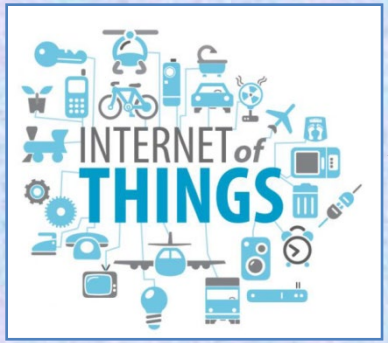
2020（第十二届）弗戈制药工程国际论坛

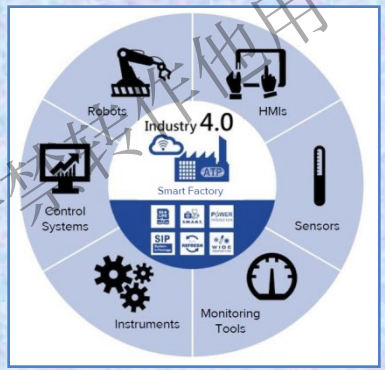
生物制药 智能工厂 的展望

The Outlook on AI-MFG Facility of Biologics



李树德 Michael Lee

2020. 09. 20



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要赢得全球的商业竞争 敢问路在何方？

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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**

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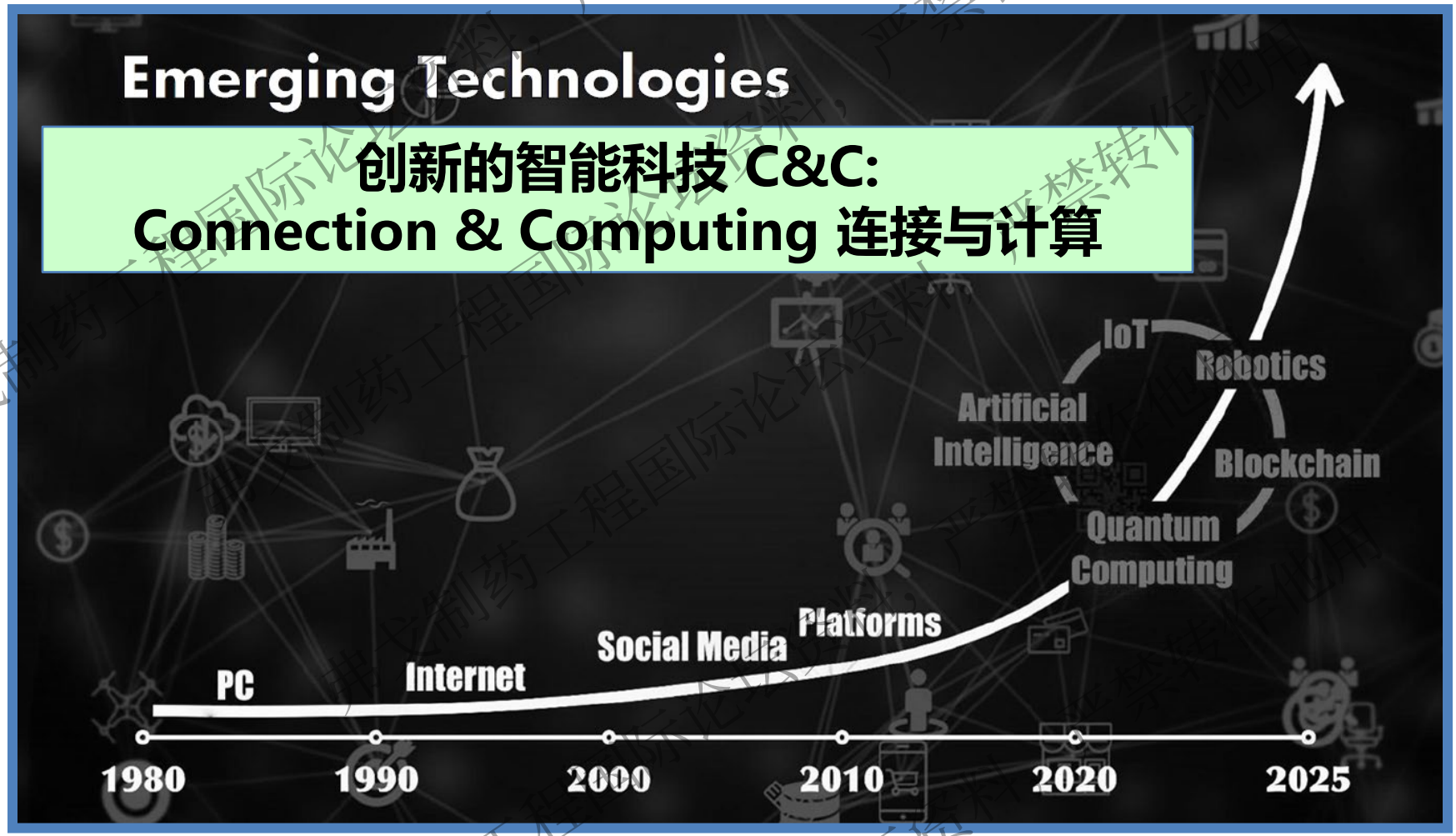
Emerging Technologies
创新的智能科技 C&C:
Connection & Computing 连接与计算
IoT
Robotics
Artificial Intelligence
Blockchain
Quantum Computing
Platforms
Social Media
Internet
PC
1980
1990
2000
2010
2020
2025

Connected World

创新的智能科技 C&C:
Connection & Computing 连接与计算

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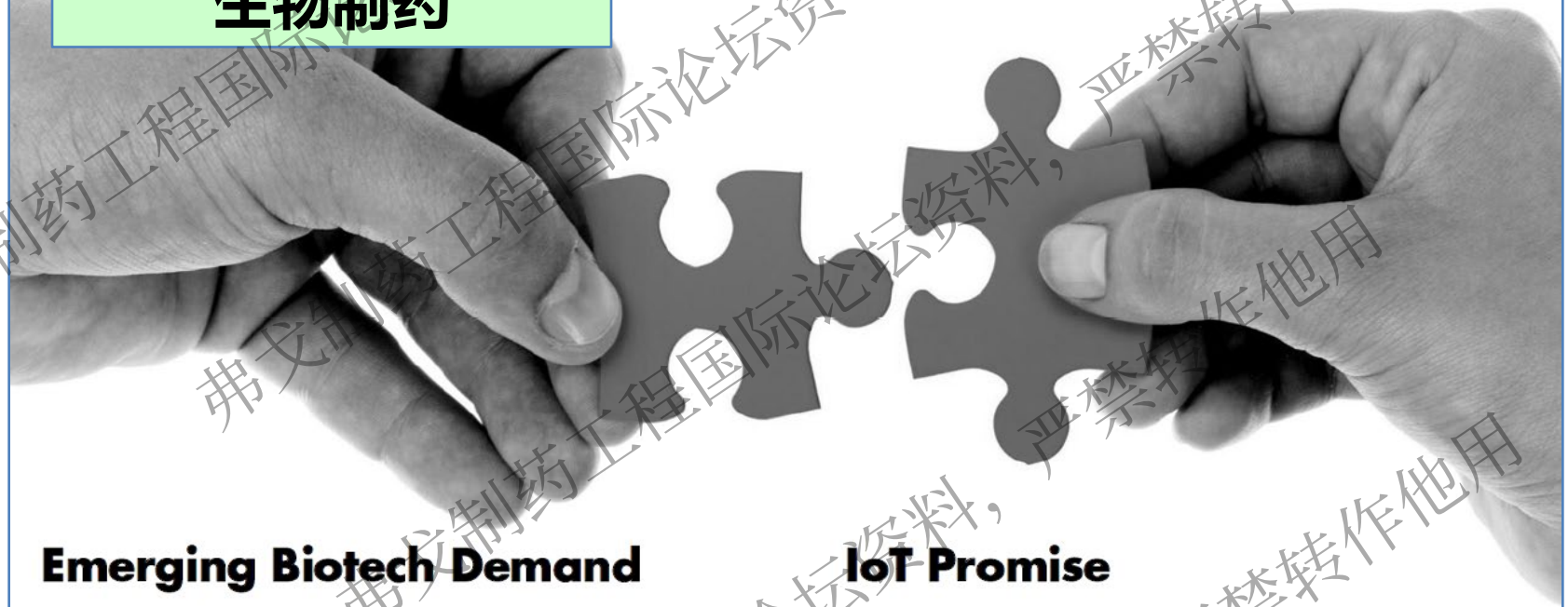
物联网 影响了 生物制药



Emerging Biotech Demand

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

IoT Promise

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

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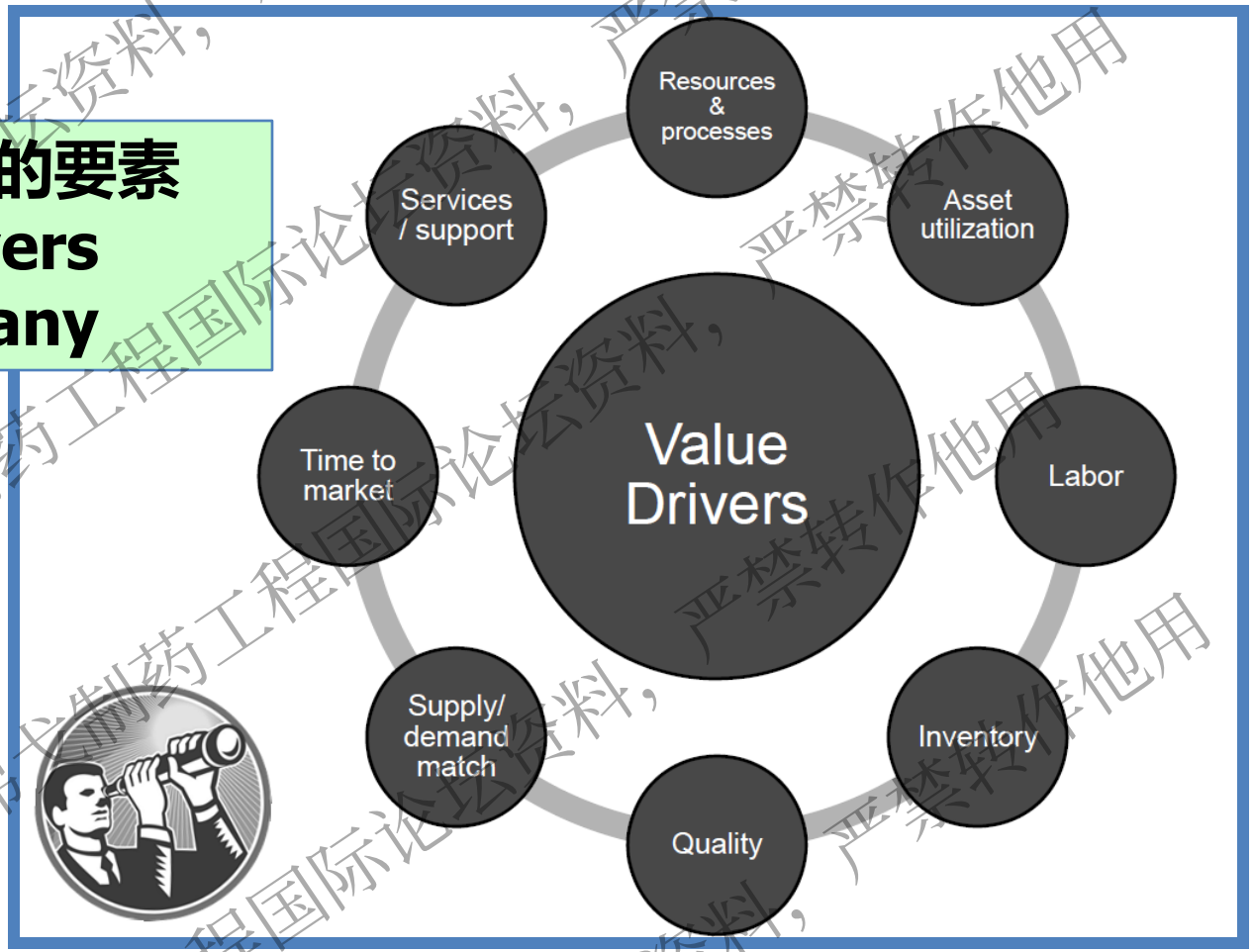
公司 价值提升的要素
Value Drivers of a company



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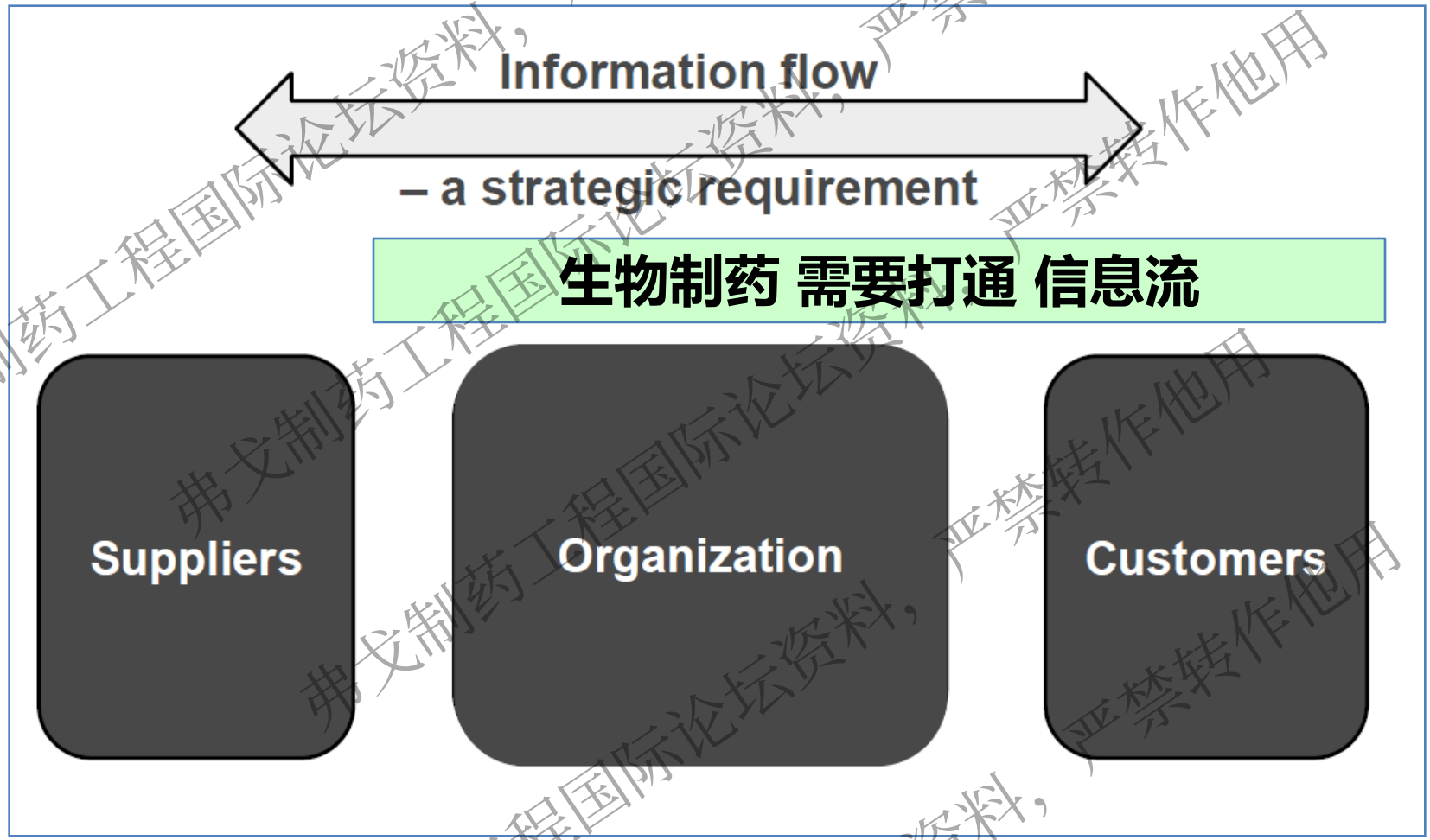

