

Research Center Pharmaceutical Engineering (RCPE) – Overview

I2APM Emerging Pharmaceutical Manufacturing Summit
Malta 2017

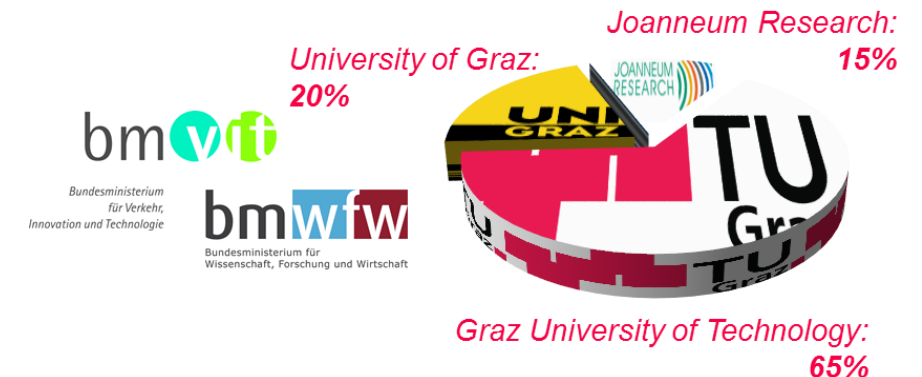
RCPE – Key Facts

- Research Center Pharmaceutical Engineering GmbH
 - Independent research center for pharmaceutical process and product development
 - A nationally-supported, public-owned Institute configures and operates as a private organisation
 - Located in Graz, Austria

- Our objectives:
 - Develop innovative science-driven platform knowledge for process and product design & development
 - Reducing costs and time in pharmaceutical development
 - Create business advantages for our partners



Head quarter with state-of-the-art laboratory facilities



Our Definition of Advanced Pharmaceutical Manufacturing

- **Controlled:** Quality is ensured by real-time monitoring of CQAs and “state of control” is maintained by advanced process control methods
- **Understood:** Mechanistic understanding of process and associated process models exist
- **Robust:** CQAs can be achieved for a broad range of materials, scales and operating conditions. Not overly sensitive to changes in materials attributes
- **Intensified:** Multiple physical and chemical transformations are carried out simultaneously (e.g., co-processing, melting and mixing)
- **Scalable:** Process is flexible with respect to the amount of product made and process can be scaled easily (e.g., time-scaling of continuous processes)
- **Economic:** Complex products and materials can be made using the processes in an economic way

Systems View of Pharmaceutical Product Development

Materials

- PSD, shape, BET, porosity, ρ
- Morphology
- Solid state, T_g , T_m
- Chemical stability
- Mechanical props.
- Flowability (ffc, etc.)
- Solubility, pKa, etc.
- Hydro/lipophilicity

Product

- Structuring
 - Molecularly mixed
 - Dispersed
 - Layered
 - Particle mix
- Mechanical interaction (friction, adhesion, etc.)
- Chemical interaction
- Thermodynamics

Processing

- Mechanical effects
 - Compactibility, hardness, porosity
- Change of morphology
- Particle/pellet synthesis (granulation, mechanofusion)
- Melting/solidification
- Redistribution

Biopharmacy

- Bioavailability
 - Liberation
 - Absorption
 - Metabolism
 - Distribution
 - Elimination
- Nano-particle uptake
- Distribution and clearance

