Continuous Manufacturing – Critical Steps and Possible Solutions
Batch Definition, Control Strategy & New PAT

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Overview of RCPE

**Research Center Pharmaceutical Engineering GmbH – RCPE**
- Independent Research Center for pharmaceutical process and product development
- Located in Graz, Austria
- 100% owned by research institutions

**Our objectives:**
- Developing the science for pharmaceutical process and product design & development
- Lowering costs and shortening times in pharmaceutical development
- Increasing quality of pharmaceutical products
Key Facts

- RCPE founded July 2008
- > 130 employees and researchers
- Turnover 2015/2016: €10 M
- > 25 Scientific Partners, > 100 Industrial Partners
- Scientific Output:
  - 6 Licenses granted, 4 Patents granted
  - 24 Patent applications
  - 200+ peer-reviewed papers
  - 9 Bachelor theses, 95 Diploma/Master theses
  - 26 PhD Theses
- 4 Spin-offs
RCPE – Scientific Area

Area I

Modeling and Prediction
- Pharmaceutical process modeling & simulation
- Granular flows
- Fluid mixing and multiphase flows
- Molecular simulations and structure optimization
- Material Science & Characterization

Area II

Advanced Products and Delivery
- Oral dosage forms
- Inhalation
- Pharmaceutical proteins
- Solubilization and nano technology
- Novel drug delivery systems
- Biopharmaceutics

Area III

Process and Manufacturing Science
- Continuous processing development and implementation
- Process Understanding & Control (including PAT)
- Process development & Scale up
- Design Space and CPPs qualification

QbD/PAT

Innovation for our partners
Some Recent News on CM

- Multiple companies have filed CM processes with FDA
- Vertex Pharmaceuticals producing since 2016 in a $30 mio 400m² CM facility in Boston based on GEA technology (for Orkambi)
- Johnson & Johnson has a conti-line in Puerto Rico for production of HIV medication
- Pfizer highly active in CM
- GSK built a $50 Mio CM plant in Singapore involving upstream technology. 100m² instead of 900 m²!
- Novartis has a plant in CH from API building blocks to final tablets, based on cooperation with MIT (and others)
- Equipment companies are ready (GEA, Glatt, Bohle, Bosch, CONTINUUS, etc.)
- Hovione entered an agreement with Vertex to produce continuously in NJ as of 2017
What are the Critical Steps?

Five critical areas:

- Materials
- Equipment
- Development
- Business case
- Regulations
Materials

- Materials need to be relatively free flowing
- No easy build-up of electrostatic charges
- Low stickiness and adhesiveness to surfaces
- Low tendency for attrition and dusting
- Reduced tendency to form agglomerates
- Hygroscopicity less critical
- Minimal segregation
- Transportable in a vacuum system
- Individual ingredients should have distinct NIR or Raman absorption bands
Equipment-specific Critical Steps

- Robust process (e.g., low-dose feeding, filtration, drying, coating)
- Process integration (e.g., buffers, interfaces)
- Process control
- Real-time quality assurance (sensors, PAT)
- OOS-handling (e.g., material diversion)
- Data-recording
- Long-term stability (material build-up, dusting, probe-fouling)
- CIP/WIP
Development Critical Steps

- Decision on dosage form (tablets, capsules, etc.)
- Time of integration of process development into drug development
- Availability of CM line for development
- Formulation design specific for CM (e.g., to minimize tribo-charging, segregation, adhesion, etc.)
Business Case

- Risk evaluation: traditional vs. continuous
- Costs for refiling in different regions
- Regulatory strategy, with some elements that come for SUPAC or any other regulatory GUIs
- Improved quality (e.g., less OOSs)
- Real Time Release: advantage vs. risk
- Business decisions based on ROI (i.e., why a senior manager should buy into CM?)
- Business wise, which are the triggers or the fundamental selling points internally?
Regulations - Critical Steps

- Batch definition
- Materials traceability
- OOS handling
- Quality systems
- State of control
- Data
- Release
- Regulatory heterogeneity
Regulatory Challenges: The Landscape
“Friendly“ Regulators for CM?

