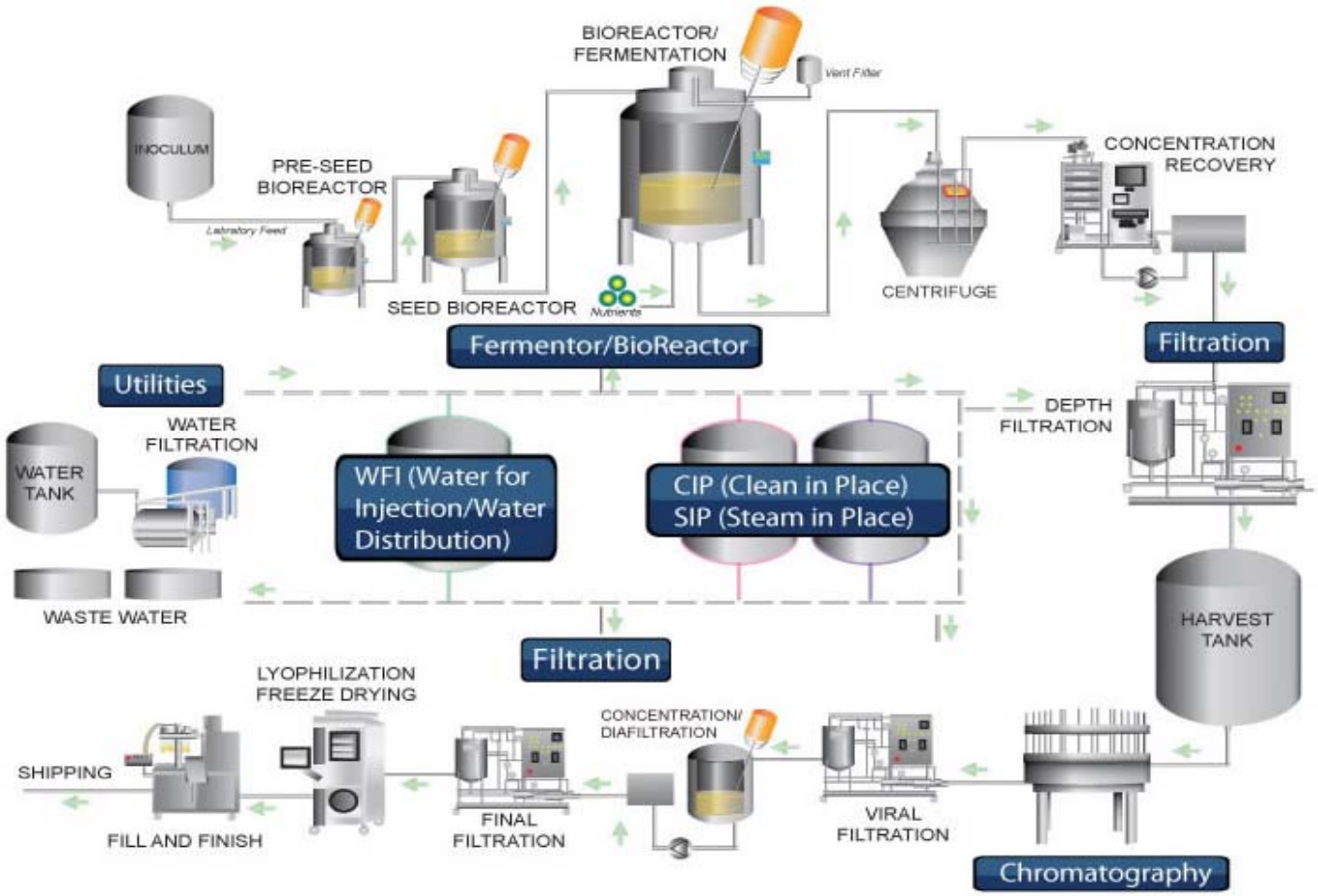
2 Hybrid系统的定义与设计

3 Hybrid系统应用案例分享

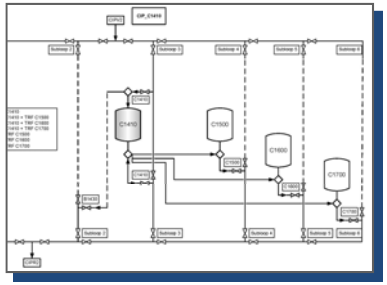
4 Hybrid系统的自动化控制

5 生物流体工艺设计新思路

工艺流程图Process Flow Diagram
抗体类药物 Recombination Products

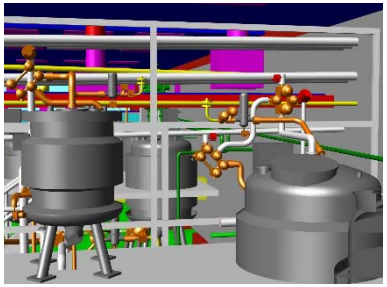


生物制药项目执行关键成功因素
Key Success Factors for Biopharmaceutical Project Execution



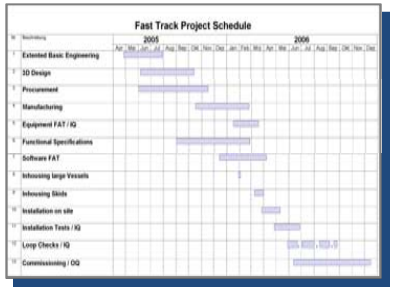
Good Process Design

- By user with support of engineering contractor / consultant
- Process identification and structuring
- Single product or multi product facility
- Design for flexibility and future modifications



Good Equipment Design

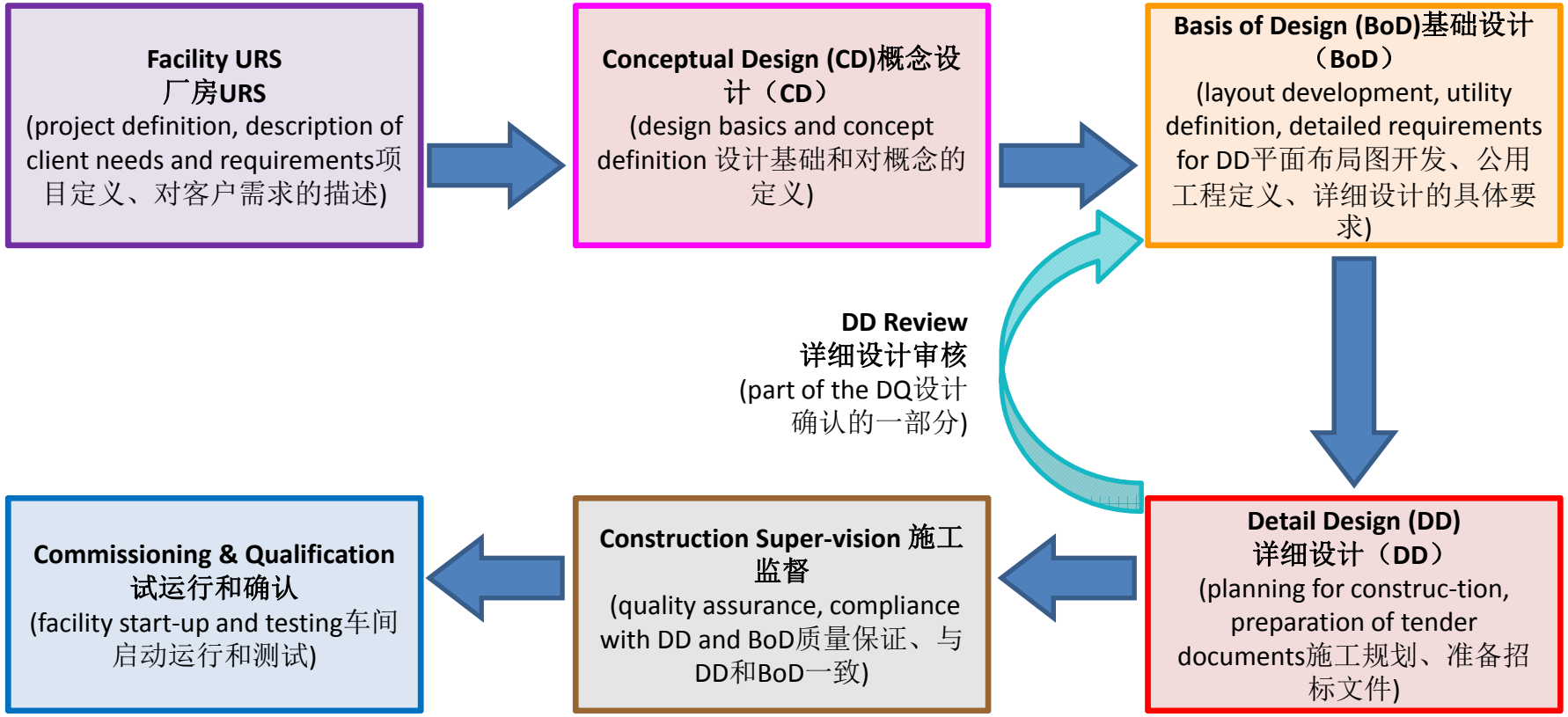
- By equipment supplier with directions from user
- Utilization of state-of-the -technology
- Equipment should fit for purpose, don’t over-engineer
- Design for suitability and future modifications



Good Project Design

- By user with support of engineering contractor / consultant
- Manage complexity in projects
- Provide all required documents for GMP operation
- Design to match cost and budget

