



# UPGRADE YOUR EFFICIENCY

“Industry 4.0” Approach in Pharma Operations:  
Continuous Manufacturing – A Trend in Pharmaceutical OSD Production  
制药“工业4.0”：连续生产——固体制剂生产的趋势

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**FETTE**  
COMPACTING

# Fette Compacting – the Global Market Leader

菲特压片——全球压片机行业领导者

- Founded 1908 by tool-maker Wilhelm Fette 成立于1908年
- HQ located in Schwarzenbek, Germany 总部位于德国汉堡附近的施瓦岑贝克
- Production facilities: Schwarzenbek Germany, Nanjing China 工厂：施瓦岑贝克，南京
- 800 employees worldwide (thereof 70 R&D and engineering)  
全球800位员工（近70位研发人员及工程师）
- 12 subsidiaries 12个分公司
- 5 Competence Centers 5个能力中心
- more than 100 technicians worldwide 全球100多位售后工程师

**> 70 years Fette tablet presses**

**> 70 Years of success since 1948 >70年成功经验**

Installed Base > 5,000 machines globally 全球5000多台装机量

Production > 260 machines p.a. worldwide 每年新生产260多台新机器

...since 111 years



# Company Profile of Fette Compacting China

## 菲特（中国）制药科技有限公司

15 Years in Nanjing – since 2004

- Fette Compacting (China) Co., Ltd. is 100% invested by Fette Compacting GmbH. Total investment is over 18 Mio. USD. The China **production started in August 2004** → Move into the new **state-of-the-art Plant in 2018**

*菲特中国是德国菲特在中国独资子公司，总投资超过1,800万美元。工厂于2004年8月开始投产，并于2018年迁至新工厂。*

- With over **1,000 sqm** and latest technology, the **Fette Compacting China competence center is the largest of its kind in Asia**, setting a true benchmark in the industry. Experienced competent teams provide **best-in-class solutions and trainings for tablet and capsule production** of all pharmaceutical, nutritional & industrial applications

....

- Nanjing is one of **Fette Compacting's global factories**, following the stringent German Fette Compacting quality standard.

*南京工厂是菲特在全球的工厂之一，严格遵循德国质量标准，确保德国品质。*



FCN – new Plant: Office Building

# Company Profile of Fette Compacting China

## 菲特（中国）制药科技有限公司

- Fette Compacting China is specialized in **manufacturing P-series** (P1010 / P2020 / P3030)

➔ high speed tablet compacting machine.

*菲特中国专业生产P系列（P1010/P2020/P3030）高速旋转式压片机。*

- All P-Series(P1010/P2020/P3030) produced in Fette Compacting China passed the “**CE**” **certification**, to ensure that the products meet the requirements of EU regulations and standards from all aspects.

*菲特中国生产的所有P系列（P1010/P2020/P3030）高速旋转式压片机都通过了CE认证，确保产品从整体到细节无一疏漏地符合欧盟法规及标准的要求。*

- Total production is **over 700 Machines at in May 2019**: over 300 customers, including more than 200 Chinese and about over 80 foreign customers (Export business).

*截止到2019年5月，P系列总产量超过700台，国内外客户超过>300家，其中国内客户>200家，海外客户>80家。*

**05.2019:**  
**> 700 P series  
produced**



**Main Office with FCN Plant  
& Competence Center**



# Global Setup of Fette Compacting

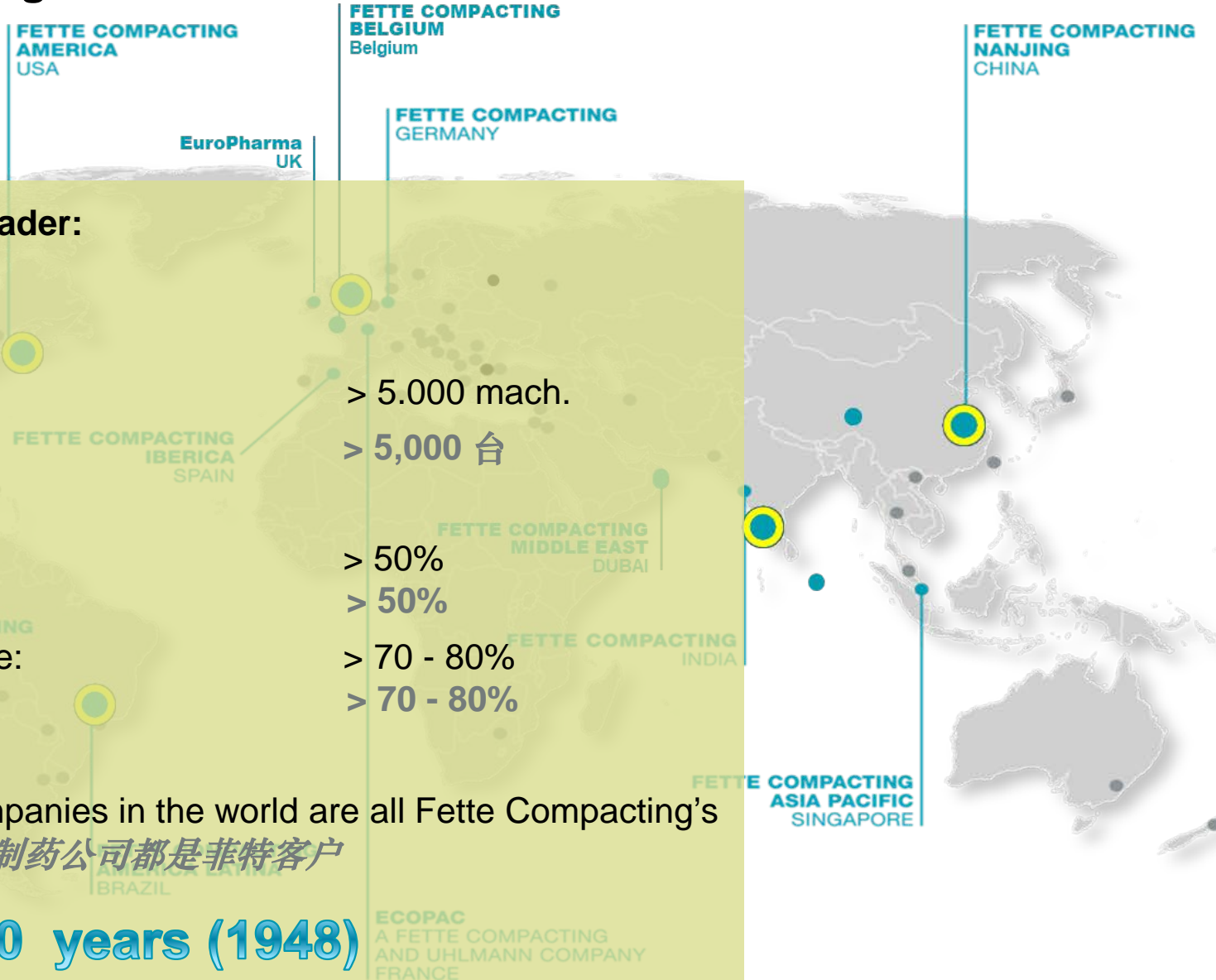
## 全球组织结构--菲特压片

### World market & technology leader:

作为世界压片机行业领导者

- Global installed base : 菲特全球装机台数 > 5.000 mach. > 5,000 台
- Global Market Share: 全球市场份额 > 50% > 50%
- high-end China market share: 中国高端市场 > 70 - 80% > 70 - 80%
- TOP 10 pharmaceutical companies in the world are all Fette Compacting's customers 全球最大10家制药公司都是菲特客户

Success since > 70 years (1948)



# Holistic offerings by Fette Compacting China

菲特中国提供的整体解决方案

The entire process chain from one single source  
(China & Export)

可以提供整个压片过程所有服务 (无论国内还是海外)



**TECHNOLOGY** stands for everything, we offer in tableting technology from tablet presses through process equipment to tableting tools.

