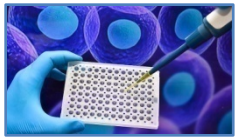
2019（第十一届）
弗戈制药工程国际论坛
2019.7.18-19 江苏·泰州



生物制药 设施的 设计、建设 与 启动

BIO-MFG New Facility: Design, Construction & Operational Readiness

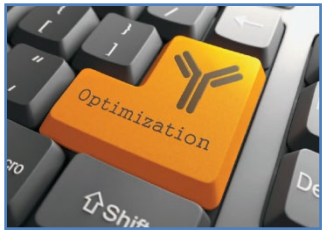
李树德 Michael Lee

2019. 07. 18

讨论 提纲 Agenda

- **Industry** ▪ FoF 未来工厂
- **Integration** ▪ 设计理念，系统整合
- **Insight** ▪ 可持续发展，创造长远的价值
- **Implement** ▪ 项目的执行

生物制药业 的 快速增长



生物制药 是现代科技中 最极致 和 最优雅 的成就之一。

生物药品 的 功效和安全性，以及它们 解决以前无法治愈的条件的能力，造成了 强劲的市场需求，也带来了 可观的利润。

生物制药 正在成为制药行业的核心，但是 生物药品的 开发与生产 却不是一项简单的任务。它在实验室、战略、技术和运营方面带来许多的转变。

生物制药 技术

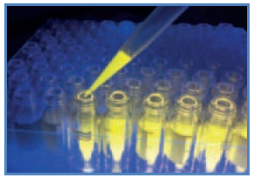
- 大规模（> 3,000L）生产
- 生物控制
- 工艺规模放大
- 技术转移
- 新厂建设
- 一次性设施工艺
- 模块化设计
- 概念设计

- 细胞培养单克隆抗体
- 微生物发酵
- 血液制品
- 疫苗
- 工艺建模
- 各国 / ICH GMP 合规
- 生物类似药
- 工艺验证

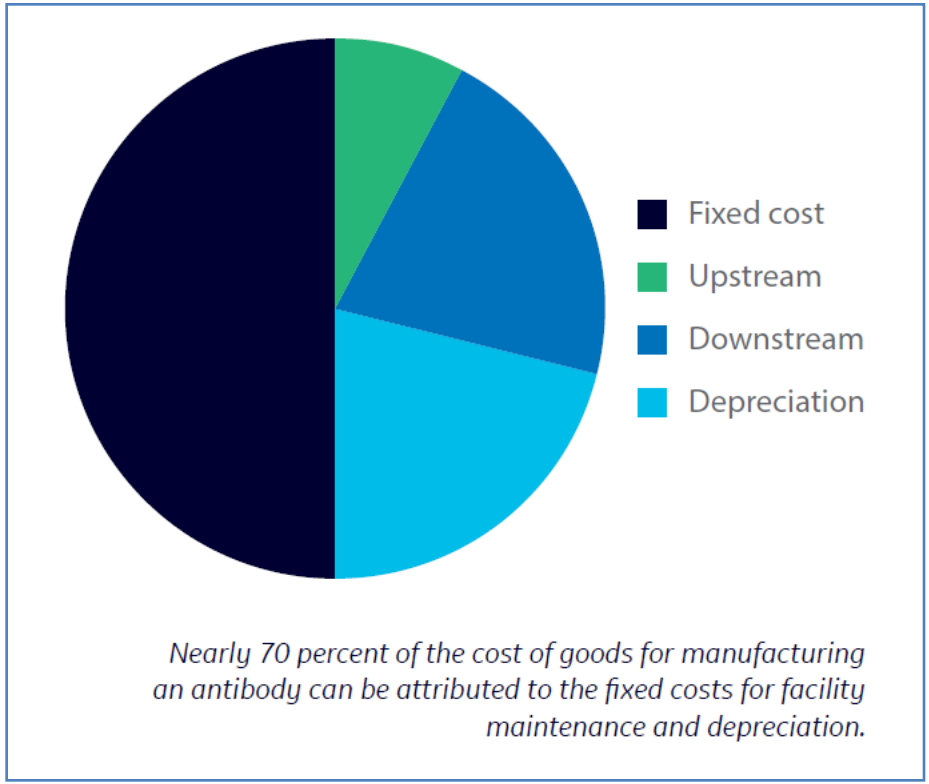
生物制药业 的成本、复杂性 和 监管

随着生物制药 从科学前沿转向商业主流，
该行业 将越来越多地 被迫面对
其他企业所面临的同样挑战：

通过 确保
“患者的可负担性 Affordability、
产品的质量 Quality, 和
公司的绩效 Performance”
来保持 企业的竞争力。



生物制药 的 COG: 70%为固定成本



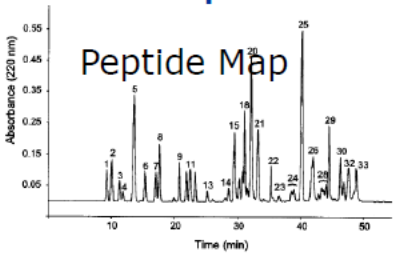
Nearly 70 percent of the cost of goods for manufacturing an antibody can be attributed to the fixed costs for facility maintenance and depreciation.

COG:
70%为 固定成本

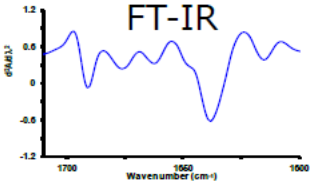
维修 与 折旧

Proteins are complex molecules that form multiple levels of structure

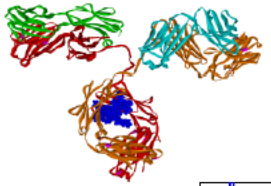
1° Structure
Amino acid sequence

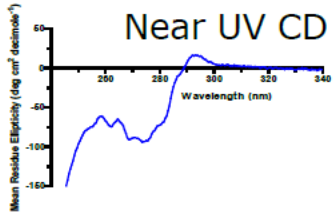


2° Structure
Sub-structure
(a-helix, b-sheet, etc.)

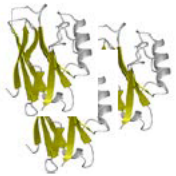


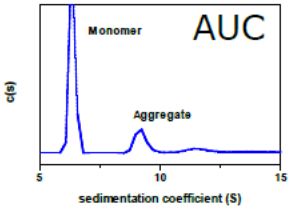
3° Structure
Three dimensional structure



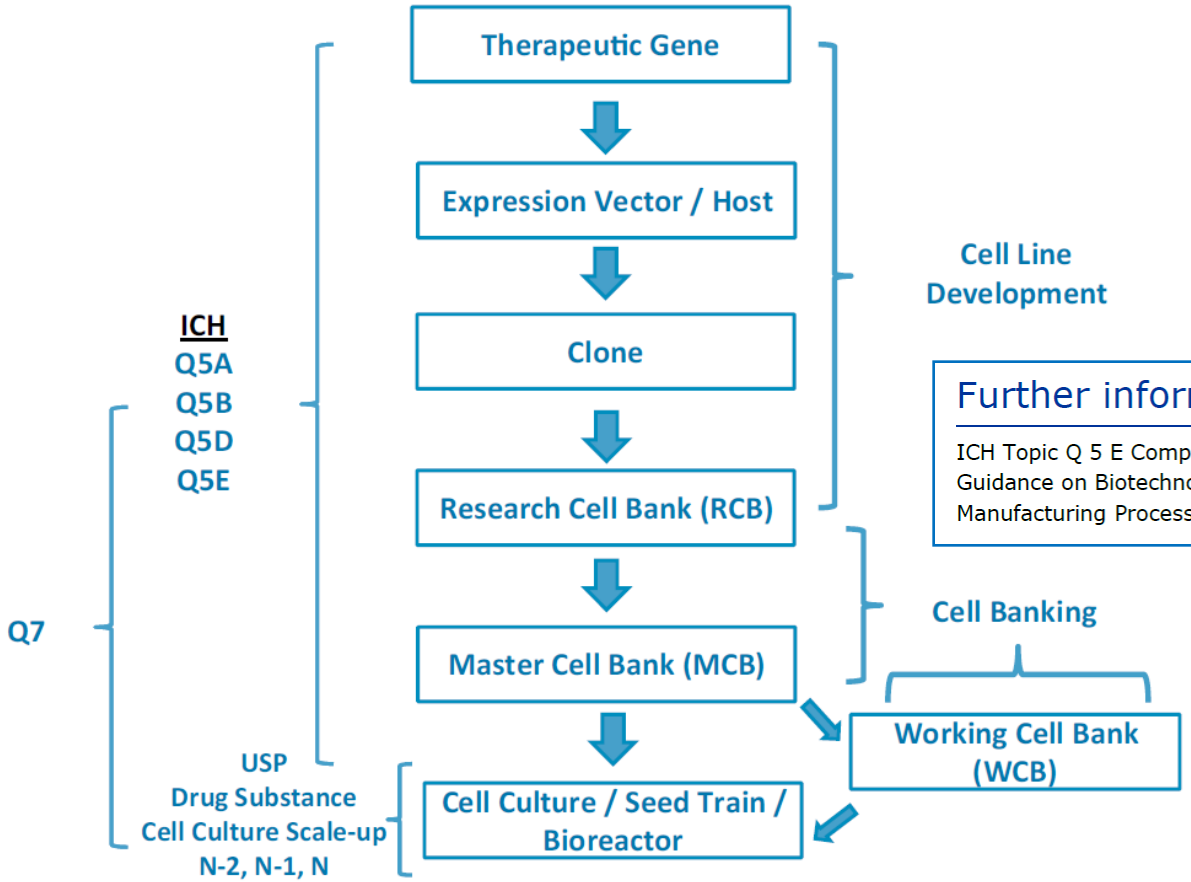


4° Structure
Self-associated structure
(aggregation)





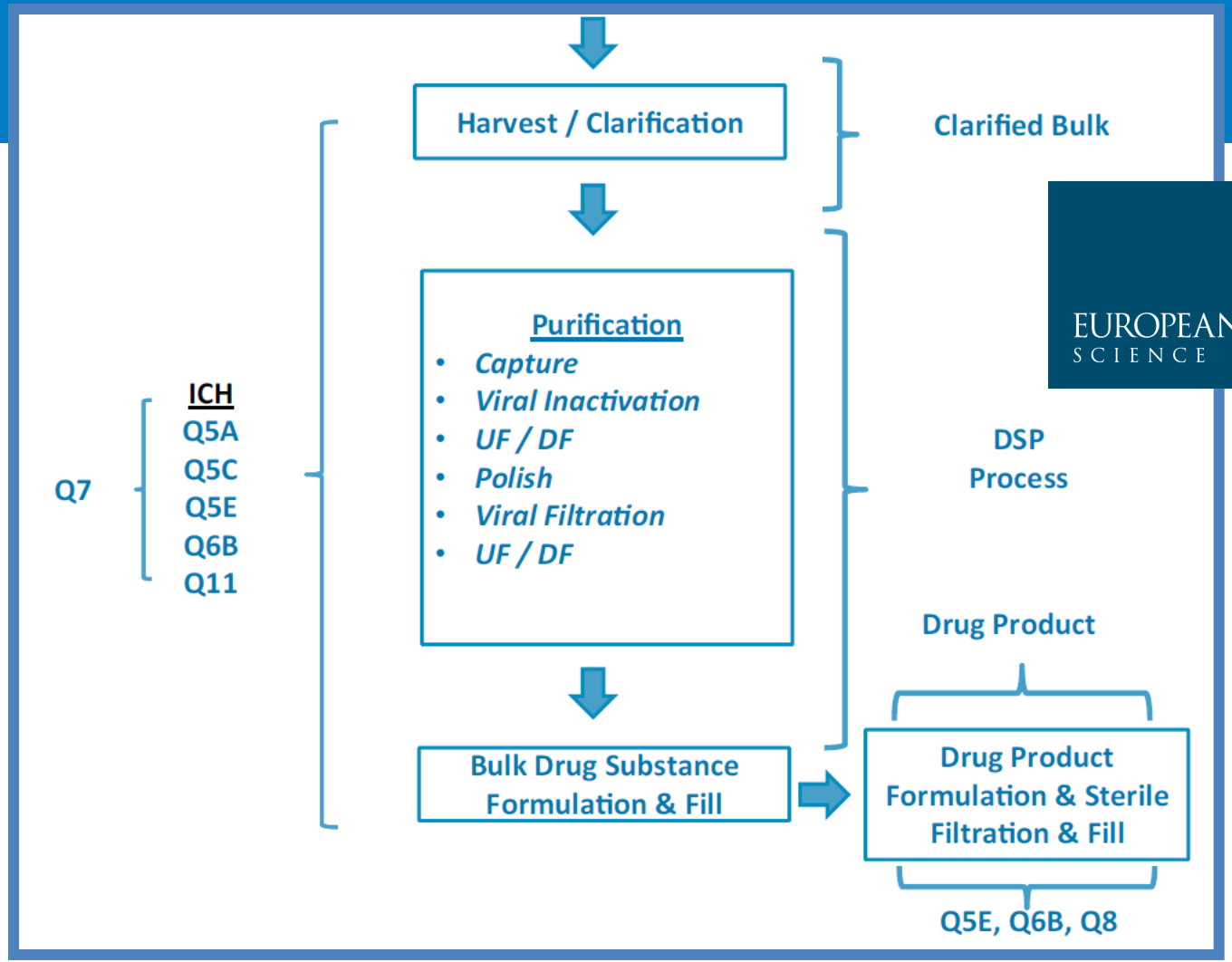
Typical Biologic Manufacturing Process Flow Diagram (Mab)



Further information

ICH Topic Q 5 E Comparability of Biotechnological /Biological Products. Note for Guidance on Biotechnological / Biological Products Subject to Changes in their Manufacturing Process (CHMP/ICH/5721/03)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH documents for biologics

- Q5 A: Viral Safety
- Q5 B: Genetic Stability
- Q5 C: Product Stability
- Q5 D: Cell Substrates
- Q5 E: Comparability
- Q6 B: Specification
- M4 / M2: CTD / e-CTD
- Q7: GMP for APIs
- Q8: Pharmaceutical development
- Q9: Quality Risk Management
- Q10: Pharmaceutical quality system
- Q11: Development and Manufacture of Drug Substances

ICH Q12: Product Lifecycle Management

ICH Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Core Guideline; Draft version Endorsed on 16 November 2017.

ICH Q12 describes an requirements using Established Conditions (ECs) structured using a PACMP (Post-Approval Change Management Protocol) within a PLCM (Product Lifecycle Management) program.

These requirements are over-and-above the manufacturing process information defined in the ICH Q8 Design Space (DS) and Control Strategy (CS) descriptions in the original CMC submissions. The process change information would be more effectively developed, easier to compile, and better communicated to regulatory agencies by amending the original CMC information within a well-organized CTD section appropriately structured for presenting well-structured DS/CS information.

ICH Q13: Continuous Manufacturing

ICH Q13: Continuous Manufacturing for Drug Substances and Drug Products, dated 2018. 11. 14

ICH Q13 that addresses Continuous Manufacturing (CM). The Q13 Business Plan suggests that CM is somehow fundamentally different than batch processes and thus must be developed and regulated differently. While they use different process technologies, both CM and batch processes are developed and controlled using nearly identical lifecycle, DS QbD/CSs control strategies to achieve the common goal of operating consistency and product quality.

ICH Q14 : Analytical Procedure Development

ICH Q14: Analytical Procedure Development and Revision of Q2 (R1) Analytical Validation dated 2018. 11. 14.

It is proposed to develop a new quality guideline on Analytical Procedure Development and to revise the ICH Q2(R1) Guideline on Validation of Analytical Procedures: Text and Methodology.

The Expert Working Group should potentially determine the feasibility to combine both documents into one for simplification and clarity.

