Better Health, Brighter Future

Facility Engineering, New Technologies and Automatization

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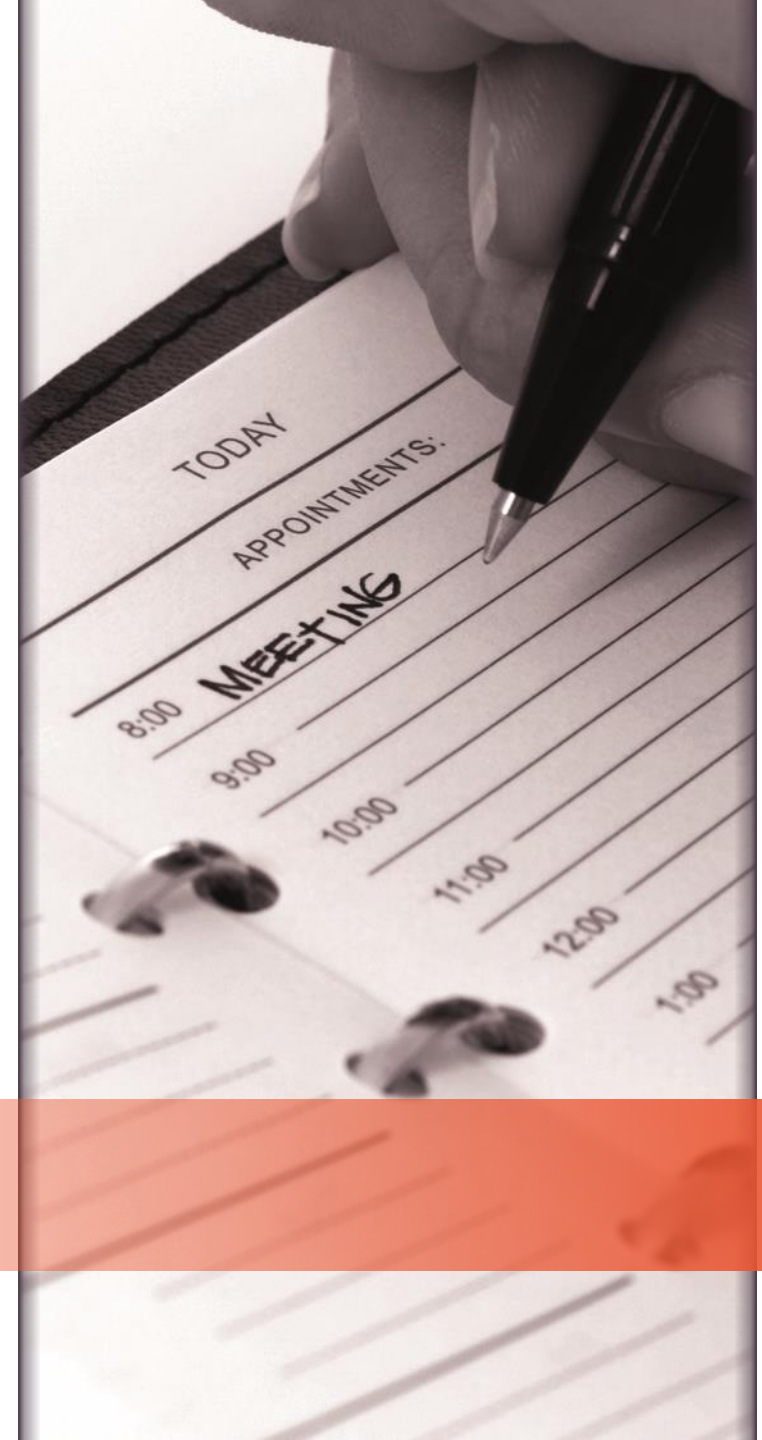
Takeda Pharmaceuticals International

Agenda

1. *Introduction*
2. Smart Facility Design
   - Green Field – Modular (Bio/regenerative medicine)
   - Brownfield – Contained (Ninlaro)
3. Digital Factory – Pathing the future
4. Outlook & Challenges



Putting the Patient at the Center

1. **Address urgent and unmet needs**
   - Provide innovative medicine for patients worldwide

2. **Innovation, partnership**
   - Faster access for those who need our medicine

3. **“Safe drug delivery & fight against counter fight products”**

Industry Trends

Globalization and competitiveness

- Outsourcing vs. Insourcing of production
- Access to new resources and markets
- Proven engineering and execution models for technology transfer into new geographic regions
- World wide networking of R&D/production sites and global planning
- Unified standardization, simplification and unification of production processes
- Global and local supply/contractor/vendor network
- Smart Factory and Digitalization (Industry 4.0, IoT)

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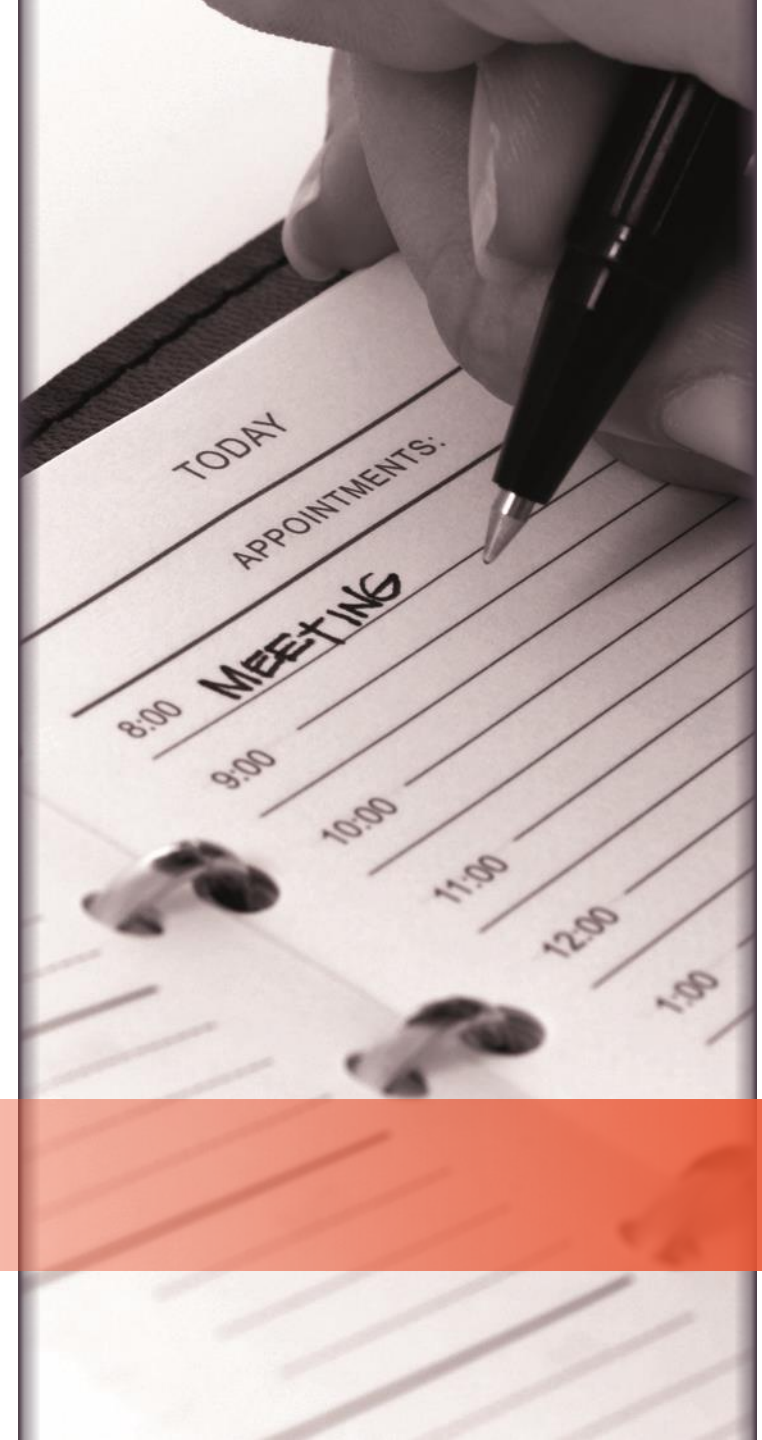


Delivering «Smart Facilities» around the globe

1. Market and Supply Chain Driven (traceability)
2. Manufacturing network – 25 sites (API, Primary, Secondary, Packaging)

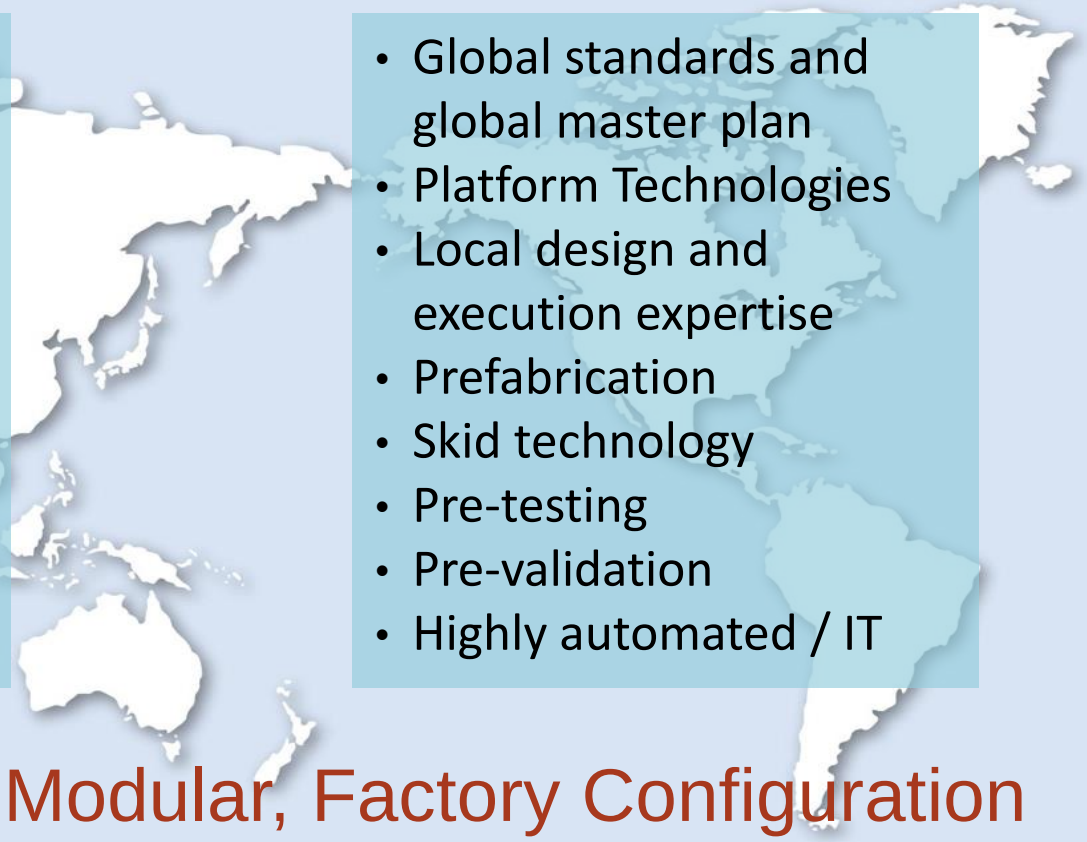
Challenges of new project deliveries

- Economical sourcing
- Different local customer needs
- Production near to market
- Availability of suppliers/technology
- Rising transportation costs
- Rising punitive duties
- Local pricing strategy
- International and local regulations
  (EMA, RZN, MOH, RPN, MIT, MHRA, FDA, ANVISA, etc.)
- National / local interest

Future Takeda smart facility solutions have to meet . . .

