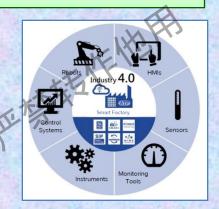
2020 (第十二届) 弗戈制药工程国际论坛

生物制药智能工厂的展望 The Outlook on

Al-MFG Facility of Biologics



李树德 Michael Lee 2020.09.20



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The opinions expressed in this presentation are my own and are not necessarily those of my employer.

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要赢得全球的商业竞争 敢问路在何方?

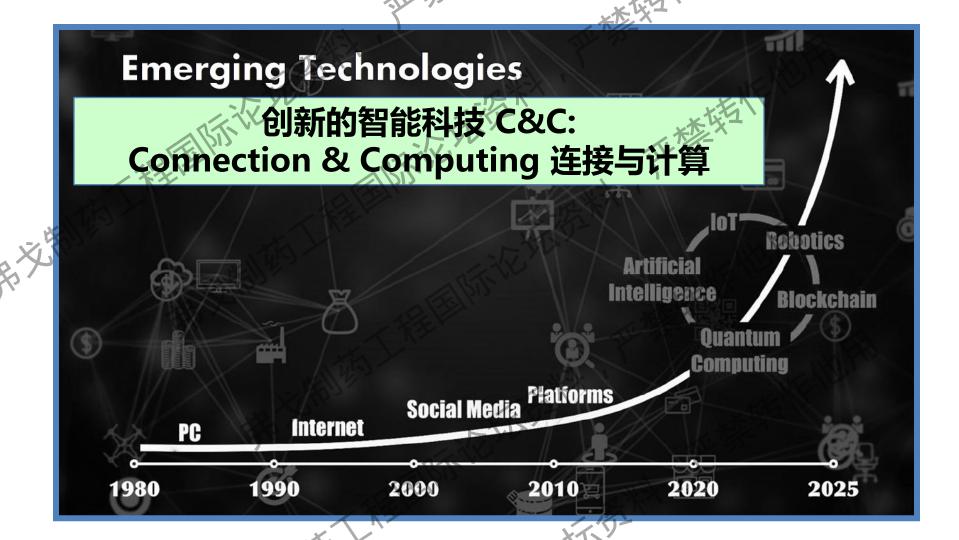


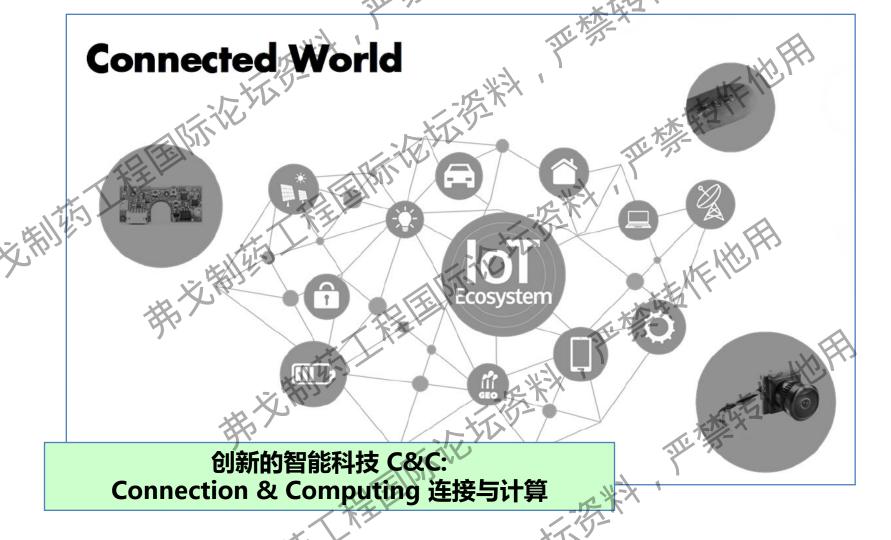
全球商业竞争的新规则 Changing Competitive Landscape

It is all about the data

- Merck smart factories
- Pfizer connected manufacturing
- Sanofi digital twins and AR
- Johnson & Johnson − Apple partner







物联网 影响了生物制药

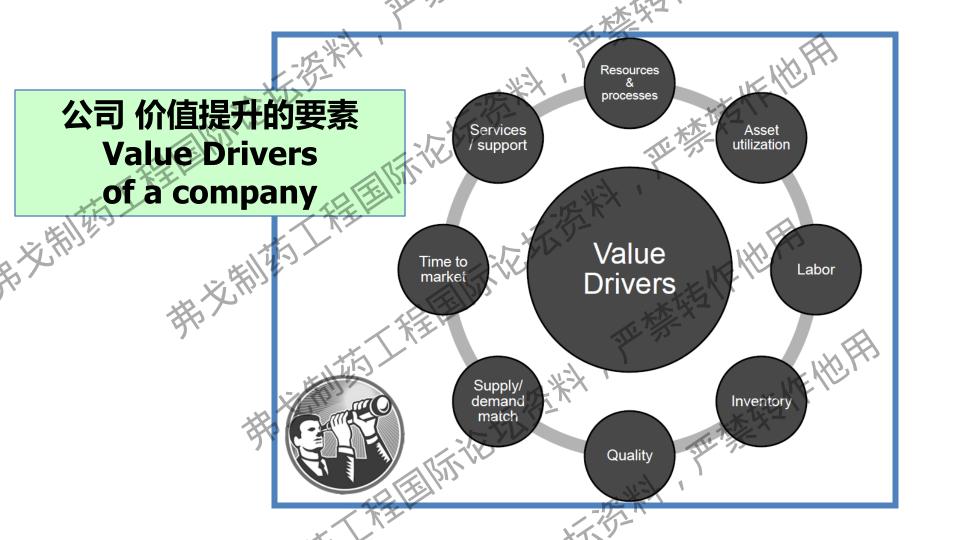
Is loT the Answer?