生物制药的技术发展 的挑战

Challenges to Biopharmaceutical Manufacturing

- Efficiency
- Quality
- OPEX: Operation
- Monitoring

生物制药行业的技术发展的工具

Enabling Technologies

Process Technologies

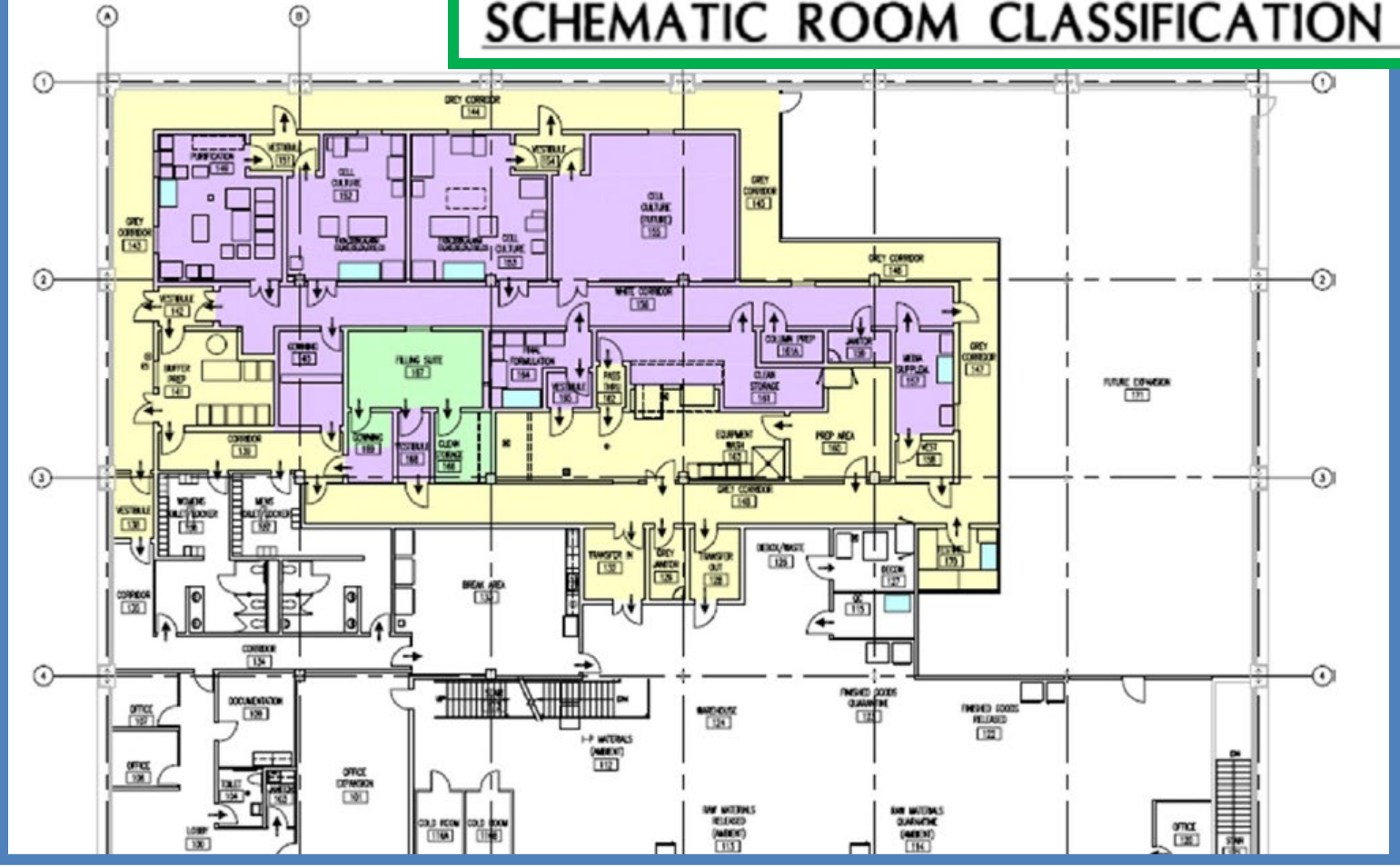
Inline Monitoring & Real time Release

Automated Facility

Knowledge Management

Supplier Partnerships

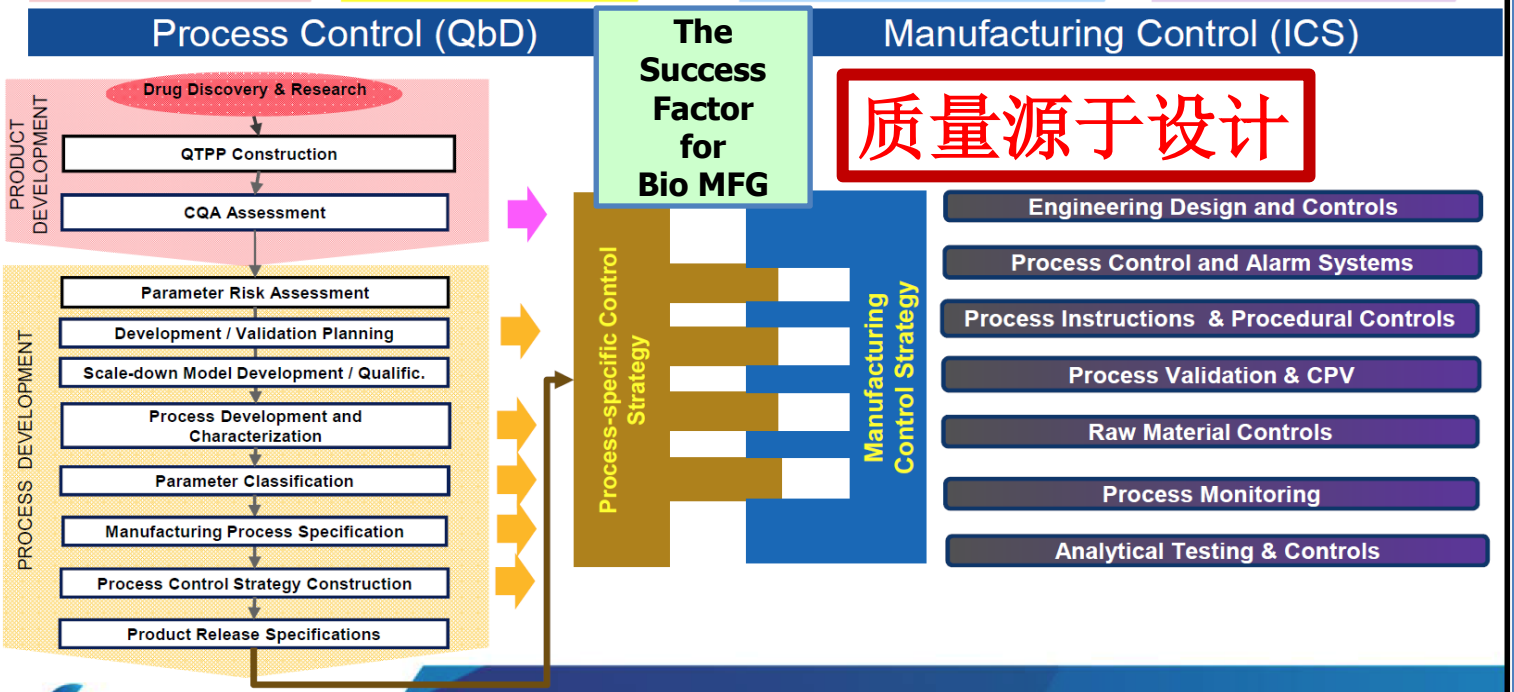
SCHEMATIC ROOM CLASSIFICATION PLAN



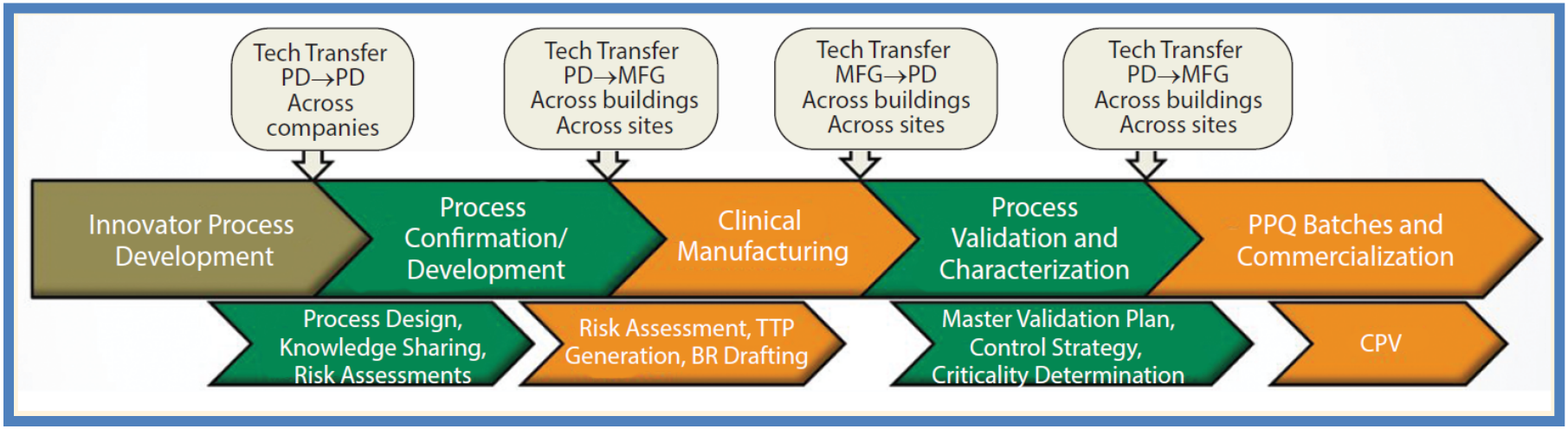
Using QbD Outputs to Build the Control Strategy

A Truly Integrated Set of Control Systems is Required Leverage QbD

Product Development → Process & Analytical Development → *Transfer* → Process & Assay Implementation → Manufacturing & Lifecycle Management

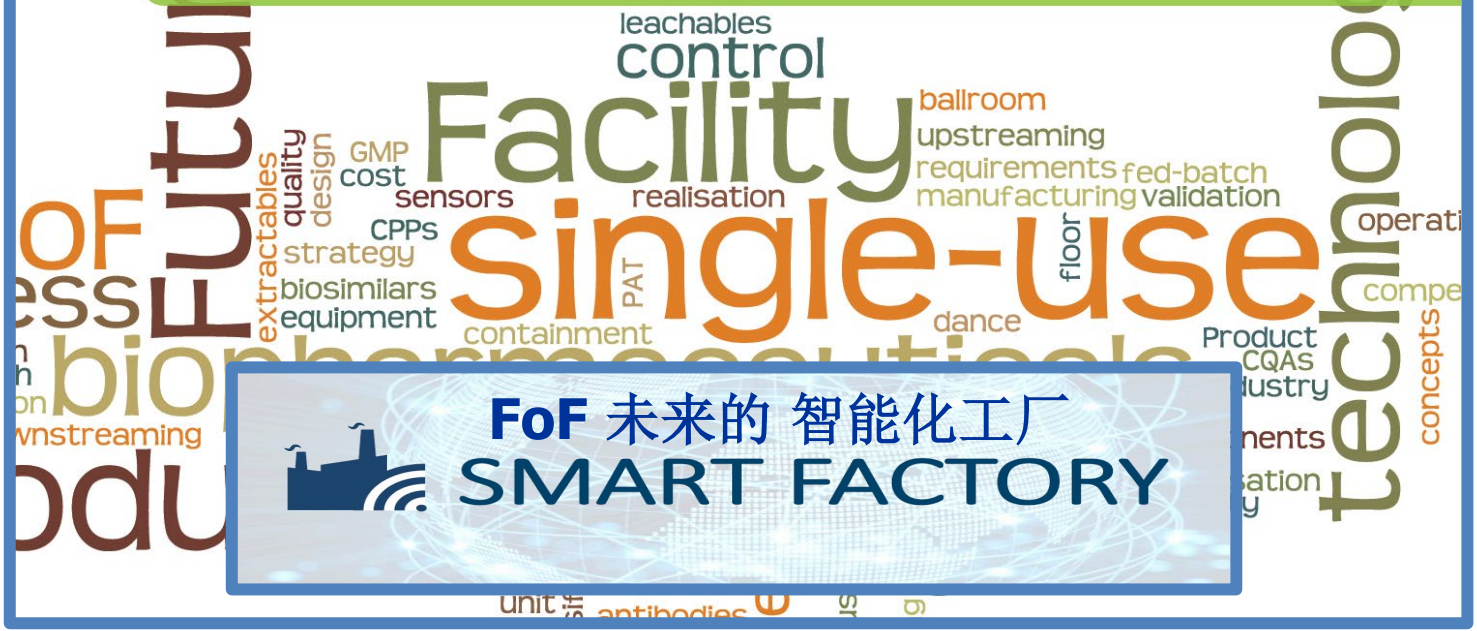


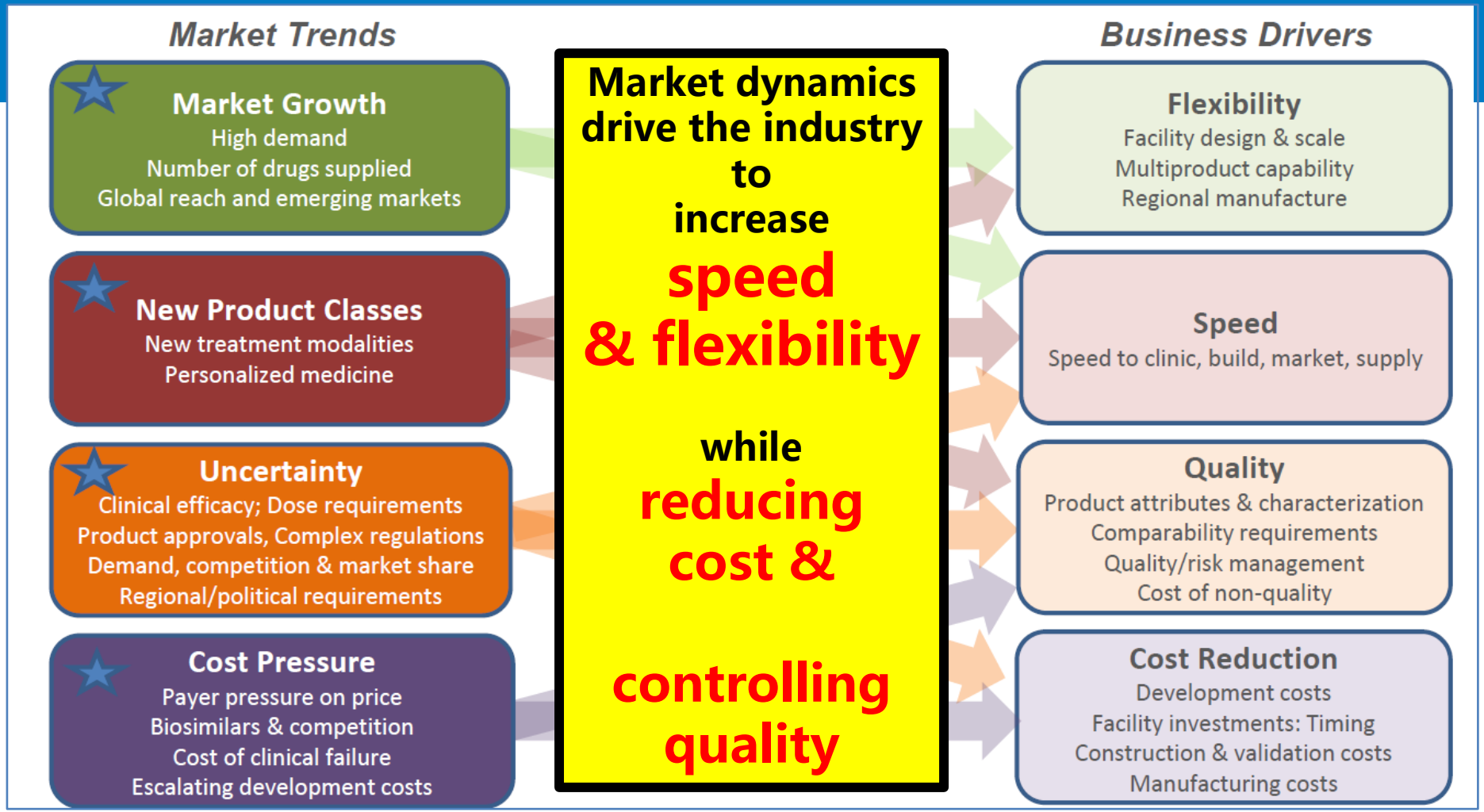
生物制药 的 生产环节


Tech Transfer
PD→PD
Across
companies
Tech Transfer
PD→MFG
Across buildings
Across sites
Tech Transfer
MFG→PD
Across buildings
Across sites
Tech Transfer
PD→MFG
Across buildings
Across sites
Innovator Process Development
Process Confirmation/ Development
Clinical Manufacturing
Process Validation and Characterization
PPQ Batches and Commercialization
Process Design, Knowledge Sharing, Risk Assessments
Risk Assessment, TTP Generation, BR Drafting
Master Validation Plan, Control Strategy, Criticality Determination
CPV

Facility of the Future

FoF 未来工厂




Market Trends
Market Growth
High demand
Number of drugs supplied
Global reach and emerging markets
New Product Classes
New treatment modalities
Personalized medicine
Uncertainty
Clinical efficacy; Dose requirements
Product approvals, Complex regulations
Demand, competition & market share
Regional/political requirements
Cost Pressure
Payer pressure on price
Biosimilars & competition
Cost of clinical failure
Escalating development costs
Market dynamics drive the industry to increase
speed & flexibility
while
reducing cost &
controlling quality
Business Drivers
Flexibility
Facility design & scale
Multiproduct capability
Regional manufacture
Speed
Speed to clinic, build, market, supply
Quality
Product attributes & characterization
Comparability requirements
Quality/risk management
Cost of non-quality
Cost Reduction
Development costs
Facility investments: Timing
Construction & validation costs
Manufacturing costs

生物制药行业的挑战 Challenges faced by Bio Industry

- 流程开发
- 分析开发
- 流程资格/验证
- 分析鉴定/验证
- cGMP制造临床前和临床材料
- 质量控制测试
- 完整的CMC文档，包括Facility Master File（CBER / CDER）

Your Future

BIOMANUFACTURING

生物制药
设施
的
规划 与 建设

OPS Requirements 工厂 作业需求

- 细胞系优化
- 细胞培养和纯化过程开发
- 蛋白质表征
- 流程优化，扩展和验证
- cGMP 临床 样品 和商业化生产
- 灌装
- 分析测定开发
- 方法鉴定和验证
- QC检测 和 稳定性试验
- 合规策略 和 产品注册