- Time to market acceleration
- Low cost of ownership
- Eco-friendly engineering and higher energy efficiency
- Labor efficient targets
- Security and safety concerns

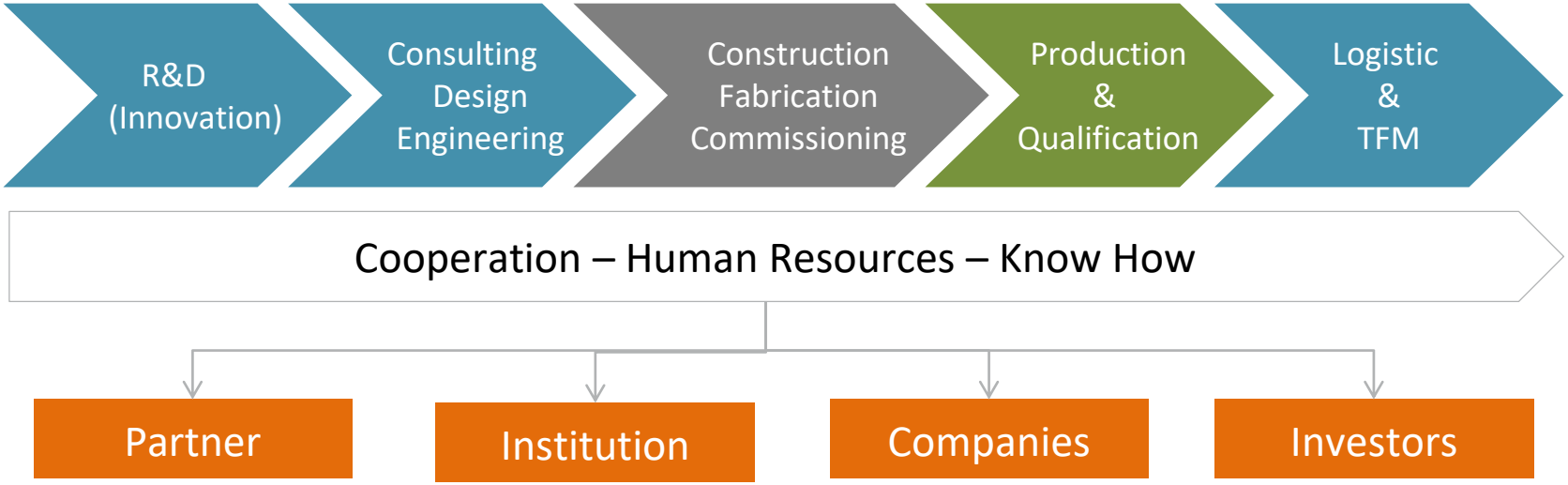
- Global standards and global master plan
- Platform Technologies
- Local design and execution expertise
- Prefabrication
- Skid technology
- Pre-testing
- Pre-validation
- Highly automated / IT



. . . Standardized, Modular, Factory Configuration

Project Execution – Industry Collaboration

- Challenge of “Integrated processes on a global basis”
- Mastering the different disciplines and processes
- Early involvement of „Experts“ and „Stakeholders” – e.g. Quality & Regulatory right from the beginning

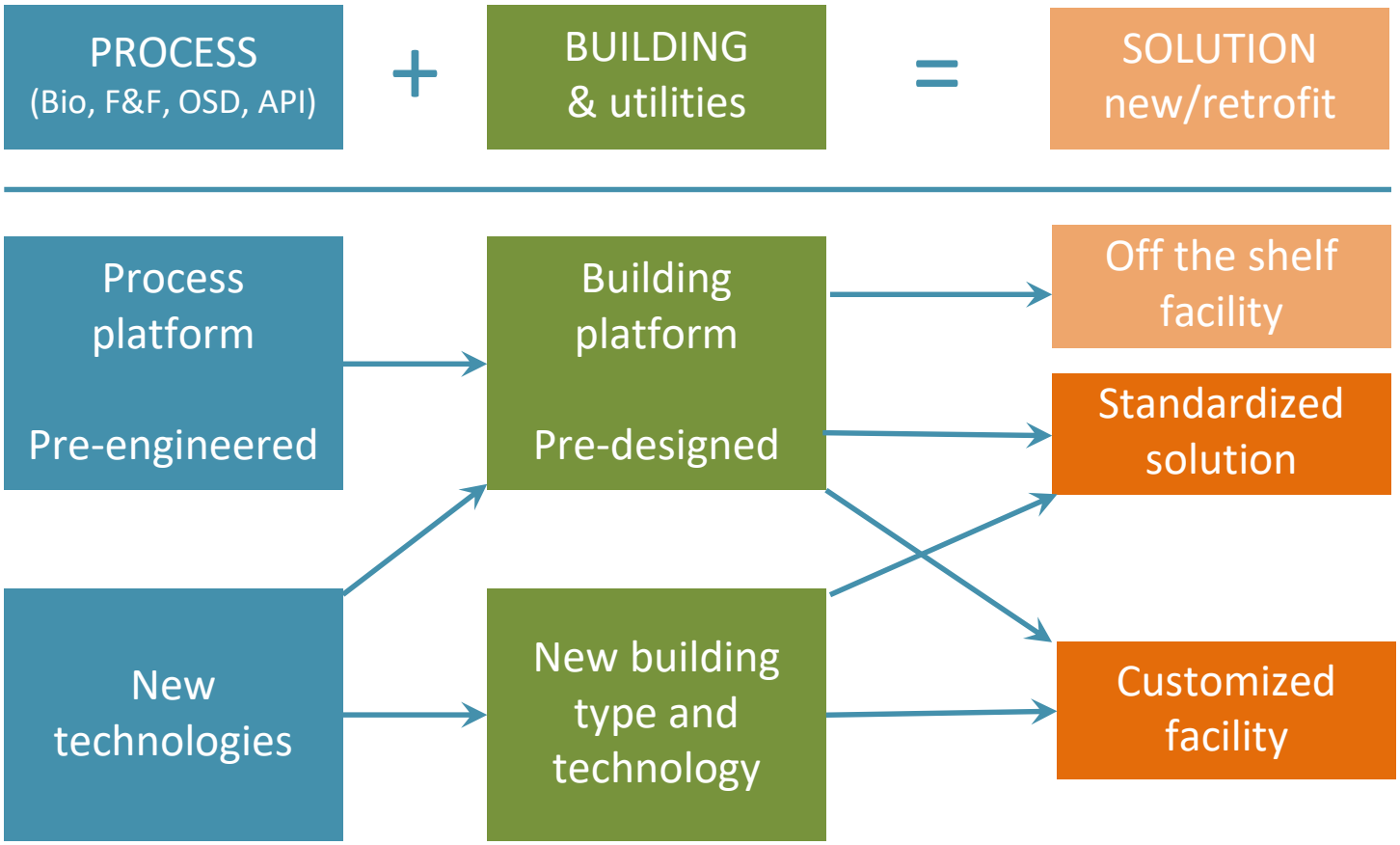


Innovation and new technology

Technology	GMP	Fast Project Realization
Bio - API – sterile filling – assembly – packaging	Track and Trace (Data Matrix und RFID)	Modular engineering and construction
Production excellence (lean manufacturing)	Implementation of production excellence	Pre-fabricated systems e.g. process skids, utility skids
Continuous processing	Interpretation, PAT (technology)	Modular and containerized building
Single use, hybrid vs. fixed installed , micro reactor	Handling of single use, hybrid	Modular and flexible IT solutions and infrastructure
Robotic system	Clean-room requirements	
Closed system & mini environment	Mini-environment, machine concept	
Quality by design	Validation and ASTM 2500	
IT - Automation	Data Analytics,, Data integrity	

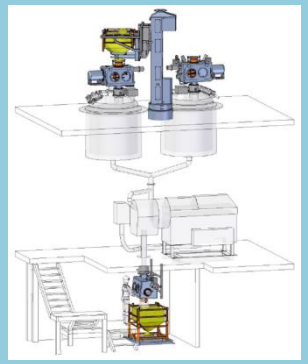
“Smart facility “design and construction

«Building Blocks» as innovative delivery model for new production facilities

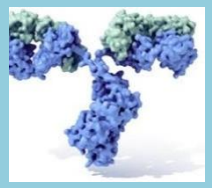


«Process Platform»
Process definition – “Unit operations”