“FDA will continue our efforts to encourage the advancement of continuous manufacturing as one of a variety of ways to enhance the quality of the medications used by the American public.” – Lawrence Yu, Ph.D., FDA’s Deputy Director, Office of Pharmaceutical Quality (http://blogs.fda.gov/fdavoice/index.php/2016/04/continuous-manufacturing-has-a-strong-impact-on-drug-quality/)

“PMDA is positive towards CM” – Yoshihiro Matsuda, Ph.D., Senior Scientist (for Quality), IMT-WG, PMDA (https://www.pmda.go.jp/files/000214436.pdf)

„While there are no guidelines specific to continuous manufacturing in Europe, continuous manufacturing fits well with existing EMA guidelines” ~ Dolores Hernan Perez de la Ossa, Regulatory/Human Medicines/Scientific Advice and Protocol Assistance, EMA, United Kingdom, http://blog.ispe.org/2016-continuous-manufacturing-conference-highlights
General Statements about CM

- Continuous Manufacturing (CM) operations must be based on QbD and PAT principles. These include:
  - Definition of TPP
  - Definition of CQAs, CMAs, CPPs based on risk evaluation (e.g., FMEA)
  - Use of risk analysis throughout life cycle
  - Online evaluation of process data and process monitoring (including data logging)
  - Risk-based control concept
  - Full validation of process and process analytical/control tools
  - Concept for QA-based release
  - Optional: design space and RTRT

- Batch definition seems to be one of the challenges perceived by companies
Batch Definition

- Batch definition is needed for:
  - a. Release based on QA decision by QP
  - b. Recall

- Any released material always subject to a quality disposition decision.

- In general, significant flexibility exists and different approaches are possible, if it can be made evident that quality is assured and materials can be tracked.

- It may be possible to operate with no pre-defined run-time, in which quantities of product are defined during operation in a flexible way, based on science and risk, subjected to a disposition decision.

- The approach needs to be included in the filing and made prior to the beginning of any manufacturing run.
Batch vs. Lot (FDA vs. EMA)

Batch

- A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture (CFR 21.4).
- In case of continuous manufacture the information about batch size in traditional terms might not be relevant; however information how a batch is defined should be provided. The expected size of one campaign (e.g. period of time) should be stated (Guideline on manufacture of the finished dosage form, EMA/CHMP/QWP).

Lot

- A batch, or specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits (CFR 21.4).
Possible Batch Definitions

• It may be possible to operate in a “push mode” or “pull mode”

• **Push:**
  • All of the material discharged between two specific times (irrespective of the amount of material produced)
  • All of the material produced between two specific process events (for example, specific process conditions)
  • All of the material stemming from one API batch or tote of drug substance

• **Pull:**
  • Batch defined on “manufacturing order” based on CFR 21 V4
  • Example: 500 kg of in-spec material produced
<table>
<thead>
<tr>
<th>Excipient A Lot 1</th>
<th>Excipient A Lot 2</th>
<th>Excipient A Lot 3</th>
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<tbody>
<tr>
<td>Excipient B Lot 1</td>
<td>Excipient B Lot 2</td>
<td>Excipient B Lot 3</td>
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<td>Excipient B Lot 4</td>
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<td>API Lot 1</td>
<td>API Lot 2</td>
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</tr>
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<td>Product Lot X</td>
<td>Product Lot X+1</td>
<td>Product Lot X+2</td>
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<td></td>
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<td>Product Lot X+3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Product Lot X+4</td>
</tr>
</tbody>
</table>

**Batch Y**

Materials from
- Excipient A Lot 1-2
- Excipient 2 Lot 2-4
- API Lot 1-2
Material Flow Through the System

Residence Time Distribution (RTD)

**Definition of RTD:**

\[
E(t) = \frac{C(t)}{\int_0^\infty C(t) \, dt}
\]

\(C(t) = \text{concentration of tracer pulse}\)

**Step-change experiment (i.e., change in excipient container):**

\[
F(t) = \frac{C(t)}{C_{\text{tracer}}}
\]

\[
F(t) = \int_0^t E(t) \, dt
\]

Example: powder blender
- Washout $W(t)$ is defined as:
  \[ W(t) = 1 - F(t) \]
- $W(t)$ is relevant for defining the time at which a certain fraction of material X has left the system, e.g., 99%
Convolution of RTDs

- Typically, multiple unit operations are in sequence, each having a unique RTD.
- The combined RTD of 2 unit-operation RTDs is called convolution.

