Continuous Manufacturing – Critical Steps and Possible Solutions

Batch Definition, Control Strategy & New PAT

Prof. Johannes Khinast

Graz University of Technology
Research Center Pharmaceutical Engineering
Graz, Austria

K1 Competence Center - Initiated by the Federal Ministry of Transport, Innovation and Technology (BMVIT) and the Federal Ministry of Science, Research and Economy (BMWFW).
Funded by the Austrian Research Promotion Agency (FFG), Land Steiermark and the Styrian Business Promotion Agency (SFG).

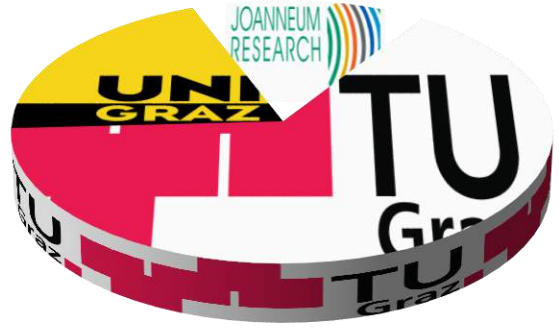
Overview of RCPE

Research Center Pharmaceutical Engineering GmbH – RCPE

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

University of Graz: ***20%***

Joanneum Research: ***15%***



Graz University of Technology: ***65%***

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

ROOM BIOTIC

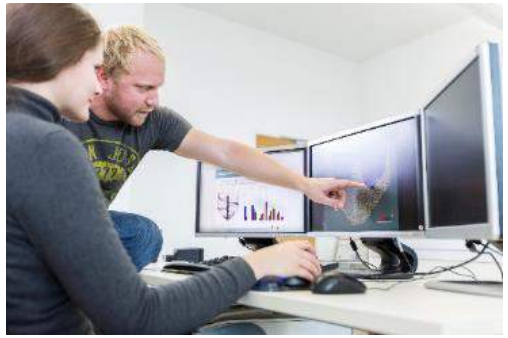
pharmaceutical and regulatory services gmbh

MeltPrep

ses-tec

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
- Solubilizatuon 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 $30mio 400m^2 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 $50Mio CM plant in Singapore involving upstream technology. 100m^2 instead of 900 m^2!
- 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
- Availibility 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

Draft: Current Recommendations for Implementing Continuous Manufacturing of Solid Dosage Drug Products in Pharmeacutical Manufacturing

This document is developed in response to an FDA invitation to prepare and submit a proposal for an FDA guidance in Continuous Manufacturing, issued by Dr Janet Woodcock during the workshop on "the Future of Pharmaceutical Manufacturing" held at Rutgers University on May 7, 2015.

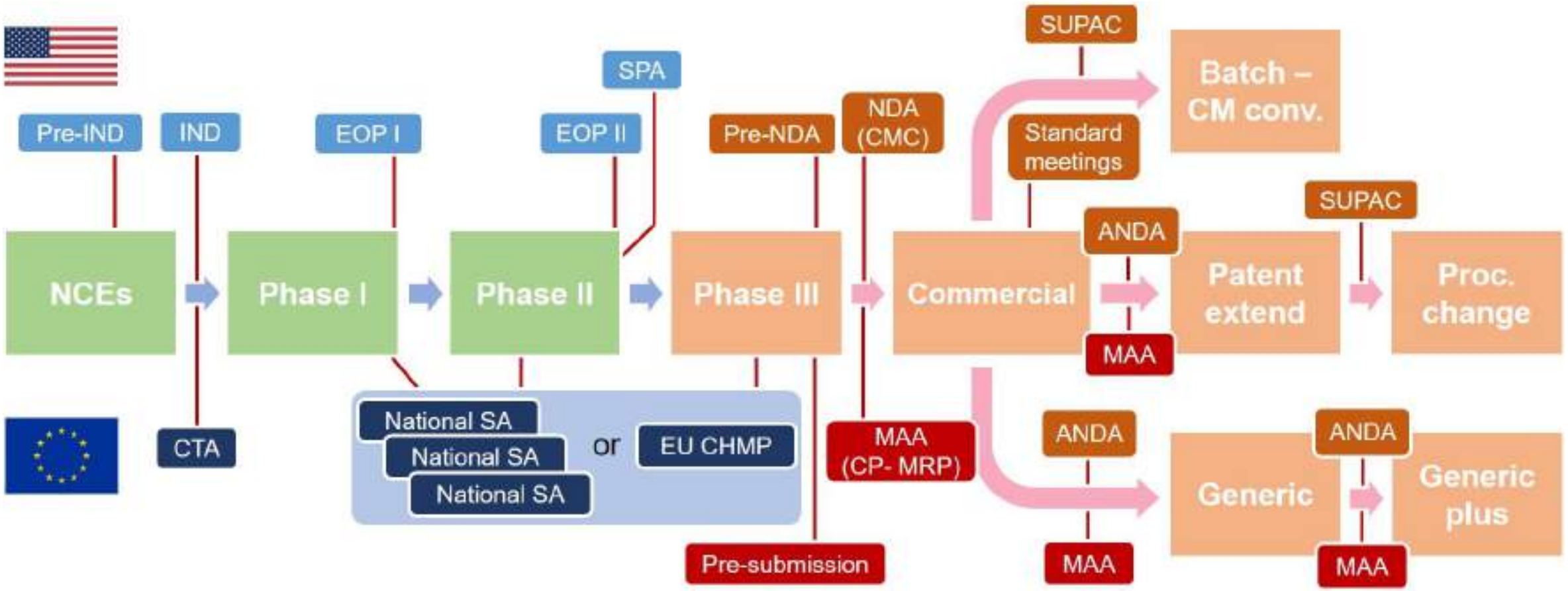
In undertaking this task, a working group convened for a series of meetings both in person and online throughout the second half of 2015. The working group was composed of representatives from more than a dozen major pharmaceutical manufacturers working on continuous processing with an open invitation for participation to all of industry. The working group split into four subgroups (Process, Sampling, Control, and Regulatory) to compose draft components. The draft presented here was merged from the subgroup draft components and has gone through a preliminary review.

At this time we are seeking comments and input from a broader pool of the industry. The group is requesting that comments and input to edits be returned to Doug.Hausner@rutgers.edu by February 12th 2015 @ 12 PM EST. You are encouraged to share this with colleagues within and outside of your organization, but we will be requesting that a single response be submitted from each corporate organization.

While this draft is circulating for comment please note that some editing work will be occurring in parallel. This will include things like ensuring that definitions for all acronyms and abbreviations are included as well as proper referencing throughout the document. Updates will be available weekly at http://tinyurl.com/CurrentRecCMD016

All inquiries should be directed to Doug.Hausner@rutgers.edu. A editable MS Word version of this document is also available in addition to this PDF.

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).

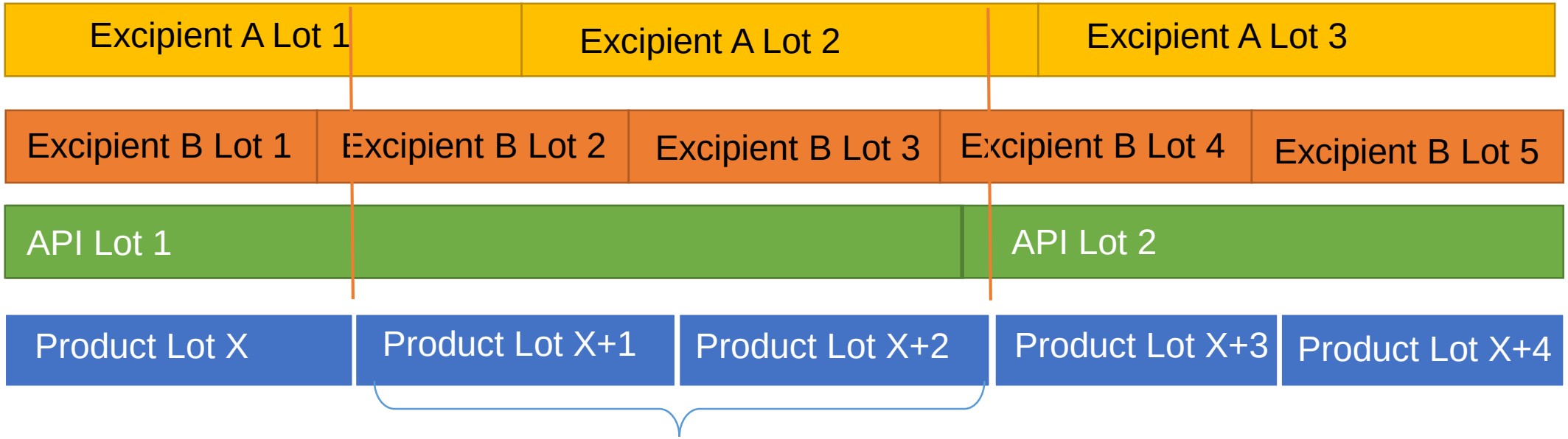
Lot

- 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

Tracebility: Bill of Materials



Batch Y

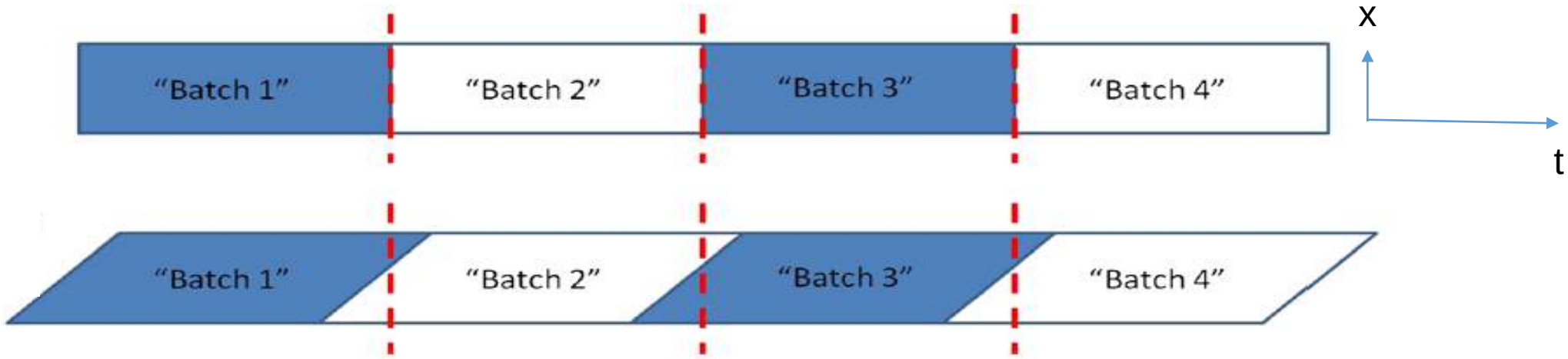
Materials from

- Excipient A Lot 1-2
- Excipient 2 Lot 2-4
- API Lot 1-2

Material Flow Through the Systen

no back mixing

with back mixing



→ need to characterize the RTD

Engisch, W. and Muzzio, F. 2016. Using Residence Time Distributions (RTDs) to Address the Traceability of Raw Materials in Continuous Pharmaceutical Manufacturing. J Pharm Innov 11: 64-81.