Synthetic API
Additives



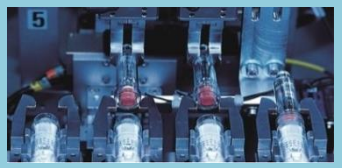
Bio API

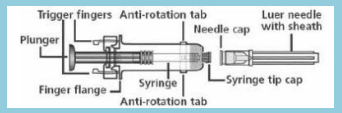


Preparation

Filling

Add. operations
Sterilization
Lyophilization
Mechanical Assembly





Packaging

«Process Platform» – Design impact

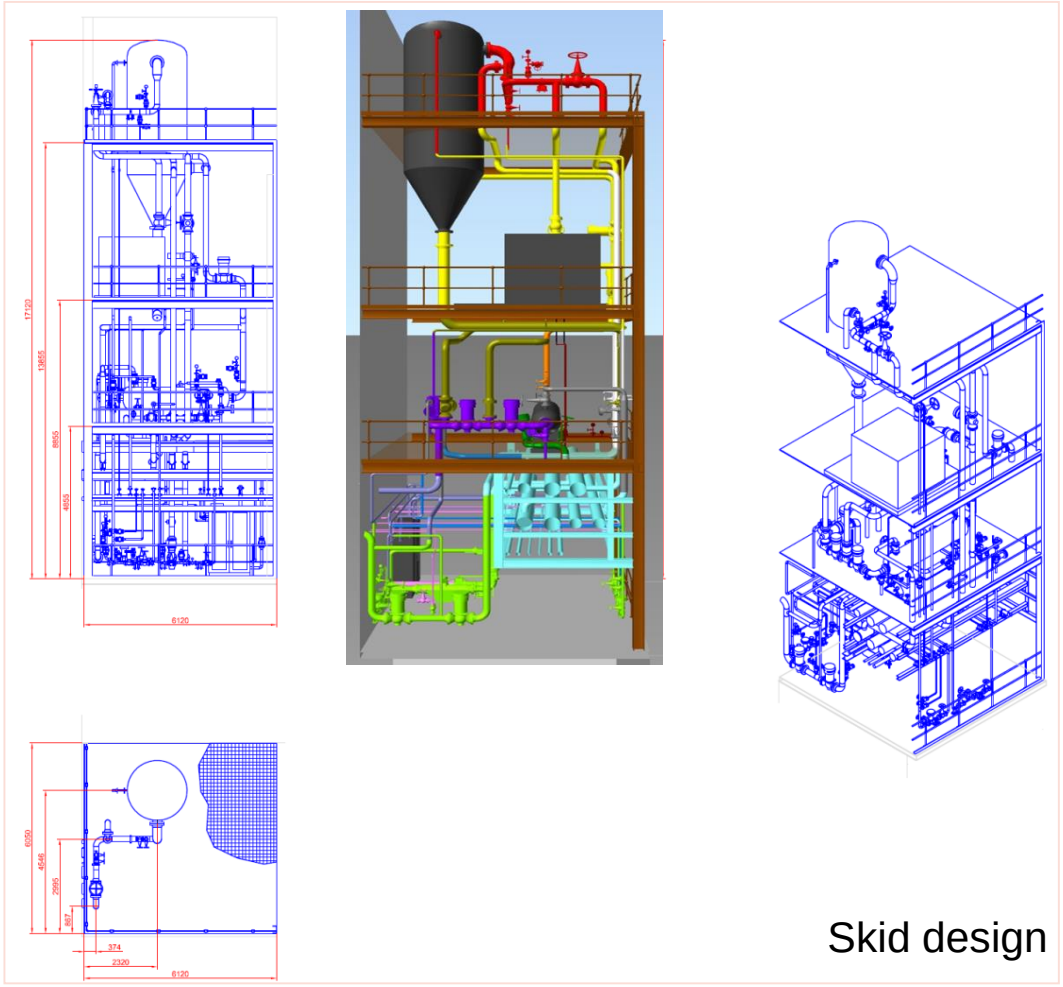
Standard clean-room
"Open System"

"cRABS - Technology"

RABS "Open System"

Isolator "Closed System"

«Process Platform» - Plug & Produce
Skid mounted process systems and machinery

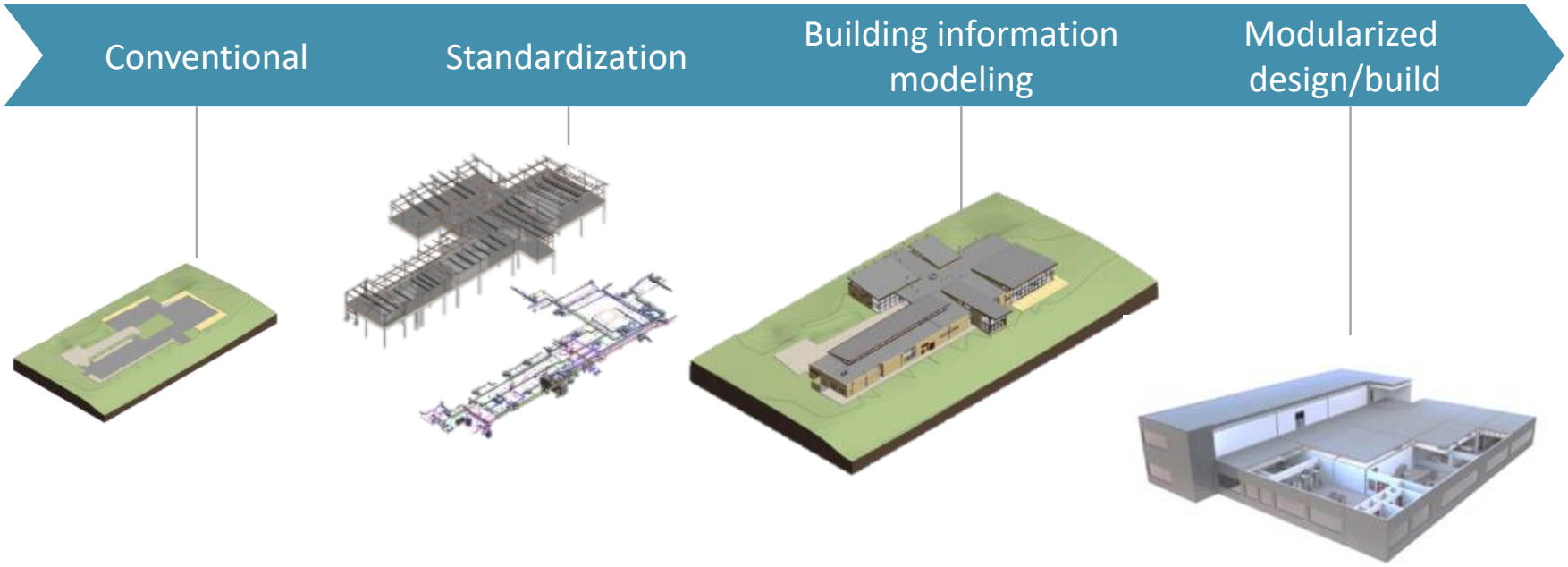


Skid design

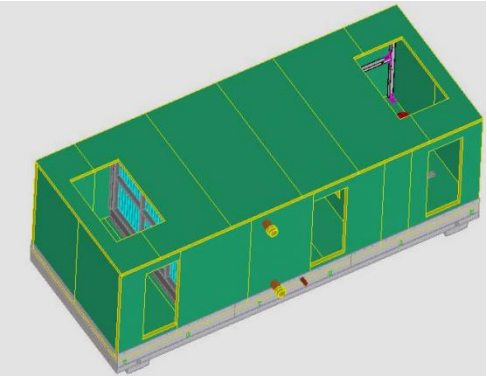
Turnkey process systems

Module / Skid fabrication assembly & integration

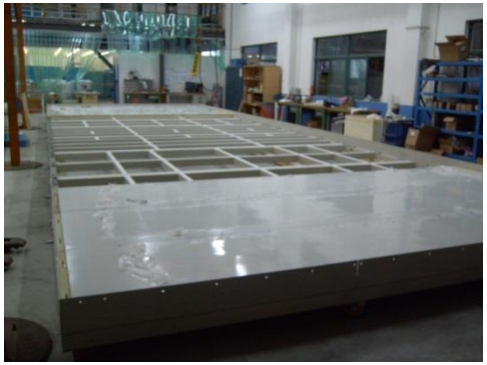
«Building Platform» – Modern tools paving the way



«Building Platform»
Skid mounted utility systems



Pre-Designed



Pre-Assembled

Installation / Start up

Smart Facility on demand – Conventional vs. modular

Solution for the most efficient facility approach

Conventional
Building

New – Greenfield

Conventional

Modular

Expansion – Brownfield (retro-fit)

Conventional

Modular

Modular
Building design
and construction

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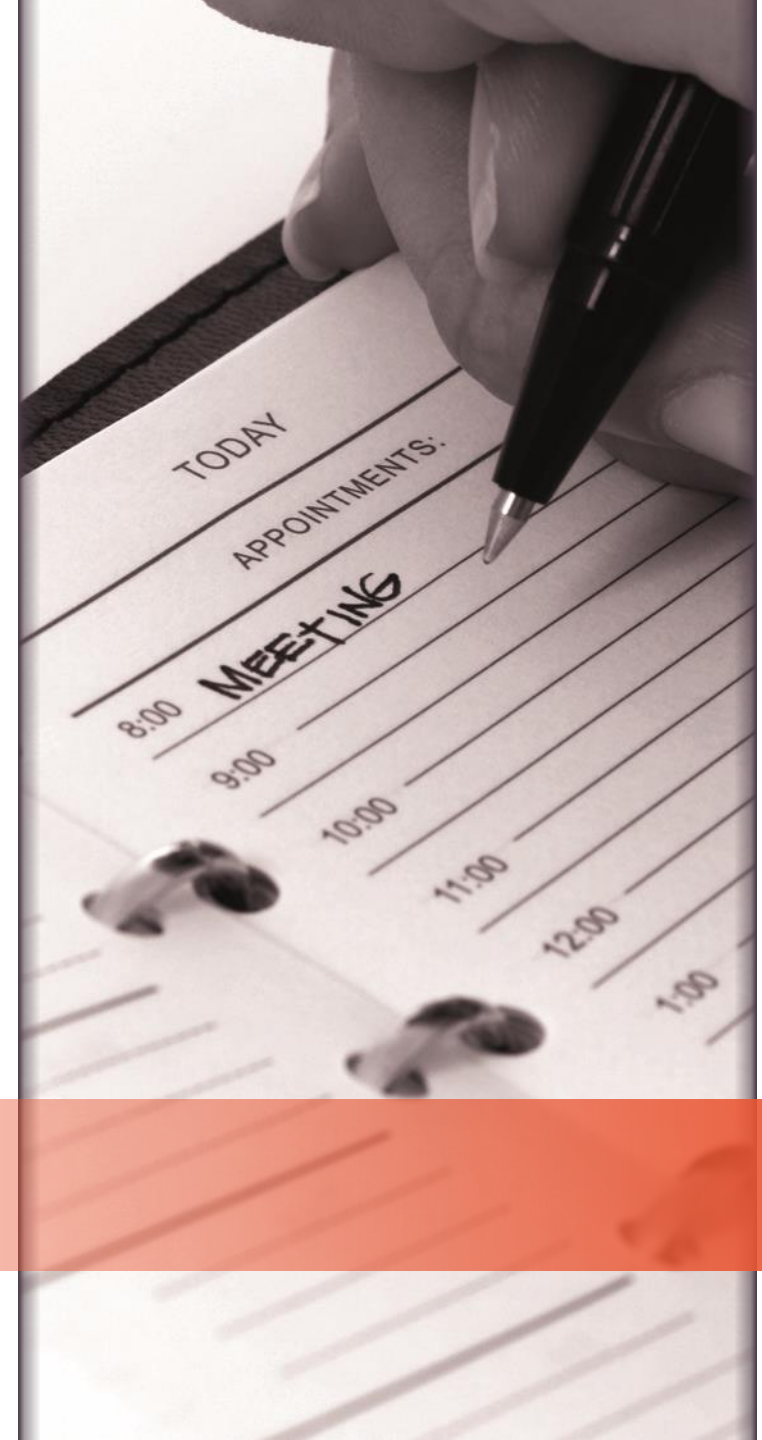