**Definition of Convolution:**

\[
(E_1 * E_2)(t) = \int_{-\infty}^{\infty} E_1(\tau)E_2(t - \tau)d\tau
\]

- RTD of whole plant (convolution) can be evaluated knowing the RTDs of the individual unit operations!
- Provides relevant information for batch definition, materials diversion and traceability.
Convolution of RTDs

Example DC line:

RTD via Experiments and/or Simulation

- RTD measurement of a roller compactor
- Simulation of dead zone using the geometries of a real LIW feeder
Experimental RTD from Color Tracer Experiments

**Characteristic values of RTD**

- \( t \) = mean residence time
- \( 2\sigma \) = broadness of probability distribution
- Skewness = asymmetry of probability distribution
- Kurtosis = pointedness
- \( t_{X\%} \) = time at which specific concentration X is reached
- \( t_D \) = dead time, delay

\[
\bar{t} = \frac{\sum_i t_i c_i \Delta t_i}{\sum_i c_i \Delta t_i}
\]

\[
\sigma = \frac{\sum_i (t_i - \bar{t})^2 E(t) \Delta t_i}{\bar{t}^2}
\]

\[
Skewness = \frac{\sum_i (t_i - \bar{t})^3 E(t) \Delta t_i}{(\sum_i (t_i - \bar{t})^2 E(t) \Delta t_i)^{3/2}}
\]

\[
Kurtosis = \frac{\sum_{i=1}^{N} (t_i - \bar{t})^4}{N \sigma^4}
\]

Graphical representation of the characteristic values

- **Kurtosis**
- **Skewness**
- \( t_D \) = dead time, delay
- \( t_{X\%} \) = time at which specific concentration X is reached
- \( t_{5\%} \), \( t_{50\%} \), \( t_{95\%} \) = time at which specific concentrations are reached
Example: HME Various Mass Flow Rates

large dead time for low mass flow

“broad” RTD for low mass flow
RTD Model Fit

- Model: $P(s) = \frac{\bar{y}(s)}{\bar{u}(s)} = \frac{k}{(1 + sT)^2} e^{-sT_t}$
  - $P(s)$ … transfer function
  - $\bar{y}(s)$ … system output, Laplace domain
  - $\bar{u}(s)$ … system input, Laplace domain
  - $\bar{y}(t)$ … system output, time domain
  - $\bar{u}(t)$ … system input, time domain
  - $k$ … gain
  - $T$ … time constant
  - $T_t$ … dead time

- Fit the model parameters $k$, $T$ and $T_t$ for the experiments mentioned above

- Investigate the influence of different mass flows on the parameters $T$ and $T_t$ / the RTD

Martinez, Horn, Khinast, submitted to J. Pharm Sci.
Example: Model vs. Tracer measurements

- Model: \( P(s) = \frac{\bar{y}(s)}{\bar{u}(s)} = \frac{k}{(1 + sT)^2} e^{-sT_t} \)
  - \( T = 17.1s \)
  - \( T_t = 79.1s \)
  - \( k = 4.8 \)
  - \( m_{\text{tracer}} = 39.2\, \text{mg} \)
RTD via Modeling: Extruder Modeling Strategy

1D-Simulation for Process Control

- profiles of process variables along the screw axis

Experiments

1D Screw Parameters

- characterization of screw elements

Material Properties

- input parameters

3D-Simulation (SPH)

- for model validation and screw characterization
Computed RTD – Example ZSK18 vs. Pharma 16

<table>
<thead>
<tr>
<th>ZSK18</th>
<th>Exp.</th>
<th>n [rpm]</th>
<th>m [kg/h]</th>
<th>Temperature profile</th>
<th>SMEC_{geo} [kWh/kg]</th>
<th>SMEC_{geo} [kWh/kg]</th>
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<th>m [kg/h]</th>
<th>Temperature profile</th>
<th>SMEC_{geo} [kWh/kg]</th>
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Diversion (Segregation) of OOS Material

- In general, material diversion is not mandatory and must be based on risk considerations
- Materials diversion optimizes the amount of in-spec material
- Must be based on understanding of RTDs
- Example: Continuous RC line
Rejection of Material (Diversion)

- Propagation of a disturbance between extraction points in the system are important to justify the amount of material at risk due to OOS event
- Process dynamics, steady-state RTD and dynamic RTD (i.e., during process changes, start/shut-down, during campaign processing, back-to-back batches) need to be understood
- Understanding via:
  - Response to a set point change around nominal states
  - Tracer experiments
  - Process simulation
- Ideally, measurement and material extraction points should be near where OOS events can occur, but downstream extraction is possible with understanding of process dynamics.
- High degree of back-mixing is positive since fluctuations are dampened. However, this can increase the amount of material at risk.
Disturbances and Required Sampling Frequency (PAT)