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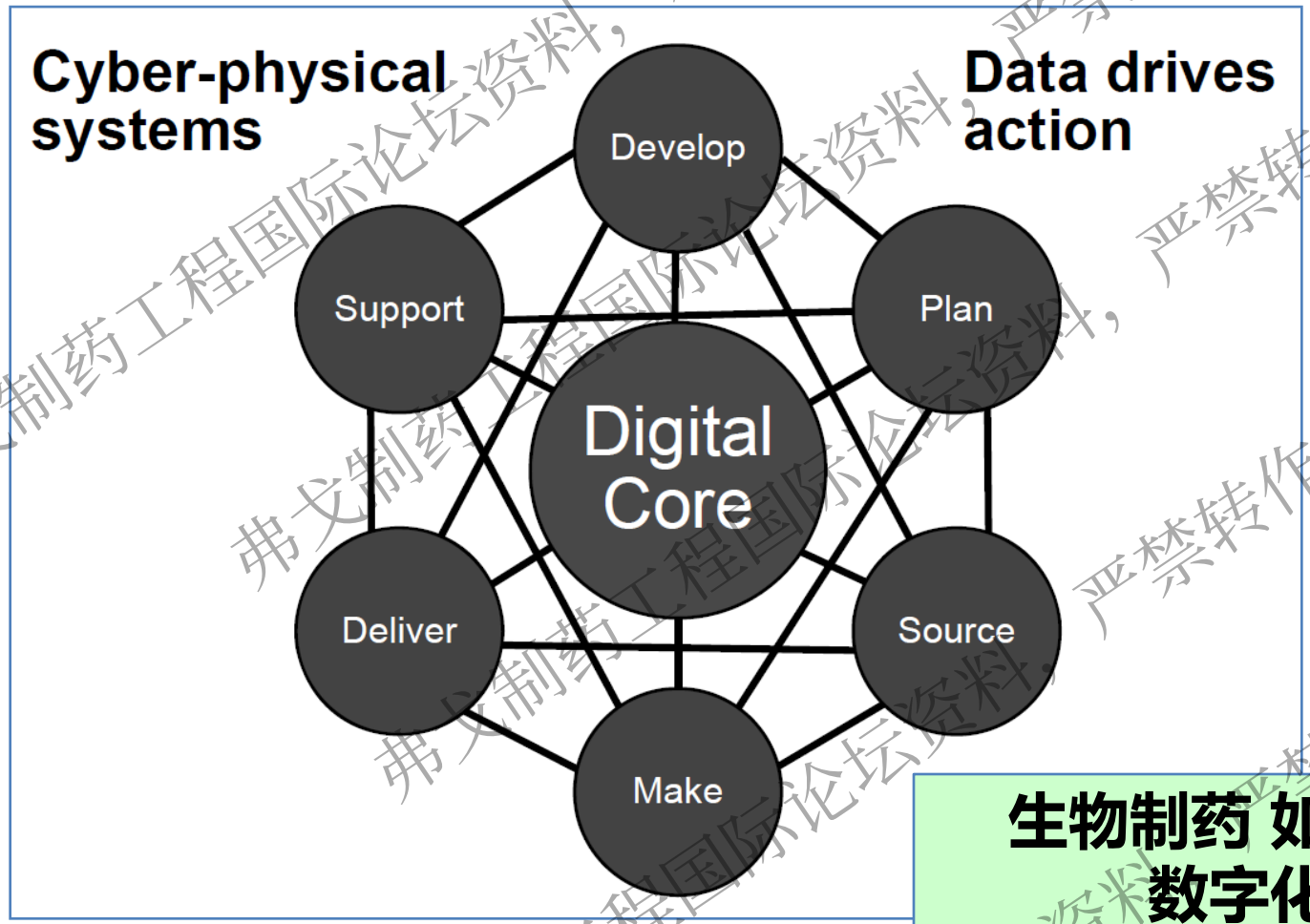

生物制药 如何 利用好 数字化技术

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

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

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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

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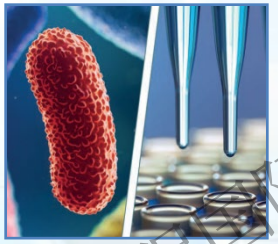
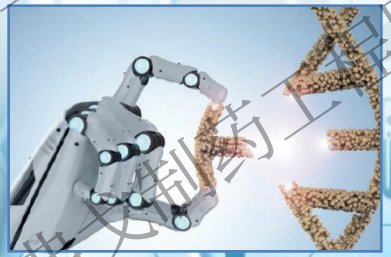
生物制药行业 的未来





FUTURE

FUTURE BIOMANUFACTURING

对人类健康的 贡献

社会对行业的 期待

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

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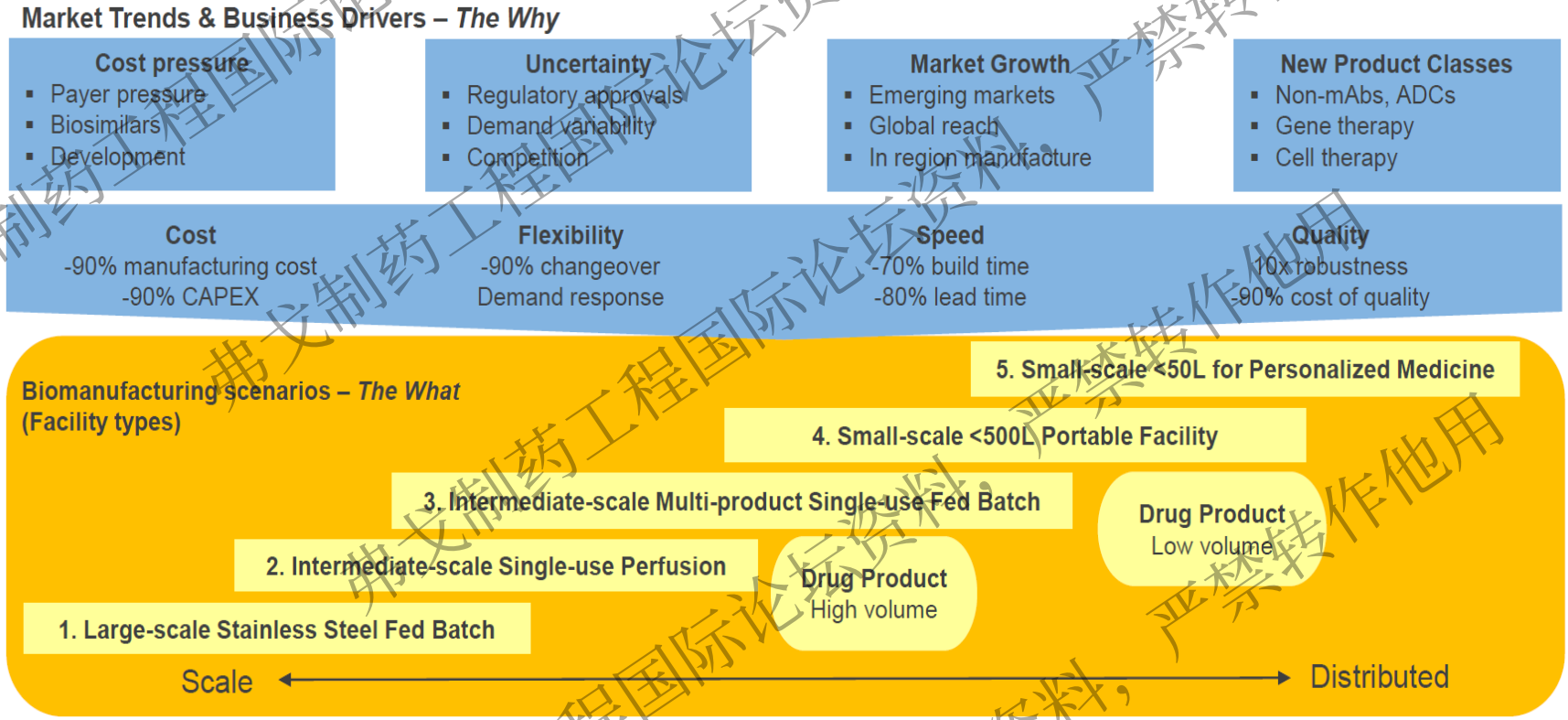
社会对行业的 期待 + 生产力的竞争



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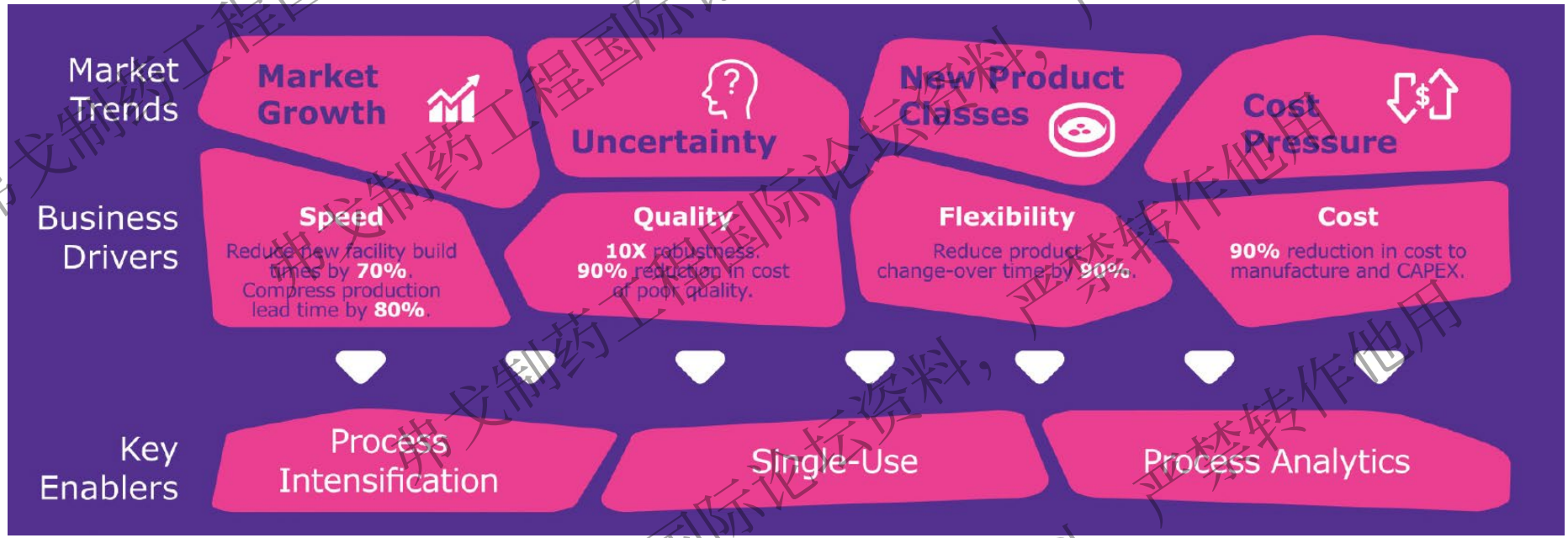
FoF to Support Next-Generation's BioProcessing with a Multidisciplinary Pursuit



展望 行业的未来

Looking to the Future

Modernizing FoF for Bio-MFG: A Continuous Effort by the Industry

BIOMANUFACTURING INNOVATION

FUTURE BIOMANUFACTURING

BIOHARMACEUTICALS

VALUE-ADDED MFG MATERIAL

ENGINEERING MATERIAL FOR FACILITIES

ADD INTEGRATED STRENGTHS IN BIOMANUFACTURING

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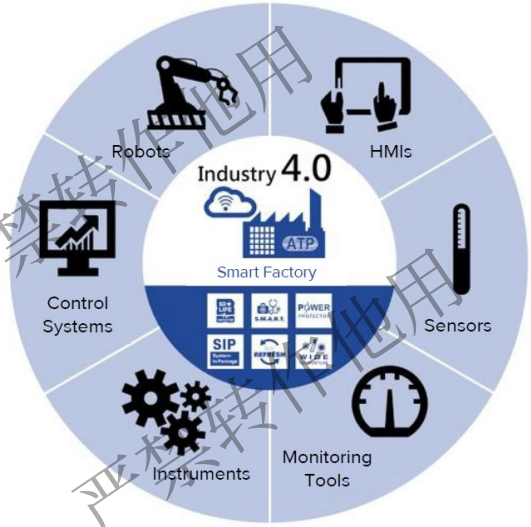
21世纪的抗体药物
新一代的生产设施

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

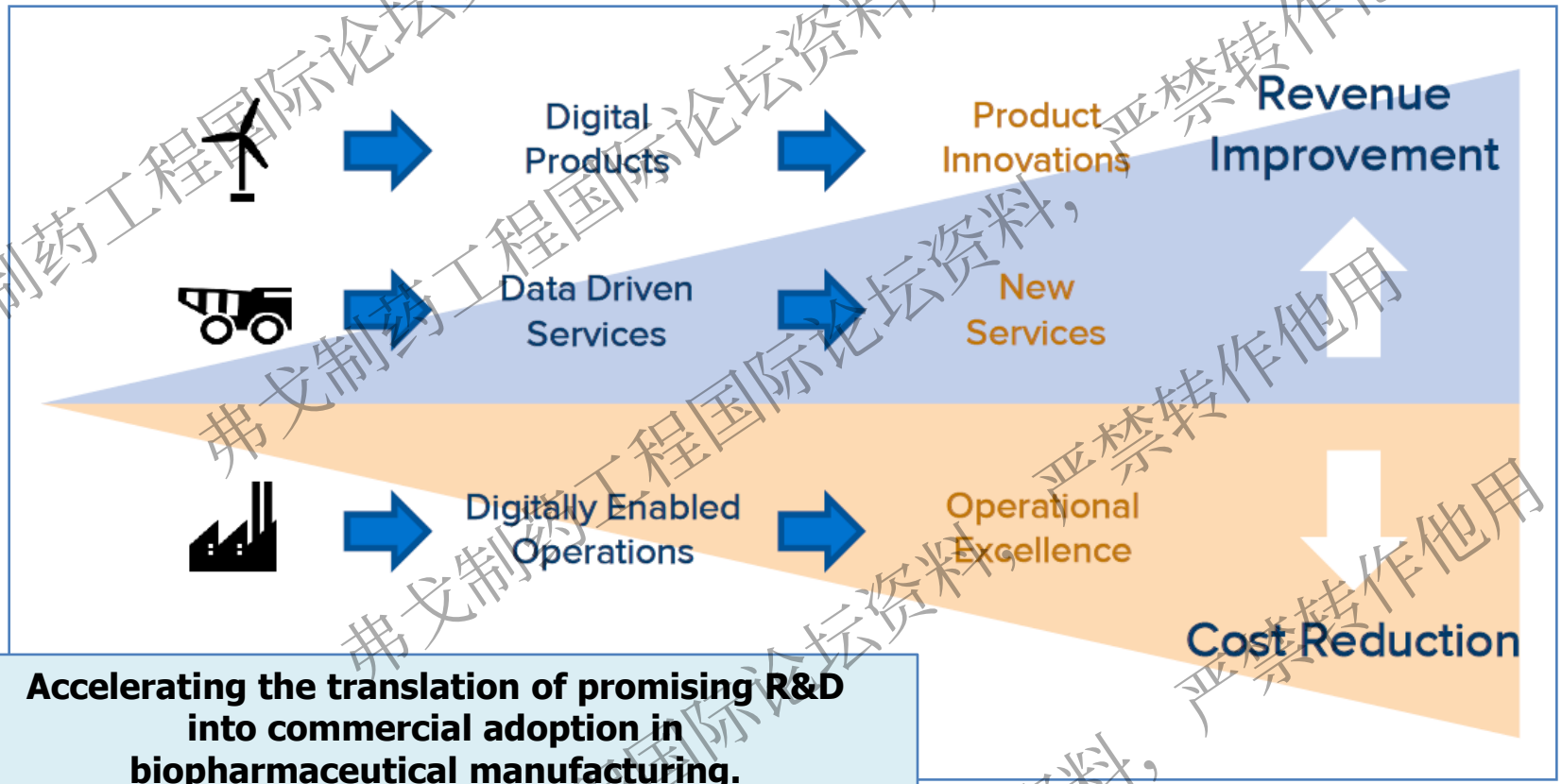
在这个世界中，数字渠道成为主要的（有时在某些情况下，也是唯一的）系统整合模型，而自动化流程则成为生产力的主要驱动力，也是灵活、及时、透明和稳定的生产管理与供应链运行的基础。

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



Accelerating the translation of promising R&D into commercial adoption in biopharmaceutical manufacturing.