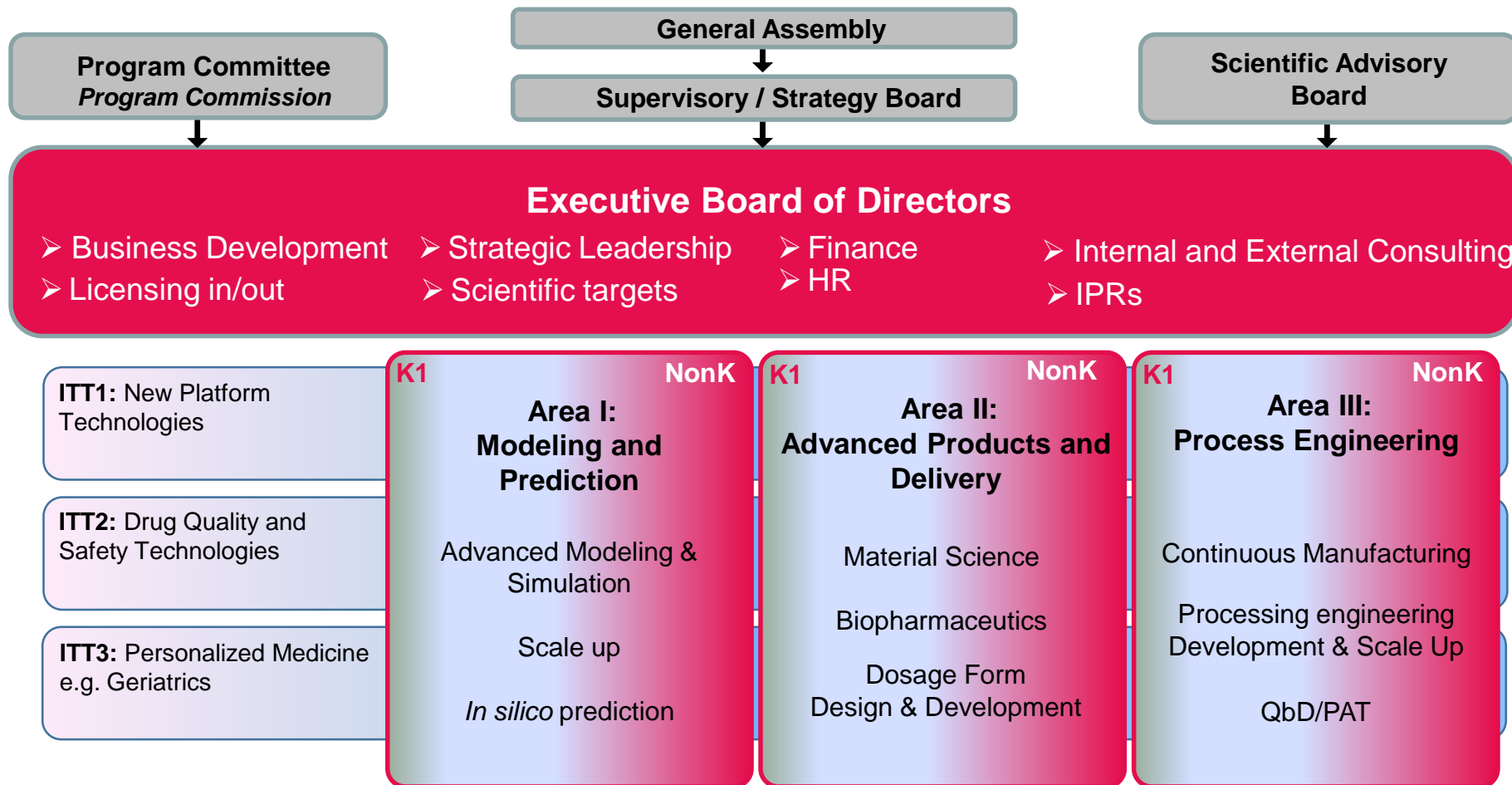
Experimental

- | | | | |
|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • Pore sizer • X-ray • Texture analyzer, etc. | <ul style="list-style-type: none"> • TEM • DSC • Powder rheology, etc. | <ul style="list-style-type: none"> • Compaction simulator • Small-scale equipment • Pilot lab | <ul style="list-style-type: none"> • In-vitro model (human cells) • Ex-vivo model (tissue) • In-vivo model (animal/human) |
|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|

Simulation

- | | | | |
|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • MD, DFT, MC • Group-contribution models | <ul style="list-style-type: none"> • MD, DFT, MC • Group contribution methods | <ul style="list-style-type: none"> • CFD, DEM, CFD-DEM • FEM, SPH | <ul style="list-style-type: none"> • IVIVC • GastroPlus • PBPK models |
|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|