项目步骤—设计和实践规划
Project Steps – Design & Realization



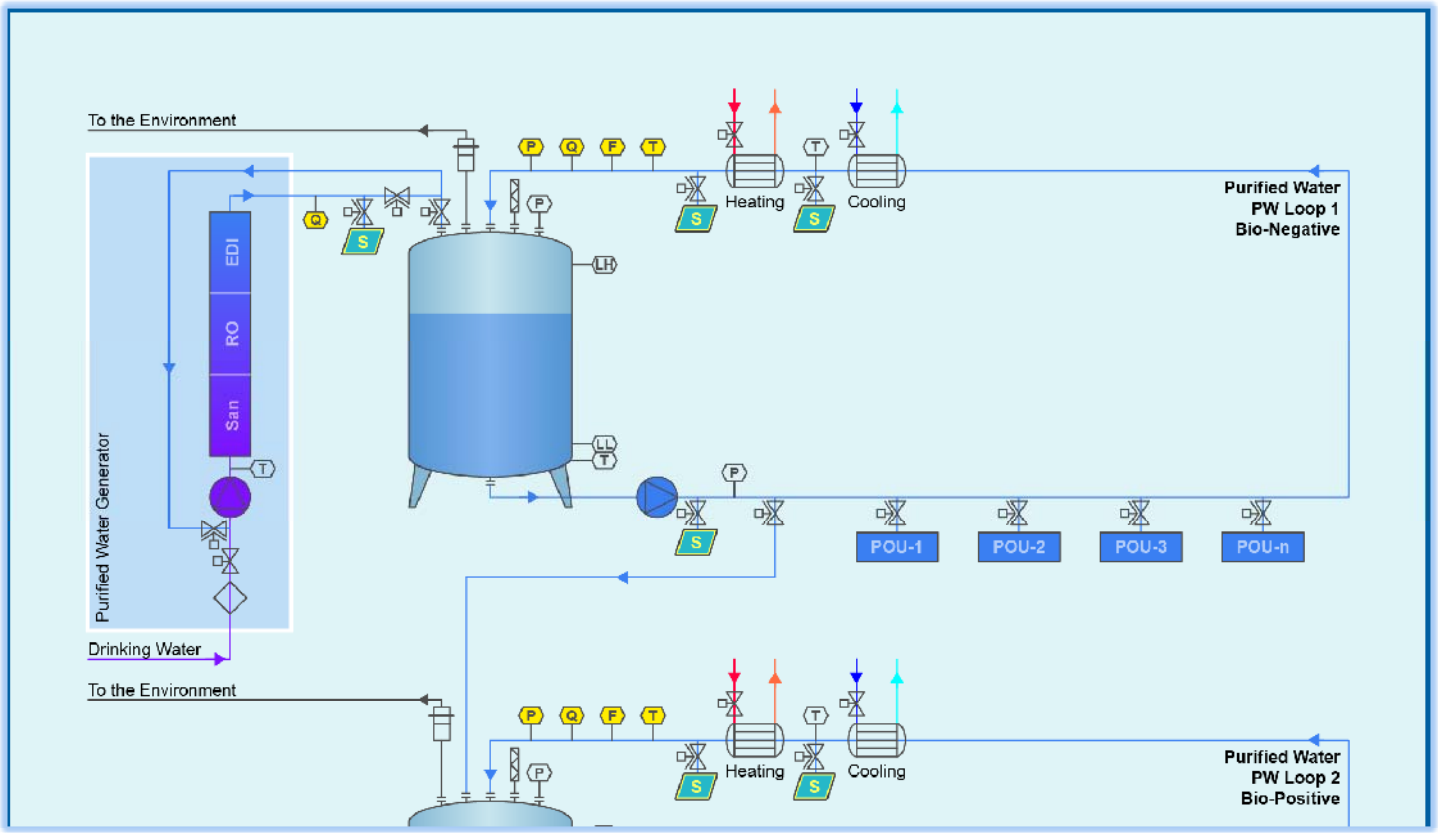
控制关键点
Control Critical Parameter

	Media Prep.	Media Hold	Buffer Prep.	Buffer Hold	Bio Reaactor	Seperator	Depth Filter	Harvest	Ultra Filter	Chromatography	Hold Versel	PW LOOP	WFI LOOP	CIP Station	Clean Steam System
Temperature	C	C	C	C	C	C		C	N		C	C	C		C
Pressure	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Level	C/N	C	C/N	C	C			C	C		C	C	C	C	
Weight	C/N	N	C/N	N	C			N	N		N				
Flow	N		N			C	C	N	C	C		C	C	C	
pH	C		C		C				C	C	C				
Conductivity									C	C	C	C	C	C	
Dissolved oxygen					C										
Stir	C	C	C	C	C			C			C				
UV										C					
Turbidity						C									

C=A Critical Variable N=A design consideration ,but not necessary = Usually not a design consideration

BoD阶段的信息输出（举例）
Output from BoD Phase (Example)

- PW system 纯化水系统



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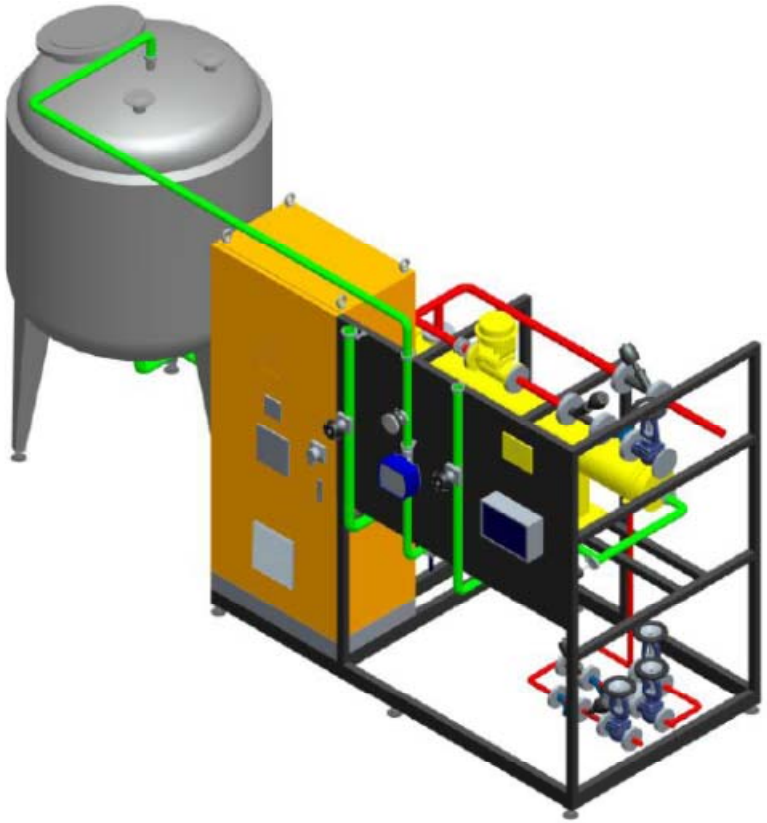
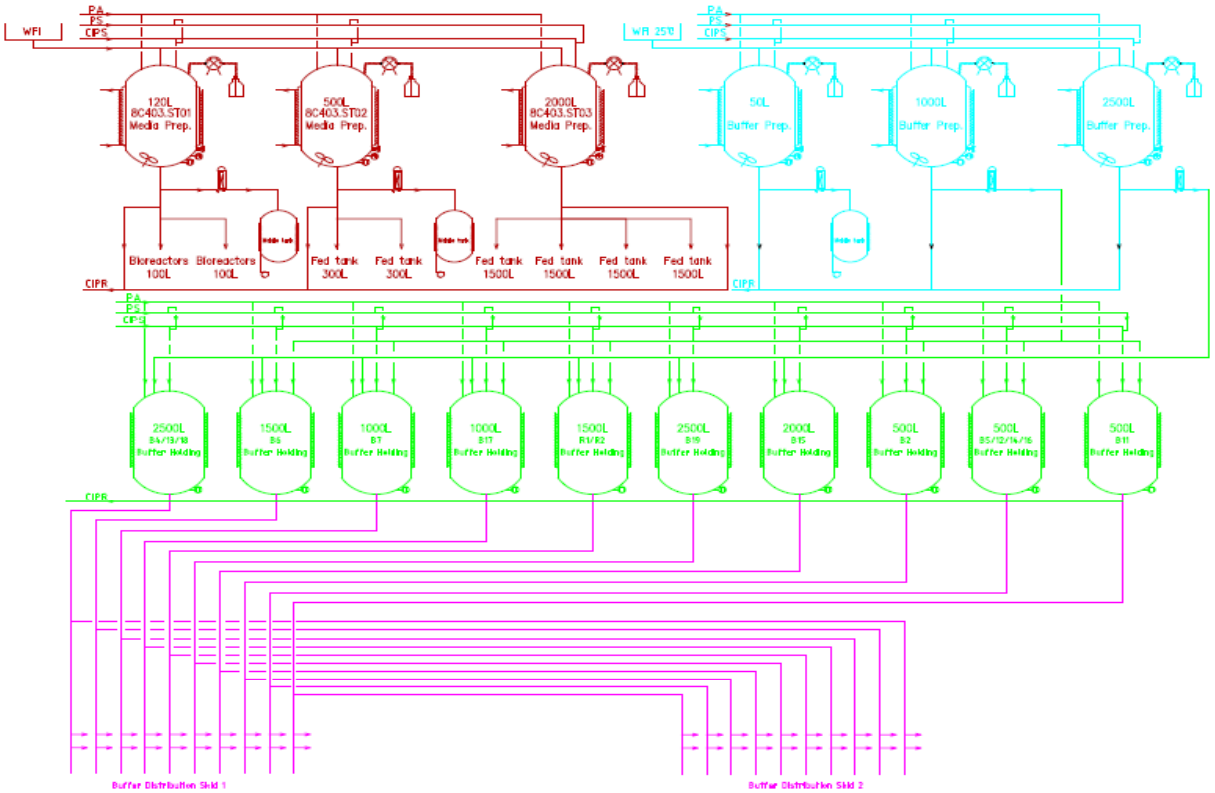