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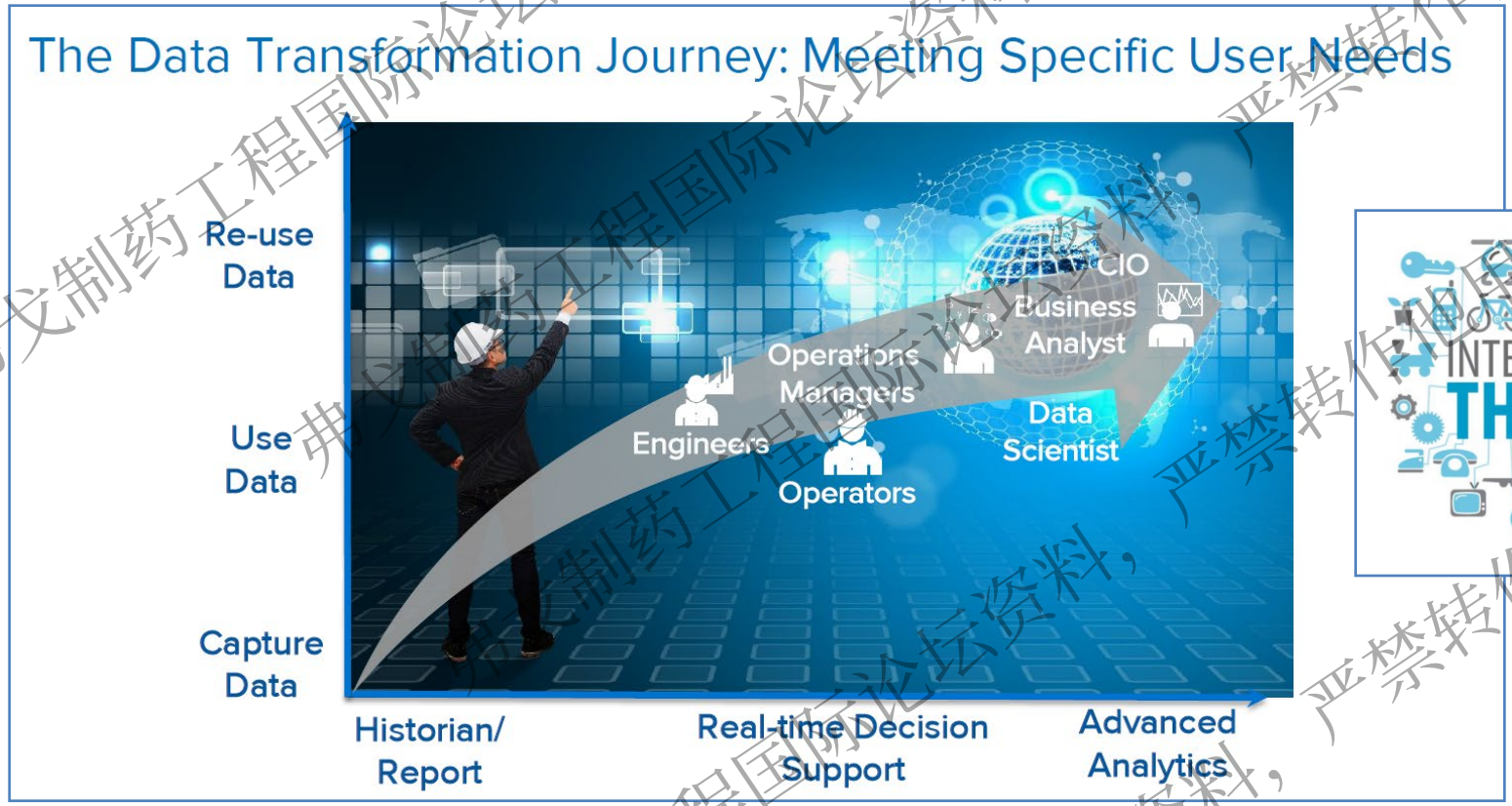
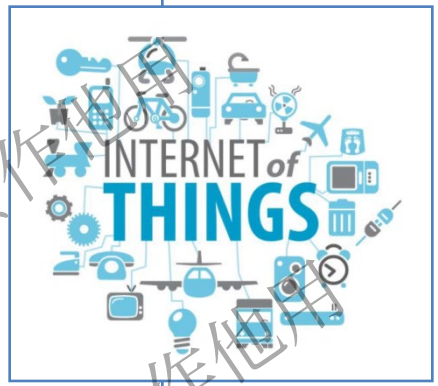
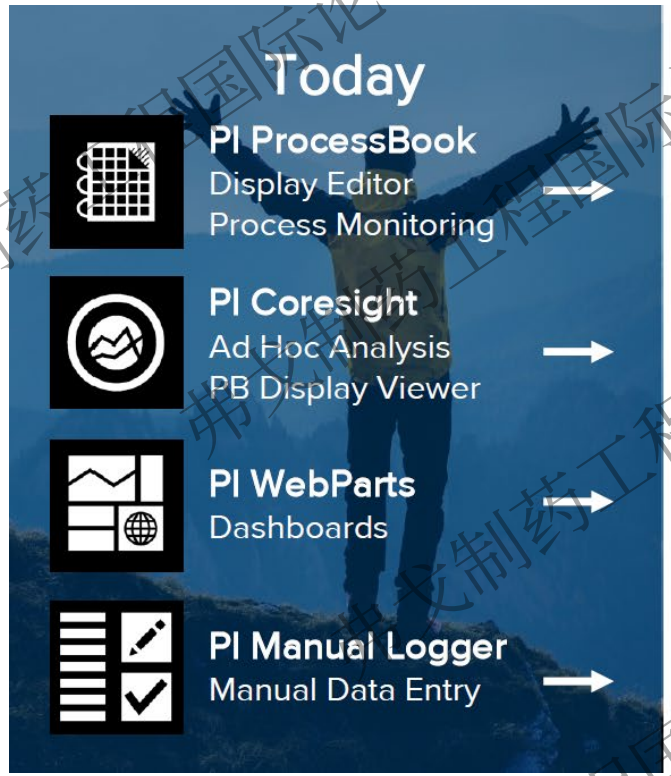
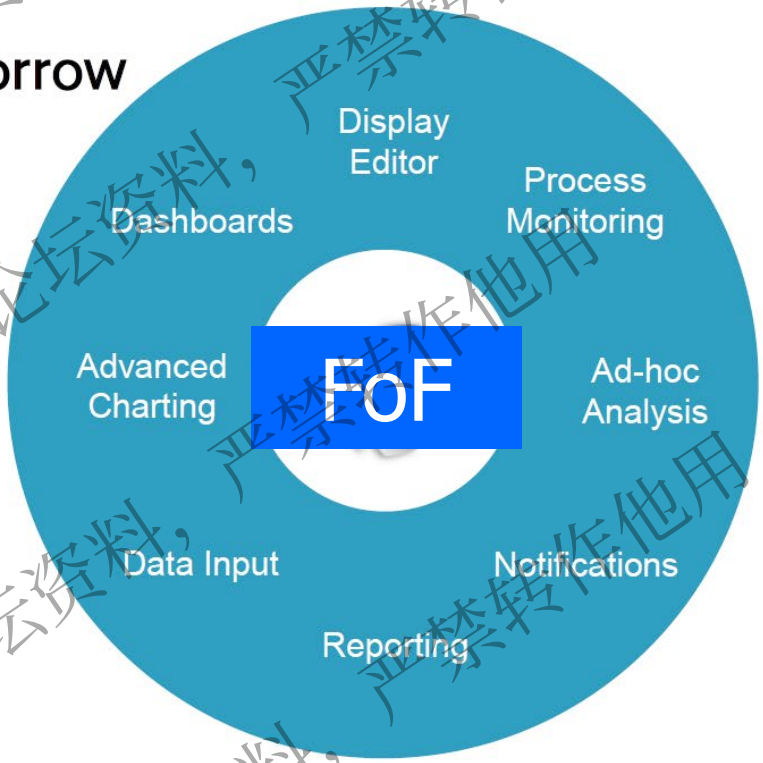
Digital Transformation 数字化 转换





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

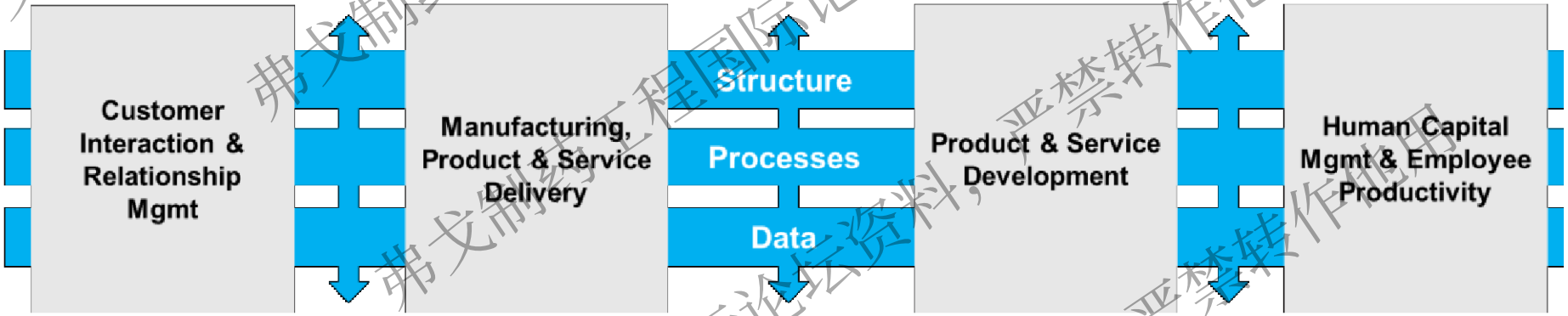
- 生物药品检测技术、工艺控制和监控、
- 与数字化转型相关的新技术，能给制药供应链带来重大变化。
- 绝大多数的生物制药公司将主数据管理（MDM）列为供应链转型的重要驱动因素。
- 数字化转型，将支持下一代工艺的开发和生物药品的制造
- 涵盖各个职能：Process Development，Analytical Method Development / QC，Tech Transfer/GMP Manufacturing，Regulatory Compliance，Outsourcing，Project Management，Operational Excellence OPEX

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



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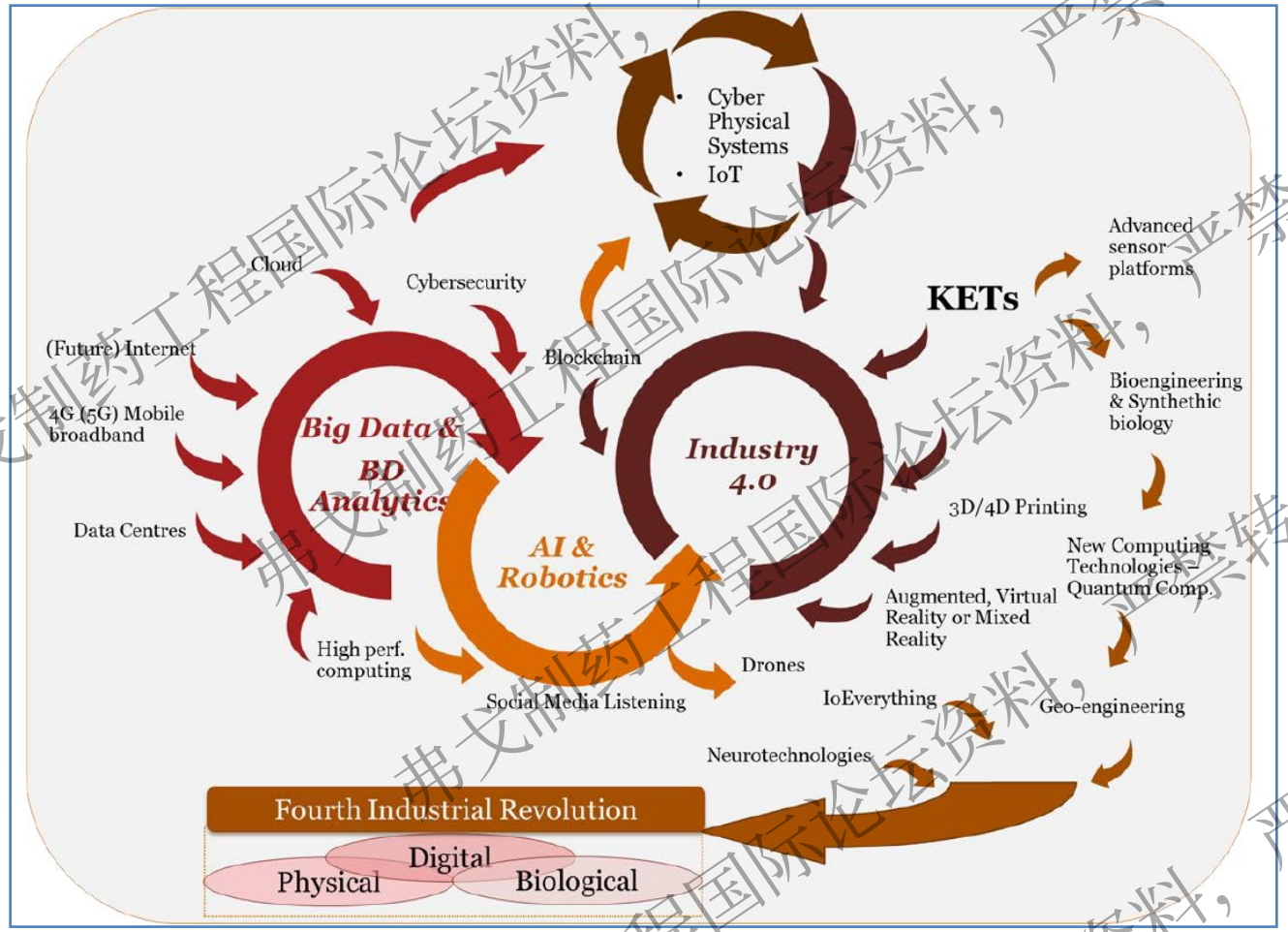
Cyber Physical Systems
IoT
Cloud
Cybersecurity
KETs
Advanced sensor platforms
(Future) Internet
4G (5G) Mobile broadband
Blockchain
Bioengineering & Synthethic biology
Big Data & BD Analytics
Industry 4.0
Data Centres
AI & Robotics
3D/4D Printing
New Computing Technologies – Quantum Comp.
Augmented, Virtual Reality or Mixed Reality
High perf. computing
Drones
Social Media Listening
IoEverything
Geo-engineering
Neurotechnologies
Fourth Industrial Revolution
Digital
Physical
Biological

第四次工业革命

高效、柔性 的 未来工厂
Efficient and flexible FoF

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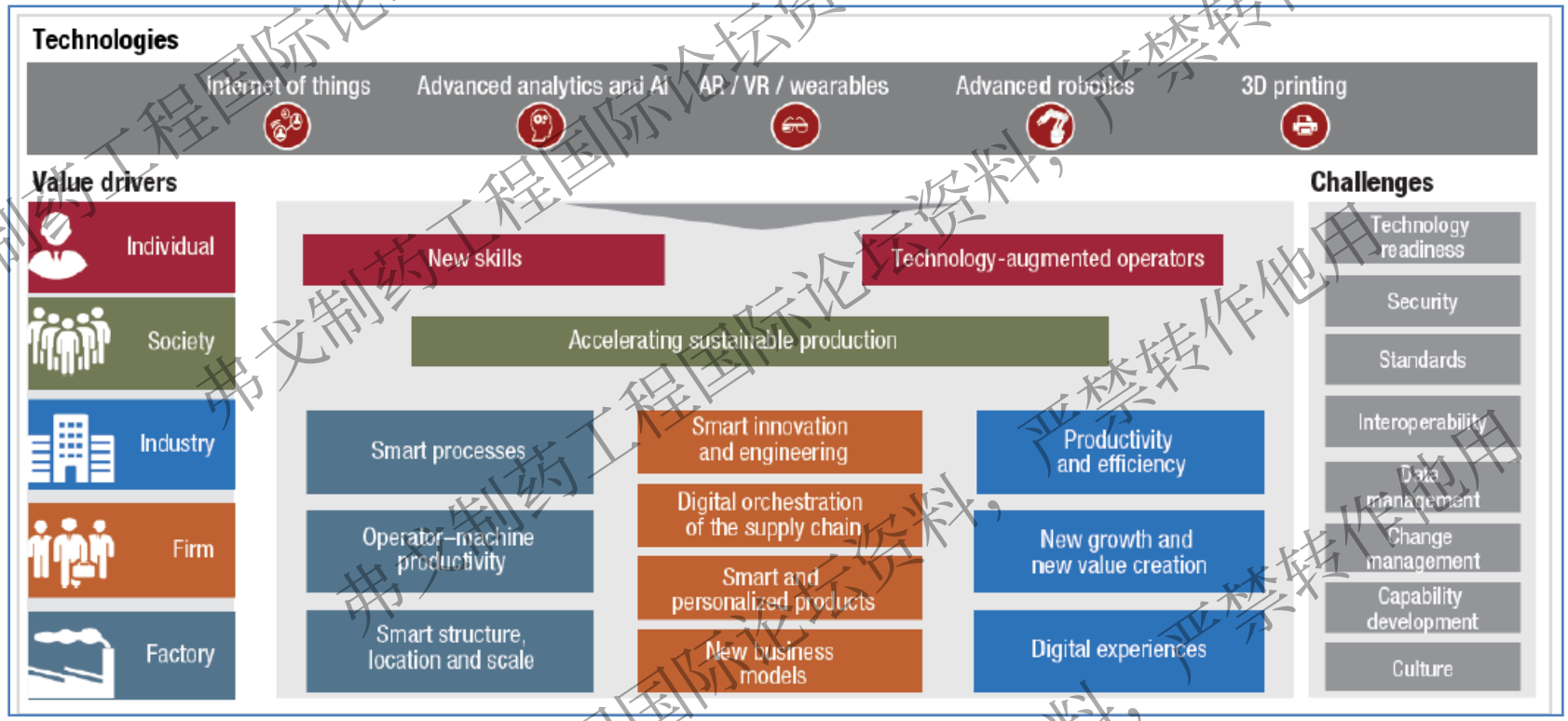
生物制药 的智能化：生产与合规