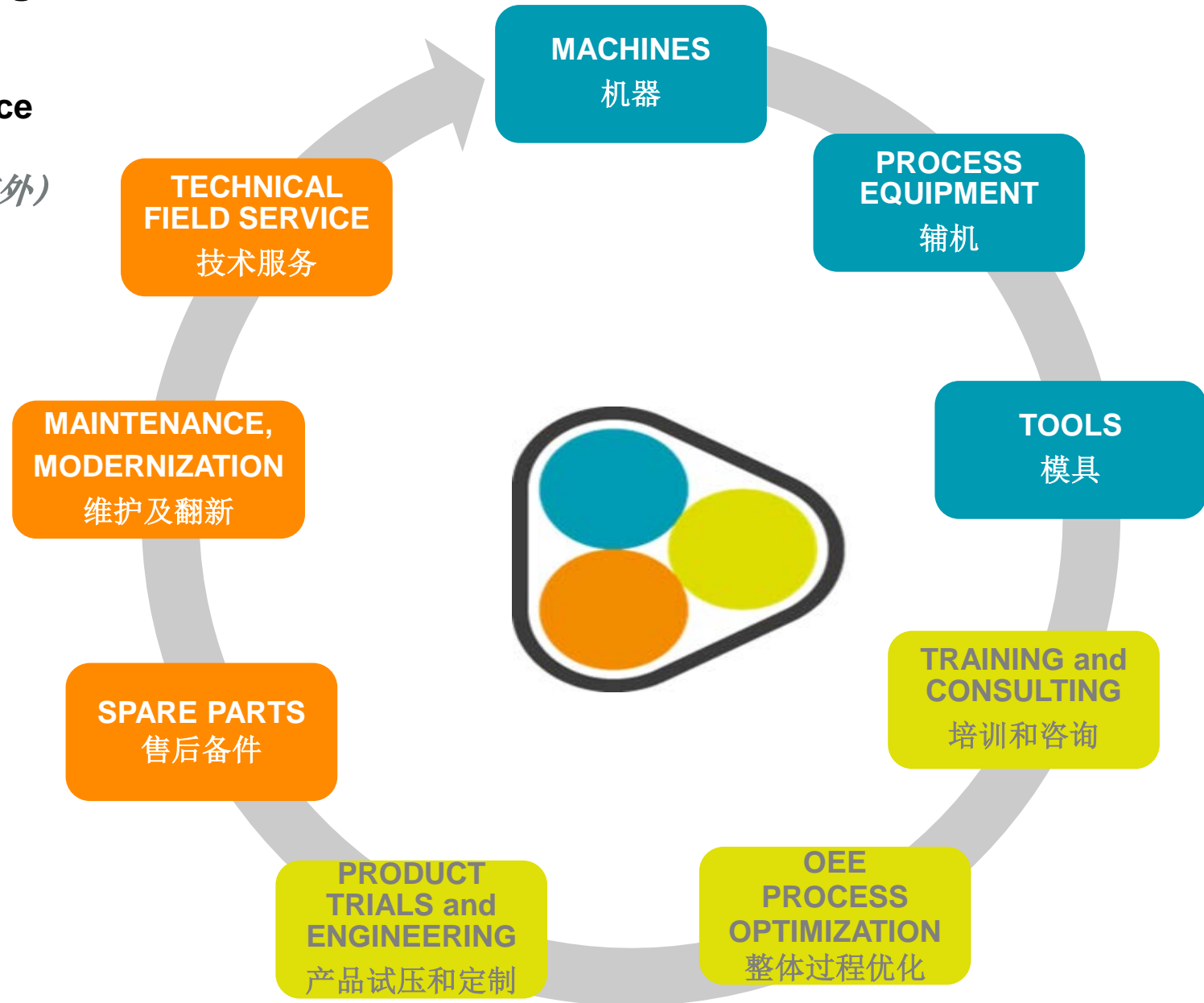
代表为片剂生产提供的所有机器、辅机和模具。

**COMPETENCE** is the overarching idea behind all our process-related services. This includes training offers, product trials, application and OEE consultation, and engineering.

代表整个流程链上可以提供的专业服务。

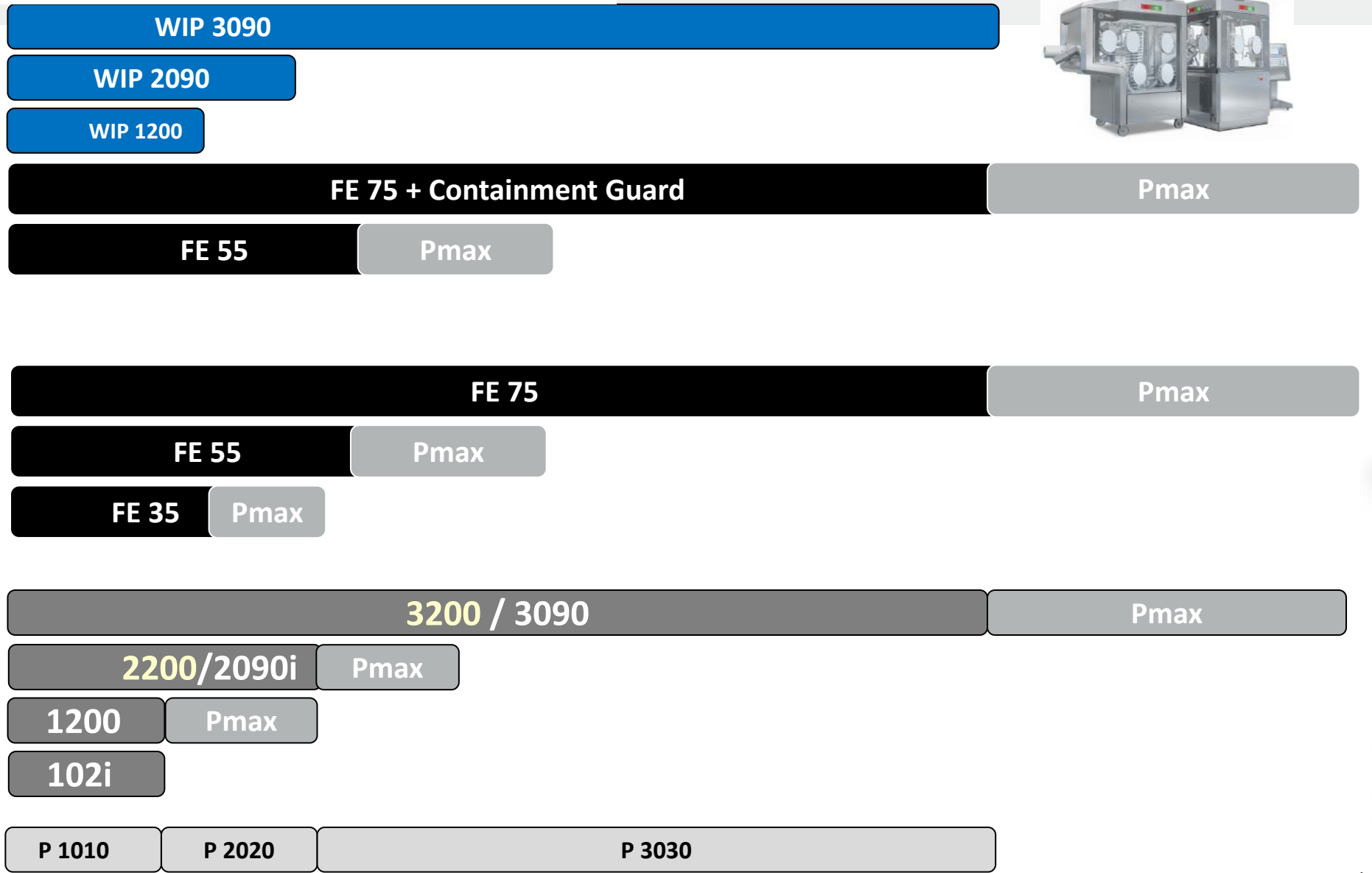
**SERVICE** includes all the services related to machines and equipment, such as the supply of spare parts, equipment modernization, and the technical field service.

包含所有机器、设备相关的服务。



# Product Portfolio 产品组合一览表

Level of Technology / Cost



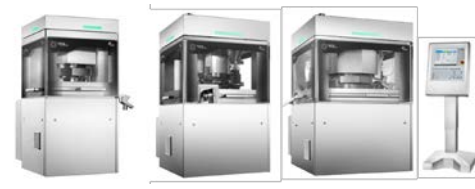
Containment Guard



FE - Series



i - Series



P - Series



150 300 450 600 750 900 1.005 1.200 1.350 1.500

Output in '1000 tablets / hr'

## New: Fette Compacting Capsule filling machines

新：菲特集团的胶囊填充机

### FEC 40

Next generation capsule filling technology

下一代的胶囊填充技术

- **Duplex Concept** for high flexibility, efficiency and performance  
*双倍理念，更灵活、更高效*
- **TRI.EASY** – for swift cleaning and turnover  
*TRY.EASY – 快速的清洁和产品切换*
- Advanced HMI for easy, intuitive operation  
*智能人机交互界面，操作更简单直观*
- Highest output up to 400,000 capsules per hour  
*最高产量可达每小时40万粒胶囊*





# Agenda

## 议程

Intro: Industry 4.0 philosophy at a glance 工业4.0观点概述

What is continuous manufacturing in Pharma Production?  
在制药行业, 什么是连续制造?