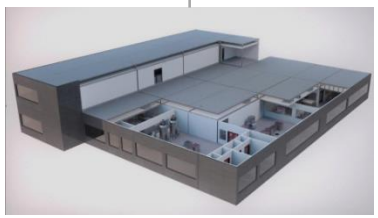
Approach for modularization

Feasibility | Concept | Basic design | Detail design construction installation | Start up qualification & validation

Early engagement & Process definition

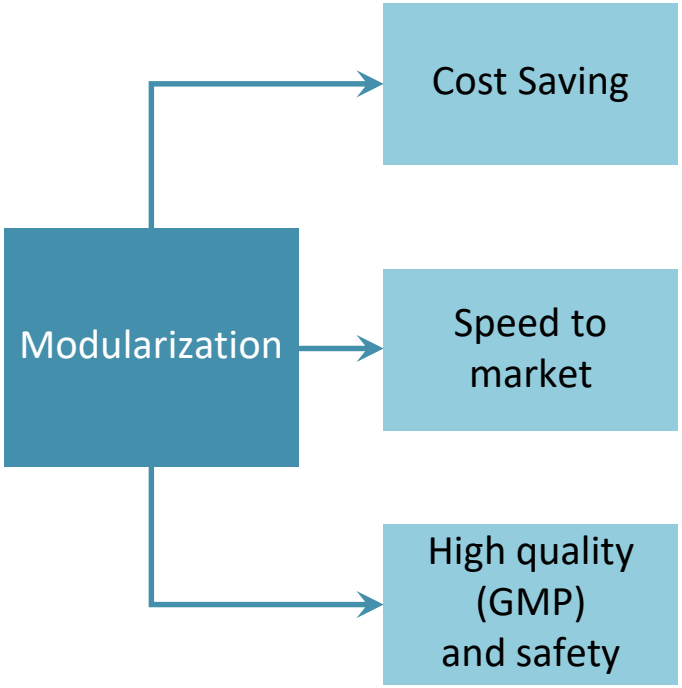
Layout (URS from Takeda)

Module Splits



Benefits from modularization

Benefits from high modularization



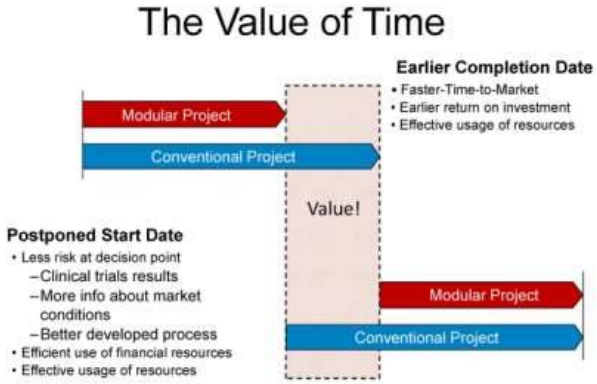
- Shop fabrication efficiency (2–3 x times field fabrication)
- Low cost labor benefit
- Reduce CM cost and tool cost (crane etc.)

- Reduce site installation time
- Reduce IQ/OQ time

- High quality and less contamination risk to sanitary equipment (sustainable)
- Improve site installation safety
- Less working hours at site

Off the shelf facility
Key metrics – Takeda

- **Modular, pre-engineered**
- **Total size:**
  approx. 3000 m^2
- **Footprint:**
  2000 m^2, two floors
- **cGMP-compliant** facility design
- Grade A and B processing
- **Disposable** system



Off the shelf facility
Key metrics – Takeda

- **Fast project initiation**
  From idea via due diligence / site selection to CAPEX within 8 month
- **“Global Delivery Model” & “Experience in project delivery”**
  Takeda can focus on process and tech transfer due to “Turn Key” approach
- **Market driven design, engineering and construction**
  In execution 4 – 6 month faster then stick build
  (18 months from concept to end of IQ/OQ)
- **Use of platform technology**
  Accelerates technology transfer – start up – staff training and validation
- **Schedule certainty for assembling program**
  Independent from weather and site interfaces
- **Quick extendable at any time**

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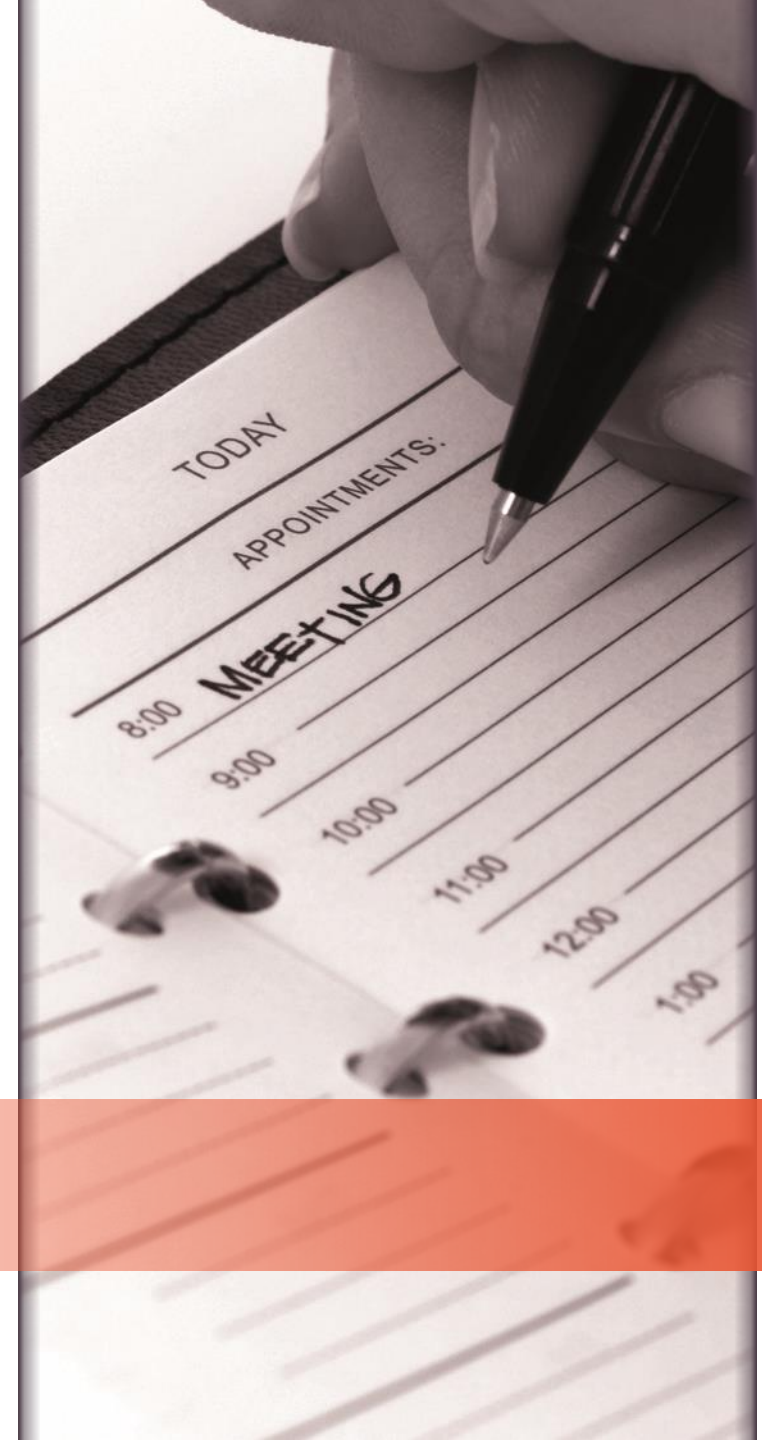


New OSD Installation – Brownfield
“High Potent Production Line”

Administration building:
1 floor – offices & canteen
2 floor – offices & laboratories
1.250sqm

Production-& Packaging building:
Solids production
Sterile production
Packaging 9.000sqm

Warehouse:
6000 pallet places
1.900sqm

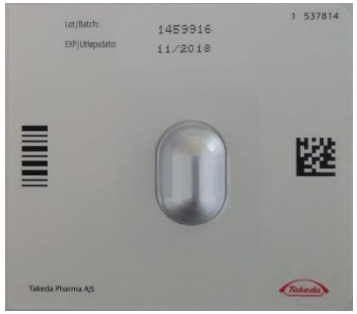
Utility building & Solvent Storage

New Capsule production
Primary & Secondary
Packaging **425 sqm**

New OSD Installation – Brownfield
Purpose of the facility

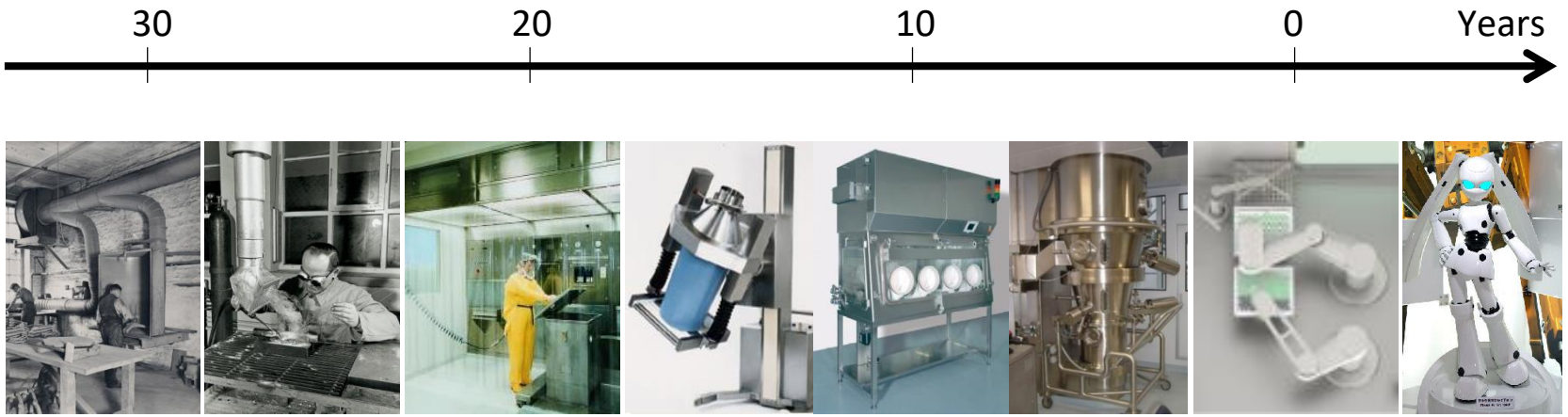
- **PROJECT Scope**
  - Future proven concept and state of the art installation
  - Technology transfer
  - Smart Design and Construction
  - Commissioning & Qualification
  - Validation & Operation