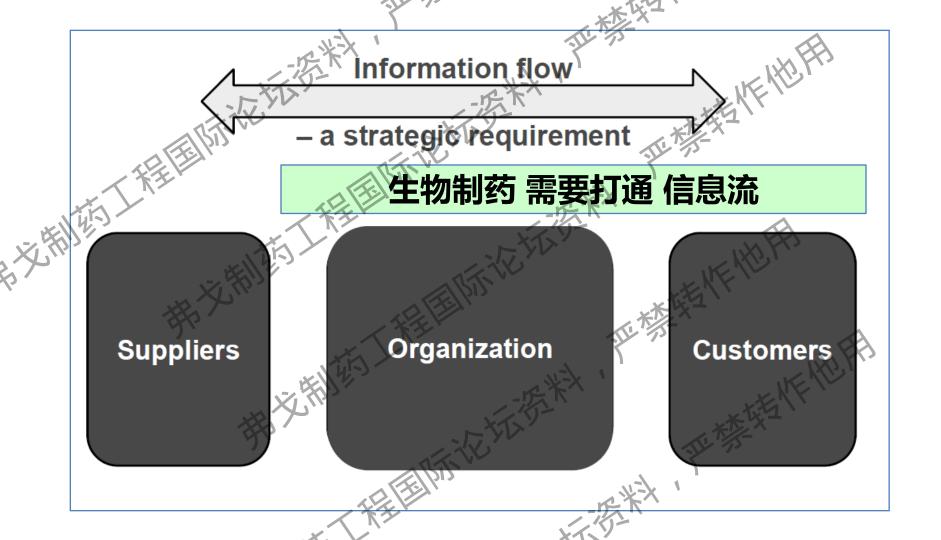
Emerging Biotech Demand

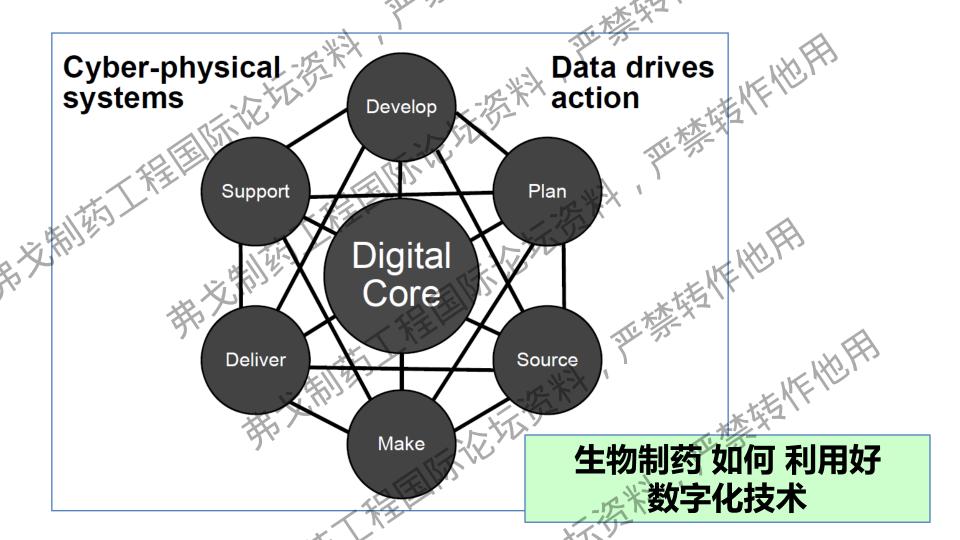
- Lower Costs
- Disposables consumables
- Reconfigurable shop floor
- Continuous Bioprocessing

loT Promise

- · Standardized, lower-cost technologies
- Auto-subscribing devices
- Smart eco-system with "location aware" devices
- Scalability from PD to Commercial







Data Itself Makes No Sense... We need INFORMATION!

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把数据 转化为 信息 把信息转化为 竞争力

Life during Industry 4.0

- Move production closer to customers
- Establish data standards for interoperability

General areas of focus in Bio-manufacturing: 公司运营管理 焦点 Large Bio-Pharma Company

- Asset Performance Optimization (APO) 资产效益
- Digital Performance Management (DPM) 数字化 绩效
- Integrated Quality & Real Time Release 质量管理 与实时放行
- Smart Factory 智能工厂
- Materials Science 材料科学



生物制药 未来的巨大变化 Bio-Pharma 4.0

BioPharma 4.0: the Next Bio-Industrial Revolution Bio-Manufacturing for **Operations Management,** Automation, Process Controls **Decision Making**

社会对行业的 期待 + 生产力的竞争

Market Trends & Business Drivers - The Why

Cost pressure

- Payer pressure
- Biosimilars
- Development

Uncertainty

- Regulatory approvals
- Demand variability
- Competition

Market Growth

- Emerging markets
- Global reach
- In region manufacture

New Product Classes

- Non-mAbs, ADCs
- Gene therapy
- Cell therapy

Cost

-90% manufacturing cost -90% CAPEX ____

Flexibility

-90% changeover Demand response

Speed

-70% build time -80% lead time

Quality

10x robustness -90% cost of quality

Biomanufacturing scenarios – *The What* (Facility types)

- 5. Small-scale <50L for Personalized Medicine
- 4. Small-scale <500L Portable Facility
- 3. Intermediate-scale Multi-product Single-use Fed Batch
- 2. Intermediate-scale Single-use Perfusion

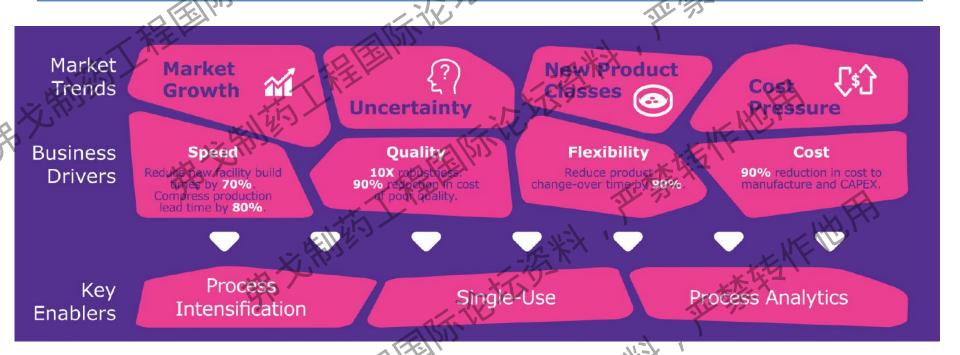
1. Large-scale Stainless Steel Fed Batch

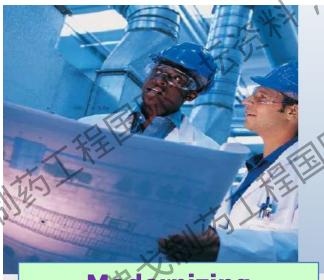
Drug Product High volume Drug Product

Distributed

Scale

FoF to Support Next-Generation's BioProcessing with a Multidisciplinary Pursuit





Modernizing FoF for Bio-MFG:

A Continuous

Effort

by

the

Industry

展藝術业的未来

Looking to the Future



BIOMANUFACTURING INNOVATION

FUTURE BIOMANUFACTURING









BIOHARMACEUTICALS

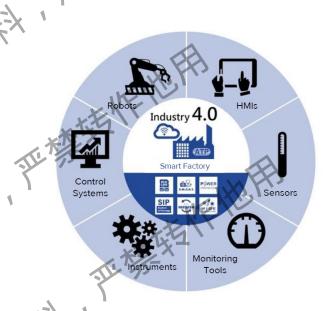
VALUE-ADDED MFG MATERIAL ENGINEERING MATERIAL
FOR FACILITIES

ADD INTEGRATED STRENGTHS IN BIOMANUFACTURING

21世纪的抗体药物新一代的生产设施

工艺技术需求的增加,对产品质量的确保,对环境的影响减小,生产成本(COG)的压力,以及生物制药行业的最新技术的发展(连续生产),极大地增加了新厂的设计、建造和工厂合规及有效运营的挑战。

21世纪,行业会不断地扩展,也对各种平台技术和系统有更多的需求。



数字化转型 Digital Transformation

在这个世界中,数字渠道成为主要的(有时在某些情况下,也是唯一的)系统整合模型,而自动化流程则成为生产力的主要驱动力,也是灵活、及时、透明和稳定的生产管理与供应链运行的基础。

