

Second Russian GMP Conference 2017
Gelendschik

FACTORIES AND PLANTS OF THE FUTURE – Global trends in GEP

Dr. Thomas Zimmer
VP European Operations
International Society for Pharmaceutical Engineering



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THE BIG PICTURE

INNOVATION AND TRENDS IN GMP AND GEP

- CHANGING PRODUCT PORTFOLIO
- FACTORIES OF THE FUTURE: FLEXIBILITY AND AGILITY
- TECHNOLOGY PLATFORMS AND END TO END INTEGRATION: PHARMA 4.0
- QUALITY & SAFETY : FALSIFIED MEDICINES, DRUG SHORTAGES
- READINESS FOR INNOVATION: PRODUCTS AND PEOPLE
- REGULATORS VIEW ON INNOVATION
- HOW CAN ISPE HELP INDUSTRY

CHANGING PRODUCT PORTFOLIO

BIOLOGICS

- mAbs – Monoclonal Antibodies
- Biosimilars
- ATMPs – Advanced Therapeutic Medicinal Products
- ADCs – Antibody Drug Conjugates (High Potent Drugs)

MERGERS AND ACQUISITIONS

- Product Transfers, Know how transfer

SHORTER PRODUCT LIFE CYCLES

- Market demand variations

BLOCKBUSTER MODEL OUTDATED

- Higher complexity of product portfolio, Orphan drugs raise

Top 20 Specialty Medicines: Mainly injectables

Rank	Product	Generic Name	Company	Pharmacological Class	WW Product Sales (\$m)			Market Status
					2014	2020	CAGR	
1.	Humira	adalimumab	AbbVie + Eisai	Anti-tumour necrosis factor alpha (TNF) MAb	12,890	13,934	+1%	Marketed
2.	Revlimid	lenalidomide	Celgene	Immunomodulator	4,980	9,640	+12%	Marketed
3.	Opdivo	nivolumab	Bristol-Myers Squibb + Ono	Anti-programmed death-1 (PD-1) MAb	29	8,182	+156%	Marketed
4.	Januvia/Janumet	sitagliptin phosphate	Merck & Co + Ono + Daewoong + Sigma-Tau + Almirall	Dipeptidyl peptidase IV (DPP-IV) inhibitor	6,358	7,525	+3%	Marketed
5.	Xarelto	rivaroxaban	Bayer + JNJ	Factor Xa inhibitor	3,366	7,466	+14%	Marketed
6.	Enbrel	etanercept	Amgen + Pfizer + Takeda	Tumour necrosis factor alpha (TNF) inhibitor	8,915	7,219	-3%	Marketed
7.	Tecfidera	dimethyl fumarate	Biogen	Nuclear factor erythroid 2-related factor (Nrf2) pathway activator	2,909	6,804	+15%	Marketed
8.	Remicade	infliximab	JNJ + Merck & Co + Mitsubishi	Anti-tumour necrosis factor alpha (TNF) MAb	8,807	6,511	-5%	Marketed
9.	Avastin	bevacizumab	Roche	Anti-VEGF MAb	7,018	6,202	-2%	Marketed
10.	Pneum 13	pneumococcal vaccine	Pfizer + Daewoong	Pneumococcal vaccine	4,297	5,833	+5%	Marketed
11.	Eylea	afibercept	Regeneron + Sanofi + Santen	VEGFR kinase inhibitor	2,972	5,826	+12%	Marketed
12.	Harvoni	ledipasvir; sofosbuvir	Gilead Sciences	Hepatitis C nucleoside NS5A & NS5B polymerase inhibitor	2,127	5,751	+18%	Marketed
13.	Imbruvica	ibrutinib	Pharmacyclics + JNJ	Bruton's tyrosine kinase (BTK) inhibitor	547	5,586	+47%	Marketed
14.	Soliris	eculizumab	Alexion Pharmaceuticals	Anti-complement factor C5 MAb	2,234	5,462	+16%	Marketed
15.	Herceptin	trastuzumab	Roche	Anti-HER2 (ErbB-2) MAb	6,863	5,313	-4%	Marketed
16.	Xtandi	enzalutamide	Astellas Pharma	Androgen receptor antagonist	1,254	5,147	+27%	Marketed
17.	Rituxan	rituximab	Roche	Anti-CD20 MAb	7,547	5,096	-6%	Marketed
18.	Orkambi	ivacaftor; lumacaftor	Vertex Pharmaceuticals	Cystic fibrosis transmembrane conductance regulator (CFTR) corrector	-	5,082	-	R&D
19.	Keytruda	pembrolizumab	Merck & Co	Anti-programmed death-1 (PD-1) MAb	55	4,988	+112%	Marketed
20.	Lantus	insulin glargine recombinant	Sanofi	Insulin analogue	8,428	4,935	-9%	Marketed