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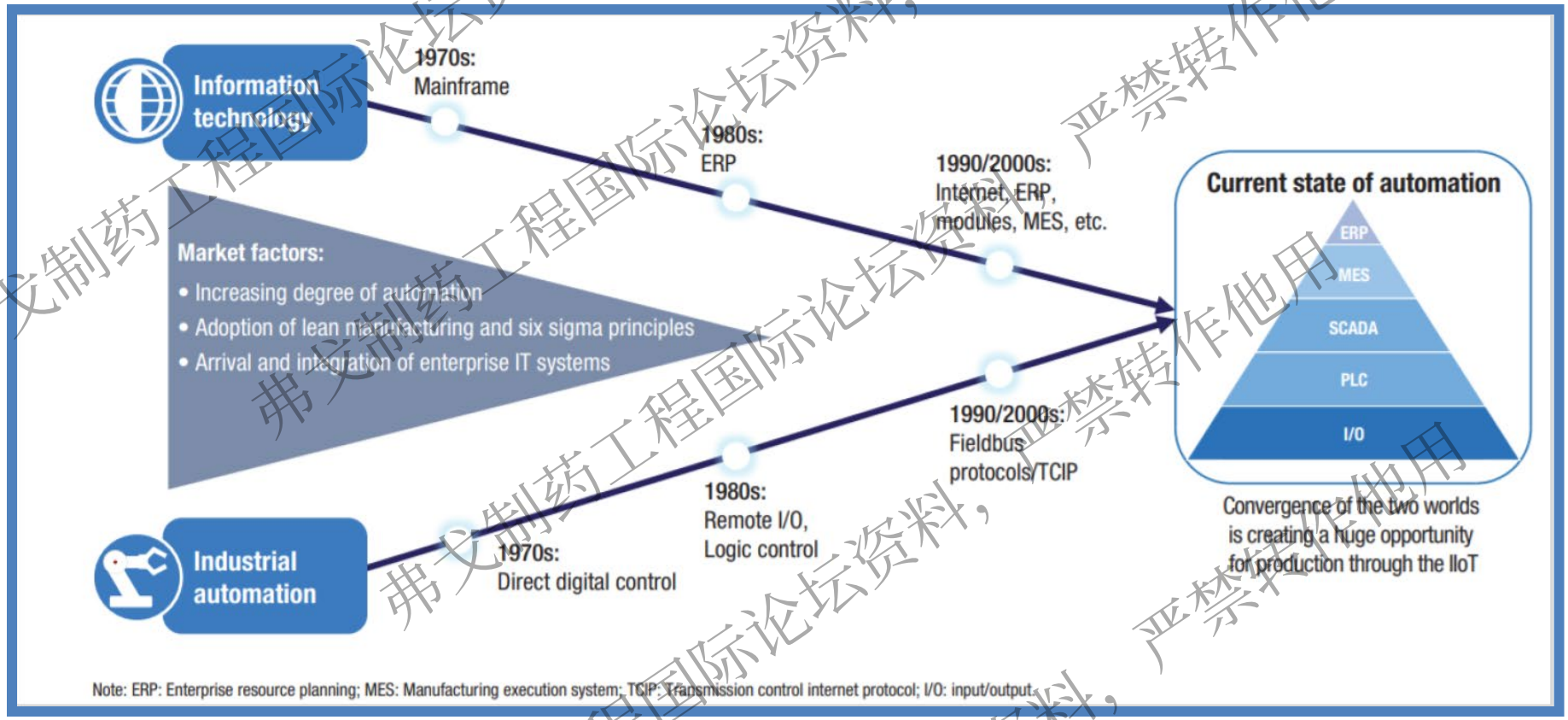
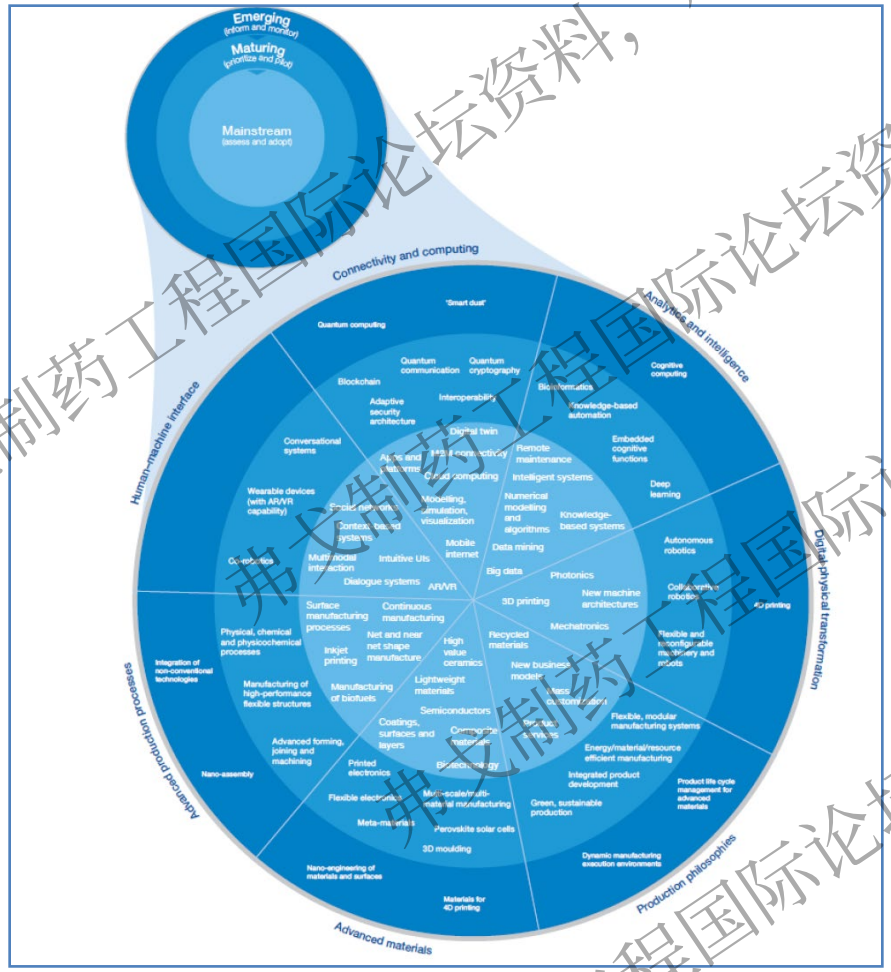
Information Technology with Operational Technologies





MFG Technology:

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

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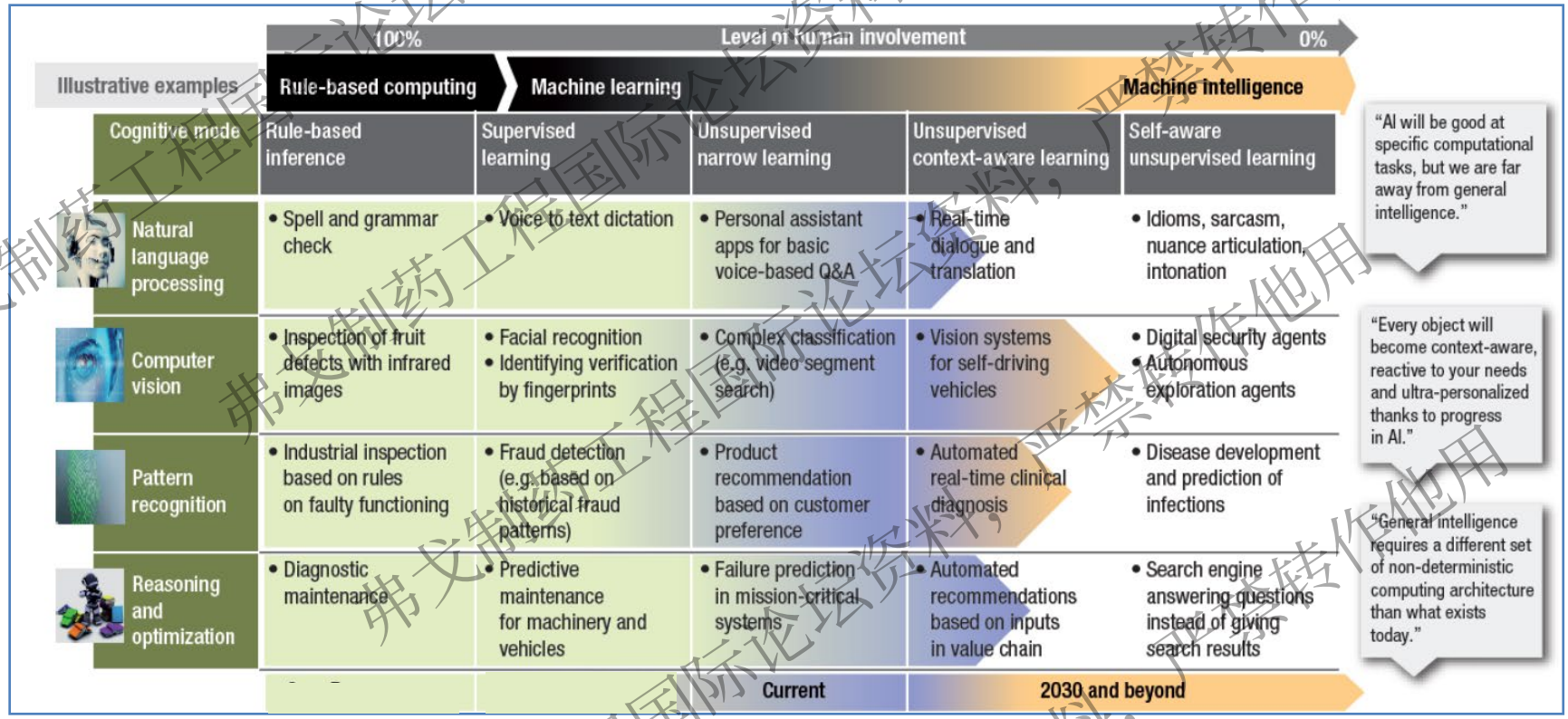
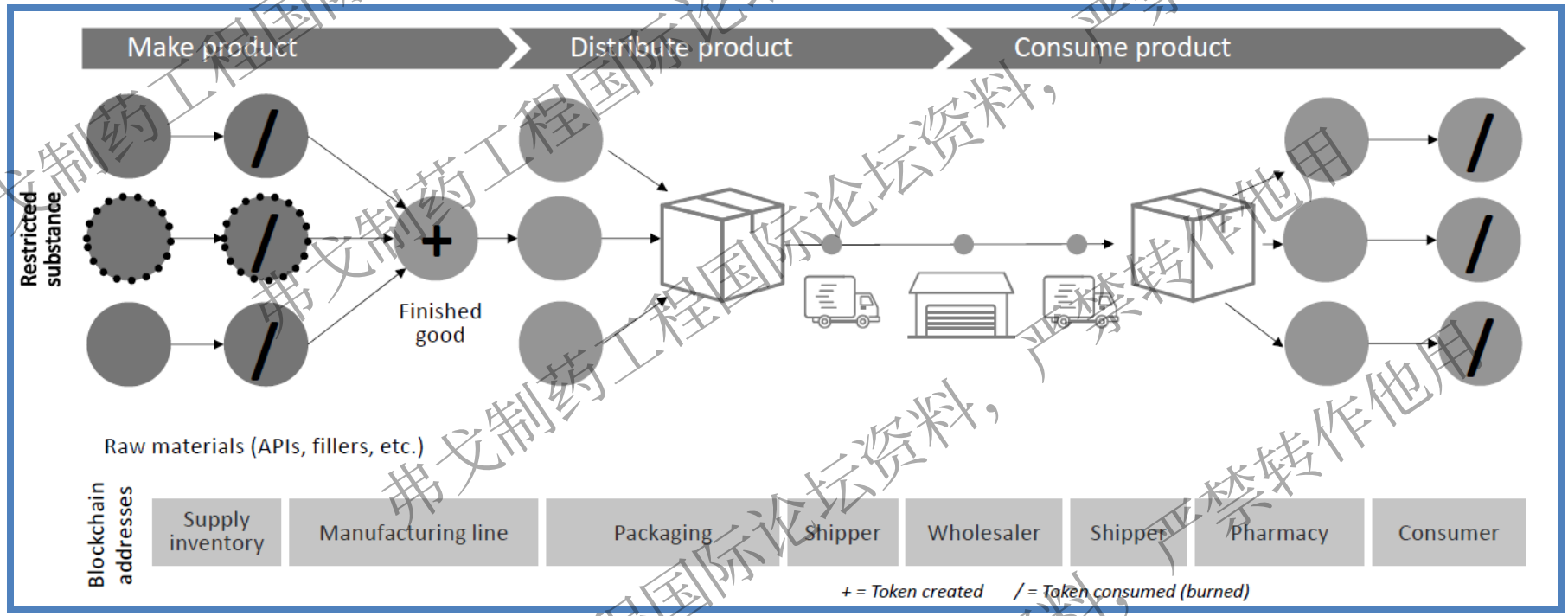
Development of AI and its future state



区块链 与 供应链管理



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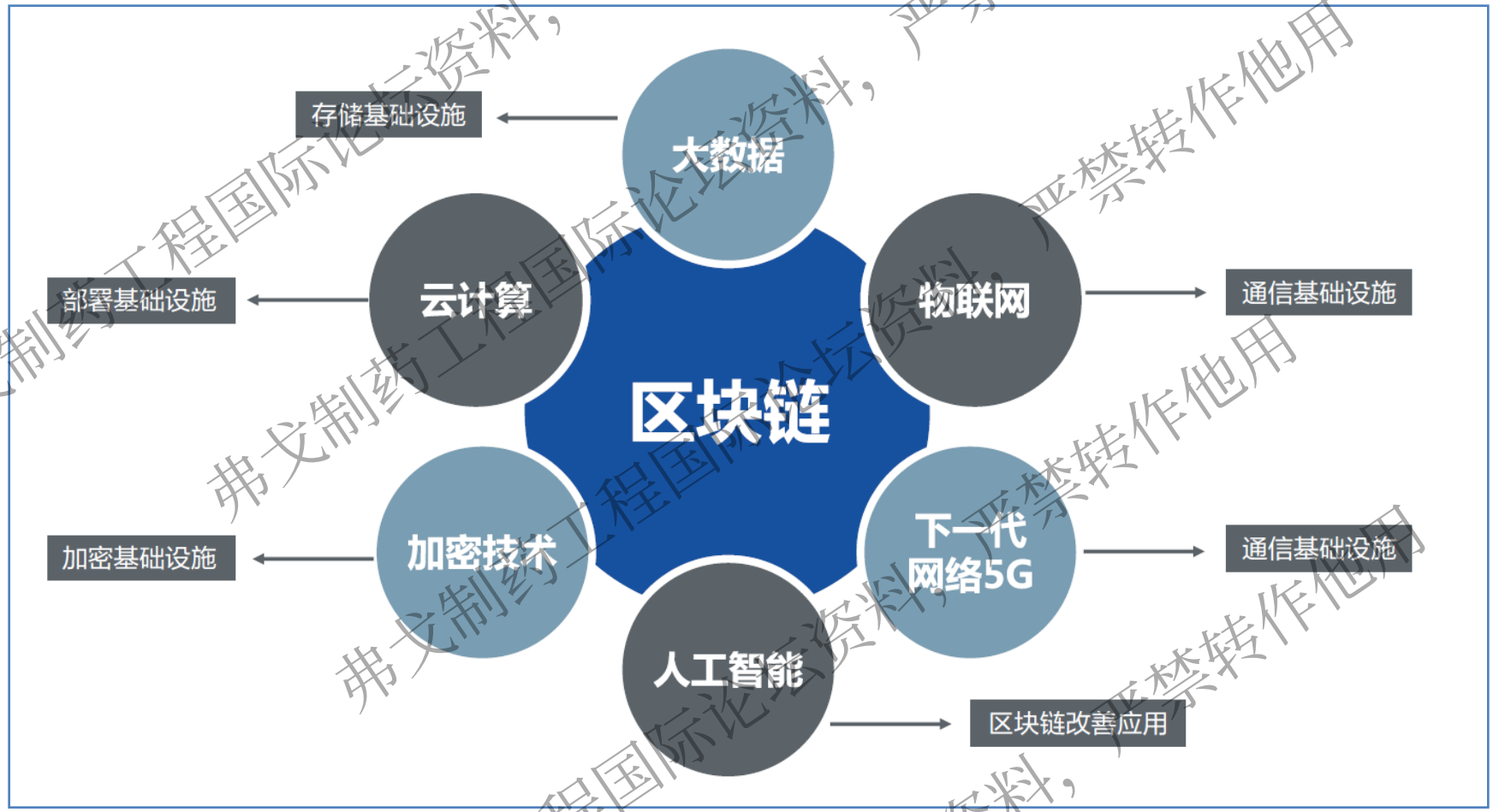