Advantages and challenges  
优点和挑战

Batch Production vs. Continuous Manufacturing  
批次生产与连续生产

Direct compression line  
直接压片生产线

PAT integration  
整合PAT技术

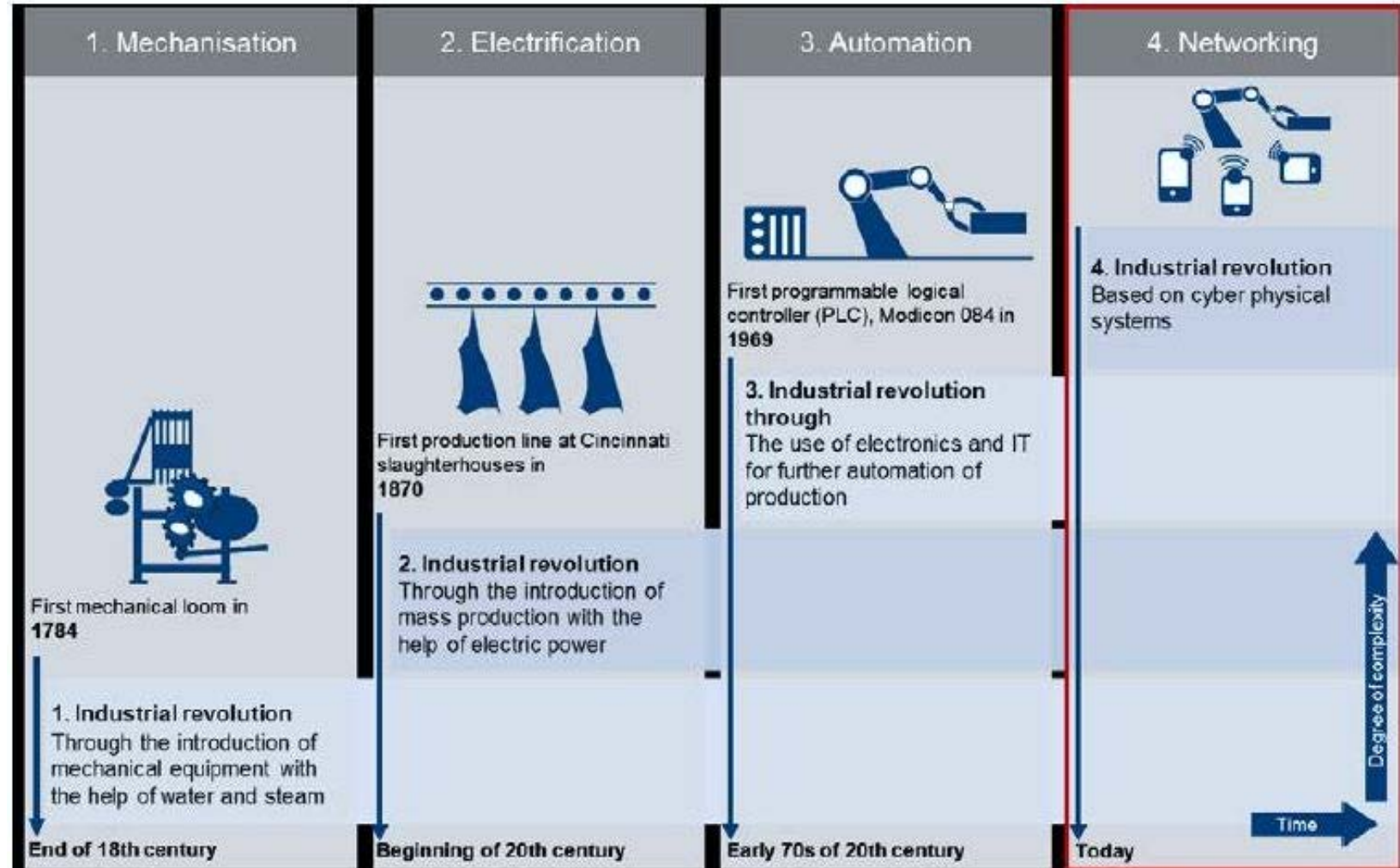
Application Example  
应用示例

Industry 4.0 – other aspects to be considered  
工业4.0 - 其他有待考虑的方面

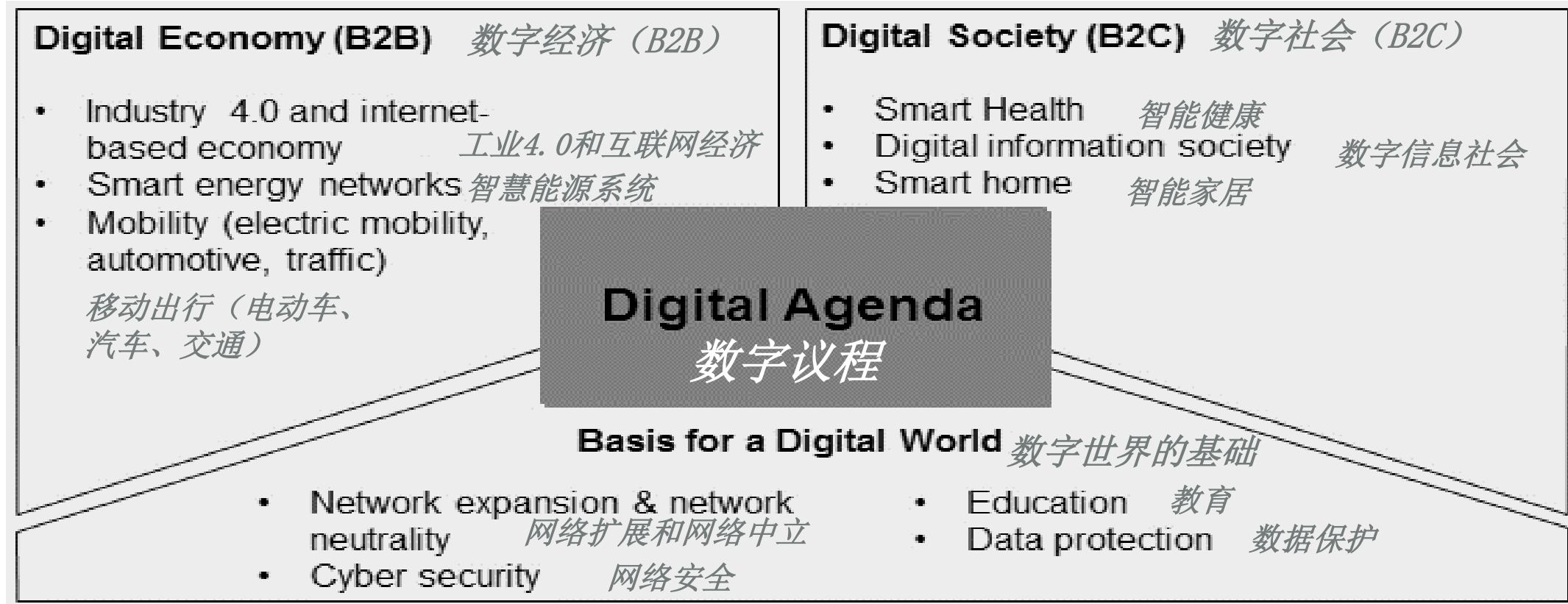
# The Characteristics of Industry 4.0

## 工业4.0的特点

- **Goal: Individualization (Lot 1)**  
at the cost of a mass product  
*目标: 用批量生产的成本实现个性化定制 (为1整批)*
- **Highly flexible, productive, resource-efficient production**  
*高度灵活、高生产力、资源节约型生产*
- **Real-time adjustment and optimization of processes**  
*实时调整和过程优化*
- **Intelligent assistant systems support the workforce**  
*支持操作员的智能辅助系统*



# The Digital Agenda and Industry 4.0 数字议程和工业4.0



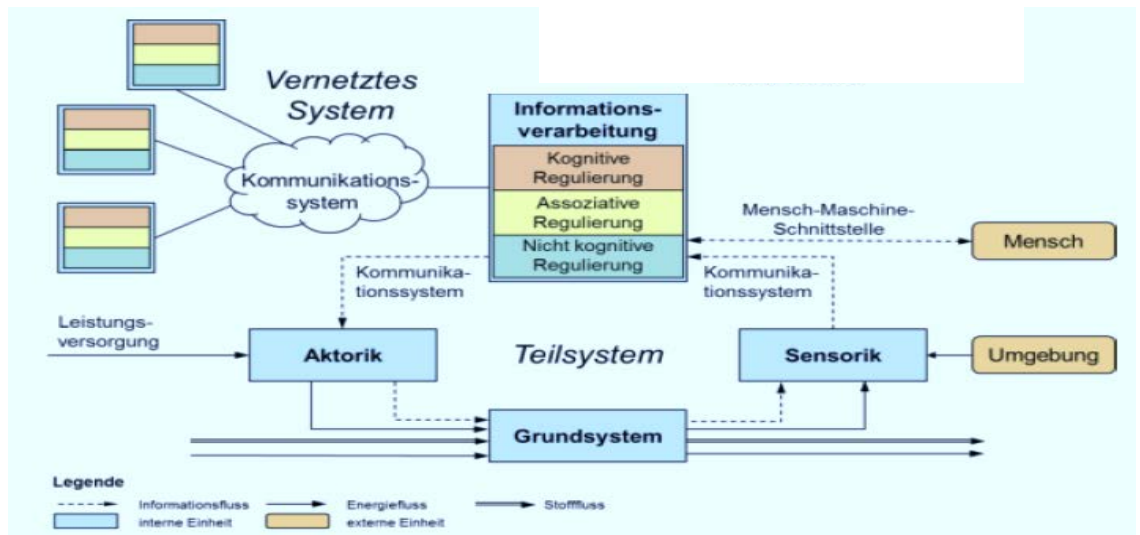
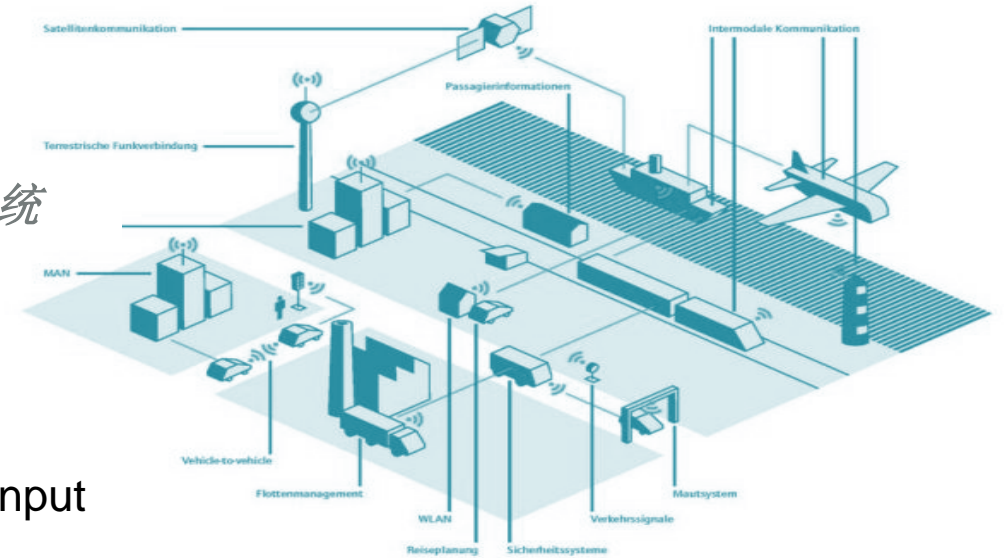
The Digital Agenda – not only a Production Topic  
数字议程 - 并非只是生产的课题

