未来制药设施的建设与运营

Delivery & Operation of the Manufacturing Facility of the Future

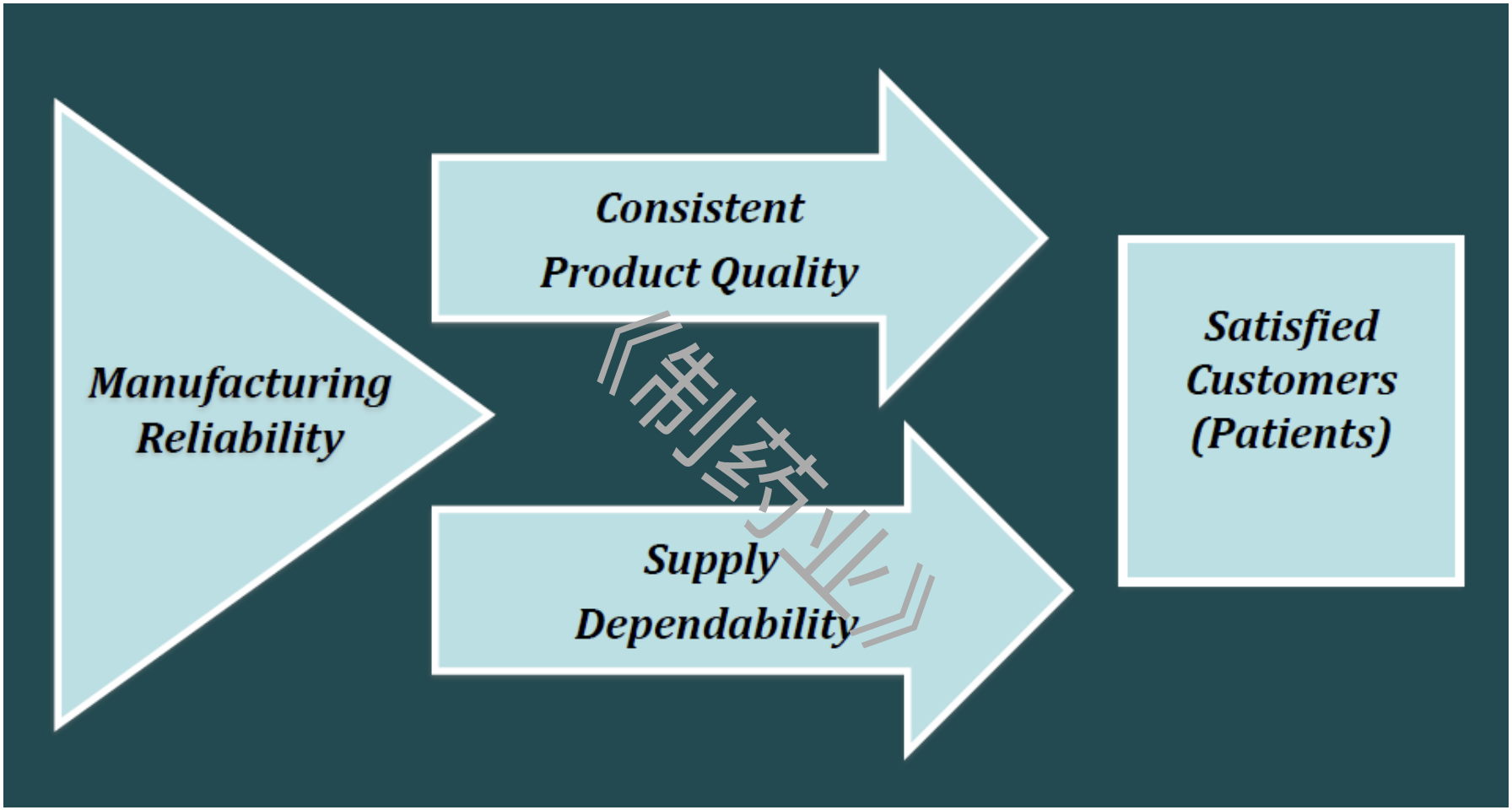
李树德 Michael Lee

May 2016

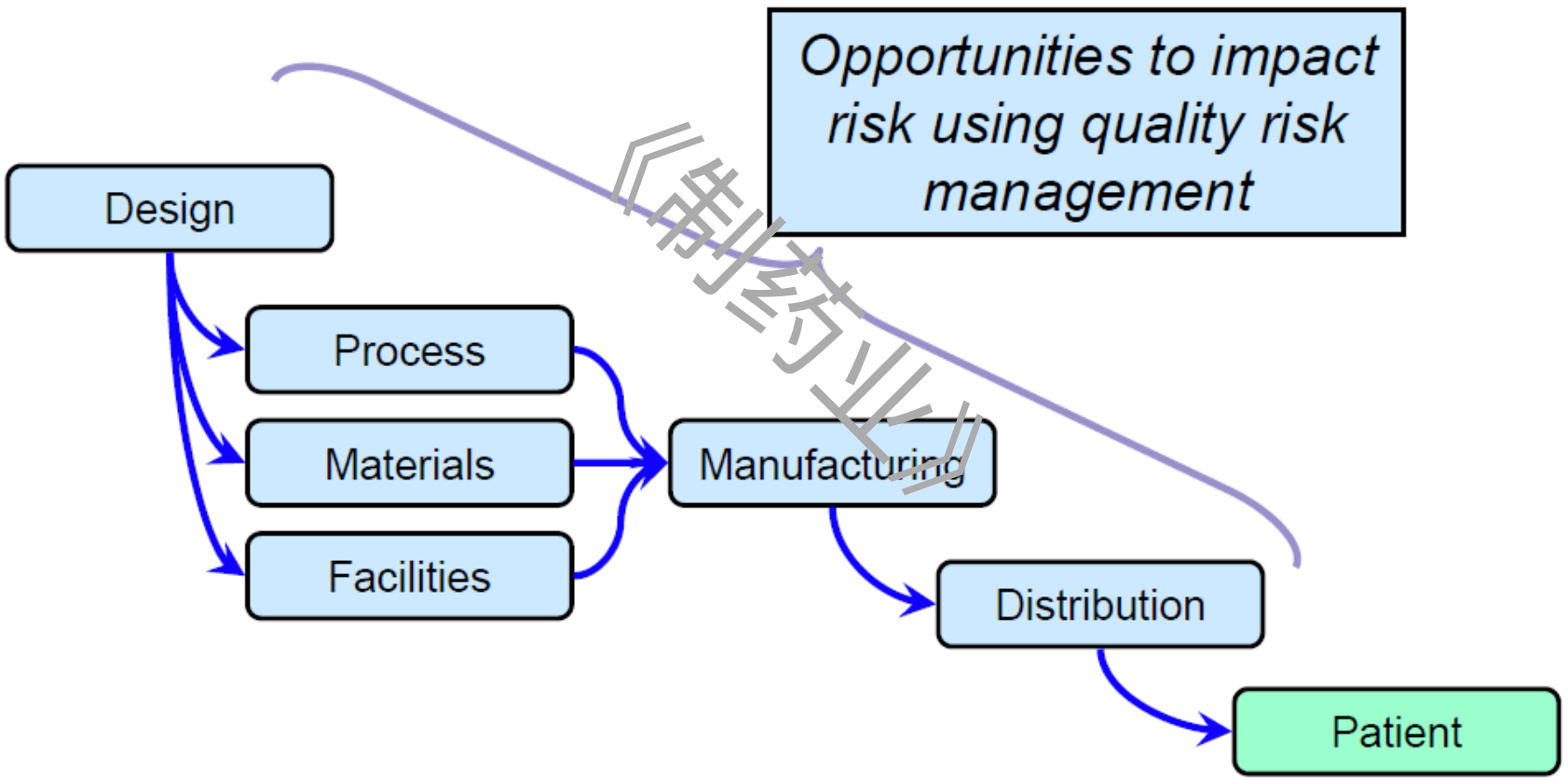
FoF

Facilities of the Future

制药企业 未来新厂


Manufacturing Reliability
Consistent Product Quality
Supply Dependability
Satisfied Customers (Patients)

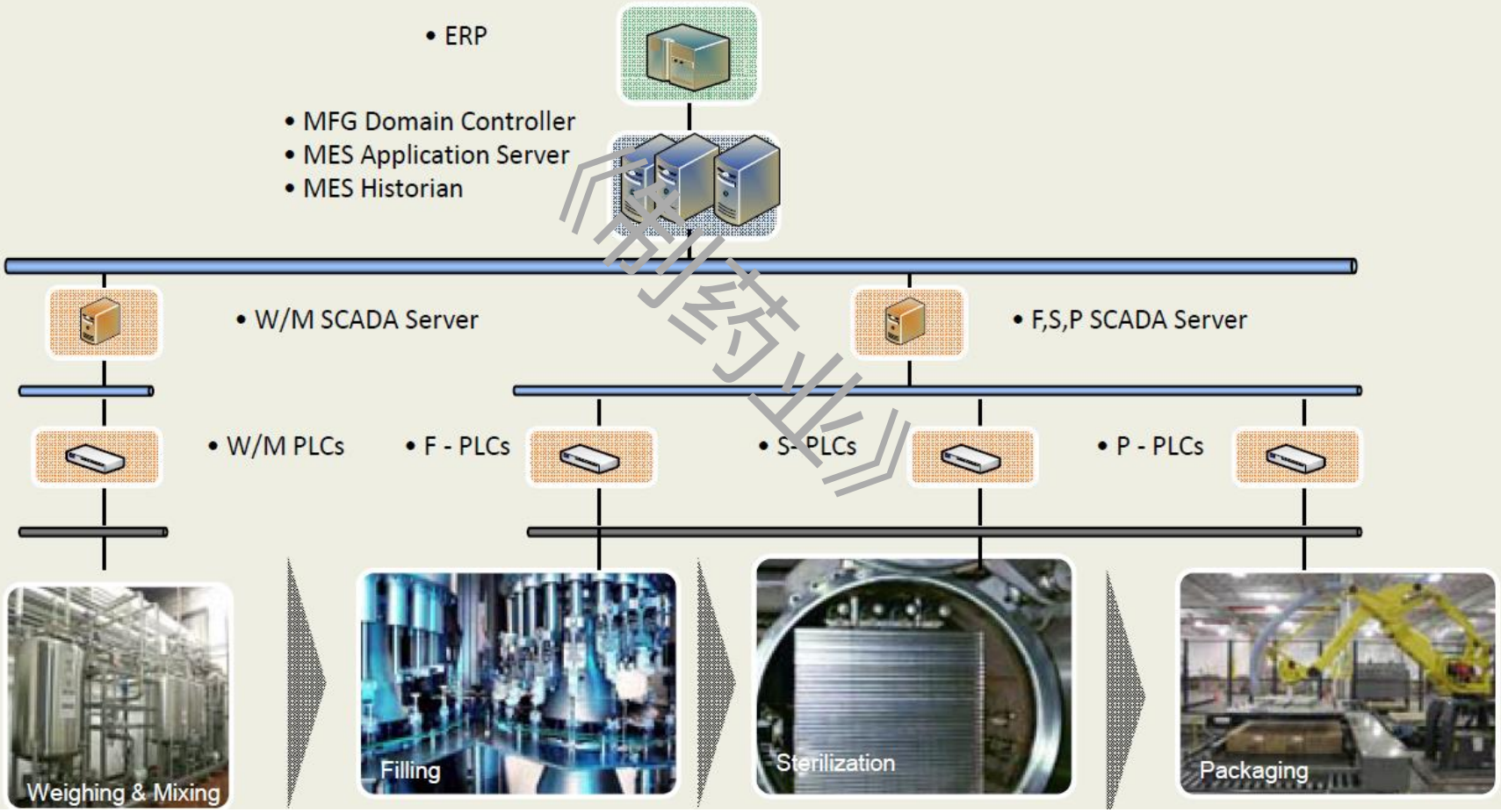
Link to Patient Safety




Pharmaceutical Development
Technology Transfer
Commercial Manufacturing
Discontinuation
Investigational products
GMP
Management Responsibilities
Process Performance & Product Quality Monitoring System
PQS elements
Corrective Action / Preventive Action (CAPA) System
Change Management System
Management Review
Enablers
Knowledge Management
Quality Risk Management

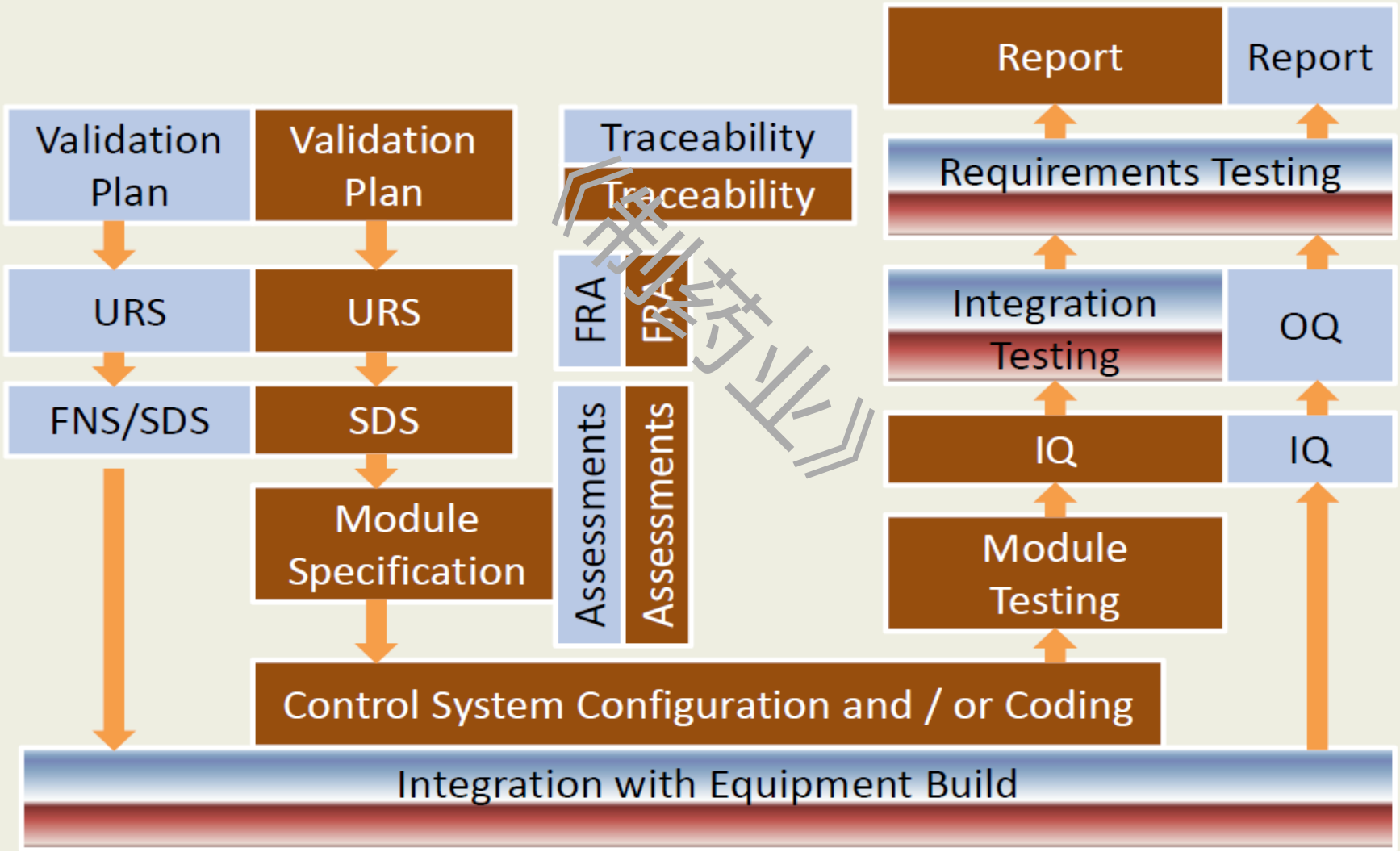
What is the architectural concept of a “Data-Driven Environment”

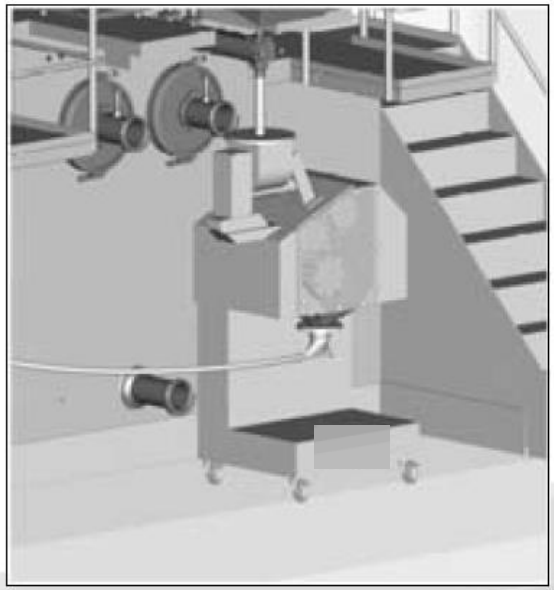
3. The Data-Driven Environment



How to Qualify the Integration ?