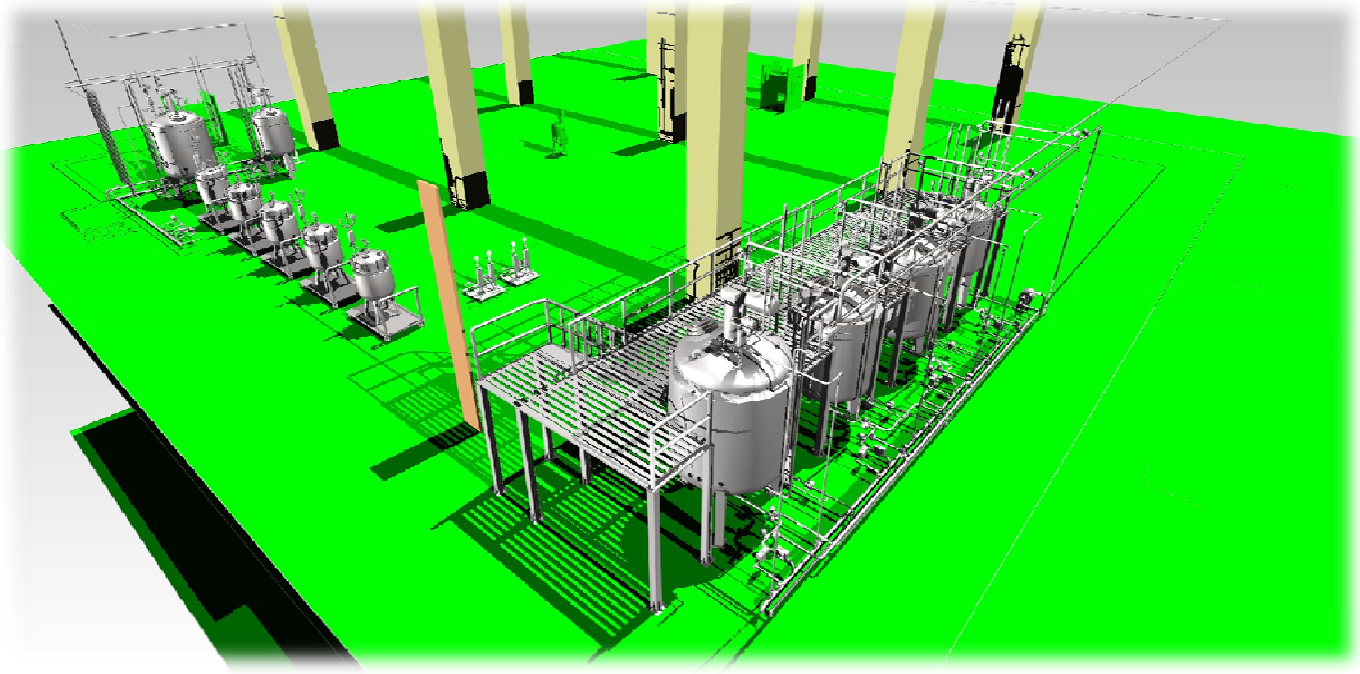
BoD阶段的信息输出（举例）
Output from BoD Phase (Example)

- Media/Buffer System 培养基与缓冲液系统



DD阶段的信息输出（举例）
Output from DD Phase (Example)

- Media/Buffer System 培养基与缓冲液系统



DD阶段的信息输出（举例）
Output from DD Phase (Example)

- Media Preparation & Transport System 培养基配制&转运系统

试运行和确认
Commissioning & Qualification

- **Commissioning 试运行**
- Documented activities for start-up and testing of NON-GMP and GMP systems.
  对非GMP系统和GMP系统的启动和测试工作都用文件记录下来。
- Within commissioning it will be verified, that all user requirements are met and that the system has been built, installed, and is functioning correctly.
  试运行时要确认是否满足所有用户需求，系统的构建、安装和性能是否正确。

→ All systems need commissioning 所有系统都要进行试运行。

- **Qualification 确认**
- Action of proving and documenting that any premises, systems and equipment are properly installed, work correctly and lead to the expected results. 采取行动证明并记录所有处所、系统和设备都安装正确、工作正常并满足所期待的结果。

→ GMP systems need qualification 所有GMP系统都需要进行确认。

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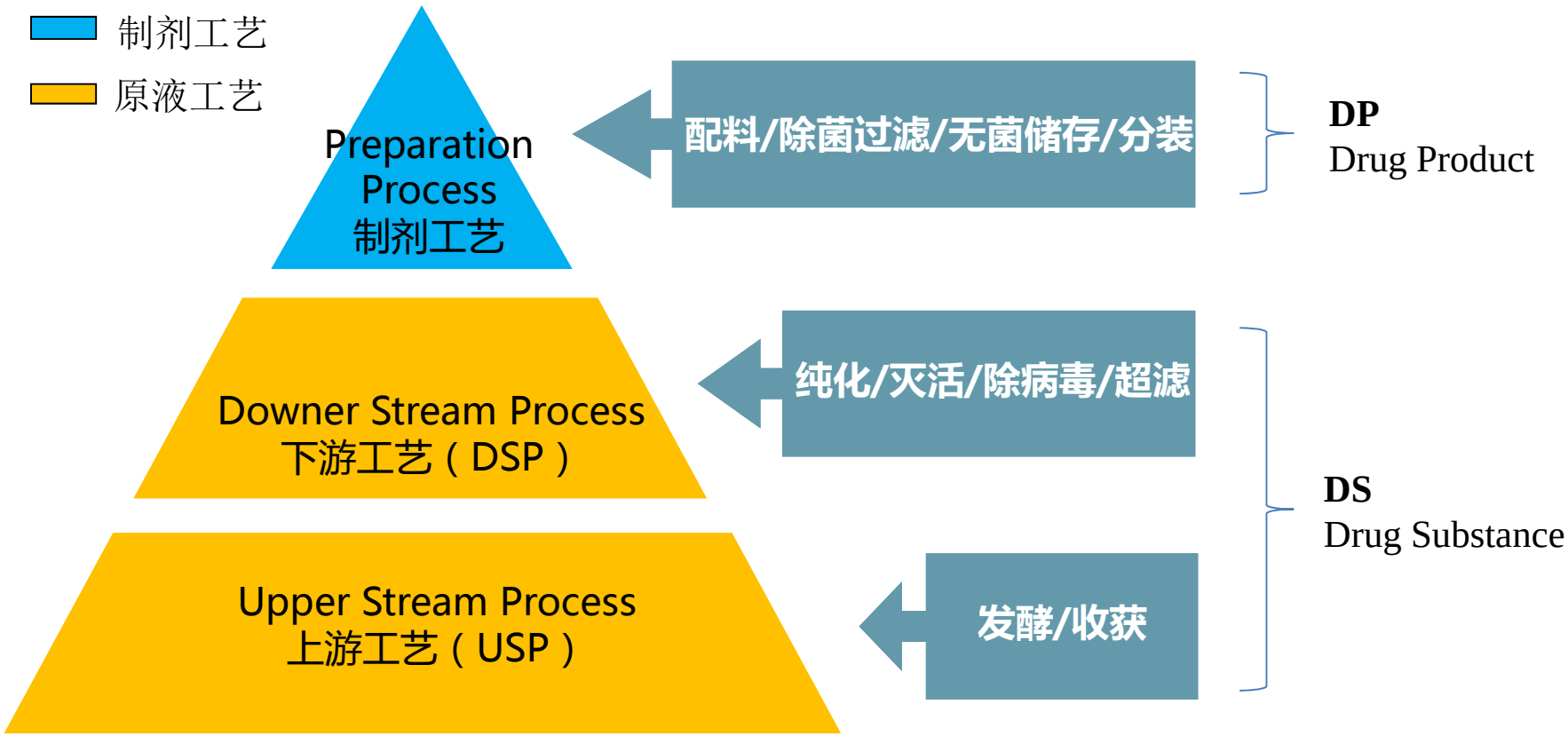
生物工艺单元
Bio Pharm. Process Units



Hybrid系统：不锈钢与一次性系统的兼容
Hybrid Systems linking Stainless Steel with Single Use

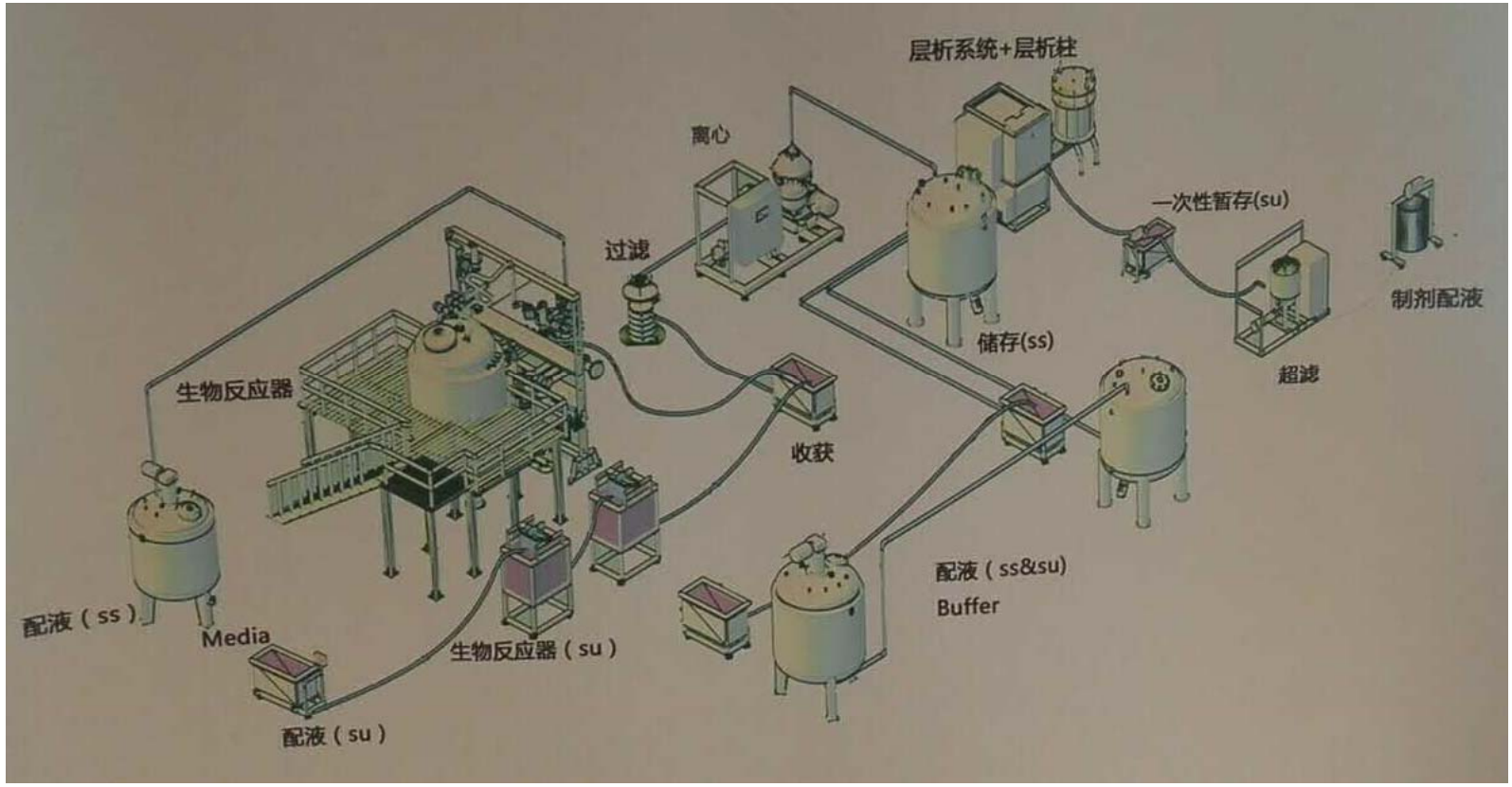
- Nowadays both technologies, Stainless Steel and Single Use are available
- Be aware of the limitations of each technology
- Consider requirements for flexibility
- Utilize stainless steel or single use where suitable or more cost effective