# The Digital Agenda and Industry 4.0 数字议程和工业4.0

Industry 4.0 工业4.0

Industry 4.0 – Cyber-Physical Systems 工业4.0 – 网络-物理系统

- Products with embedded hard- and software / Traceability  
搭载嵌入式硬件和软件/跟踪的产品
- Sensors and actuators responding to the physical environment / input  
响应物理环境/输入的传感器和驱动器
- Use of Internet protocols and services to networking  
互联网协议和联网服务的使用
- Interaction across application borders  
跨应用程序边界的交互
- Control business and complete value creation networks in real-time  
实时控制业务和完整的价值创造网络



Source: [www.acatech.de/cps](http://www.acatech.de/cps) und Gausemeier

What does this mean for the Pharmaceutical OSD Production

对制药生产的意义

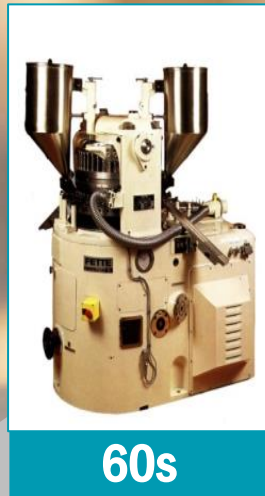
INDUSTRY 4.0 OR “MADE IN CHINA 2025”  
IN THE PHARMACEUTICAL INDUSTRY

制药工业的  
工业4.0 或是 “中国制造2025”



# Evolution of Tableting Technology

## 压片技术的革新



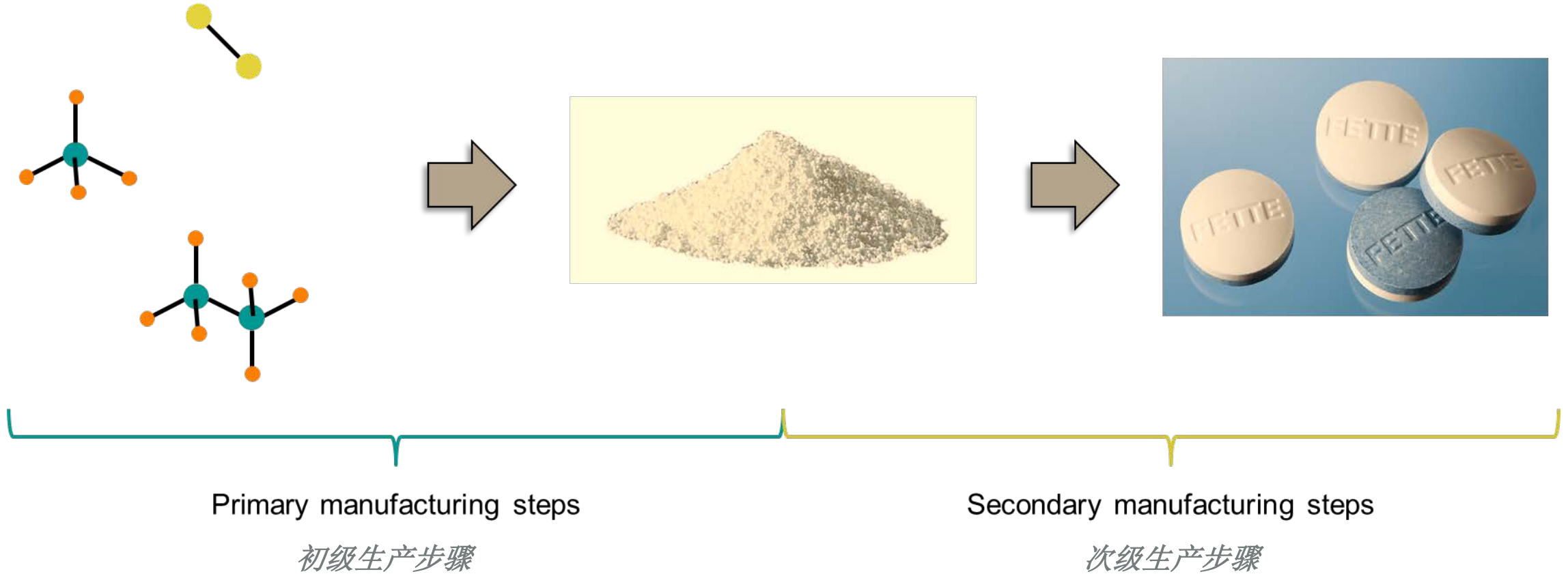
„Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. **It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing.**“

如今，来自20世纪50年代的药品生产专家，能轻而易举地识别出现代的制药工艺。可以预见，在未来的25年，现在用的制药工艺将会被更加清洁，灵活，更加高效的连续制造所替代。

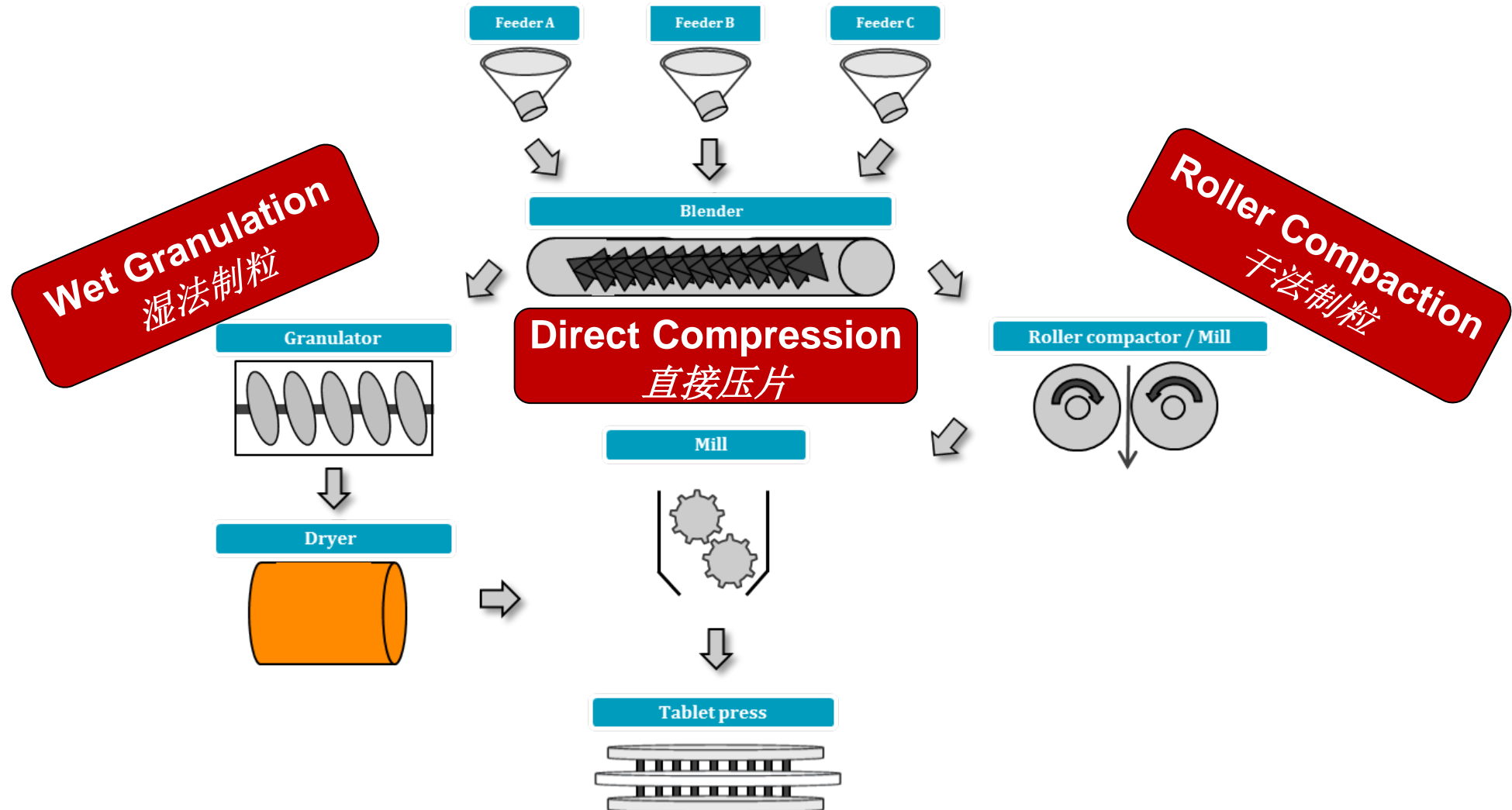
Dr. Janet Woodcock, US FDA, October 2011

# Continuous Pharmaceutical Production

药品连续生产



# Routes of Manufacturing 生产路线图





## Continuous Manufacturing - Key Facts *药品连续生产——重要事实*

1

**Big Pharma has widely evaluated CM in the last 5 to 10 years.**

*在过去的5到10年中，大型制药公司广泛评估了CM。*

▶ The point-of-no-return has been crossed!