2. Deliverables





- Auto W&D
- Granulation
- Drying/Milling
- Blending
- Compression

4400

9800

2350

Linking Process - Product - Patient

Patient

Product

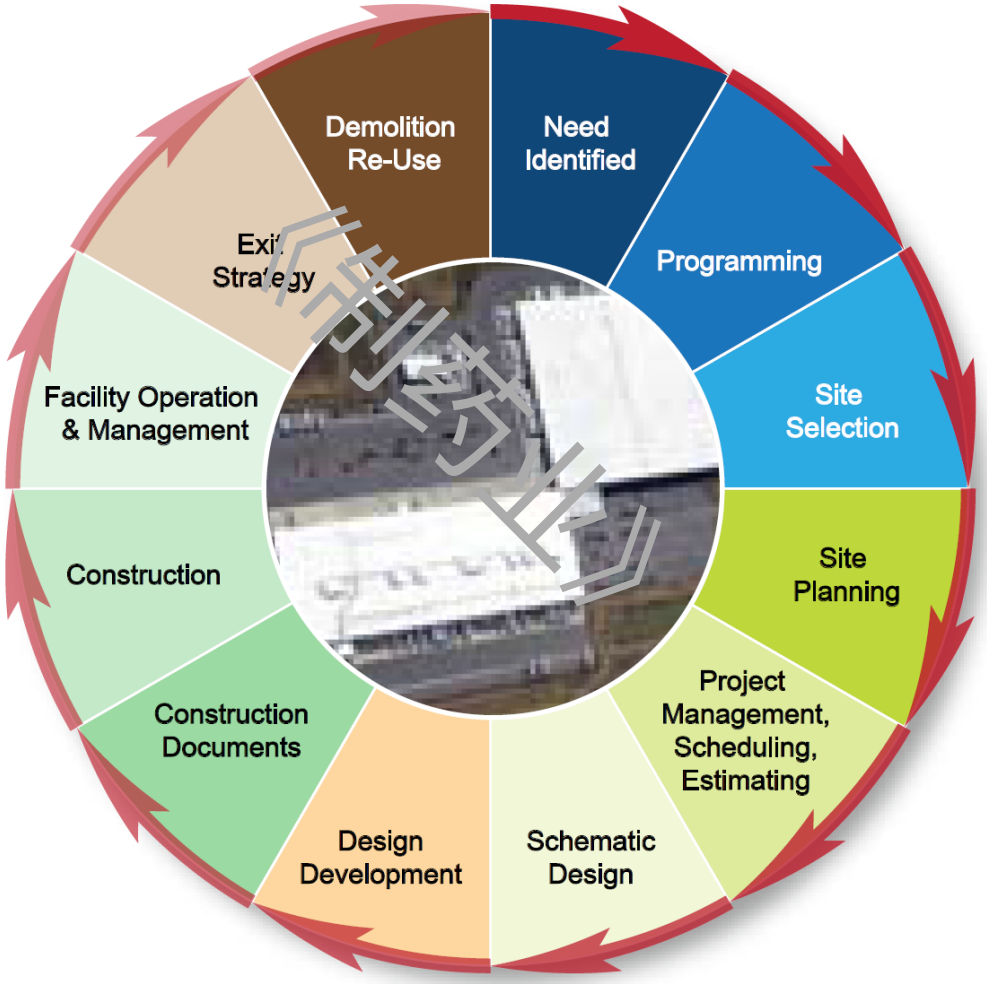
Process

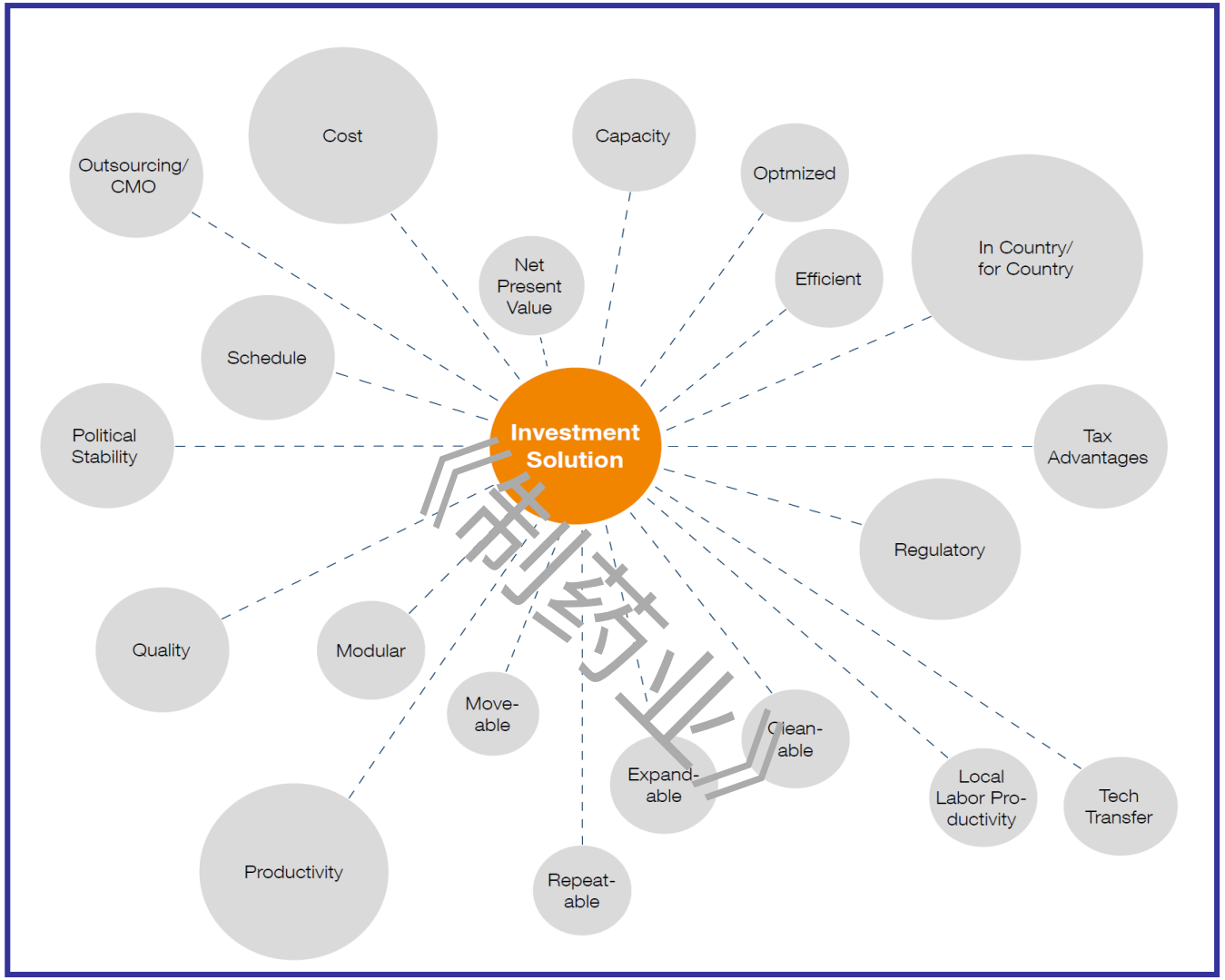
Quality Target Product Profile

Critical Quality Attributes

Material Attributes & Process Parameters

Facility Life Cycle

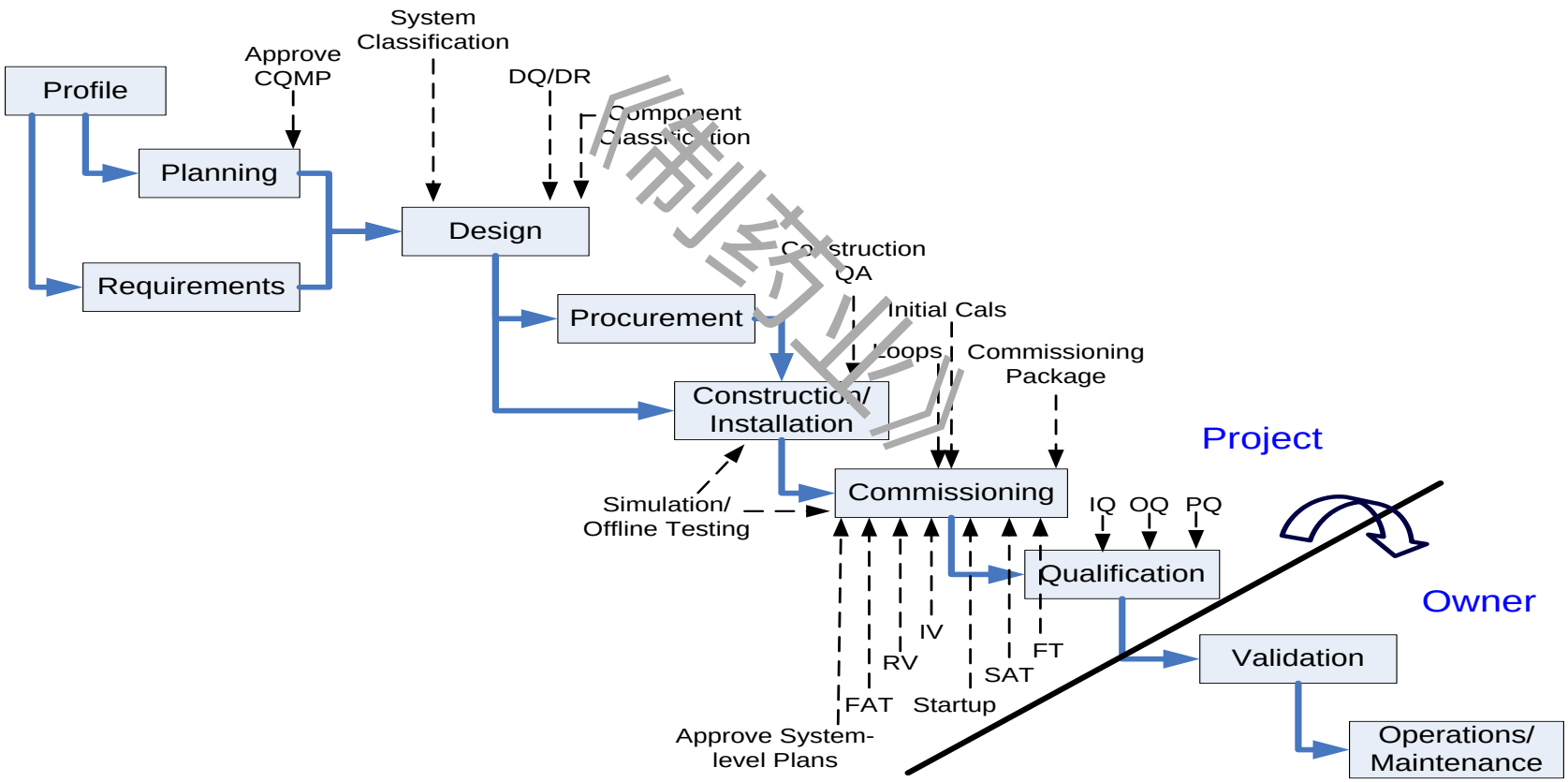




项目的投资决策

Project Investment Decision

Facilities Project



A bridge to the future for Manufacturing with the advanced Facility Planning & Project Delivery

良药苦口（病患）（工艺、设备）
苦口婆心（药监局）（合规）
心想事成（药厂）（FoF 未来工厂）

Ethical Business Supported by Technology, Engineering and OPX Operation

三工：工艺技术、工程设计 与 工厂运营

OPX: Operational Excellence

卓越的工厂运营

- Higher R&D activities
- Distinction between launch and production facilitiy
- Personalized medicines
- Smaller and individual production
- Reduction of ‘time to market‘
- Small batch sizes
- More dedicated products with high-potent technology
- Continuous and Lean-manufacturing
- Flexible facility solutions

FoF Trend
未来工厂的趋势

- **GMP-Requirements**

<u>Production of high-potent products:</u>

- **Personalized medicine**
- **Safety and Environment**
- **Qualification and Validation**
- **HVAC and Cleanroom applications (hygienic zoning concepts)**
- **Personnel training**
- **Process Automation and Controls**

Challenges of FoF
未来工厂 的 挑战

Flexible Production and smaller batch-sizes

Life Cycle Cost Consideration

- Energy Efficiency and enviornmental foot-print are of higher importance
- Return Air-Units including high efficiency heat-recovery systems
- Qualification / Validation strategy

Time to market

- Fast project execution scenarios
- Project schedule and budget

Challenges of FoF

未来工厂 的 挑战

Challenges facinging
pharmaceutical companies
with respect to:
Design, Construction & Operation of Plants

FoF is to deliver on unexpected targets and respond rapidly to changes.

未来新厂的挑战：
设计、建设与营运

Higher titers, smaller batches, higher potency products, complex delivery forms all challenge the traditional paradims in the way we design and operate manufacturing facilities.

未来新厂的挑战：
设计、建设与营运的新思路；
多、快、好、省。

Drivers for FoF

- **Business Drivers – impact of property, plant, and equipment on the bottom line; reduced depreciation targets across asset base.**
- **Capital Drivers – limited future capital availability, need to improve cash flow objectives to achieve lower overall cost of new assets.**
- **Asset Utilization – provide higher utilization of manufacturing assets.**
- **Timelines – reduce construction timelines to defer capital spending and enable emerging market development of new assets.**

制药行业的工厂的角色
支持业务的发展、投资回报、
资产利用率、建厂的效率

Excellence and Compliance

FoF is to maintain a facility that uses operational excellence to remain in compliance with appropriate regulatory guidelines.

Current Good Manufacturing Practices (cGMPs) and process validation define standards for regulatory inspections and product submissions for approval.

Manufacturing excellence is a set of requirements necessary to be compliant with pharma regulatory guidelines and in combination of complete knowledge, understanding, and implementation of all other applicable guidelines (e.g. HSE) to assure full compliance at all times.

绩效 与 合规

Investment & Operating Costs

In terms of pharmaceutical manufacturing facilities, the overall cost of manufacturing a product can be viewed as a combination of operating and capital costs.

With the current cost pressures on the industry as a whole, understanding and controlling both of these costs is critical.

固定成本、运营成本

Despite the growing plant automation, the flexibility, People, With the decision-making capabilities will stay as the core competency.

自动化 与 人才

Flexible Facilities

- Lower cost of expansion and scalability
- Enables fast-track construction
- Compliant engineering turnover package
- Multiple technologies and products
- Configurable systems
- Flexible process systems
- Pre-engineered solutions

弹性化的设计、快速的建设与合规的运营：
成本节约、技术、软件、工艺

Manufacturers will have to achieve the globally-standardized plant floor, harmonizing, supervising, and coordinating execution activities across the company's and suppliers' global SCM network .

全球一致化的车间设计、
全球一致化的供应链管理网络。

The factory of the future will be measured according to its production capability and flexibility.

车间设计 的 产能规划与 调整 弹性 。

More companies expect that their production processes will be largely or completely automated/computerized in the years to come.

自动化的程度 持续提升

（德国）工业4. 0

中国制造2025

智能化 制造

More and more companies will give up to make-to-stock (MTS) and will be heading toward make-to-order (MTO).

未来工厂的 生产计划 从 MTS 安全库存 导向 转为 MTO 订单生产 导向。

Energy – Waste – Water – Emission

Optimization of energy efficiency in classified cleanrooms

Monitor air exchange rates with continuous counting of particles

Adjust the air exchange rates in accordance with the user profiles

Adjust the air exchange rates in accordance with the personnel flow

Adjust the ISO class according to open and closed processes

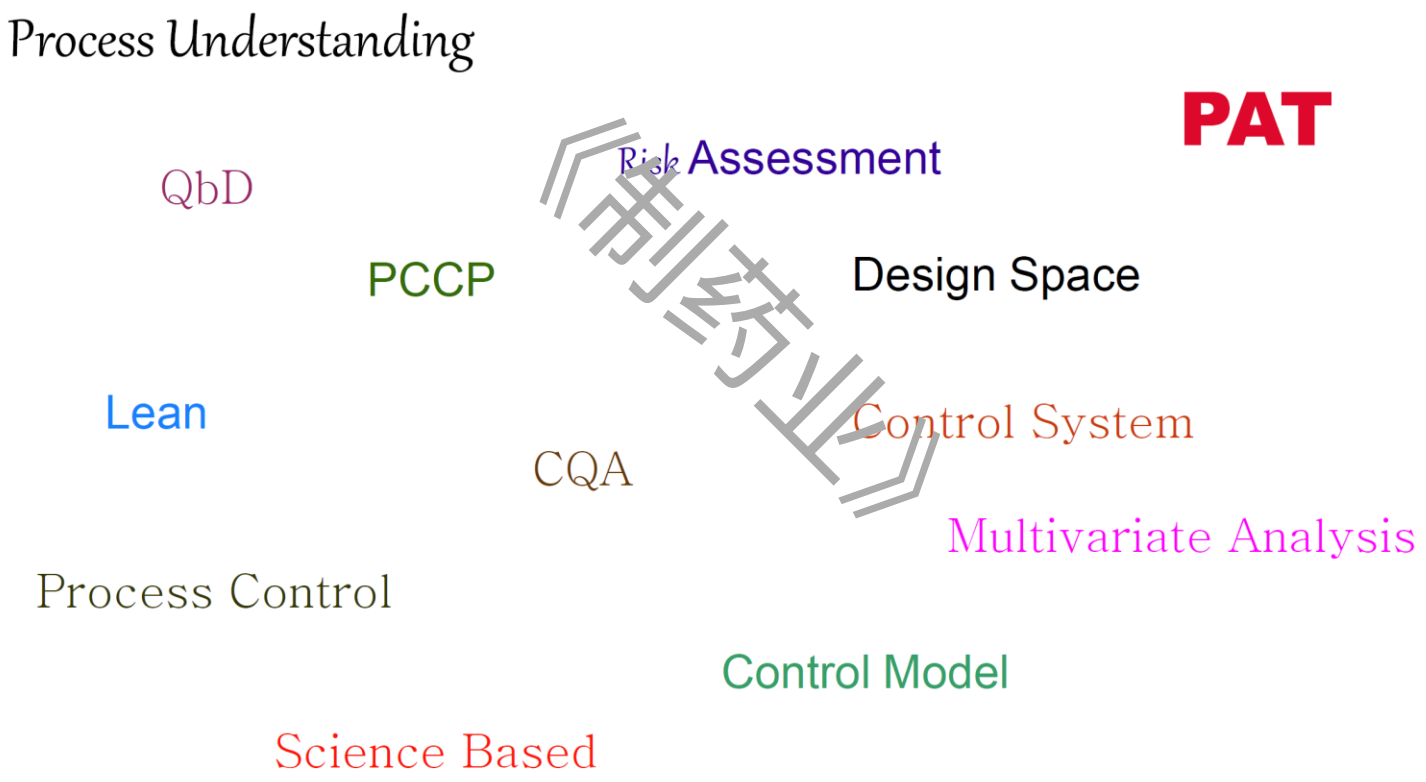
Adjust the lighting according to the user profile

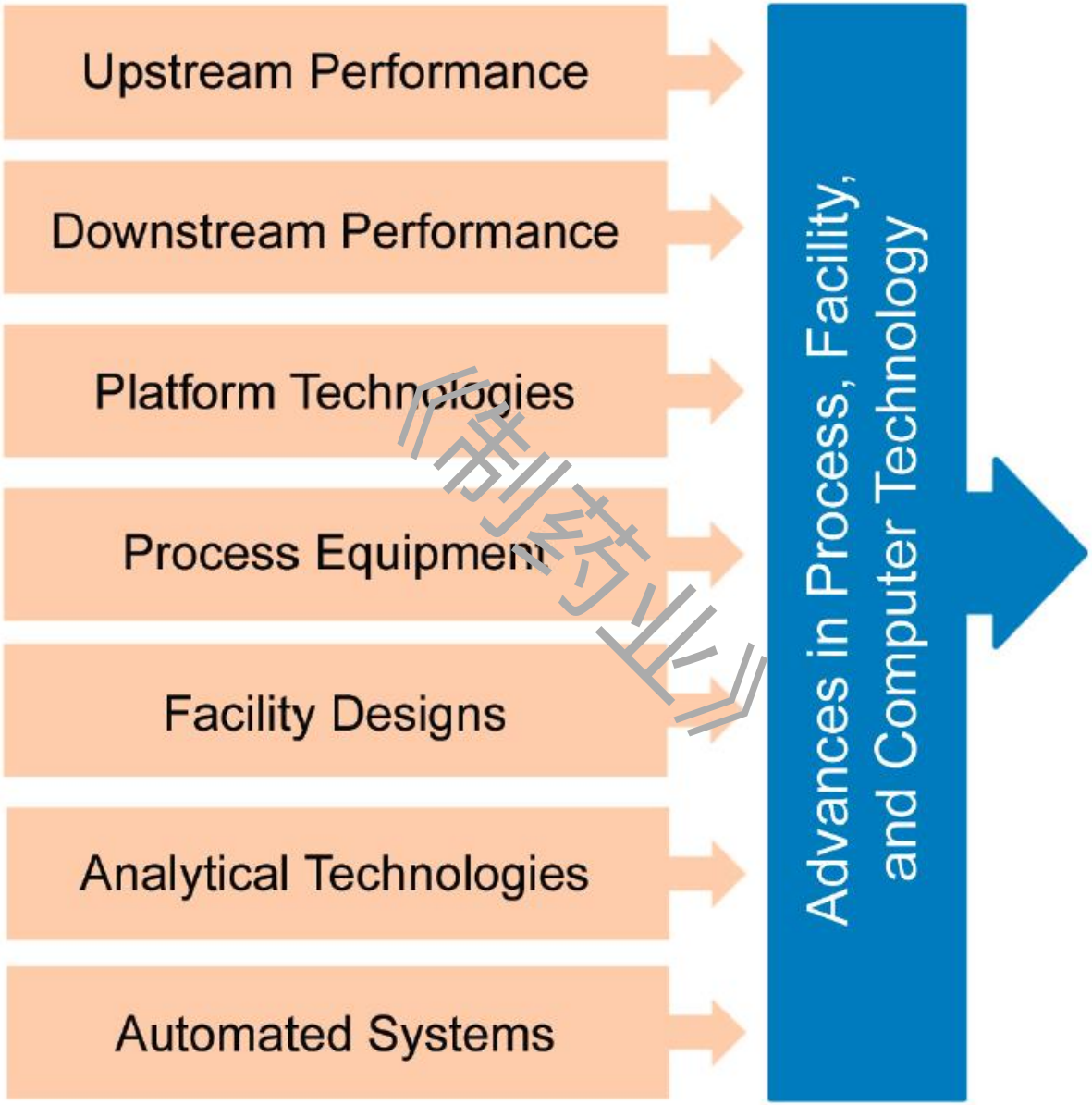
Use the design space to regulate temperature and humidity