➢ **No religious wars what's better, combine both technologies in the best way !**

➢ **Stainless steel and single use are complementary technologies !**

➢ **Automation is the glue that links both together !**

Hybrid系统：不锈钢与一次性系统的兼容
Hybrid Systems linking Stainless Steel with Single Use



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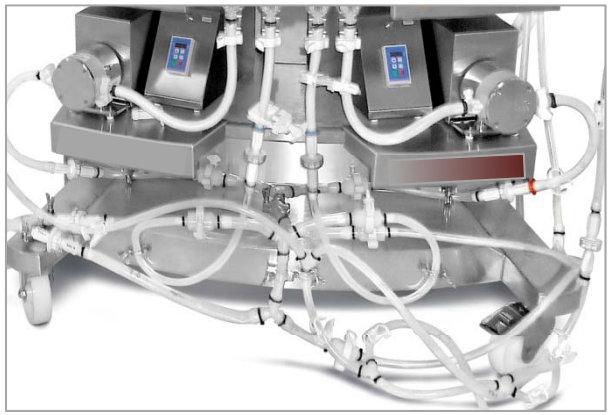
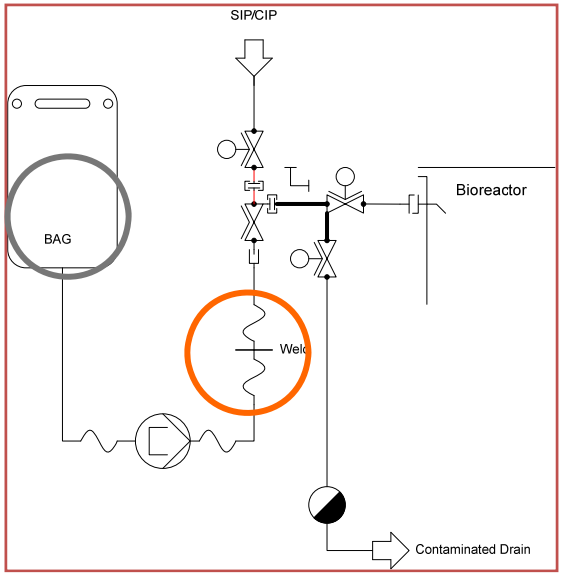
一次性系统设备设计
Equipment Design for Single Use Equipment

The good, ... the bad .....and the ugly !



- Clear arrangement of single-use flow paths
- Automated pinch valve
  - for reproducable operation
  - as anchor points for tubing sets
- Easy set up reduces operator errors
- Hoses at the floor should be avoided

混合型系统方法：灭菌阀门和管道焊接
The Hybrid Approach, Autoclaved Valve and Tube Welding



- Common method for sterile connection of addition bags to Bioreactors
- Re-usable valve with sealed thermoplastic tubing (TPE) sterilized in autoclave
- SIP of addition port after hook up of autoclaved valve
- Connect tubes from sterile bag assembly and autoclaved valve by sterile tube welding
- Max. tube size 3/4 inch ID (tube welder)

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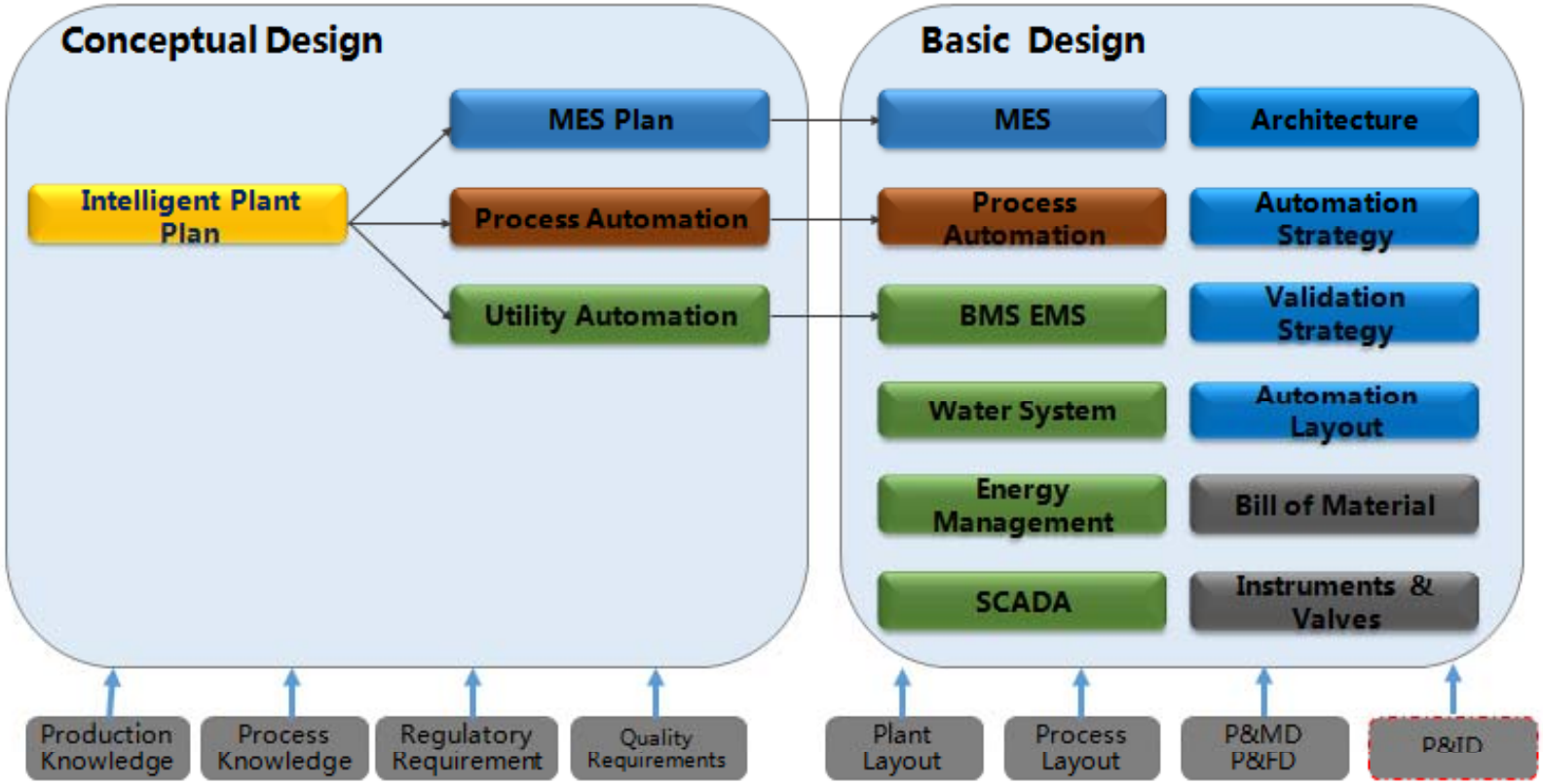
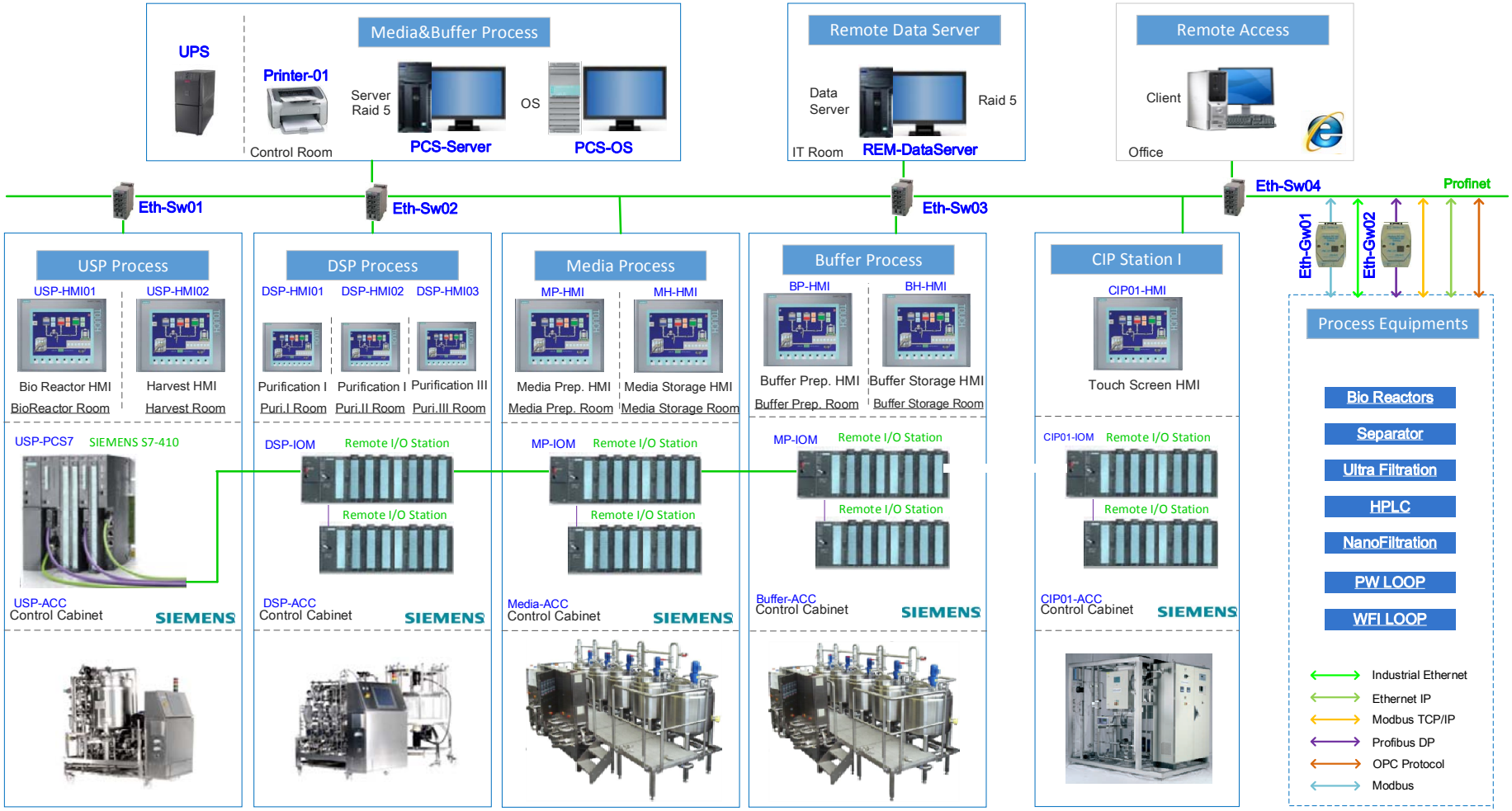
自动化与信息化的设计流程
The Design Procedure of Automation and Information