- **OBJECTIVES**
  - Produce capsules physically and chemically stable
  - Monitor critical features and process parameters
  - GMP & EHS Compliant (by-products and waste)
  - State of the art process technology
  - Synergies between R&D and technical development
  - Track and Trace (UPI) implementation
  - Sustainable



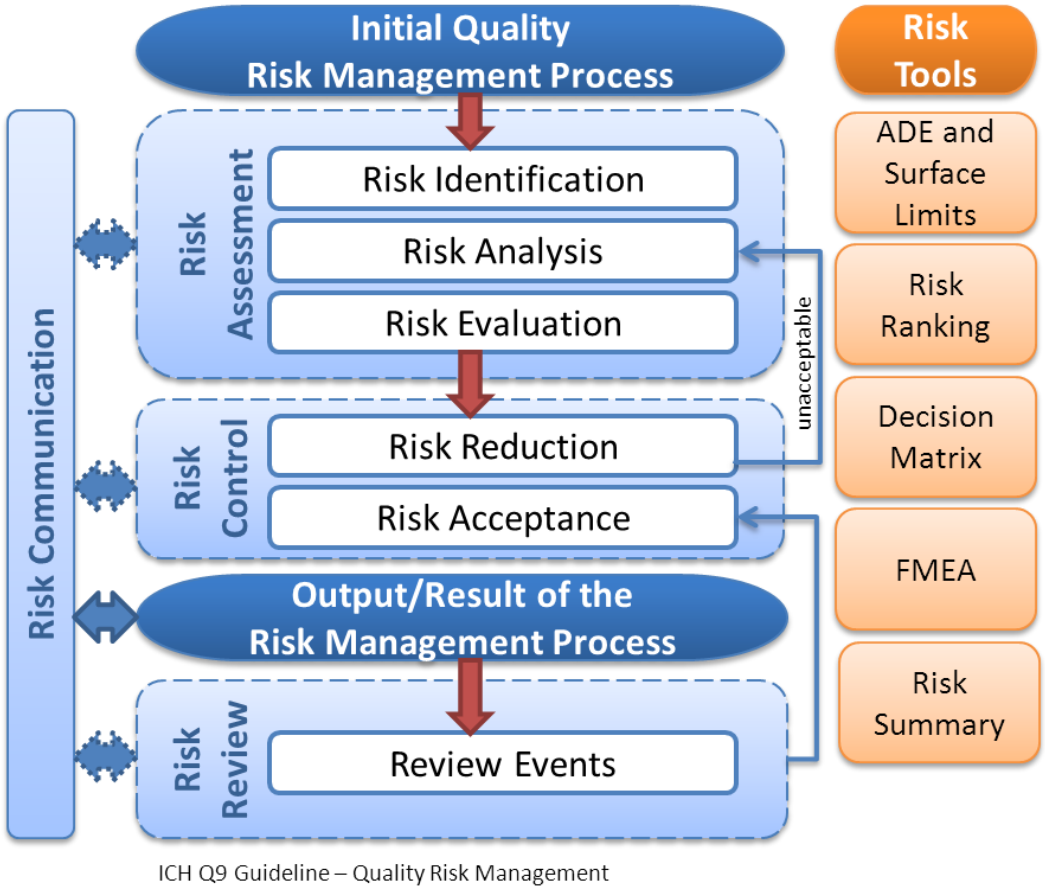
Technological development and innovation
Evolution in Containment

- Evolution in Containment



- Potential to cause occupational illness
  - Opiates, Antibiotics, Hormones, Cytotoxic, Novel Drugs

Risk based approach- Protection Product Operator and Environment EHS/IH vs. cGMP

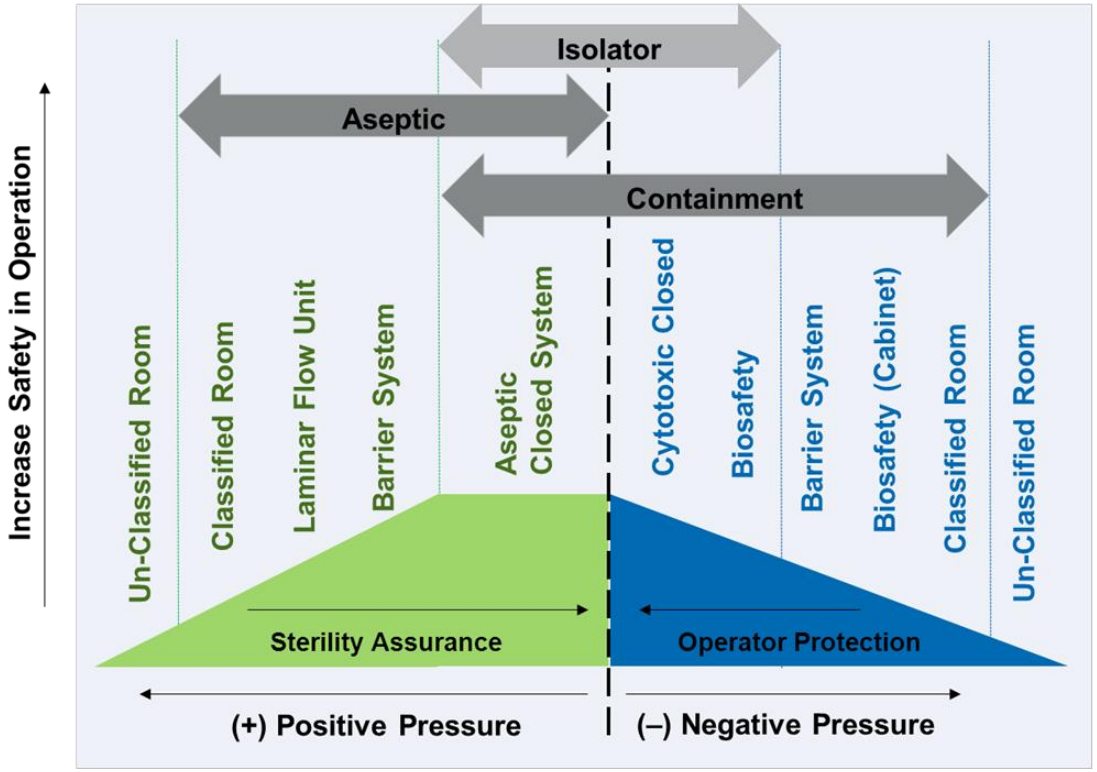


ICH Q9 Guideline – Quality Risk Management

- Holistic View
  - Drug Metabolism
  - Pharmacokinetics
  - Toxicologists
  - EHS
  - Cleaning Experts
  - Quality/Regulatory
  - Engineering
  - Production
  - Operators

Protection Product, Operator and Environment „PDA Isolation Continuum“

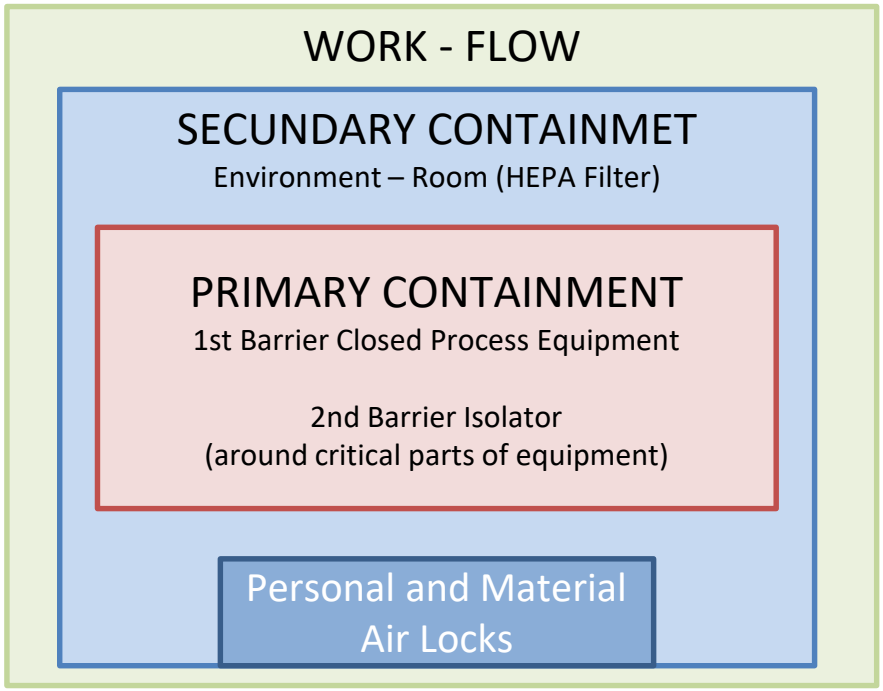
- Containment (OEB 1-5 /OEL [µg/m³]) and Biosafety (BSL) Solutions



2013 “By M+W modified PDA Isolation Continuum“
James Agalloco and James Akers.: Advanced Aseptic Processing Technology, informa healthcare New York London, 2010

Criteria for Barrier
Primary and Secondary Containment

- Category 3: one physical barrier
- Category 4/5: two physical barriers



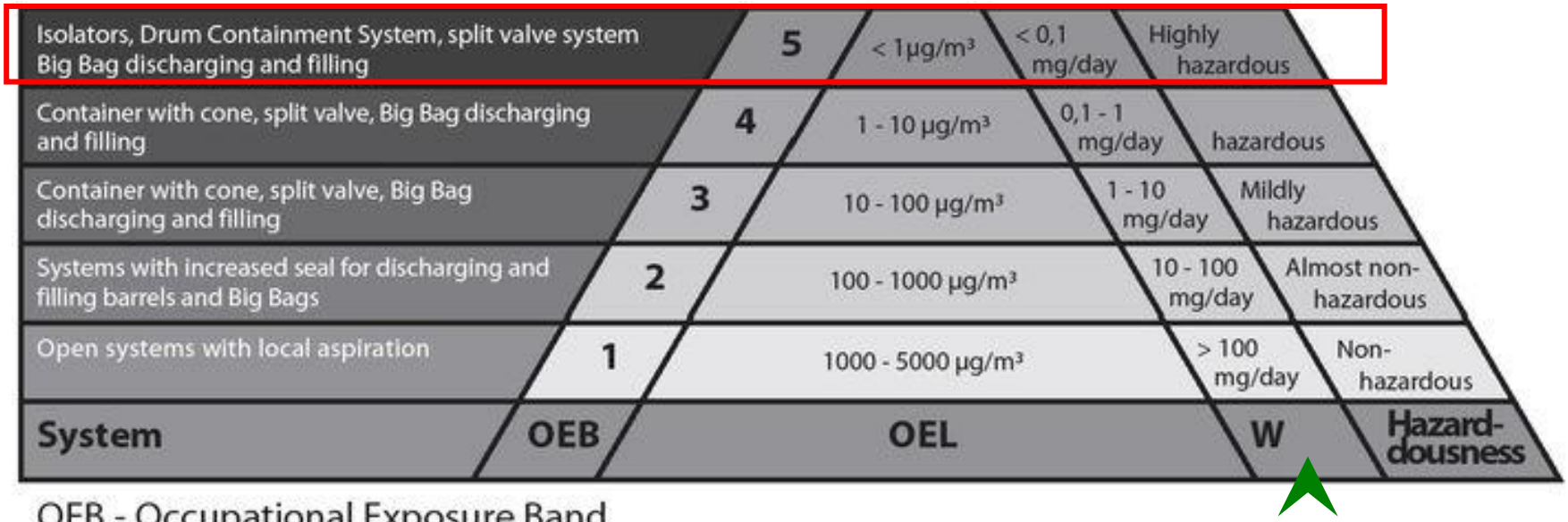
- SOPs
- Gowning Procedure, Material / Equipment/ Personal flow
- Training /Maintenance
- etc.