Cell line optimization

Cell culture and purification process development

Protein characterization

Process optimization, scale-up and validation

cGMP clinical and commercial manufacturing

Bulk filling

Analytical assay development

Method qualification and validation

QC release and stability testing

Regulatory strategy and submission

Simple to plan

Cheap to procure

Facile to program

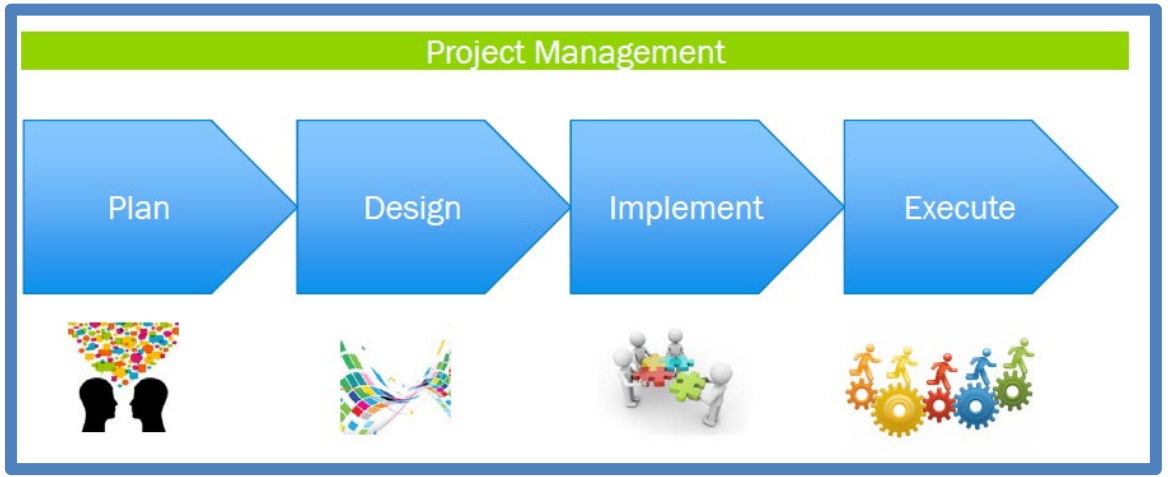
Readily to commission

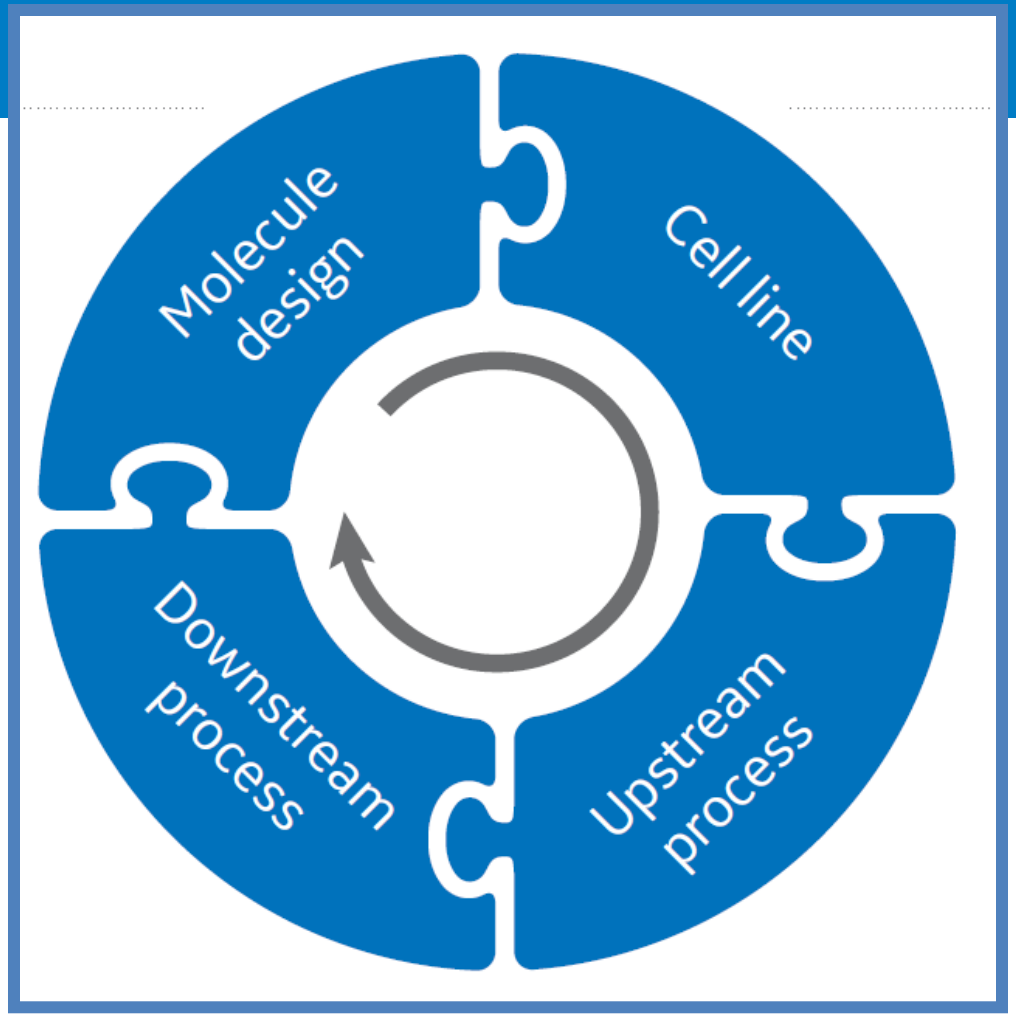
Straight to validate

Safe to operate

Easy to maintain

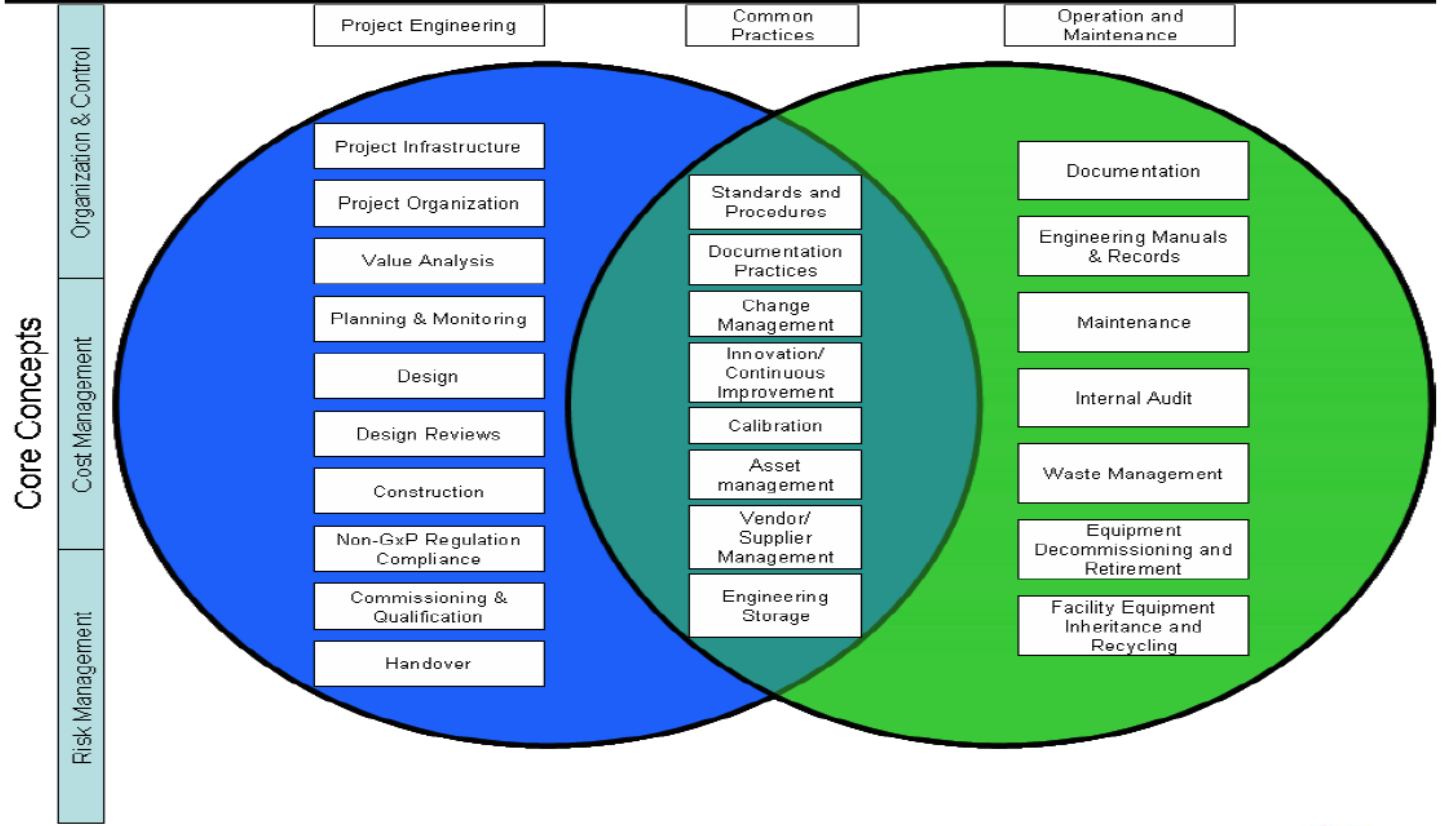
生物制药 设施 的 规划 与 建设



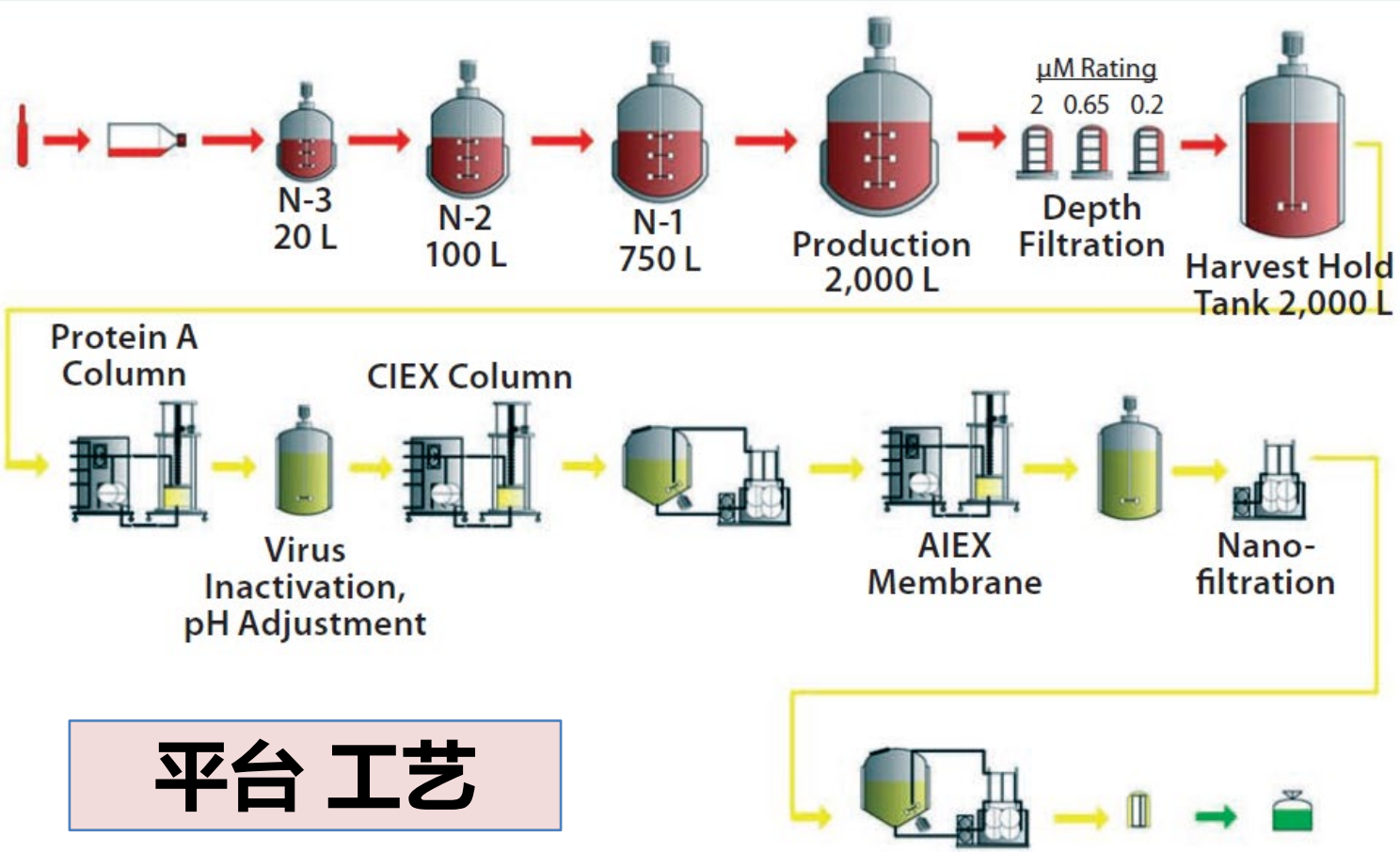

Molecule design
Cell line
Downstream process
Upstream process

Best Practice Commissioning and Start-Up

Good Practice Guide - GEP, 良好工程规范



Standard monoclonal antibody platform manufacturing process



平台 工艺

项目管理 的 铁三角

The Iron triangle scheme

The Project Management Triangle is used to analyze projects.

Principles:

- The quality of work is constrained by the project's budget, deadlines and scope (features).
- The project manager can trade between constraints.
- Changes in one constraint necessitate changes in others to compensate. Otherwise, quality will suffer.

项目 的 设计 与 文件

成功的设计 和 实现 FDA 可验证的设施 不是偶然发生的。

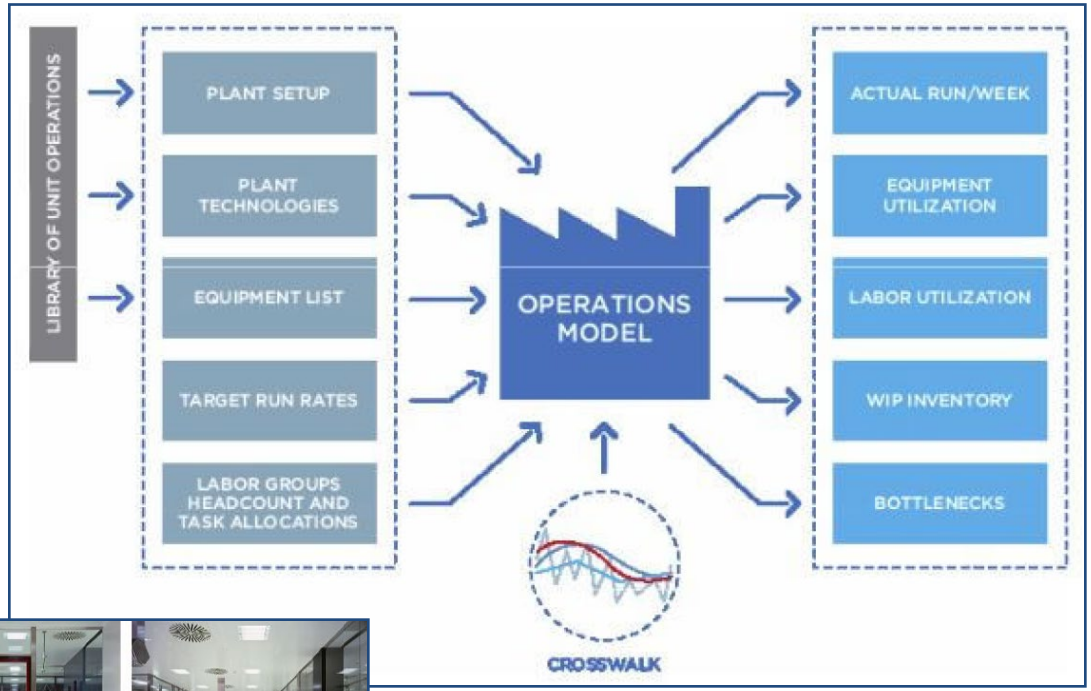
所有相关方之间的 早期协调 和 沟通 至关重要，
从流程设计 和 放大 到 cGMP布局，
FDA预建 设计审查，
调试，验证 和 监管机构的现场检查。

完整的“设计基础”文件，
对于 优化 稀缺资源的利用 是必要的。

在“建设”阶段之前，
在前端所进行的设计优化 其所花费的时间 是必须的。

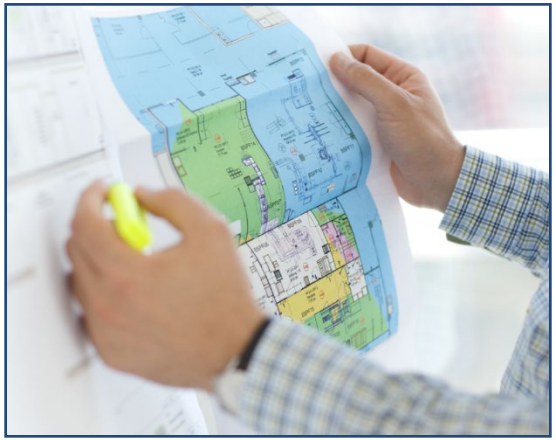
Optimizing Biomanufacturing in Real Time

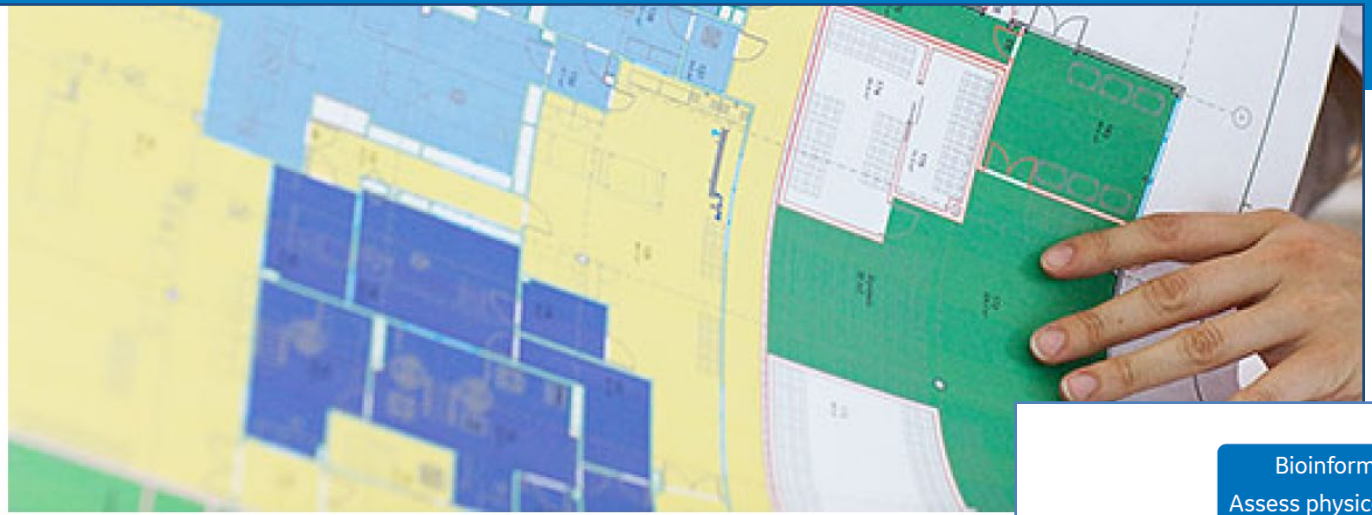
The successful design and realization of small and large scale facilities are only possible if work is done together by interdisciplinary teams.



Biomanufacturing Facility Engineering

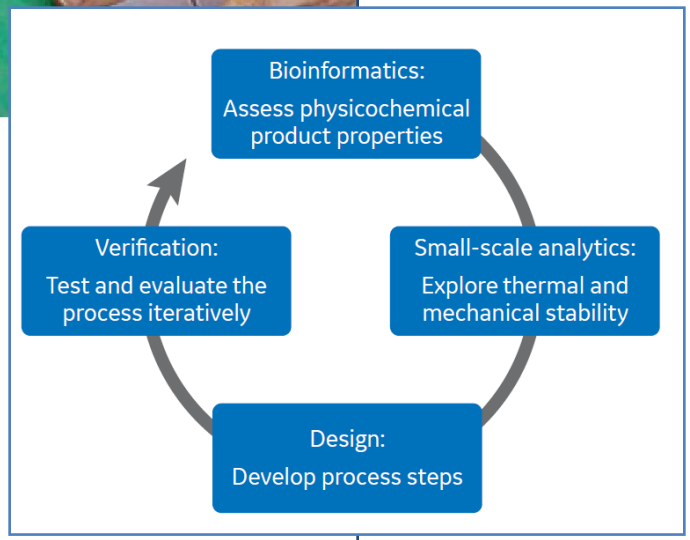
- Project management (cost, quality & time)
- Process-orientated building concepts & layouts
- Clean room & HVAC technology
- Aseptic processing
- Biosafety, containment and barrier technology
- Biowaste inactivation
- GMP compliance
- Qualification & validation
- Automation
- Process support and utility systems (e.g. CIP, purified water, WFI, clean steam)





Design phase

- Site master planning and site evaluation
- Feasibility studies
- Conceptual design
- Basic engineering
- Detailed engineering



Implementation of Facility Delivery

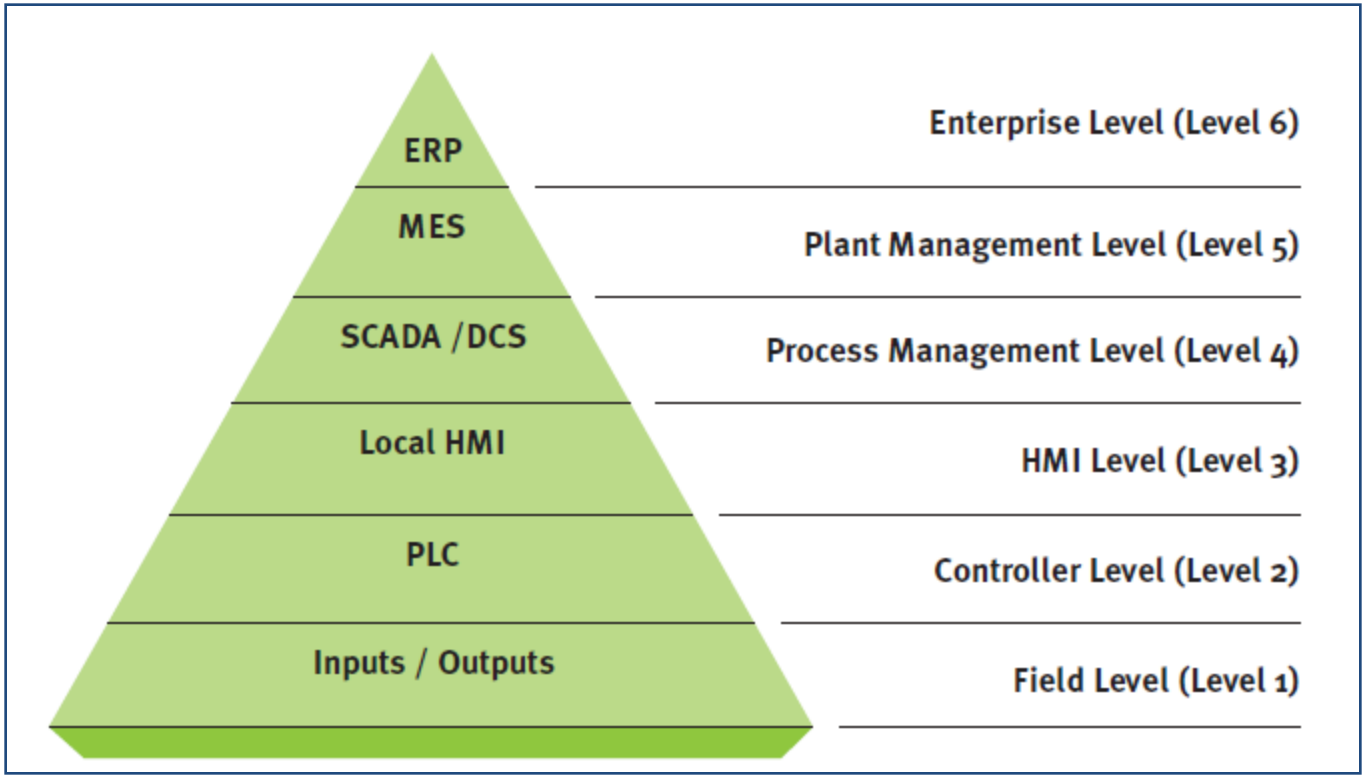
Realisation phase

- Procurement
- Construction management
- Project controlling (quality, cost, time)
- Commissioning
- Operator training
- Qualification and validation

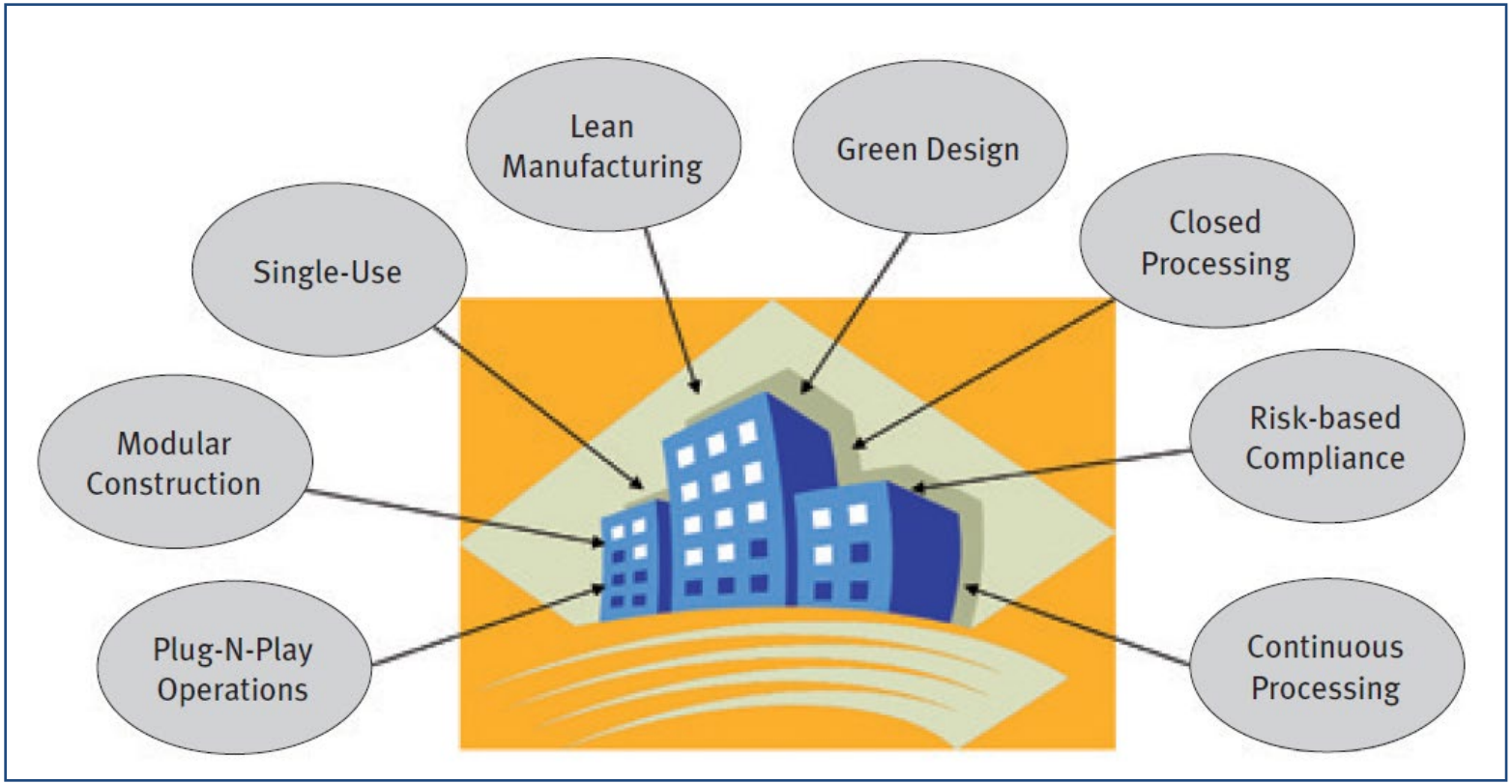
Supplementary services

- Process simulation and optimisation
- Biosafety concepts and environmental impact analysis (EIA)

Requirements of Automation Systems



Total Requirements of FoF



1. What can current stainless steel technology deliver?
2. What is the potential for modular single-use facilities?
3. What is the potential for continuous processing facilities?