RCPE Organization



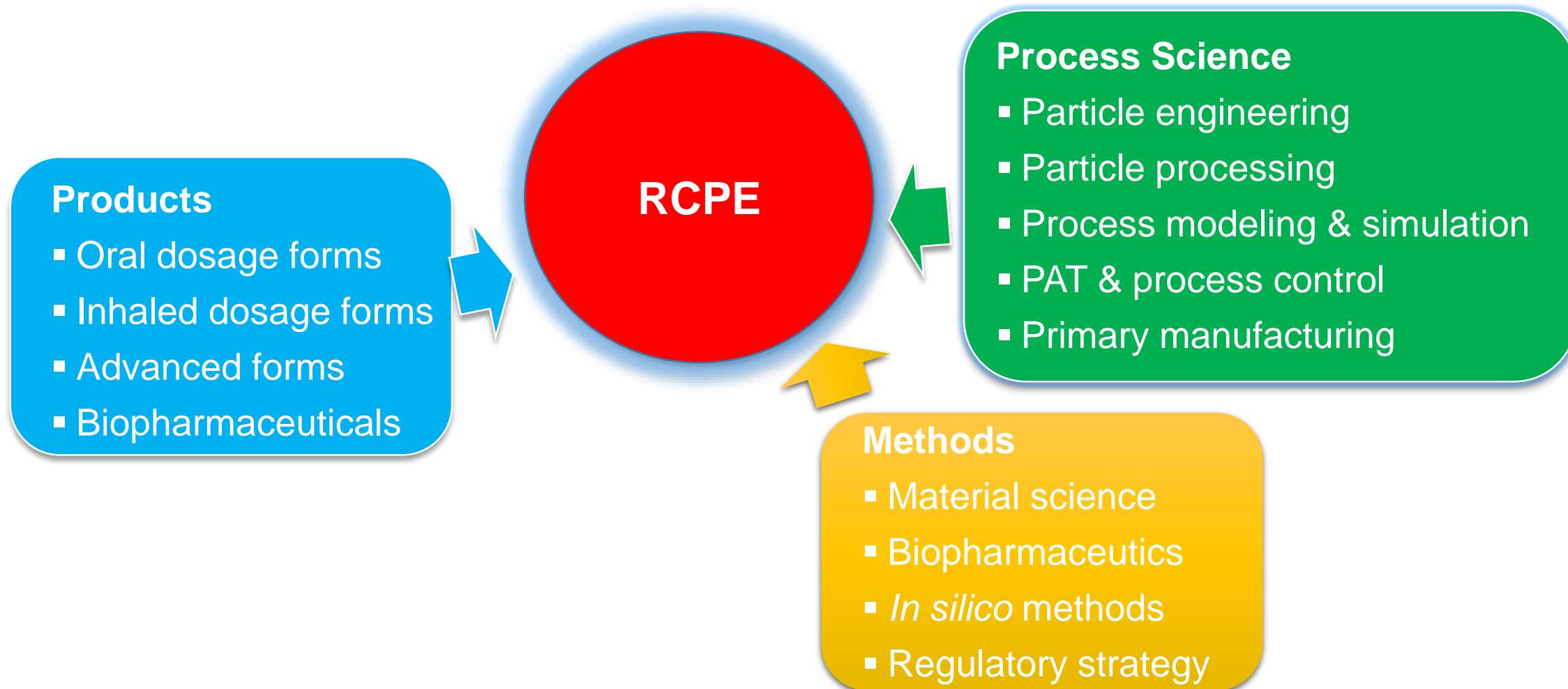
Key facts

- 140 Researchers,
- Legal entity is GmbH
- Clear IPR strategy
- 11 MIO per year turnover
- 30 peer-reviewed publications per year