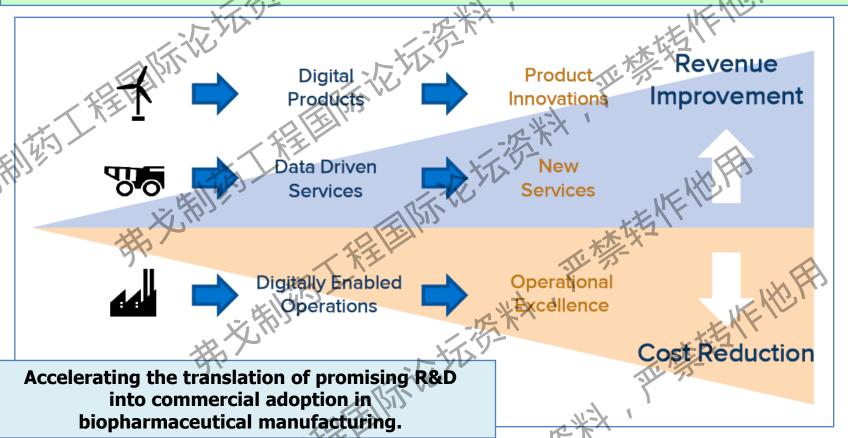
ICT: Information & communication technology (ICT)-enabled technologies

通信,计算,人工智能,和生产自动化方面的创新,都是使我们进入一个以前只能想象的世界。生物制药行业不能免于这种快速变化的步伐。这包括工艺和设施的设计与操作。当今最先进的生物制药工厂正在以前所未有的速度全面变化。从药物的开发到最终的制剂生产,未来的设施(FoF)在所有的这些领域中,都将拥有新的东西。

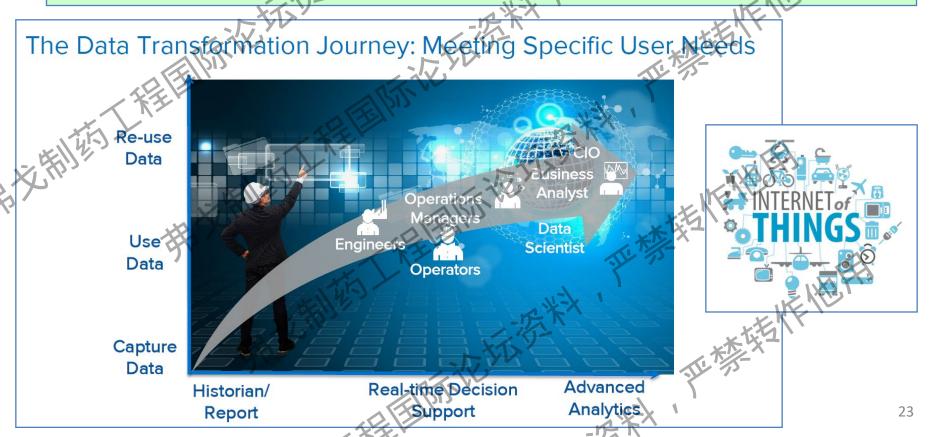
作为生物制药 4.0 (B4.0) 联盟,波士顿咨询集团 (BCG) 和爱尔兰 国家生物加工研究与培训学院 (NIBRT),在都柏林建立了 数码化运营创新中心 (ICO) Digital Innovation Center in Operations.



Digital Transformation 数字化 转换

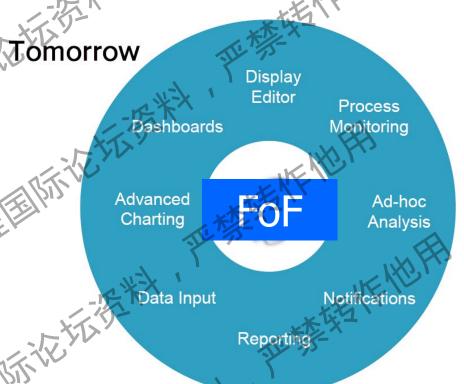


Digital Transformation 数字化 转换



信息的及时、可视化 (在FoF 未来工厂)





数字技术集成在整个站点中,包括企业资源计划系统ERP与电子生产记录MES, 过程控制系统PCS,数据库和实验室信息管理系统LIMS的集成。这个数字平台 简化了产品的制造MFG、检测QC和放行QA。它还支持强大的数据管理,以支持 开发活动和工艺表征。

公司的系统,可以管理:

- ●利用一次性设备和数字设备、跟踪生产情况,可以快速重新配置空间。
- 多个灵活的cGMP生产套间,用于制造: mRNA药物、 配制原料药、无菌药品、 个性 化癌症疫苗 (PCV)、 关键原材料,
- 原料发酵和缓冲液制备
- 包装,贴标签和存储西林瓶产品的空间
- 进出产品的温度控制仓库
- 品管实验室
- 规模化和毒理学生产的中试车间
- 研究级mRNA的生产空间
- 洁净公用系统,包括纯水和注射用水



FOF设施会越来越容易使用。它将可能是具有灵活设计的模块化设施,该设施利用某种形式的连续制造和封闭系统,来消除当前配置的高级别洁净室的必要性。_______

本地化的控制和自动化,将有可能被越来越开放的源代码集中控制的制造系统所取代。由于采用了实现这些目标的新方法,并且工艺变得更加连续,由于无菌保证和可清洁性技术的发展,将使得批次的失败变得越来越少。

未来的设施将利用物联网(IoT)来建立数字化发展。这将使生产过程中的人工干预最少。FOF将通过高度优化的一次性工艺流程实现更高的滴度生产,并提高产品产量。

通过生物制药工艺的开发和执行产生了大量的数据。预计随着制造商和制造商将新型传感器、智能材料、过程分析技术和过程自动化集成到实验室和制造工厂中,生物制造数据的数量和复杂性将成倍增长。数字化战略结合了包含AI、预测建模和可视化的结构化数据集成和分析平台,以及数字转换,来推动下一代的智能化生物制药。

FoF 智能化 解决方案

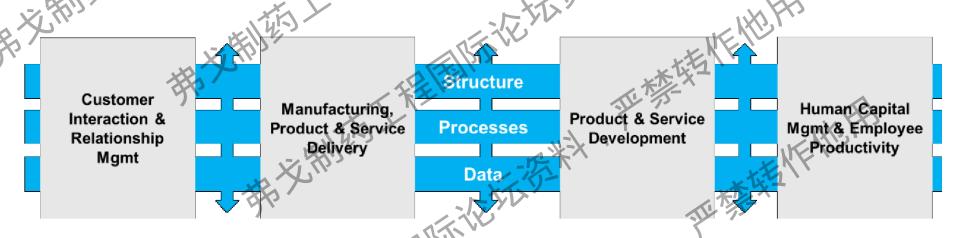
- 生物药品检测技术、工艺控制和监控、
- 与数字化转型相关的新技术,能给制药供应链带来重大变化。
- · 绝大多数的生物制药公司将主数据管理 (MDM) 列为供应链转型的 重要驱动因素。
- 数字化转型、将支持下一代工艺的开发和生物药品的制造
- 涵盖各个职能: Process Development, Analytical Method Development / QC, Tech Transfer/GMP Manufacturing, Regulatory Compliance, Outsourcing, Project Management, Operational Excellence OPEX