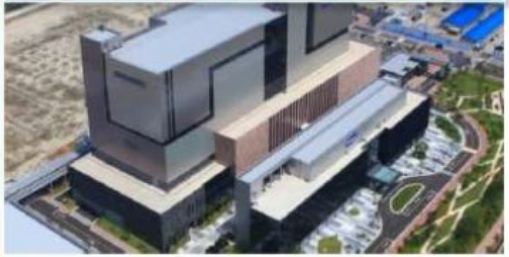
设施 的 选项：

不锈钢的设施、一次性的设施

生物制药
不锈钢设施
的
规划 与 建设

Plant No. 1 (2011 ~ 2013)

"Industry Standard"



Total capacity	• 30,000L (6 x 5,000L)
Capex	• US$300 mm
Construction	• 25 months to cGMP ready

Plant No. 2 (2013 ~ 2016)

"The Largest Single Plant"(1)

Total capacity	• 152,000L (10 x 15,000L / 2 x 1,000L)
Capex	• US$650 mm
Construction	• 29 months to cGMP ready

Plant No. 3 (2015 ~ 2018)

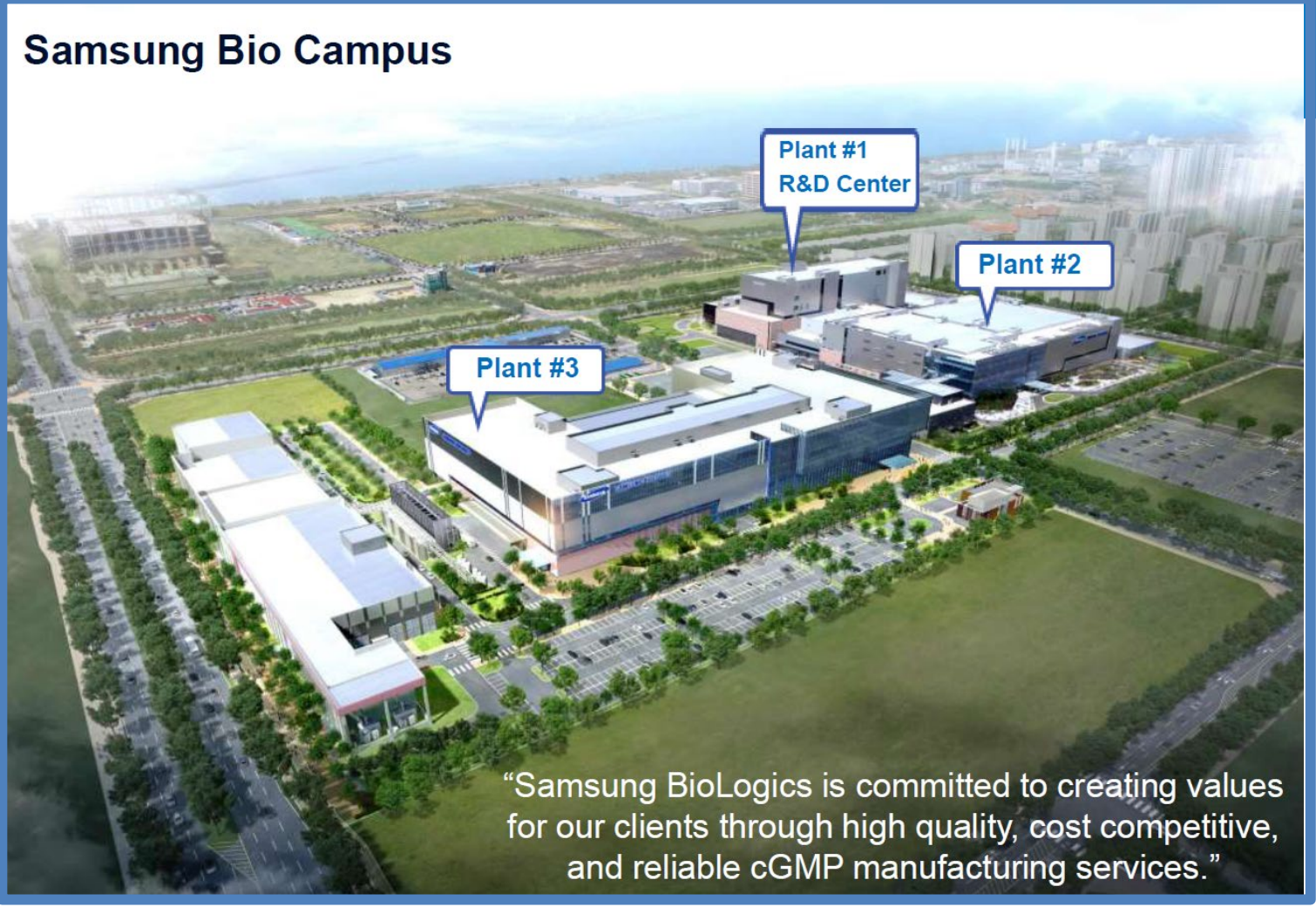
"The Most Competitive Plant"

Total capacity	• 180,000L (12 x 15,000L)
Capex	• US$740 mm (estimate)
Construction	• 35 months to cGMP ready

CMO Capacity Comparison (KL)(2)

Note: (1) Excluding Boehringer Ingelheim's Bibearch plant (196KL) which has 2 downstream process for 12 x 15KL bioreactors; (2) Peers' capacity as of 2015; (3) Plant No. 3 expected to become operational by 2018
Source: BioProcess Technology Consultants, Company data

Samsung Bio Campus



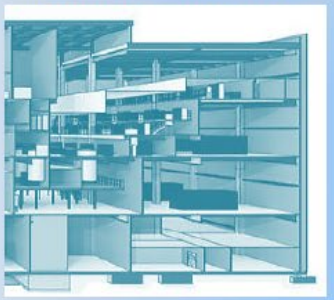
Samsung BioLogics headquarters and production facilities in Songdo, Incheon

Total Site

Space Management

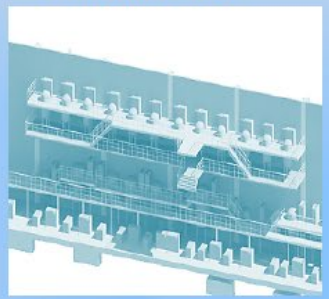
Process Flow

- *Gravity flow*
- *Minimal Product Loss*



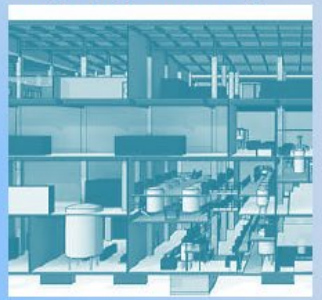
Personnel Access

- *Operational Freedom*
- *Personnel Flow*



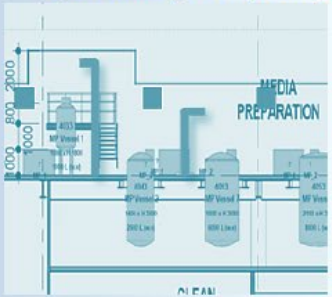
Utility Support

- *Short Distances*
- *Logic pipe routing*

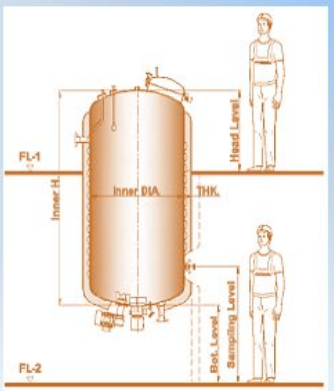


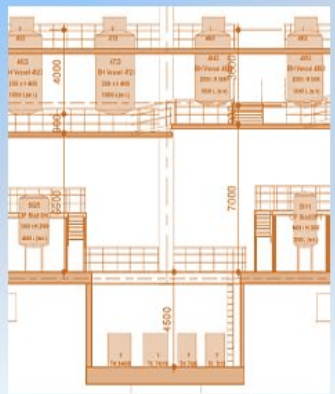
Material Flow

- *Lean Logistics*
- *Separated from pers.flow*



Operation & Compliance

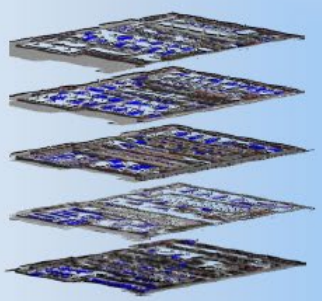




Room Concepts

Optimal Layout

- *Gravity flow*
- *Minimal Product Loss*

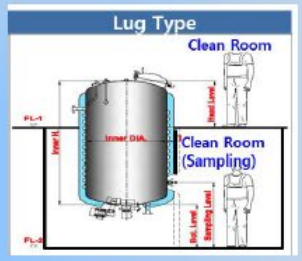


Efficient Zoning

- *Operational Freedom*
- *Personnel Flow*

Floor Height

- *Optimize room volumes*
- *Operation & Mainten.*



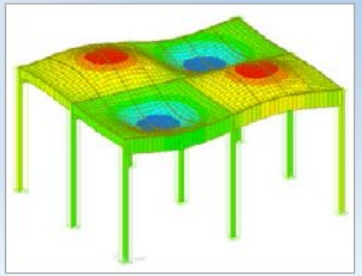
GMP room finish

- *Cleanability, Durability*
- *BioBurden Control*

Structure & Civil

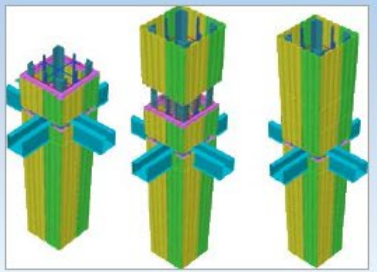
Structural System

- *Load Optimization*
- *Structure Simulation*



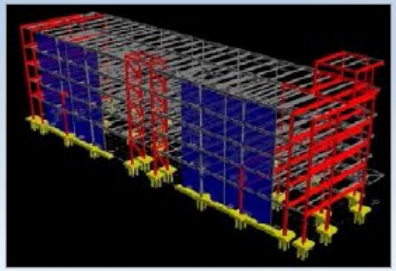
New Methods

- *Cost & Time reduction*
- *Earth quake safety*



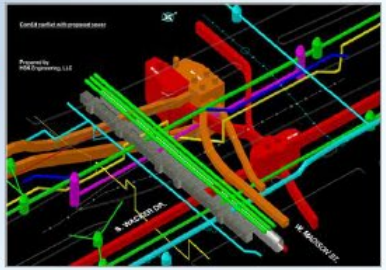
Foundation Design

- *Stability Improvement*
- *Pile Capacity optimum*



Drainage U/G

- *U/G Utility opt. design*
- *Reflect regional situation*



Organization & Documentation

Organization

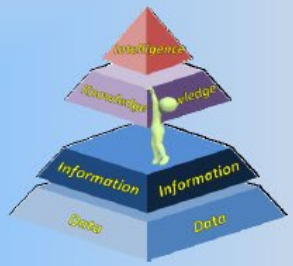
- *Fast manpower mobil.*
- *Efficient Hierarchy*

Scheduling

- *Smart & flexible*
- *Tight expediting*

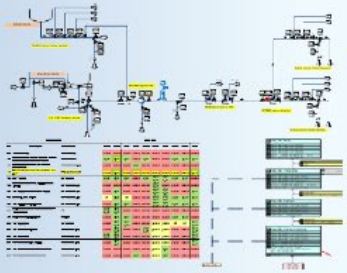
Knowledge Management

- *Leverage information and expertise*



FDS

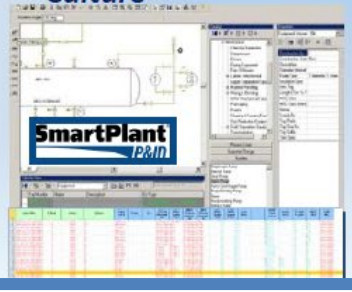
- *SA88 adapted concept*
- *All plant systems in one hand*



Calculations & Simulations

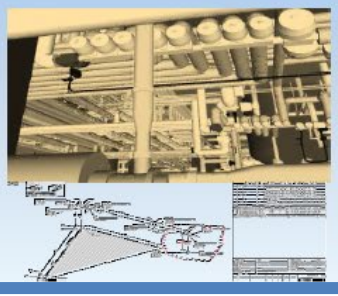
P&ID

- *Data Based smart PID*
- *Best PID as Engineering Culture*



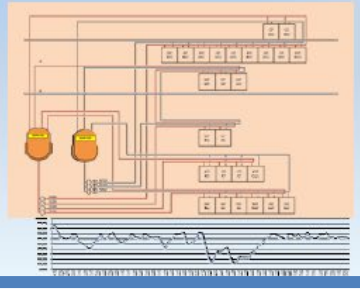
3D Modeling

- *3D CAD (PDS)*
- *Comprehensive PIMS*



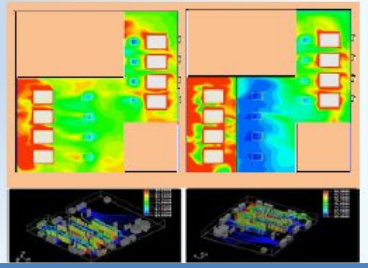
Utilities

- *Consumption Analysis*
- *Peak simulations*

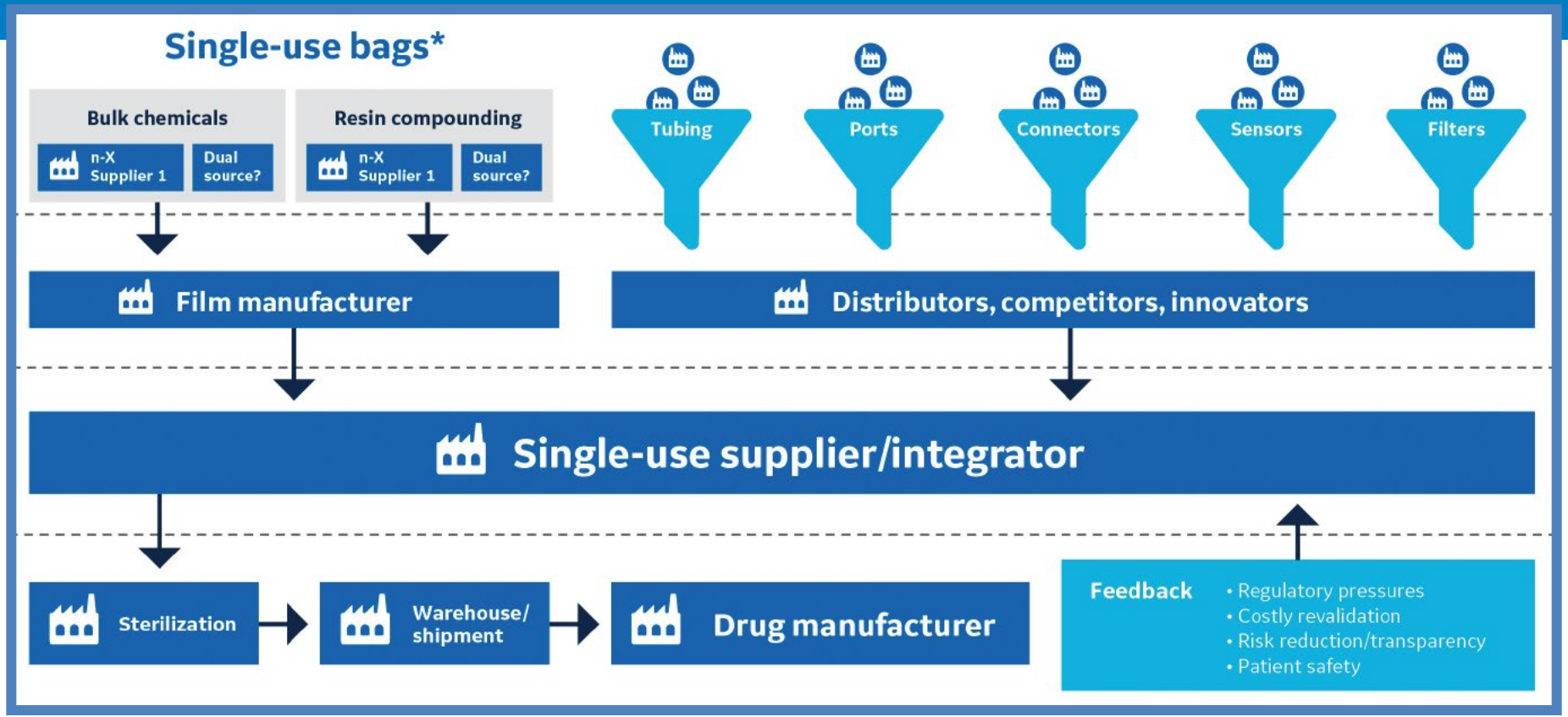


HVAC

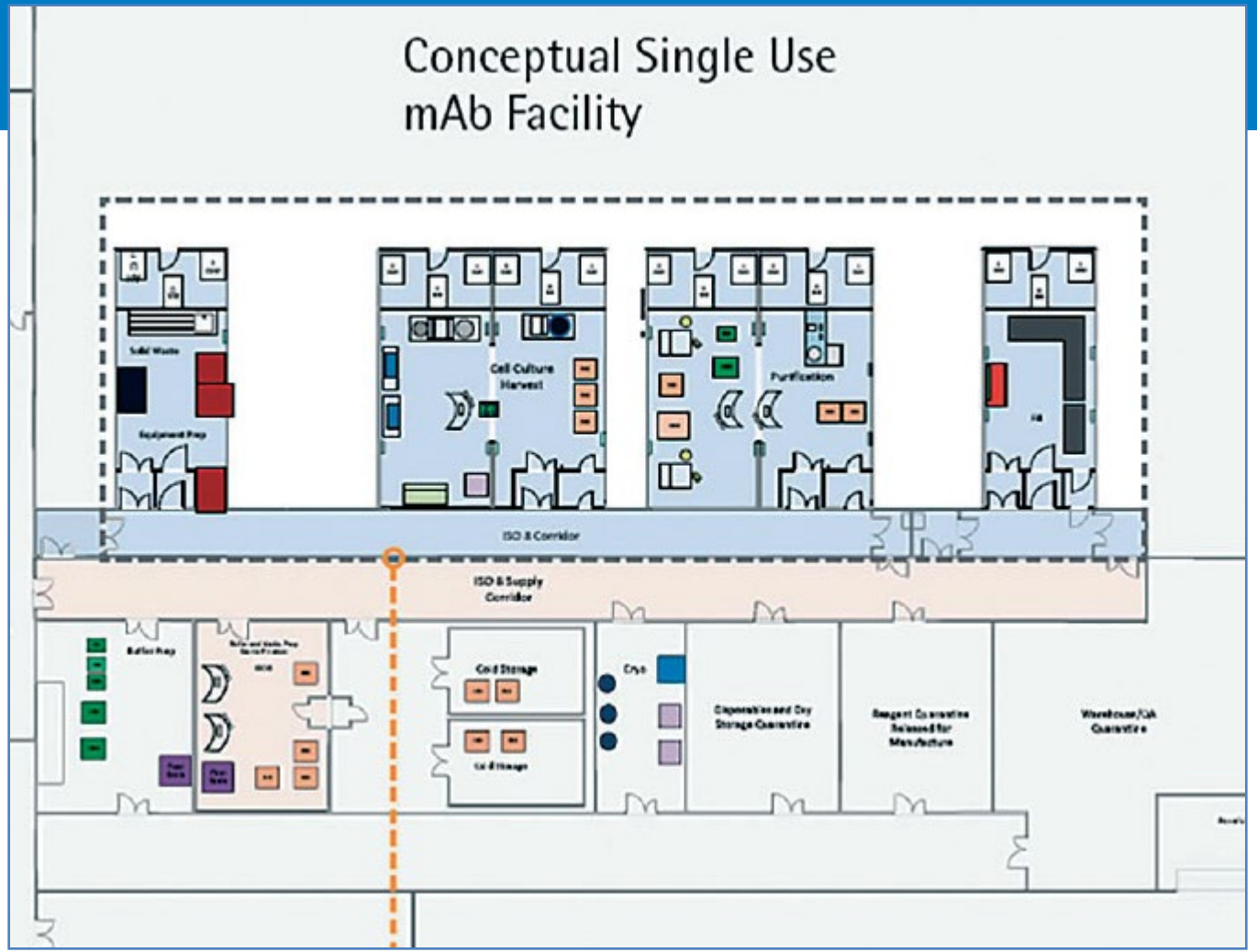
- *Load Analysis*
- *Air flow simulations*