- Many disturbances are caused by feeder fluctuations, including:
  - Feed rate fluctuations of non-cohesive powder due to the discontinuous nature of solids and screw patterns
  - Downspout accumulation, triboelectricity
  - Feeder bearding
  - Feeder refill (switch to volumetric mode)
- Sampling frequency must be based on detectability of disturbances
- Blender and other unit operations (granulator, extruder, etc.) filter short-term fluctuation.
- “Filterability” of a specific disturbance pattern (e.g., sinusoidal) can be computed based on RTD.
- Large fluctuations are not filtered and can be treated as pulse
- Risk analysis based on maximum API pulse size (e.g., largest chunks or beards breaking off) at smallest possible intervals.
Filterability of a Process

Example: Dry Granulation (Roller Compactor) Line
Filterability of a Process

Example: Dry Granulation (Roller Compactor) Line

Feeder characterization  RTD Blender  RTD Roller Compactor
Filterability of a Process

Impact of a Pulse Function of the API Feeder

![Graph showing API concentration over time with different outlets: feeder outlet, blender outlet, roller compactor outlet.](image-url)
Filterability of a Process

Impact of API feeder interruption 1 min

![Graph showing API concentration over time](image-url)
Filterability of a Process

Impact of API feeder interruption for 10 sec

API concentration

- concentration in %
- time in s

-100 0 100 200 300 400 500 600 700 800

feeder outlet
blender outlet
roller compactor outlet
Feeder Refill

- During feeder refill weight signal is lost
- Thus, feeding rate cannot be controlled
- For the 5% API product with +/-5% permitted deviation, a 10 s complete feeder interruption does not lead to OOS product.
- Neither does a doubling of feed rate for 10s
- Thus, refill should be <10s to minimize risk for OOS material
- Moreover, refill should not occur on empty feeders, as the feed rate is drastically increased (20% is a good choice)
Summary: Understanding of RTD

Application of RTD

- Understanding the backmixing of material (incl. deadzones, etc.)
- Tracking material back to original raw material tote or IBC (traceability)
- Various limits for “wash out” can be set: 5% typical, yet 1% or 0.5% also possible
- Basis for diversion strategy (material segregation)
- Basis for BOM (bill of materials)

Tables with material which was OOS during manufacturing
CM Control Strategy Options

General Control Strategy

Level 1 – Input Output
Considers the total Input/Outputs. The CQAs that are visible at the I/O level are the CQA’s of the final product.

Level 2 – Intermediate
Considers the interactions between the unit operations.

Level 3 – Process Unit
Represents the process at the most detailed level. Separate considerations for every involved unit.
Some Relevant Control Strategies

- **Open system:**
  - No active controls but may trigger external action
  - Needs clear rules of engagement with the process. (e.g., separation of non-conforming material and/or operator adjustment).

- **Feed back:**
  - Output information is used to automatically trigger upstream action

- **Feed forward:**
  - Input/output information used to automatically trigger control action
  - Need knowledge of process dynamics (i.e., a model) to automatically adjust process in order to compensate for the event. (e.g., run the press differently, if detected granule density is high).
  - MPC is advanced form of feed-forward control
Control of Unit Operations via Model-Predictive Control (MPC)

- Often combinations of feedback (PID) and model predictive control loops are used.
- MPC includes real-time process information.
- Model predicts future values of control variables and control action.
- Models can be mechanistic or statistic.
- Process dynamics can be understood (startup, shutdown, etc.)

![Diagram showing past, future, reference trajectory, measured control variable, predicted control variable, past manipulated variable, and predicted manipulated variable.](attachment:image.png)
Types of Models

- **Most detailed**
  - First Principles
    - Quantum Mechanics
    - Discrete Element Models
    - Finite Element Models
    - Computational Fluid Mechanics
  - Multi-Dimensional Models
    - Population Balance Models
    - Dispersion Models
    - Meso-Scale Lumped Models
  - Engineering or Semi-Empirical
    - Residence Time Distribution Models
    - Macroscopic Mass and Energy Balances
  - Empirical and Reduced Order Models
    - Surrogate Based Models
    - Statistical Models

- **Most expensive**

- **Least detailed**

- **Least expensive**

Figure courtesy Ierapetritou group at Rutgers University
Control Example: Blending speed adaption (via MPC)

- Outlet mass flow should be kept constant to a reference value of 20 kg/h.
- Mass hold-up must stay between the given limits.
- Blender speed $\omega$ is computed by model predictive control (MPC) strategy.