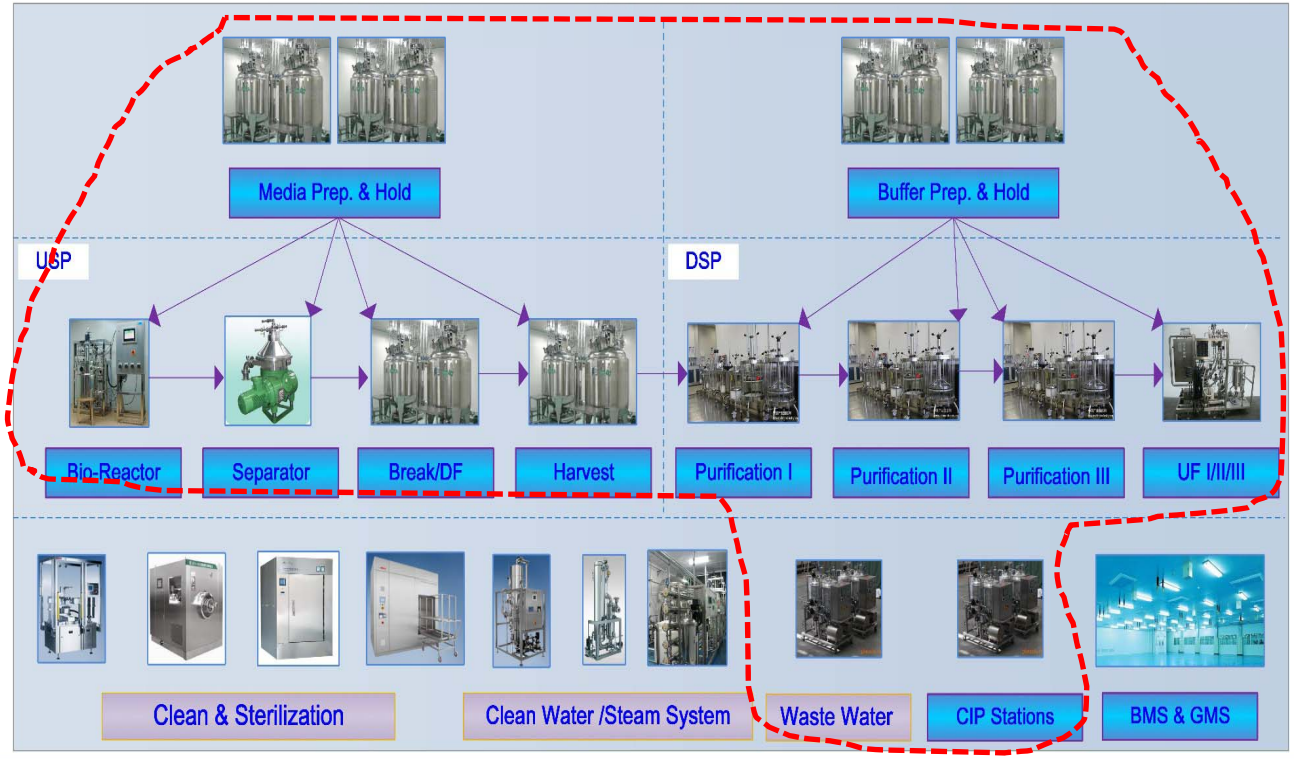


Process Control System Network Architecture



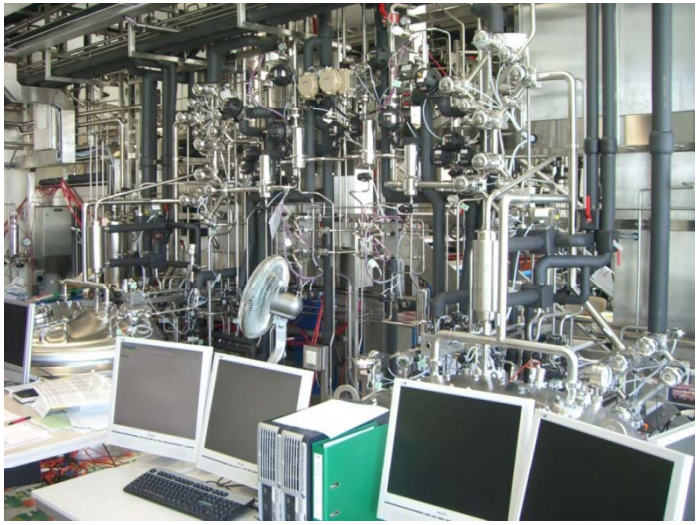
工艺控制系统功能
Bio Process Control Functions

- CIP/SIP: Units and Pipes 单元设备及管线的在线清洗及在线
- Transfer： Unit to Unit 单元设备转料
- Preparation： Media and Buffer and Reactor 培养基、缓冲液配制以及反应单元配制反应
- Storage： Media and Buffer and USP DSP 培养基、缓冲液、上游、下游物料存储
- Interface： Process Equipment 与关键工艺设备及其他系统的接口功能



一次性和不锈钢系统自控对比

Automation Structures Stainless Steel vs. Single Use



- High I/O count
- Complex SIP and CIP operations
- Complex transfer systems
- Target for high degree of automation
- Mature system architectures
- PLC / DCS / Batch / MES
- Full 21 CFR Part 11 compliant

- Low I/O count
- No need for SIP/CIP at Single-Use Systems
- Transfers by moveable bag containers
- Step backwards to more manual operations
- Still evaluating phase
- Local controls at process skids (start/stop)
- Lack of 21 CFR Part 11 compliance

➢ **How to combine those two worlds in Hybrid Systems ?**

专业的调试团队

生物制品工程
Bio-pharm. Engineering

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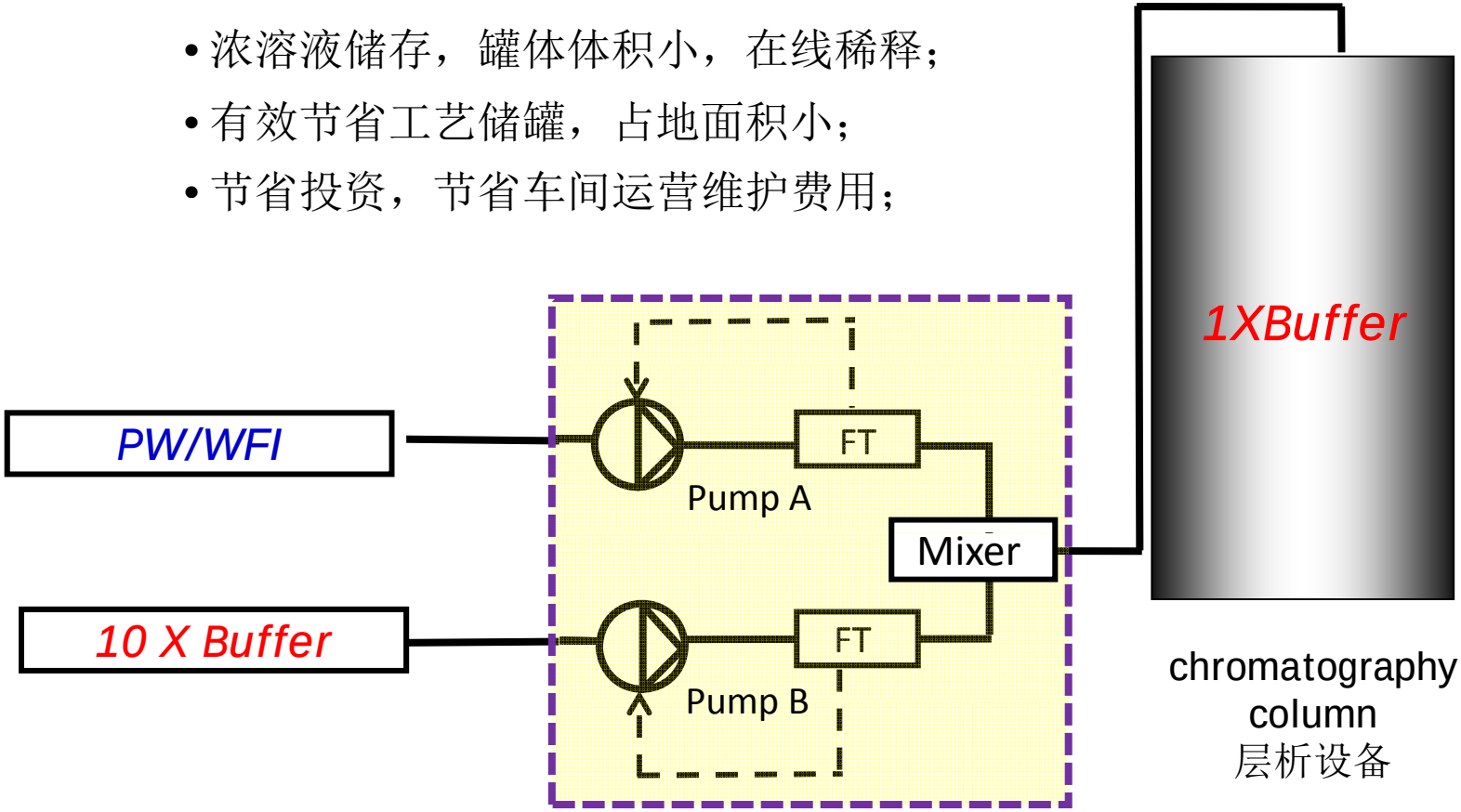
在线稀释法--缓冲液配料新技术