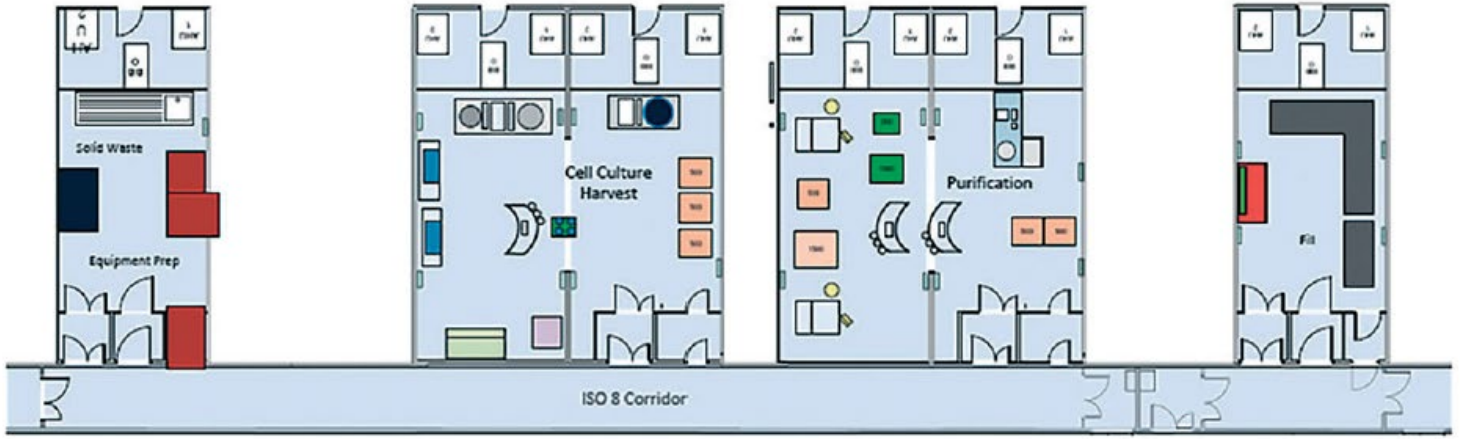


生物制药
一次性设施
的
规划 与 建设


Single-use bags*
Bulk chemicals
n-X Supplier 1
Dual source?
Resin compounding
n-X Supplier 1
Dual source?
Tubing
Ports
Connectors
Sensors
Filters
Film manufacturer
Distributors, competitors, innovators
Single-use supplier/integrator
Sterilization
Warehouse/ shipment
Drug manufacturer
Feedback
• Regulatory pressures
• Costly revalidation
• Risk reduction/transparency
• Patient safety

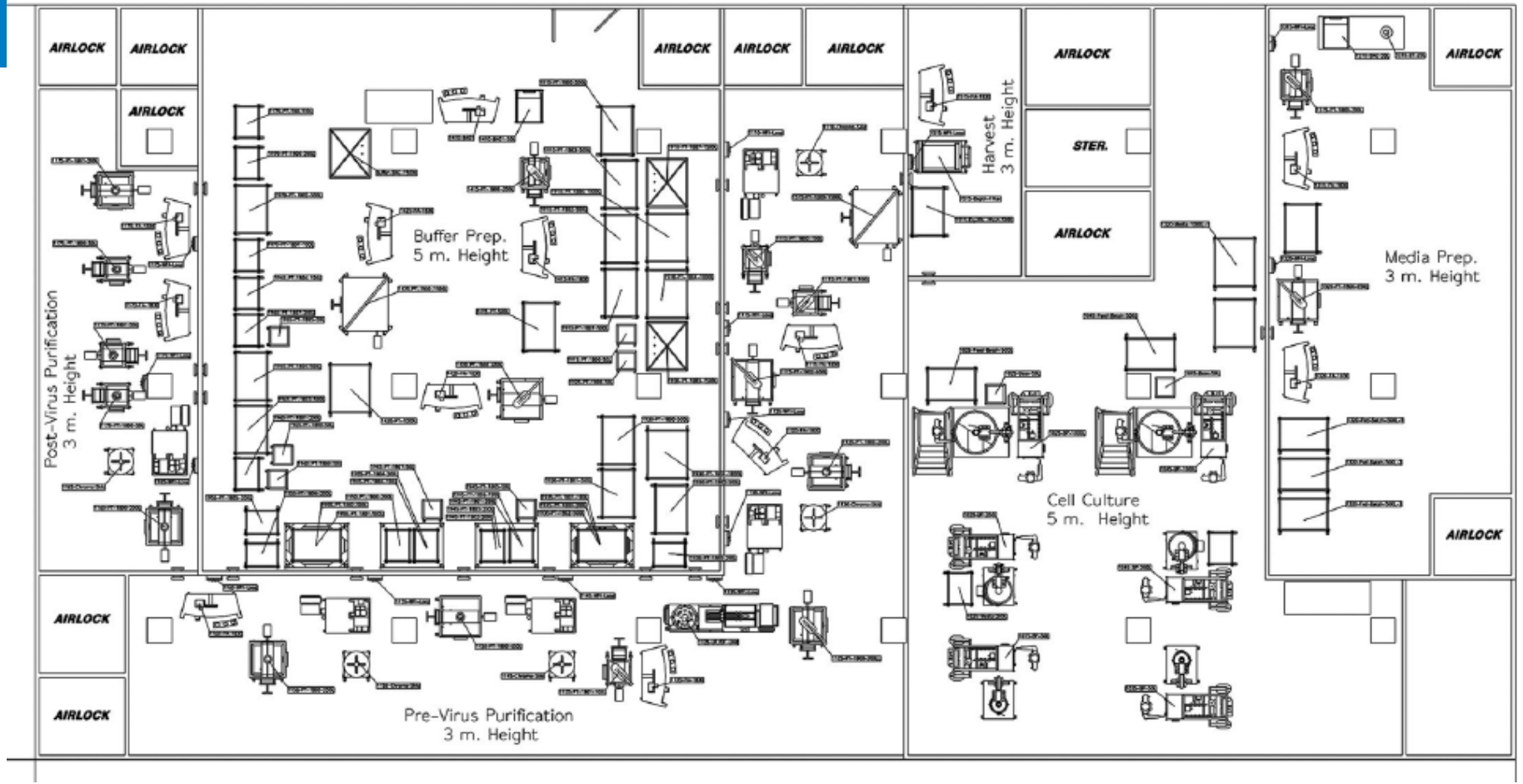
Conceptual Single Use mAb Facility





Legend

	-Drum		Pass Through		Equipment Washer		1000 L STR Bioreactor
	LAF		Bench		10 Liter CultiBag		50 | 200 L Twin STR
	Biological Safety Cabinet		4 C Storage		500 Liter Palletank Storage		UF
	Chromatography Skid		-70 C Storage		FlexAct®		
	Liquid Nitrogen Dewar		Autoclave		Palletank Mix		


AIRLOCK
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STER.
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AIRLOCK
AIRLOCK
Buffer Prep.
5 m. Height
Harvest
3 m. Height
Media Prep.
3 m. Height
Post-Virus Purification
3 m. Height
Cell Culture
5 m. Height
Pre-Virus Purification
3 m. Height

Upstream

- 100% single use bioreactors
- 250L - 2000L Fed Batch
- 50L - 500L XD®
- 50L - 250L perfusion
- Separate media prep suite
- Annual output up to 500 kg

生物制药 设施 的 一次性平台 实例

Downstream

- Single use, multi use
- Column and membrane chromatography
- Depth, Dead-End, TFF, micro and nano-filtration
- Output up to 10 kg per batch
- Clarification and/or RHOBUST®

Thaw
(Equilibrate)

Pool &
Compound

Bioburden
Reduction
Filter

Hold

Dual Sterile
Filter

Fill

Lyo
(if needed)

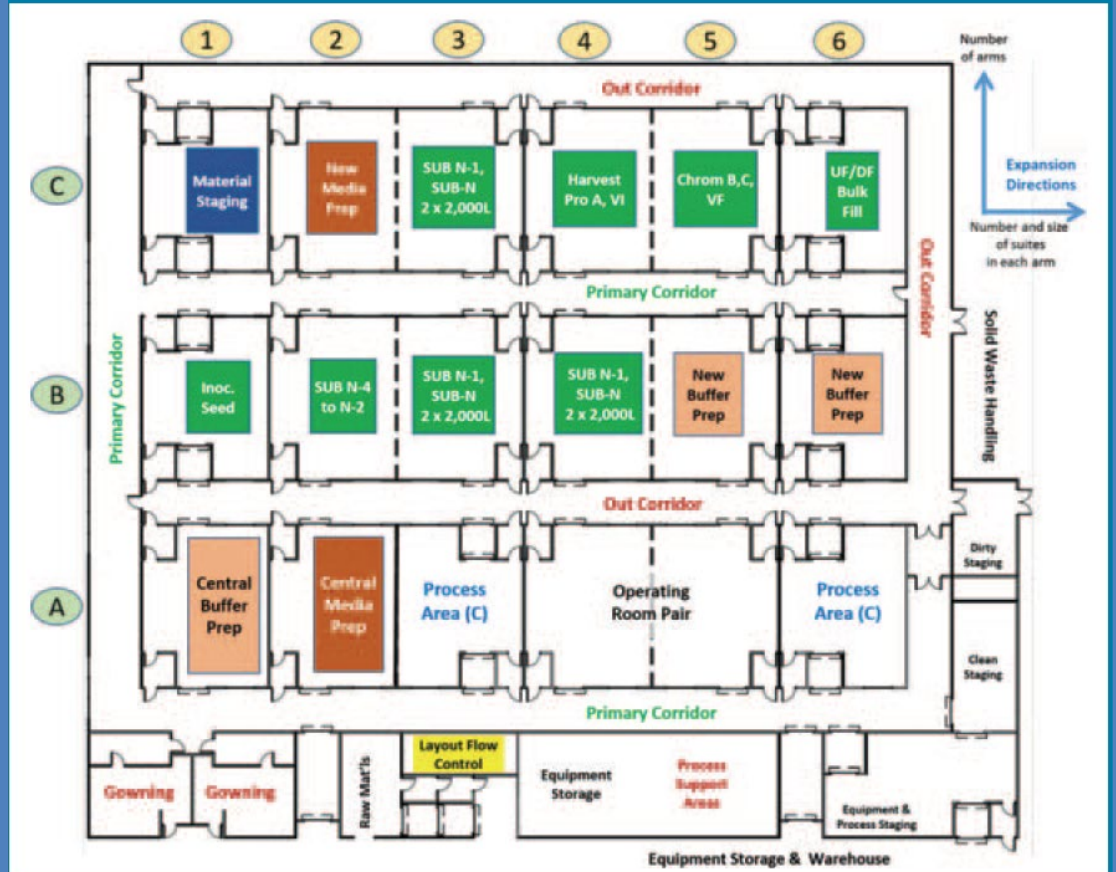
Cap

Inspect

Generalized Drug Product Process (with Lyophilization)

Development Activity								
Freeze / Thaw Studies	Pooling Stress & Mixing Studies	Filter Sizing Studies	Hold Time Support, Material Compatibility & Process E/L	Filter Sizing, Design Space, Flush Studies & Validation	Pump, Fill Vol Ppk, Density, Needle selection, VHP Evaluation & Drying Studies	Cycle Development & Robustness	Capping Pressure & CCI Method Validation	Defect Library Support

One possible logical operating unit (LOU) arrangement for the large-scale, 6 x 2000-L monoclonal antibody (mAb) process. Support LOUs are added as needed.



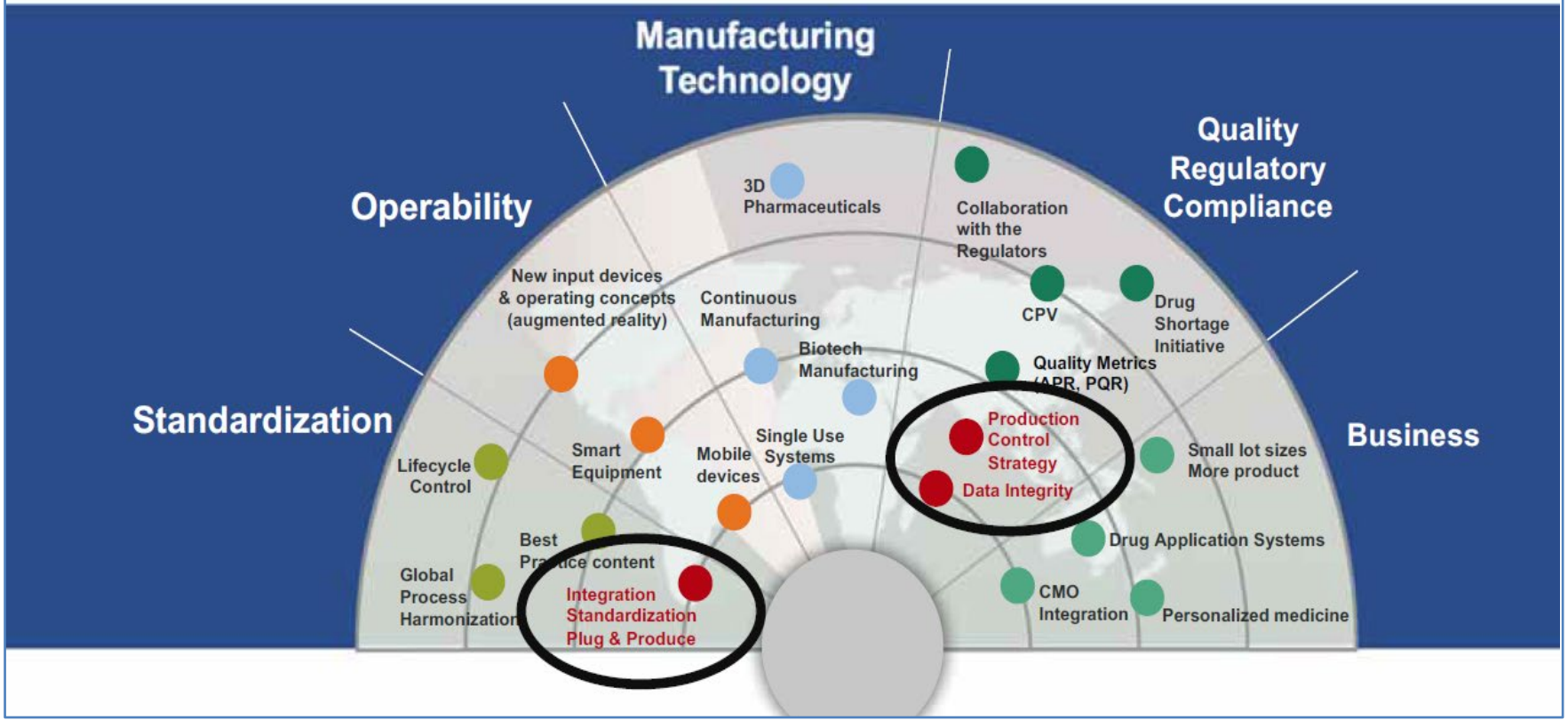
Multi-Purpose

Bio-MFG Facilities

provide the process and capacity flexibility

生物制药设施 的作业 及 监控系统

Smart Factory 智能化的生物药厂
Production Control Strategy - Pharma 4.0 Trend Radar



生物制药行业 的 智能化工厂
Bio FoF: Facility of Future for Biomanufacturing

生物制药智能工厂 要实现的 八大关键技术：

包括1）企业物联网；2）生产设备智能化、工作站化；3）机器人技术、智能传感器技术的应用；4）符合制药行业特点，满足GMP要求的智能化管理系统；5）大数据技术、云计算技术应用；6）互联网与智能工厂的融合；7）数据安全；8）生物制药智能工厂的标准化。

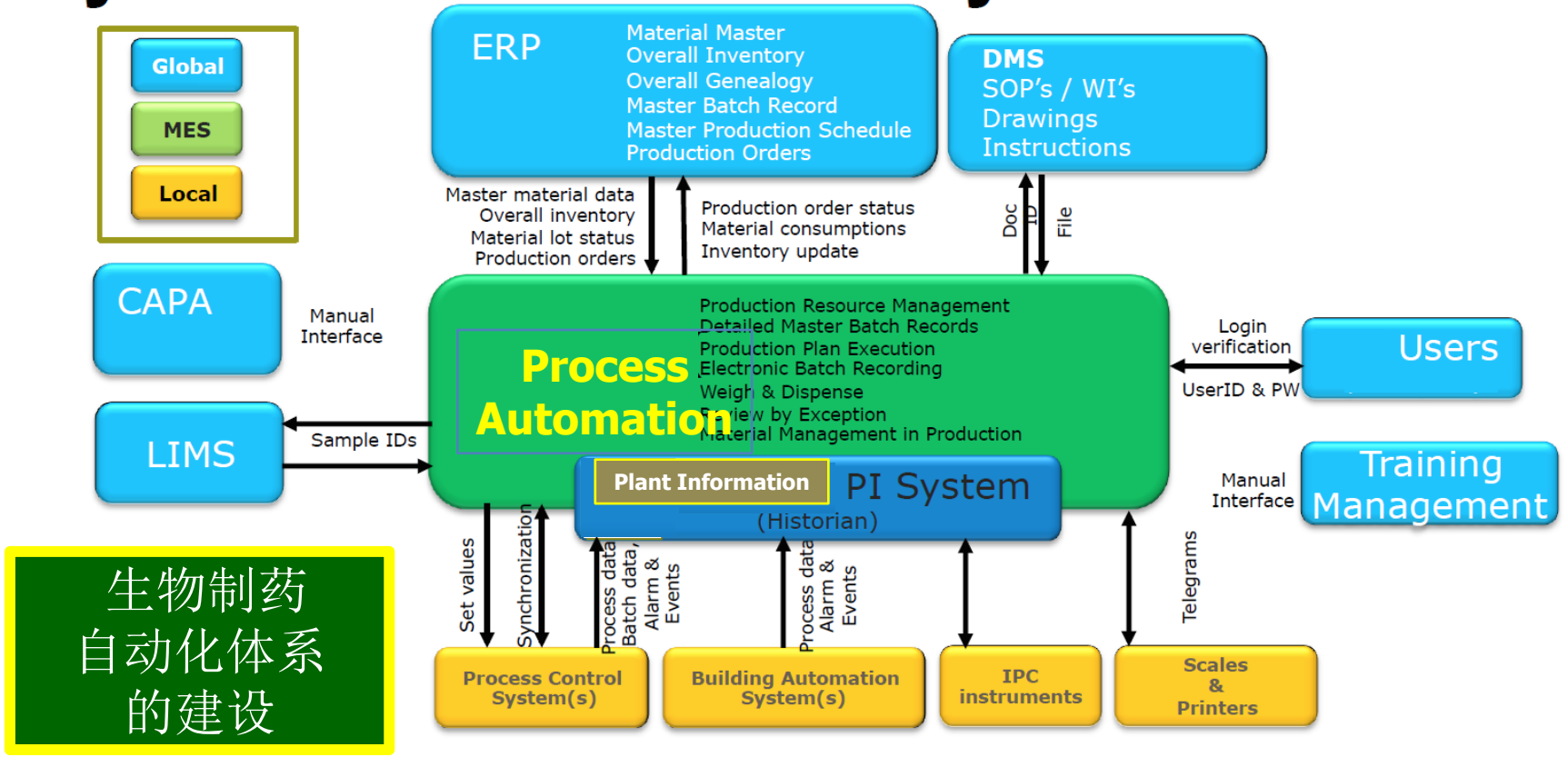
生产工艺：从产品开发上讲，产品设计决定了生产工艺，而生产工艺决定了生产设备。一些医药企业通常只关注到设备或软件，而往往忽视了工艺，更不会去在意设计以及概念。一套体系化的产品设计理念和产品开发平台，才是生物制药企业成功实现《工业4.0》转型的最基本前提。

生物制药
的
精益生产

Integrated Bio MFG toward OPEX: Operational Excellence at an FoF: Facility of Future