Laboratories and Pilot Plant

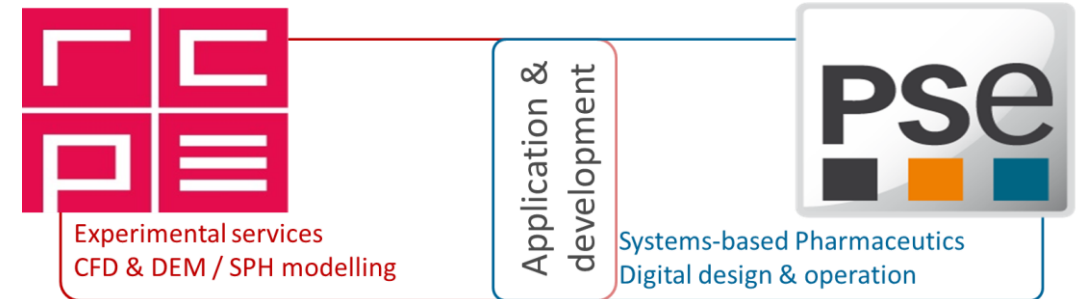
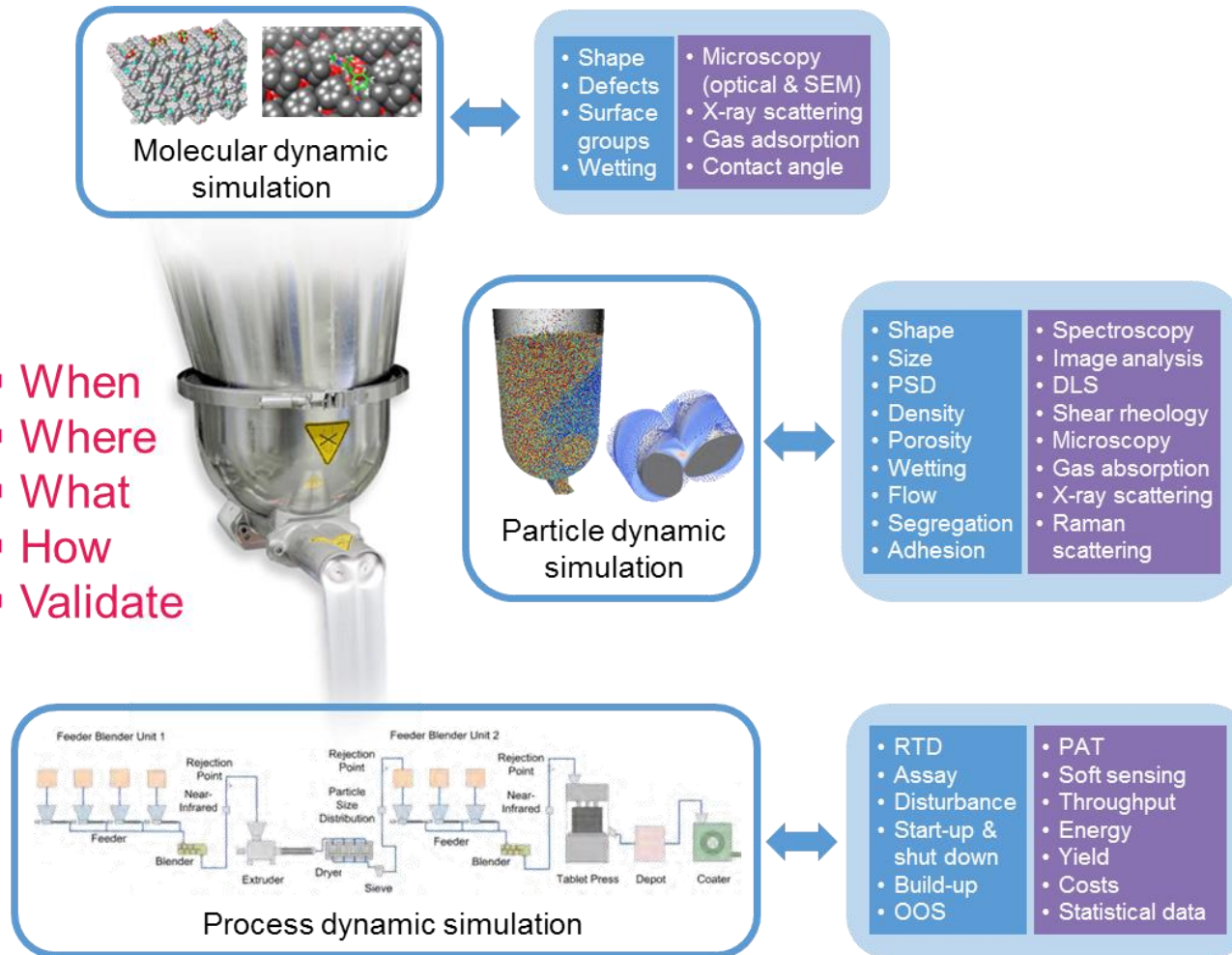
- OEB 3 - 4 and controlled substances
- Material Science
- Analytical Science
- Stability
- Pre-clinical and clinical manufacturing in collaboration with AMS

RCPE Scientific “Space”