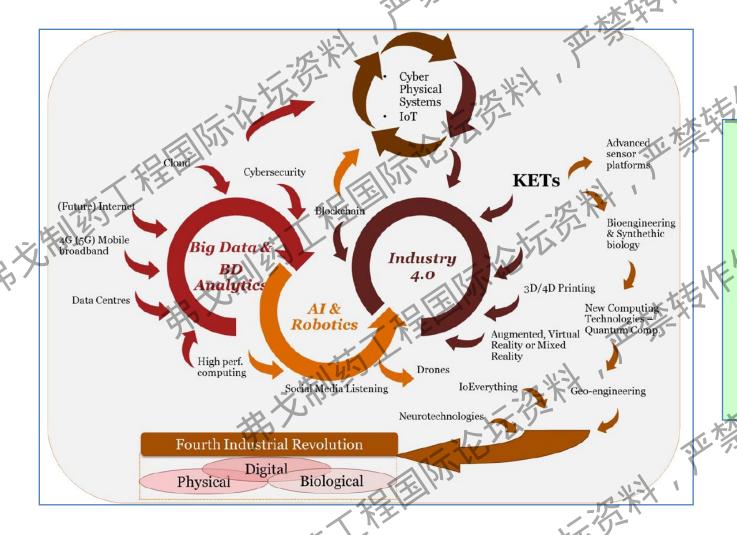
生物制药 行业的挑战: 生产与合规

- · 以分布式控制系统 (DCS) 为基础,构建未来设施。选择并安装合适的解决方案和设备,包括增强现实和实现高级分析等创新技术。
- DCS,建立在开放式以太网上,可为移动设备提供智能工作站和无缝的即插即用连接。它提供从ERP到车间的统一集成,并提供实时仪表板。
- 当员工在整个工厂中拥有可以跟随他们的 平板电脑或移动屏幕 以进行生产管理时,他们的工作会更加有效。
- · 总的来说,由于设备都已连接,数字化系统会减少对系统操作的人为 干预和报警的工作。

数字化转换

Digital transformation of the company is a deep transformation





第四次工业

高效、柔性 的 未来工厂 Efficient and flexible FoF

Smart supply network

Efficient supplier network that enables optimized decision-making

loi sepabled

Integrated sensors in process stream data continuously

Al-enabled

Real time analytics with own engine for decision-making

Mobile workforce

Workforce enabled with wearable technology uses AR/VR

Digital-physical systems

Advanced robotics and 3D printing complement processes

Advanced materials

Nanotechnology and new materials used extensively

Smart products

Products carry information to manufacture themselves

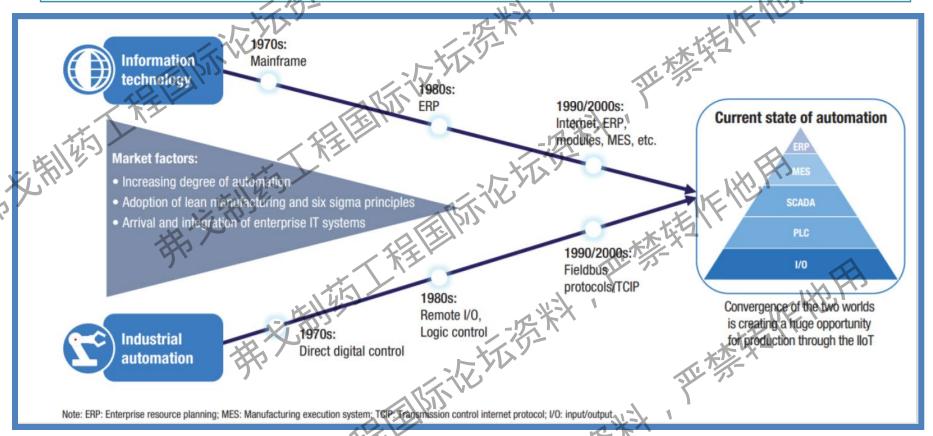
Smart products

Customer interaction through the process chain

生物制药 的智能化: 生产与合规



Information Technology with Operational Technologies





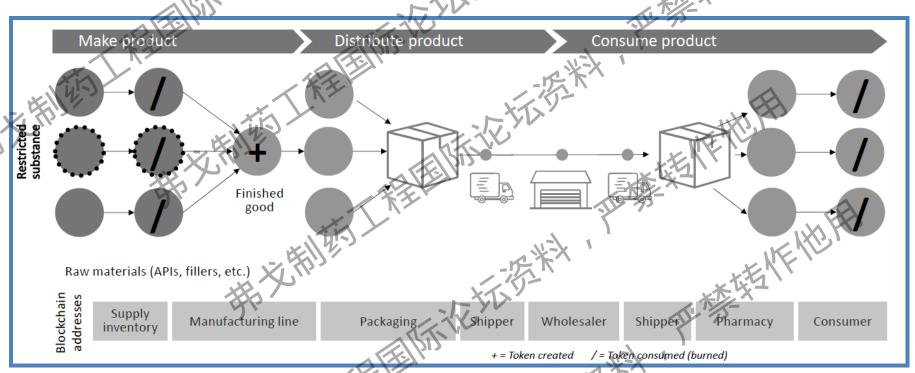
MFG Technology:

connectivity and computing, analytics and intelligence, human machine interface, digital physical Transformation, advanced materials, Advanced manufacturing processes; manufacturing philosophies, sustainability.