2

**Generic manufacturers are behind Big Pharma but currently start to invest.**

*仿制药厂家落后于大型制药公司，但现在也已开始投资。*

3

**Wet Granulation and Direct Compression are both important.** *湿法制粒和直接压片都很重要。*

▶ Wet Granulation (WG) is at the moment the dominant route of manufacturing

▶ Direct Compression (DC) is often selected for first investment in CM as it is simpler than WG

4

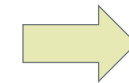
**CM is relevant for new drugs and also existing batch products!** *CM与新药和现有批次产品紧密相关!*

▶ Vertex got FDA approval for a new drug Orakambi

▶ J&J got first FDA approval for shift from batch to CM for Prezista in early 2016

5

**CM is promoted by FDA.** *FDA在推广CM。*



6 Drug Products already approved by FDA  
6个药品已获批

6

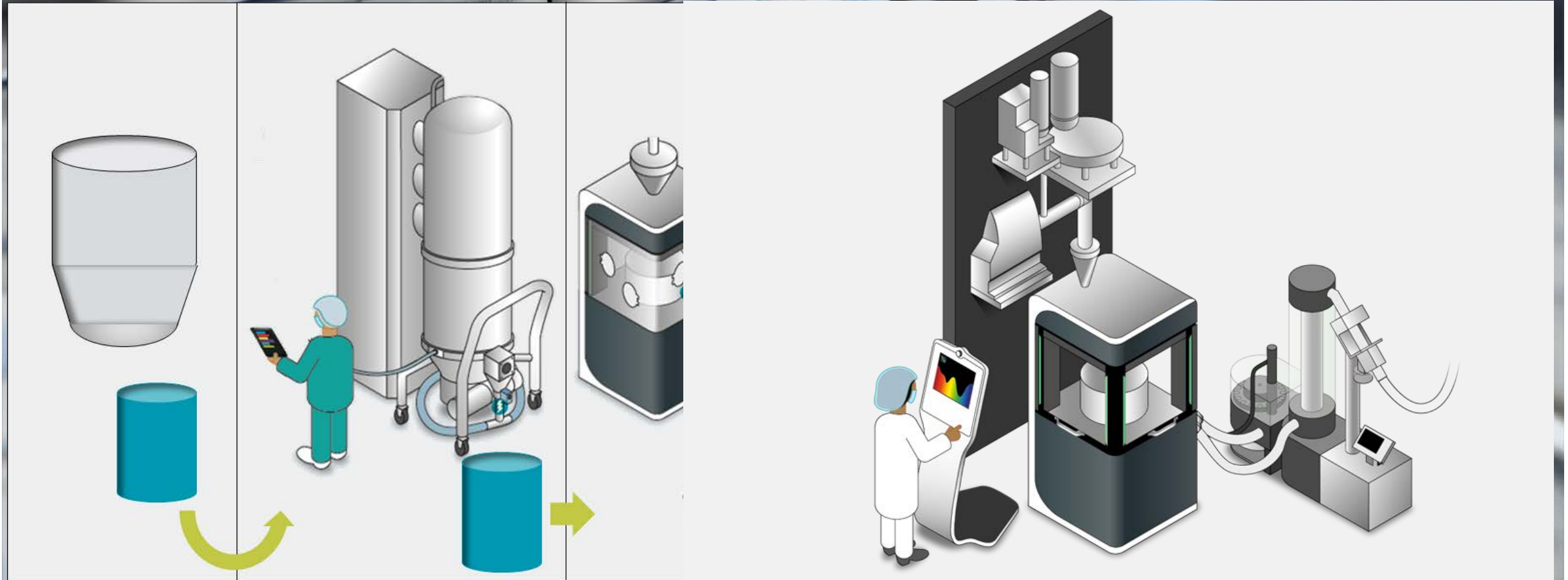
**Equipment suppliers have started to develop CM technologies and equipment:**

Fette Compacting, Glatt, GEA, Bohle, Bosch,

*设备供应商已经开始开发CM技术和设备: GEA, Glatt, Bohle, Bosch Fette Compacting.*

# Batch vs. Continuous Manufacturing

批次生产 vs. 连续生产



Source: Siemens: Continuous manufacturing – Moving towards real-time release

## Batch vs. Continuous Manufacturing

批次生产 vs. 连续生产

### Batch Manufacturing 批次生产

- Spatially and temporally independent production processes  
*工艺过程相对独立*
- Individual control of unit operations  
*单元设备独立控制*
- Storage of intermediates waiting for release and downstream processing  
*工艺上下游, 有等待期, 需要对中间体进行存储*

### Continuous Manufacturing 连续生产

- Mechanically interlinked production processes resulting in a single material stream  
*连续的工艺流, 物料流*
- Central control of different unit operations  
*集中控制各组成设备*
- No storage of intermediates  
*无需对中间体进行存储*

# Motivation & Drivers

## 动机和驱动力

- Less material handling is required 所需的材料处理更少
- Smaller footprint leads to less energy consumption 占地面积小, 能源消耗低

No intermediate product storage  
无需对中间体存储

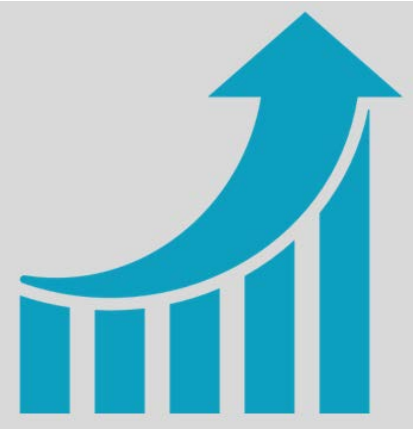
**Safety and Eco Footprint**  
安全和生态足迹

**Lead Time**  
交货时间

CM to reduce costs  
CM可减少成本

**CapEx & OpEx**  
资本支出和运营支出

**Time-to-Market**  
投放时间



# Motivation & Drivers

## 动机和驱动力

**Product Loss and QA Cost**  
产品损耗和质量保证成本

**Product Quality**  
产品质量

Explore a wider range of process parameters with less material and in less time 以 fewer 的材料和更少的时间探索更广泛的工艺参数

**Batch Size**  
批量大小

Possibility of producing virtually any required batch size with smaller equipment range  
可以在较小的设备范围内生产几乎所有需要的批量

**Scale-Up**  
可按比例增加

Flexible batch size determined by time and production capacity  
可由时间和生产能力灵活决定批量大小

Process performance	Yield
2-sigma	69.2%
3-sigma	93.3%
4-sigma	99.4%
5-sigma	99.98%
6-sigma	99.99966%

Implementation of PAT and APC to achieve higher process stability 采用PAT和APC, 获得更高的工艺稳定性

# Technical challenges

## 技术挑战



## Direct Compression line by Fette Compacting 菲特直接压片生产线

- Based on advanced FE series with integrated controls for the whole DC line  
*基于先进的FE系列设备，可对所有单元进行控制*
- Easy to operate  
*操作简单*
- Flexible setup suitable to process material of 5 up to 300 kg/h  
*生产能力：5~300Kg/h*
- Integrated inline analytics for real-time monitoring of API concentration  
*实时监控药物含量变化*
- Test facility available for products trials  
*硬件可开展产品试验*



# Technical Aspects of the Core - Tablet Press

## 压片机技术现状



# Control system & Process Automation

## 控制系统及自动化



Recipe: Standard    Operator: FetteAdmin    Batch: Sample Batch    14:08:08 17.11.2017

1.242.000    00:00:00    19 / min

Main menu > Functions > Feeder 1    FE55.249999    Standard run

### Feeder 1

No.	Parameters	Set	Actual
1000	Lead time	s	0
1001	max. Feedrate	kg/h	0,000
1002	Feedrate	kg/h	10,000
1003	Totalizer	kg	0,000
1004	Control command	%	0,000
1005	Motor speed	rpm	0,000
1006	Feedfactor	kg/h	1,270
1007	Weight	kg	5,000
1008	max. Refil level	kg	0,000
1009	min. Refil level	kg	0,000
1011	Operating mode		0