Residence Time Distribution (RTD)

Definition of RTD:

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)dt}$$

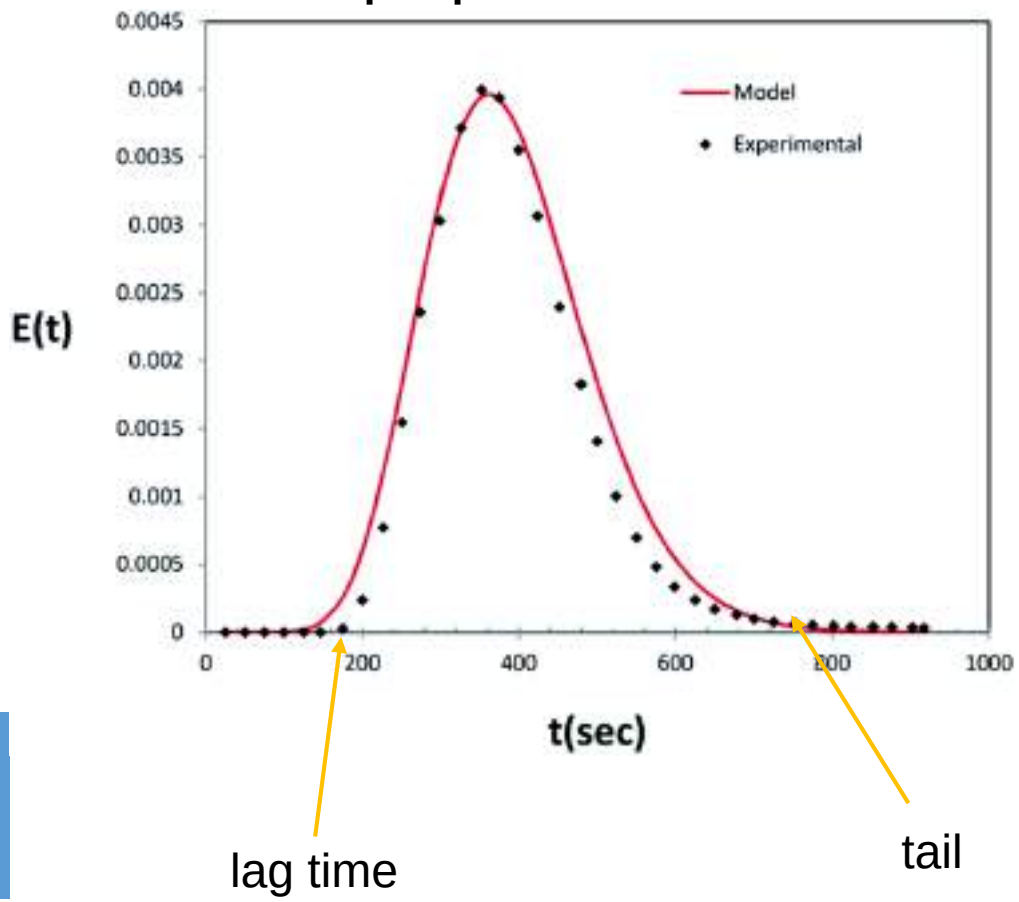
C(t) = concentration of tracer pulse

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

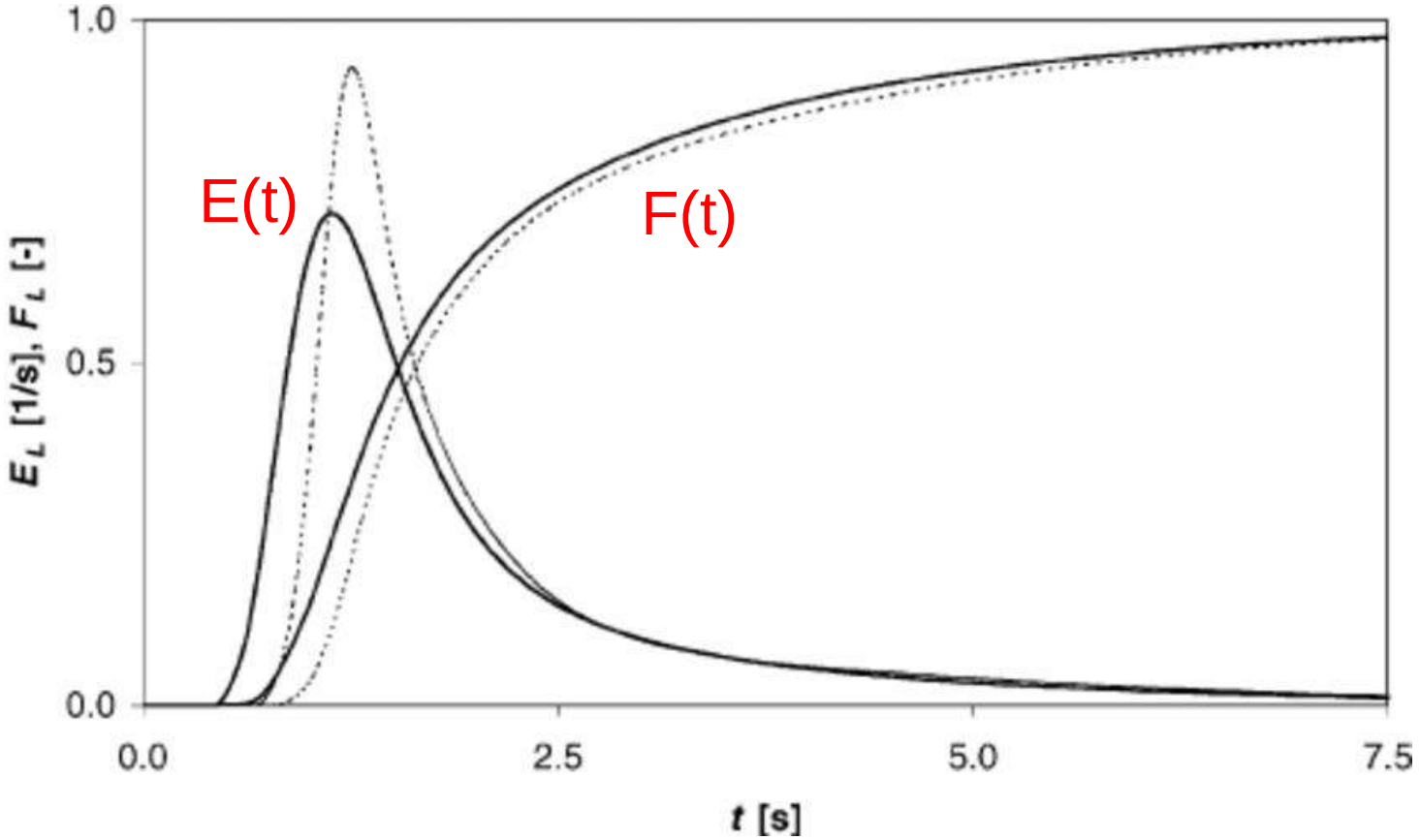
$$F(t) = \frac{C(t)}{C_{tracer}}$$

$$F(t) = \int_0^t E(t)dt$$

Example: powder blender



RTD and Cummulative RTD



- 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:

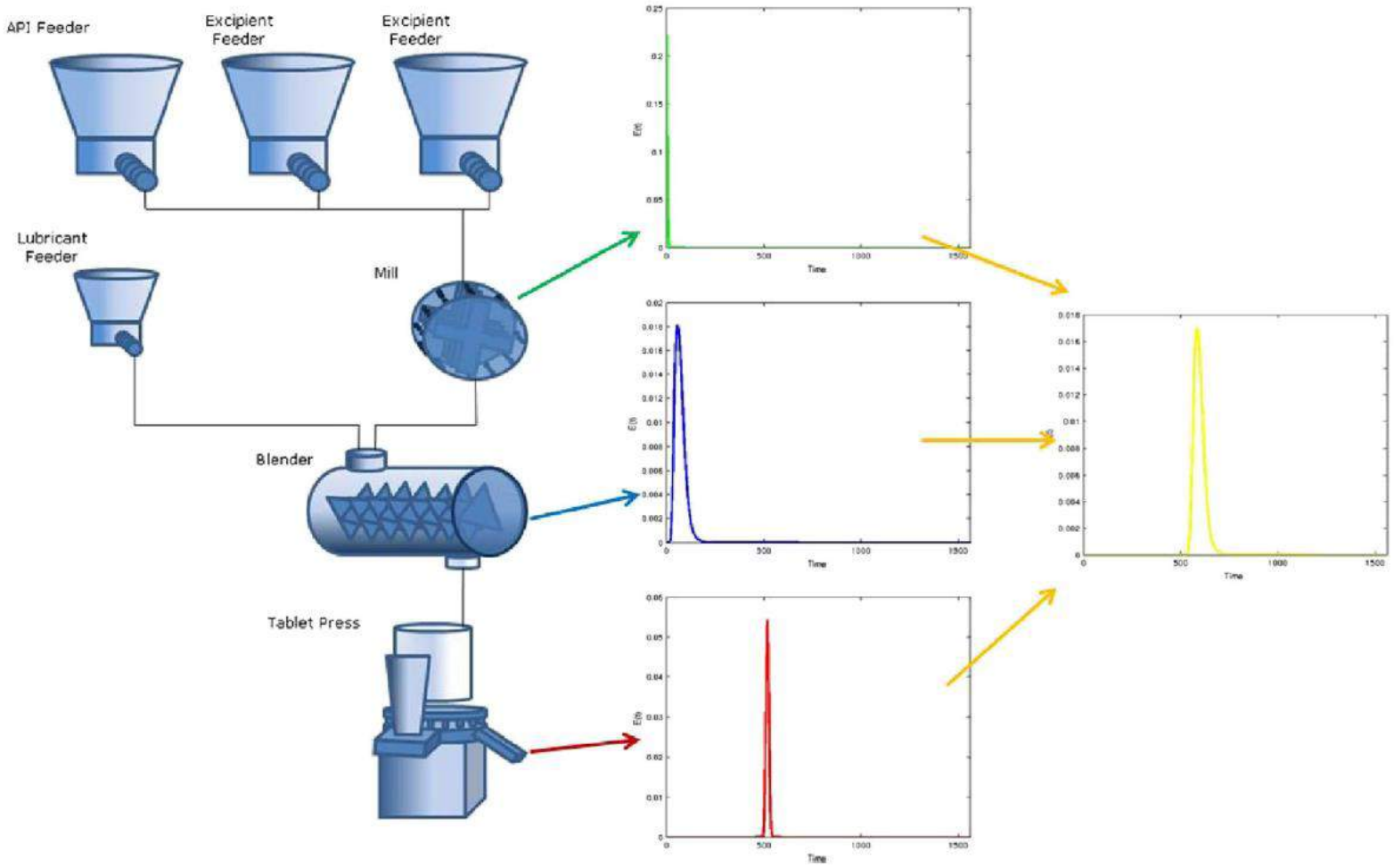
$$(E_1 * E_2)(t) = \int_{-\infty}^{\infty} E_1(\tau) E_2(t-\tau) d\tau$$

E_i: RTD of unit operation i

- 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.

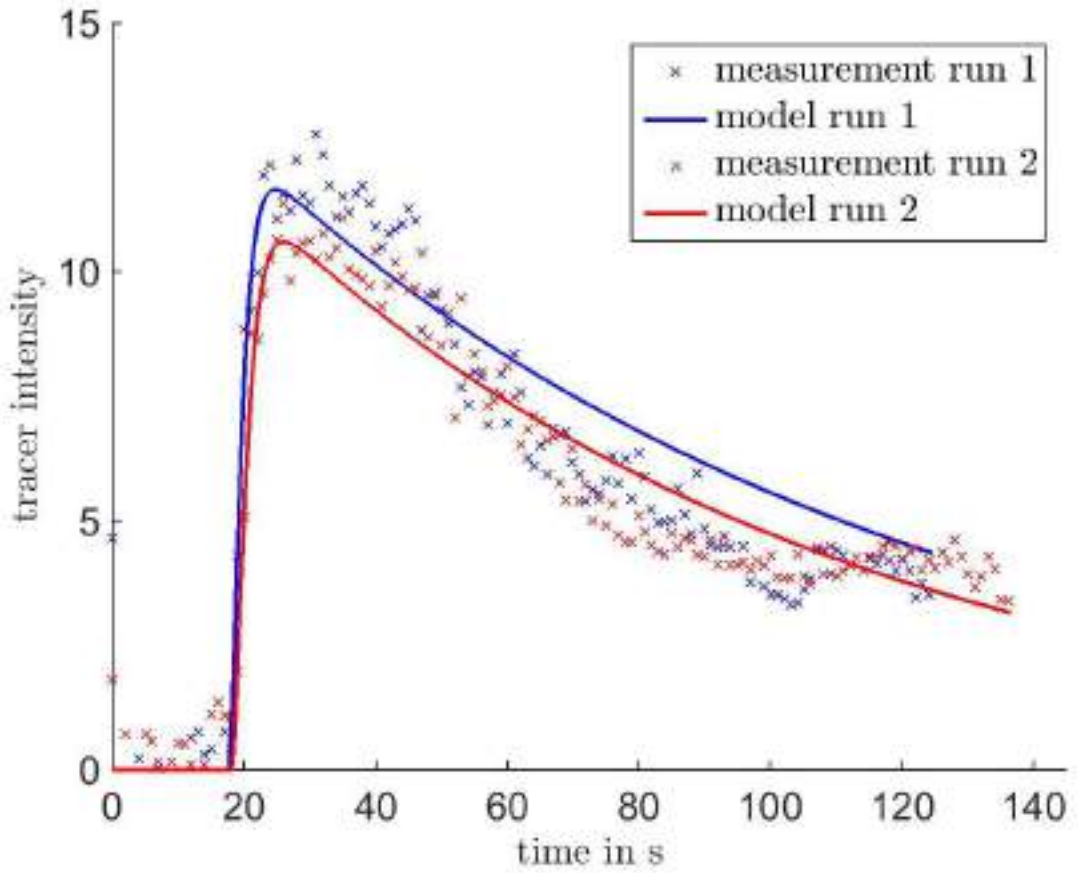
Convolution of RTDs

Example DC line:

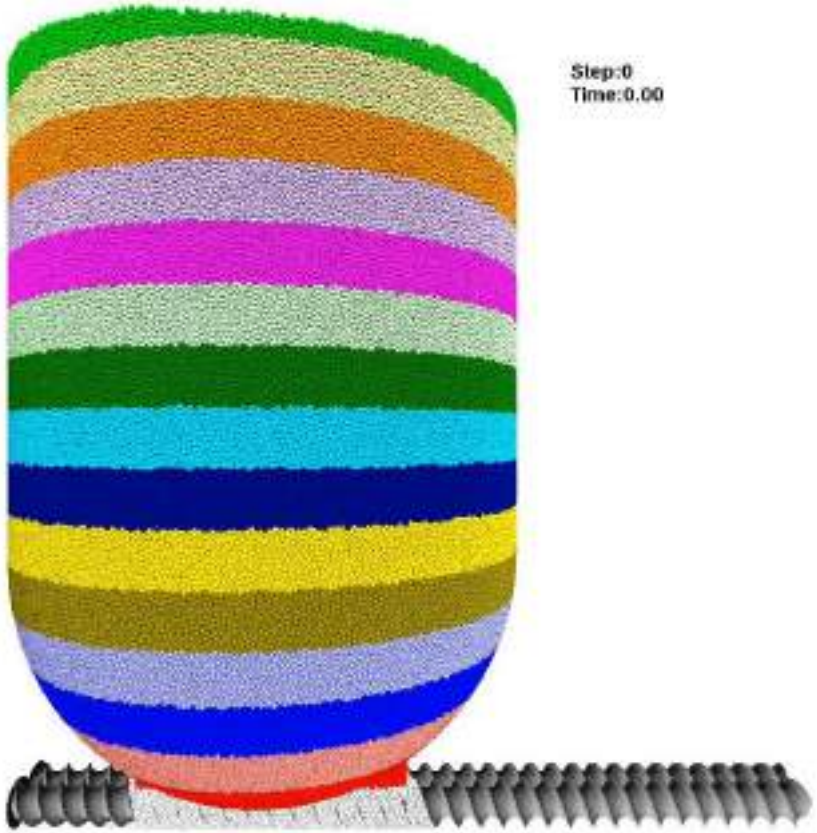


Engisch, W. and Muzzio, F. 2016. Using Residence Time Distributions (RTDs) to Address the Traceability of Raw Materials in Continuous Pharmaceutical Manufacturing. J Pharm Innov 11: 64-81.

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

- $\bar{t}$ = mean residence time

$$\bar{t} = \frac{\sum_i t_i c_i \Delta t_i}{\sum_i c_i \Delta t_i}$$

- 2σ = broadness of probability distribution

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

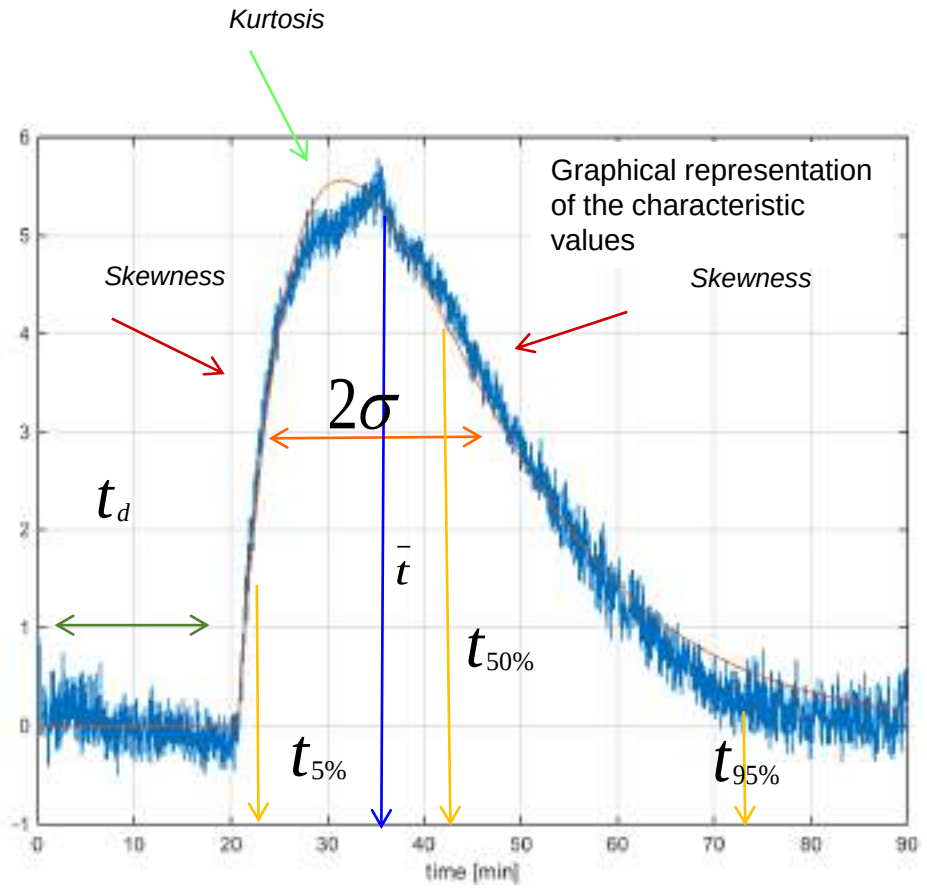
- Skewness = asymmetry of probability distribution

$$Skewness = \frac{\sum_i (t_i - \bar{t})^3 E(t) \Delta t_i}{\left(\sum_i (t_i - \bar{t})^2 E(t) \Delta t_i\right)^{3/2}}$$

- Kurtosis = pointedness

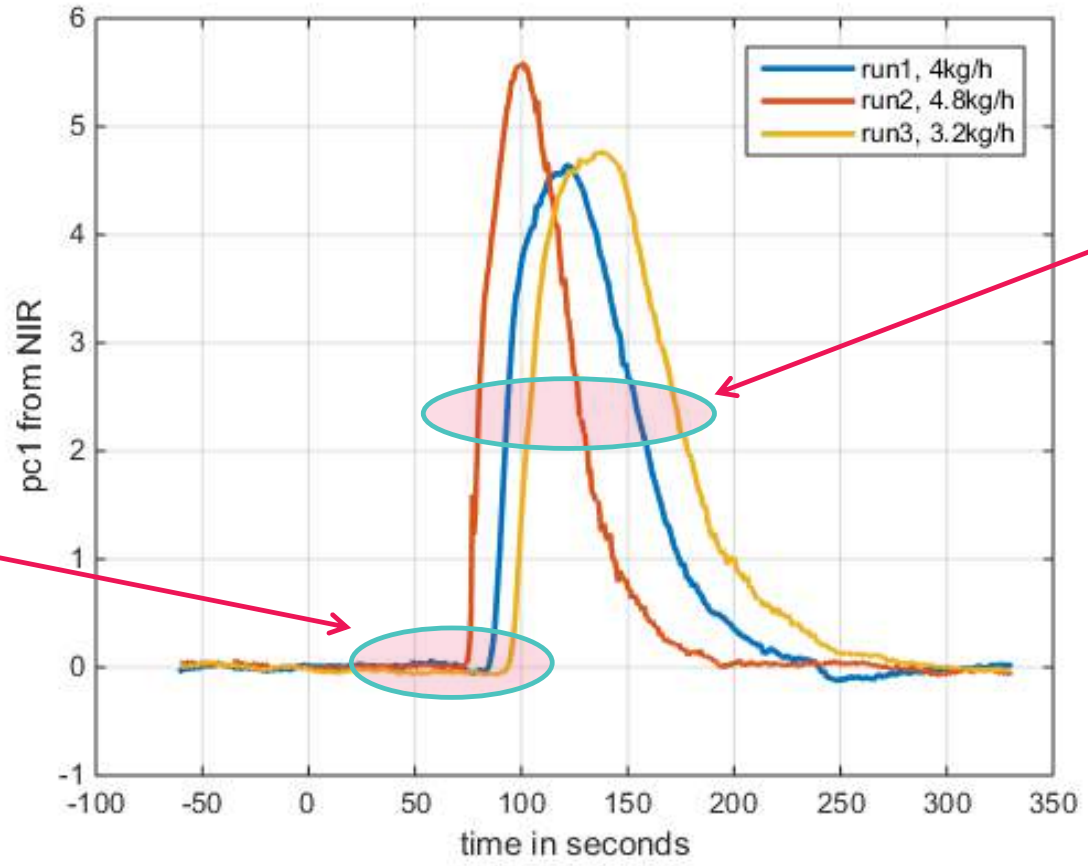
$$Kurtosis = \frac{\sum_{i=1}^{N} \frac{(t_i - \bar{t})^4}{N}}{\sigma^4}$$

- $t_{X\%}$ = time at which specific concentration X is reached
- t_D = dead time, delay



Example: HME Various Mass Flow Rates

large dead time
for low mass flow



"broad" RTD
for low mass flow

RTD Model Fit

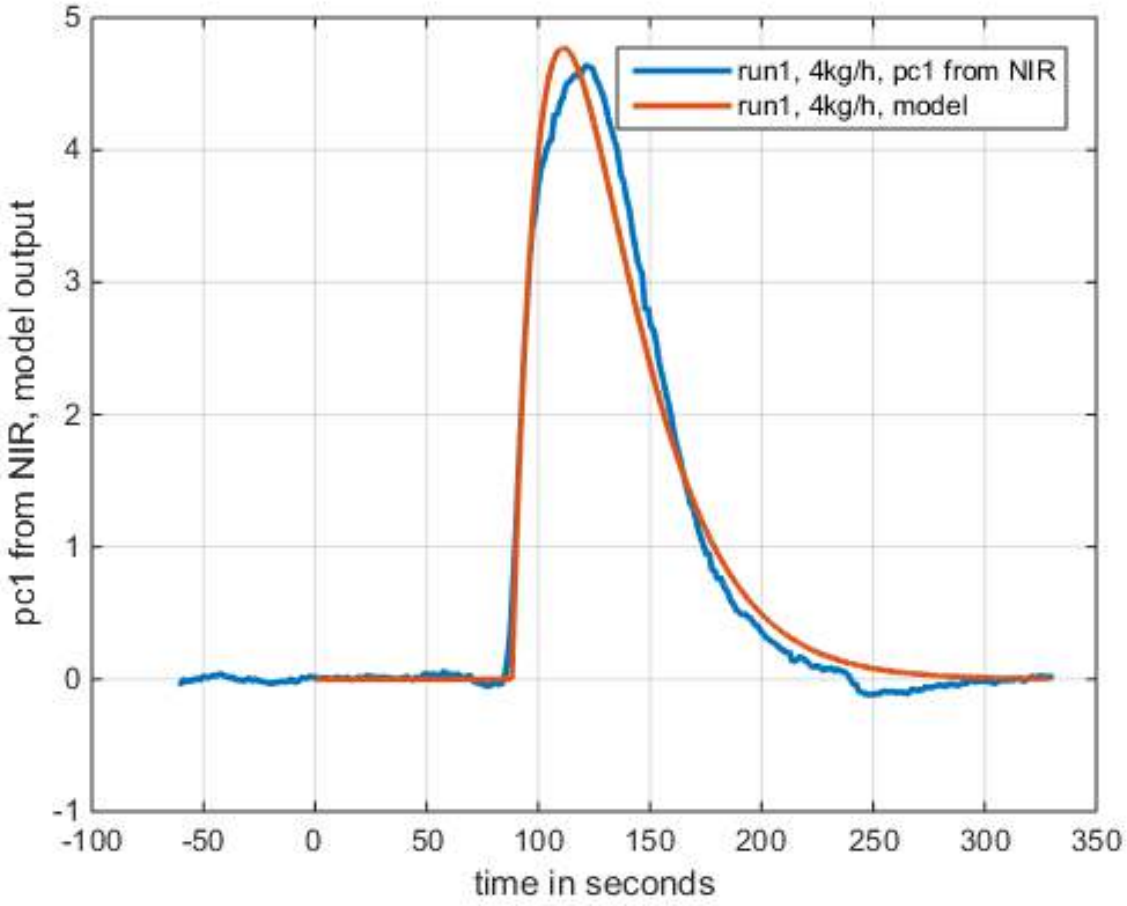
- Model: $P(s) = \frac{\bar{y}(s)}{\bar{u}(s)} = \frac{k}{(1+sT)^2} e^{-sT_t}$
  - $P(s)$ … transfer function
  - $y(t)$ …system output, time domain
  - $u(t)$ … system input, time domain
  - $\bar{y}(s)$ … system output, Laplace domain
  - $\bar{u}(s)$ … system input, Laplace domain
  - k … gain
  -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