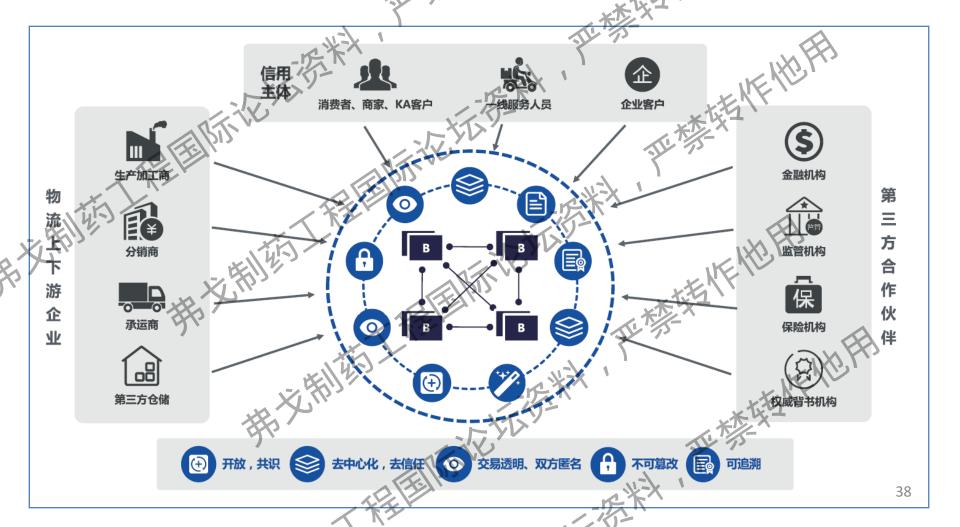
Development of AI and its future state

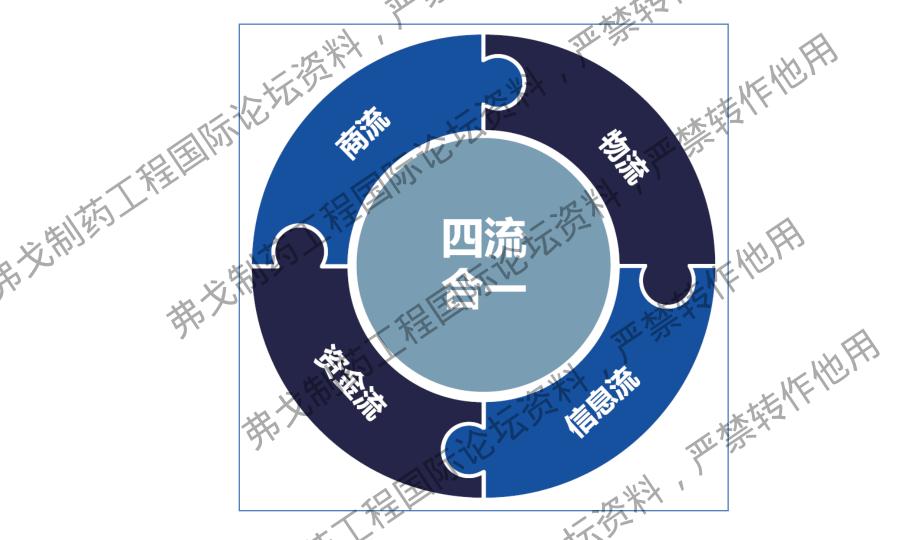
	<u>'</u>				
(00%	Leval of Guman involvement		vement	0%	
Illustrative examples Rule-based computing	Machine learning	2,512		Machine intelligence	
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Supervised learning	Unsupervised narrow learning	Unsupervised context-aware learning	Self-aware unsupervised learning	"Al will be good at specific computational tasks, but we are far away from general
Natural language processing	• Voice to text dictation	Personal assistant apps for basic voice-based Q&A	• Real-time dialogue and translation	Idioms, sarcasm, nuance articulation, intonation	intelligence."
	 Facial recognition Identifying verification by fingerprints 	Complex classification (e.g. video segment search)	Vision systems for self-driving vehicles	Digital security agents Autonomous exploration agents	"Every object will become context-aware, reactive to your needs and ultra-personalized thanks to progress
Pattern recognition • Industrial inspection based on rules on faulty functioning	Fraud detection (e.g. based on historical fraud patterns)	Product recommendation based on customer preference	• Automated real-time clinical diagnosis	Disease development and prediction of infections	"General intelligence requires a different set
Reasoning and optimization	Predictive maintenance for machinery and vehicles	Failure prediction in mission-critical systems	Automated recommendations based on inputs in value chain	Search engine answering questions instead of giving search results	of non-deterministic computing architecture than what exists today."
/- \-		Current	2030 and		

区块链 与 供应链管理











MFG Process 生产工艺的核心事项

上游的

优化细胞培养条件以最大化细胞密度和产量。

下游

监控缓冲液的组成和过程,例如色谱和过滤,以确保蛋白质的纯度和产量。

制剂

监控并验证API和赋形剂的浓度,以满足内部质量和 法规要求



细胞系开发

确保培养条件与您的束缝和细胞培养系统制容,从而有助于获得最佳的细胞密度和质 是



缓冲液制备

检查缓冲液的成分是否正确。以进行有效 理以及最佳质量和产量。



配方开发

优化配方浓度和稳定性、以高产量生产。



培养基

检查培养基的组成,以获得最佳的细胞。 长



色谱法

保持药物中间体的纯度,并识别和处理可能 损害产品收率的偏差。



最终配为

监测和/或验证赋形剂的浓度。确认配方中 的可溶性成分。减少注射部位的疼痛。



细胞培养监测

确保培养条件适合细胞正常生长和健康。这 促进了最大的密度和产量。



缓冲液交换

监控缓冲液的组成并验证适当的交换以优化 中空的数量,并以最高的质量获得最高的产 品产量

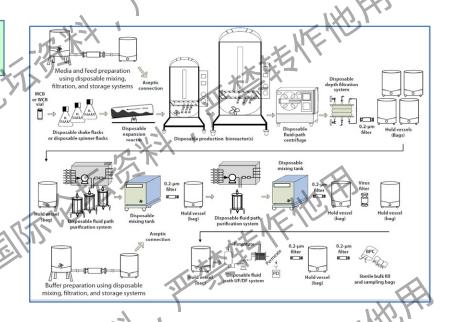


过滤和填充

关键的药品发布规范,以确认产品的稳定 性。 生物制药的未来设施 FoF: The facility of the future

FoF: Beyond MFG Process 不只是《生产工艺





Bio-Manufacturing Organization

生产信息的智能化 Manufacturing Intelligence (MI)

Right First Time

Processes are defect-free and free from workarounds. Visibility to poorly performing processes and methods enables the organization to align on improvement activities.

Targeted Continuous

Improvement of Mfg

Leverage data from internal and

external sources to enable long

term process improvements and

cross-site comparability. Utilize

dashboards to identify and

measure the greatest improvement

opportunities.

Processes X

Countinued Process Validation Life Cycle "QbD"

Clearly demonstrate control of risk to product quality and assure continually that the process remains in a state of control.

Sustainable Process Knowledge

Easy access to technical and production documentation.
Centralize and share product data and know how across the functions and across sites.

Real-Time Predictive Process Control

Real-time control and optimization of the processes and alerts through predictive analytics allows operators to adjust parameters enabling higher yields and reduce loss

Enable Learning Organization

Enable continuous learning throughout product & process lifecycle to learn from development through qualification and commercialization across all functions and networks.

Optimize External Manufacturing Process

Evolve to a seamless distributed external partner network through a free-flow of data exchange, process collaboration, and product knowledge enabling early detection & improvement, oversight, and control visibility to performance

Predictive Maintenance

Utilizing a connected factory
(Internet of Things) and self
diagnostic capabilities, monitored
machinery has the ability to ensure
predicted product quality and
automatically schedule just-in-time
(JIT) maintenance and calibration
to minimize equipment downtime

Core Asset: process /equipment data and product knowledge

生物制药的未来设施的功能 Functions of FoF









Descriptive

- Visualization
- · Dimension reduction
- Abnormality & Trend detection
- Alert systems

Diagnostic

- Process
 Understanding
- Failure analysis
 - Trend & pattern explanation
- Decision support

Predictive

- Forecasting
- · Soft Sensors
- Simulation & Scenario analysis
- Maintenance
- Planning support

Prescriptive

- Proactive decision support
- Process Control
- Process Automation
- Smart Factory

Model complexity

Requirements for the FoF Lean **Green Design** Manufacturing Closed Single-Use Processing Risk-based Modular Compliance Construction Plug-N-Play Continuous Processing Operations

Sanofi, Location: Framingham, Massachusetts, USA Project: Sanofi Digitally Enabled Integrated Continuous Biomanufacturing Facility