Reduce the pressure differential by precisely measuring the air flow

洁净室的热效率

Key Concepts of Modern Pharmaceutical Manufacturing




Upstream Performance
Downstream Performance
Platform Technologies
Process Equipment
Facility Designs
Analytical Technologies
Automated Systems
Advances in Process, Facility, and Computer Technology

Facilities in Gray Space


《制药业》

Bio Mfg Operations

Introductory

- Cell biology
- Molecular biology
- Bioprocessing
- Glycobiology
- Biopharm eng
- Biopharmaceuticals

Upstream

- Animal cell culture
- Fermentation
- Bioreaction proc
- Bioreaction design
- Modelling
- Scale up, TT
- Contamination
- Sterilisation

Downstream

- Protein purification
- Chromatography
- Column packaging
- Integrity testing
- TFF

Bioanalytics

- PAT
- QbD
- Glycobiology
- Analytical techniques

Aseptic Manufacture

- Aseptic fill finish
- Cleanroom
- Fill finish
- Formulation
- Pharmacology

GMP compliance

- Reg Affairs
- Risk assessment
- Biovalidation
- Drug discovery and dev

Facilities, utilities

- CIP
- Energy Mgt
- Facility design
- Instrumentation
- Purified water
- Engineering

Business skills

- Lean sigma
- Project mgt
- Supervisory mgt
- Documentation
- Op Ex

Hot topics '11

- Single Use
- Biocatalysis
- Viral inactivation

Process Analytical Technologies

Raw Materials Analysis
Spectroscopy
Microscopy
FCS
Mass Spectrometry

Glycan Analysis

Intermolecular Interactions
Static and Dynamic Light Scattering
Small angle X-ray Scattering
Phase Diagrams

Process Analytical Techniques (PAT)

ize Analysis
D[illegible]t Scattering
HPL[illegible]
Analytical U[illegible]gation
Transmission E[illegible]icroscopy

Cell Culture Design

Protein Solution Stability
Static and Dynamic Light Scattering
Differential Scanning Calorimetry
HPLC, Analytical Ultracentrifugation
Phase Diagram

Structural Characterisation
X-ray crystallography
IR/CD spectroscopy
Small Angle X-ray scattering
NMR

Cell Medium Design

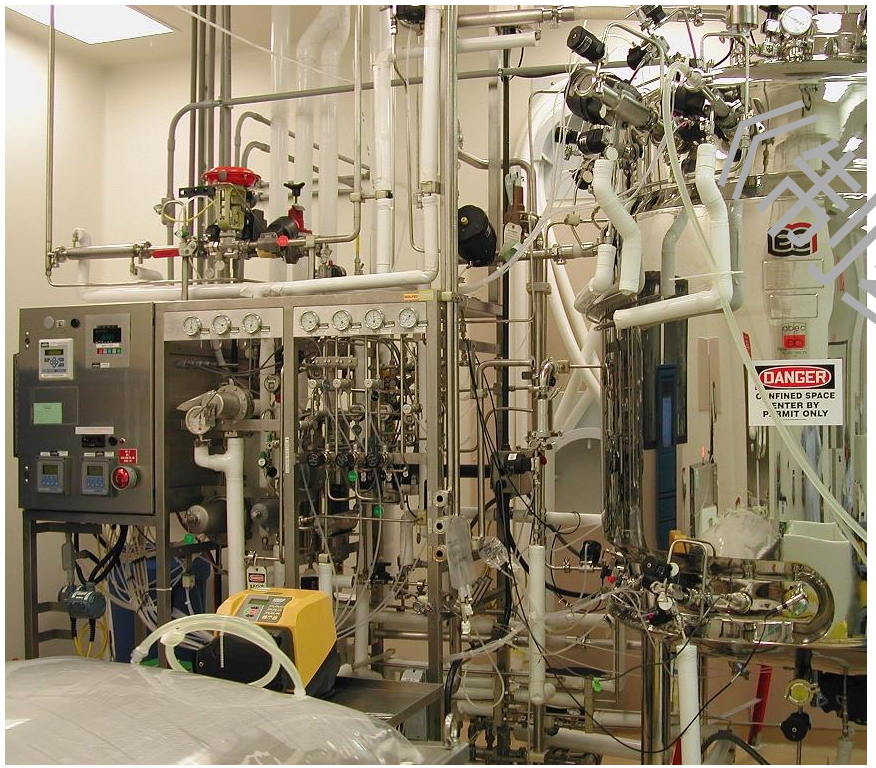
Objectives:

- Provide a complete range of analytical methods required to fully characterize a recombinant protein and to define whether it meets requirements.
- Understand each stage of a bioprocess and identifying the conditions which may affect product stability/ aggregation.
- Design systems to monitor and control the process at each stage, in order to maintain product stability/aggregation.


《制药业》

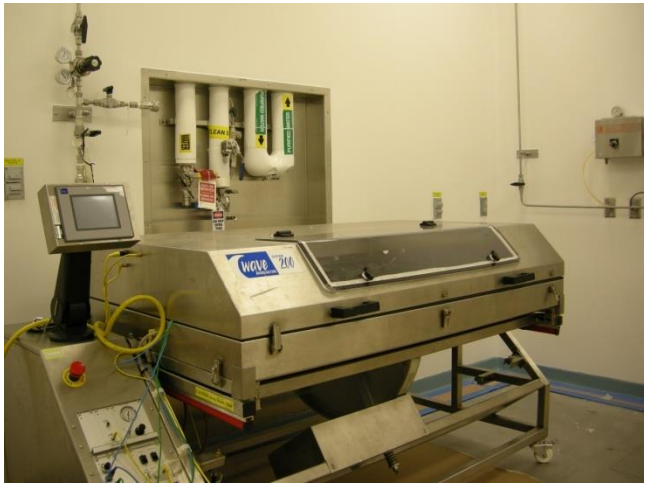
Manufacturing Facility

Process Area 1 x 1600 L Bioreactor



Flexible Process Design

Process Area – 2 x 3000 L Bioreactor

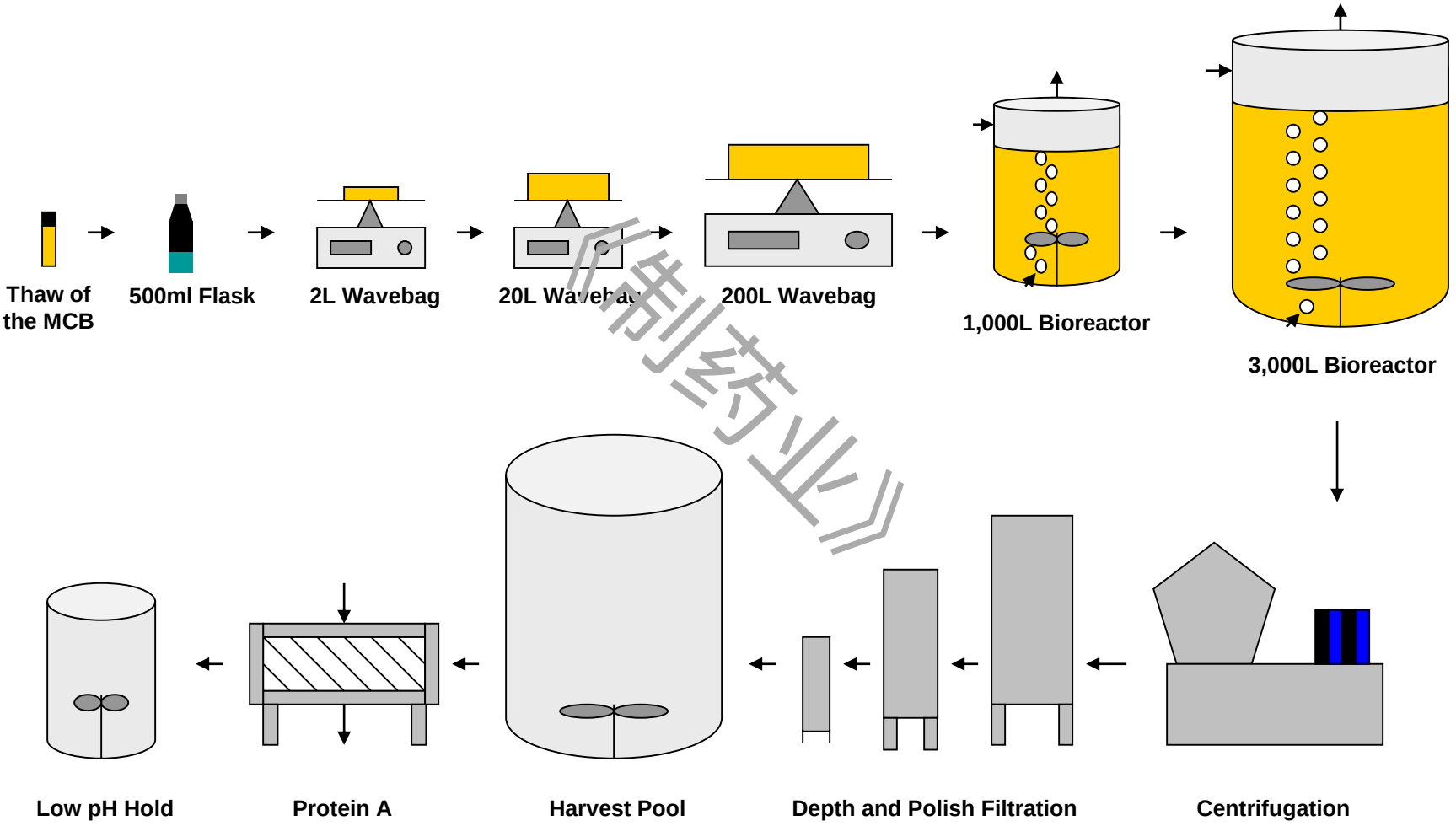


- **Focus on characterizing and understanding the process**

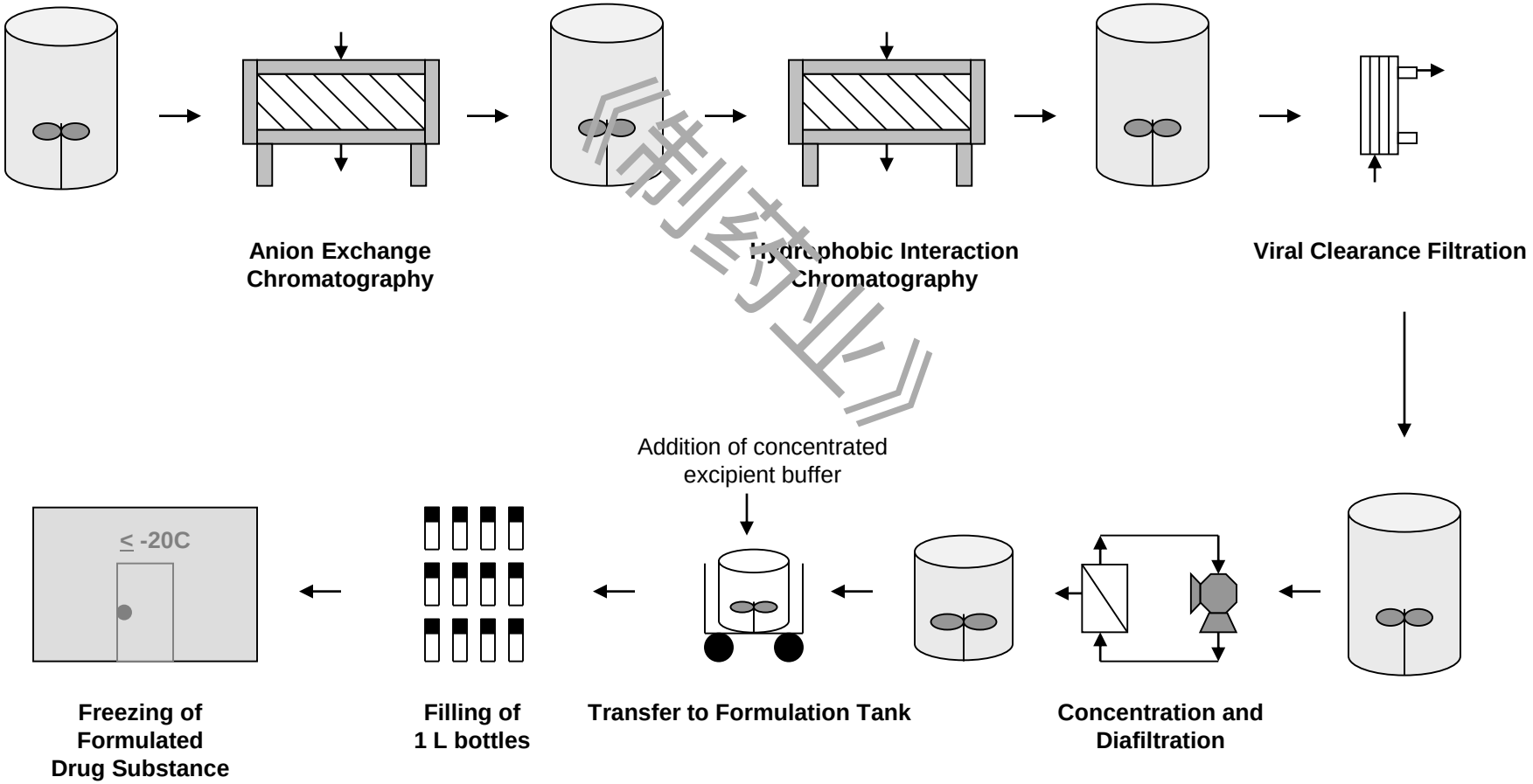
Process Area

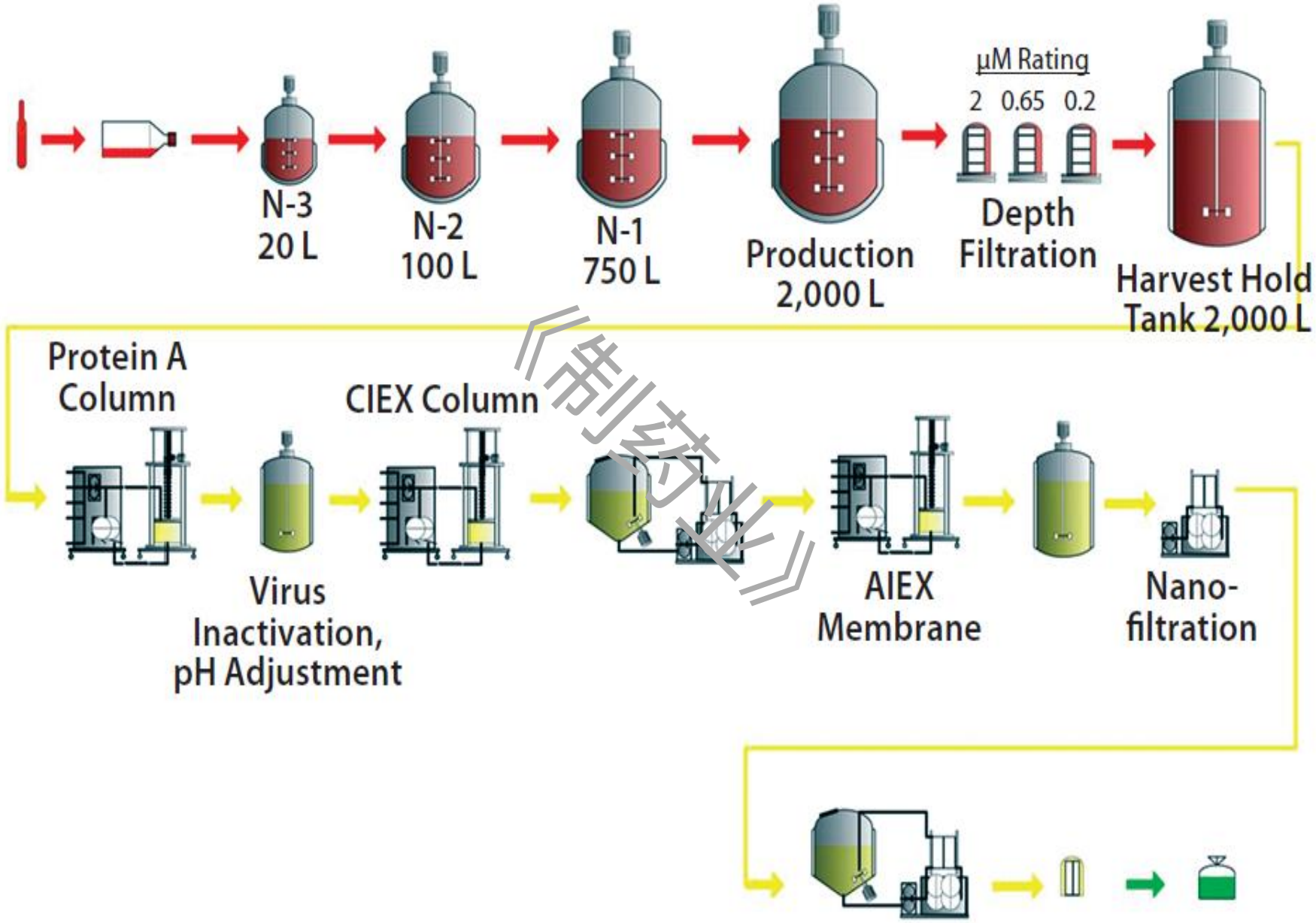
Manufacturing Capacity

Drug Substance Manufacturing
Upstream Operations

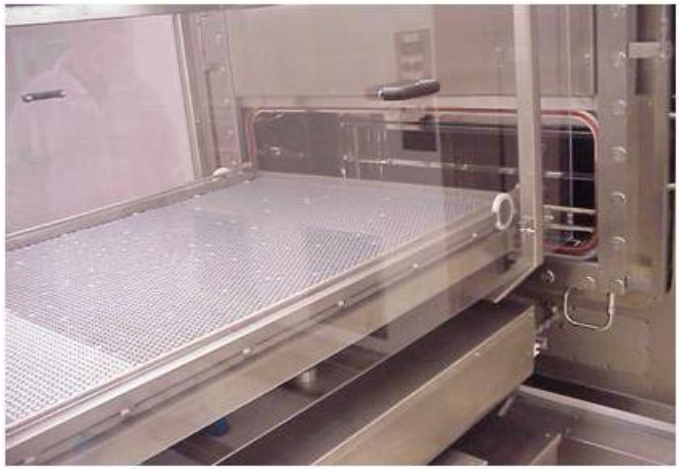


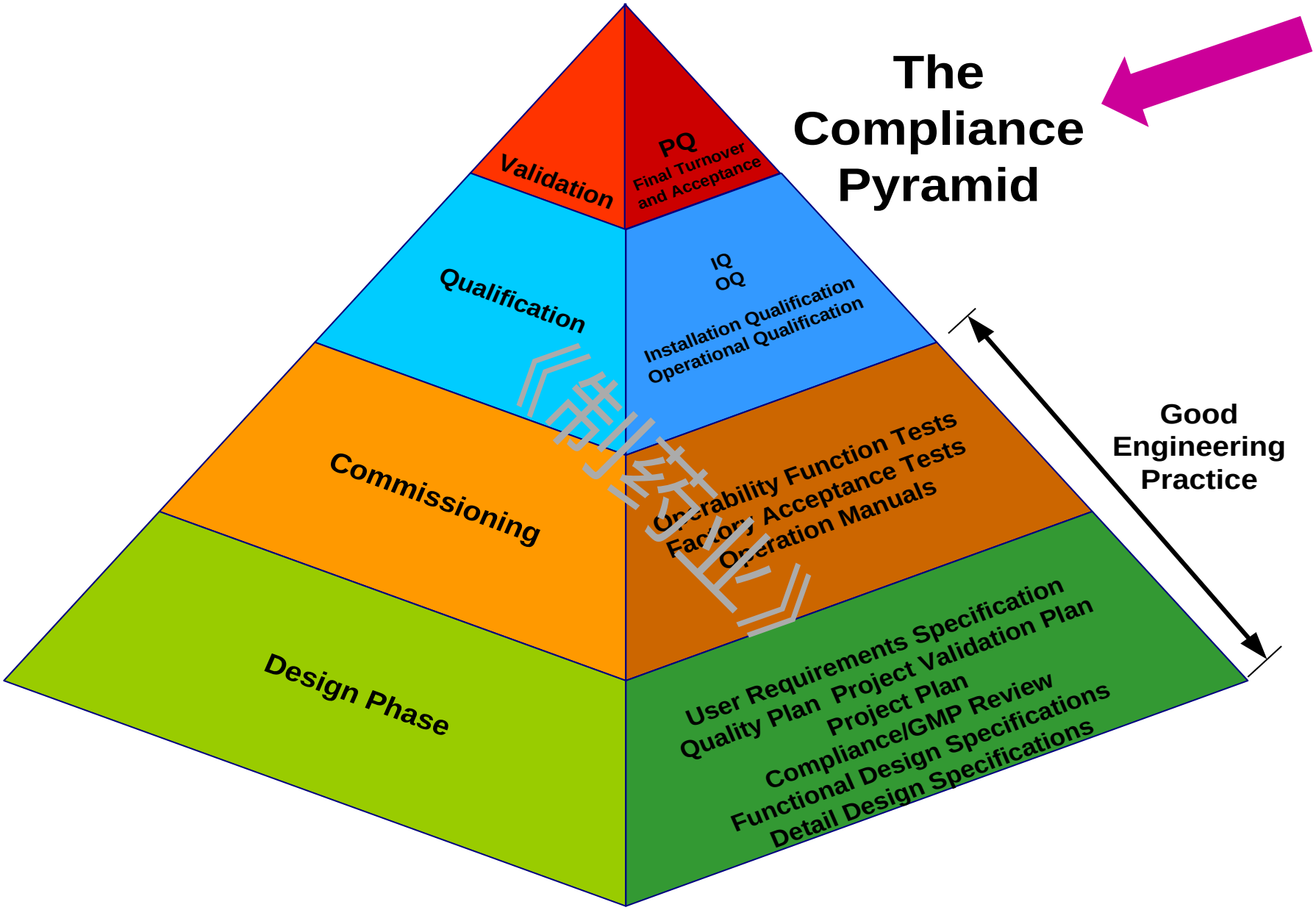
Formulated Drug Substance Manufacturing
Downstream Operations