Buttons: Acknowledge Alarms, Clear Alarms, Stop and preserve alarms, Stop and clear alarms, Start and clear alarms, Clear totalizer, Gravimetric mode, Volumetric mode, Tare feeder, Calibrate, Empty feeder, Refill feeder



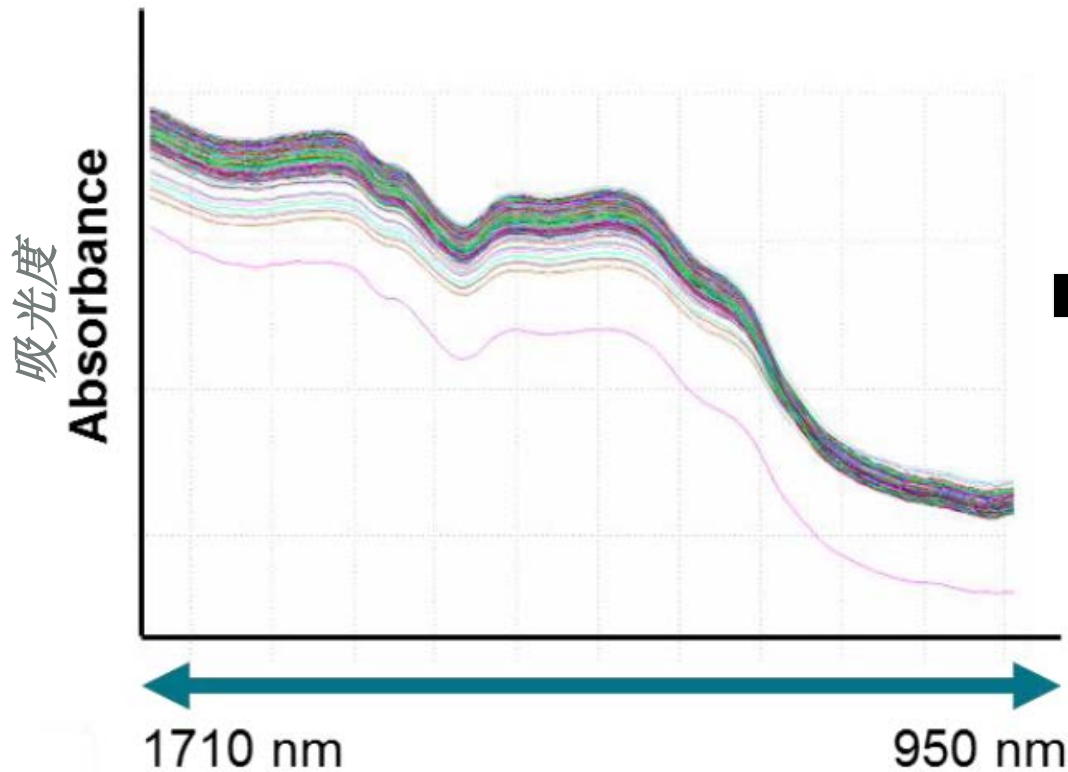


# NIR Data Analysis

## NIR数据分析

Raw spectra

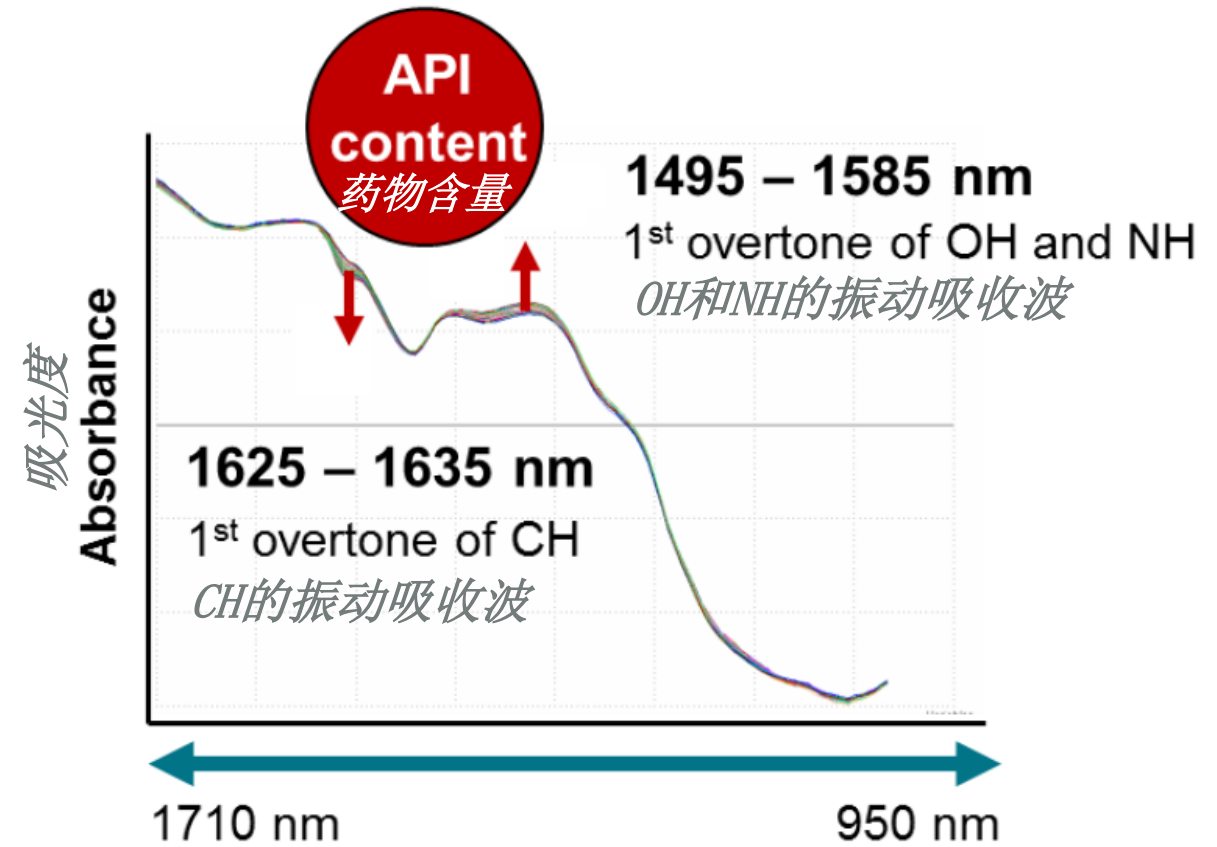
原谱



Calibration spectra (SNV)