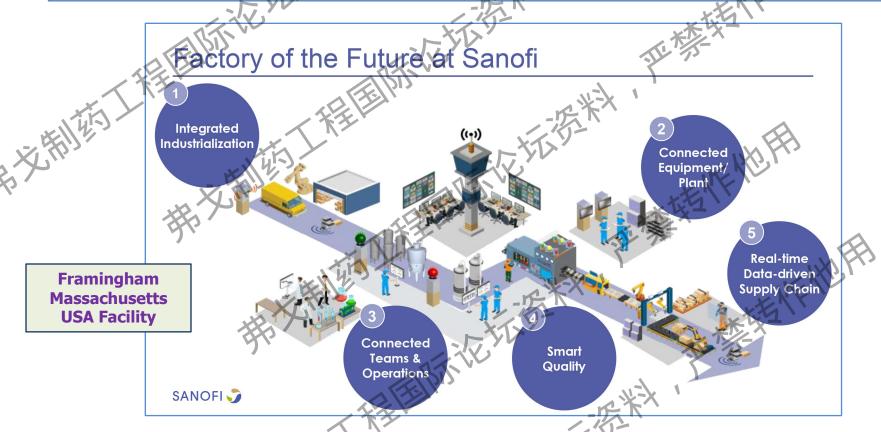
- From the early design phases Sanofi was dedicated to incorporating a full set of lean operations principles into the design. They have broken new ground in digital integration. The entire facility is run using a comprehensive suite of digital solutions.
- Plant performance is managed through electronic boards that allow real time visibility of performance metrics
- Issues are automatically escalated
- Trending of key metrics is available on electronic boards throughout the facility
- Full integration of PCS, MES, Historian, ERP systems with automated data transfer
- Electronic work instruction using pictures and videos
- Fully electronic batch records enabling review and release by exception
- Wireless instrumentation and RFID technology
- Common user interface and user experience across all suites, processes, and utilities

Digital Transformation 数字化 转换

They have pushed the concepts of digitization to fully integrate process control, data collection, and analytics.

This combined with a commitment to a "born lean" design philosophy has created an industry factory 4.0 lighthouse.

Digitally Enabled Integrated Continuous Biomanufacturing Facility



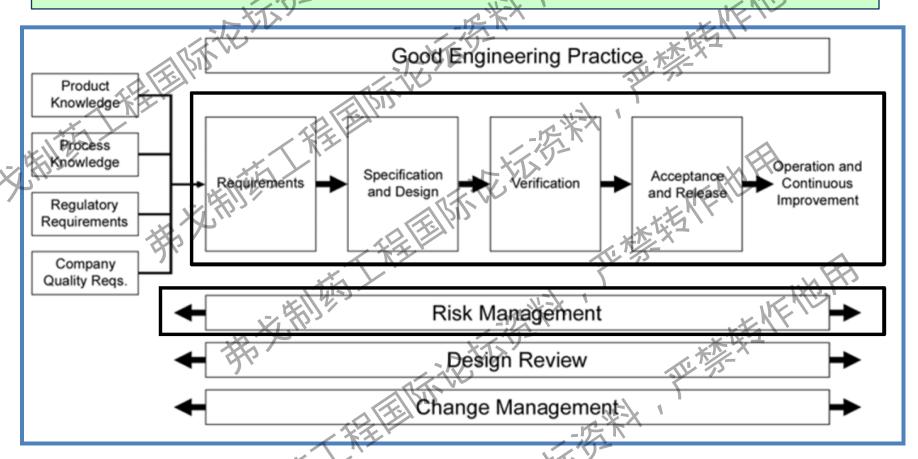


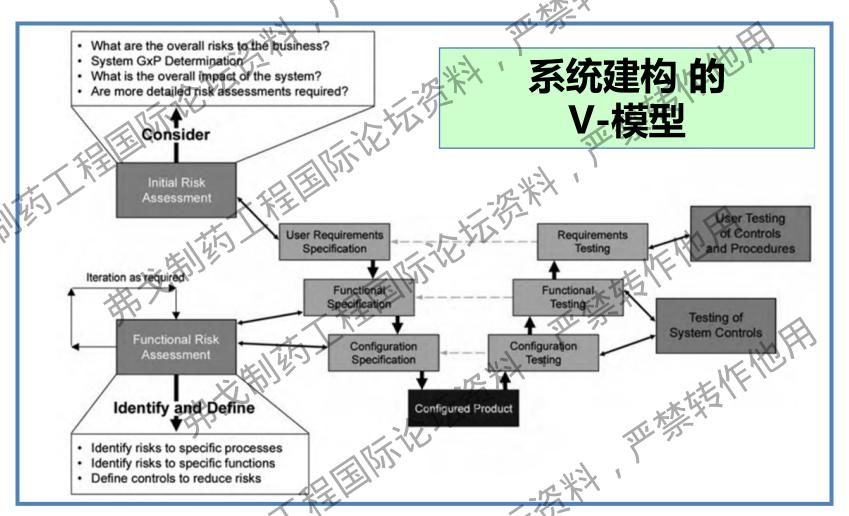




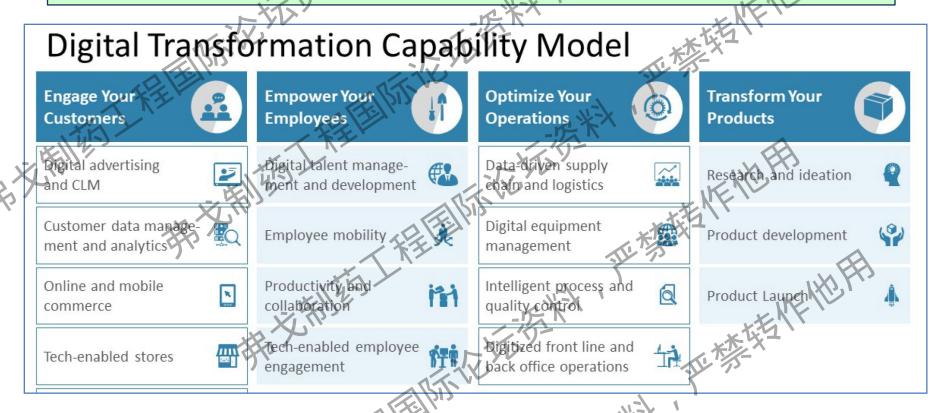


以GEP来 建设 FoF 未来设施





DT 数字化转型 的效益









设施



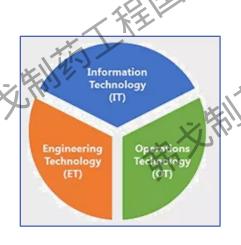


Technician interaction with Electronic Batch Records (EBRs) using Human Machine Interface (HMI).