- Decontamination
- Cleaning and Disinfection Procedures for Clean Rooms
- Proof of Cleaning

Product contacted parts
- Single Use vs. fixed installed
- Product specific
- Multi-use/purpose (Cleaning Validation required)

Measures

- Define Project Containment



System	OEB	OEL	W	Hazard-dousness
Isolators, Drum Containment System, split valve system Big Bag discharging and filling	5	< 1µg/m³	< 0,1 mg/day	Highly hazardous
Container with cone, split valve, Big Bag discharging and filling	4	1 - 10 µg/m³	0,1 - 1 mg/day	hazardous
Container with cone, split valve, Big Bag discharging and filling	3	10 - 100 µg/m³	1 - 10 mg/day	Mildly hazardous
Systems with increased seal for discharging and filling barrels and Big Bags	2	100 - 1000 µg/m³	10 - 100 mg/day	Almost non-hazardous
Open systems with local aspiration	1	1000 - 5000 µg/m³	> 100 mg/day	Non-hazardous

OEB - Occupational Exposure Band
OEL - Occupational Exposure Limit
W - API content

Source: Online GMP Berater, Chapter 4.J-2

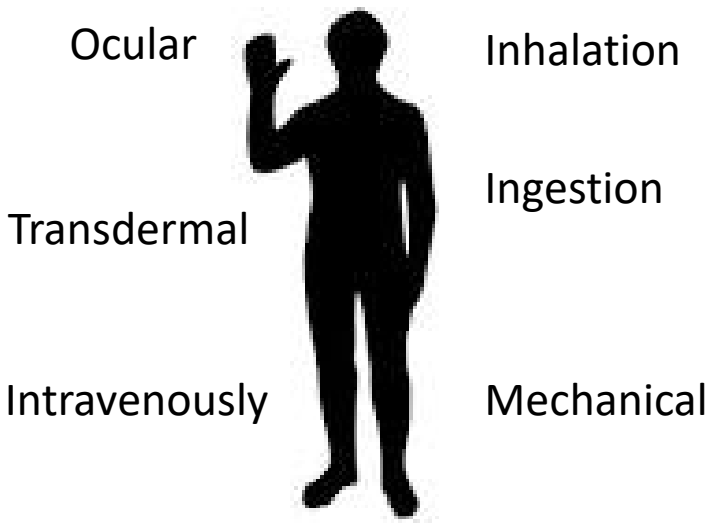
TWA – Time Weighted Average

Containment Strategy – Exposure Potential
Allocation of Exposure

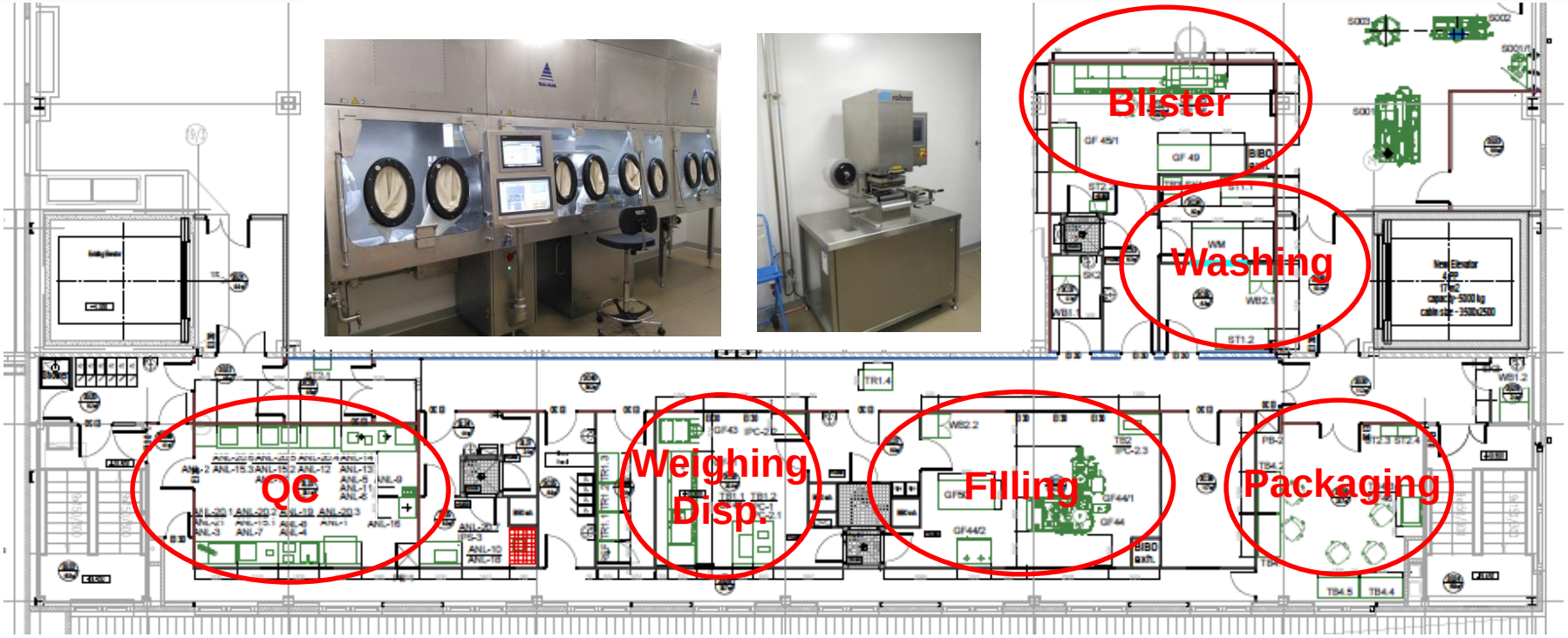
Factors that effects exposure

Wet Product	Dry Product
Large P. / Dense	Small P./Light
Closed	Open
Single Transfer	Multiple Transfer
Poorly Maintained	Well Maintained
No explosion risk	High explosion risk
No energy/velocity	High energy/velocity
No technique required	Highly technique required