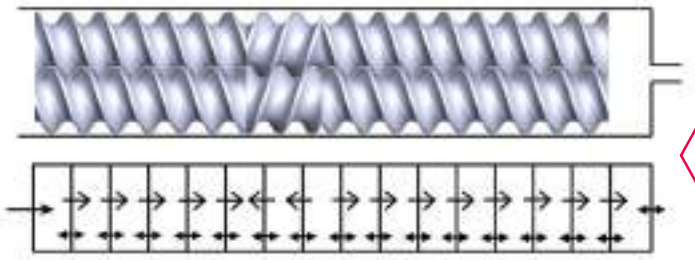
Example: Model vs. Tracer measurements

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



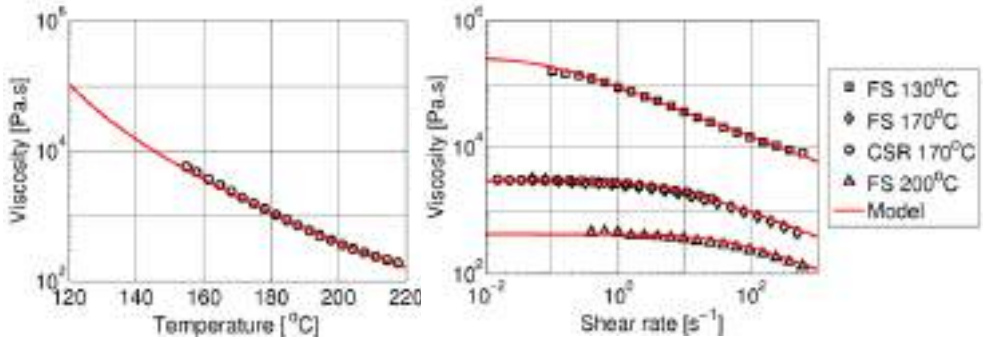
RTD via Modeling: Extruder Modeling Strategy

1D-Simulation for Process Control



profiles of process variables along the screw axis

Material Properties

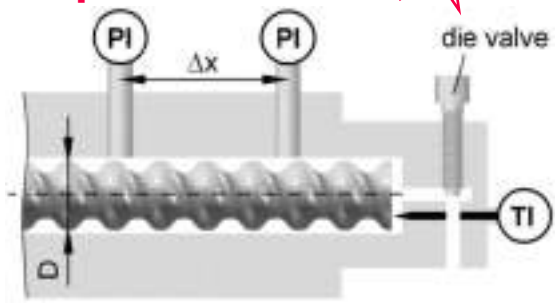


input parameters

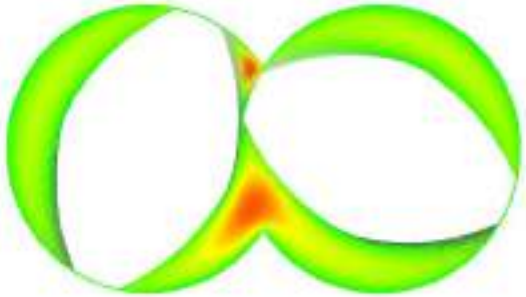
1D Screw Parameters

characterization of screw elements

Experiments



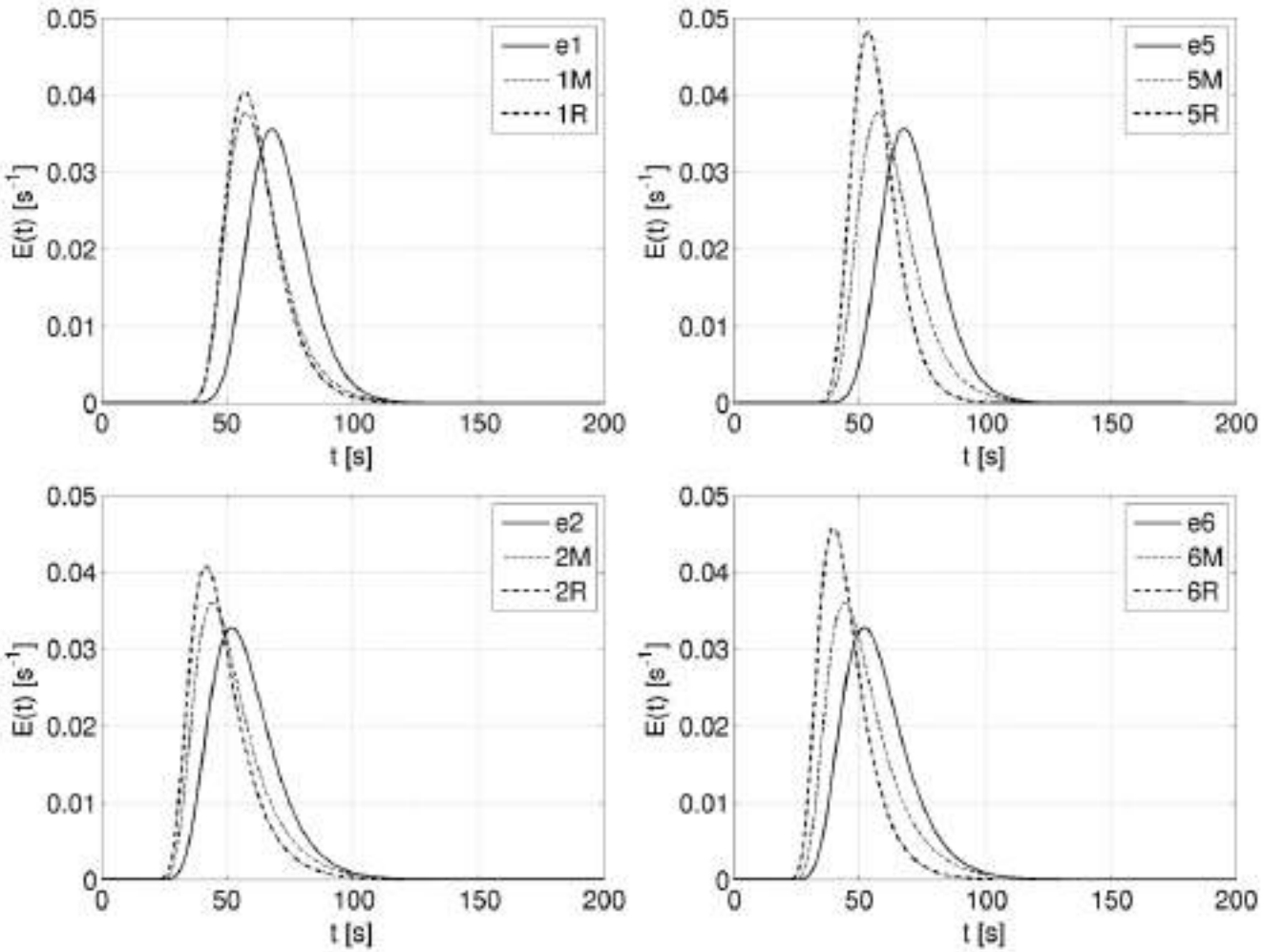
3D-Simulation (SPH)



LIGGGHTS

for model validation and screw characterization

Computed RTD – Example ZSK18 vs. Pharma 16



ZSK18

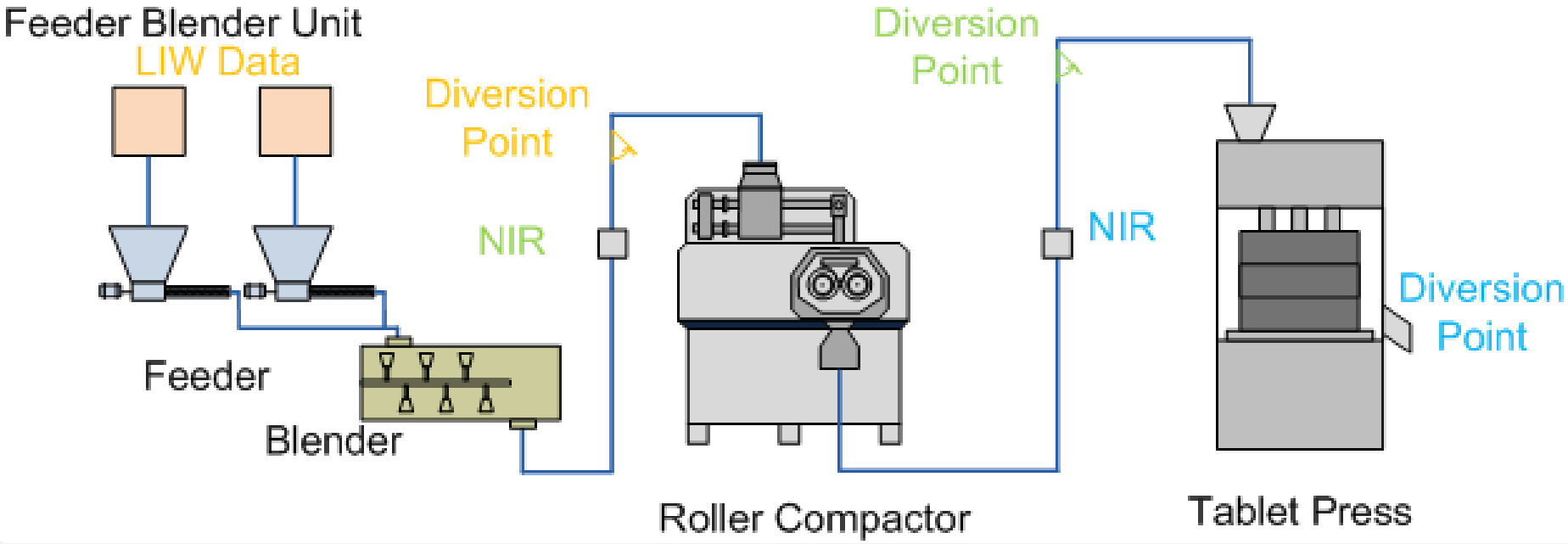
Exp.	n	ṁ	Temperature profile	$SMEC_{exp}$	$SMEC_{1D}$
	[rpm]	[kg/h]	[°C]	[kWh/kg]	[kWh/kg]
e_1	120	2	60/80/100/100/100/110/110/110/110/120	0.184	0.133
e_2	200			0.285	0.230
e_3	600			0.855	0.790
e_4	1000			1.267	1.425
e_5	120	2	60/80/115/115/115/125/125/125/125/135	0.120	0.116
e_6	200			0.214	0.199
e_7	600			0.736	0.685
e_8	1000			1.188	1.239
e_9	120	2	60/80/130/130/130/140/140/140/140/150	0.076	0.097
e_{10}	200			0.150	0.167
e_{11}	600			0.594	0.578
e_{12}	1000			1.069	1.051

Pharma16

Exp.	n	ṁ	Barrel temperature profile	$SMEC_{exp}$	$SMEC_{1D}$
	[rpm]	[kg/h]	[°C]	[kWh/kg]	[kWh/kg]
1M	145	1.6	60/80/100/100/100/110/110/110/110/120	0.154	0.140
2M	240	1.6		0.239	0.241
1R	140	1.7		0.139	0.129
2R	240	1.8		0.209	0.218
5M	145	1.6	60/80/115/115/115/125/125/125/125/135	0.102	0.121
6M	240	1.6		0.186	0.208
5R	140	2		0.088	0.099
6R	240	2		0.159	0.173

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)

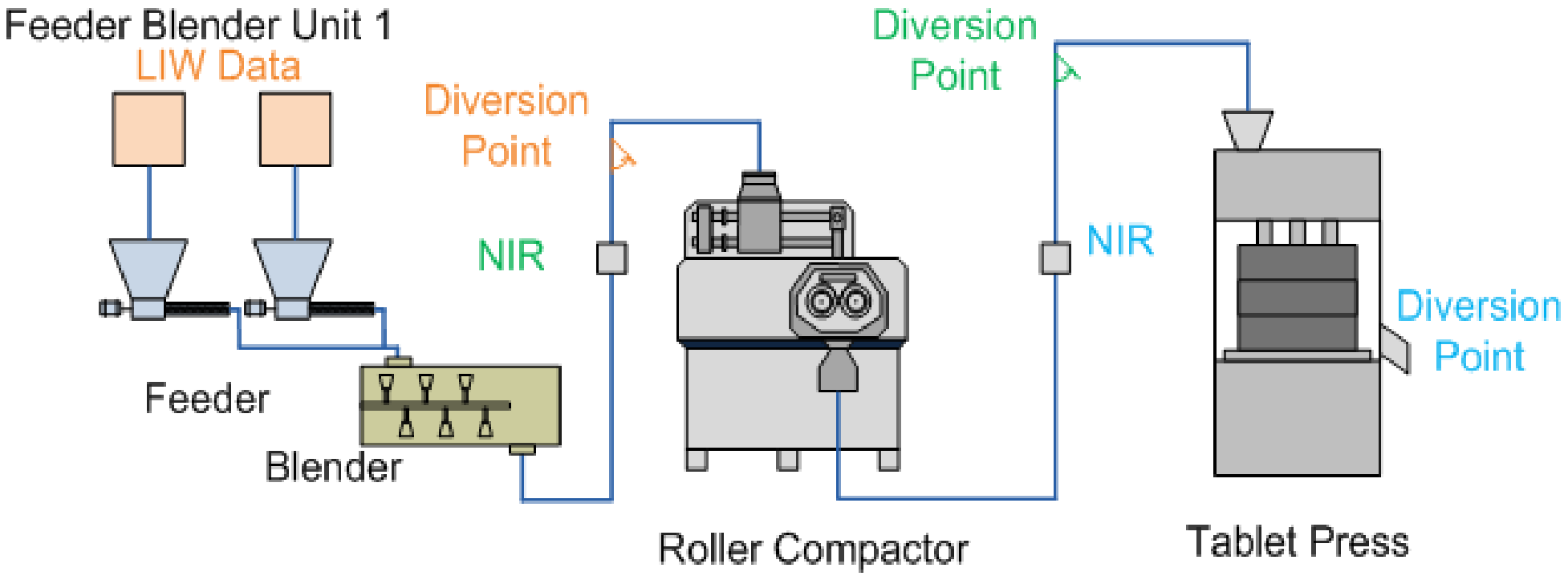
- Propagation of a disturbance between extraction points in the system are important to justify the amount of material at risk due to OOS event
- Process dynamics, steady-state RTD and dynamic RTD (i.e., during process changes, start/shut-down, during campaing processing, back-to-back batches) need to 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.