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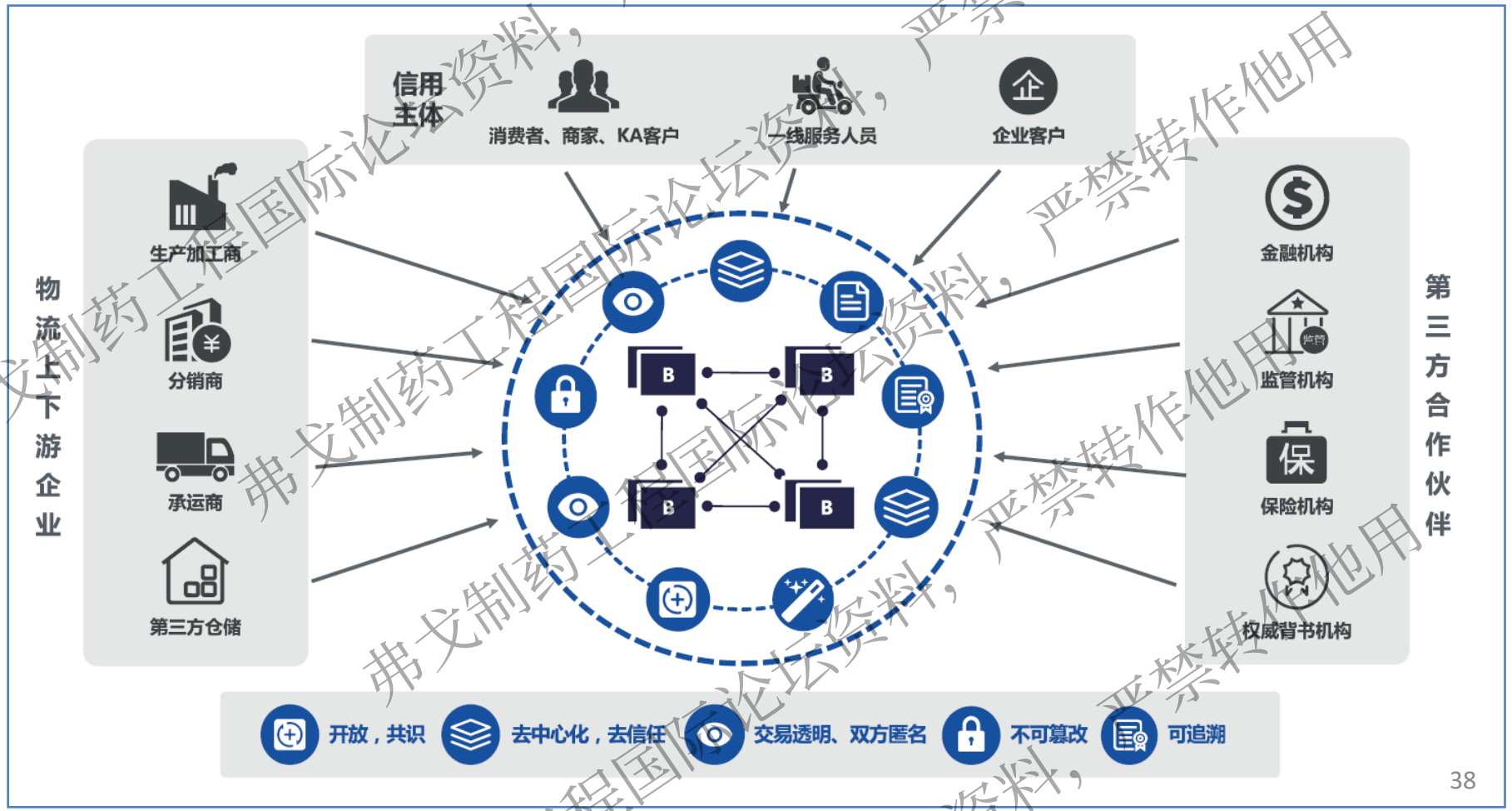

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MFG Process 生产工艺的核心事项

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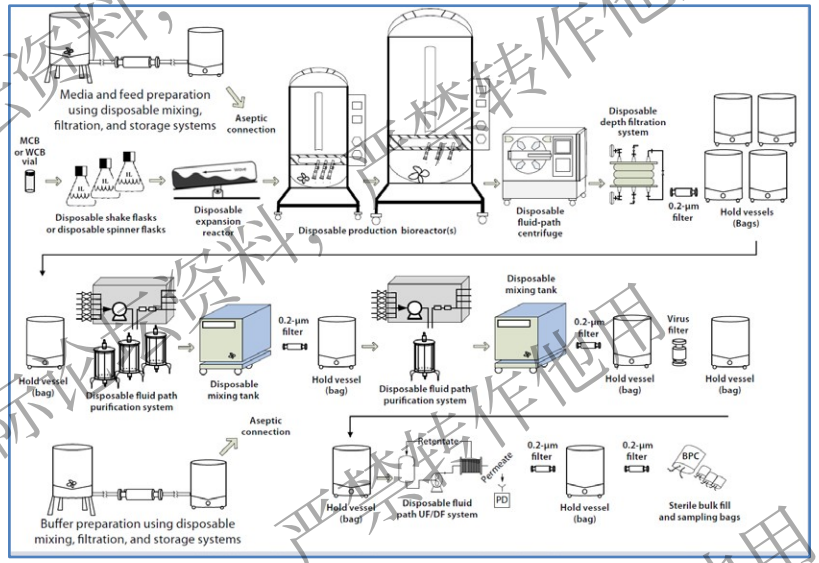
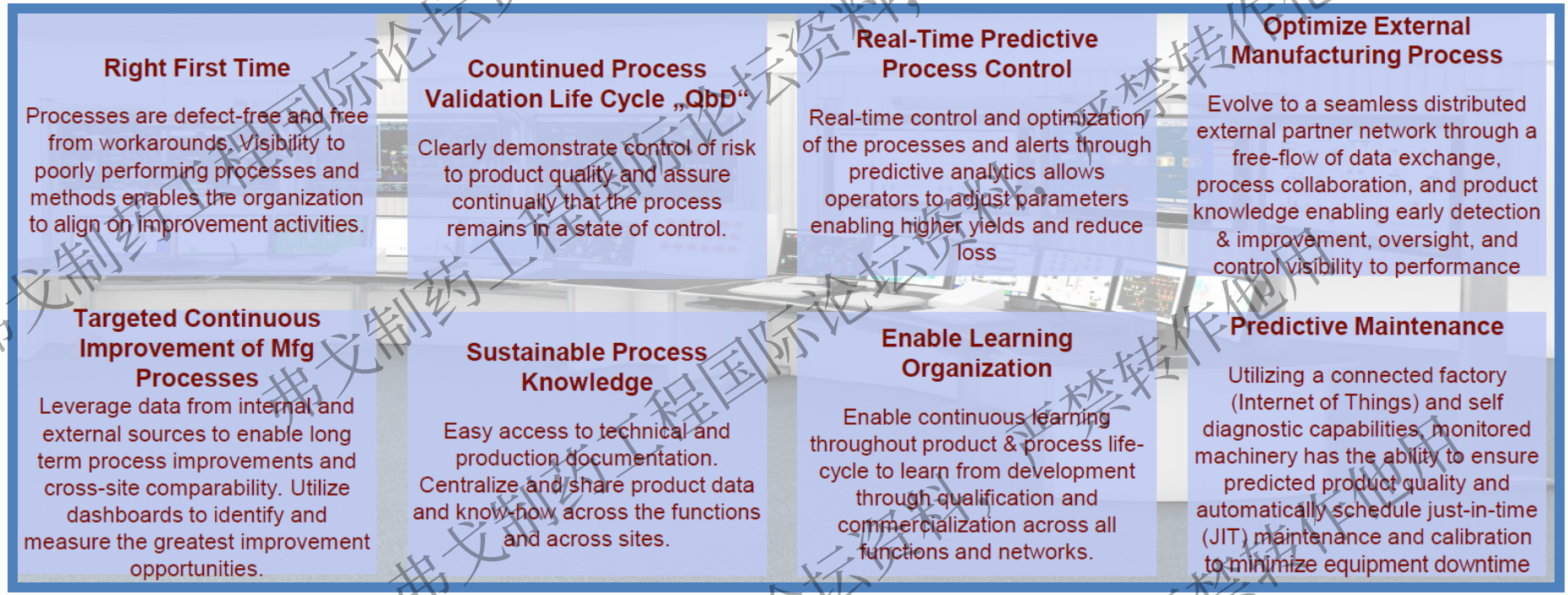
生物制药的未来设施
FoF: The facility of the future

FoF: Beyond MFG Process
不只是生产工艺



Bio-Manufacturing Organization

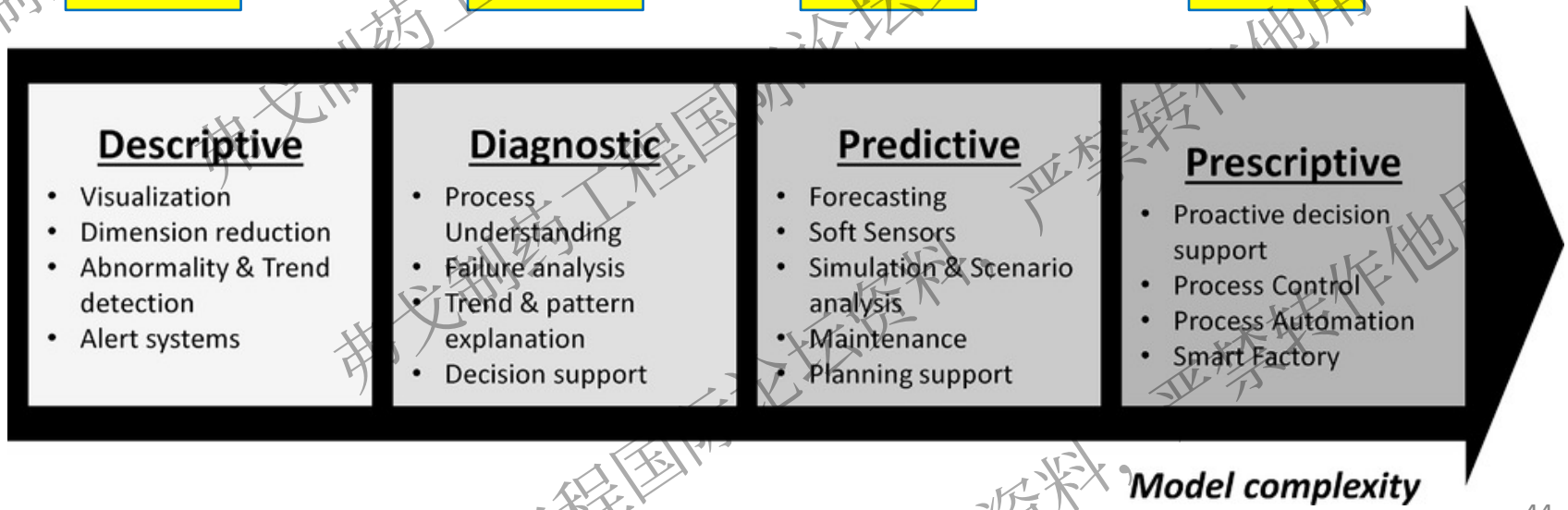
生产信息的智能化 Manufacturing Intelligence (MI)



Core Asset: process /equipment data and product knowledge

生物制药的未来设施的功能
Functions of FoF

告知 **诊断** **预警** **防控**



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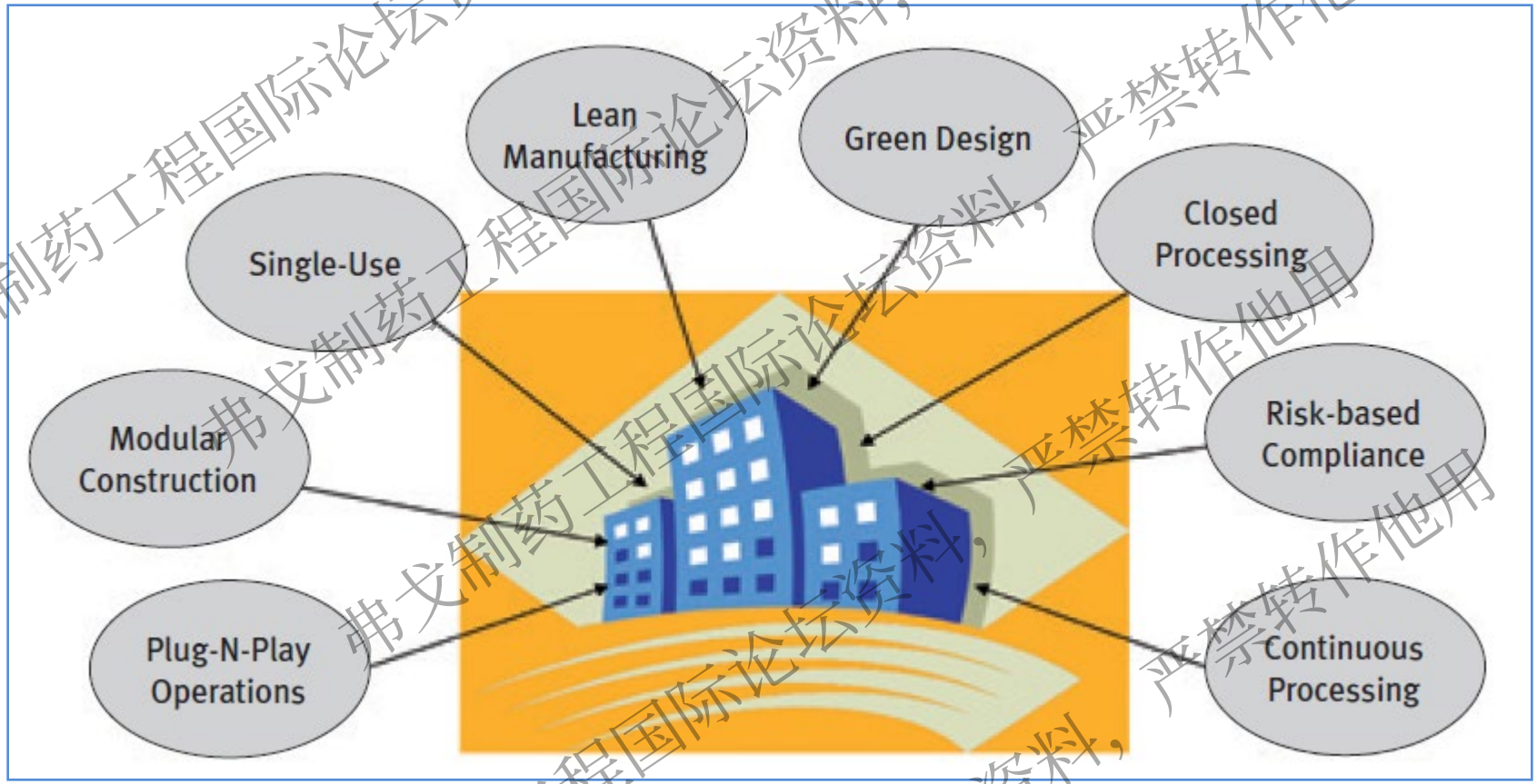
Requirements for the FoF



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

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- **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**

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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.