The Best Success Factor for Bio MFG

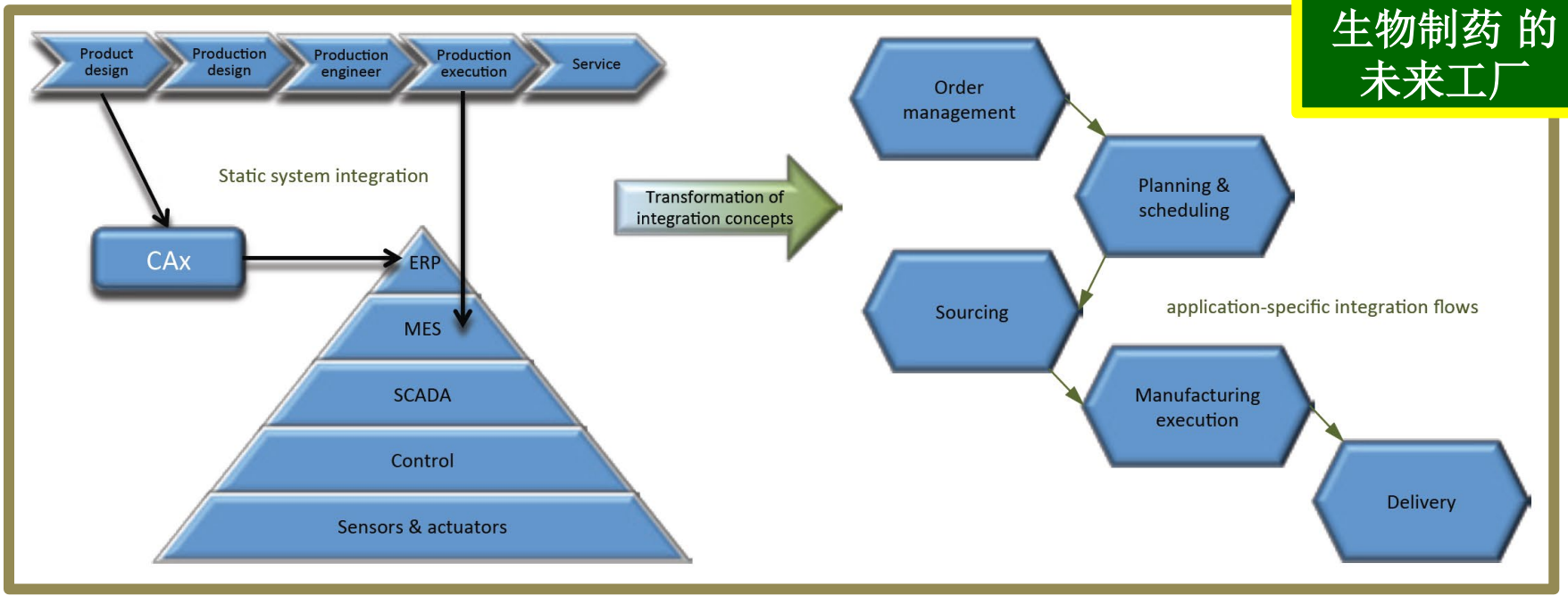
System Architecture – System Overview



生物制药
自动化体系
的建设

Smart FoF: Requires Systems Integration

智能化
生物制药 的
未来工厂




ANTIBODY

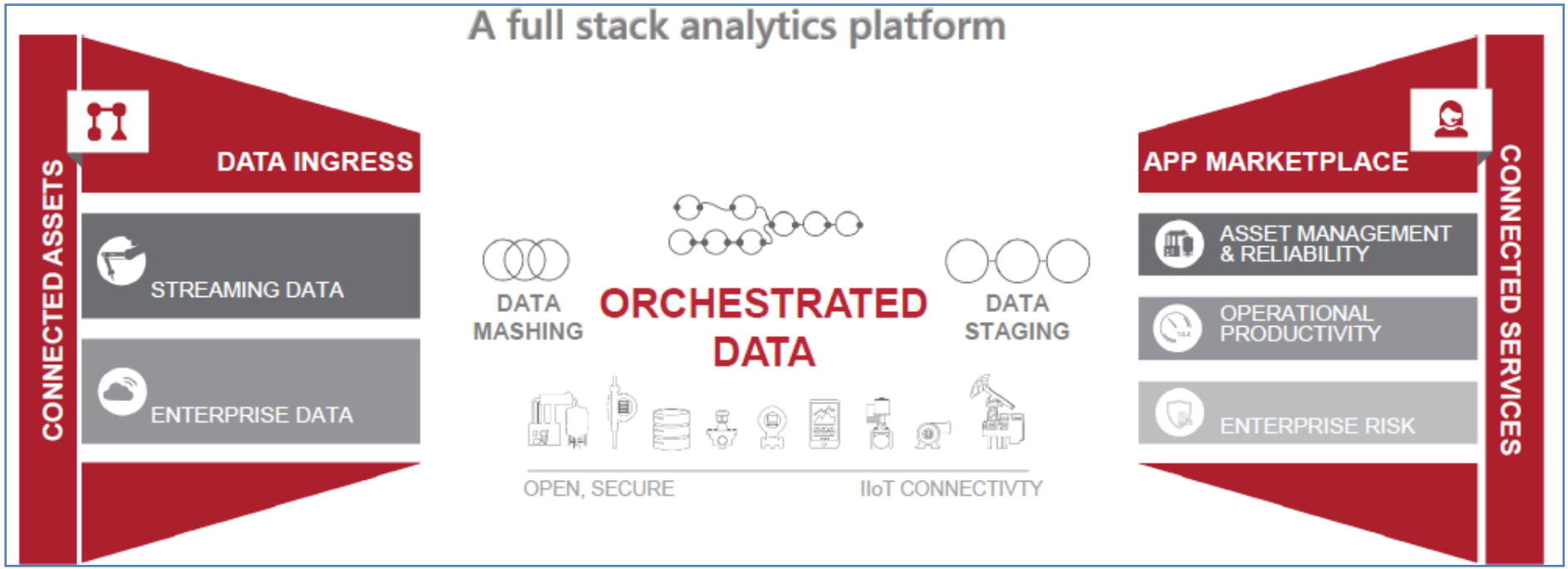
智能化 的 未来工厂 AI FoF

Next Generation of Biologics Manufacturing Facility

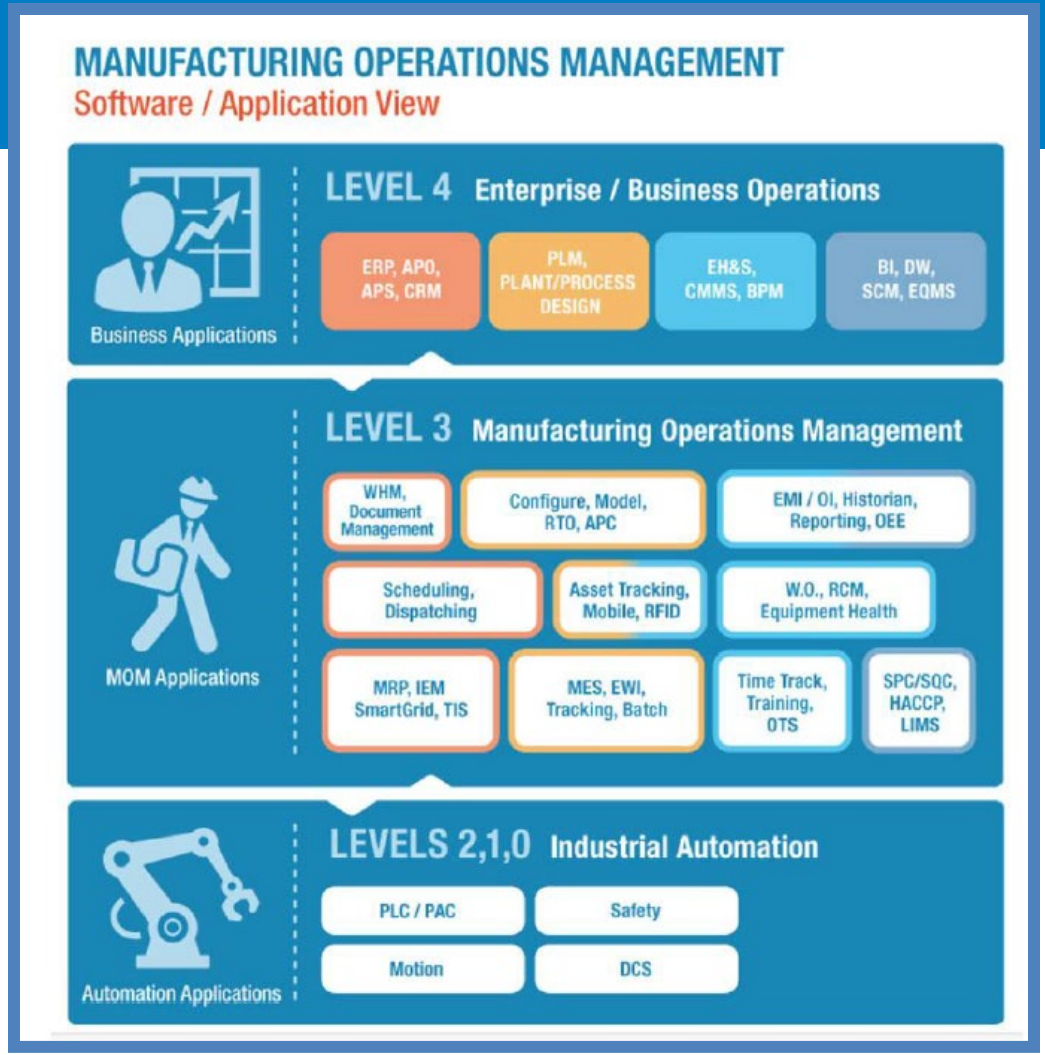
1. 数字化转型 将改变 生物制药
Digital Transformation is Revolutionizing Bio-Manufacturing

2. 生物药品的连续化生产
Continuous Processing for Biologics
IMPROVING PROCESS INTENSIFICATION AND CONTROL

to a data driven organisation



Current State	Future State
Manual Data Gathering	Data collection and transformation into control charts and process
Data Reaction	Data Prediction
Alarm Reaction	Early Warning Signal Culture
Pass/fail criteria for measurements	Trending/SPC for monitored measurements to indicate potential issues/trends



The technology storm is developing

Industry 1.0

Mechanical production equipment, steam and water power

Industry 2.0

Electricity, mass production, assembly line

Industry 3.0

Computers and automated production

Industry 4.0

Cyber-physical systems

智能化 AI Keywords 关键字

智能化，改变文化，并改善 绩效

强大，可扩展 和 安全 的 平台

数字化 的 定义：将某些东西 从 模拟形式 转换为数字形式，而不对流程本身进行任何更改的过程。

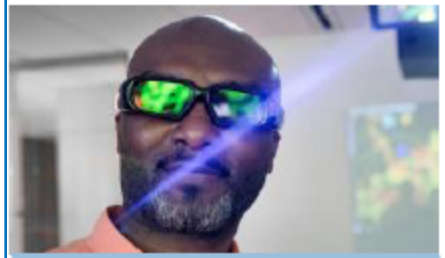
数字化 的 价值

通过从 传统纸张 转向 数字数据，我们可以开始设计 自动化 和 简化业务流程 的解决方案。

数字化 为企业更快速地 跨多个系统访问和利用数据奠定了基础。但是，没有数据的数字化，就不可能进行 业务流程数字化 或 企业运营 数字化的转换。

数字化 的 转换

Advancing an enterprise-wide Digital Transformation

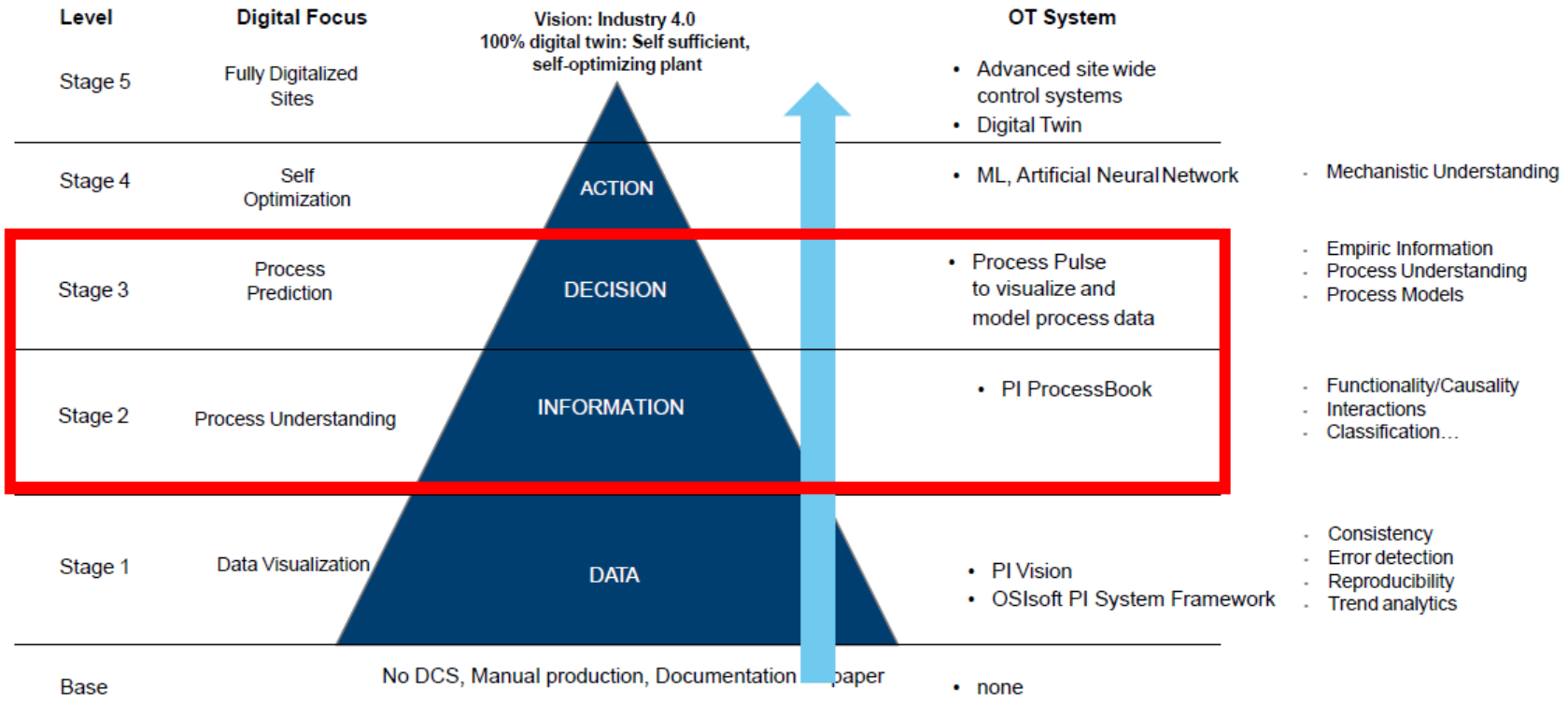


Data & Digital Leadership

- Scale top 5 digital initiatives across the company
- Upskill digital capabilities in all units and functions

Operations Digitalization Pyramid

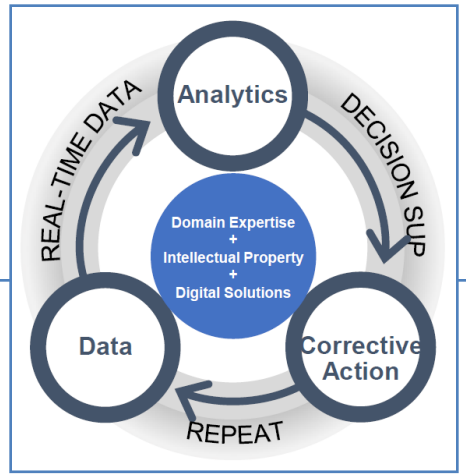
Following a Maturity Level Approach



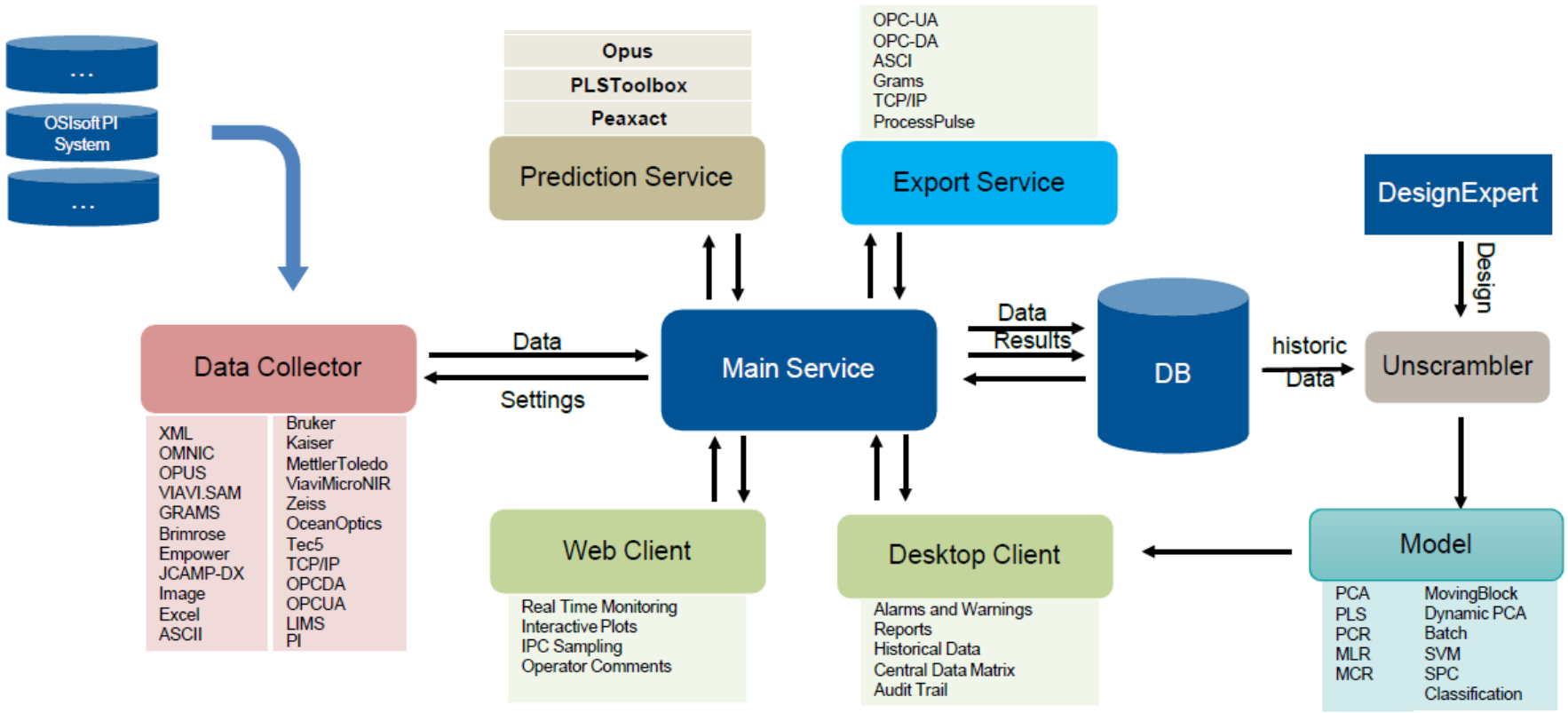
Road Map 项目计划

Evaluation	Aim/Specifications Strategy	Project Organization Realization	Development	Implementation

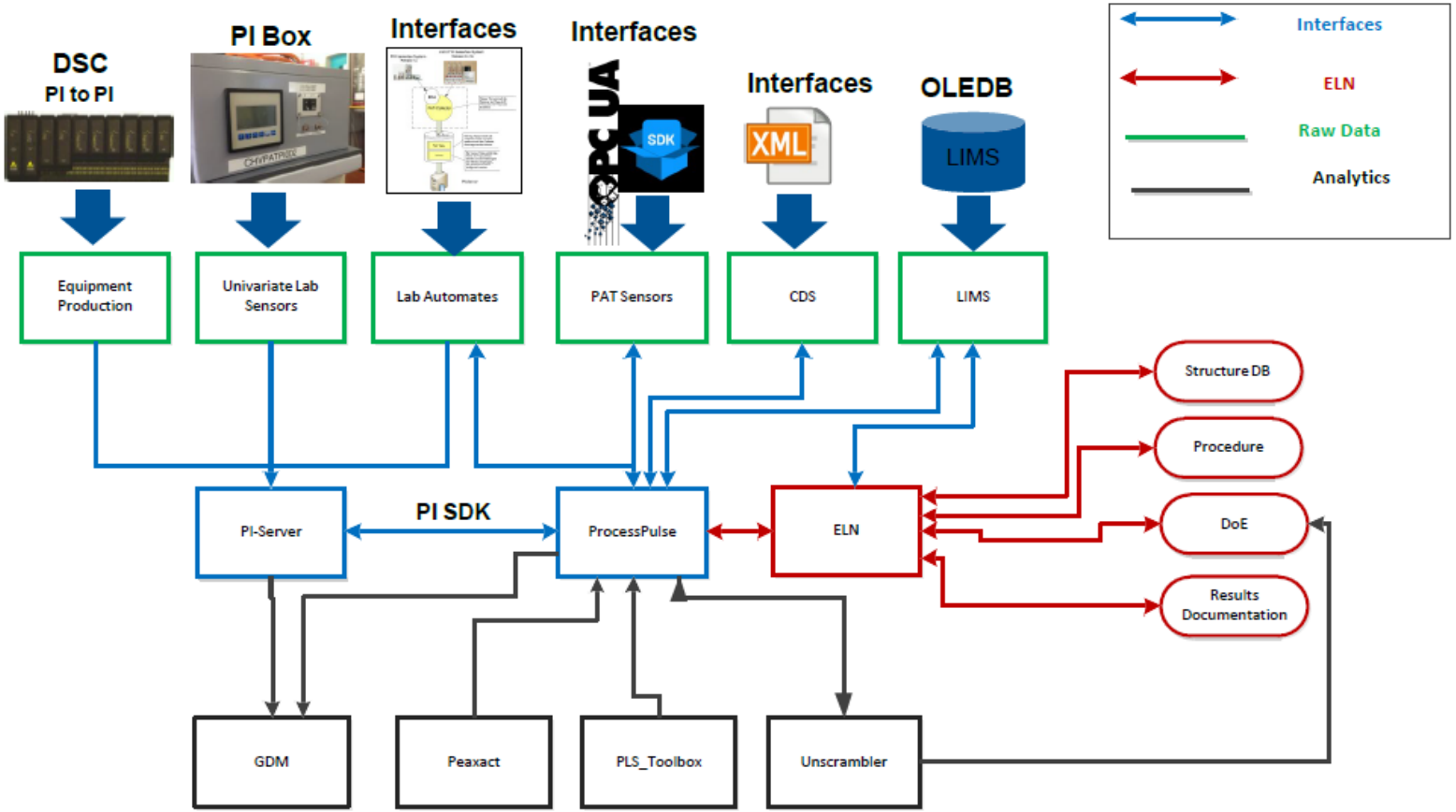
▪ Needs
▪ Requirements
▪ Costs/benefits
▪ Risks
▪ Market screening
  ▪ SIPAT
  ▪ SynTQ
  ▪ xPAT
  ▪ PP
	▪ Aim definition
	▪ Specifications
	▪ Feasibility
	▪ Alternatives
	▪ Concept
	▪ Project layout
	▪ Risk analysis
		▪ Budget
		▪ Business Case
		▪ Realization plan
		▪ Time line
			▪ Project team
			▪ Interfaces to ELN
			▪ Concept for LA
				▪ Pilots
				▪ PAT Group
				▪ Fermentation Group