N-3
20 L
N-2
100 L
N-1
750 L
Production
2,000 L
µM Rating
2 0.65 0.2
Depth
Filtration
Harvest Hold
Tank 2,000 L
Protein A
Column
CIEX Column
Virus
Inactivation,
pH Adjustment
AIEX
Membrane
Nano-
filtration

Today's State of the Art Technology Uses Automated Systems To Transfer Product From Production Line Into the Freeze-Dryer

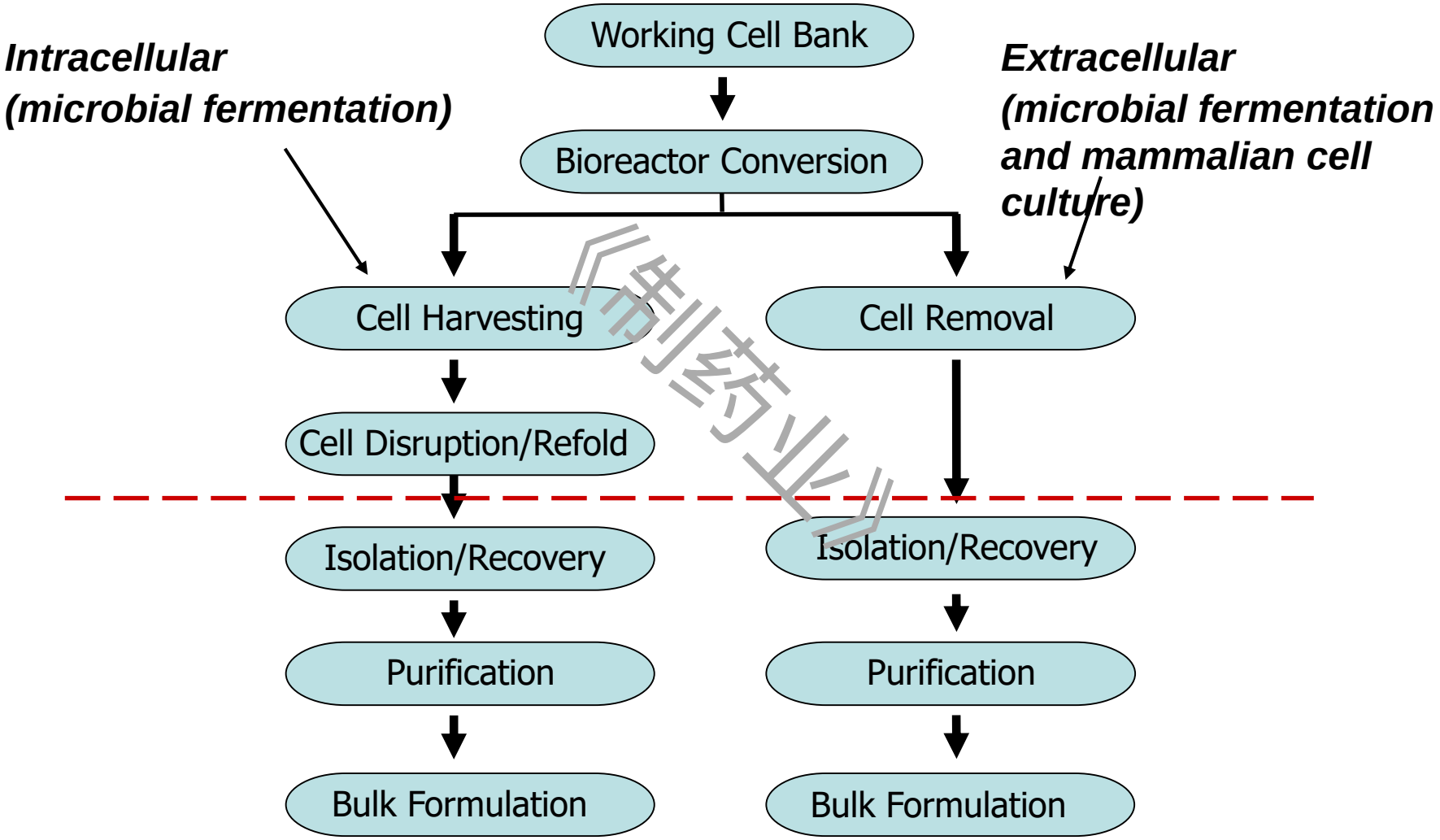



The Compliance Pyramid
Validation
PQ
Final Turnover and Acceptance
Qualification
IQ
OQ
Installation Qualification
Operational Qualification
Commissioning
Operability Function Tests
Factory Acceptance Tests
Operation Manuals
Design Phase
User Requirements Specification
Quality Plan Project Validation Plan
Project Plan
Compliance/GMP Review
Functional Design Specifications
Detail Design Specifications
Good Engineering Practice


《制药业》
Manufacturing
Intelligence

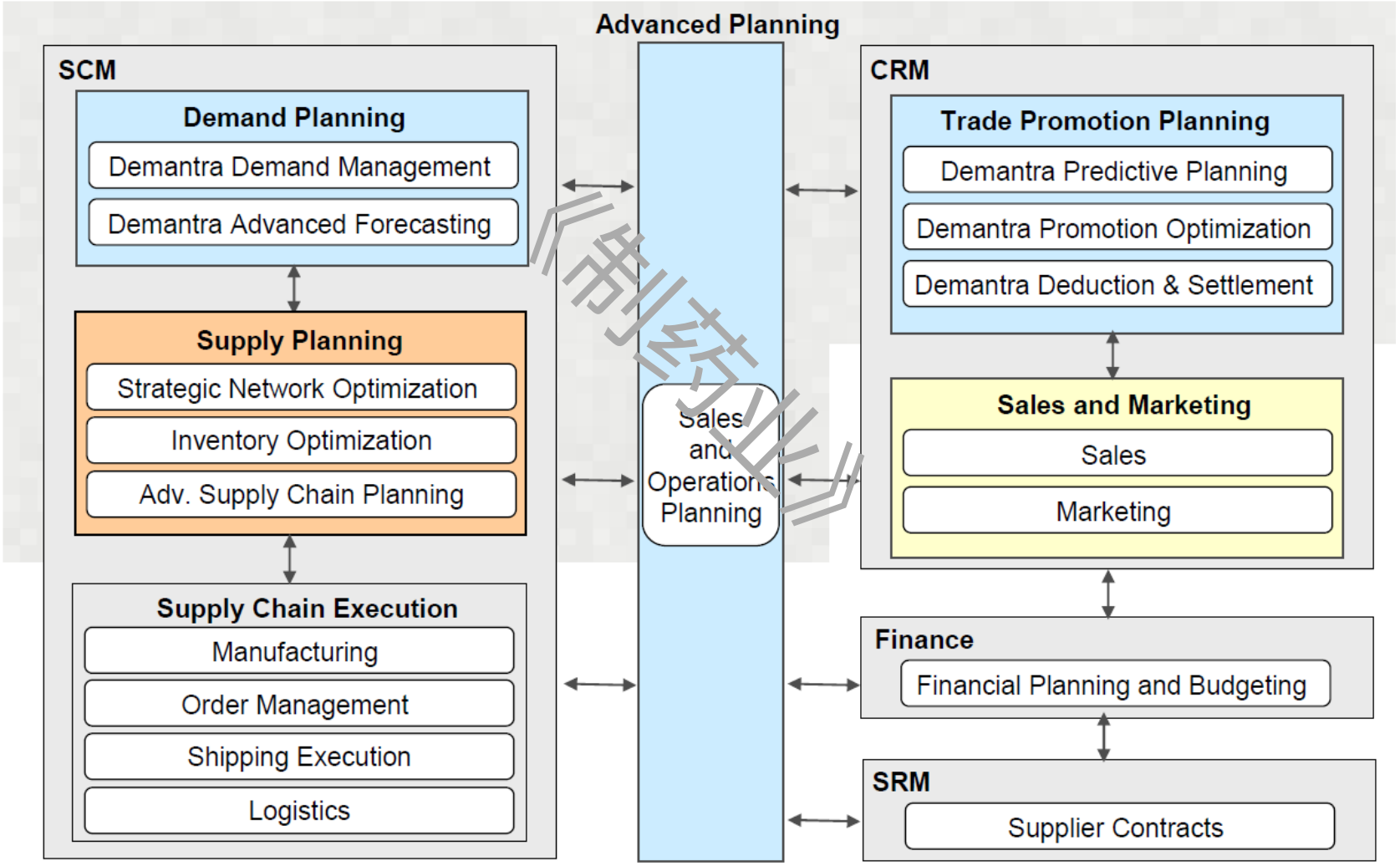

Manufacturing
Execution Systems

"Upstream" Process

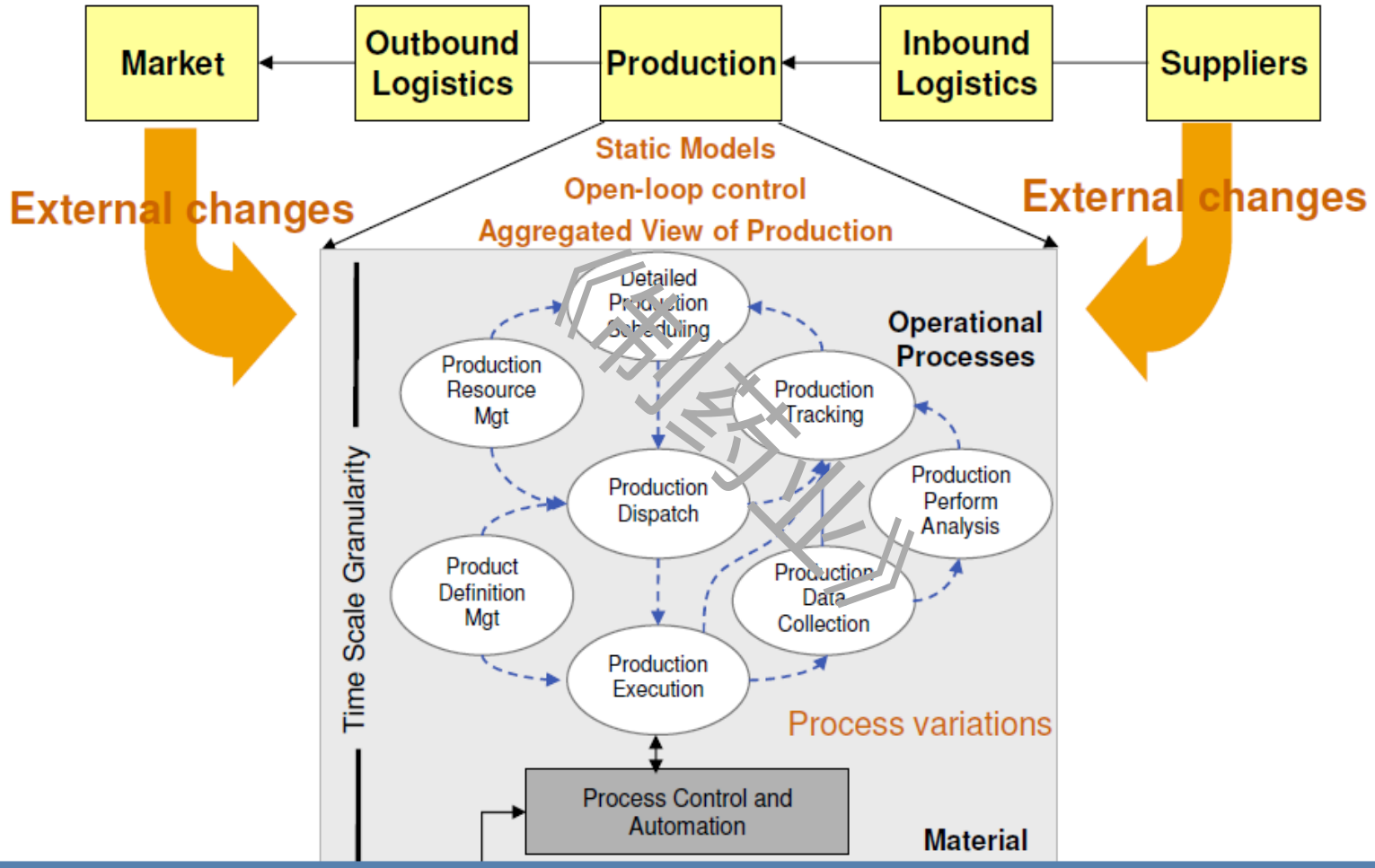


"Downstream" Process

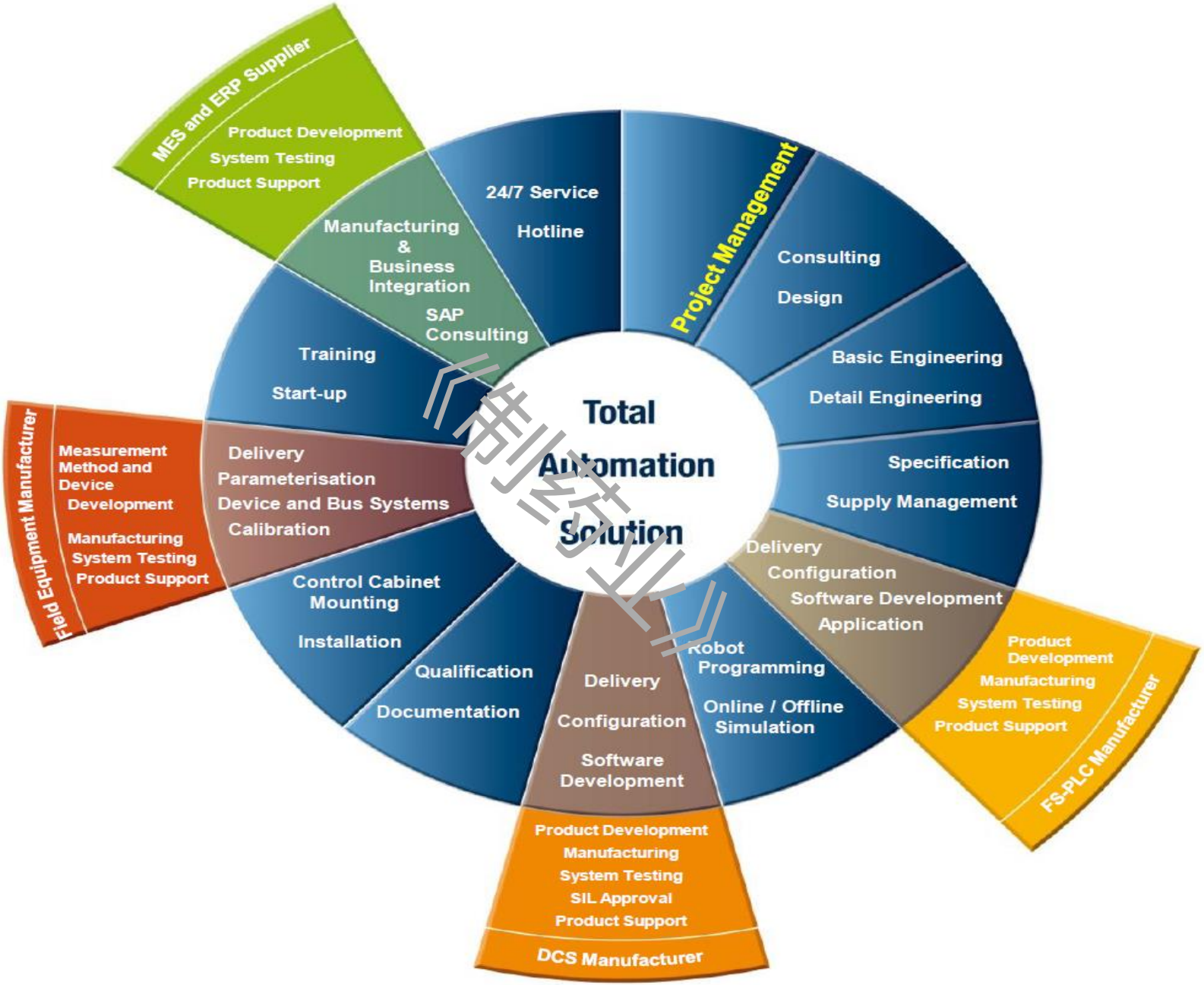
Business Process Integration Plan



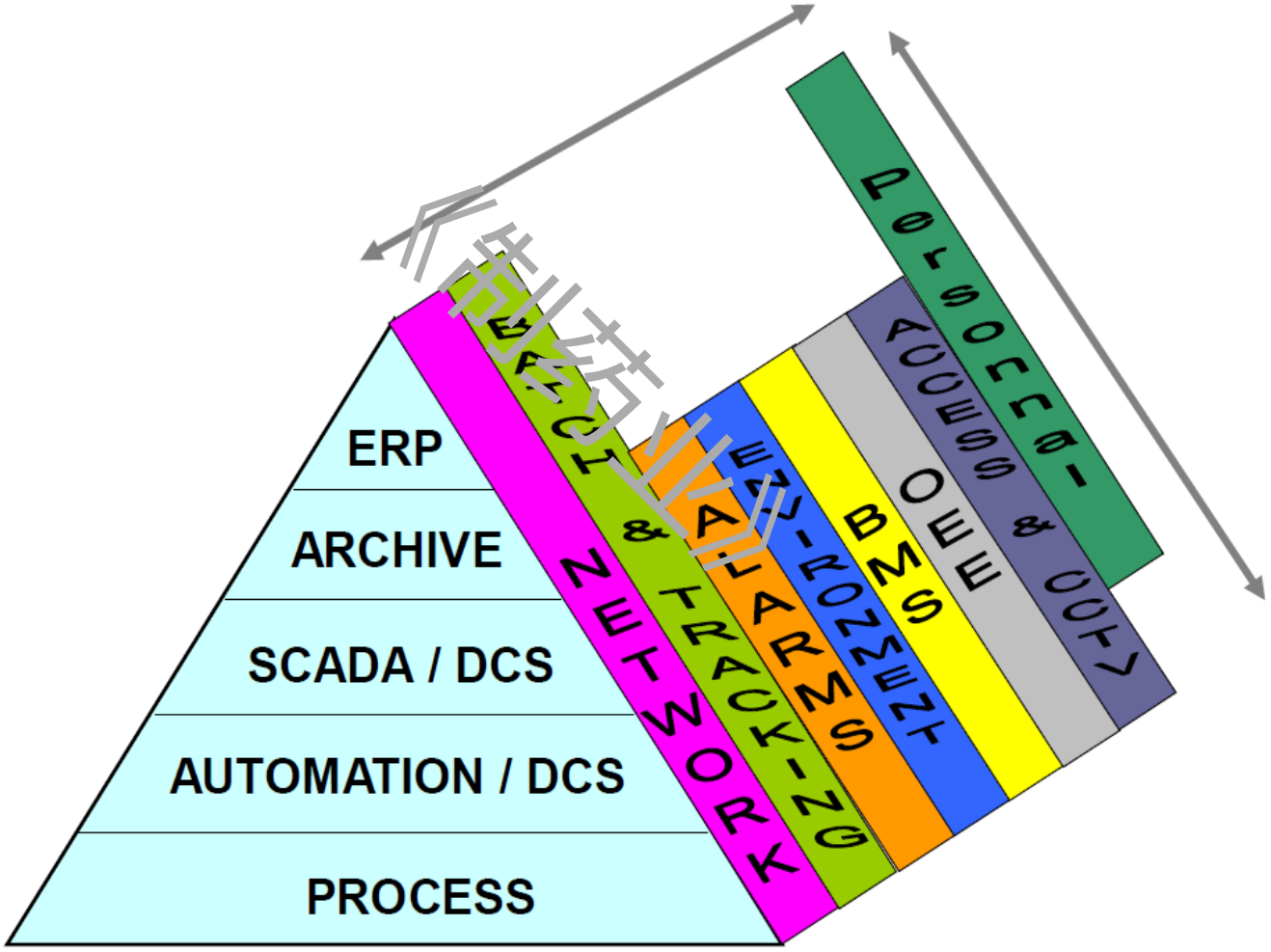
Supply Chain Processes: Traditional View of Manufacturing