Simulation Capability and RCPE-PSE CoE

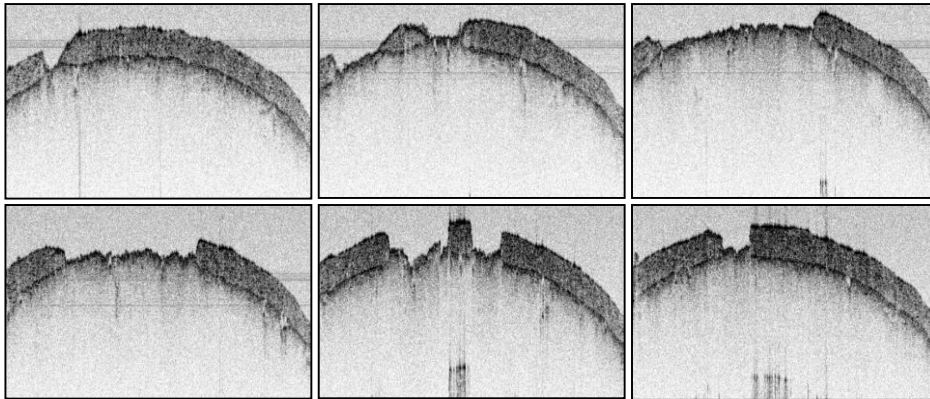
- When
- Where
- What
- How
- Validate



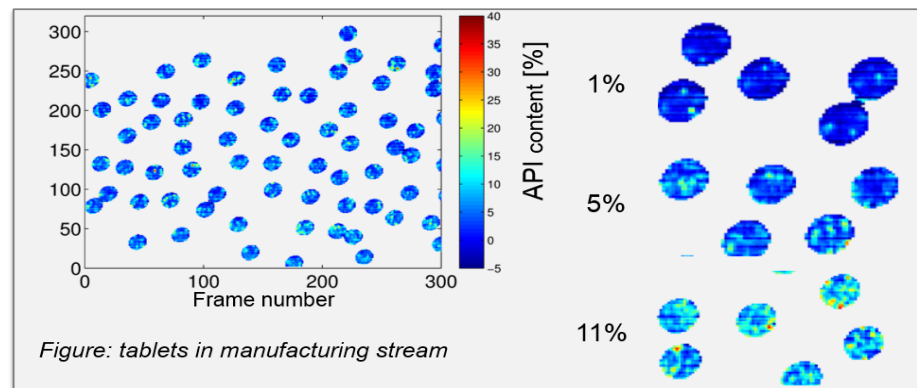
The Centre of Excellence for Pharmaceutical Formulation & Manufacture provides a “one-stop shop” that **combines model-based analytical technology** and **experimental services**.

This helps **accelerate the development of drugs** and **design of their manufacturing processes**

Process Analytical Technology (PAT)



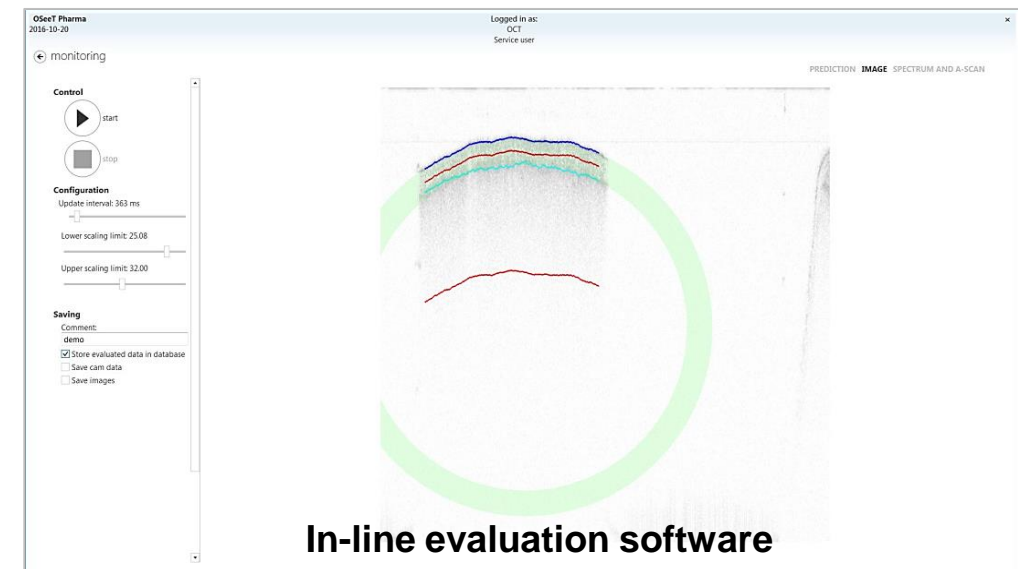
Optical Coherence Tomography



NIR Imaging



OCT Pharma 1D probe in hygienic design



Continuous Manufacturing at RCPE

- **European Consortium on Continuous Pharmaceutical Manufacturing (ECCPM):** RCPE leads consortium with AZ, UCB, Bayer, GEA, Siemens, Automatik, EVK, University of Gent, U. of Eastern Finland, U. of Duesseldorf, TU Graz
- **International Institute for Advanced Pharmaceutical Manufacturing:** RCPE (A), CMAC (UK), C-SOPS (USA)
- **Continuous Hot-melt Extrusion and Pelletization:** Bayer (D)
- **Continuous filtration, cake washing & particle drying:** Novartis (CH)
- **Continuous drying of crystallization slurries:** Novartis (CH)
- **Fully continuous plant for dry, wet and melt granulation:** LLB Bohle Germany (D)
- **Integrated upstream-downstream continuous process**
- **Continuous capsule filling system**
- **Printing of Drugs**