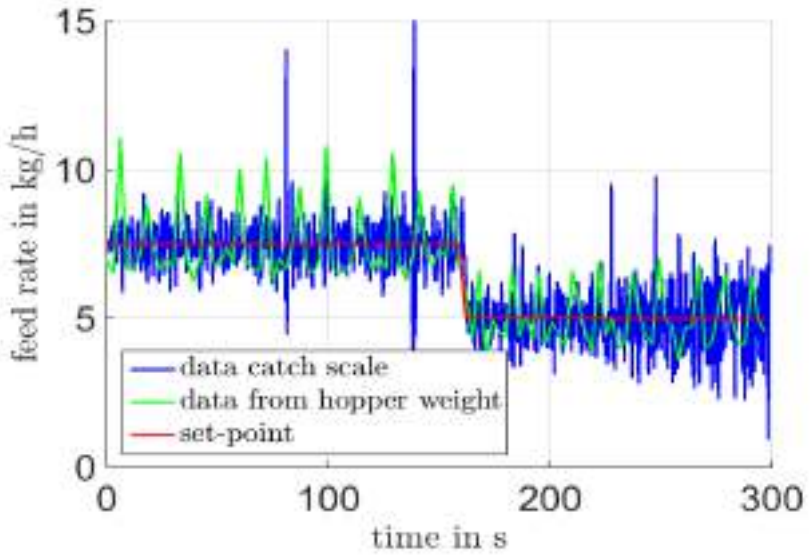
Filterability of a Process

Example: Dry Granulation (Roller Compactor) Line

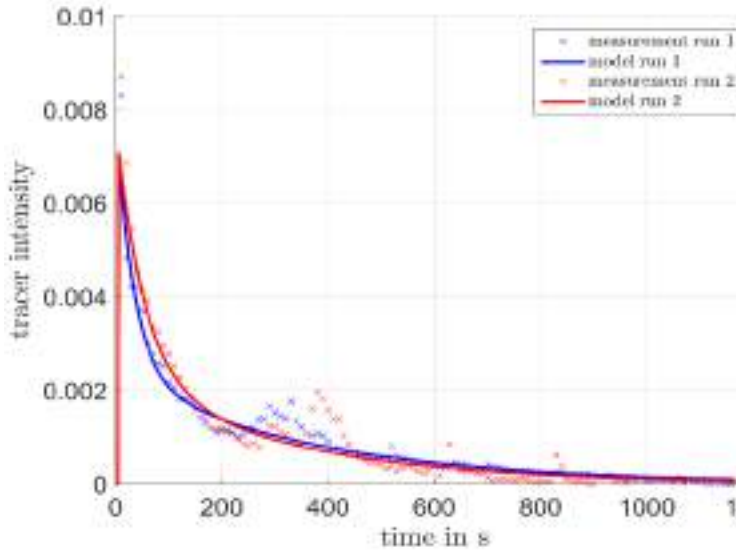


Filterability of a Process

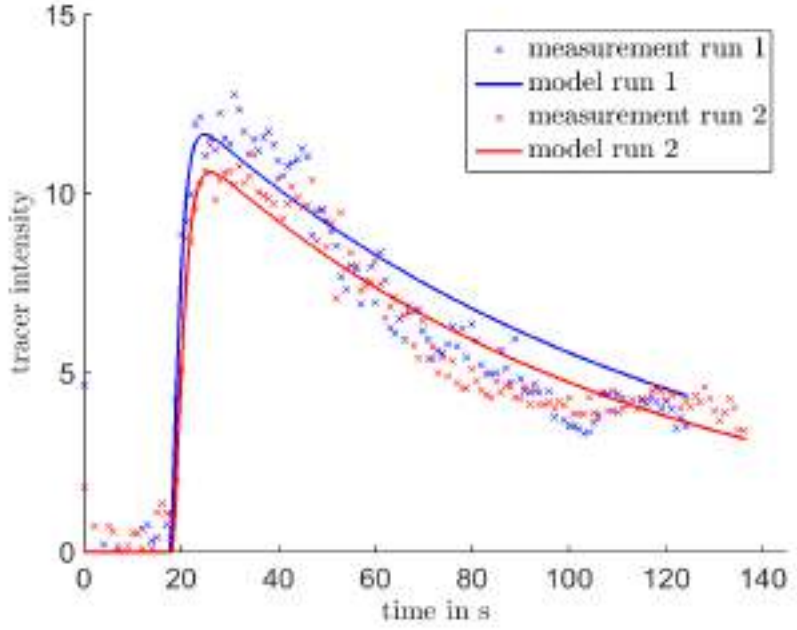
Example: Dry Granulation (Roller Compactor) Line