Next generation injectables includes biosimilars

Cosentyx

Novartis
Psoriasis



Remicade

J&J
2 applications
Immunosuppressant



Repatha

Amgen
Dyslipidemia



Humira

AbbVie
4 applications
Immunosuppressant



Praluent

Sanofi/Regeneron
Dyslipidemia



Enbrel

Amgen/Pfizer
2 applications
Immunosuppressant



Toujeo

Sanofi
Diabetes



Lantus

Sanofi
2 applications
Diabetes



Tecentriq (atezolizumab)

Roche
Cancer



Rituxan

Roche
2 applications
Cancer

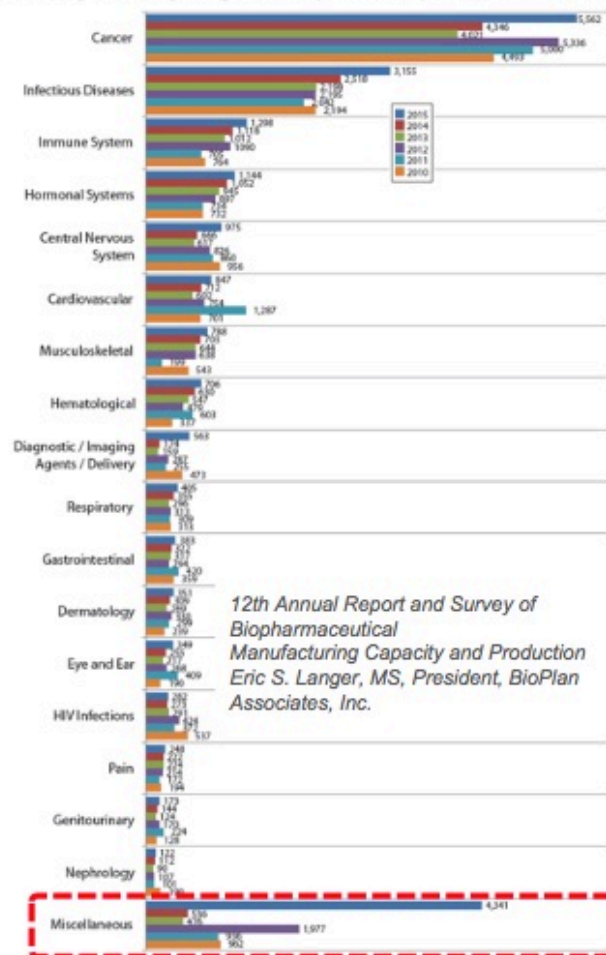


Zenapax (daclizumab)