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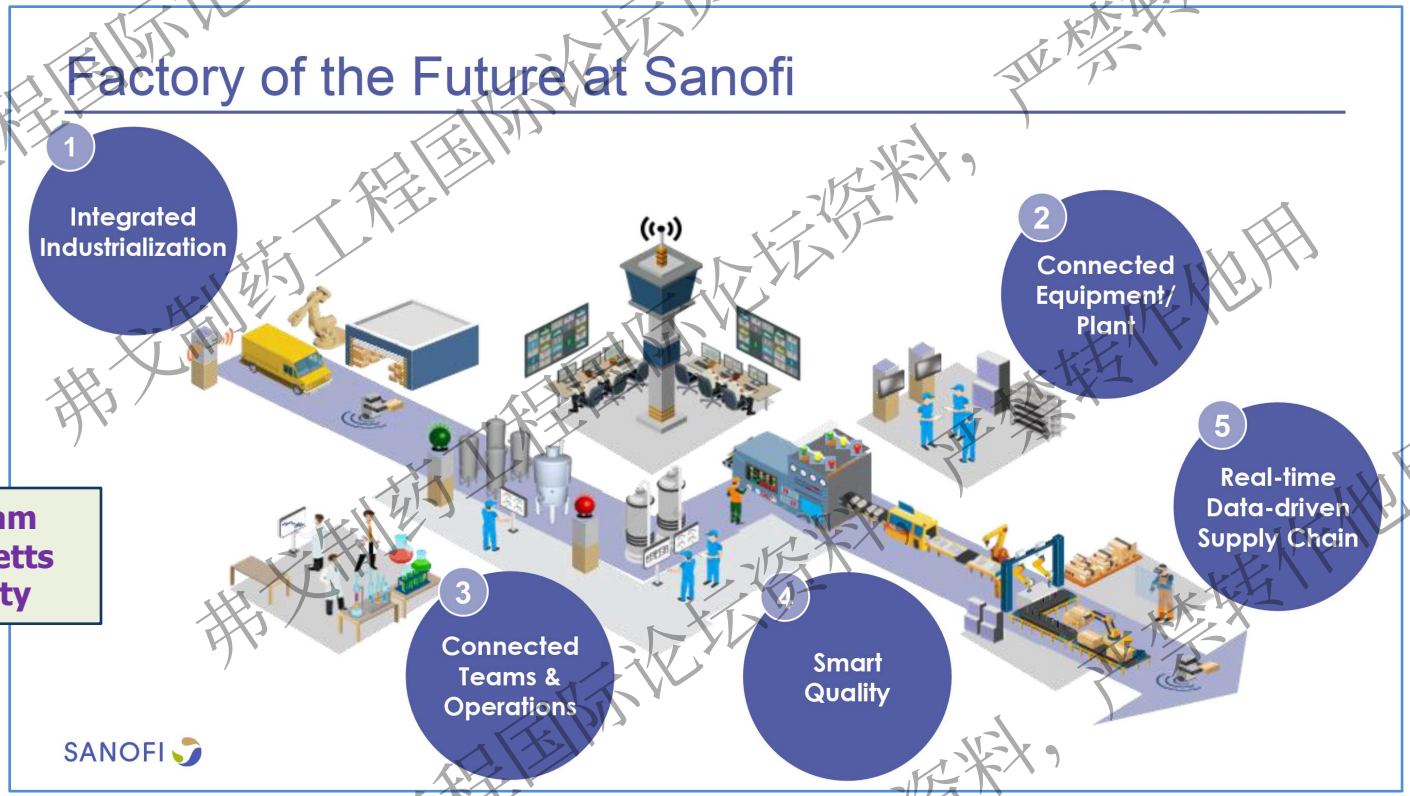
Digitally Enabled Integrated Continuous Biomanufacturing Facility



Framingham Massachusetts USA Facility

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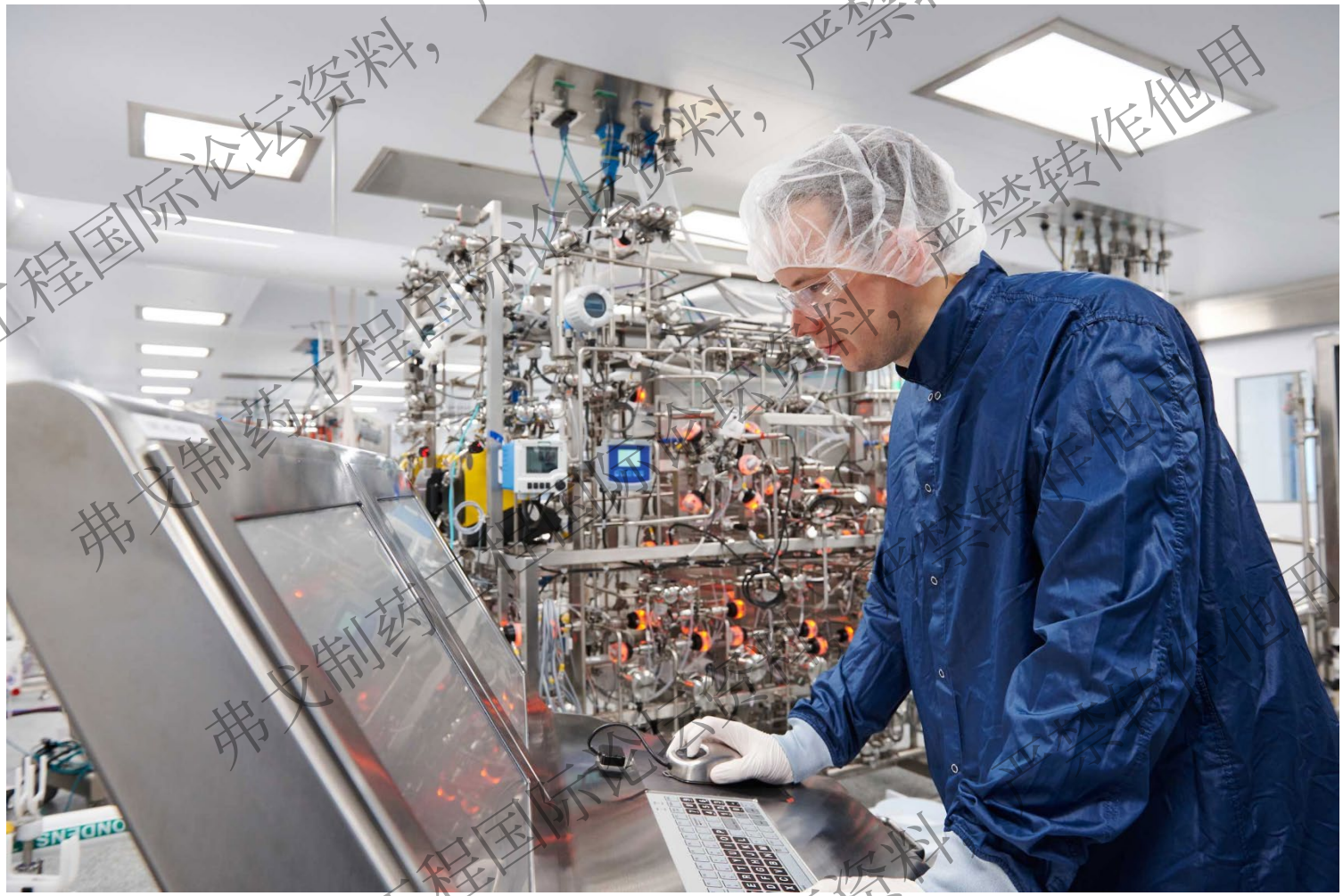

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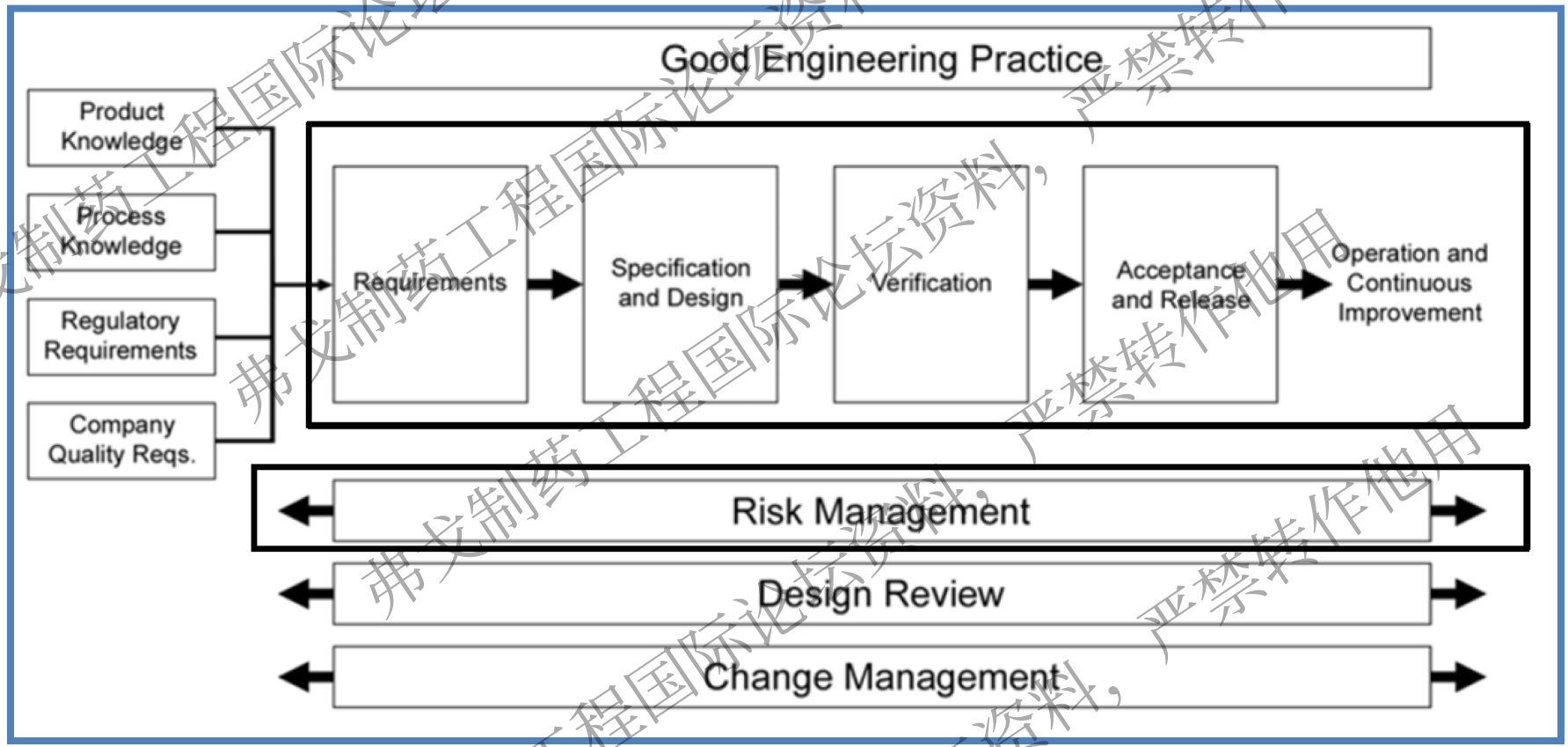
以GEP来 建设 FoF 未来设施



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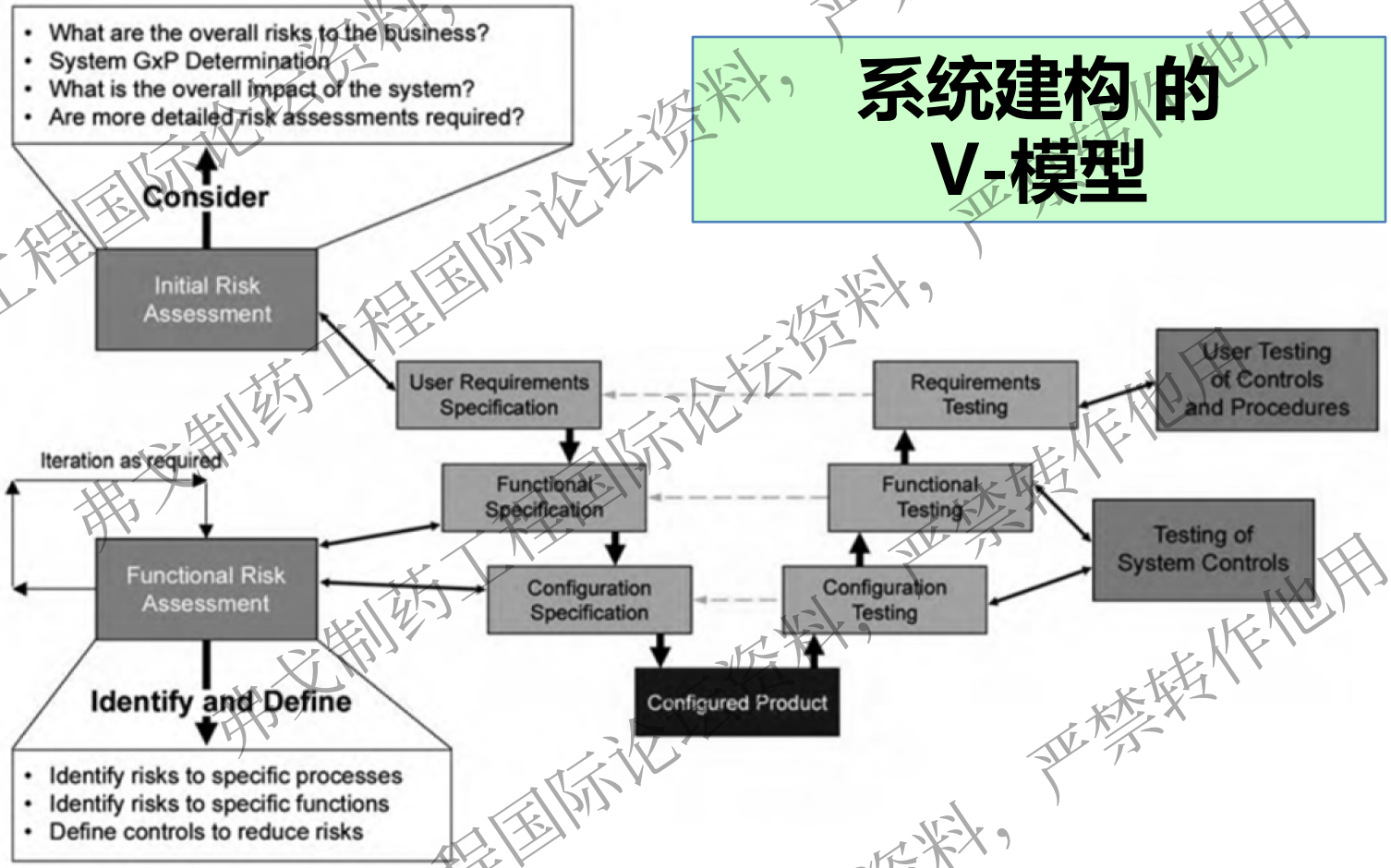
系统建构 的 V-模型



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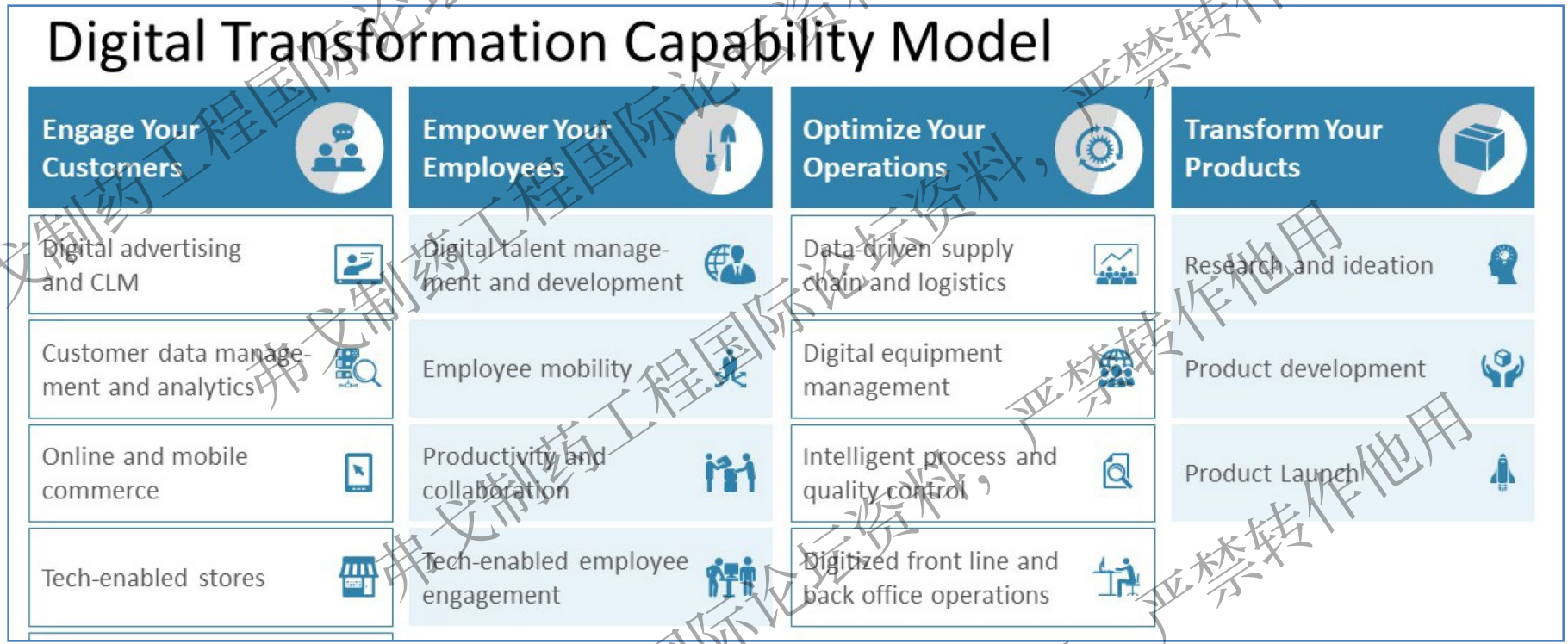
DT 数字化转型 的效益