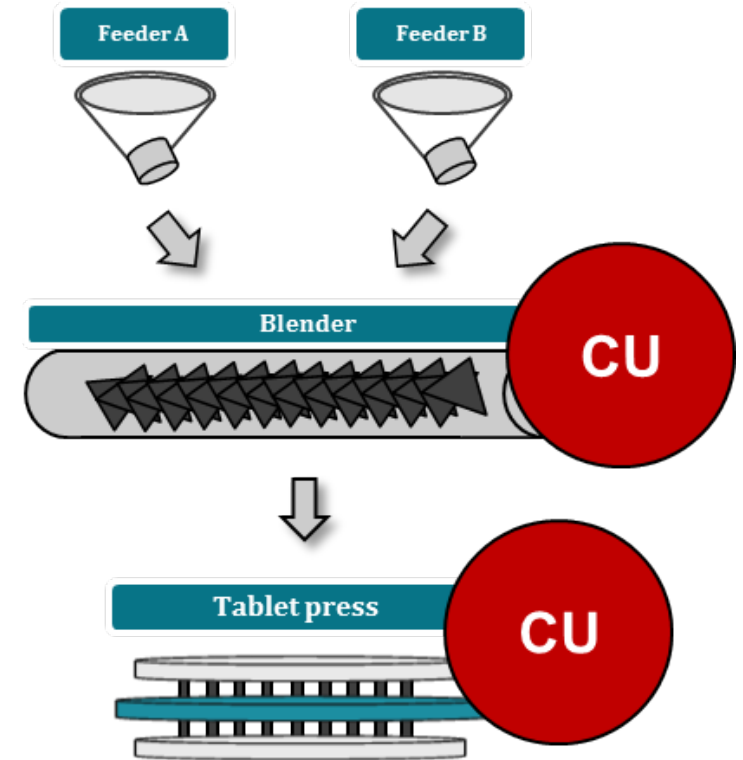
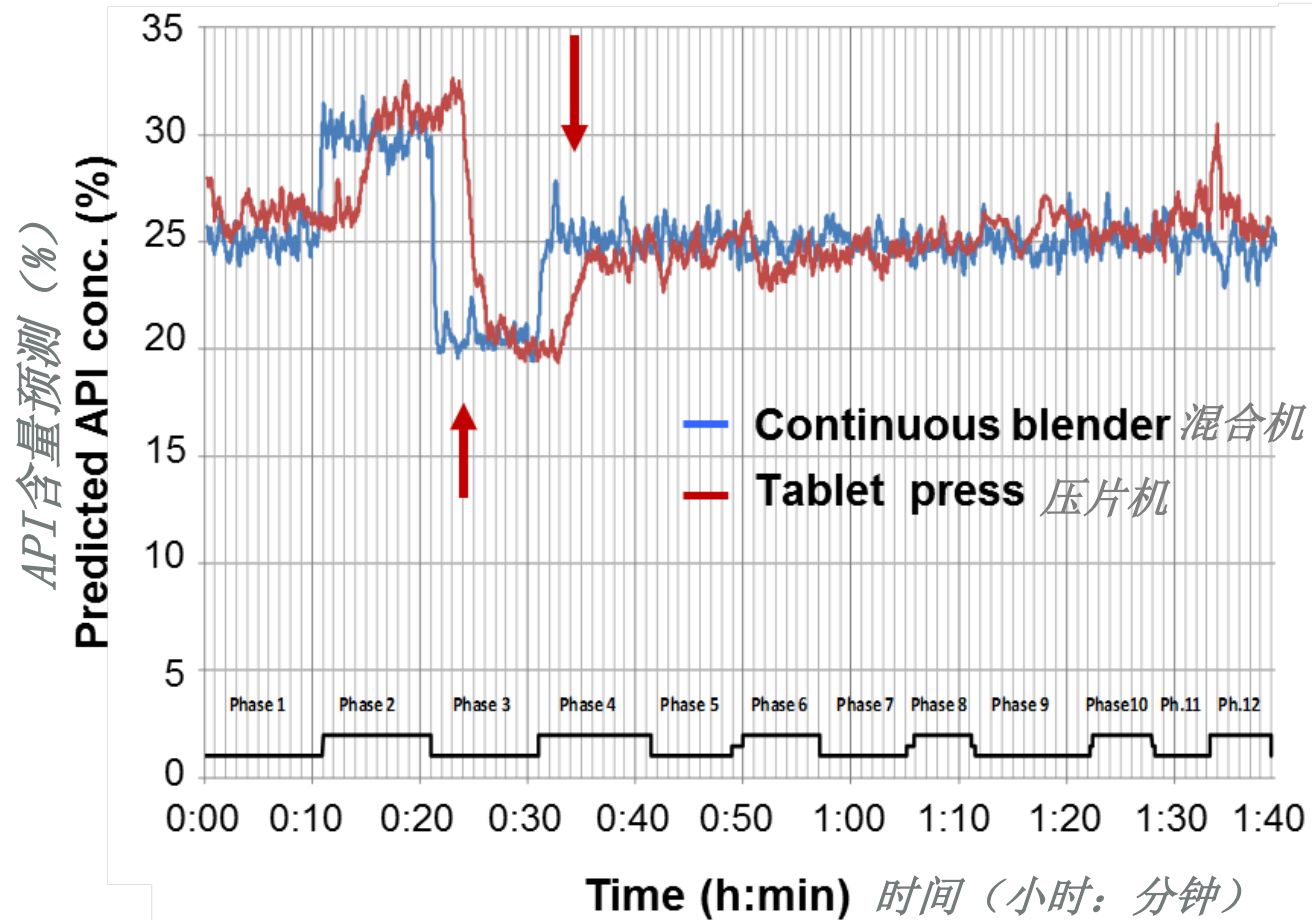
With different API concentrations

不同API浓度的校准光谱 (SNV)



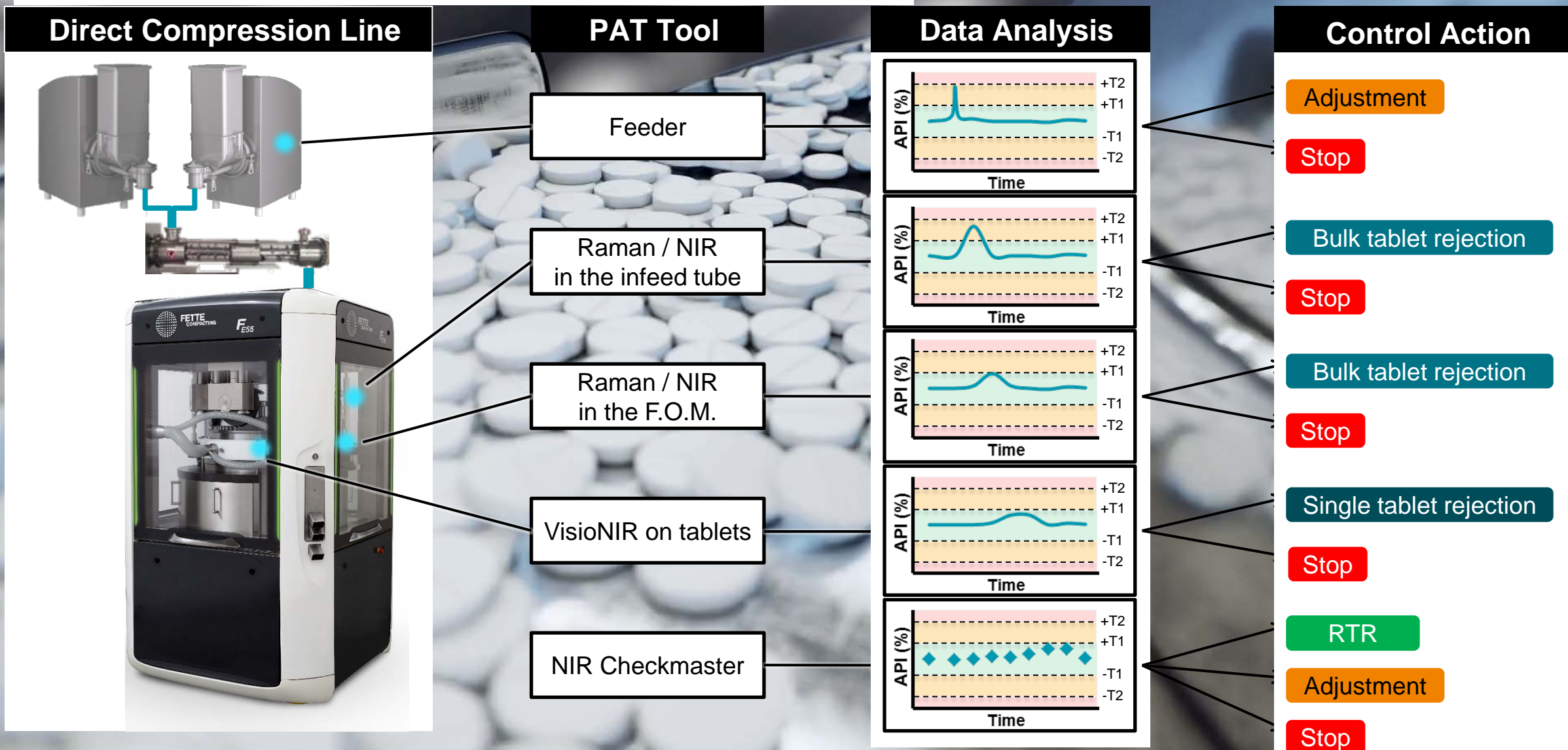
# Prediction of API Content During the Test Run

试运行期间药物含量预测



# PAT implementation in the direct Compression line

在线分析技术在直接压片中应用

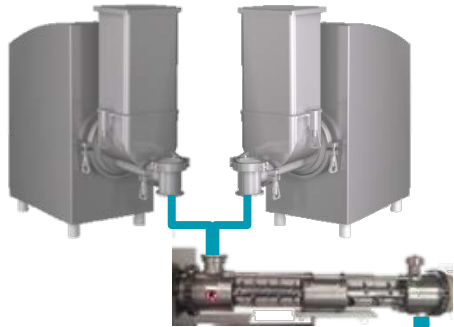


Part of overall OOS and rejection strategy

# Application Example – In line measurement in Tablet Production

应用示例——药片在线检测

## Direct Compression Line



## PAT Tool

Raman  
in the infeed tube

NIR  
in the F.O.M.