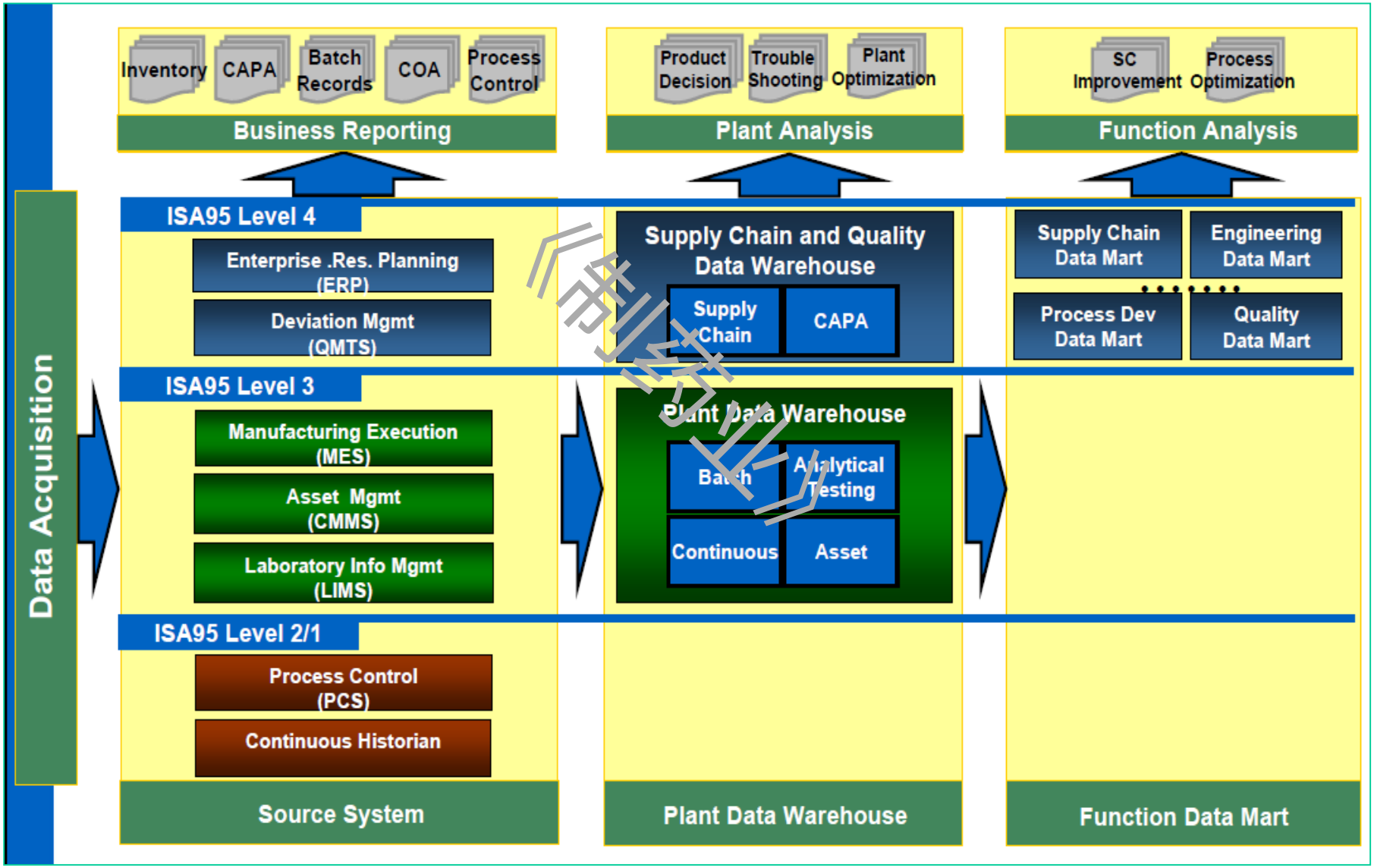
Traditional Models of Open-loop Operations Lead to disconnect between the Plant and Business Processes

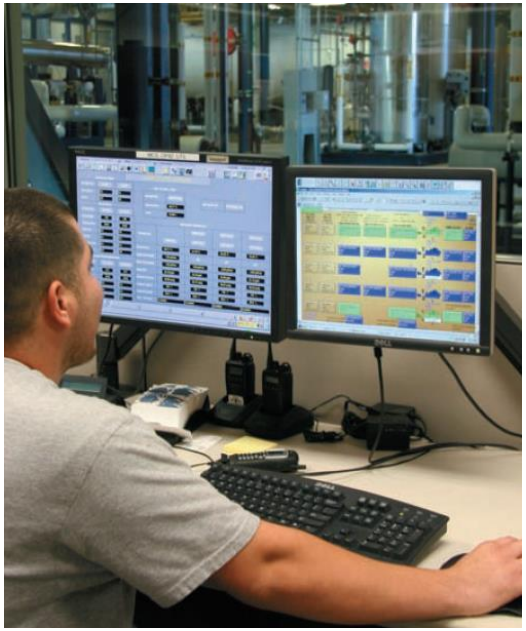

MES and ERP Supplier
Product Development
System Testing
Product Support
24/7 Service
Hotline
Project Management
Consulting
Design
Basic Engineering
Detail Engineering
Specification
Supply Management
Delivery
Configuration
Software Development
Application
Product Development
Manufacturing
System Testing
Product Support
FS-PLC Manufacturer
Robot Programming
Online / Offline Simulation
Delivery
Configuration
Software Development
Product Development
Manufacturing
System Testing
SIL Approval
Product Support
DCS Manufacturer
Control Cabinet Mounting
Installation
Qualification
Documentation
Delivery
Parameterisation
Device and Bus Systems
Calibration
Measurement Method and Device Development
Manufacturing
System Testing
Product Support
Field Equipment Manufacturer
Training
Start-up
Manufacturing & Business Integration
SAP Consulting
Total Automation Solution

Data Management



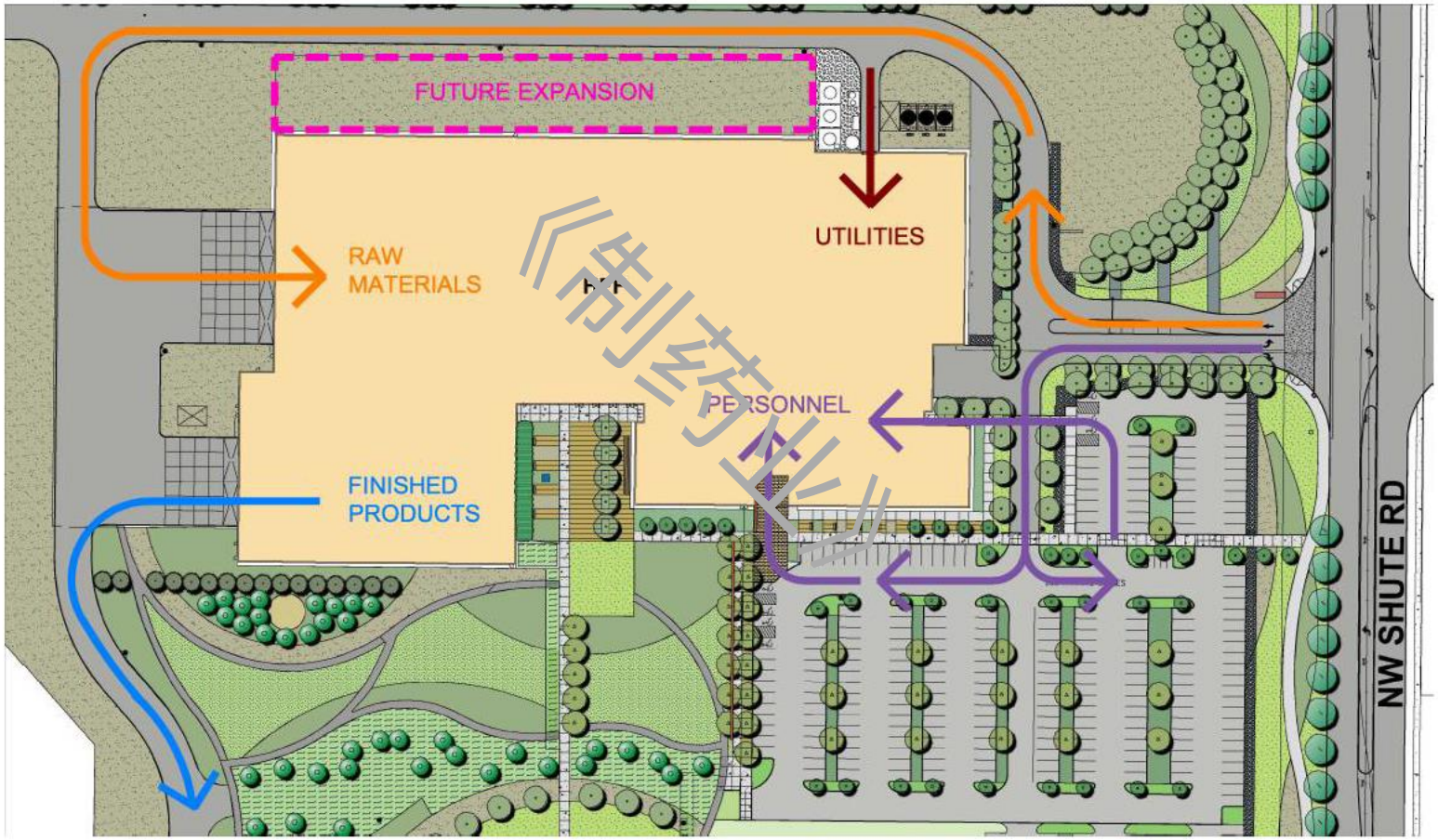
Plant Data Warehouse Is To Be Integrated





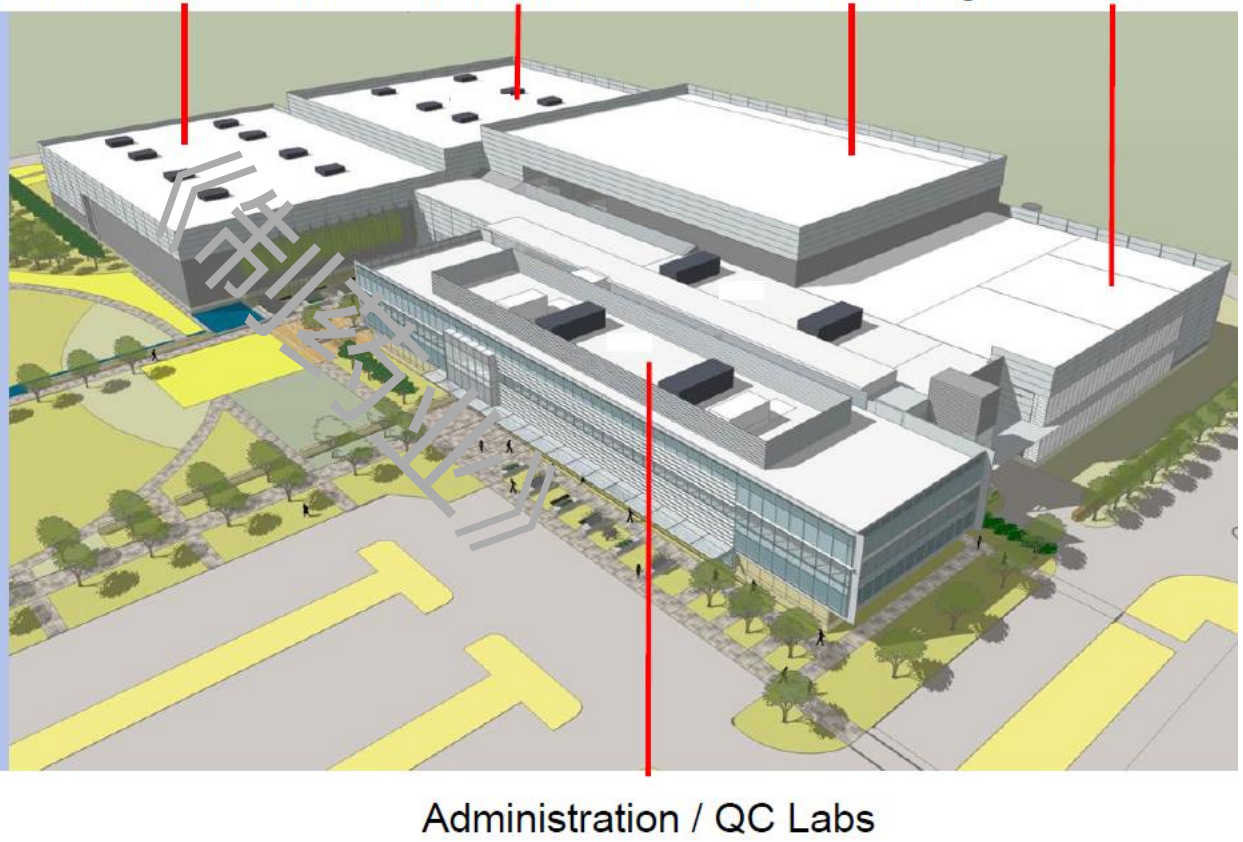
- Project Business Drivers
- Scope Alignment
- Capital Effectiveness
- Cost Impact Elements
  - Technology
- Delivery Method

Preliminary Design – Site Flows



Preliminary Design – Approval Requirements

- Regular review of flow diagrams
- Clear communication of design intent
- Include authorities in design development
- Get early buy-in from Building Department on exceptions (UL)