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设施

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

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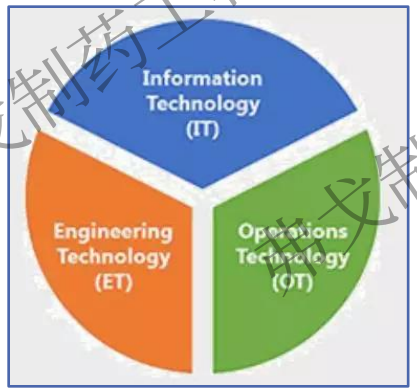
信息技术 IT & OT 运营技术 的融合



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电子批记录 EBR

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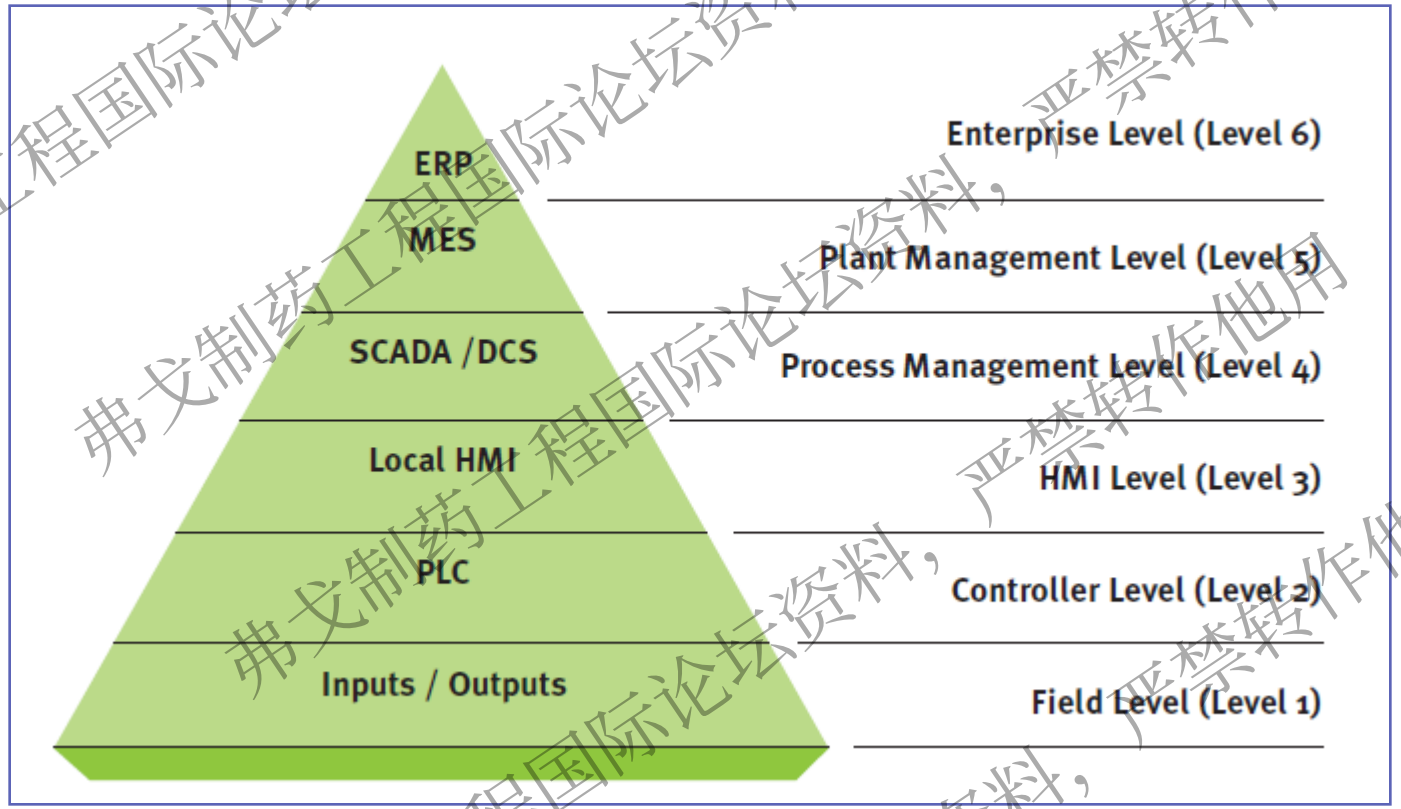
自动化 金字塔 The Automation Pyramid



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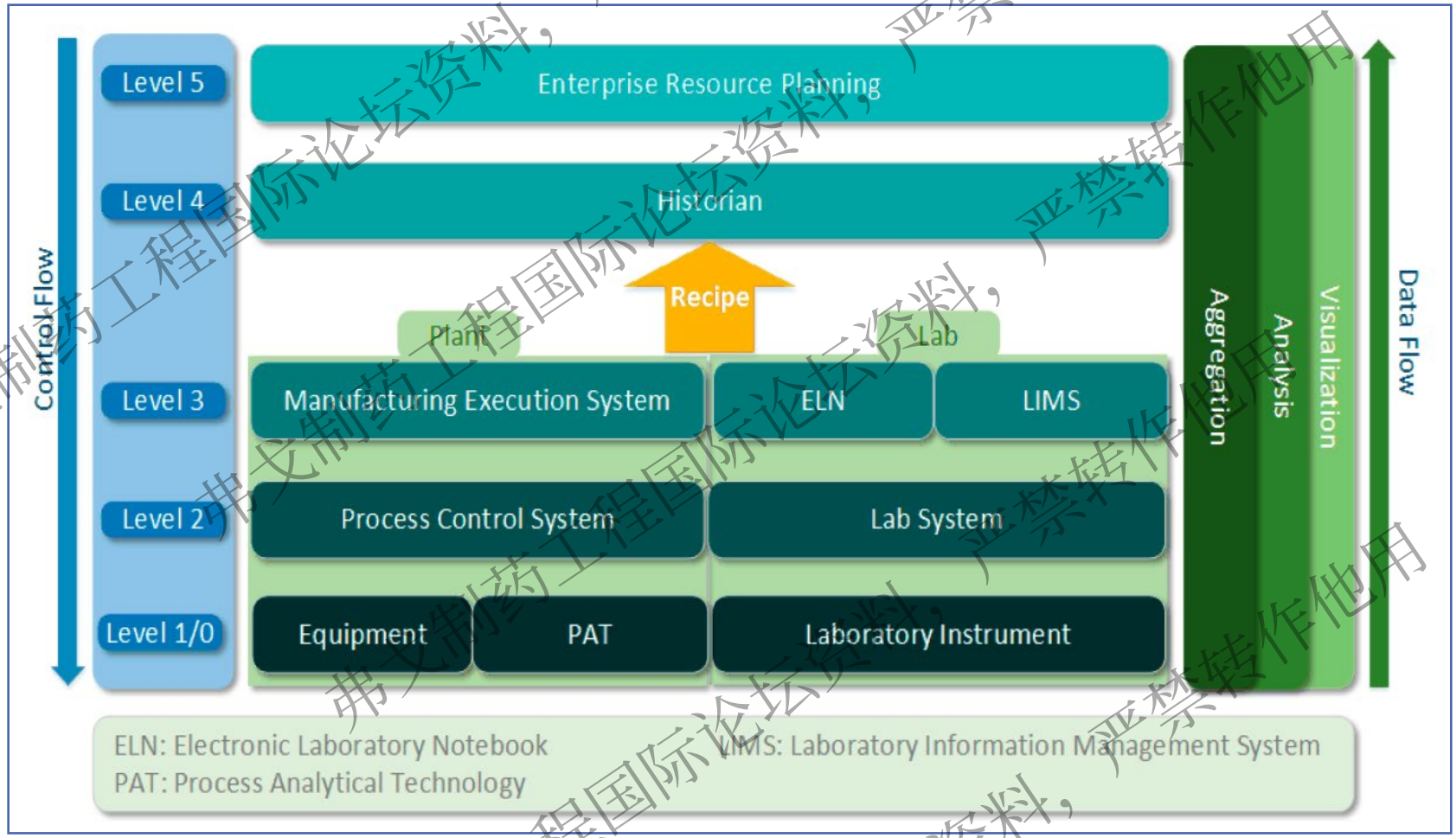

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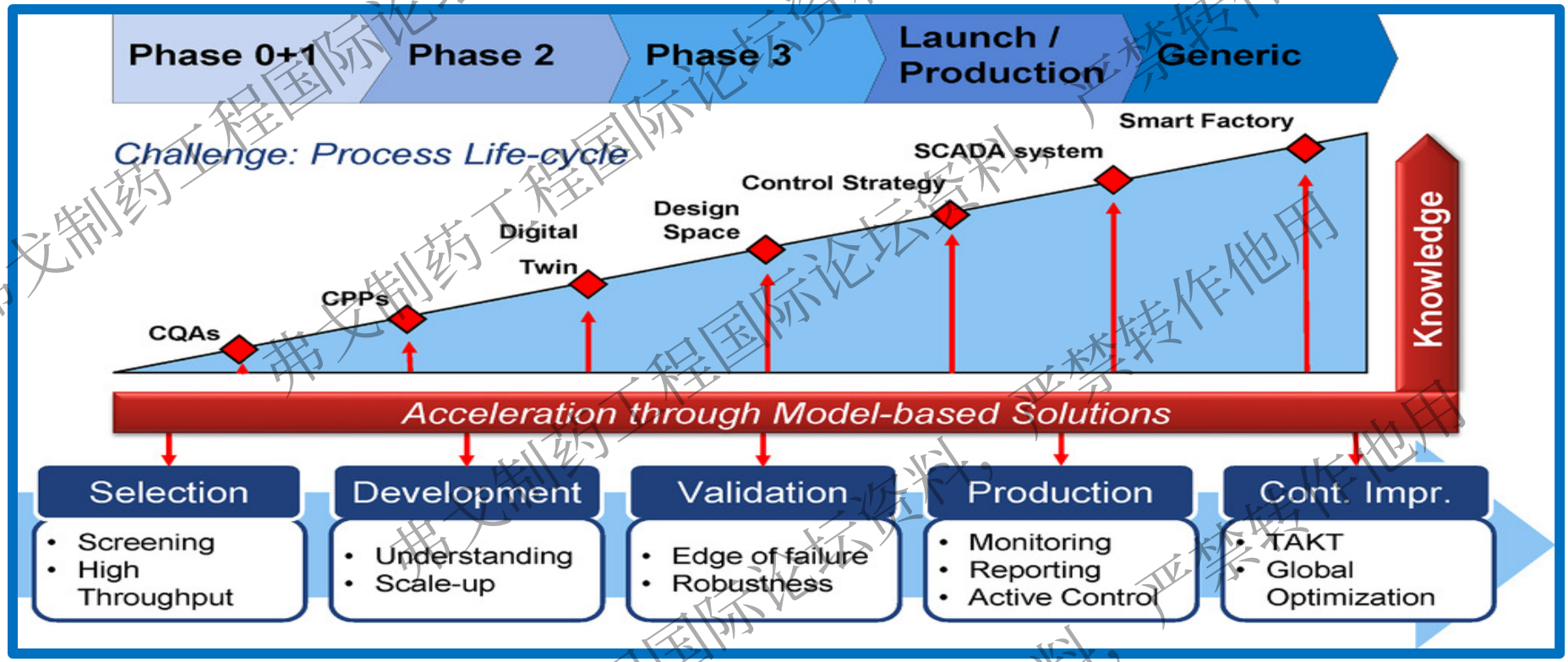
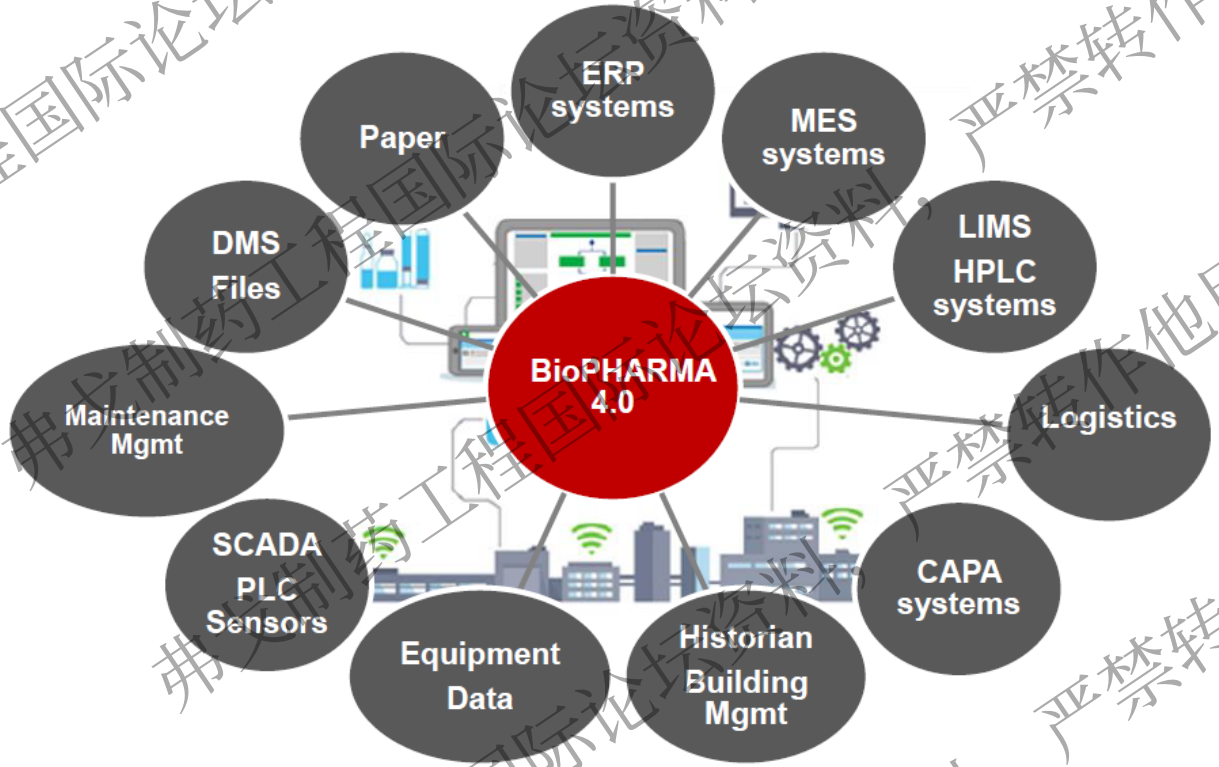
生物制药 数位化生产的时代 Bioprocessing in the Digital Age: The Role of Process Models 工艺模块的角色



End to End, Vertical & Horizontal Integration

Big Data: Overall Data Collection



Across the product lifecycle

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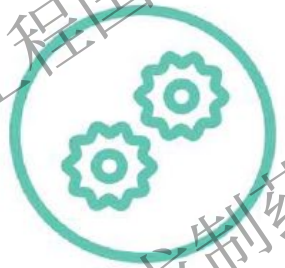
数字化转型助力生命科学企业的机遇



高效
执行

加强各项流程的数字化与合理化程度，从而提升效率、节省成本，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，打造并开展有针对性的互动活动，以满足客户/患者/员工的需求，提升忠诚度