Roche/Biogen
MS

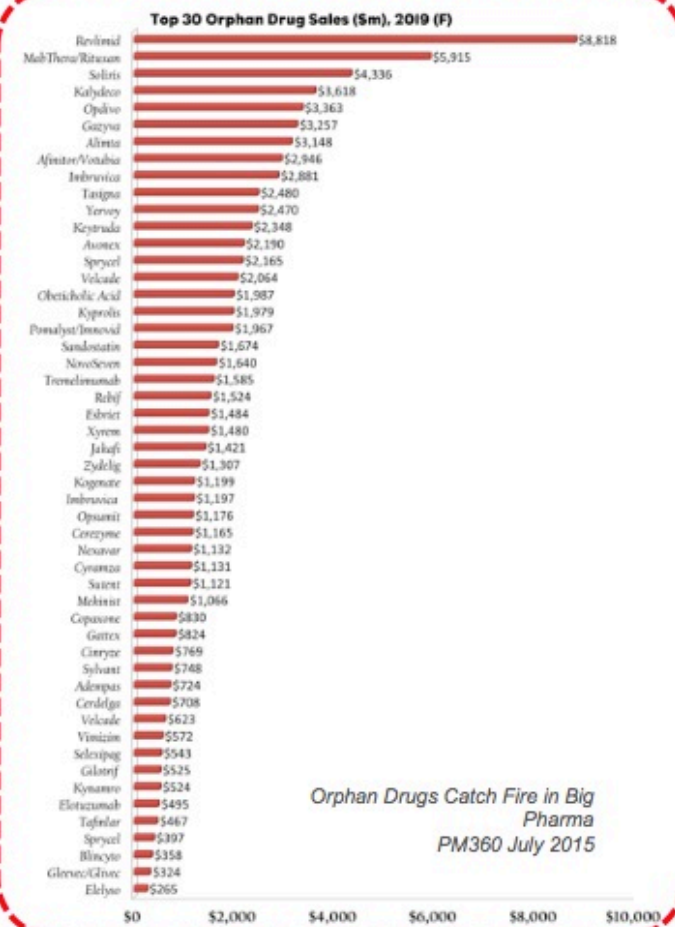


Fig 1.1: Investigational Drugs: Large Molecule (Protein Therapeutics), Worldwide, 2010 - 2015



12th Annual Report and Survey of
Biopharmaceutical
Manufacturing Capacity and Production
Eric S. Langer, MS, President, BioPlan
Associates, Inc.

The
"long tail"
of
therapeutic
areas



Orphan Drugs Catch Fire in Big
Pharma
PM360 July 2015

Source: BioPharm Insight, www.infinita.com/biopharma-solutions/by-product/biopharm-insight.html, February 2015



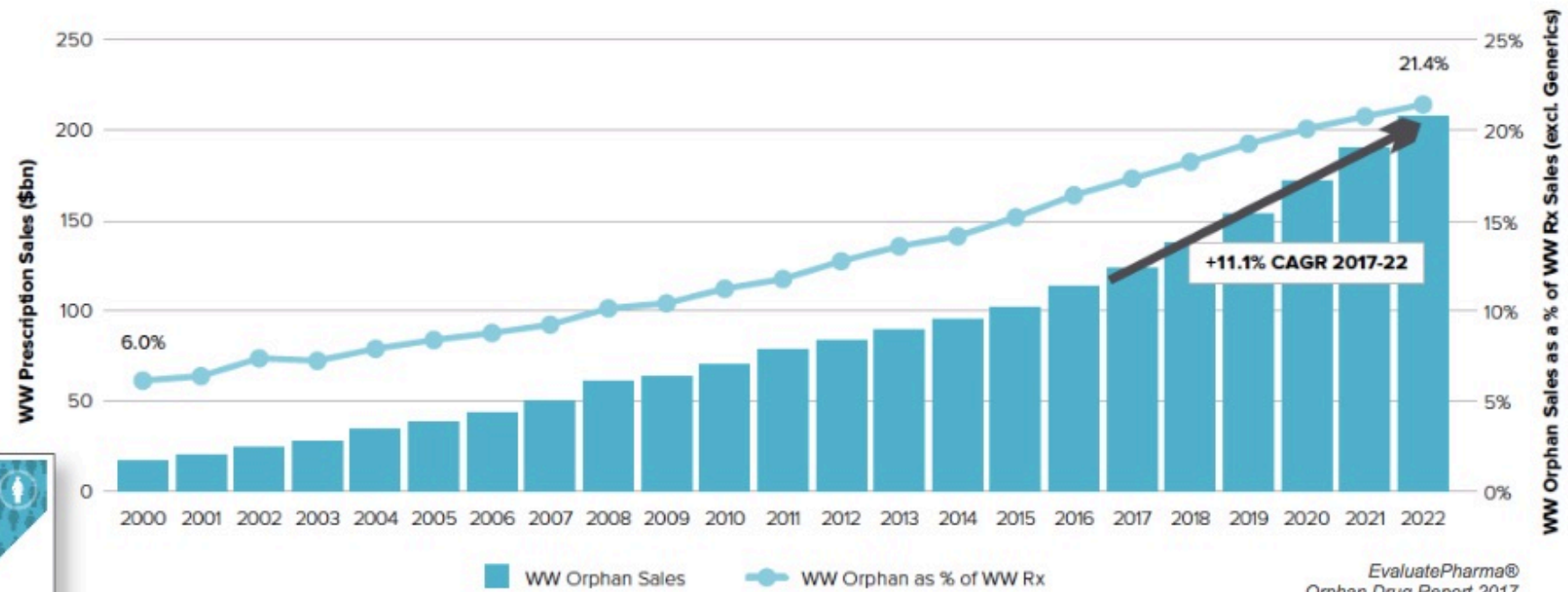
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Orphan Drug Sales Growth

Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2000-2022)

Source: EvaluatePharma® February 2017



FACTORIES OF THE FUTURE

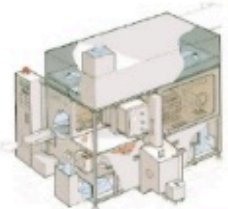
FLEXIBILITY AND AGILITY

- Shorter product change over times
- Modular factories (ISPE conferences)
- Operational excellence (ISPE guideline, Training ITEM)
 - Business processes
 - Technical processes
 - IT supported documentation
- Good Engineering Practice (ISPE guideline)
 - Project management capabilities (ISPE guideline)
- Workforce of the Future

Agility Challenge: Isolator Technology Example

Evolution of Isolator Technology Pioneer Days – the first steps in Isolator Technology

- ▶ First Hardwall Barrier System in late 1980's
- ▶ No Biodecontamination System included
- ▶ Surrounding Cleanroom Class B
- ▶ Manual Spray and Wipe Sanitization



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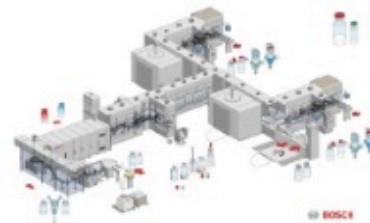
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Evolution of isolator technology over the last decade – and its influence on biodecontamination
Matthias Angelmaier, Bosch Packaging Technology, ISPE Aseptic Conference 2017



Evolution of Isolator Technology 21st Century - Nowadays high-end solutions

- ▶ Total Cycle Time down to 0,1 ppm in approx. 135 Minutes (2 Hours 15 Minutes)
- ▶ Total Cycle Time down to 0,05 ppm in approx. 195 minutes (3 Hours 15 Minutes)



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Enabling technology examples for a paradigm shift



Staubli Aseptic Robot



Sartorius Stedim Cultibag



Metall+Plastic E-beam sterilizer



Factbird Internet of Things



Manufacturing ballroom



Vanrx Aseptic Filling Workcell



GEA Consigma (OSD)



Medtronic MedLink



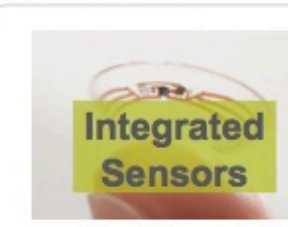
Pall Allegro filling needles



Ompi EZ fill tub solution



Bosch Flexible Assembly Platform



Google, Novartis SmartLens

Facilities of the Future in API, OSD and Biotech

What is Continuous Manufacturing?

Continuous Manufacturing
- directly related to Intense Processes

= maximised material processing in a smallest process room

Example:

Granulation in high shear granulation vessel today in batch - intrinsic process independent of size



Space process takes place in

© 2015 ISPE. Continuous Manufacturing (CM) 100

NOVARTIS

Markus Krumme, Novartis: Continuous Manufacturing - what is unique about it and how to control quality, ISPE EU Annual Conference Frankfurt 2015

Solution

Current, 2015: Best of Lab/Plant. Modularisation at Controllable sub-unit level. Separated Feeds.



© 2015 ISPE. Continuous Manufacturing (CM) 100

Flavien Susanne, GSK: Implementing a Three Stage Continuous API process to IG Grade, ISPE EU Annual Conference Frankfurt 2016

Commercial Line - Line Design

Validate the product on the high volume commercial line Consigma 100 and develop the Operational model

Commercial Line Design

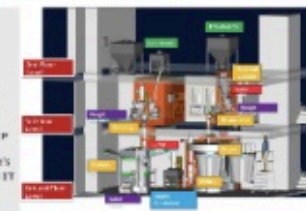
1. Layout: Horizontal and Vertical configuration
2. Line throughput: 100 t/h
3. Automatic rejection systems
4. 80% of the line CIP/WIP
5. Fully integrated with Site's Material Handling and IT Systems to operate the line with two people



Initial Performance Assessment

DOE & Validation

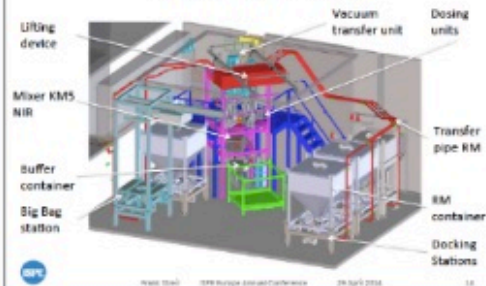
Operational Model



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Leonardo Panetti, Janssen/JnJ: Continuous Manufacturing of OSD at Johnson & Johnson, ISPE EU Annual Conference Frankfurt 2016