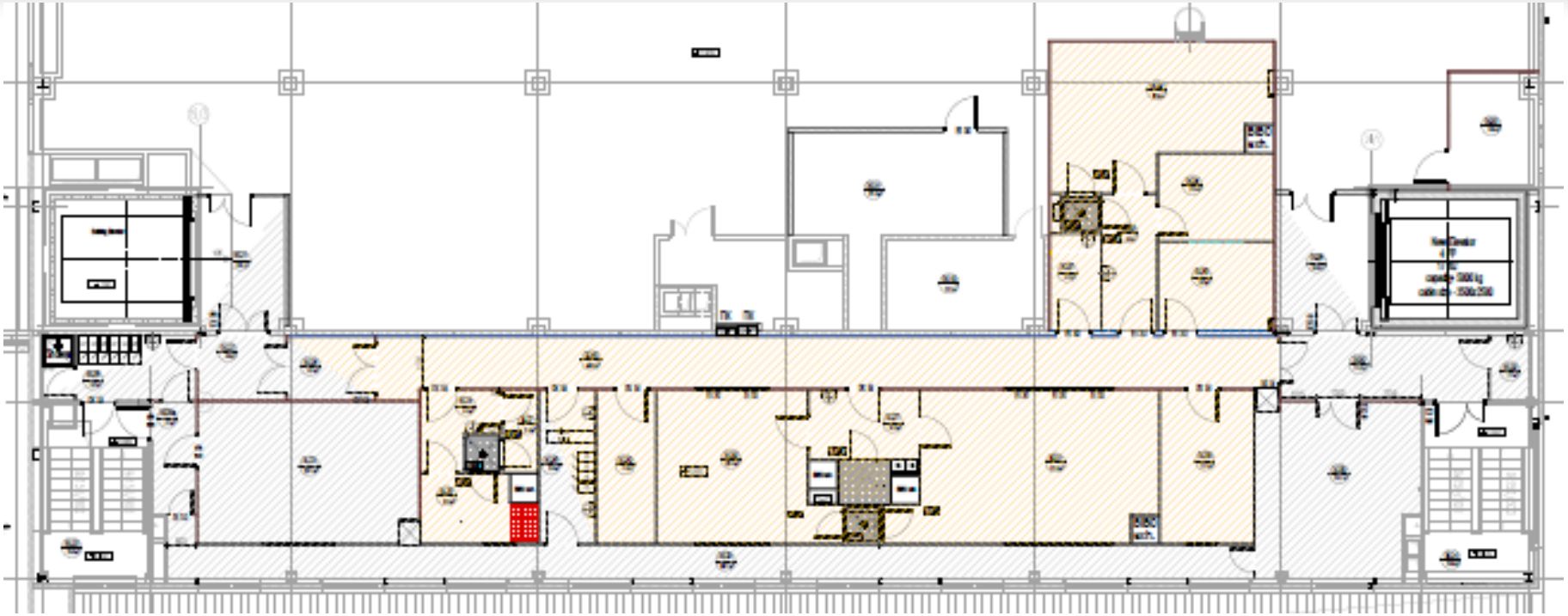
Occupational

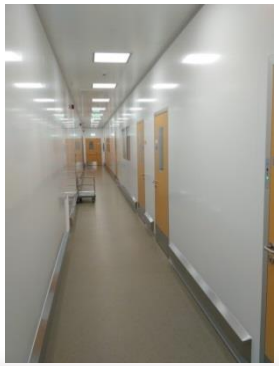


Production and packaging of Capsules
Layout and production areas



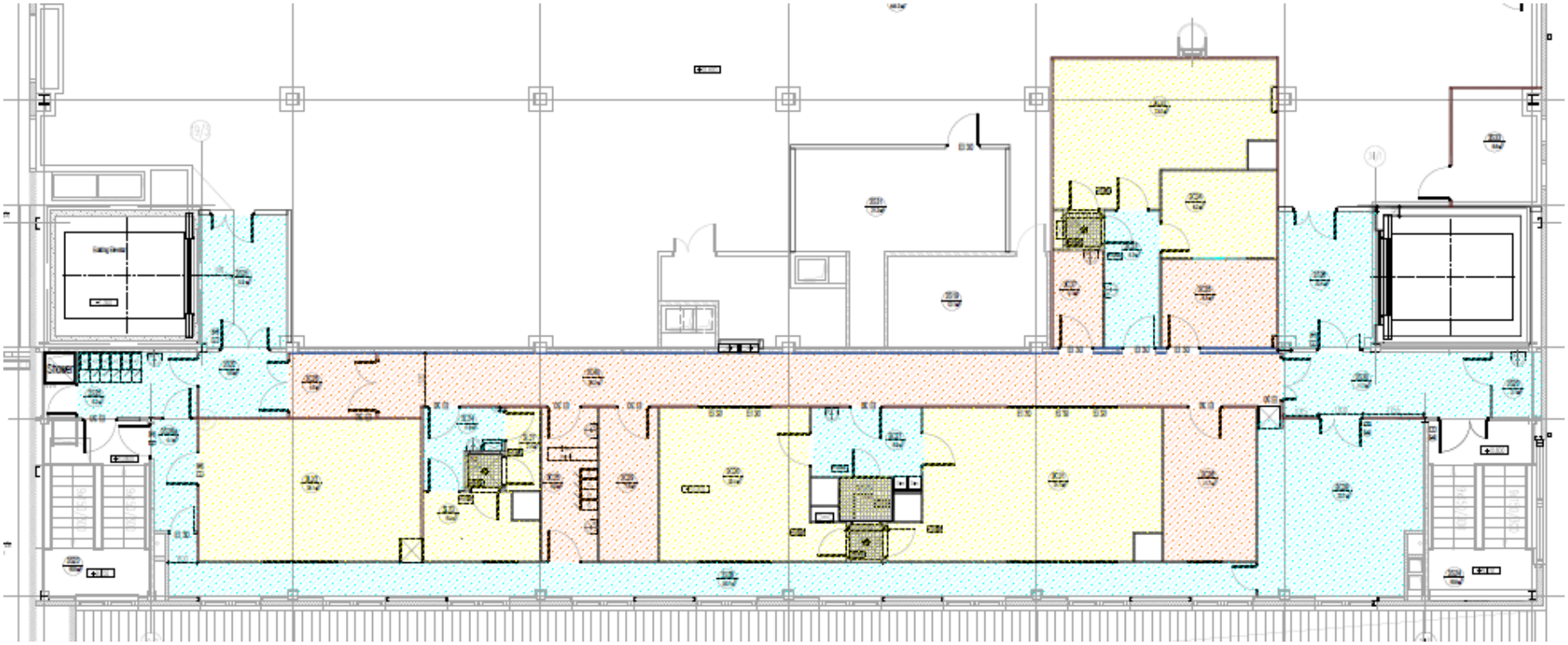
Segregation of Areas (GMP, EHS)
Clean Room Classification





Условные обозначения	
Символ:	Описание:
	Класс чистоты D
	Контролируемая зона (CNC)
	Неконтролируемая зона (NCA)
	Ламинарный поток/Laminar flow (LF)

Segregation of Areas (GMP, EHS)
Pressure Zones



Условные обозначения:	
Символ	Описание
	-15 Pa
	0 - +5 Pa
	15 Pa

Suits – Secondary Containment,
OEB: class 5

Brownfield
Key metrics – Takeda

- **"Turn Key Delivery Model" for fit-out and infrastructure**
  Takeda focus on process integration and tech transfer

- **"State of the art construction" – 425 m^2 Production space**
  "All functions" built into an existing warehouse with optimized flow

- **Use of global process platform technology (High Potent)**
  Accelerates technology transfer – start up – staff training and validation

- **Followed risk based approach**
  to operate highly potent drugs (GMP vs. EHS)

- **Track & Trace**
  to meet Russian regulatory requirements

Country	Health Toxicity
Europe	Harmful
Canada	Toxic
New Zealand	Hazardous
China	Non Hazardous

Example - Worldwide possible difference in the classification of a substance with LD50 = 257 mg/kg (oral)

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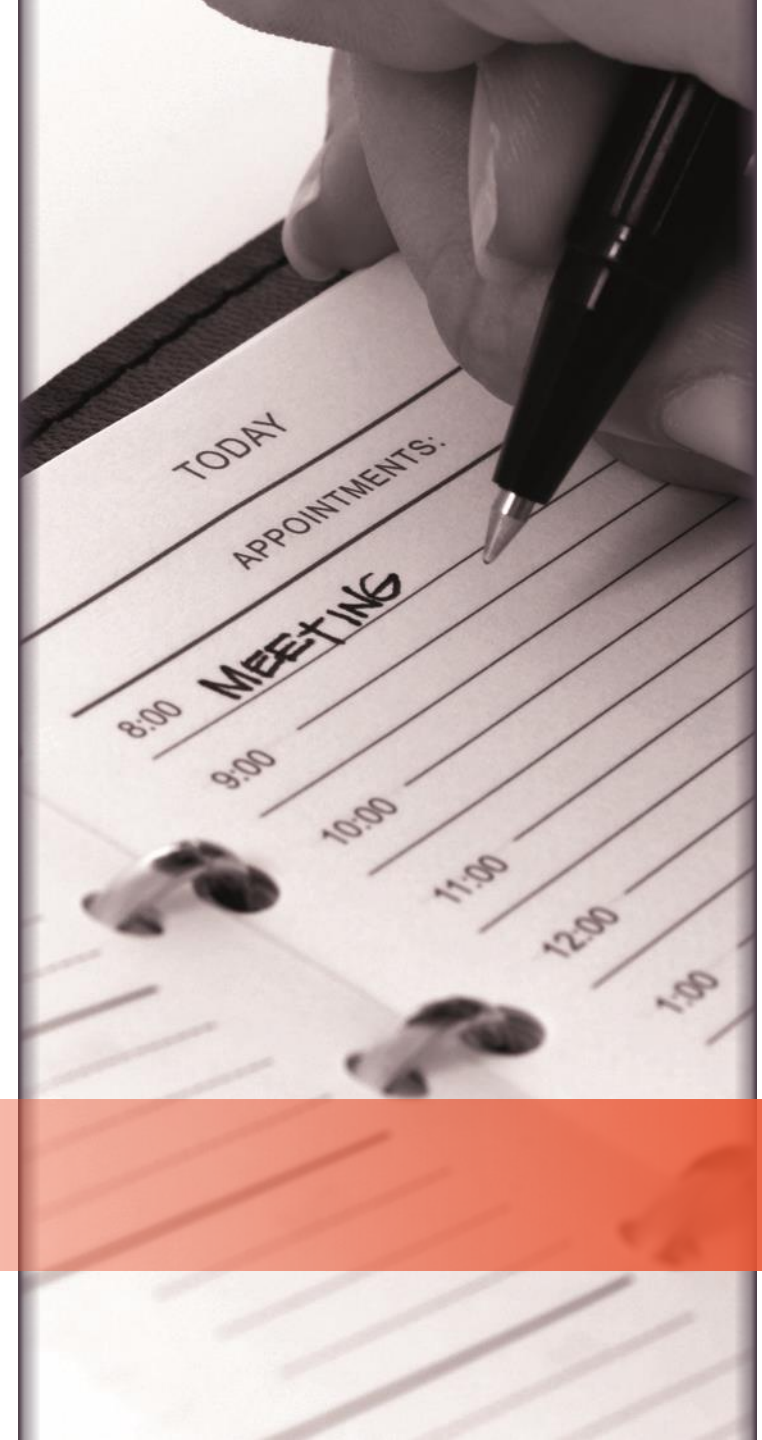


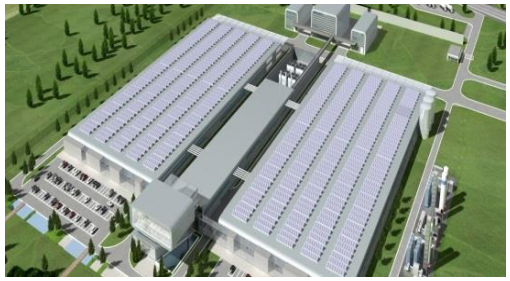
«Digital Factory» Integration without limitations (Industry 4.0 – Internet of Things IoT)

Robust Networks

- Mobile Devices / Connected workers
- Mobile Communications
- Broadband

Smart Factory

- Plug and Produce
- Low Cost Automation
- HMI
- Virtualization (VR/AR)
  Augmented Reality
  Virtual Factories and Equipment
  Process development
- Predictive Maintenance
- Social Machines
- Artificial Intelligence



Cloud Computing

- Real time data
- IPv6
- Apps
- Big data

Security

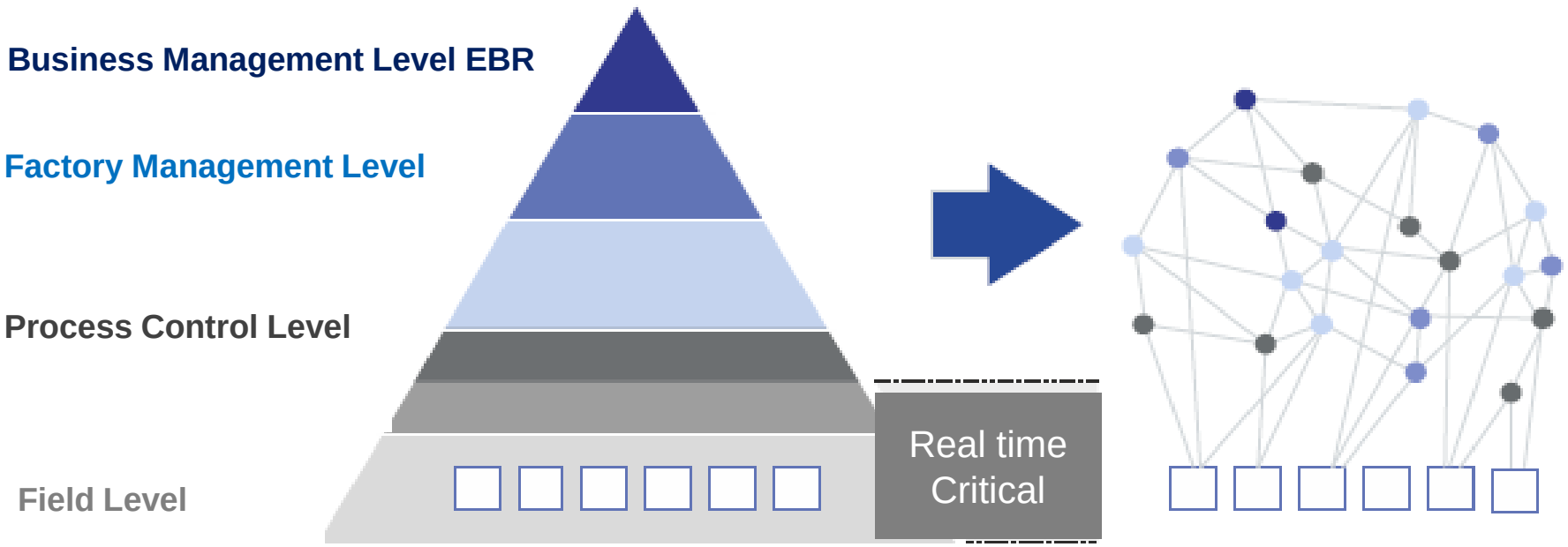
- Data Protection / Data Integrity
- Information security