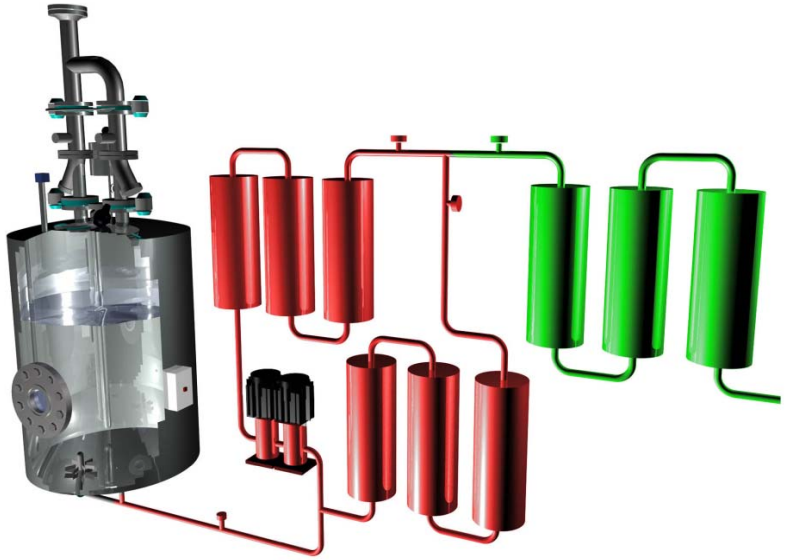
- 缓冲液在线稀释技术
  - 浓溶液储存，罐体体积小，在线稀释；
  - 有效节省工艺储罐，占地面积小；
  - 节省投资，节省车间运营维护费用；



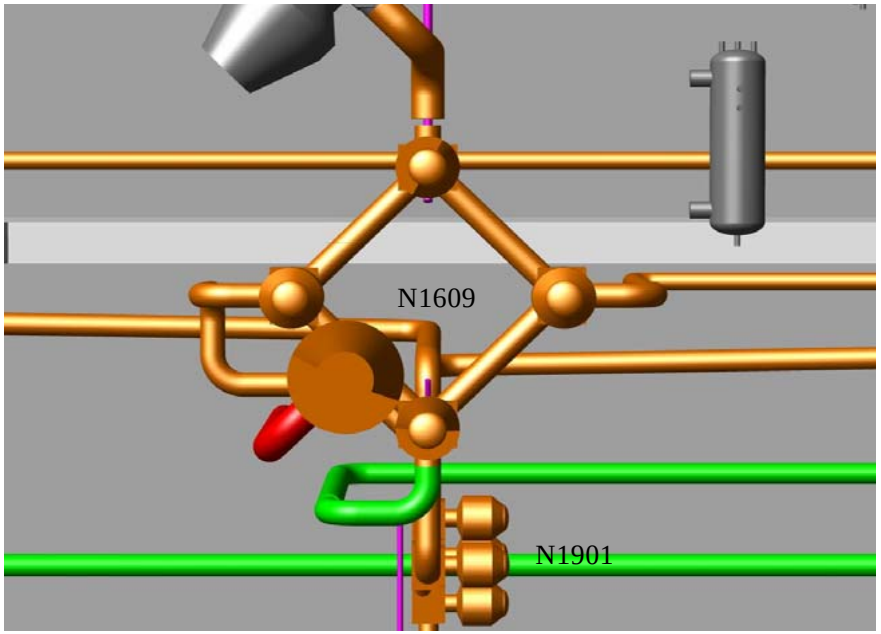
生物废水灭活的节能技术（连续操作）

连续废水灭活技术（CED）

- 连续废水灭活Continuous Effluent Decontamination, CED；
- 处理量大，只需一个小型储罐，占地面积小；
- 性能可靠，高温灭活设施一备一用，冷却至60度后排放；



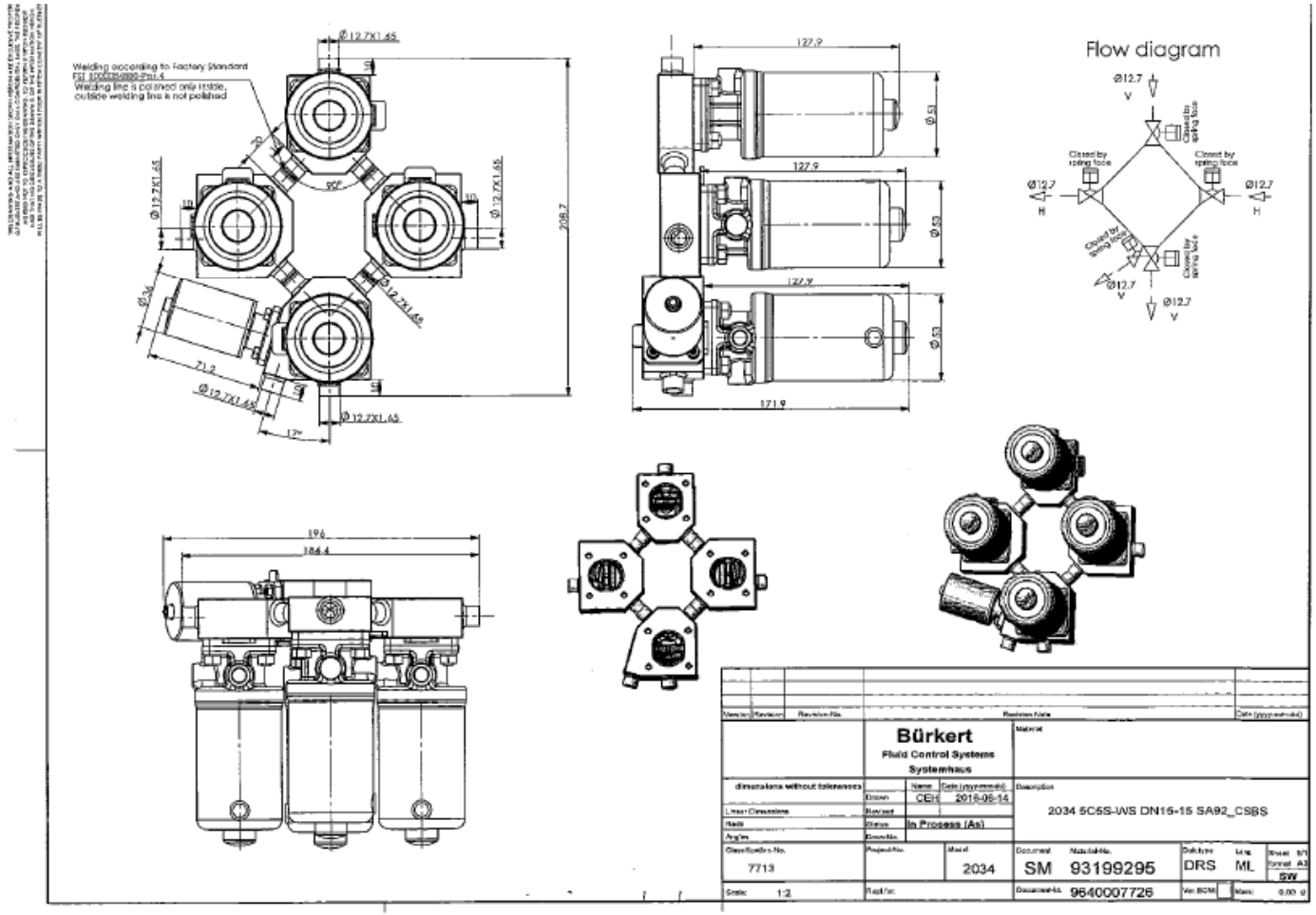
不锈钢系统设备设计-阀环
Equipment Design for Stainless Steel Systems, Valve Rings



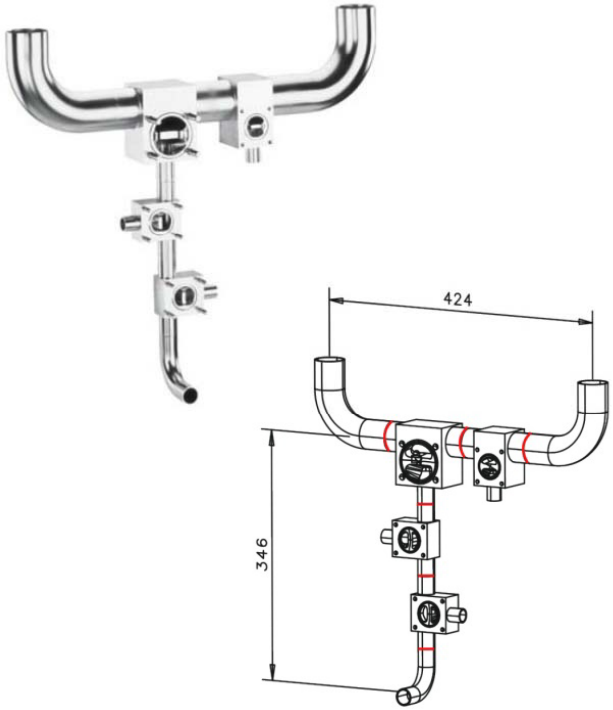
- State-of-the-art technology for high quality bio-pharmaceutical equipment
- Allows clear segregation of SIP and CIP circuits
- No dead ends for good cleaning performance
- Easy 3D designs by following simple rules
- Allows pre-manufacturing for fast project execution