Cost Appropriate Solutions

. . . functional

. . . public

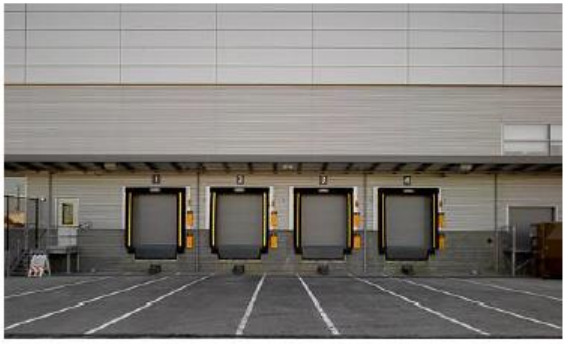
. . . manufacturing

Exterior Strategy

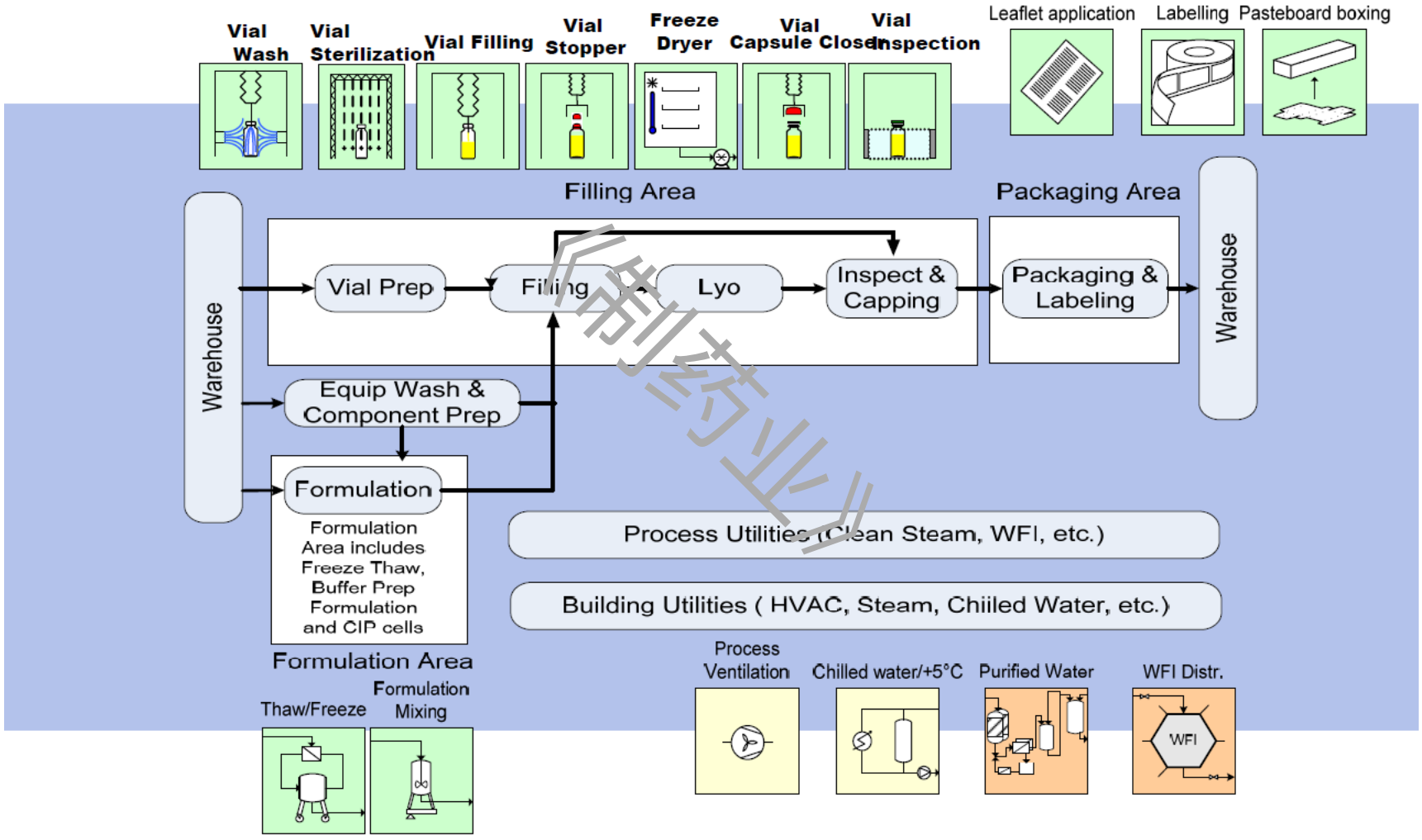
. . . material availability

. . . corporate image

. . . functional requirements

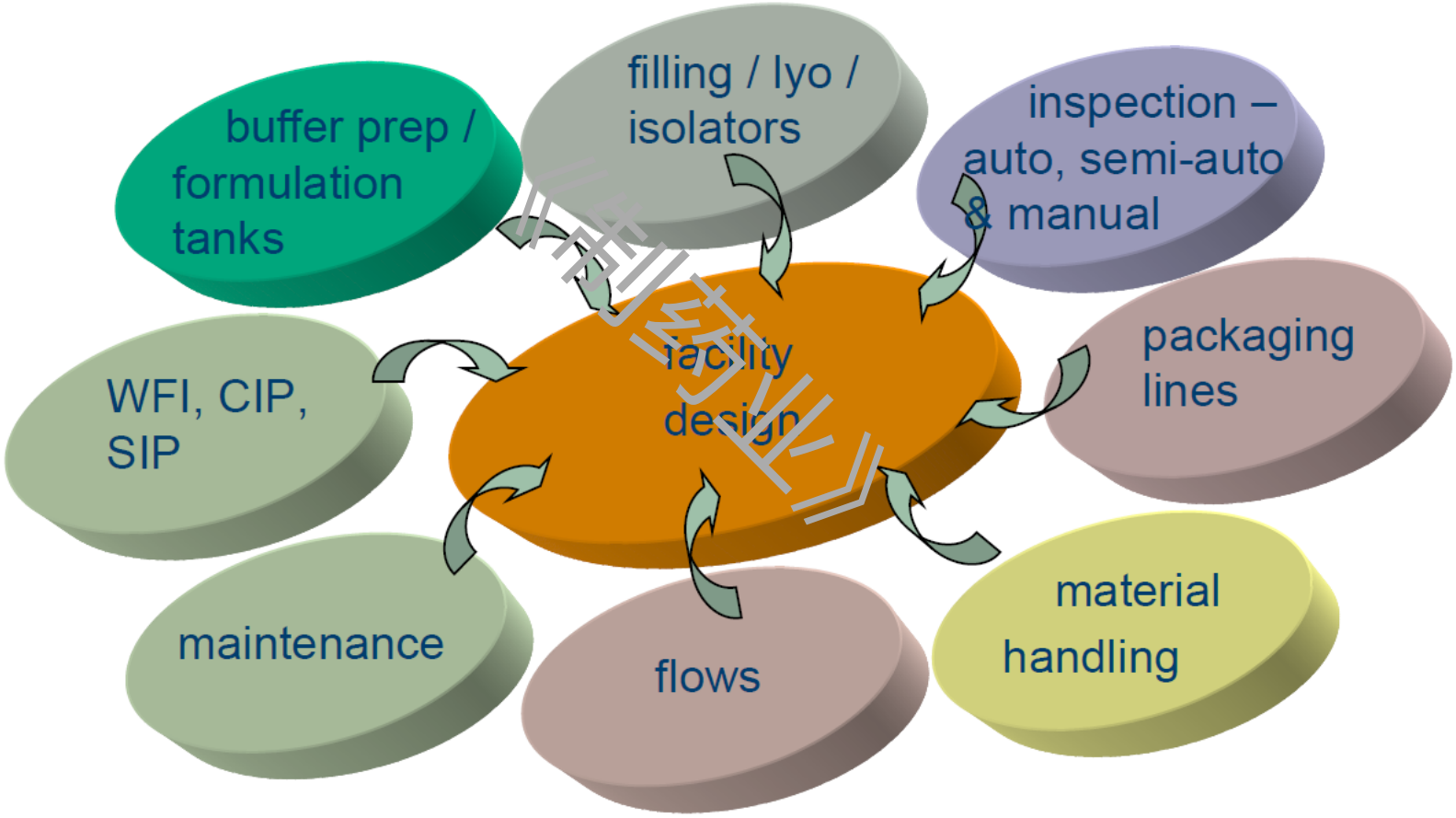


Process Flow



Design Process – Equipment Interface

vendors. . .providing the solutions

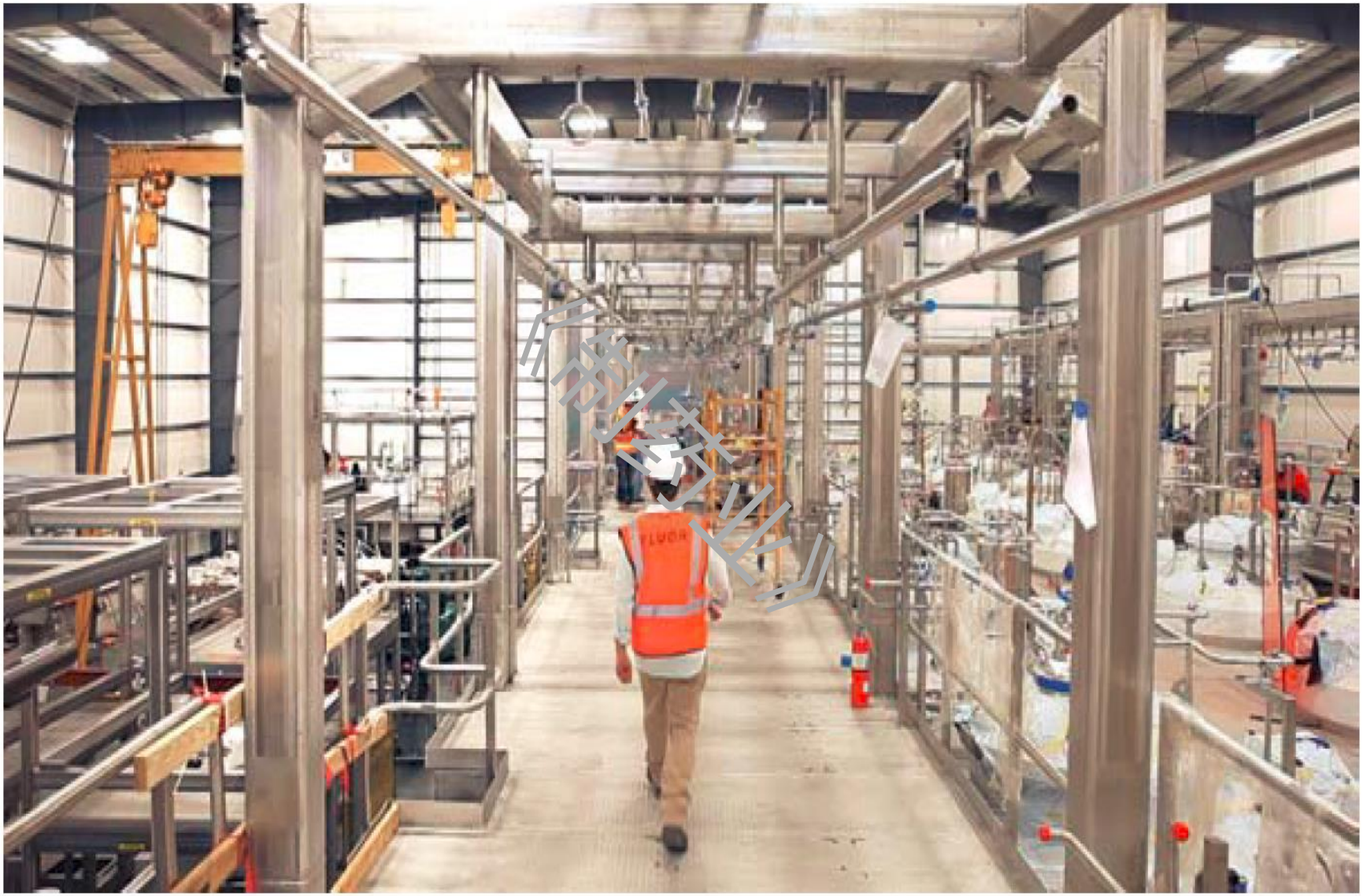



MedImmune

GlaxoSmithKline's USD 412million Vaccine Plant in Singapore

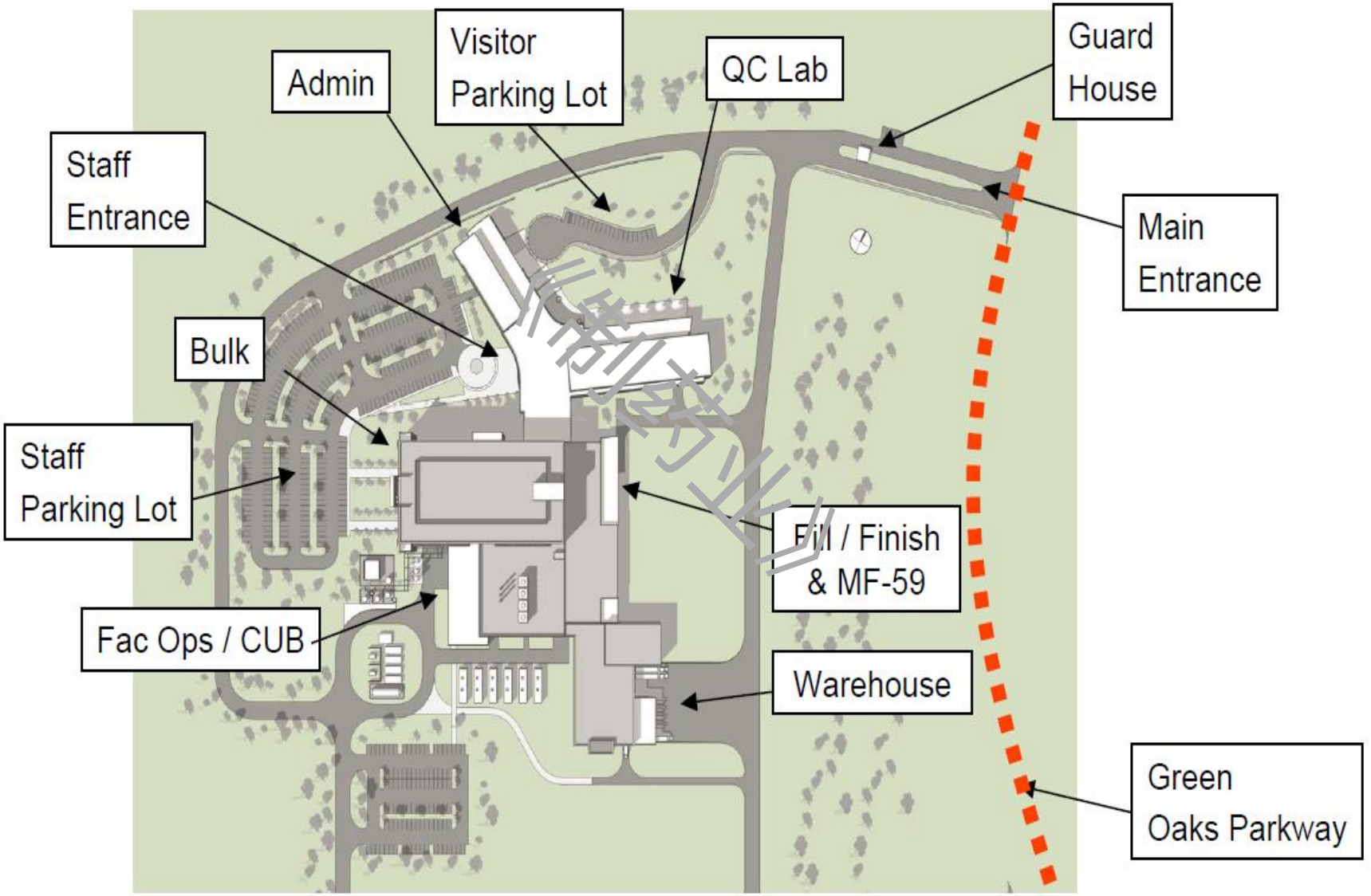
Merck, Vaccines Manufacturing Facility. A €200 million state-of-the-art vaccines mfg and R&D facility in Carlow, Ireland. Located on a 65-acre site, the plant facility floor area is 17,000 sqm.

CLEAN STEAM
CLEAN IN PLACE SUPPLY
PROCESS
CLEAN IN PLACE SUPPLY

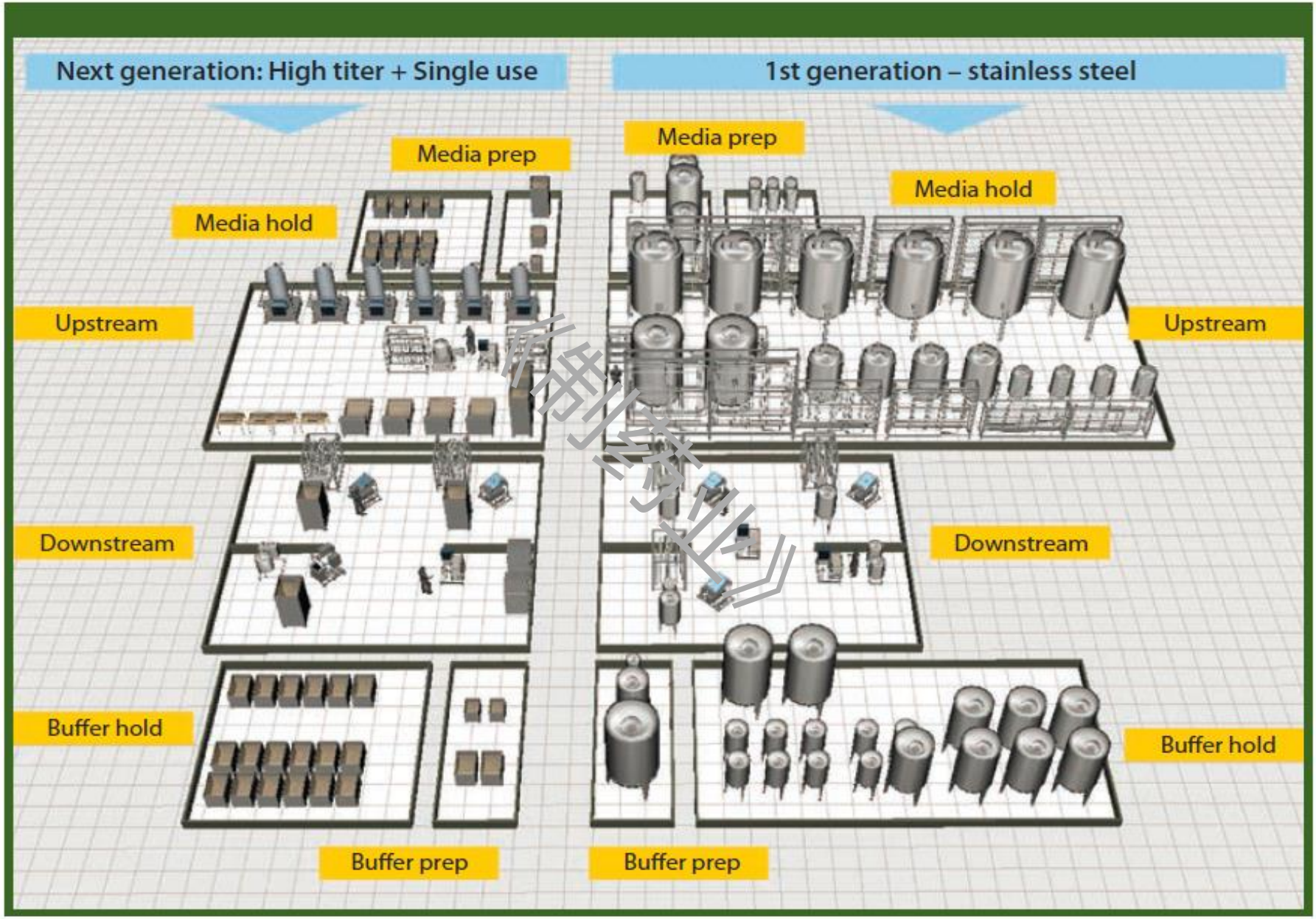


Cell culture harvest train.

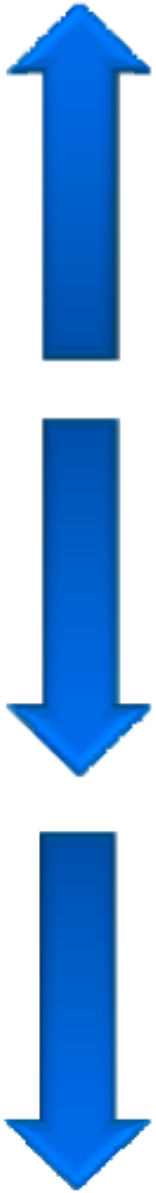
Project Scope Summary – Facility Layout




PACIFIC
PACIFIC


Next generation: High titer + Single use
1st generation – stainless steel
Media prep
Media hold
Upstream
Downstream
Buffer hold
Buffer prep
Media prep
Media hold
Upstream
Downstream
Buffer hold
Buffer prep