Feeder characterization



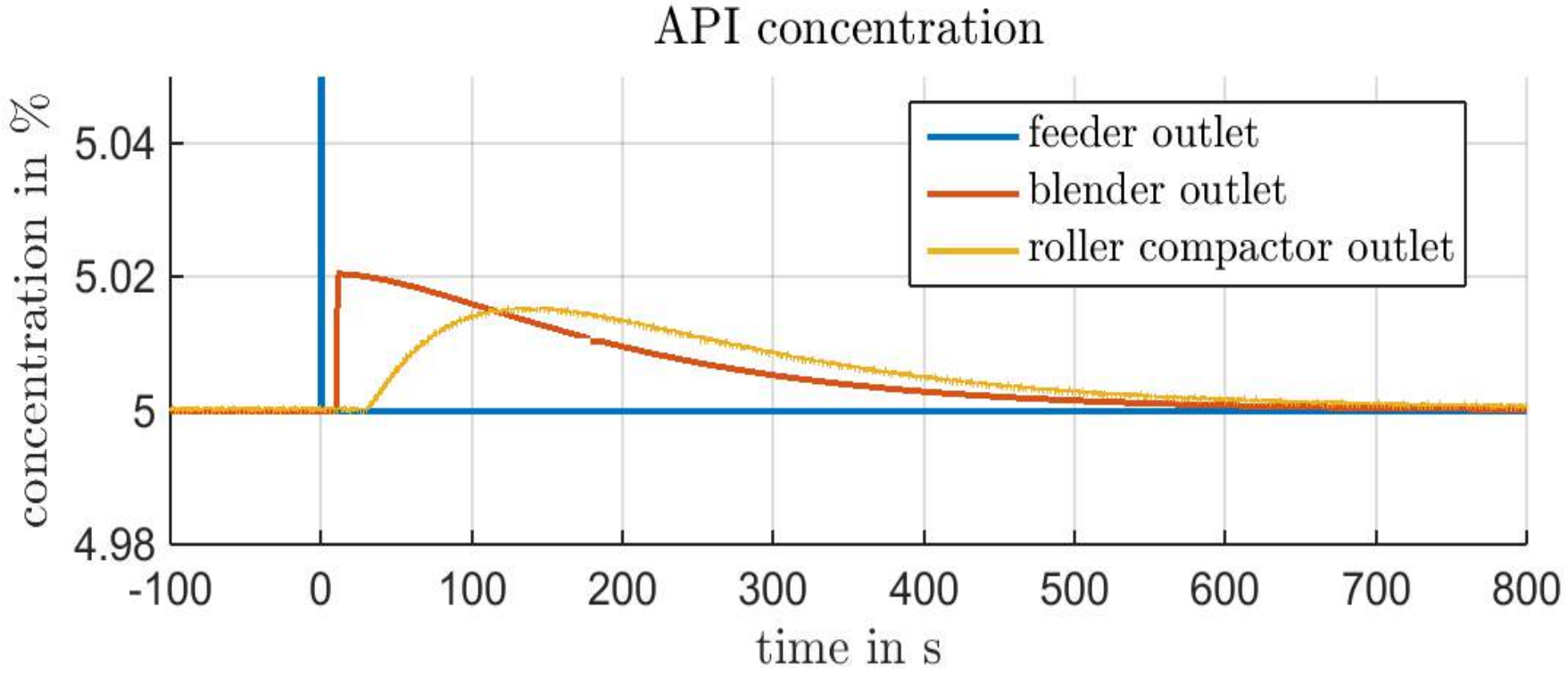
RTD Blender



RTD Roller Compactor

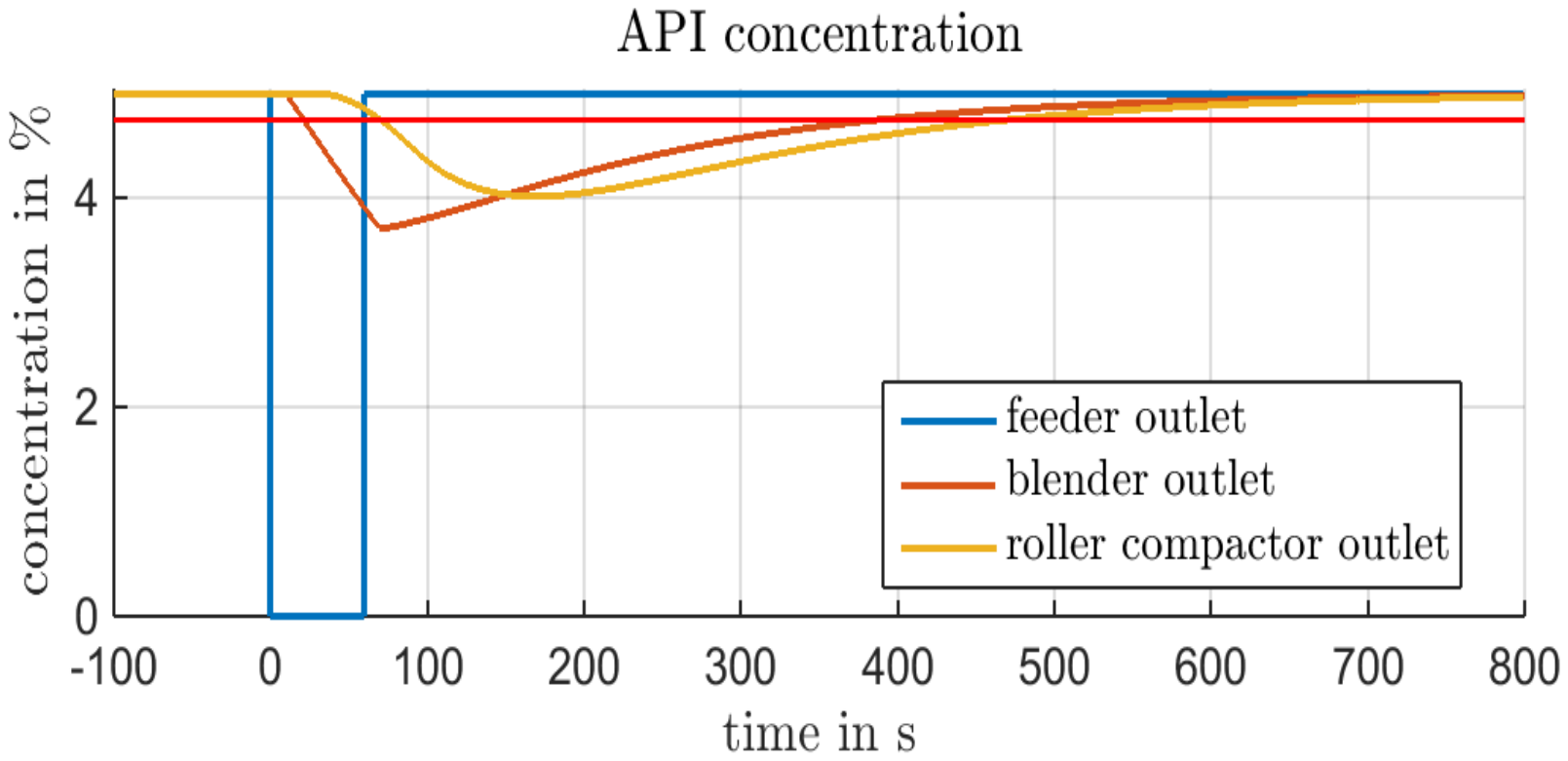
Filterability of a Process

Impact of a Pulse Function of the API Feeder



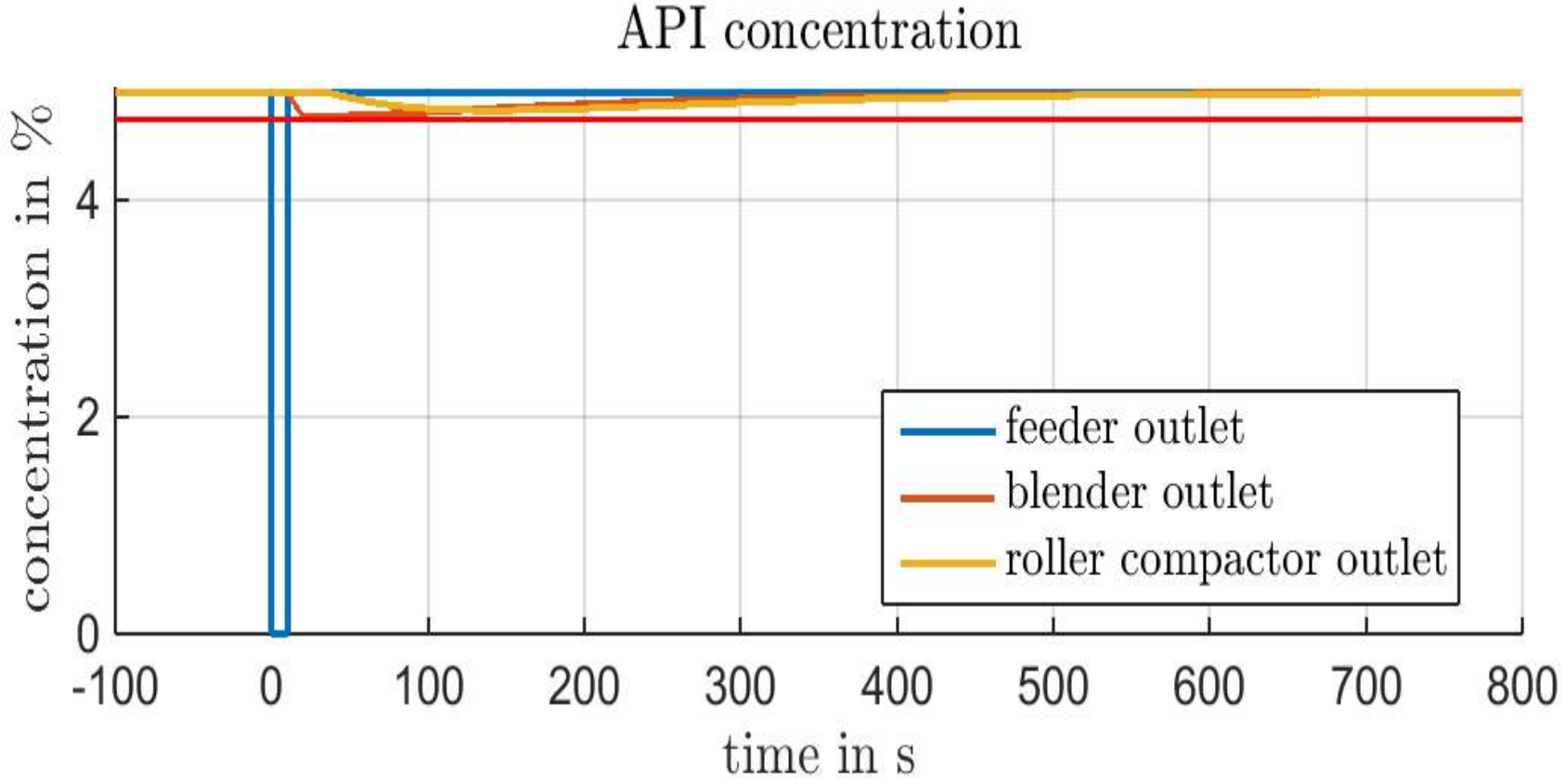
Filterability of a Process

Impact of API feeder interruption 1 min



Filterability of a Process

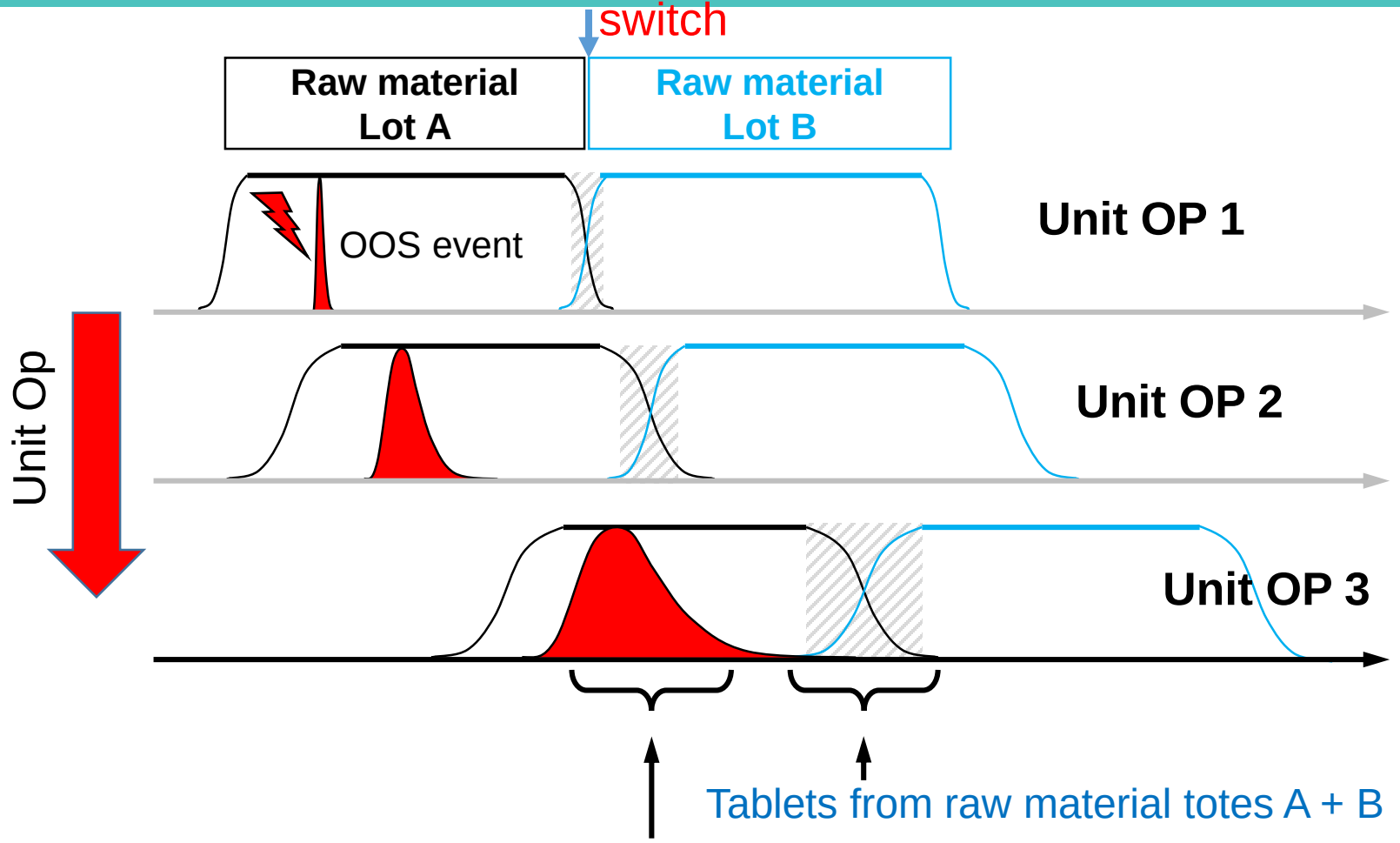
Impact of API feeder interruption for 10 sec



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)

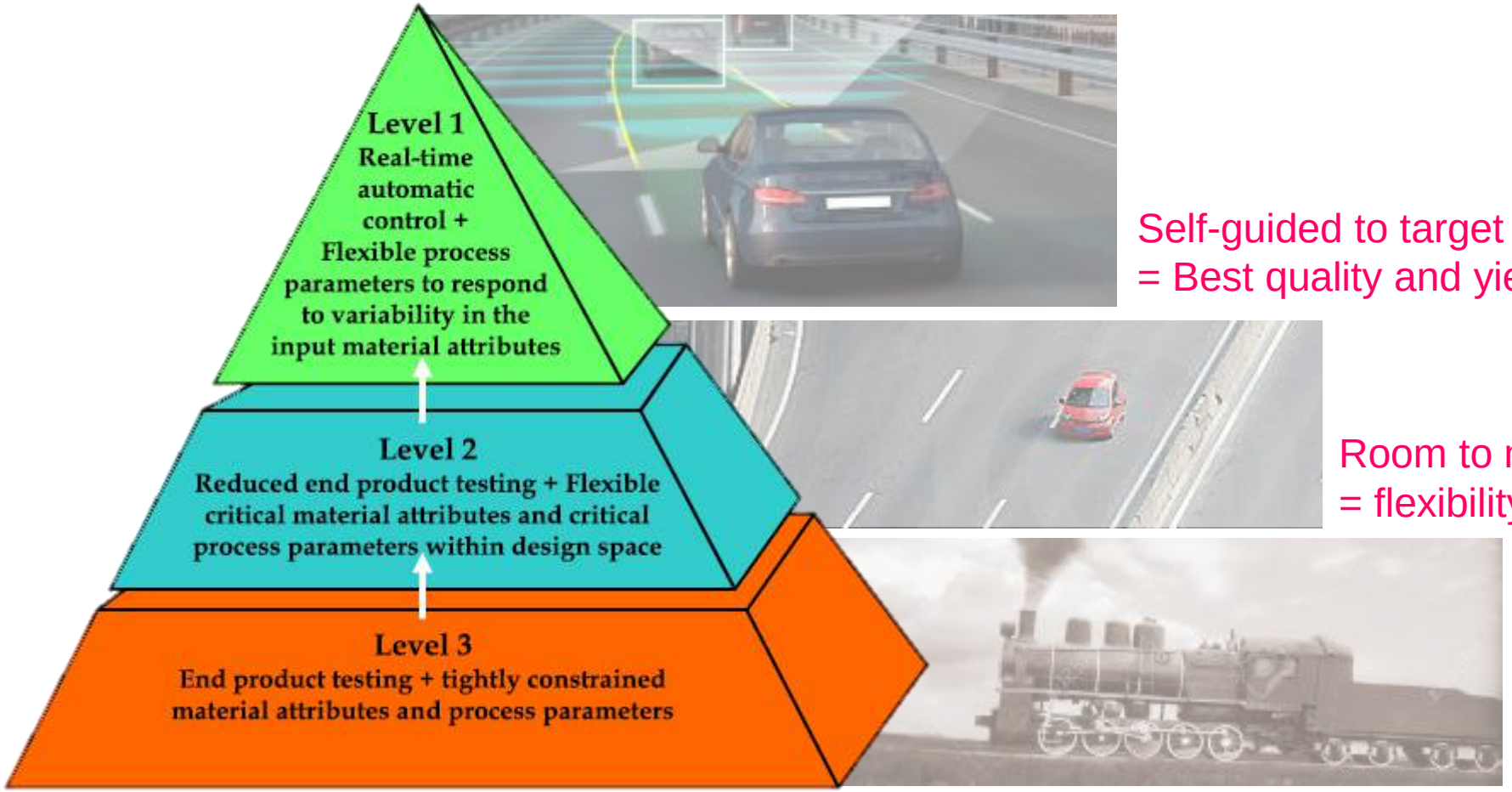
Summary: Understanding of RTD



Application of RTD

- Understanding the backmixing of material (incl. deadzones, etc.)
- Tracking material back to orginal 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)

CM Control Strategy Options



Self-guided to target
= Best quality and yield

Room to manoeuvre within the set limits
= flexibility to adapt

Fixed aims and approach
= minimal flexibility

Yu, L.X. et al. 2014. Understanding Pharmaceutical Quality by Design. AAPS 16(4): 771-783.

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.