VisioNIR on tablets

## Setup of Study

Based on 5 blends with different API concentration

基于5种成分，不同药物浓度的配方

Claimed API conc.: 3%

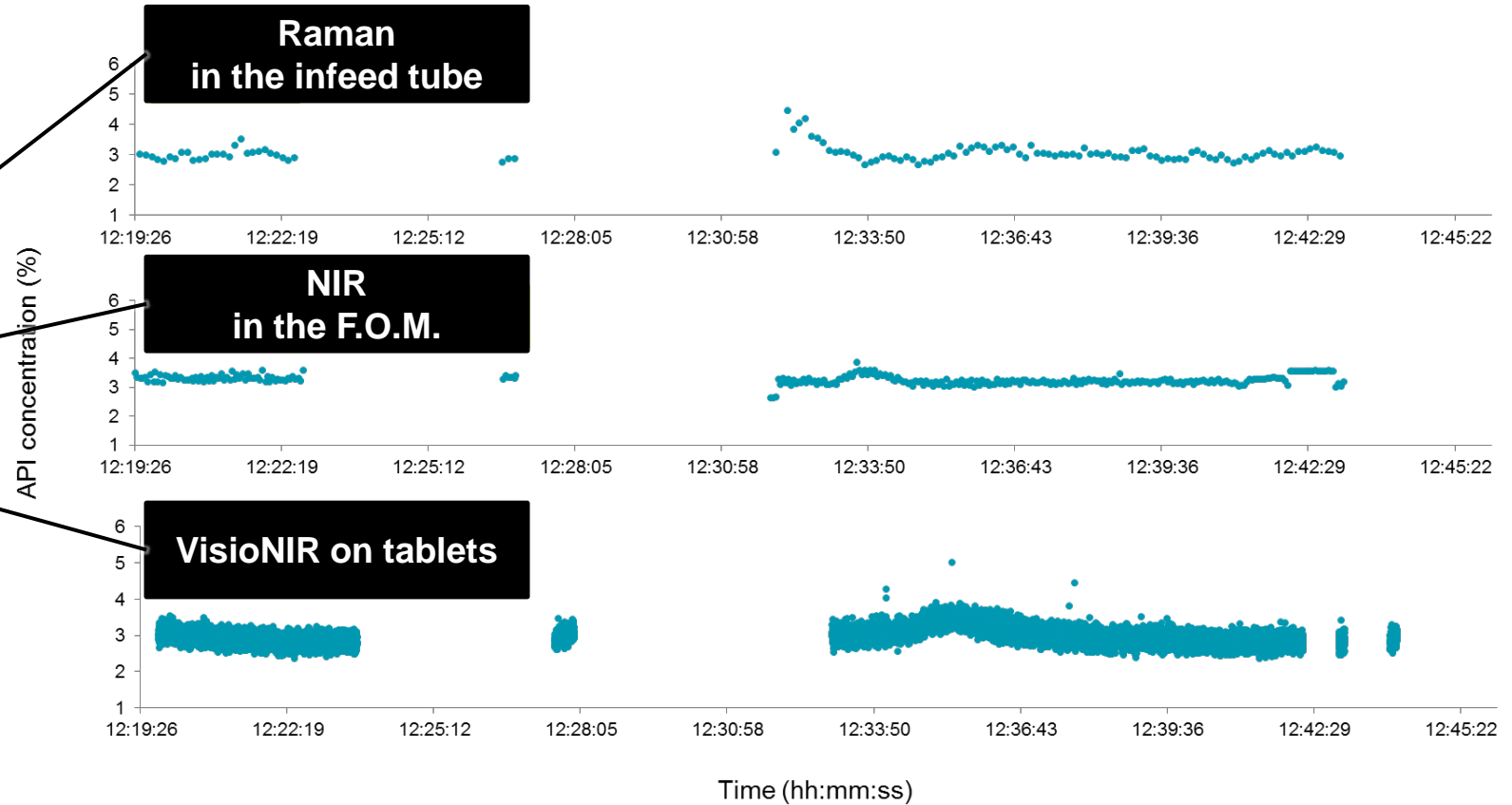
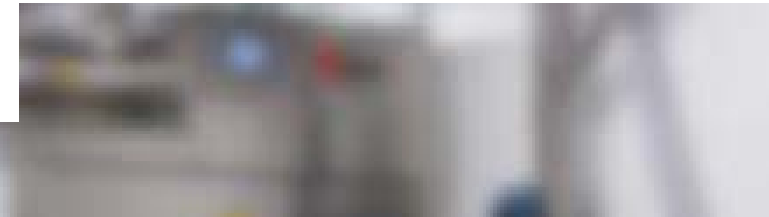
主药标示量：3%

3 PAT tools in the line

3处在线分析点

# Application example - Data analysis of in-line PAT sensors

## 应用示例——在线检测器数据分析



# Industry 4.0 is more than just Technology ... it is a holistic concept

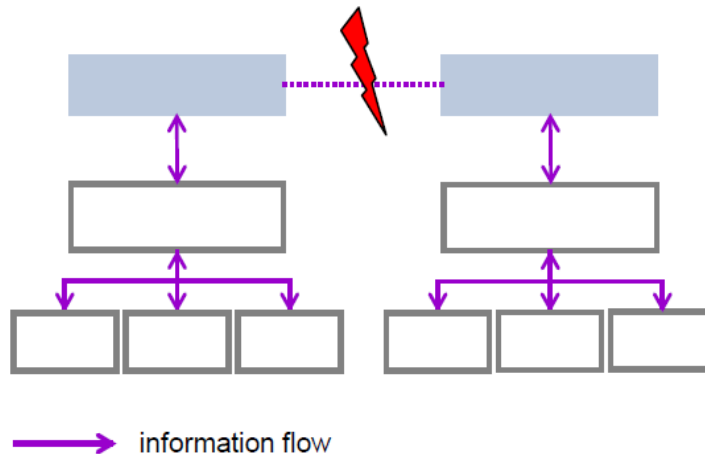
工业4.0不仅只是技术，更是一种整体观念

## 现在的信息使用

- 间接信息流，互不关联
- 极少记录数据，常手动转换数据
- 无/低效使用现有数据
- 工业领域很少使用“分析学”

## Information usage today

- Indirect information flow, non-connected
- Few data is recorded, often converted manually
- No / inefficient usage of available data
- Few usage of “Analytics” in the industry sector

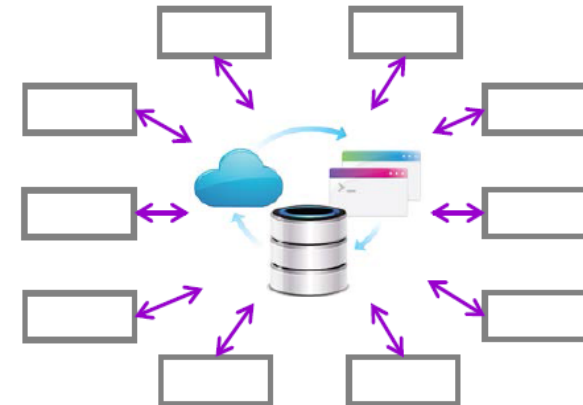


## Information usage tomorrow

- Direct information flow
- Central high-scale collection and processing of heterogeneous data
- Digital copies of machines and factories
- “Big Data”, “Analytics”, and simulations
  - > Real time monitoring and predictions
  - > Maintenance and reliability forecasts
  - > New after-sales services

## 未来的信息使用

- 直接信息流
- 大规模集中收集、处理异构数据
- 机器和工厂的数字副本
- “大数据”、“分析学”和模拟
  - > 实时监控和预测
  - > 维护和可靠性预测
  - > 新型售后服务



## Industry 4.0 implementation

The major challenges are still in the field of IT

工业4.0实施 IT领域仍存在重大挑战

### Unique identification 唯一标识

- > IPv4 addresses are used up (4.3 bil.)
- > IPv6 is hardly applied by corporations
- > IPv6 is essential for the "Internet of Things"

Basis for  
Internet of Things

物联网基础

### Intercommunication 交互性

- > many protocols available
- > no standard protocol determined
- > industry-specific solutions on the way
- > Combination of IT security and operational safety

Basis for  
Industry 4.0

工业4.0基础

### IT security and trust 信息安全信任

- > Access control → available, applied
- > Usage control → available, hesitation of industry

Basis for  
Digital Factories /  
Additive Manufacturing

数字化工厂/  
附加加工基础

# Successful implementation of Industry 4.0 requires to address and overcome challenges

成功实施工业4.0需要克服各种挑战

## Human aspects 人员方面

- > Employees' acceptance of the new technology
- > Qualification and Training
- > Motivation and continuous learning

## IT and legal aspects 信息技术和法律方面

- > Hesitation towards changing a running system
- > Hesitation towards transparency among the supply chain
- > Slow establishment of norms and standards

## Exotic products 国外产品

- > The whole supply chain / manufacturing process needs to be pre-planned and digitalized  
→ potential effort / output gap

## Data quantity and quality 数据数量和质量

- > Limited real-time processing capability
- > Selective data processing
- > Users' resistance towards continuous machine monitoring and analytics by the manufacturer

## Organizational aspects 组织方面

- > From "central planning" to "decentralized control"
- > Changing processes and functions
- > Cooperation with workers councils

**A real paradigm shift for personnel development:  
"Industry 4.0" cannot be realized with Users &  
Operators on "level 2.0 / 3.0"**

真正的范式转变：  
“2.0/3.0的用户和经营者无法实现工业4.0”



## Summary & Take aways

### 总结

- Continuous Manufacturing is evolving and promoted by FDA with 6 drug products being already approved  
*FDA不断推动连续生产，已批准应用此技术生产6个药品*
- CM is relevant for new drugs and also existing batch products – a clear future trend  
*连续生产不仅可用于新药开发，也可用于现有品种生产——趋势显而易见*
- Lean production process with Direct Compression leveraging full efficiency potential  
*直接压片实现精益生产，效率潜力无限*
- Fette Compacting provides fully integrated turn-key solutions with flexible outputs of 5 up to 300 kg/h  
*菲特压片拥有一揽子的连续生产压片方案，产量灵活：5到300公斤/小时*
- Advanced Process Intelligence with continuous adjustment by integrated control system allow DC even with variation of powder quality  
*即便物料性质多变，智能的过程监测系统能够及时作出调整，保证压片顺利进行*
- Fette Compacting Test facility is available for products trials  
*菲特压片随时欢迎您来进行产品试压*

**THANK YOU!**