不锈钢系统设备设计-阀环

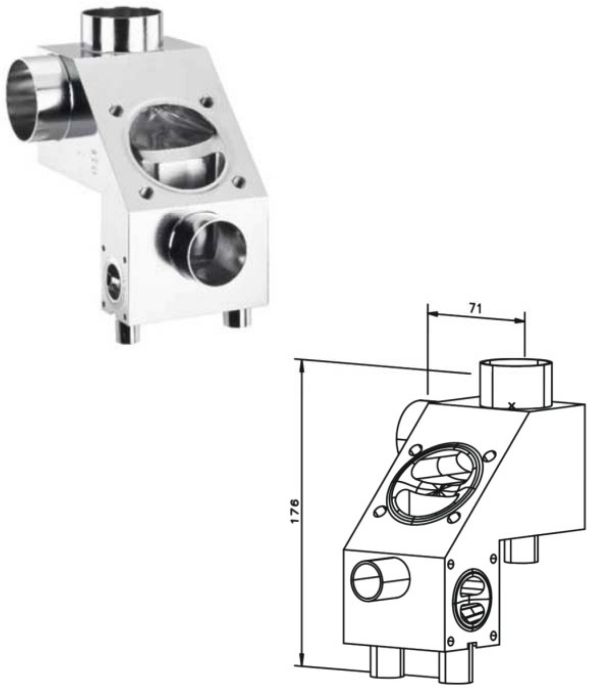
Equipment Design for Stainless Steel Systems, Valve Rings



不锈钢系统：死角控制技术1-Block阀门的应用



（a）传统设计



（b）Block设计

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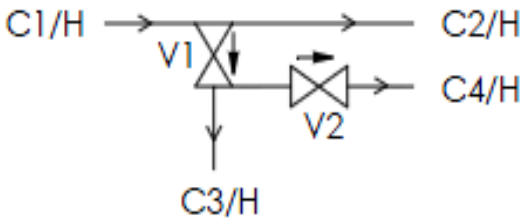
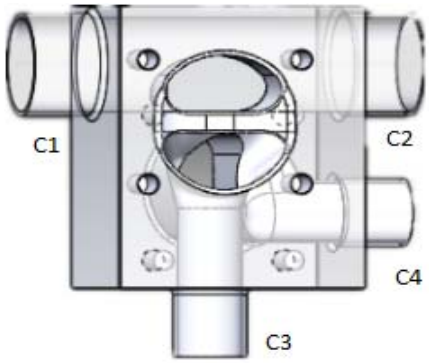




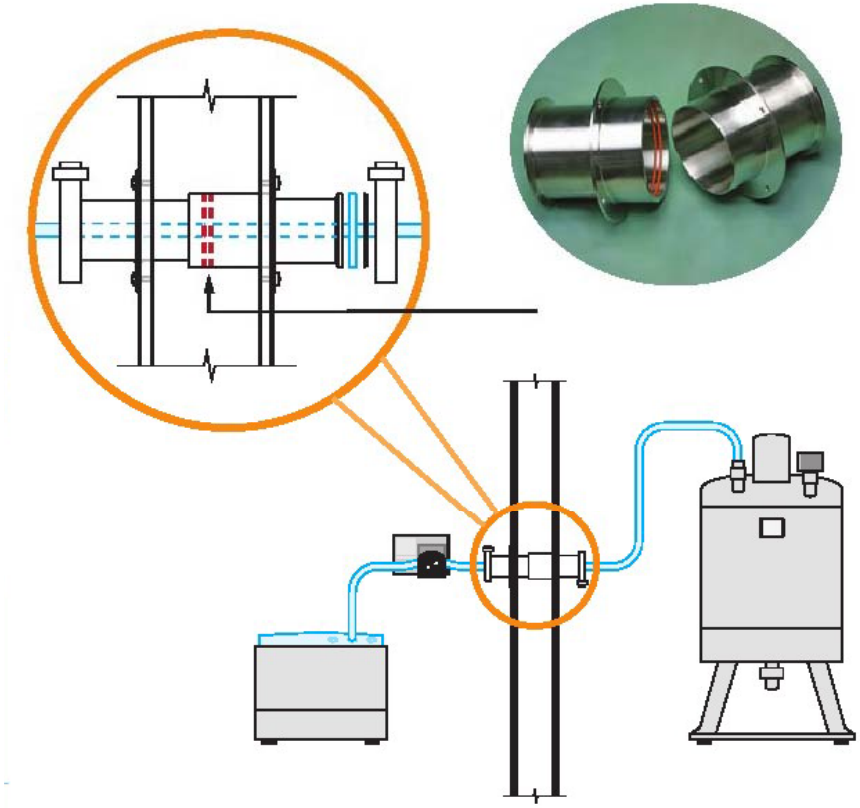
不锈钢系统：死角控制技术2-流通式传感器

（a）插入式

（b）流通式

穿墙技术

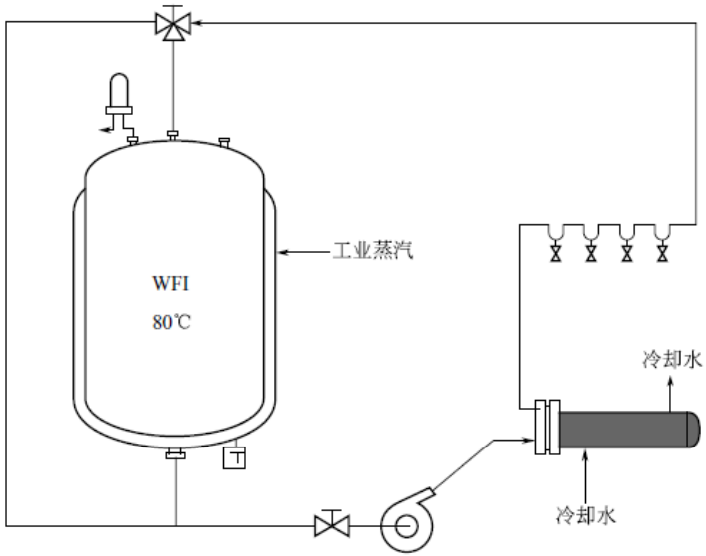
- 跨区转运-穿墙技术 Advance pure-自主创新



核心技术与专利

WFI SKID-热储存、旁路冷循环技术—奥星自主发明创新

- WFI储罐始终高温；循环管网工作模式常温、待机模式高温；
- 采用过热水灭菌技术，节省纯蒸汽的使用；



注射用水制备新工艺

优点：

纯化法制备，可纯蒸汽灭菌，可单套设备制备PW与WFI；WFI出水温度可设计为高温或常温；初期投资低；

缺点：

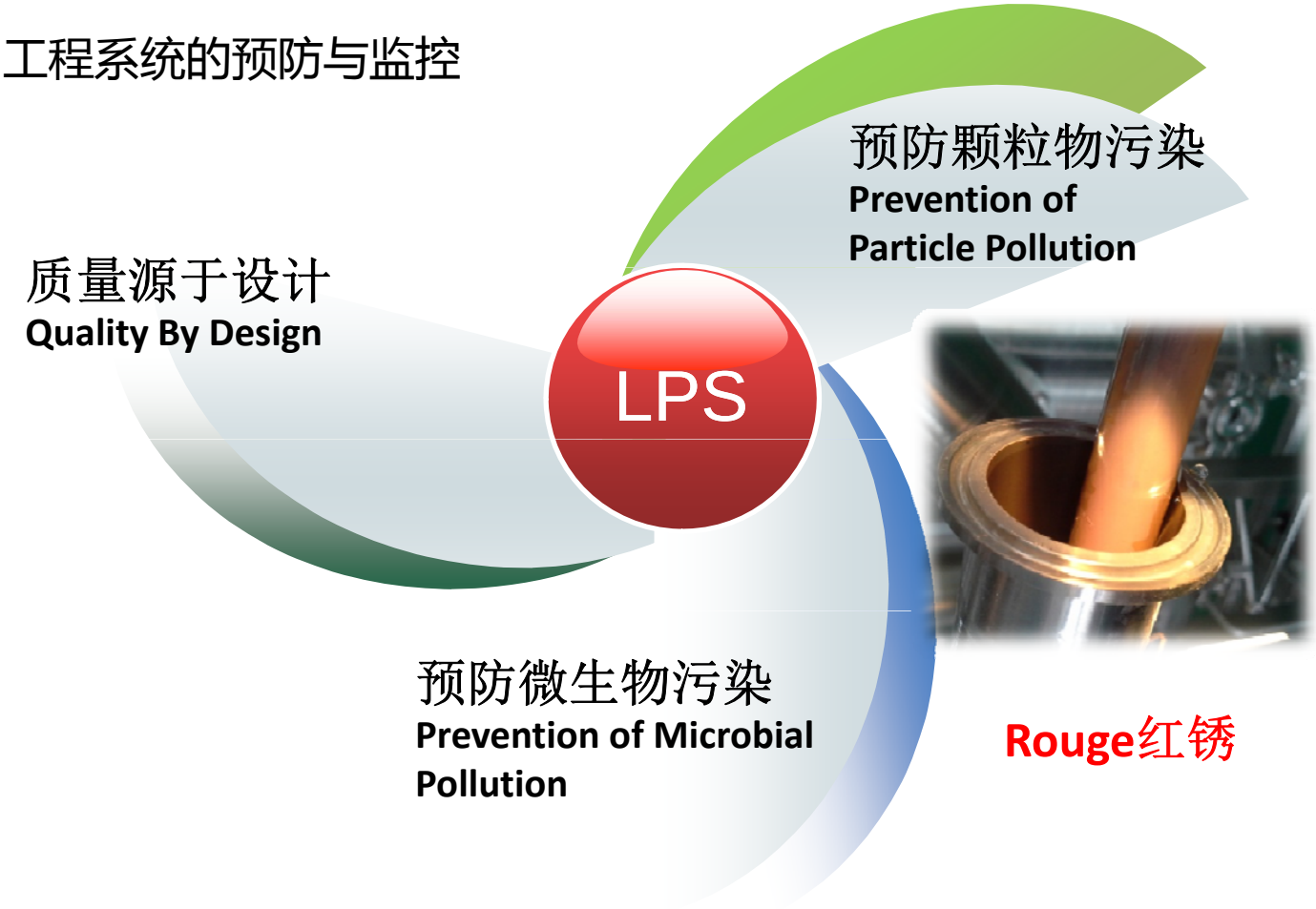
欧、美、日等国家药典已认可，中国药典未认可；微生物控制压力大，设计上需严谨；维保投入大。