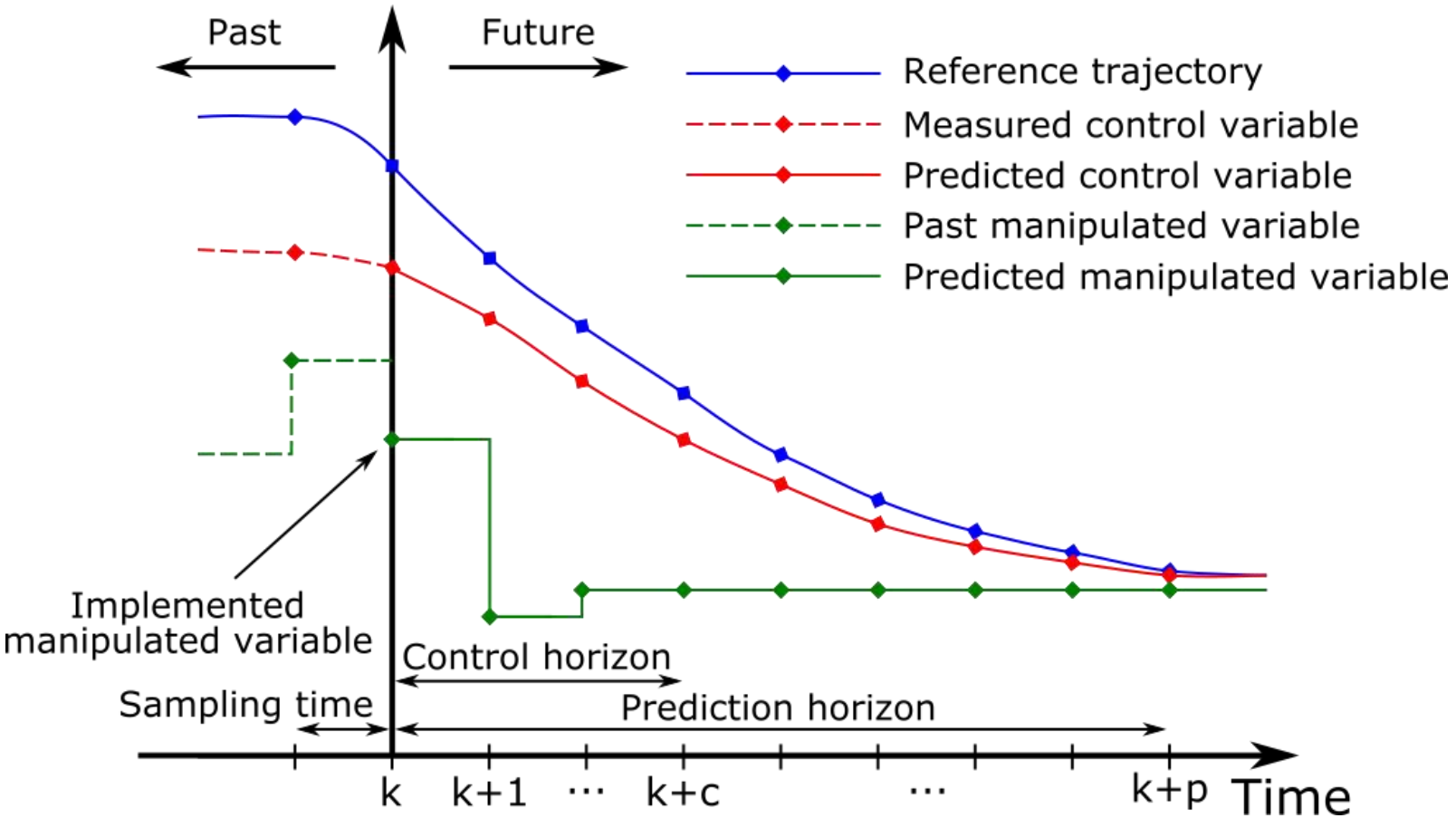
Level 3 – Process Unit
Represents the process at the most detailed level. Separate considerations for every involved unit.

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.)



Types of Models

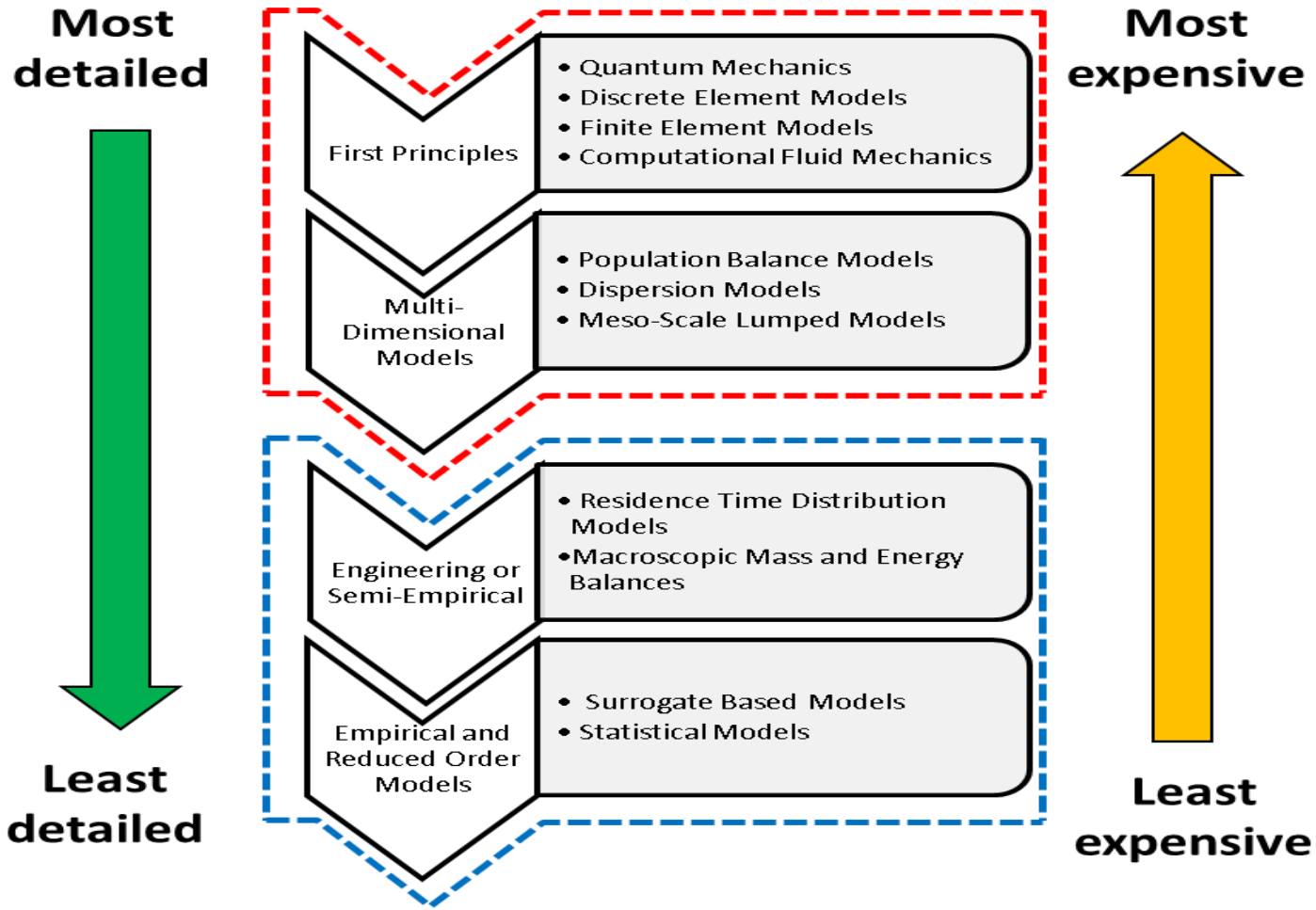
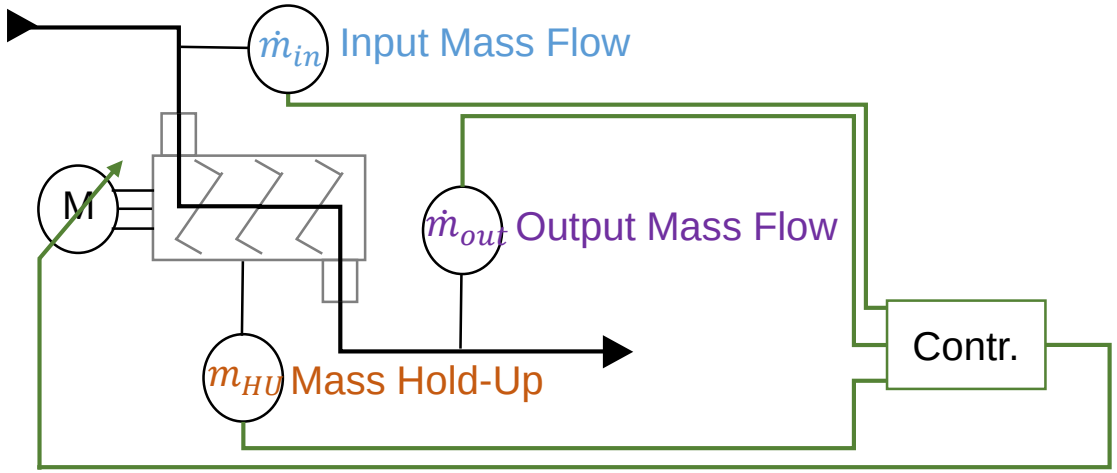
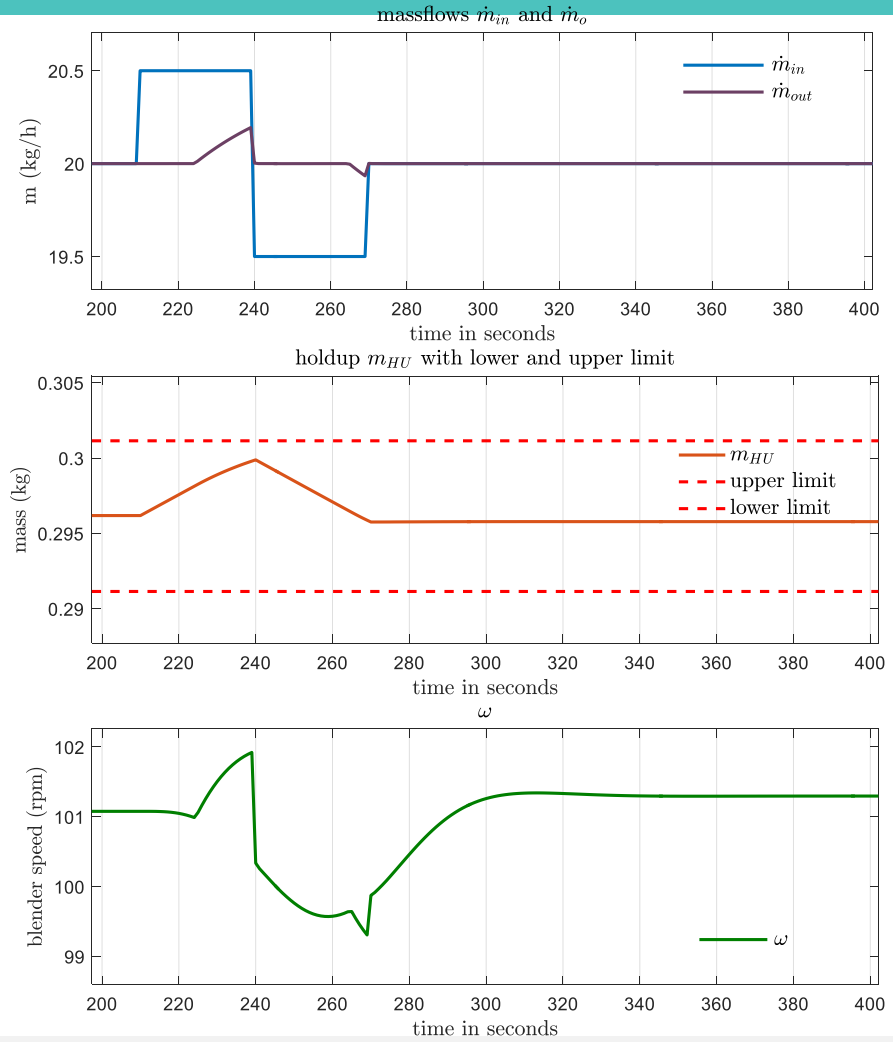


Figure courtesy Ierapetritou group at Rutgers University

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 ω 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

(granular & fluidized systems)

SPH

(extruders, melts, mixing)

PowCom

(tableting, compaction)