Development of a Model-Based Control Concept for a Direct Compaction Process; J. Kruisz, J. Rehrl, M. Martinetz, S. Sacher, M. Horn, J. G. Khinast; Partec. April 2016, Nürnberg.
Control Model Development: Model Simplification

First principles

- PowCom (granular & fluidized systems)
- SPH (extruders, melts, mixing)
- XPS (extruders, melts, mixing)

Model simplification

Fast control models

- Fluid bed granulator
- Fluid bed dryer
- Fluid bed coater
- GEA coater
- Drum coaters
- Hot-melt extruder
- Wet extruder
- Tableting
- Blenders/hoppers/feeders
Center of Excellence RCPE-PSE

- 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 development of drugs and design of manufacturing processes.
True-Shape DEM

Included:
- 1.8 Mio TS objects
- 500 kg total mass
- 5 fan-shaped sprays
- Convective heat
- Conductive heat
- Spray cooling

C. Radeke, P. Böhling and J.G. Khinast, manuscript in preparation, 2017
Fluid Bed Coater
Wurster Coater: CFD-TFM vs. CFD-DEM (Full Model)

CFD-TFM

CFD-DEM
Process Analytical Technology

I. Modern process analyzers

II. Multivariate tools for design, data acquisition and analysis

III. Process control tools

IV. Continuous improvement and knowledge tools
I. Modern Process Analyzers

**Univariate process measurements**
- Time, temperature, weight, pressure, conductivity, pH, pO2, outgas O₂ / CO₂, stirrer speed, power, foam level, etc.

**Full process analysis with PAT tools**
- Chemical composition
- Polymorph monitoring
- Nucleation & crystal growth
- Particle properties
- Blend homogeneity
- Identification of impurities
- Etc.
New Methods
Optical Coherence Tomography: Novel PAT-Tool for Monitoring of Tablet Coating

- System is modularly designed
- Light source: SLD Broadlighter
  - Central wavelength: 832 nm
  - FWHM spectra bandwidth: 75 nm
- Lateral resolution: ~14 µm
- Axial resolution: ~4 µm
- Acquisition rate: ~62 kHz (~62 fps)
OCT Capabilities: Coating Thickness, Variability & Defect Detection

Online Integration

Online Measurements

Real-time Coating Distribution

Defect Detection
In-line Monitoring of a Pan Coating Process

- Mean coating thickness of each analysed tablet.
- Relative standard deviation (RSD) of coating thickness for each analysed tablet.
- Corresponds to intra-tablet coating variability.
OCT Technology is GMP Ready

- The systems include:
  - **1D imaging probe** (CE and ATEX conform)
  - **3D imaging probe** available mid 2016
- GMP conforming hardware and documentation/software available
- System can be purchased as of 2017 from Phyllon GmbH (Graz, Austria)
NIR Hyperspectral Imaging – How does it work

HELIOS G2 NIR
NIR Hyperspectral Imaging – How does it work

- Spatially resolved spectroscopic data is converted in real-time to „chemical colors“.

- Concentrations of chemical constituents can be measured non-invasively at high product speeds.

Camera internal classification and RGB visualization (chemical color representation) of chemical differences for real-time analysis.
HELIOS Chemical Color Image (CCI)

Original (VIS)  HSI preview (mean intensity)  HELIOS CCI
PAT for Continuous Manufacturing
100% Monitoring of Tablets with Chemical Imaging

Mapping of tablets

Time averaged API content
Sorting System

- Smart HSI Camera HELIOS feeds classified data to a sorting engine
- The sorting engine controls valves or claps to sort out e.g. tablets not meeting the quality specs, triggers an alarm or evaluates product statistics.
Take Away Message

Take-away points:

- Regulatory bodies such as FDA’s ETT are supportive and increasingly knowledgeable as more CM applications are filed.
- Regulators at EMA are open to discuss applications within MAA (CMC)
- Batch definition and material traceability depends highly on how well-behaved the RTDs of the unit operations and the complete line are.
- Furthermore, RTD behaviour likely depends not only on system configuration, but on material attributes as well.
- Control concepts complex.
Thank You