ECCPM - Structure

Prof Johannes Khinast
Scientific Director

ECCPM

Massimo Bresciani
Director BD/Sci Op

RCPE Scientific and Communication Lead: Wen-Kai Hsiao

Pre-Competitive: Work Shop Series

Use-case I Hot Melt Extrusion

Bayer
Maag Automatik
Siemens
EVK
IPPT
RCPE

KR:
Johannes Khinast

RCPE:
Jakob Rehrl
Isabella Aigner

Company Specific

Use-case II Wet Granulation

UCB
GEA
Ghent University
RCPE

KR:
Thomas de Beer

RCPE:
Dave Doughty
Wen-Kai Hsiao

Company Specific

Use-case III Direct Compaction

Astra Zeneca
University of Eastern
Finland
RCPE

KR:
Jarkko Ketolainen
Ossi Korhonen

RCPE:
Wen-Kai Hsiao

Company Specific

ECCPM – Workshop Series

- Successful workshop September 2015 on PAT & RTR
- Successful workshop July 2016 on process control and control strategy
- More than 45 participants at each workshop
- High level speakers
 - Steve Hammond, Pfizer Inc. (USA)
 - Sonja Sekulic, Pfizer Inc. (USA)
 - Martin Warman, Vertex Pharmaceuticals Inc. (USA)
 - Mauricio Furtan, Janssen (USA)
 - Jochen Thies, Glatt (CH)

Workshop Series

“Going Continuous”

Topics for the next workshop:

- Developing a risk-based PAT strategy: from sensors to Real Time Release (RTR)
- What are the challenges for monitoring?
- What advanced process control is needed?
- Regulatory requirements and measurement

WORKSHOP 2

Topic: Advanced PAT and Real Time Release
Date: September 16th and 17th, 2015
Location: Graz, Austria

Workshop Series

“Going Continuous”

Topics for the next workshop:

- Continuous Manufacturing process control, important prerequisites
- Control strategies designed for Continuous Manufacturing
- Fit for purpose process control
- Regulatory requirements and opportunities in the field of Continuous Manufacturing and associated process control

WORKSHOP 2016

Topic: From Control Strategy to Process Control
Date: July 5th, 2016
Location: Graz, Austria

INTERNATIONAL EXPERTS:

- Prof. Fernando Muzzio (Rutgers University)
- Dr. Ivo Backx (Siemens)
- Mauricio Furtan, Ph.D. (Vice President Advanced Technology, Janssen Supply Group, LLC)
- Prof. Horn (University of Technology, Graz, tentative)

Event organized by
www.rcpe.at
Telefon +43 (0) 316 – 873 – 30901

Registration for invited participants only
Registration fee €750 per participant

For any Input/Questions

please contact:
Isabella Aigner (RCPE)
isabella.aigner@rcpe.at

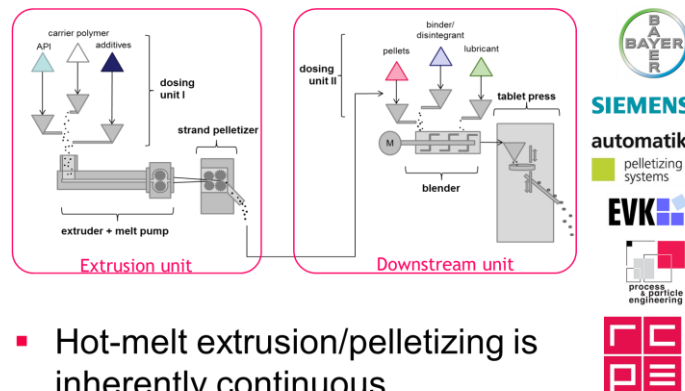
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ECCPM - Industrial Use Cases

Use Case 1: Hot-melt Extrusion



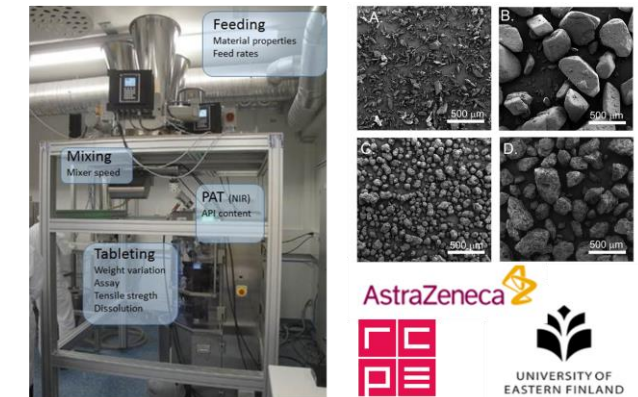
- Hot-melt extrusion/pelletizing is inherently continuous
- Solubility enhancement for poorly water soluble compounds with IR tablet as targeted product
- Challenges:
 - Formulation and process development for successful pelletizing
 - Formulation for fast dissolution (pellet)
 - Formulation and process development for successful tableting (elastic pellet)
 - Develop PAT solution and control strategy