Engineering Design



Frank Streil, Teva: Continuous Manufacturing of Direct Compression Tablets, ISPE EU Annual Conference Frankfurt 2014

Biofacility of the Future Design principle 1: Continuous Processing



Stefan Sievers, Bayer: A concept for the biofacility of the future, ISPE EU Annual Conference Frankfurt 2015



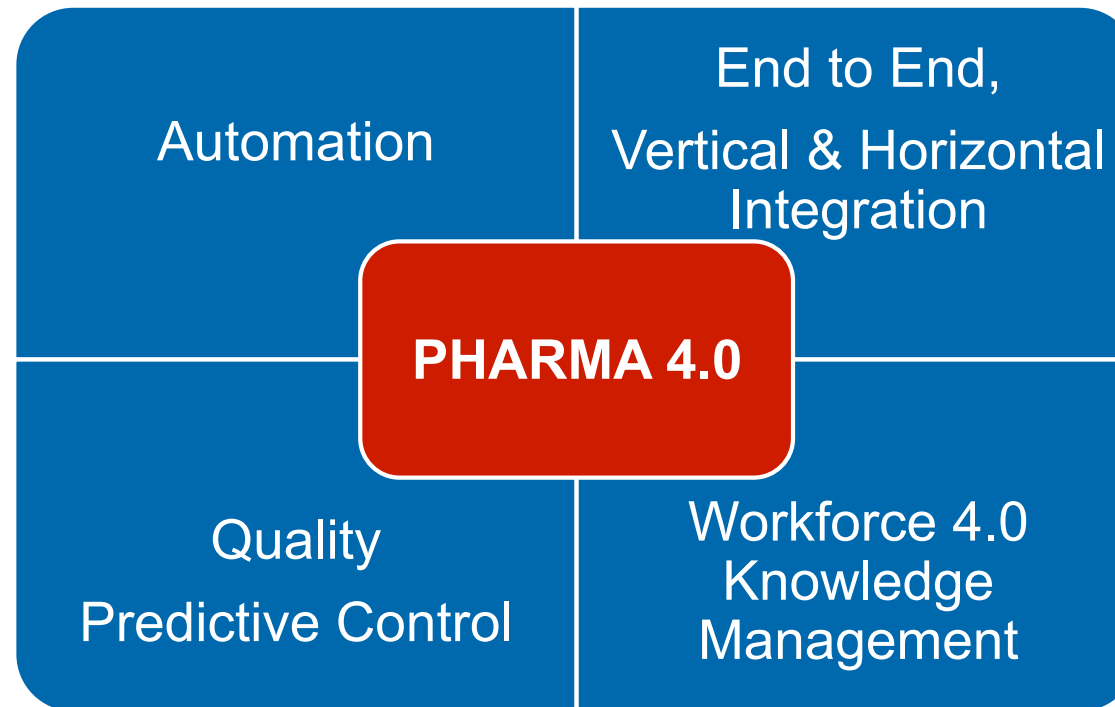
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TECHNOLOGY PLATFORMS AND END TO END INTEGRATION – PHARMA 4.0



Industry 4.0 and Pharma 4.0 DIGITIZATION

Information available everywhere

In the company

In all countries

In all business units

In all departments

In all involved service providers

In all involved regulatory authorities

Electronic data interchange

Within the company

With all involved countries

With all business units

With all departments

With all involved service providers

With all involved regulatory authorities

Digitalization Entering the Pharmaceutical Industry

Change the Way of Doing Business

→ Transforming to semi-software companies

- Unified ERPs with Real-time User Experience
- Next level eCommerce & Digital Marketing
- Smarter Lab and Devices' Management



The Future...