Facilities of the Future



Flexibility

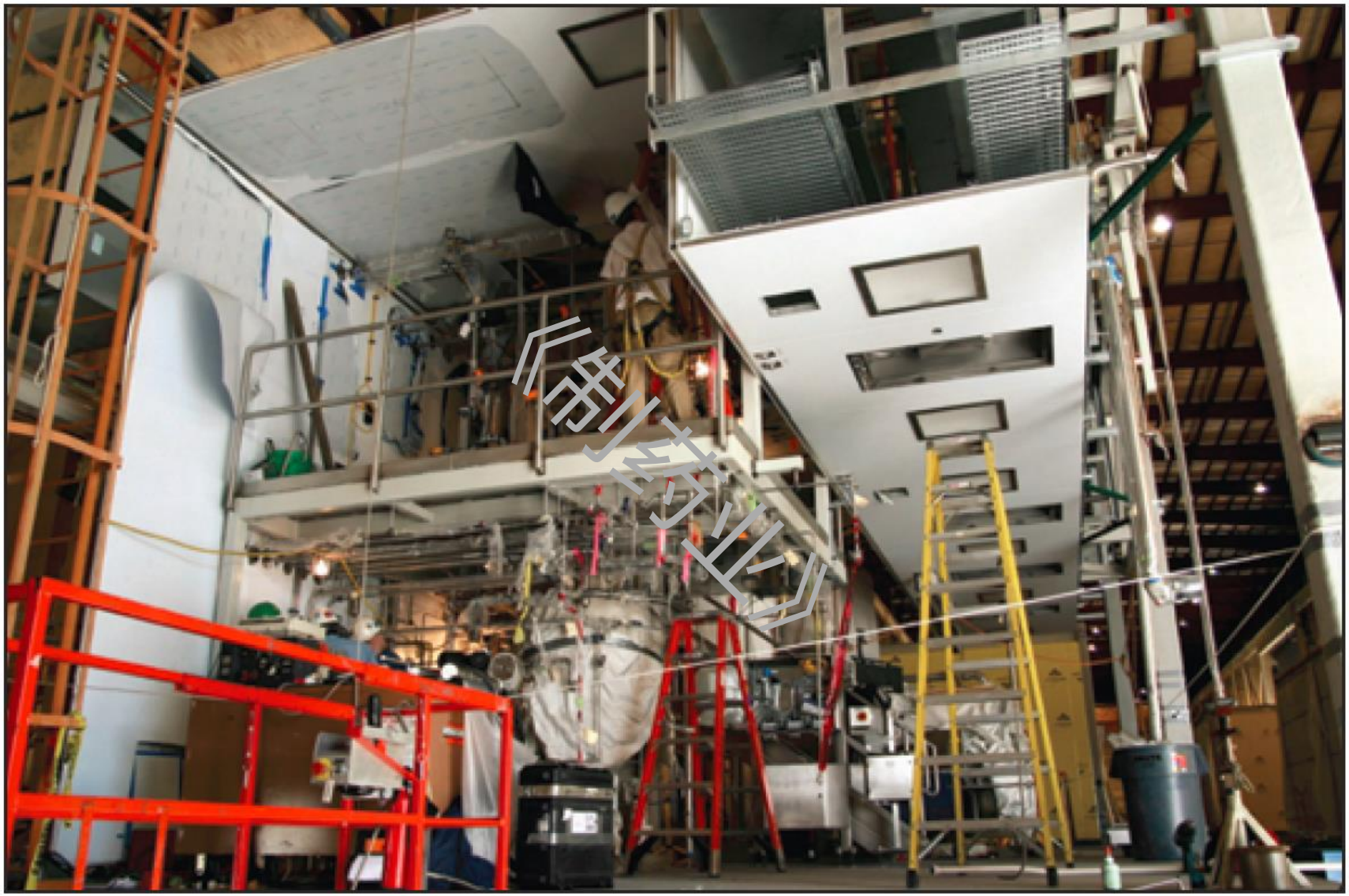
- for optimizing plant capacity

Capital Cost

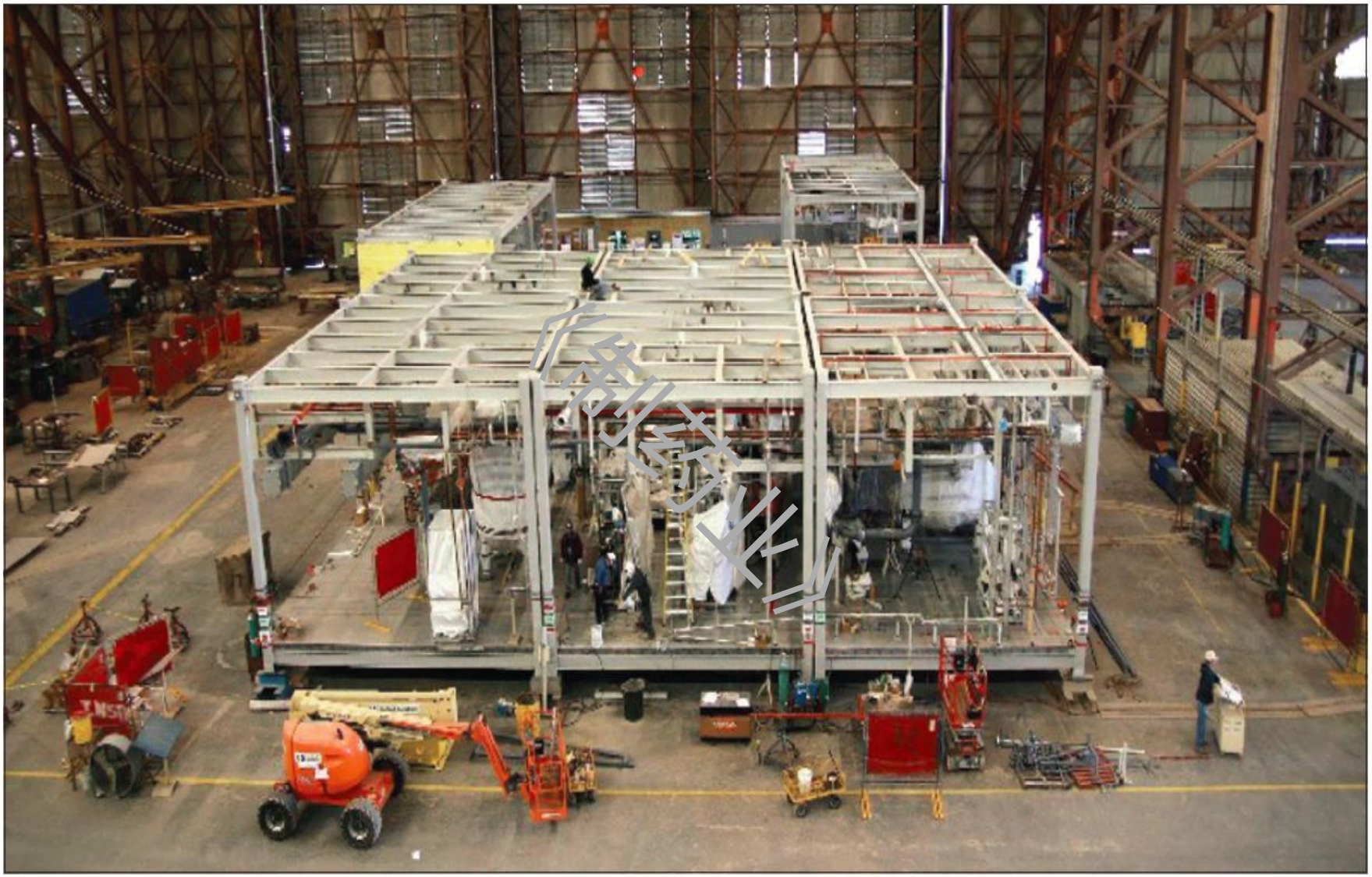
- engineering construction
- materials

Operating Cost

- utilities
- maintenance
- environmental control/monitoring



Module fabrication shop.



Modules staged in final layout.

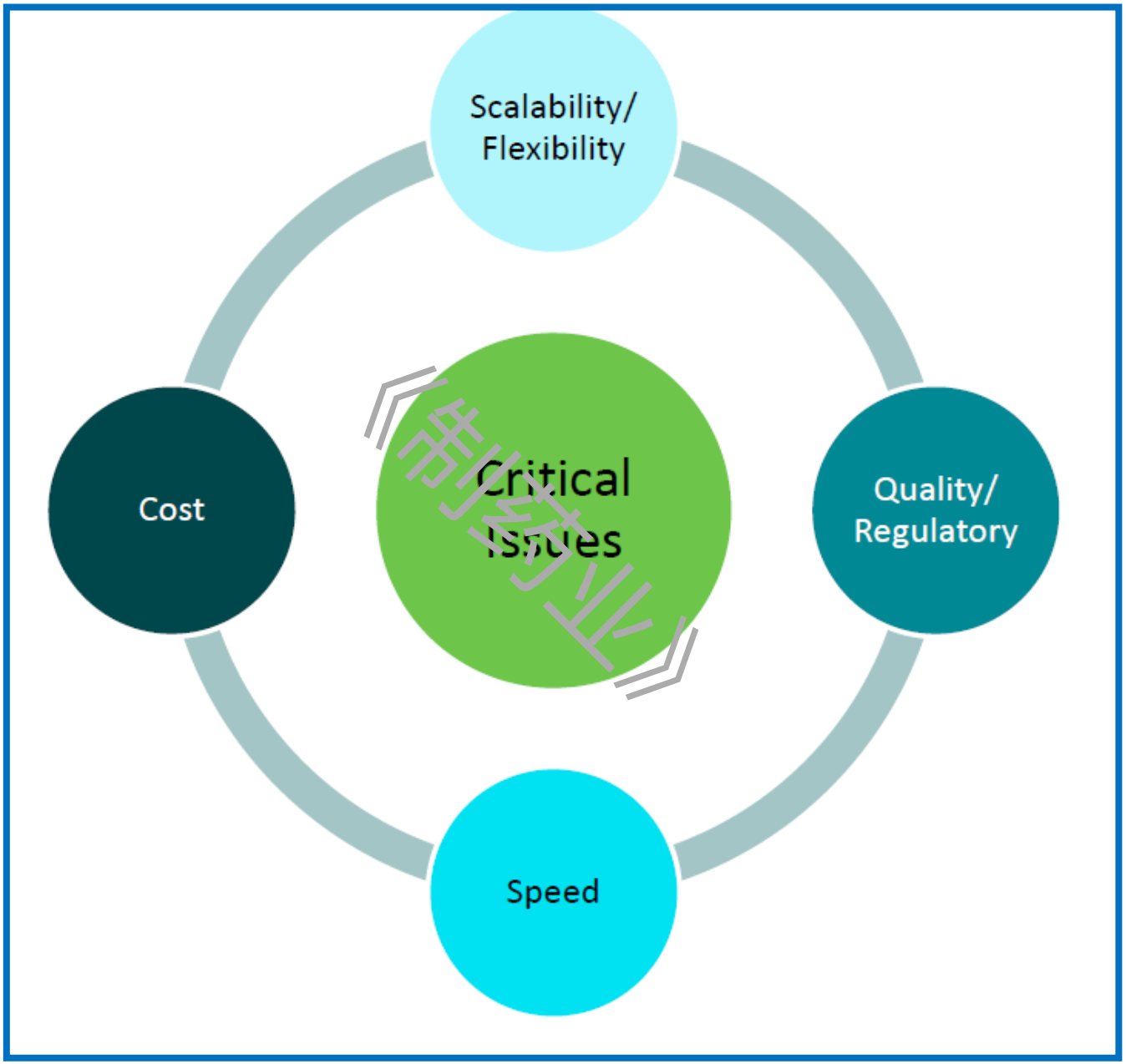
Modular skid.

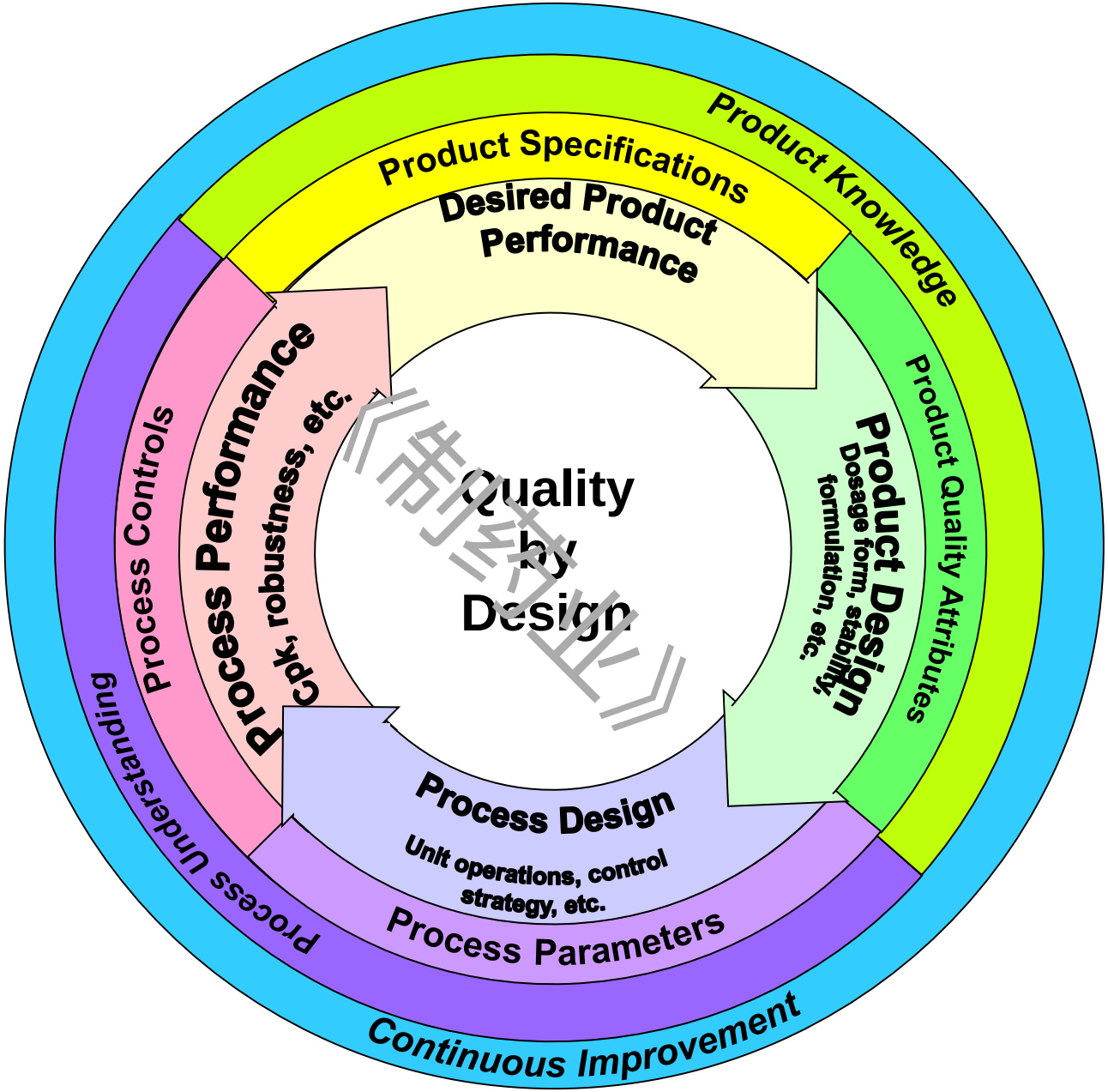
Degree of Integration

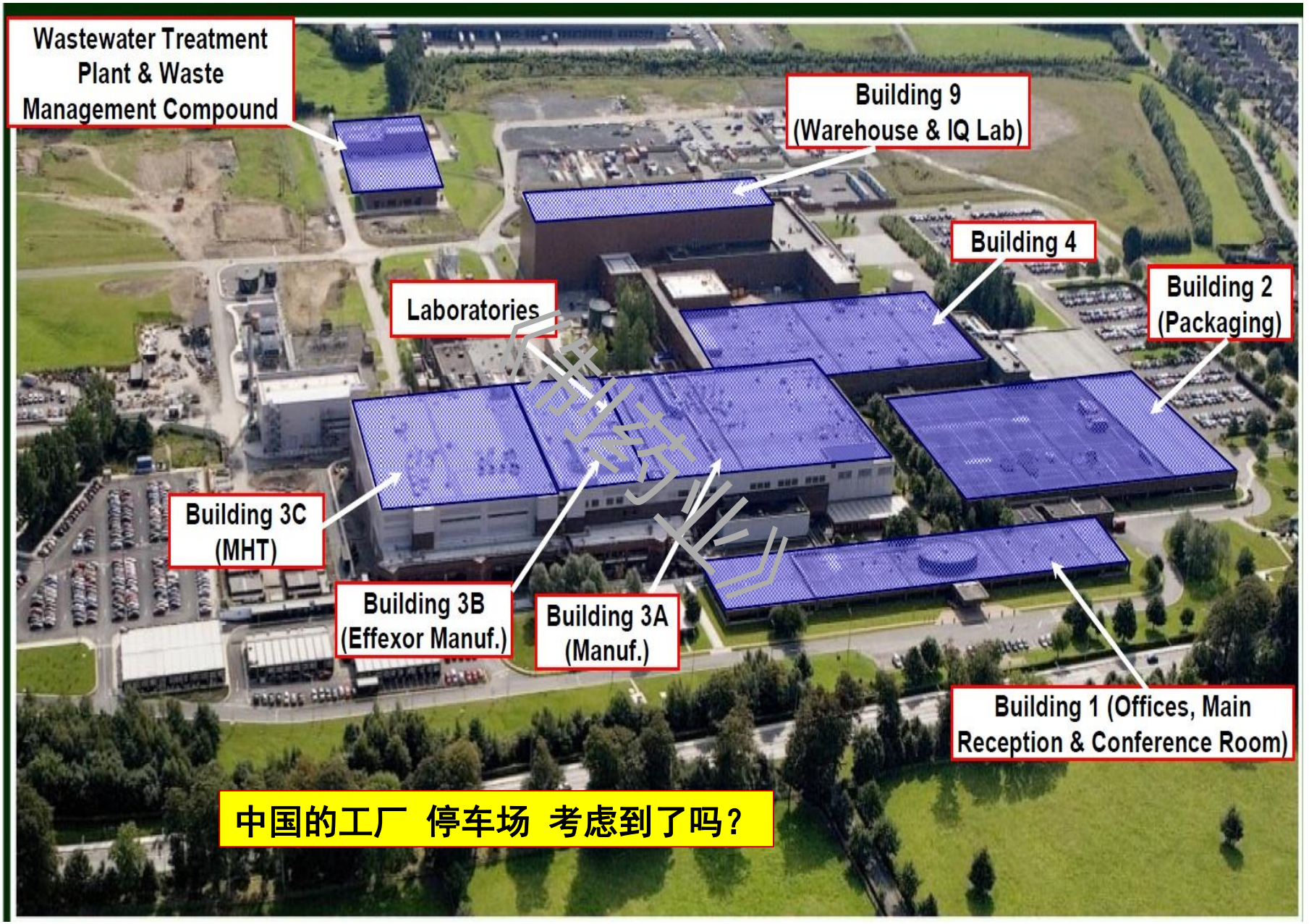
- **Comprehensive Prefab**
  - integrated prefab structure / facility / process

- **"Box-in-a-Box"**
  - integrated pre-fab facility within a stick-built structure

- **Partial Prefab**
  - prefab assemblies for insertion in stick-built structure and facility


Scalability/
Flexibility
Cost
Critical
Issues
Quality/
Regulatory
Speed

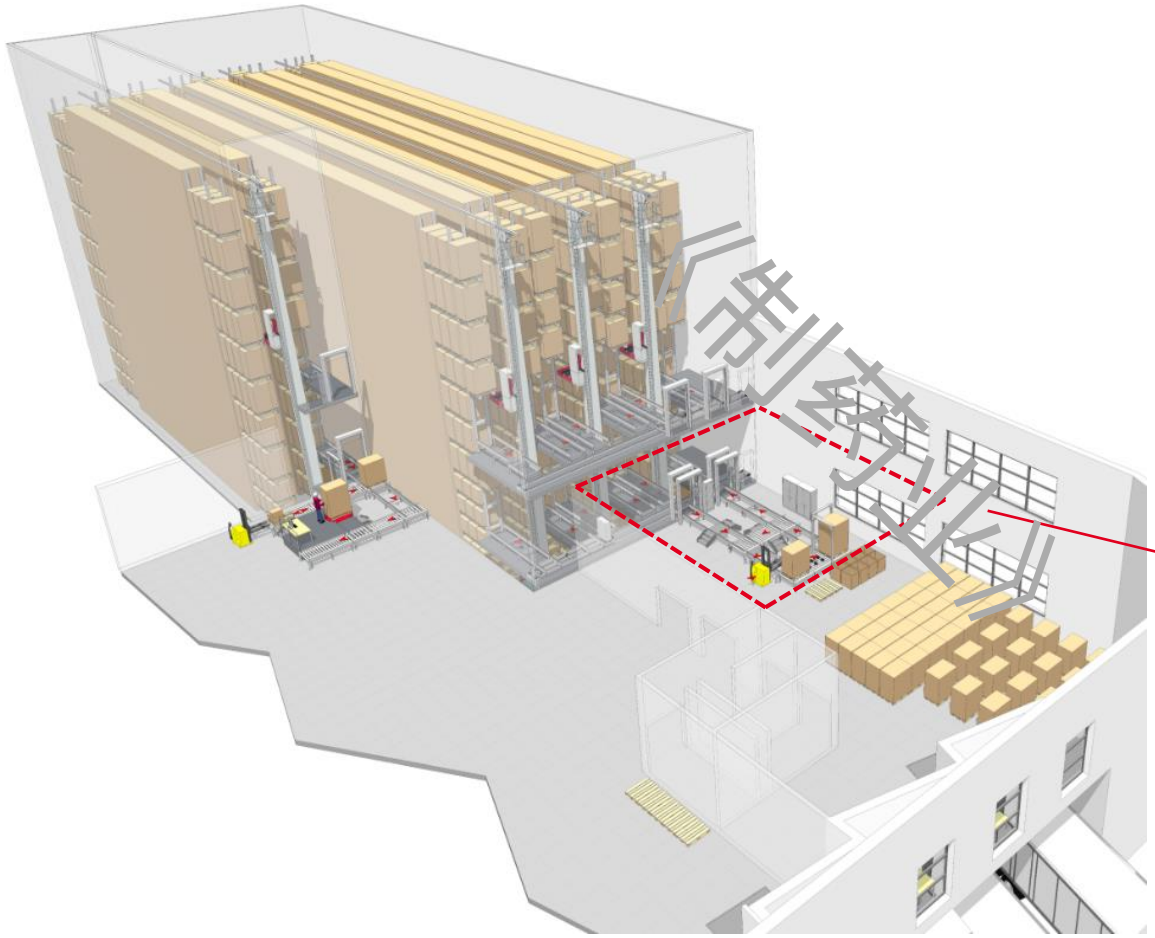

Product Knowledge
Product Specifications
Desired Product Performance
Product Quality Attributes
Product Design
Dosage form, stability, formulation, etc.
Process Performance
Cpk, robustness, etc.
Process Controls
Process Understanding
Quality by Design
Process Design
Unit operations, control strategy, etc.
Process Parameters
Continuous Improvement