Use Case 2: Wet granulation



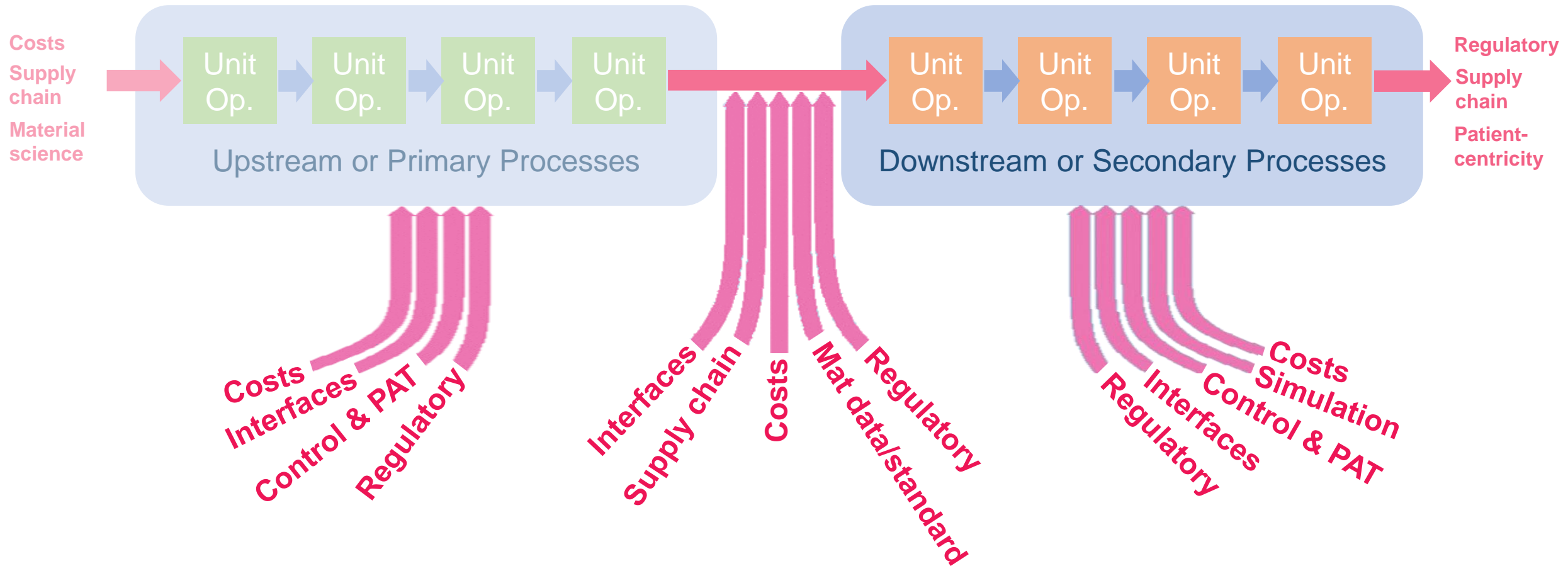
- CM equipment available based on wet extrusion granulation (GEA ConsiGma)
- Support migration from batch to continuous processing
- QbD approach to process development
- Challenges:
 - Formulation and process development to mitigate variability in API batches
 - Individual unit operation trial and optimization
 - Technology/process transfer
 - Full line operation support

Use Case 3: Direct compaction



- Simplest process path to CM
- Minimal back-mixing and buffer to damp out disturbance
- Highly dependent on material processability
- Challenges:
 - Interfaces (residues and dead zone)
 - Long run process robustness/effects
 - In-line PAT method development