Envision the unified data pipeline

→ Everything will be connected

- Consistent, real-time correlated access to results
- Lab inventory & order management
- Safety & Compliance
- Bioinformatics & data analysis
- On-premise commerce & collaborative shipping

Digitalization at Merck Life Science

Four connected platforms

→ SAP NEXT enables

- E2E commerce
- Digitization for lab & bioprocessing
- Future digital business models



Merck

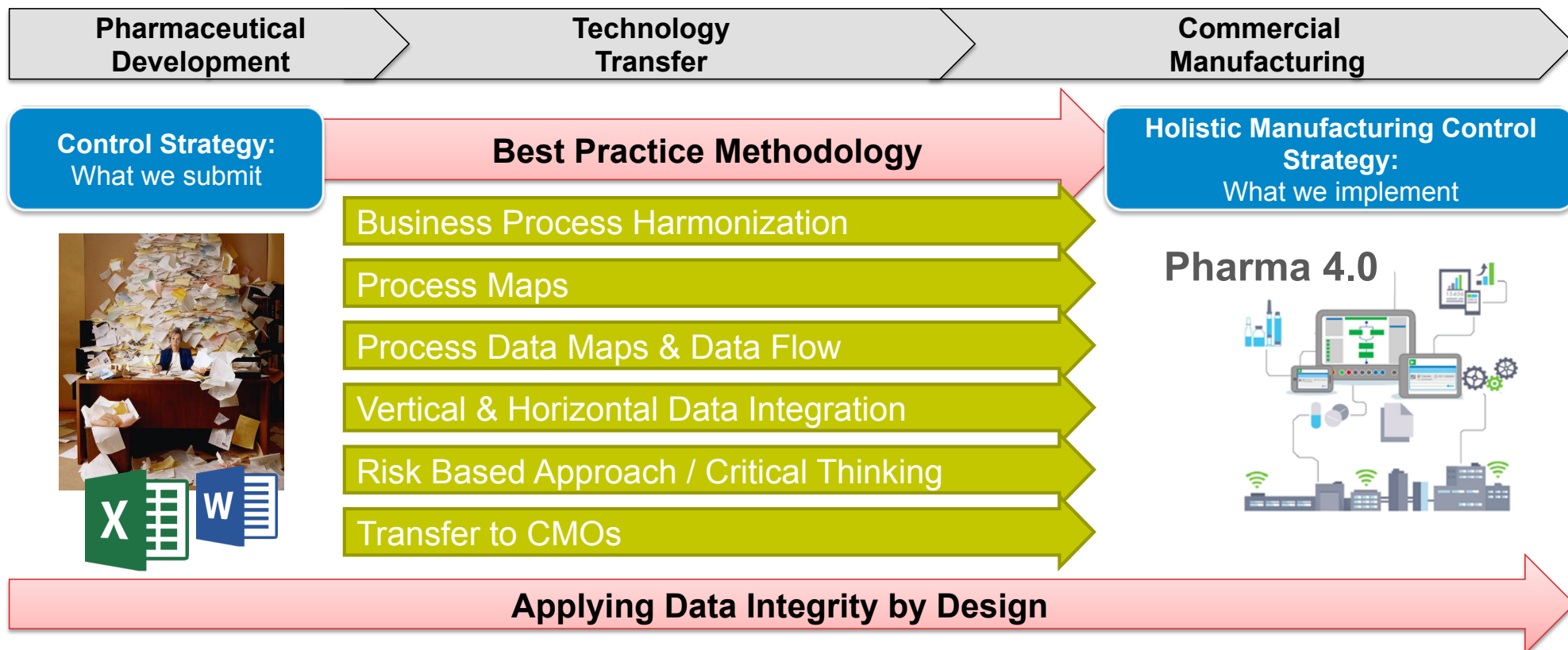
ISPE has started 2 Special Interest Groups
to define a practical way
from industry 4.0 to pharma 4.0