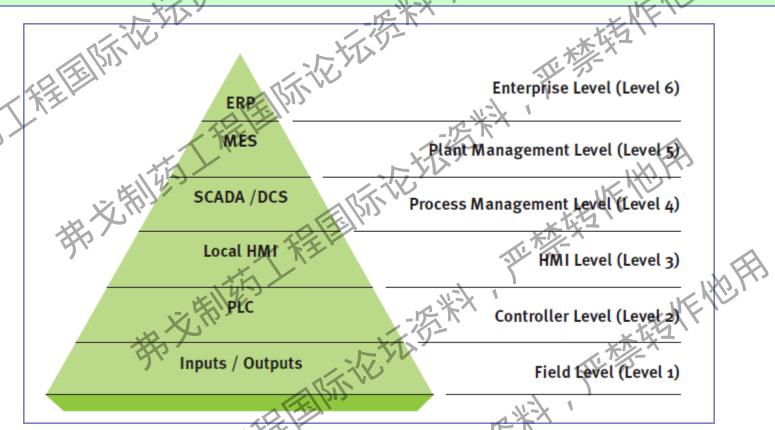
信息技术 IT & OT 运营技术 的融合

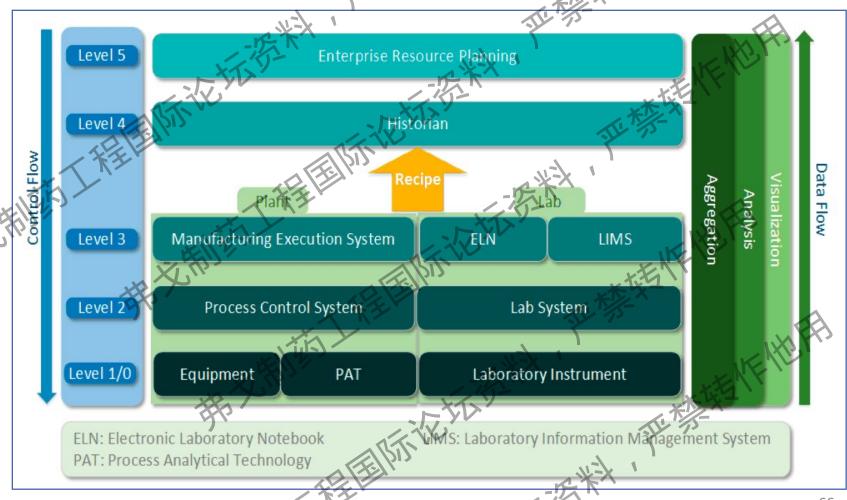




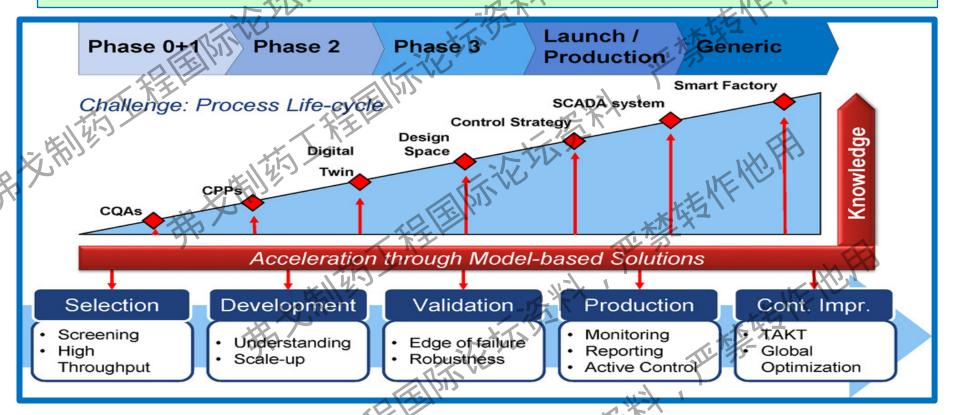


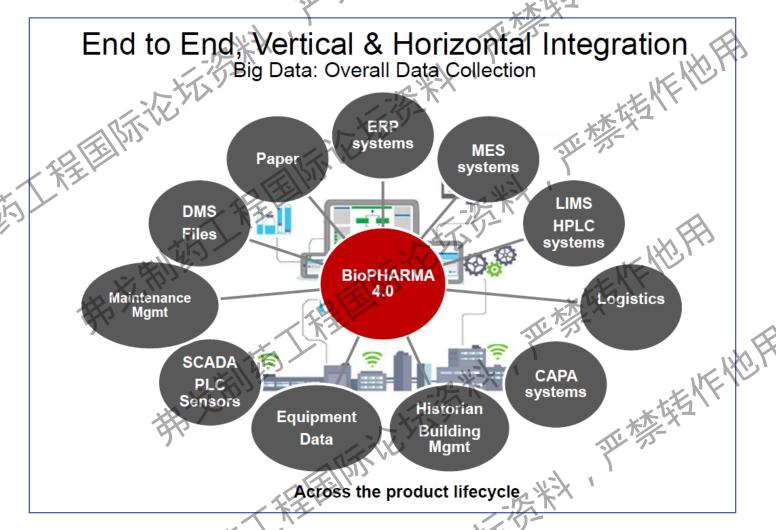
自动化 金字塔 The Automation Pyramid





生物制药 数位化生产的时代 Bioprocessing in the Digital Age: The Role of Process Models 工艺模块的角色







FILE CONTRACTOR OF THE PARTY OF

加强各项流程的数字化与合理 化程度,从而提升效率、发信 成本,打造数字化文化、培养 全新思维方式与能力

高效互动

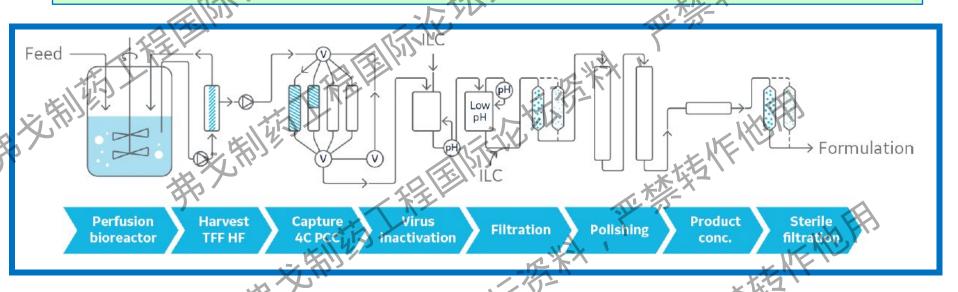
建立全新互动模式, 打造人开展有针对性的互动活动, 以满足客户/患者/员工的需求,提



产品与服务

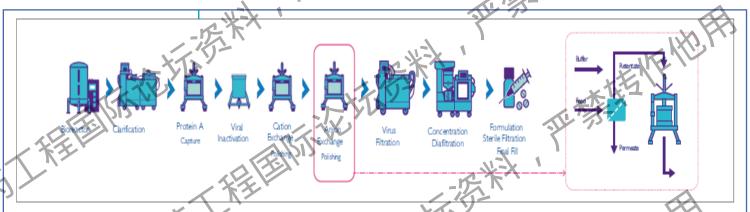
加速开发产品、服务以及新的业务模式, 运用数据与创新不分为客户增创价值

End-to-end upstream and downstream continuous processing



TFF: tangential flow filtration; HF: hollow fiber;

4C PCC: 4-column periodic counter current chromatography



Intensified polishing compared to conventional AEX polishing in a mAb process, intensified polishing utilizes a SPTFF pre-concentration step to reduce process volumes and improve resiminates loading.



Figure 2. Laboratory set-up of the continuous production of a monoclonal antibody. ATPE (aqueous two-phase extraction), SPTFF (single-passion), dial flow filtration), IPC (interprocess communication), iCCC (integrated counter-current chromatography), DF (diafiltration), Lyophil (lyophilization).