紫外灯的作用

- 杀菌：南方客户尤其适用（夏天）
- 臭氧破除：臭氧消毒的PW Loop系统
- 除余氯：与超滤组合，替代机械过滤器与活性炭过滤器，国外新技术
- 降解TOC：制药用水行业应用较少

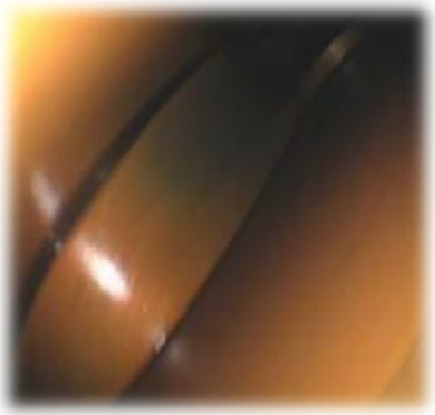
除锈与钝化服务

- 工程系统的预防与监控



除锈与钝化服务

- 除锈方法的对比

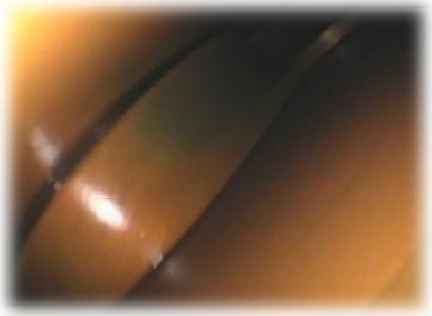


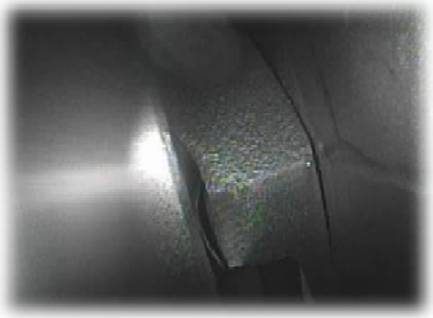
柠檬酸法 Citric Acid	硝酸/氢氟酸法 HNO_3/HF	环保节能法 CIP200

Note: Pictures from Austar Derouging for WFI System of Biopharmaceutical.

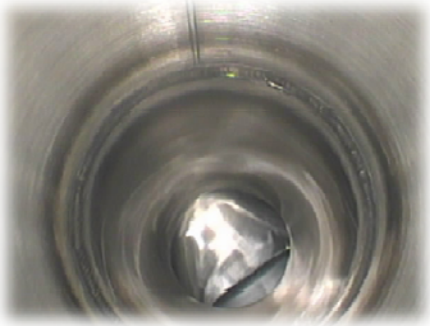
除锈与钝化服务

Pump





Piping

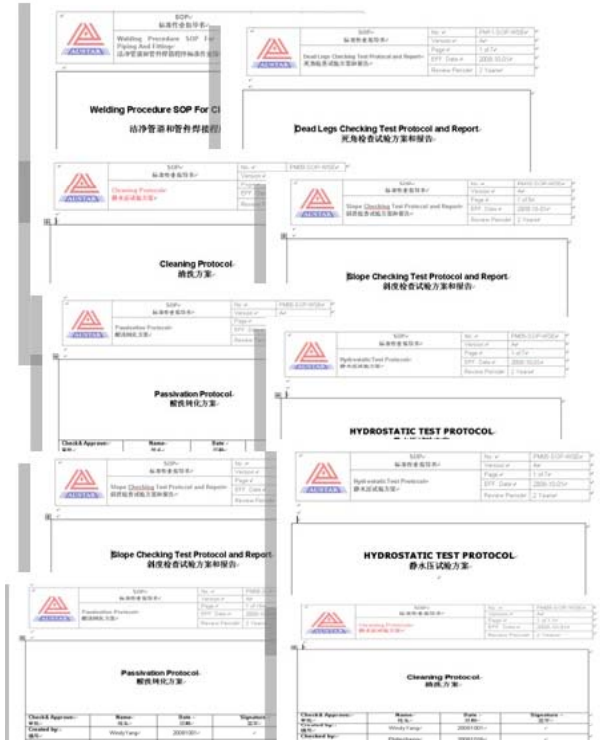


除锈与钝化服务

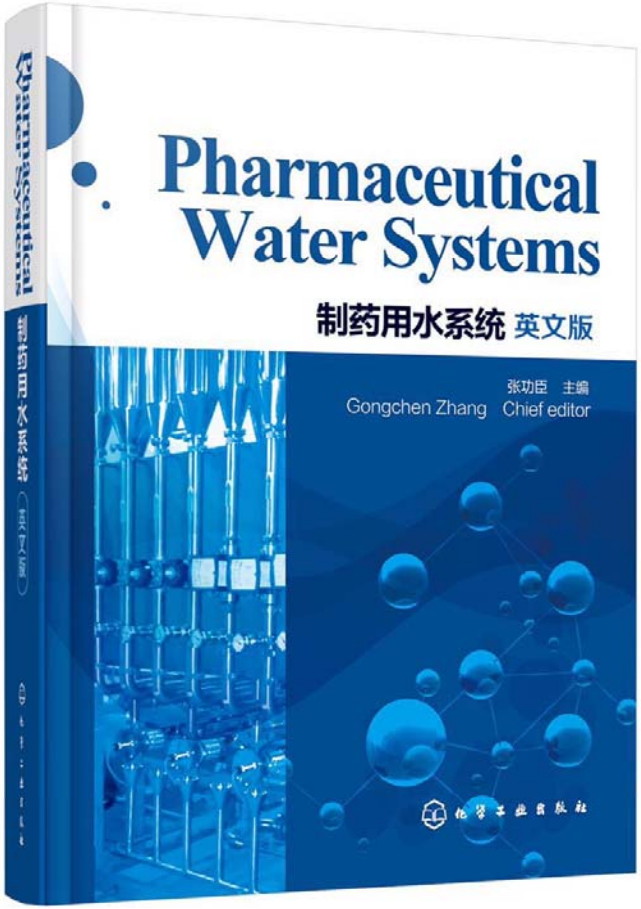
节能型除锈维保机制

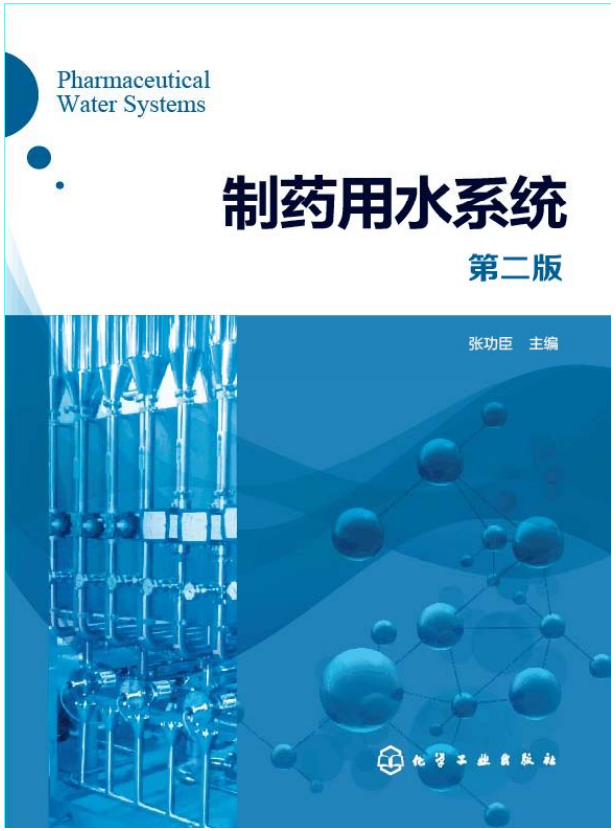
- 周期性维护除锈和钝化，增加系统运行可靠性，符合FDA质量度量理念；
- 在I类红锈或II类红锈早期进行干预，除锈效果最佳；
- WFI系统：除锈周期1-2 年/次；
- PW系统：除锈周期2-3 年/次；
- CIP/配液系统：除锈周期2-3 年/次；

数据完整性 Data Integrity



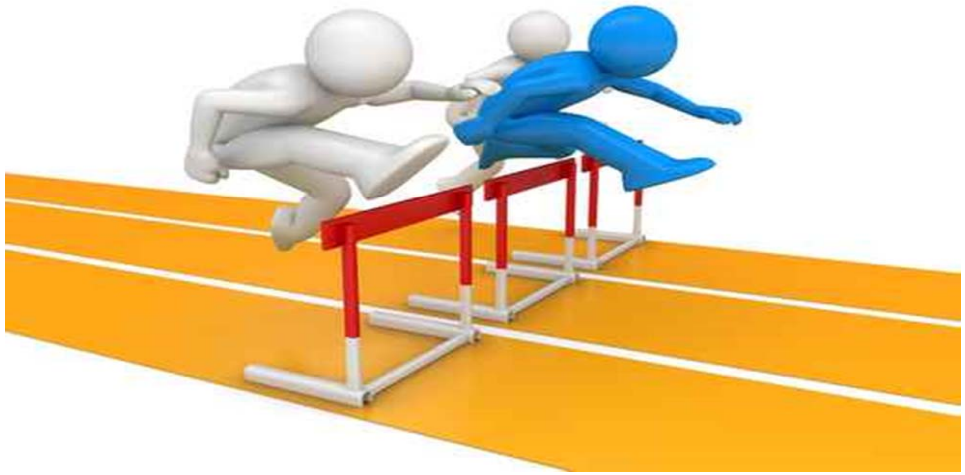
行业著作-《Pharmaceutical Water Systems》





结束语 Closing

制药用水系统
PHARMACEUTICAL WATER SYSTEMS
制药工艺
验证实施手册
制药洁净室
微生物控制
制药流体工艺
实施手册
欧盟GMP/GDP
法规汇编



Thank you!