1. HOLISTIC MANUFACTURING CONTROL STRATEGY

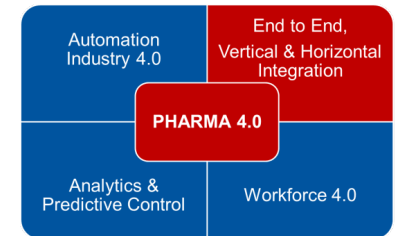
2. PLUG AND PRODUCE

HOLISTIC MANUFACTURING CONTROL STRATEGY

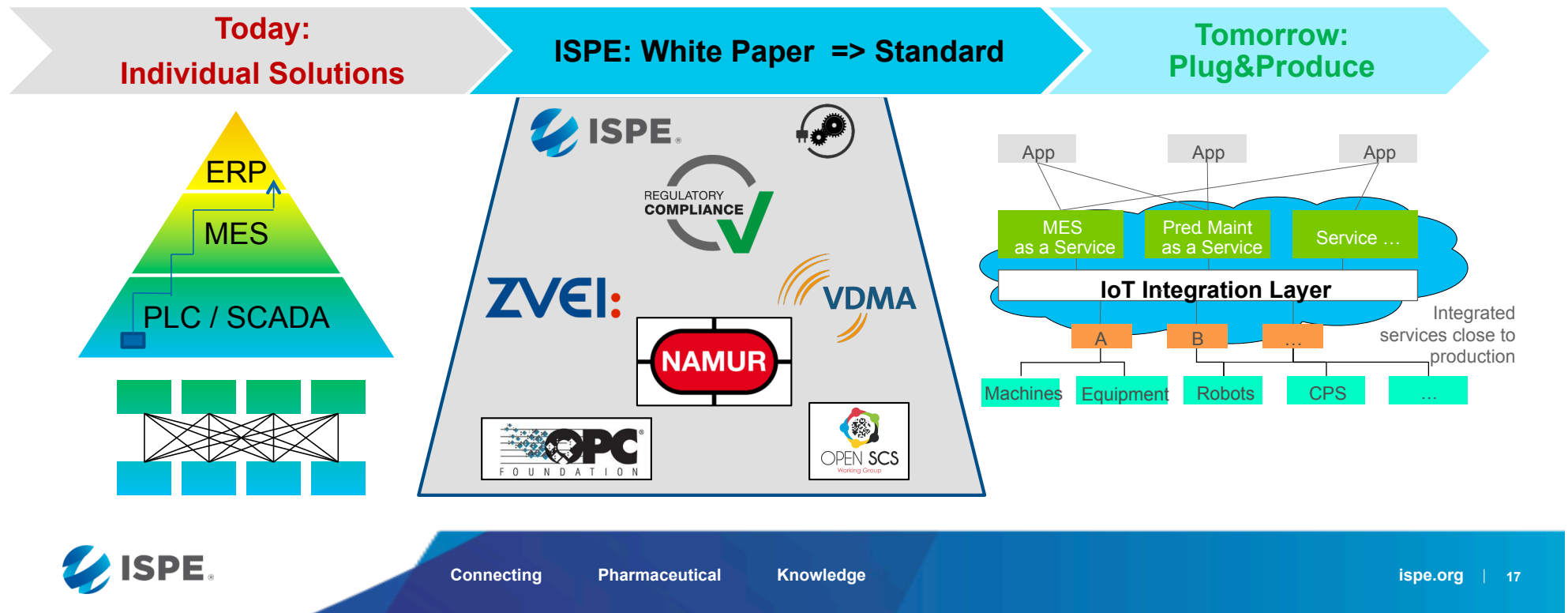
What We Need: Best Practice Implementation Methodology



Problem Statement for Plug and Produce: Complex and Cost Intensive Equipment Integration, Pharma Standard is Missing



Simplify, reduce engineering & increase usability



READINESS FOR INNOVATION

LEGACY PRODUCTS

- Developed for different target profiles
- Not suitable for automated processes
- Upgrading or re-development needed
- Portfolio pruning as a condition

QUALITY AND SAFETY

FALSIFIED MEDICINES DIRECTIVE

- Mass serialisation on pharmaceutical packaging
- End to end integration along the value chain: verification of originator product based on ISPE GAMP standard