创新
产品与服务

加速开发产品、服务以及新的业务模式，运用数据与创新平台为客户增创价值

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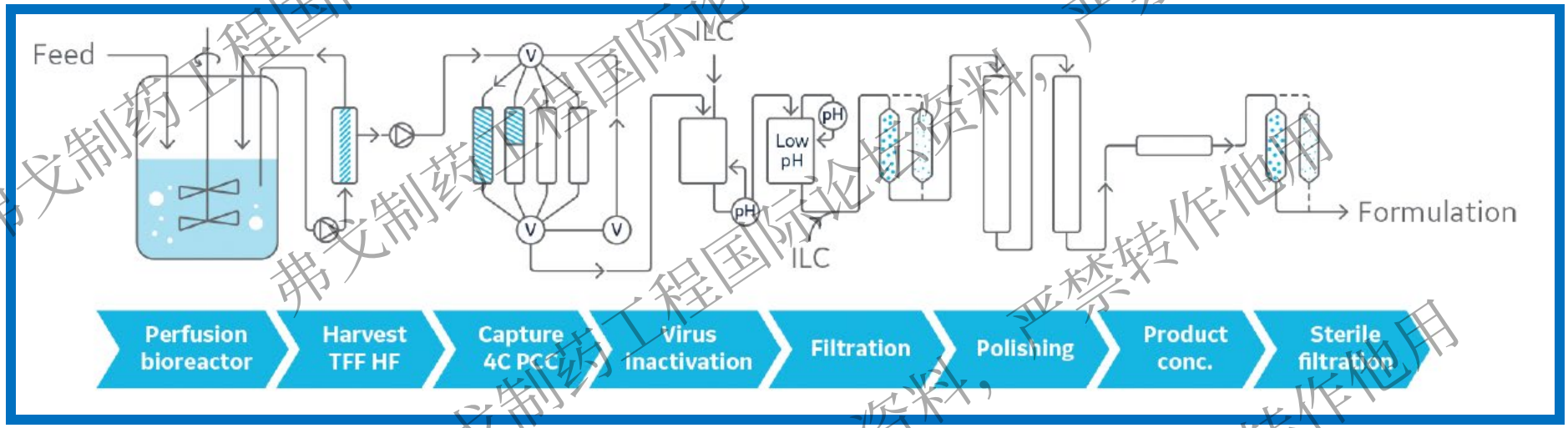
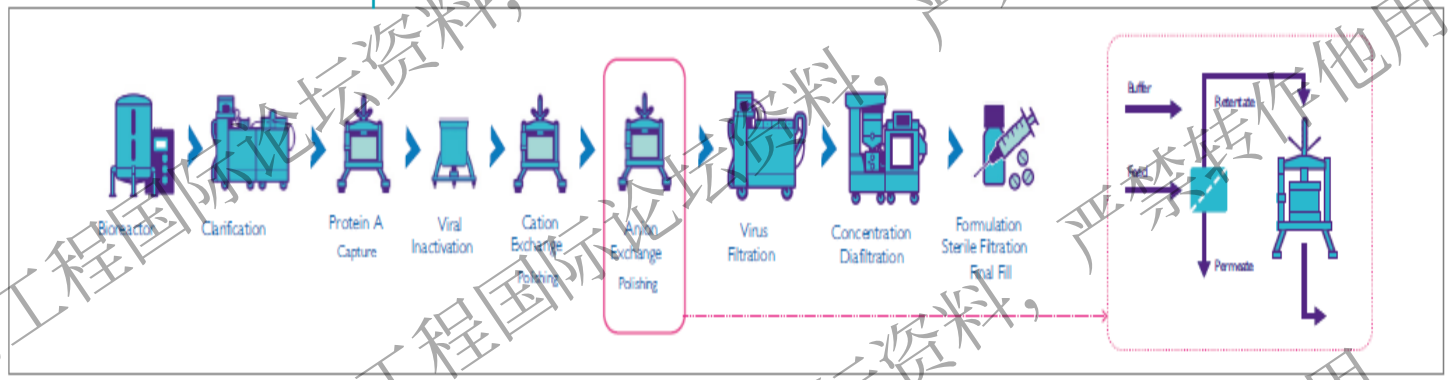
End-to-end upstream and downstream continuous processing



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 resin mass loading.

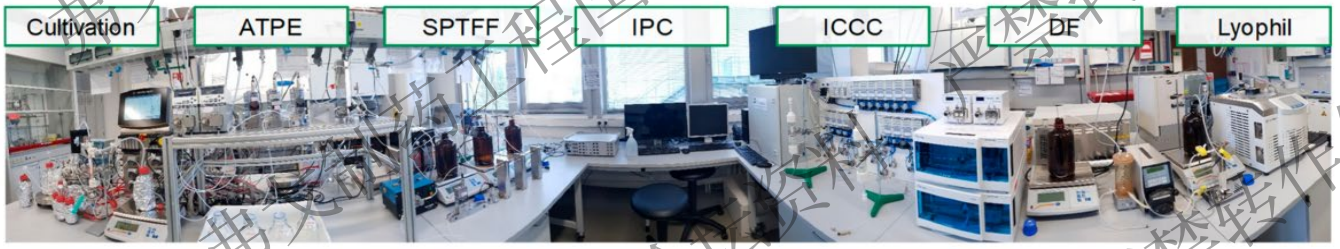


Figure 2. Laboratory set-up of the continuous production of a monoclonal antibody. ATPE (aqueous two-phase extraction), SPTFF (single-pass tangential flow filtration), IPC (interprocess communication), iCCC (integrated counter-current chromatography), DF (diafiltration), Lyophil (lyophilization).

FoF 未来设施 建设基础

FoF Project Enablers

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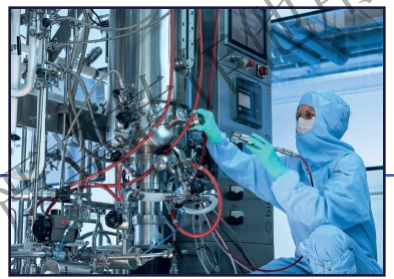
生物制药的未来设施 的实践： 体系

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



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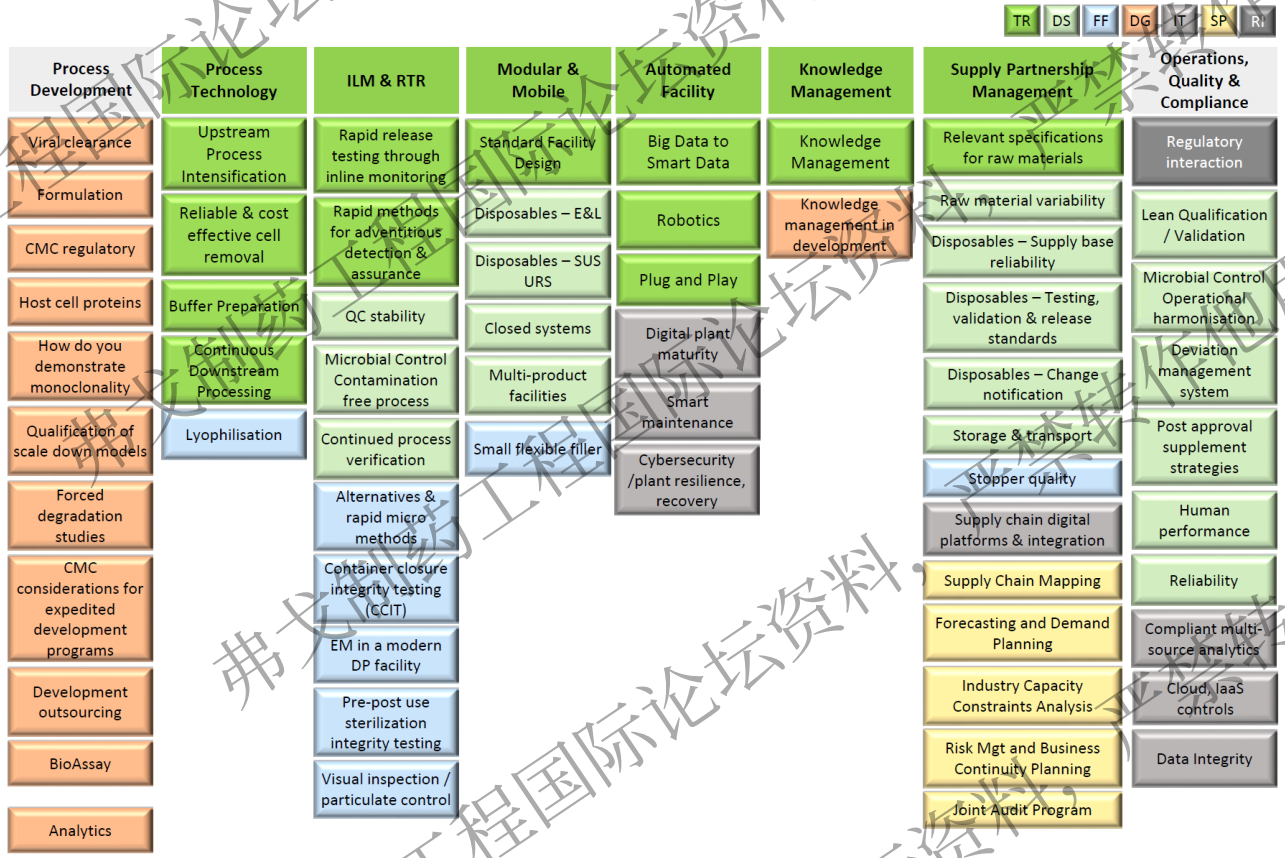
In-Line / Advanced Testing to support Bio-Manufacturing

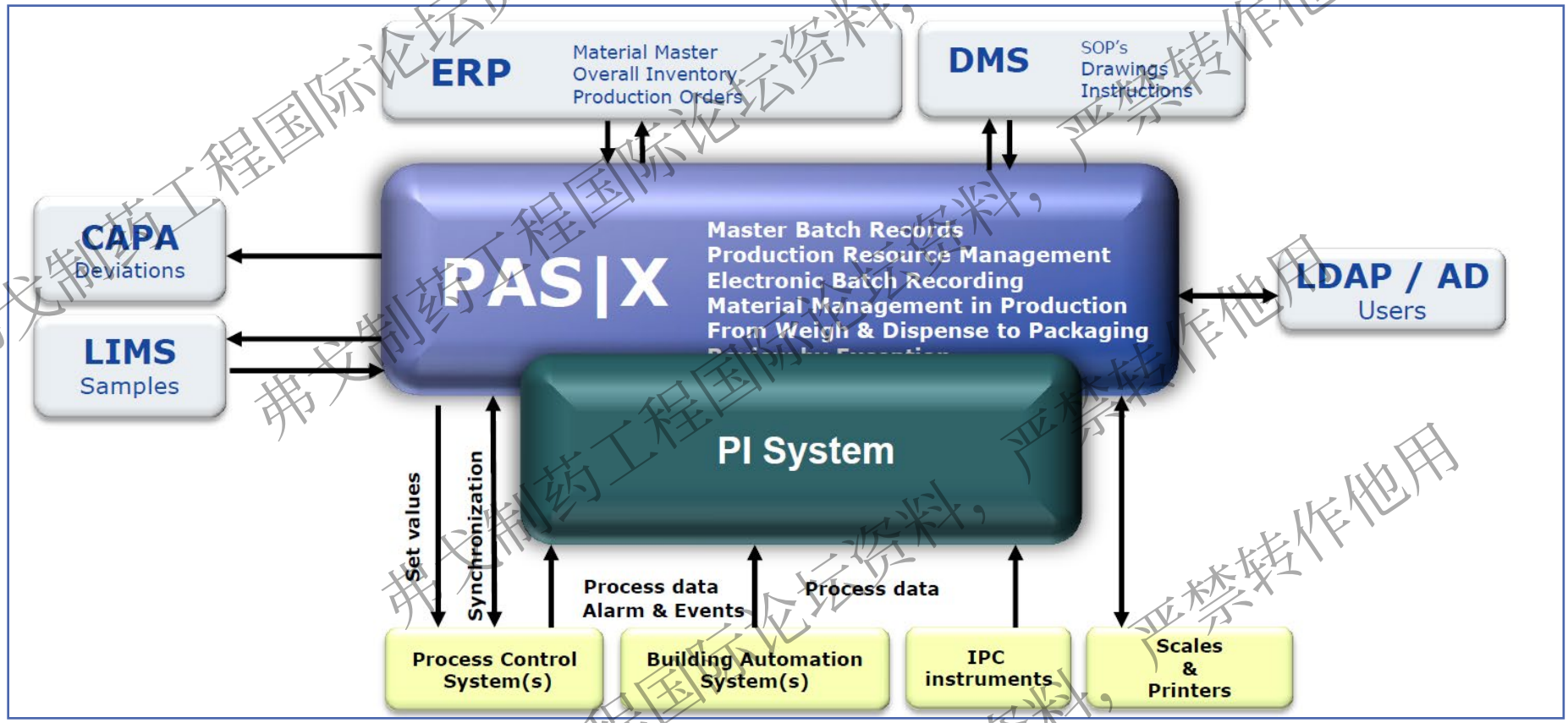
Current State		
Category	**What**	**Where**
General	pH	QC Lab
	Osmolality	
	Color (visual)	
	Turbidity (visual)	
Quantity	Protein Conc by RI	
Identity	ICIEF & Binding Assay	
Purity/Impurities	UPLC-SEC	
	Non-Reducing CE-SDS	
	Imaging Capillary IEF	
Biological Activity	Binding Assays	
Safety	Bioburden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

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



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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

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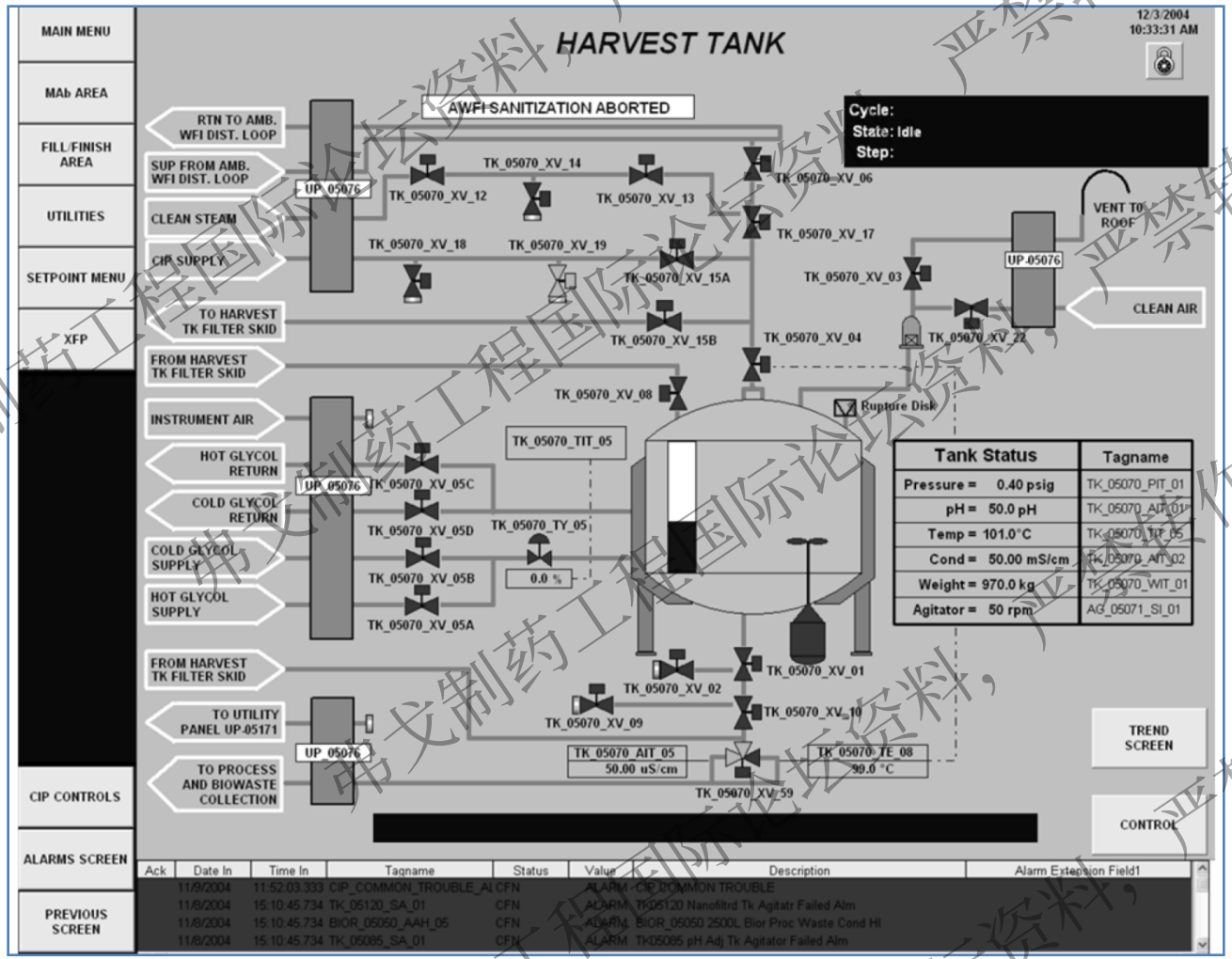

自动化系统的演变

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Automation Advancements – S88 (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.

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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.

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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

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Portable Wireless Workstations

移动式
工艺
控制站

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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).

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Business / MFG Intelligence

BI / MI 秀才不出门

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