FoF 未来设施 建设基础

FoF Project Enablers Technology standards Real time Release `Vendor interaction

Supplier Management

Regulatory-

X Keep workforce capable > Multi-use and flexible facilities

生物制药的未来设施 的实践: 体系

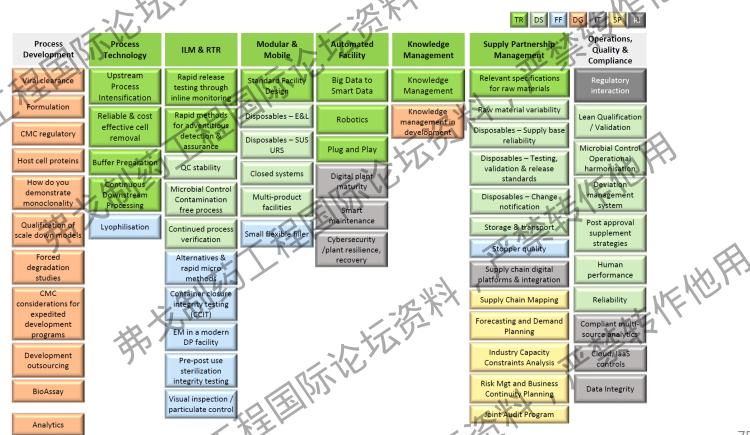
Process Modular & Automated Supply Knowledge ILM/RTR Partnership Technology Mobile Facility Management Management Reliable and cost Data analysis to Managing Standard Rapid release testing evolve from big effective cell removal Product and Facility Design through inline data to smart options for higher Process monitoring data density processes in Knowledge across biomanufacturing the Lifecycle Robotic Rapid methods for technologies in adventitious **Buffer Preparation** biomanufacturing detection & sterility assurance Continuous lug & Play Downstream Processing

In-Line / Advanced Testing to support Bio-Manufacturing

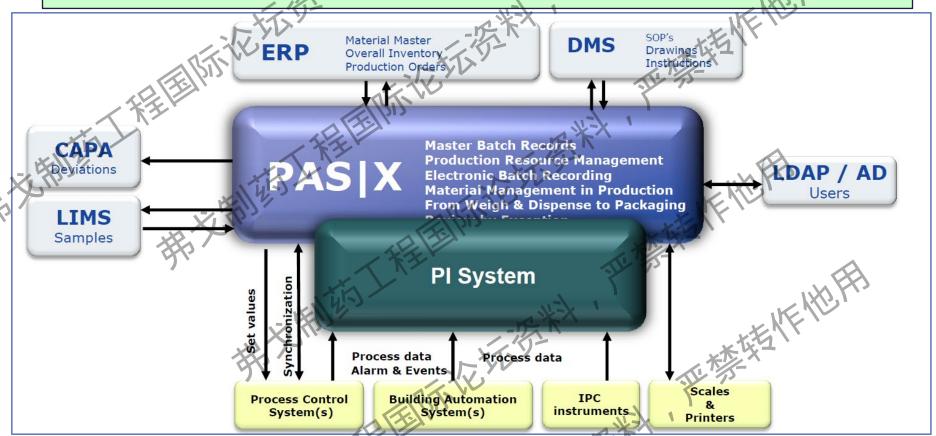
Current State		
Category	What	Where
General	pΗ	7/3/
	Osmolality 7	1
	Color (visual)	
	Turbidity (visual)	
Quantity	Protein Conc by RI	
Identity	ICIEF & Binding Assay	45
Purity/Impurities	UPLC-SEC	QC Lab
	Non-Reducing CE-SDS	
	Imaging Capillary IEF	
Biological Activity	Binding Assays	ĺ
Safety	Bioburden (plates)	
	Endotoxin (turbidimetric)	
	In-Vitro Adventitious Virus	

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

生物制药的未来设施 的实践: 工艺、知识管理、供应链



数字化转型的 系统搭配



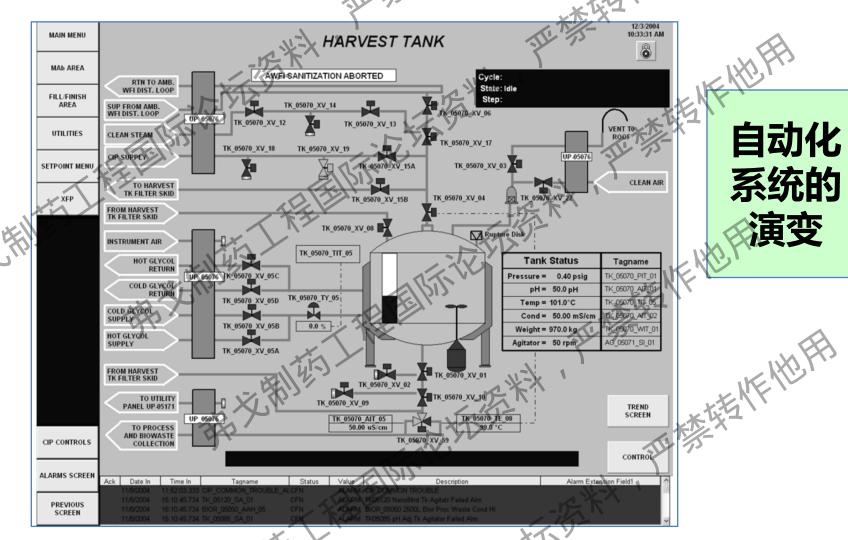


PC based Operator Interfaces

- PC 1981 IBM
- Late 80's Window to the PLC
 Replaced pilot lights, pushbuttons
 and selector switches
- 1990's DCS systems Hybrid



自动化 系统的 演变



自动化

Automation Advancements – \$88 (ISA 88, Batch Control)

自动化 系统的 演变

Problem – Every batch control system programmed separately.

Solution - S88, shorthand for **ANSI/ISA-88**, a standard addressing batch process control. A design philosophy for describing equipment and procedures. It was approved by ISA in 1995. It was adopted by the IEC in 1997 as IEC 61512-1.

S88 provides a consistent set of standards and terminology for batch control and defines the physical model, procedures, and recipes.

自动化 系统的 演变

Automation Advancements – Server Technology

- •Servers have dedicated functionality such as web servers, print servers, domain servers, database servers
- •Servers have a faster CPU, and often, redundant hard drives, power supplies and network connections for disaster recovery.



Automation Advancements – MES

Manufacturing Execution System - a control system for managing and monitoring work in process on a factory floor to improve productivity and reduce cycle-time. Often integrated with ERP software.

Typically Include

- Scheduling
- Security Basics
- Equipment Tracking
- Materials Management
- Inventory Management
- Recipe Authoring
- Order Management
- Weigh and Dispense
- Electronic Batch Records
- Electronic Signatures
- Genealogy and Traceability

Software

- Werum
- Syncade
- Elan
- PMX
- Simatic IT
- Plant Apps

生产管理 系统的 开发

Portable Wireless Workstations





移动式 工艺 控制站

UE HUFF

生物制药的未来 Biotech Manufacturing: The Future

- Smaller, flexible, multiproduct, multiplatform facilities.
- Entirely disposable or hybrid systems following standards for interconnection.
- Current batch manufacturing will shift toward continuous manufacturing like other matured processing industries (oil, commodity chemicals, paper).