DRUG SHORTAGES

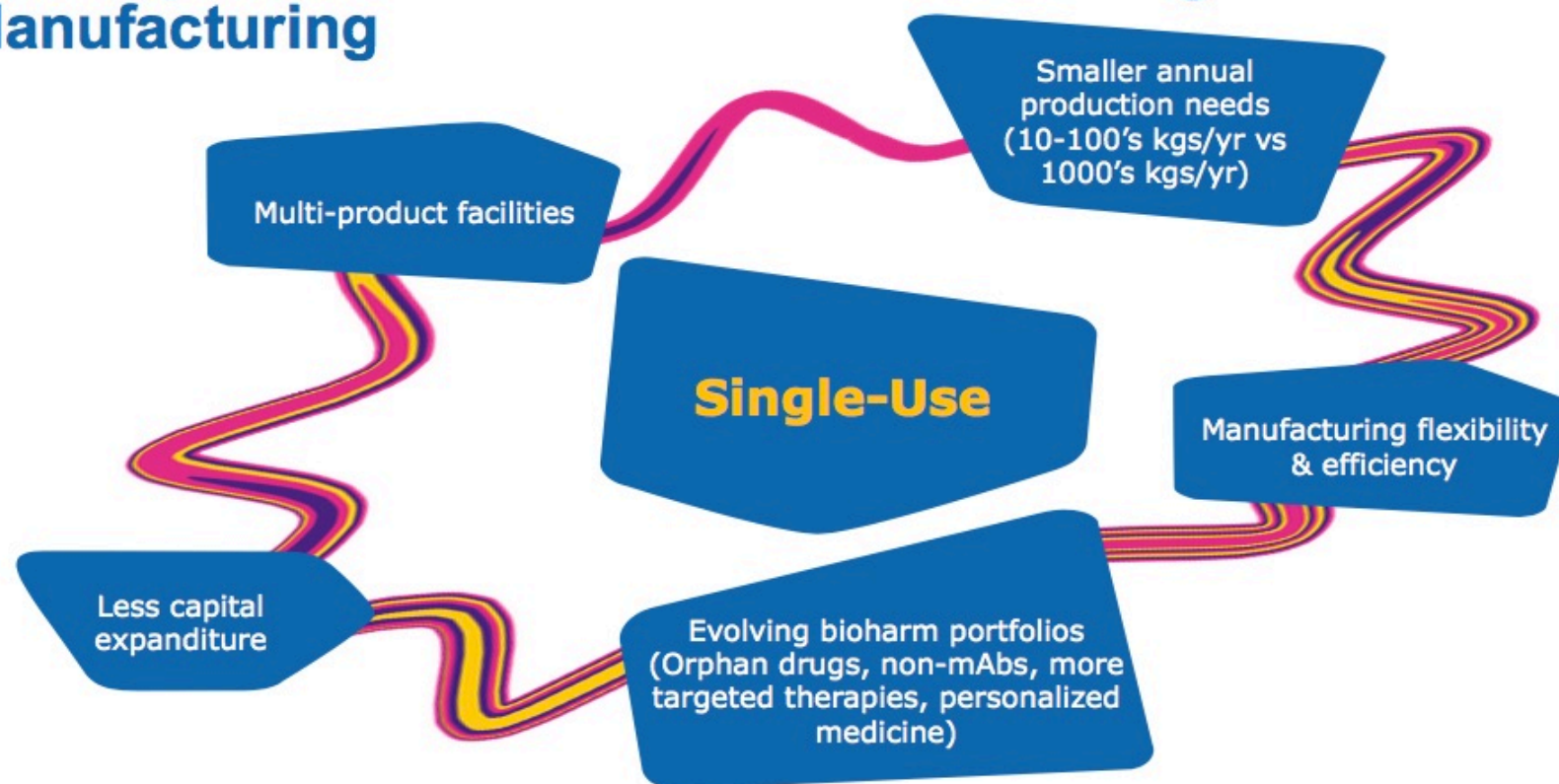
- ISPE Drug shortage survey
- ISPE Drug shortage prevention plan
- ISPE Drug shortage gap assessment tool

REGULATORS VIEW ON INNOVATION

NO COMPROMISES FOR QUALITY AND SAFETY

- Continuous manufacturing to improve market availability of drugs
 - API, Biologics, big volume products
 - Small products: personalized medicine?
- Avoid contamination (ISPE Containment Manual)
 - Single use technologies
 - No cleaning validation
 - Containment
 - Isolators
 - Aseptic processing (Annex 1 EC GMP Guide)

Consequence 1: Continued Growth of Single-Use Manufacturing



MERCK

Consequence 2: Process Intensification towards Continuous Processing

Standard mAb Process Template



Improved upstream process efficiency
necessitates Higher productivity
downstream solutions



Further needs for cost reduction
driving fully connected and
continuous process

>2025
€C



Requires:

- In-line sensors
- Holistic process controls

MERCK

SUMMARY

INNOVATION AND TRENDS IN GMP AND GEP

- Product portfolio drives speed to innovation
- Factories of the future need careful investment consideration, there is no more a standard solution but a lot of elements to combine
- Digitization will disclose potentials never achievable before
- Quality and safety cannot be compromised
- READINESS FOR INNOVATION: PRODUCT design AND PEOPLE capabilities are of the essence

ISPE offers the platform for dialogue with all stakeholders !

Спасибо

Thank you