Evolving Challenges for CM

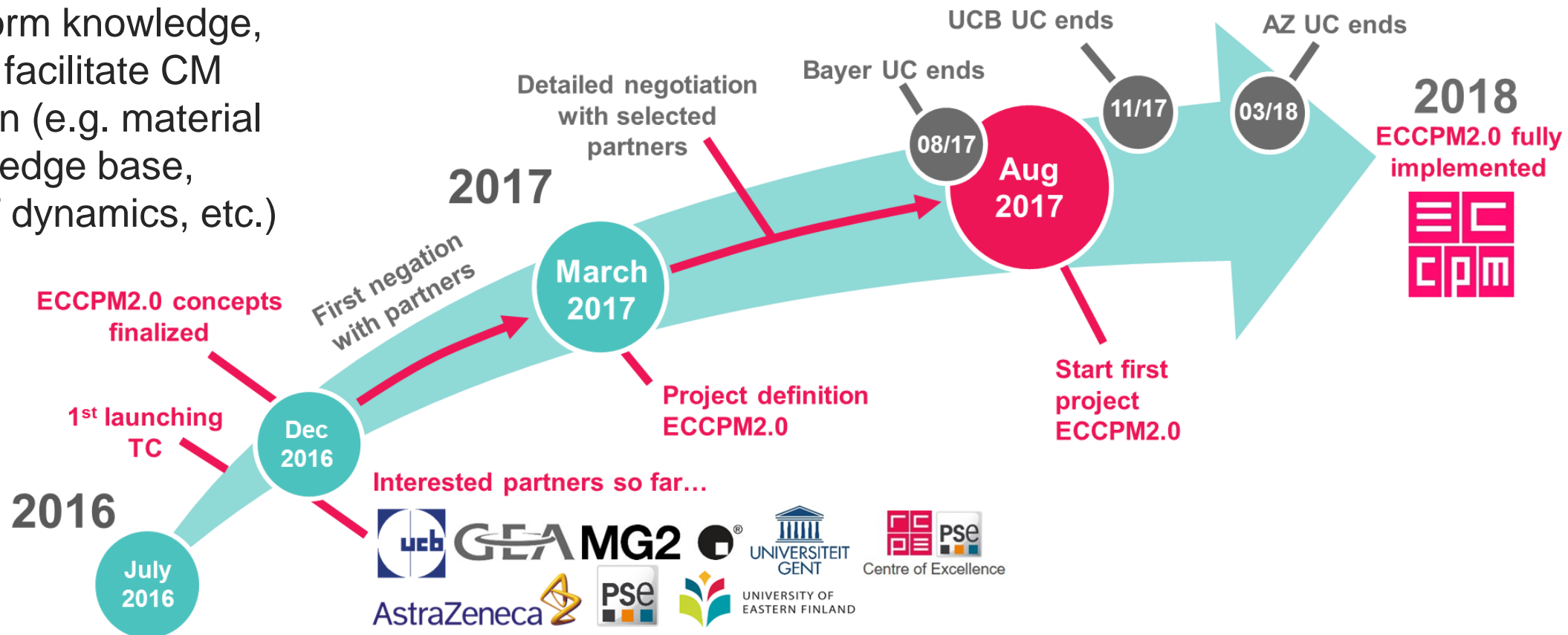


Continuous Manufacturing – What's Next?

- Integrating CM early on in pharmaceutical development, i.e., “What formulation strategies enable CM?” or “How can CM simplify formulations?”
- Standardization of selected materials for CM (e.g., MCCs, MgSt, etc.) with USP
- Integrating continuous API synthesis and secondary manufacturing (e.g., spray drying and filling into capsules or NANEX)
- Co-processing and multi-functional materials
- Individual manufacturing for patients based on personal needs, i.e., “fresh medicines”
- Adaptive formulations based on excipient variability
- Open innovation
- **ECCPM 2.0**

ECCPM 2.0

- Consolidation of lesson learnt
- Develop platform knowledge, i.e. tool kits to facilitate CM implementation (e.g. material science knowledge base, long-term PAT dynamics, etc.)

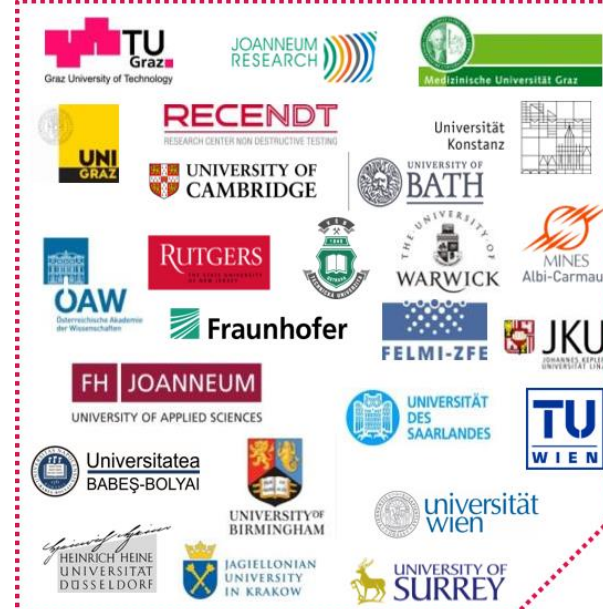


RCPE – Expanding Collaboration

Industrial partners



Scientific partners



Support partners



Contacts



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