Concept of Process Pulse



Development of Interfaces



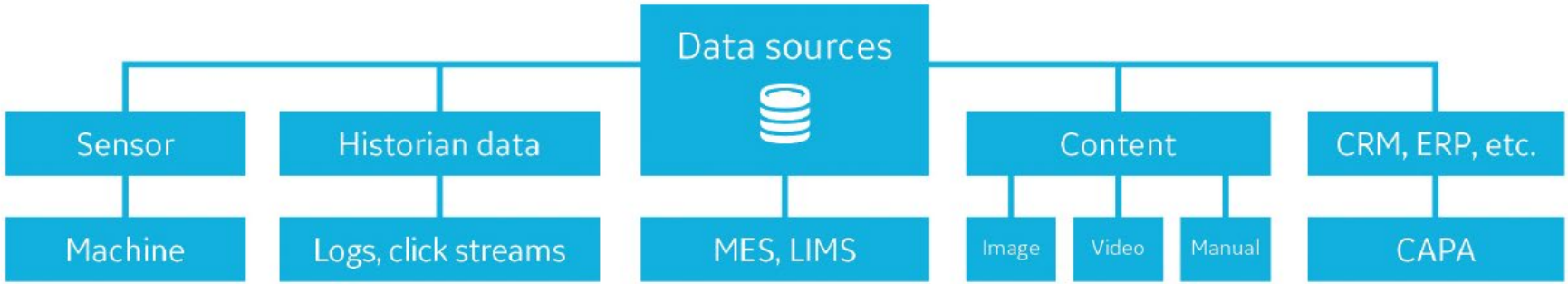
Targeted business applications

Engineering

Manufacturing science

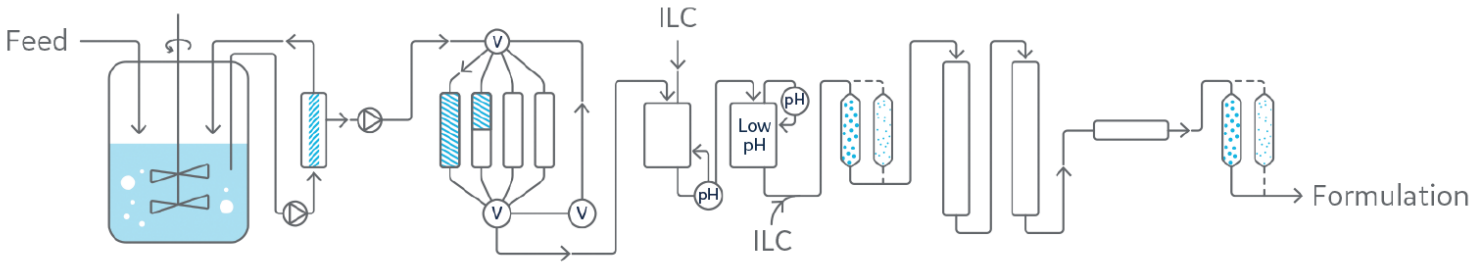
QA/RA

Business
Management and commercial



Next Generation Manufacturing

Real-time process monitoring → • Signal detection • Batch prediction • Deviation detection → **Batch-to-batch and multivariate data analysis**



TFF: tangential flow filtration; HF: hollow fiber; 4C PCC: 4-column periodic counter current chromatography
End-to-end upstream and downstream continuous processing

Parameter	Method
Structural characterisation	
Primary structure	RP-HPLC-UV based peptide mapping LC/MS based peptide mapping LC/ESI-MS/MS based sequencing Amino acid analysis
Secondary structure	CD spectroscopy
Tertiary structure	FL spectroscopy NMR spectroscopy
Disulphide bridges	LC/ESI-HRMS
Free thiol groups	Colorimetric assay (FL)
Intact molecular weight	LC/ESI-HRMS
Glycosylation site mapping	LC/ESI-MS/MS
Glycosylation pattern	HILIC-UHPLC-FL
Monosaccharide composition analysis	RP-HPLC-FL
Thermodynamic stability	DSC
Identification tests for active substance	
Determination based on hydrophobicity	RP-HPLC UV detection
Determination based on size	Reducing/non-reducing chip-electrophoresis
Determination based on charge	Capillary isoelectric focusing
Purity	
Variants and impurities with different molecular weight	SEC-HPLC Reducing/non-reducing chip-electrophoresis
Aggregation	Dynamic light scattering
Variants with different charge	IEX-HPLC
Fab/Fc-related purity	IEX-HPLC
Assays	
Active substance content	RP-HPLC UV detection
Sialic acid content	RP-HPLC-FL

Safety, Efficacy Imperatives:

- Product Quality
- Excellence and Compliance

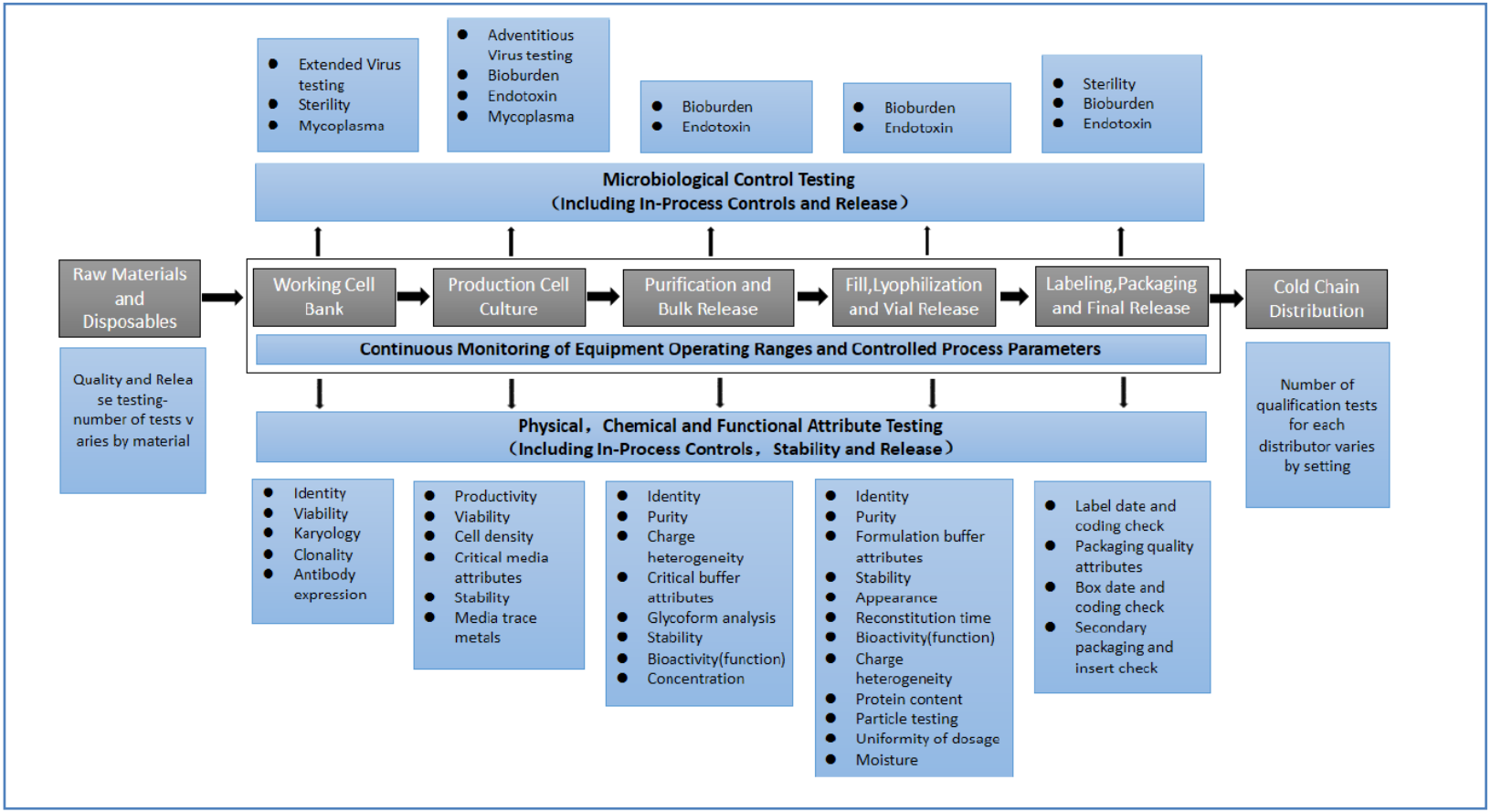
- Product
- Process
- Timeline
- Capacity
- Regulatory

	Parameter to be tested	In vitro assay (Method)
Binding to target antigen	Binding to CD20	CD20 binding assay (SPR)
Binding to representative isoforms of FcγR, FcRn and complement	Binding to all Fcγ receptors	CD16a binding assay (SPR)
	Binding to all Fcγ receptors	CD32a binding assay (SPR)
	Binding to all Fcγ receptors	CD64 binding assay (SPR)
	Binding to FcRn receptors	FcRn binding assay (SPR)
Fab-associated functions	Receptor activation	Apoptosis inducing property on CD20 expressing cells (Cytotoxicity assay)
Fc-associated functions	ADCC	ADCC effector assay on CD20 expressing cells (Calcein release assay)
	CDC	Complement-dependent cytotoxicity measurement (Viability assay)
	Complement activation	Complement activation assay (ELISA)

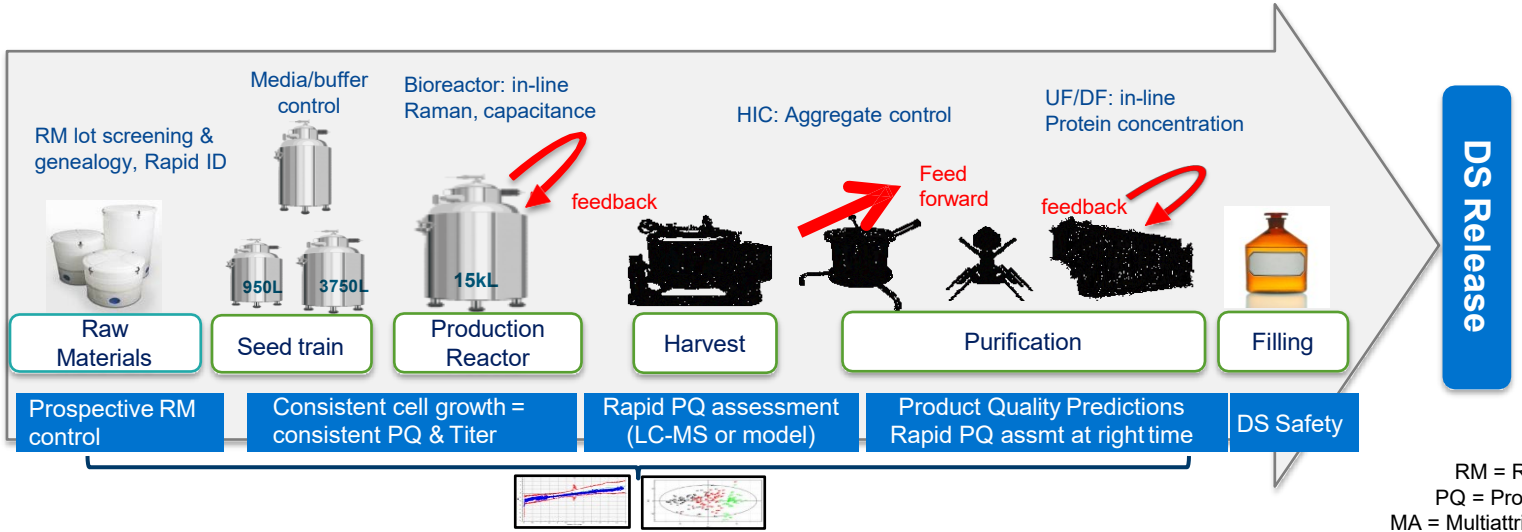
	Parameter to be tested	In vitro assay
Binding to representative isoforms of FcγR, FcRn and complement	Binding to all Fcγ receptors	Binding to FcγRIIb (CD32b) (SPR)
	Binding to all Fcγ receptors	Binding to FcγRIIIa (CD16a) high affinity (SPR)
	Binding to all Fcγ receptors	Binding to FcγRIIIb (CD16b) (SPR)
	Binding to complement[a]	C1q binding assay (ELISA)
Fab-associated functions	Receptor activation	Inhibition of cell proliferation through CD20 receptor (Viability assay)
Other	Cytokine release[a]	Release of IL-6, IL-8, IFNγ, TNF (Whole Blood Assay)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

全过程的质量监控
Control Of Quality Throughout The Manufacturing & Supply Process

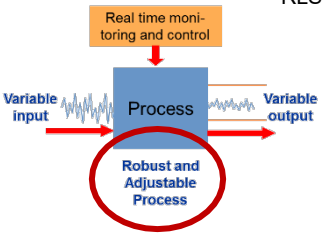


Delivering a Robust and Adjustable Process with Advanced Process Controls



Multivariate analysis for process monitoring and disposition decisions
Predictive model for product quality and/or feed forward control

RM = Raw material
PQ = Product Quality
MA = Multiattribute assay
DS = Drug substance
RLS = release



Foundation:

- Extensive understanding of raw materials, process, and product characterization
- A fully-integrated control system

Next Generation Drug Substance C of A

Current State		
Category	**What**	**Where**
General	pH	QC Lab
	Osmolality	
	Color (visual)	
	Turbidity (visual)	
Quantity	Protein Conc by RI	
Identity	ICIEF & Binding Assay	
Purity/Impurities	UPLC-SEC	
	Non-Reducing CE-SDS	
	Imaging Capillary IEF	
Biological Activity	Binding Assays	
Safety	Bioburden (plates)	
	Endotoxin (turbidimetric)	
	In-Vitro Adventitious Virus	

Future State		
Category	**What**	**Where**
General	Inline pH	In-line
	Inline Conductivity	
	Color by HunterLab	At-line
	Turbidity Meter	
Quantity	Protein Conc by SoloVPE	
Identity	Dot Blot ID	
Purity/Impurities	UPLC SEC	
Safety	Endotoxin by EndoSafe	
Purity/Impurities	LC/MS Peptide Map	High Tech Lab
Biological Activity	Binding w/ Automation	
Safety	Bioburden by GrowthDirect	
	NGS for Adventitious Virus	

Self-sufficient **right-time testing** and **exceptions-based review** for instant disposition

Next Generation Manufacturing is driving the evolution of the company

Current State:

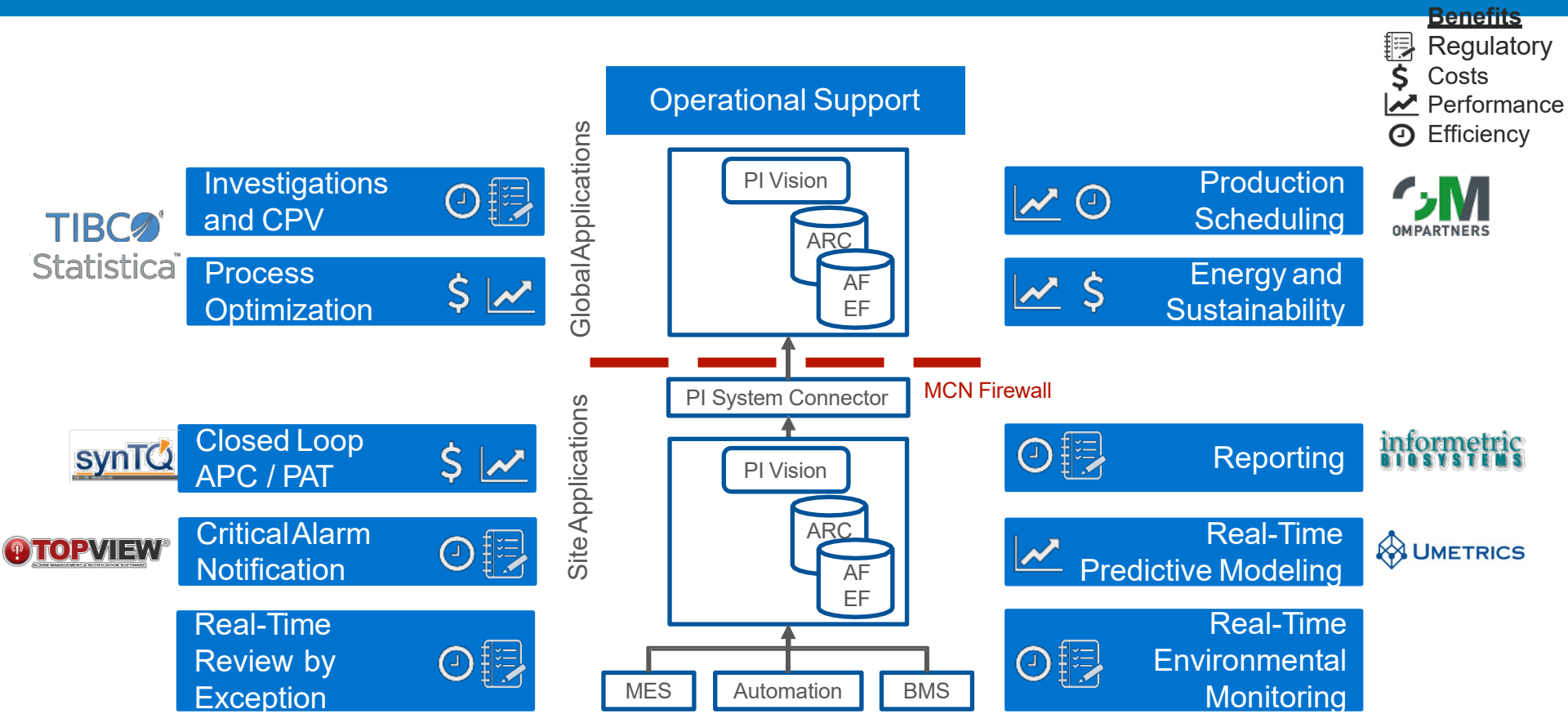
- Manufacturing relies on paper records and manual activities
- Records are reviewed in their entirety for batch release
- Test data and supporting documentation transcribed

Future State:

- Integrated systems make information available real time
- Batches are released by exception
- Transcription of data is eliminated
- Reduction in time required and error

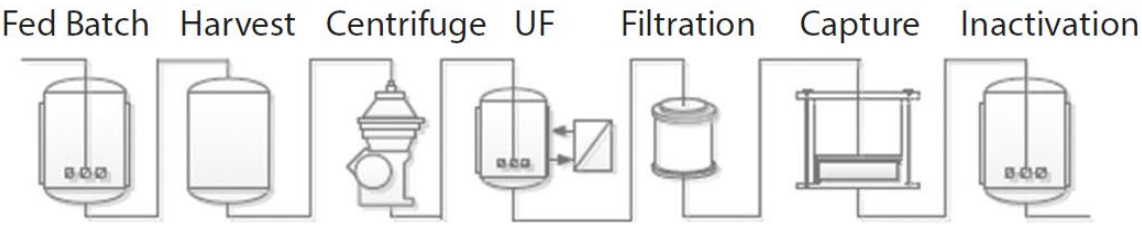
1. Eliminate Manual Activities
2. System to System Interfaces
3. Data Rich Environment

Capturing a single version of truth enables critical business processes

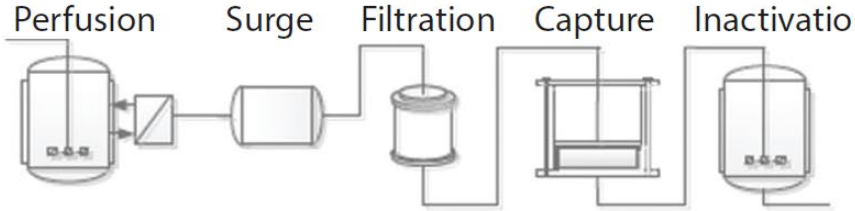


Process configuration options

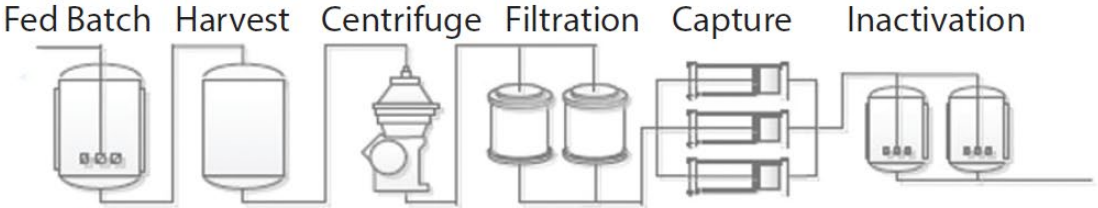
Fed Batch, DSP Batch



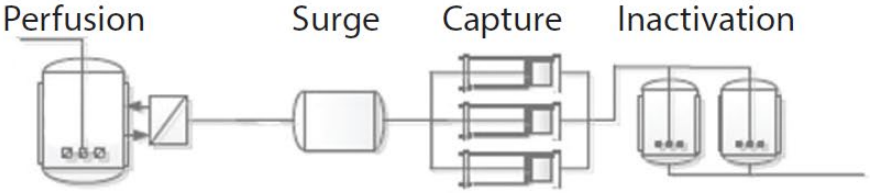
Perfusion, DSP Batch



Fed Batch, DSP Continuous



Perfusion, DSP Continuous



Next Generation

Monoclonal Antibody

Manufacturing: Delivering the Vision

MAB FoF: Next-Generation Facility

- Bio-Manufacturing Cells (BMC)
  - Initial: 2 BMCs, ~10 Metric Tons
  - Expandable to 35 Metric Tons
- 3X platform – up to 15 g/L CC titer
- 55,000 m^2 in Phase 1
- Integrated Execution Systems