Embedded Systems CPS

- Connected equipment (constant collection, monitoring, control and optimization)
- Robotics
- Intelligence Products
- M2M
- Sensors and Actors

«Digital Factory» - Be networked (horizontal integration)
Move to Data Warehouse

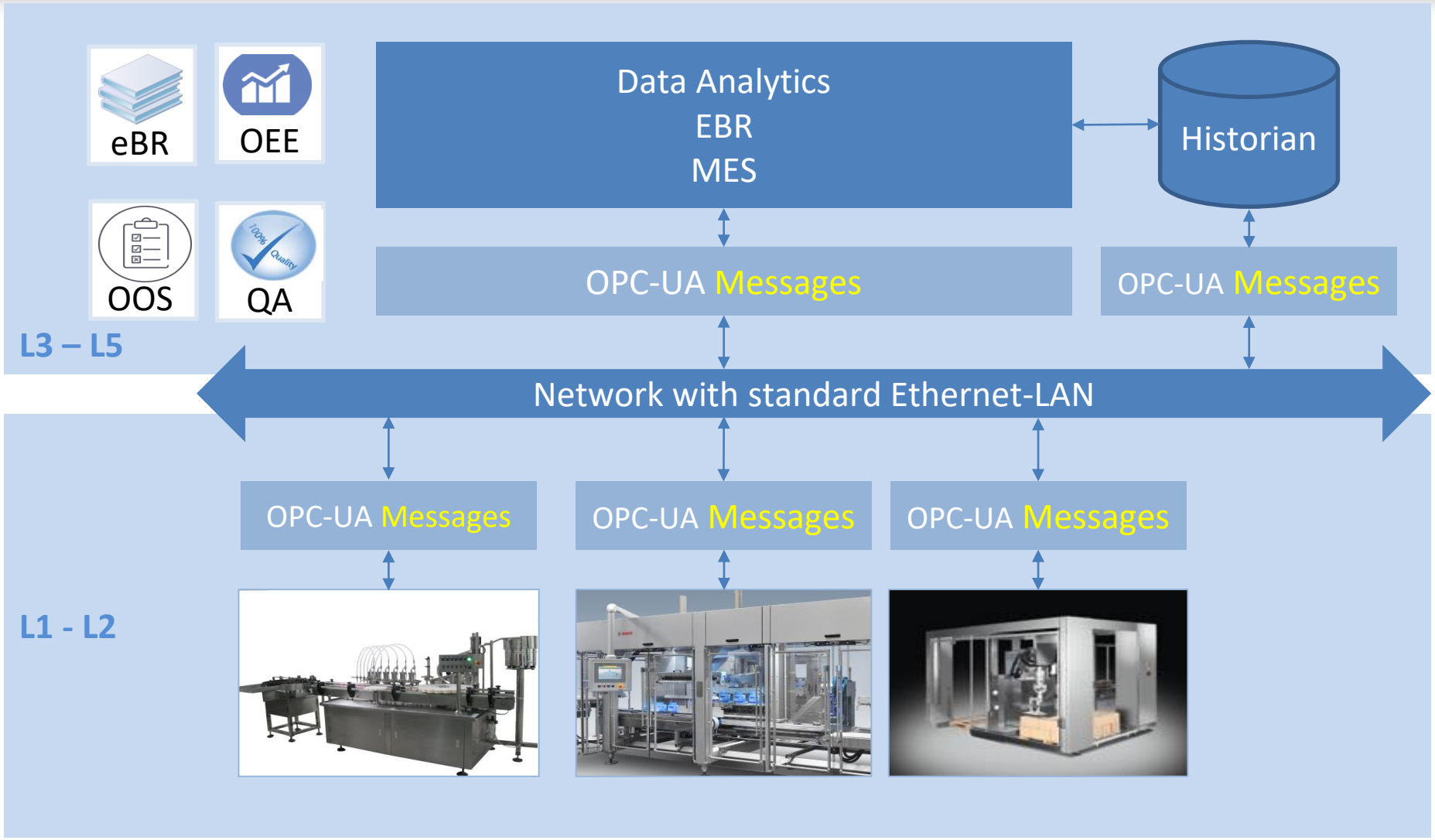
- **Resolution of the Hierarchical Pyramid of Automation**



Pyramid of Automation

CPS based Automation

«Digital Factory» - Message based data transfer
« Plug and Produce»



«Digital Factory»
«Key Metrics and automation/IT/technology fit»

- Level 1: MANUAL / PAPER
  - » Paper instructions and written records.
  - » Manual analysis of data.
- Level 2: Low Automation / PAPER
  - » Manual batch recording and partially specific reports
  - » Some automated process data analytics (SPC)
- Level 3: Automation / LESS PAPER
  - » Automated data capture and storage, partial MES/PI
  - » Descriptive analytics
- Level 4: Full Automation integration / Paperless
  - » Process Data Warehouse and Diagnostic, eBR/MBR
  - » Descriptive + Predictive analytics
- Level 5: Digitalization / Paperless – PAPERLESS
  - » Integrated, digital ecosystem within the enterprise
  - » Diagnostic/predictive/prescriptive analytics
  - » Artificial Intelligence

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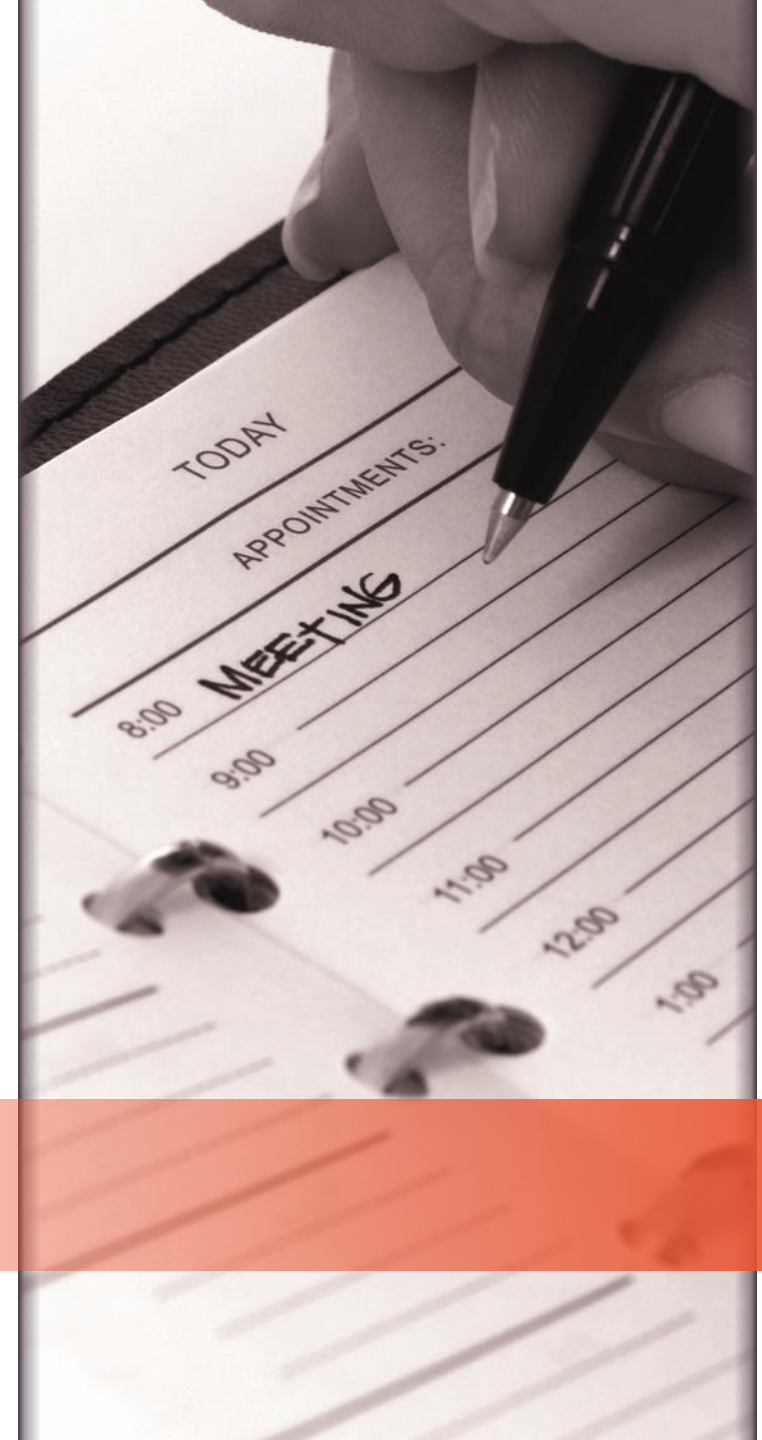
4. *Outlook & Challenges*



Outlook & Challenges

- Find the right strategy for smart facility design and execution and move to „Integrated project and flexible product delivery“
- „Agile“, „Sustainability“ and „Life Cycle Consideration“ during planning and operation
- Easy use of platform technologies and out of the shelf equipment
- Experience in project delivery model & organizational set-up (Safety – Quality/GMP/GAMP5 – Sustainability)
- Be full digital is not pre-requisite for a state of the art facility and compliant production
- IoT (Internet of Things) and Automation drives efficiency & quality

Successful T&T pilot installation for serialization in Russia!

Q & A

Thanks a lot for your attention & stay smart!

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