Wastewater Treatment Plant & Waste Management Compound
Building 9 (Warehouse & IQ Lab)
Building 4
Building 2 (Packaging)
Laboratories
Building 3C (MHT)
Building 3B (Effexor Manuf.)
Building 3A (Manuf.)
Building 1 (Offices, Main Reception & Conference Room)
中国的工厂 停车场 考虑到了吗？

Solution Example 空间利用

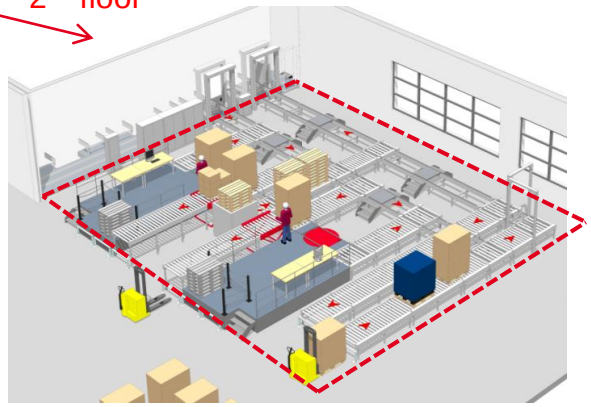
Manufacturing site for global BioPharma Company

Solutions



- 1 storage aisle for frozen storage
- 3 aisles for ambient storage
- Goods to Person picking in ambient and in frozen
- AGV's to / from production
- **Goal: cold storage and safety under control**

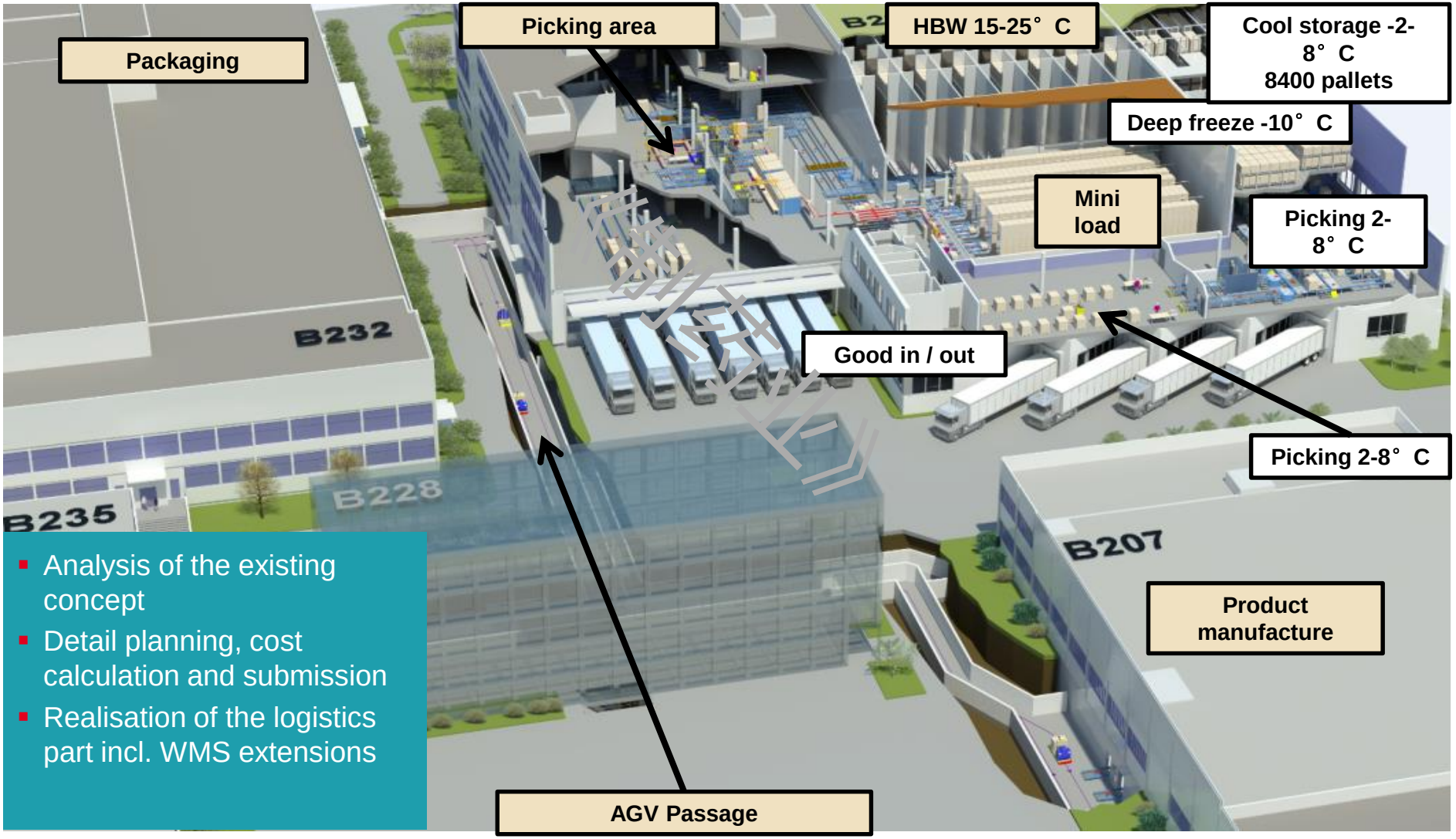
2nd floor



冷库的扩展

The Solution: Cold Storage Warehouse Extension

Solutions

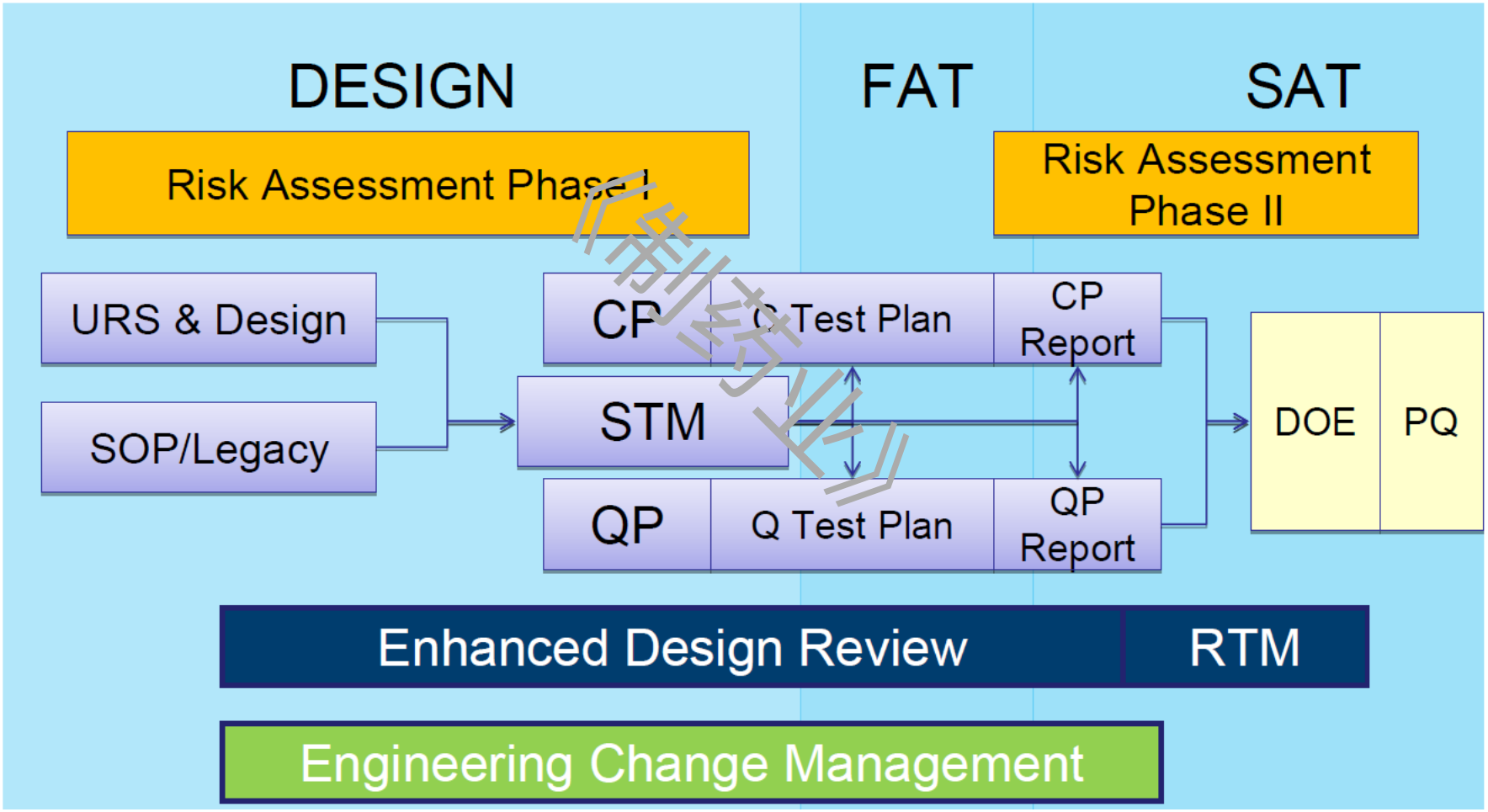


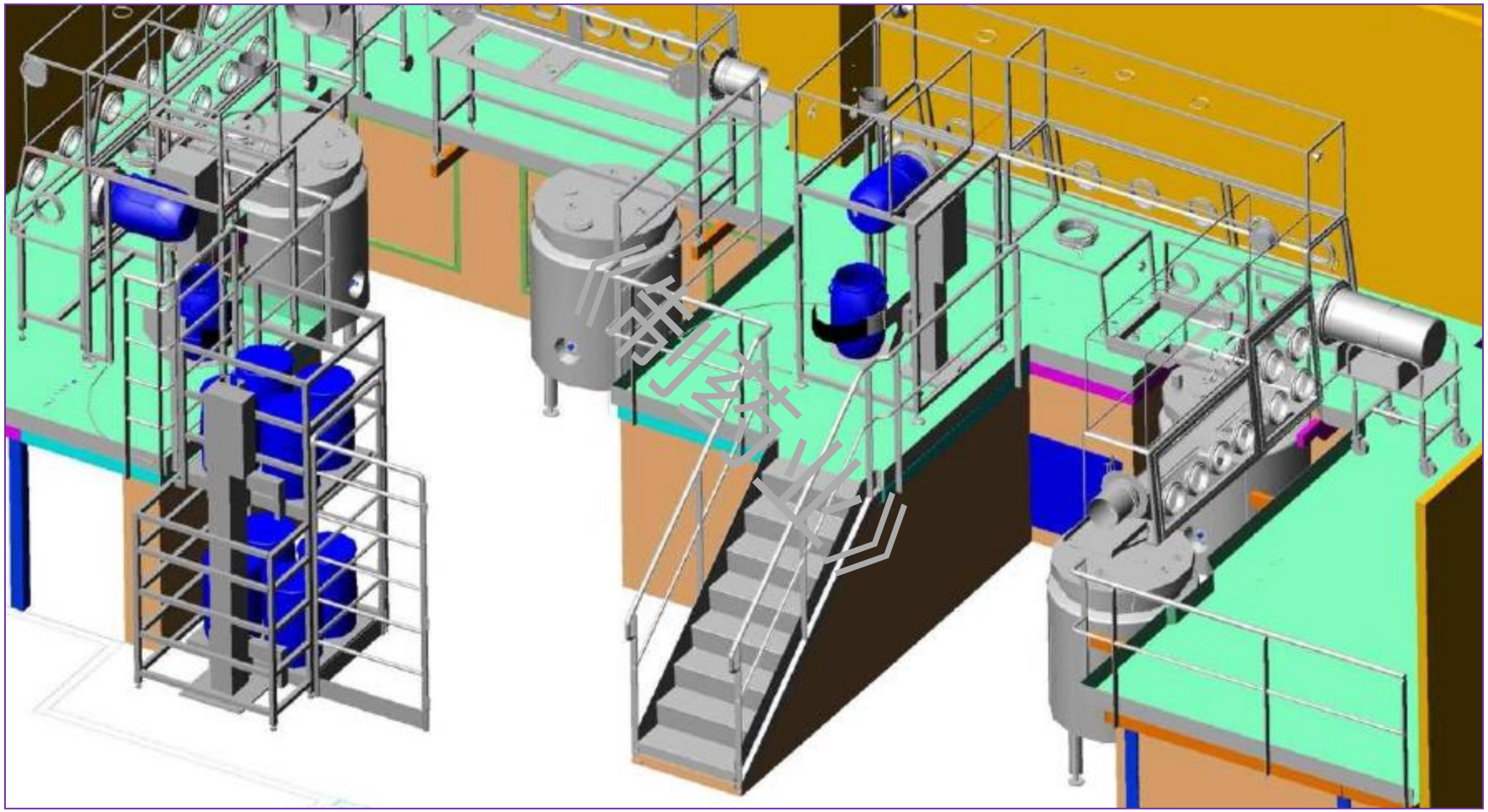
- Analysis of the existing concept
- Detail planning, cost calculation and submission
- Realisation of the logistics part incl. WMS extensions

Get The Right People Involved!

- Consider:
  - Training
  - Qualifications
  - Recognition
  - Accountability
  - Communication Skills

Process Flow Supporting C&Q





Productivity, Efficiency

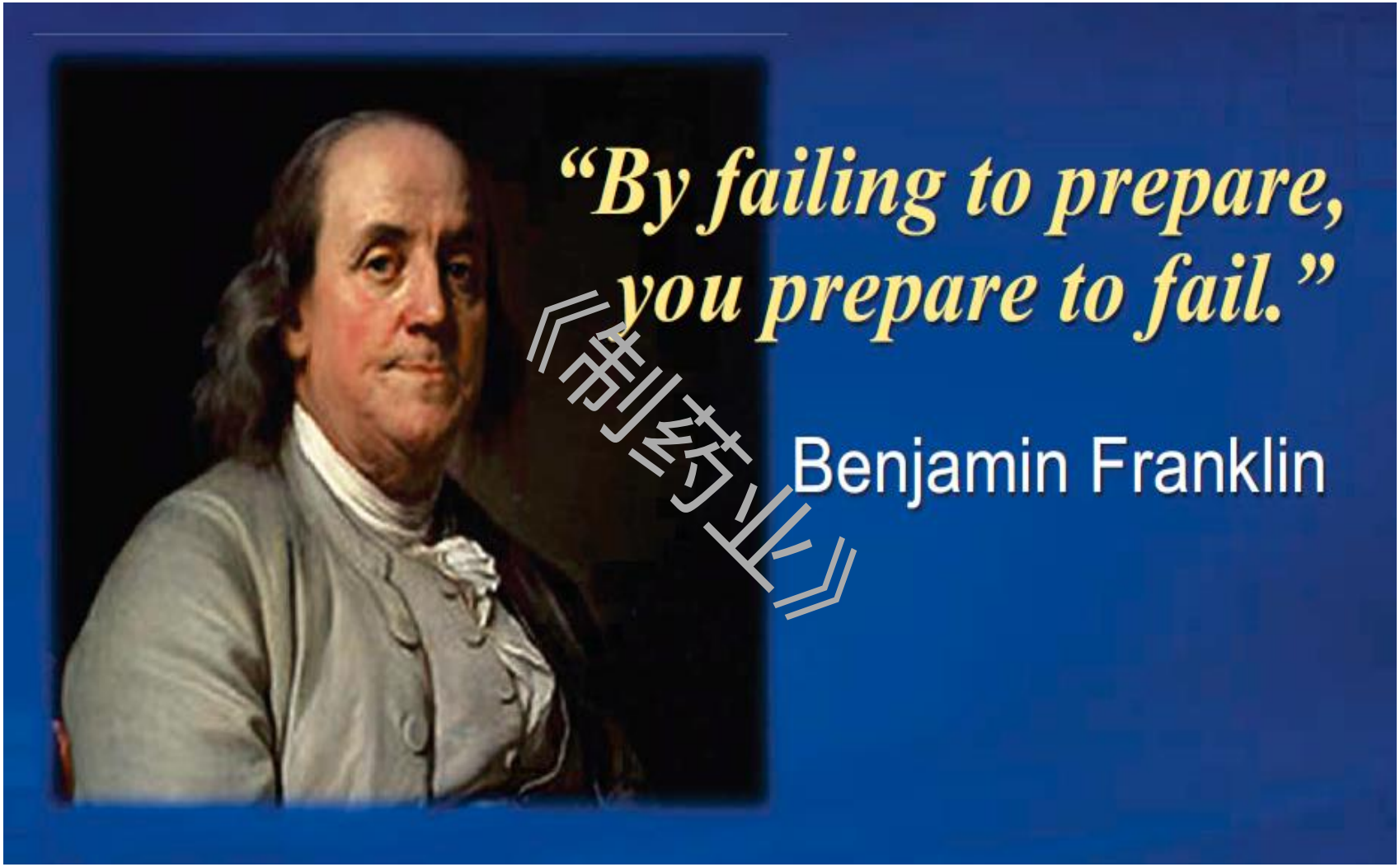
Documentation
Quality, Compliance

IP Protection, Security

Designed to be modular, fast and expandable, the IDT Biologika facility is now one of the most flexible biologics operations in the world certified to biosafety levels (BSL) 1 and 2 for live vaccines.

Success Factors for the Facility of Future

- Process Automation & Controls
- HMI (Human-Machine Interface)
- URS
- Bio-Mfg Process Development
- Products Portfolio
- Project Phases Definition
- Select System/Equipment Suppliers


“By failing to prepare, you prepare to fail.”
Benjamin Franklin

How to successfully manage Your New Facility Project

- Early planning and organizing
- Stakeholder communication and project controls integration
- Continuously improving your chances of project success

Keys to Project Success

- Assign the project team early
- Choose the right project delivery strategy
- Develop realistic estimates
- Actively manage project risks

Actively manage project risks-1

- **Technical risk**: How mature is the proposed technology? What happens if the technology fails?
- **Scope risk**: Is the project scope defined adequately in sufficient detail?
- **Schedule risk**: Are activity durations reasonable? What is our risk of extending the project?
- **Cost risk**: Are cost estimates based on current market pricing? Have we included allowances for undefined project components, design development, escalation, and other contingencies?

Actively manage project risks-2

- **Human resources risk**: Will we have sufficient skilled resources when we need them? How do we retain them for the duration of the project?
- **Regulatory risk**: Have all regulatory risks been defined? Are any permits or approvals on the project's critical path?
- **Safety and security risk**: Is craft labor trained in construction safety procedures? Is the project in a locale where there is a significant security risk to personnel and property?
- **Political risk**: Is the project subject to periodic funding approvals? Does the project have strong political approval and backing?

mikeleeck@126.com