BIOMANUFACTURING TECHNOLOGY

Enterprise system integration

- SAP
- CMMS
- Labeling

Data visualization and reporting

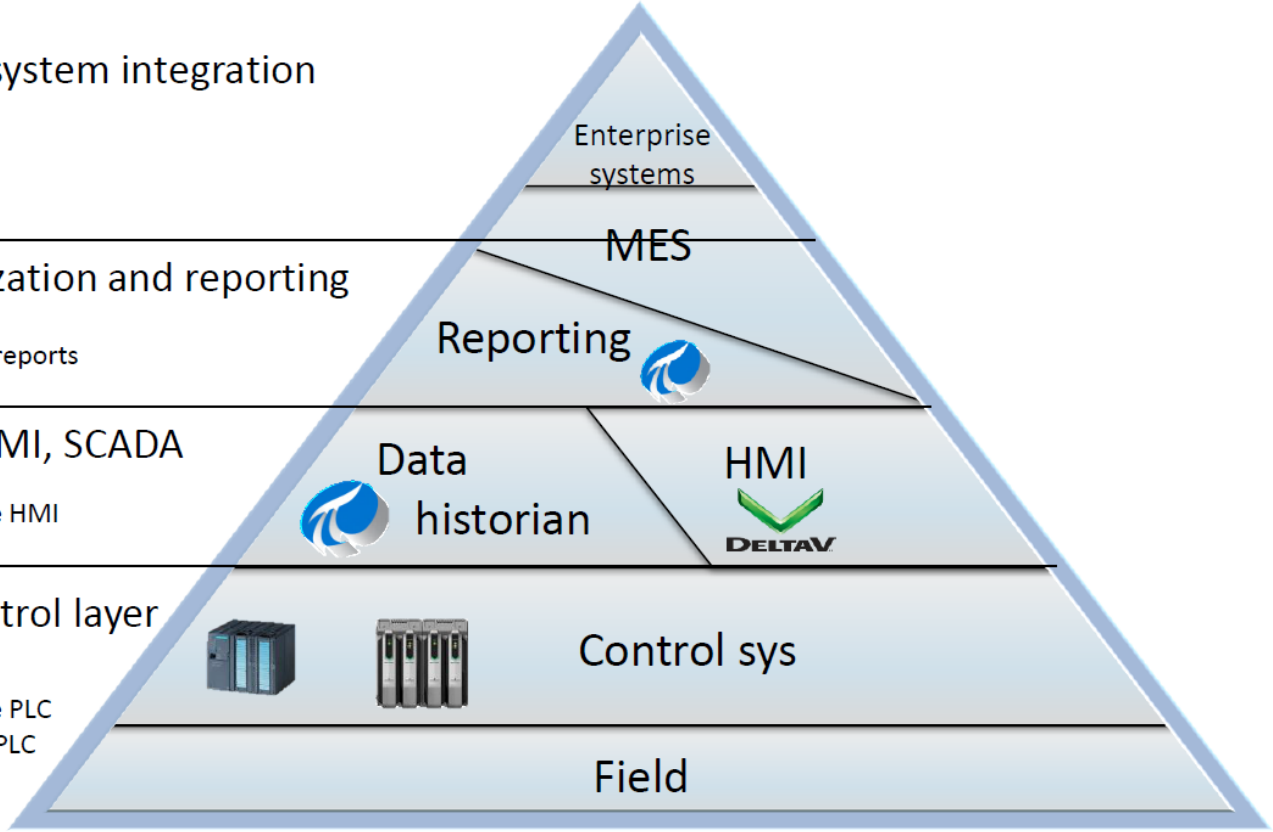
- RtReports
- Dedicated reports
- eBR

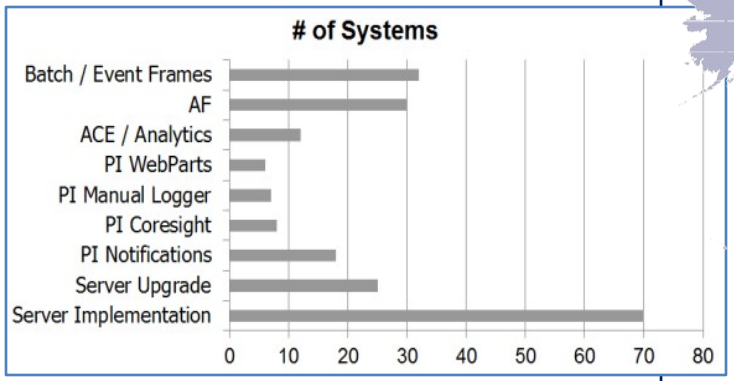
Historian, HMI, SCADA

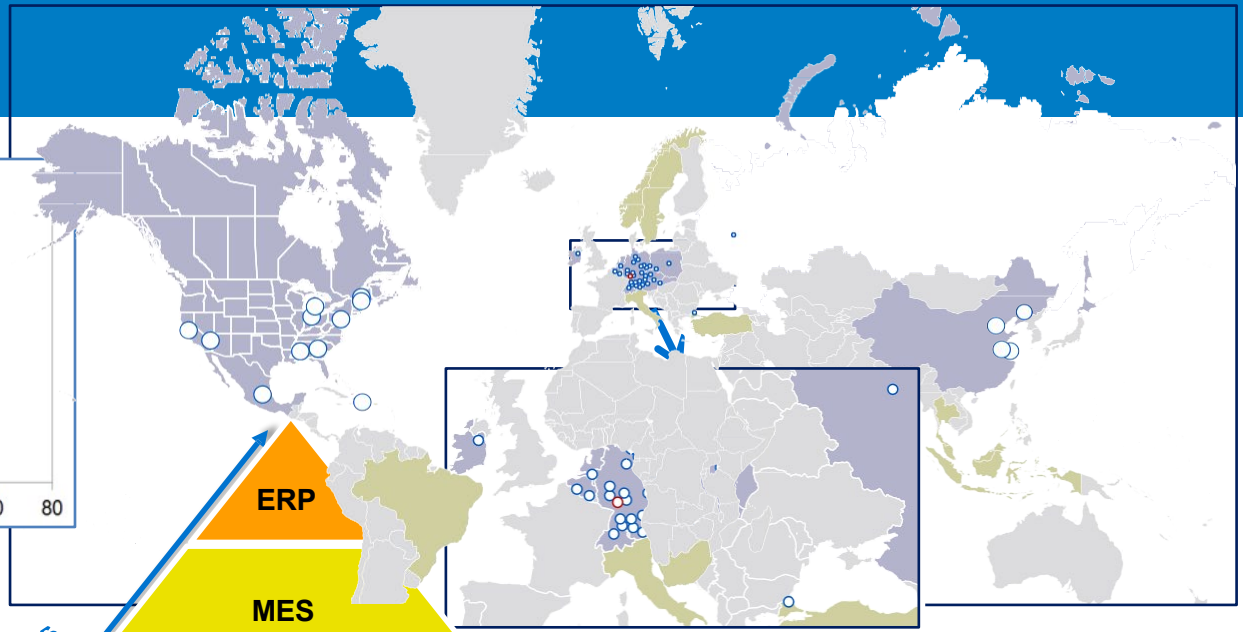
- DeltaV
- Stand alone HMI
- SCADA

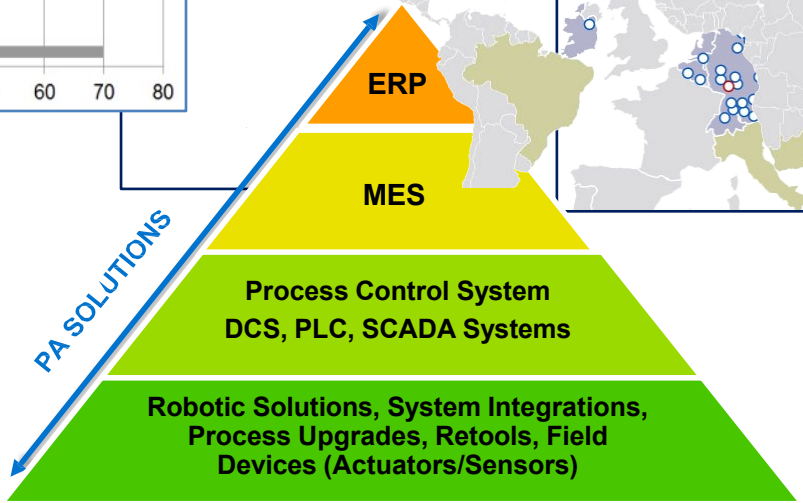
Process Control layer

- DeltaV
- Stand alone PLC
- Integrated PLC




# of Systems
Batch / Event Frames
AF
ACE / Analytics
PI WebParts
PI Manual Logger
PI Coresight
PI Notifications
Server Upgrade
Server Implementation
0
10
20
30
40
50
60
70
80

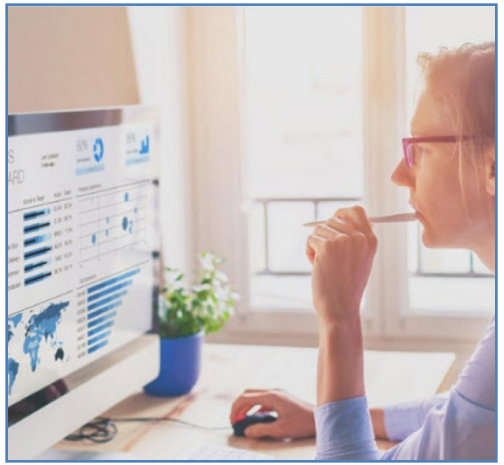



ERP
MES
Process Control System
DCS, PLC, SCADA Systems
Robotic Solutions, System Integrations,
Process Upgrades, Retools, Field
Devices (Actuators/Sensors)
PA SOLUTIONS

信息 洞察能力

大数据内的信息洞察能力，将是产业智能的未来。数据的战略使用，已成为各企业的致胜关键。采用支持数据\驱动决策的商业智能（BI）应用程序，已成为赢得数据战略的要素。

智能体系 也将为 生物制药业的提高生产效率提供助力。其标志之一是设备传感器和过程分析技术（PAT）收集的“大数据”。在生物制药工厂，传感器会产生大量的数据点。通过分析这些数据，可以发现 潜在的偏差 并迅速纠正。通过自适应过程控制策略 来提高产量，




NALYTICS
ASHBOARD
Last Updated:
3 min ago
92%
95%
Products positioning


+6.5%
78%
95%

Vision

Integrated Data Management

Continued Process Verification
- Automated Data Collect
- Multiple Sources/ One Solution
- CQA's
- CPP's

Efficiency
- Batch Reporting
- Automatic Data Capture
- Energy Monitoring
- Batch Cycle Time Analysis
- Lean Team Integration

One reliable source of integrated data, available anywhere, anytime, to anyone

Standardise | Enable | Implement

Globally
to add significant Business Value

Design to Value

Visualisation
- Real Time & Historical
- Standard Process Graphics
- Standard Energy & Utility Graphics
- Standard Asset Structure

Process Analytical Technology (PAT)

RELIABILITY

抗体药物 设施
的
工艺 验证

三阶段 的 工艺验证

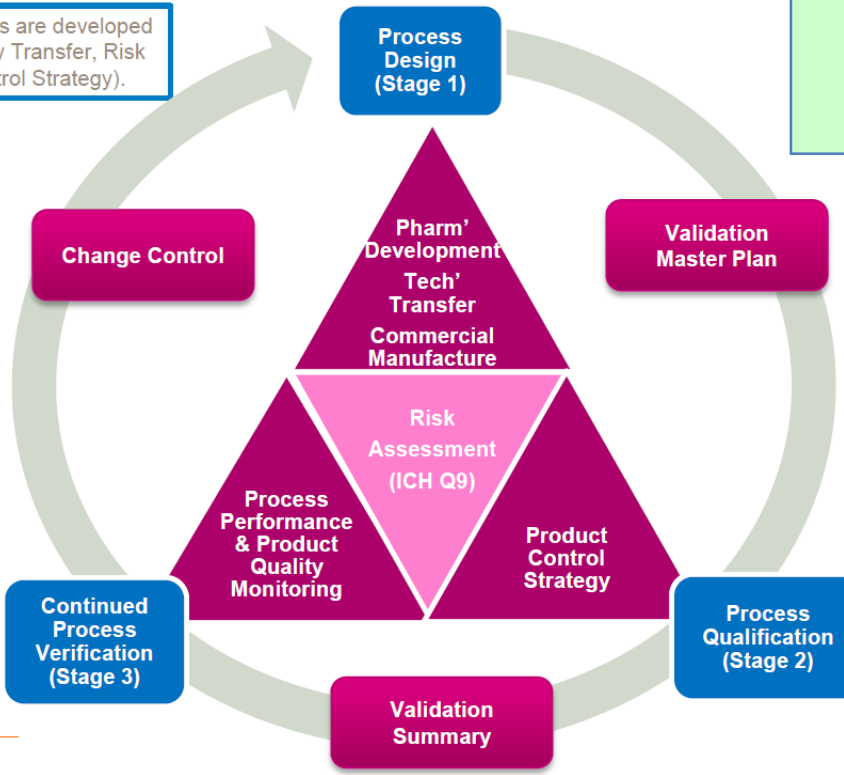
FDA current thinking on PV revolves around

- The concept of product lifecycle:
  - **Stage 1** – product and process development;
  - **Stage 2** – the manufacturing process qualification;
  - **Stage 3** – continued process verification
- Integrates the ICH Q8, Q9 and Q10 guidelines
- Ties PAT technology to process validation

Validation Lifecycle Approaches (ICH Q10)

以 生命周期 来管理 工艺验证

Stage 1 Process Design documents are developed (Development History, Technology Transfer, Risk Assessment, Draft Product Control Strategy).

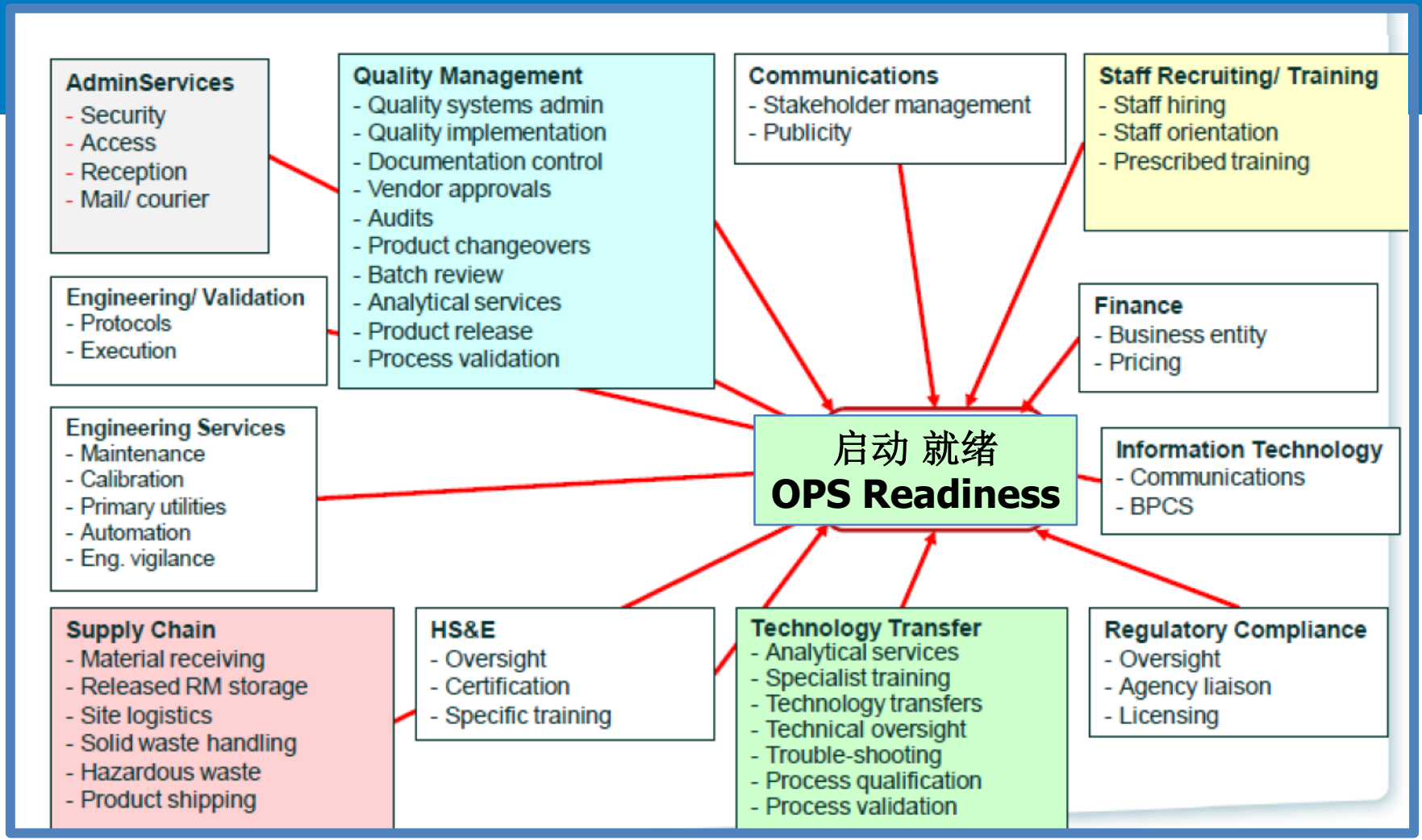


For Existing Products - Pragmatic Start with Stage 3 (Data Trending)

Stage 3 is used to capture changes, trend and demonstrate that the process is still operating in a state of control.

Stage 2 the Product Control Strategy is demonstrated to be fit for purpose.

抗体药物 设施
的
启动
Operational Readiness


AdminServices
- Security
- Access
- Reception
- Mail/ courier
Quality Management
- Quality systems admin
- Quality implementation
- Documentation control
- Vendor approvals
- Audits
- Product changeovers
- Batch review
- Analytical services
- Product release
- Process validation
Communications
- Stakeholder management
- Publicity
Staff Recruiting/ Training
- Staff hiring
- Staff orientation
- Prescribed training
Engineering/ Validation
- Protocols
- Execution
Finance
- Business entity
- Pricing
Engineering Services
- Maintenance
- Calibration
- Primary utilities
- Automation
- Eng. vigilance
启动 就绪
OPS Readiness
Information Technology
- Communications
- BPCS
Supply Chain
- Material receiving
- Released RM storage
- Site logistics
- Solid waste handling
- Hazardous waste
- Product shipping
HS&E
- Oversight
- Certification
- Specific training
Technology Transfer
- Analytical services
- Specialist training
- Technology transfers
- Technical oversight
- Trouble-shooting
- Process qualification
- Process validation
Regulatory Compliance
- Oversight
- Agency liaison
- Licensing

ONGOING BIOPHARMACEUTICAL TRENDS…

- More global biopharma facilities
- More biological products; often w/smaller markets
- More continuous processing, including downstream
- More multi-product facilities
- Modular facilities-new enabling technologies, re-purpose spaces
- More efficient bioprocessing – titers and yields continue to increase
- More high-tech expression systems and engineering advances
- More automation, monitoring and process control
- More bioprocess modeling
- More process automation
- More complex regulation

Bio-MFG


Current state
Future state
Monoclonal antibody focus
Range of modalities
Stainless steel fed-batch
Flexible and agile capacity
Conventional QC
Real-time release
Long lead times in supply chain
Responsive supply chain
Facility capital > $600 million
Facility capital ≥ 50 MUSD
Fixed cost focus
Variable cost focus
Separate upstream and downstream processing
Integrated process platform

Enablers for Bio Industry

Human Capital

World-class research standards

Next generation technologies

Close gaps in Innovation Cycle

Leadership framework

National priorities

Communication

Access global IP & knowledge pools

Ethical framework

Align regulations

Incentives and funding

THANK YOU!

谢 谢!

감사합니다 谢谢 Danke Merci Gracias Thank You ありがとう Спасибо Obrigado

CONTACT INFORMATION:

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