Model simplification

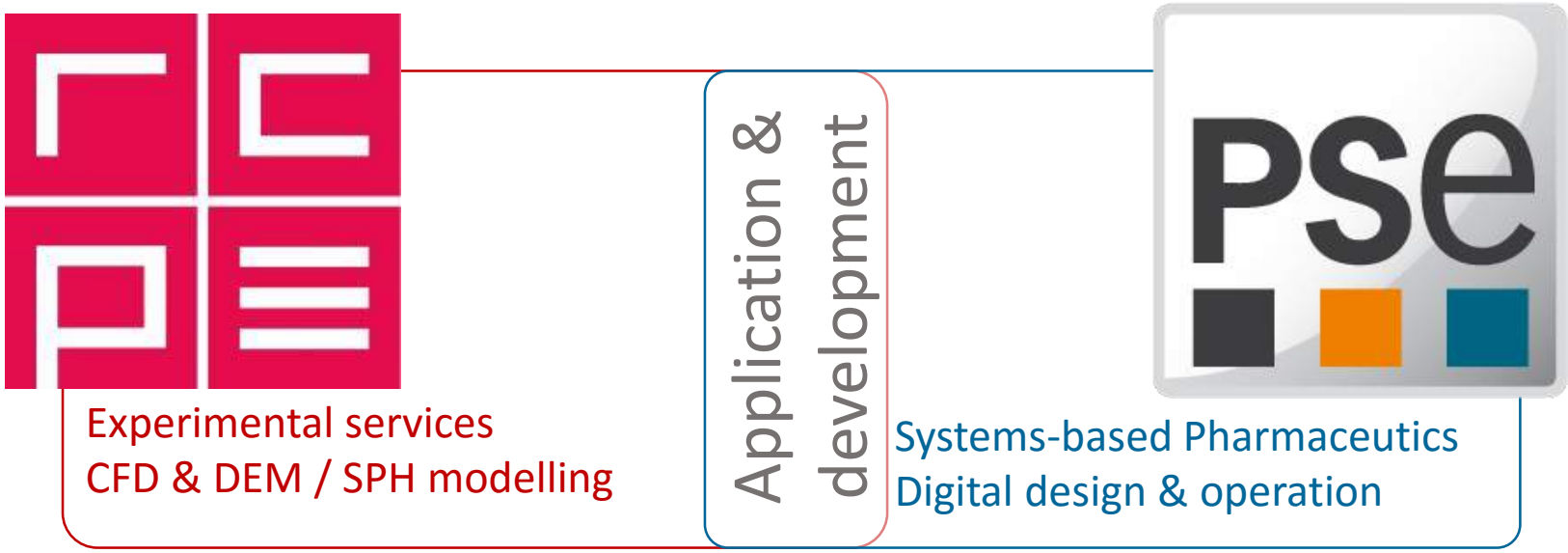
Fast control models

- Fluid bed granulator
- Fluid bed dryer
- Fluid bed coater
- GEA coater
- Drum coaters
- Hot-melt extruder
- Wet extruder
- Tableting
- Blenders/hoppers/feeders

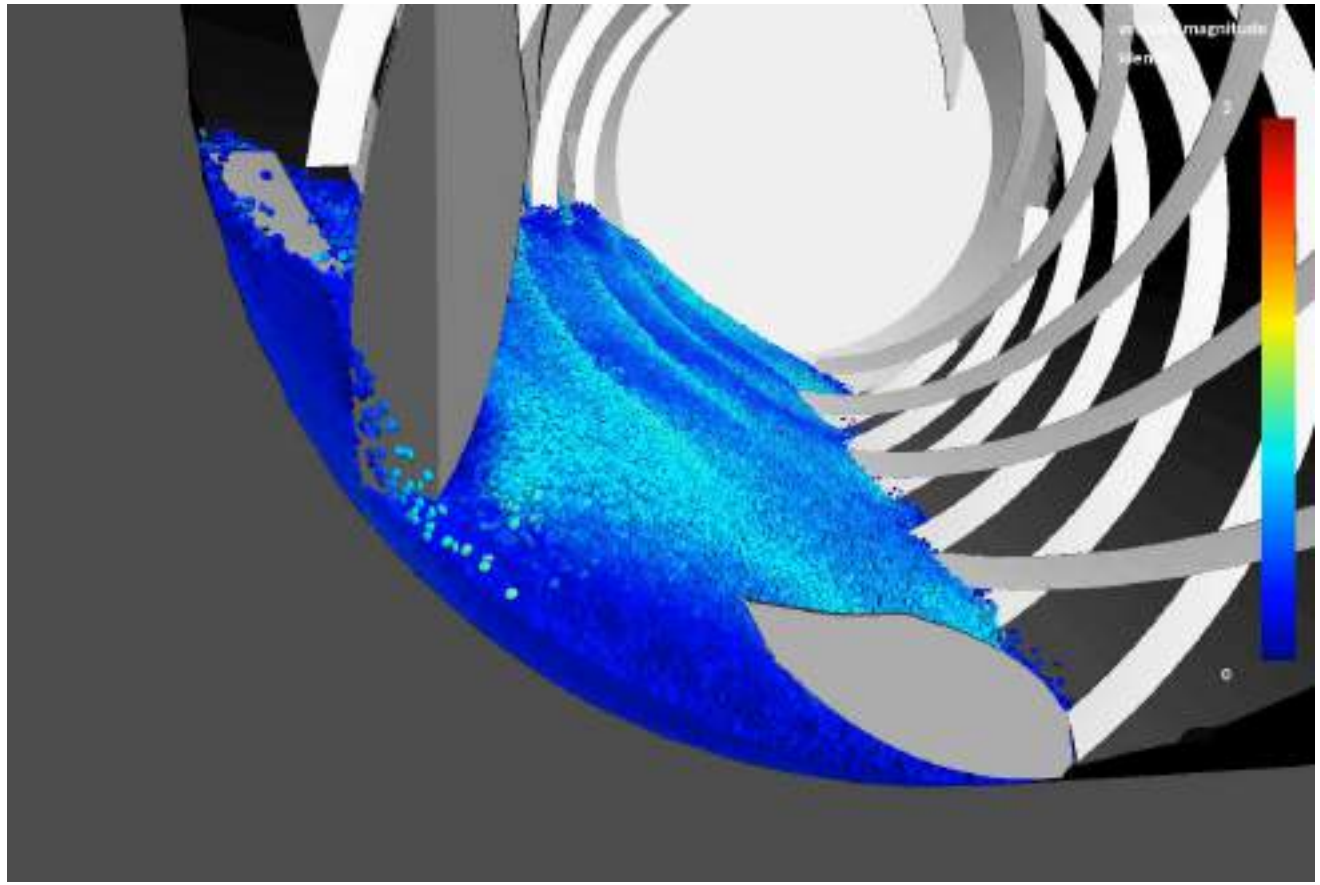
gSOLIDS

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

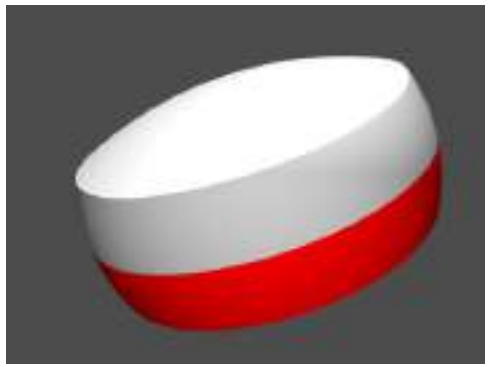


True-Shape DEM

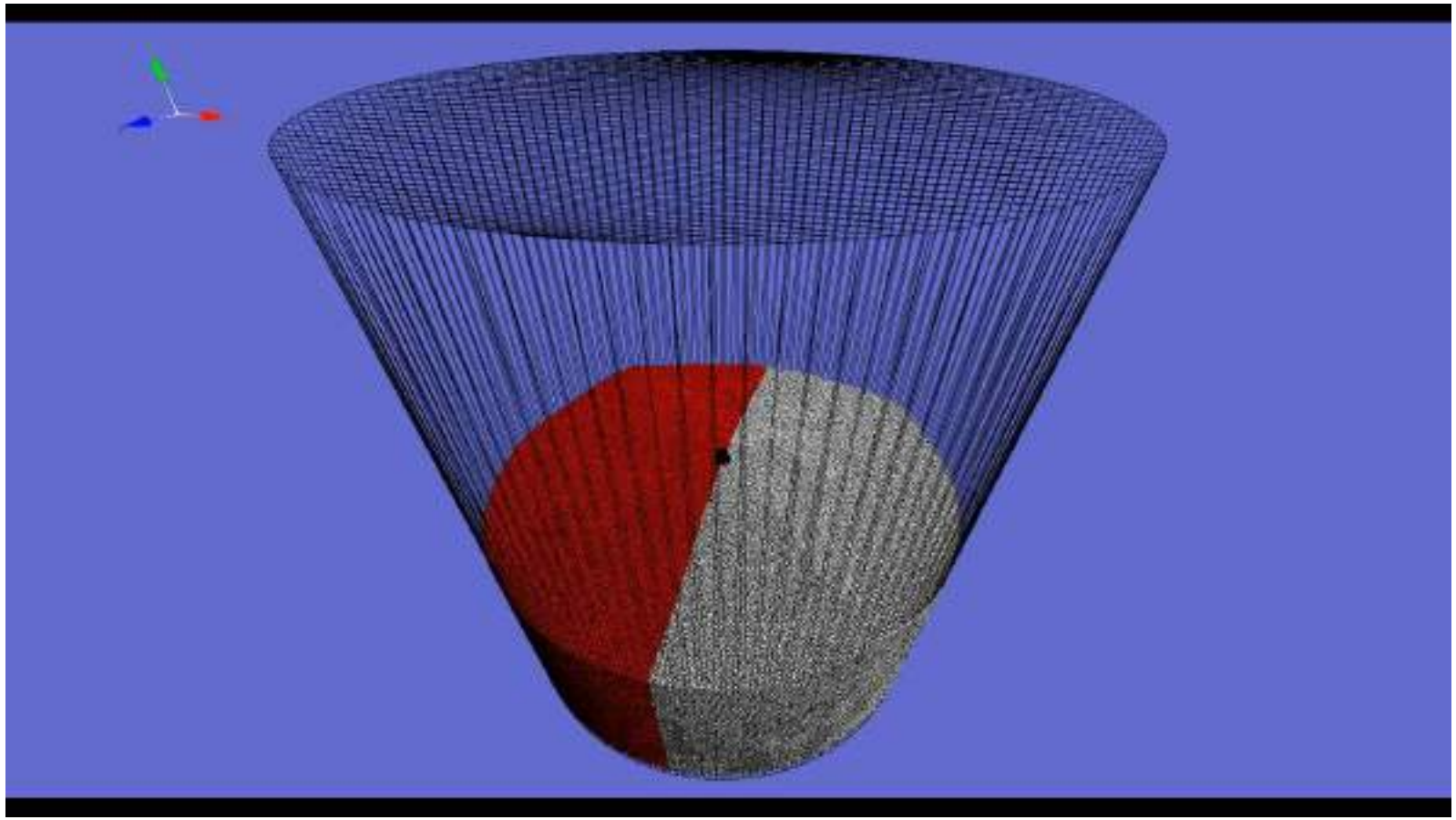


Included:

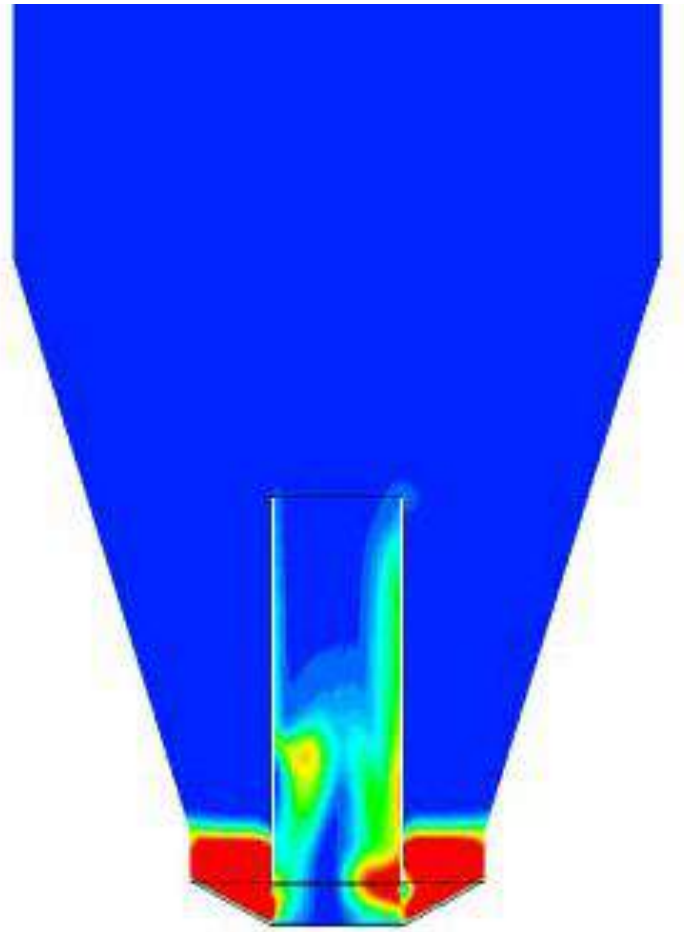
- 1.8 Mio TS objects
- 500 kg total mass
- 5 fan-shaped sprays
- Convective heat
- Conductive heat
- Spray cooling



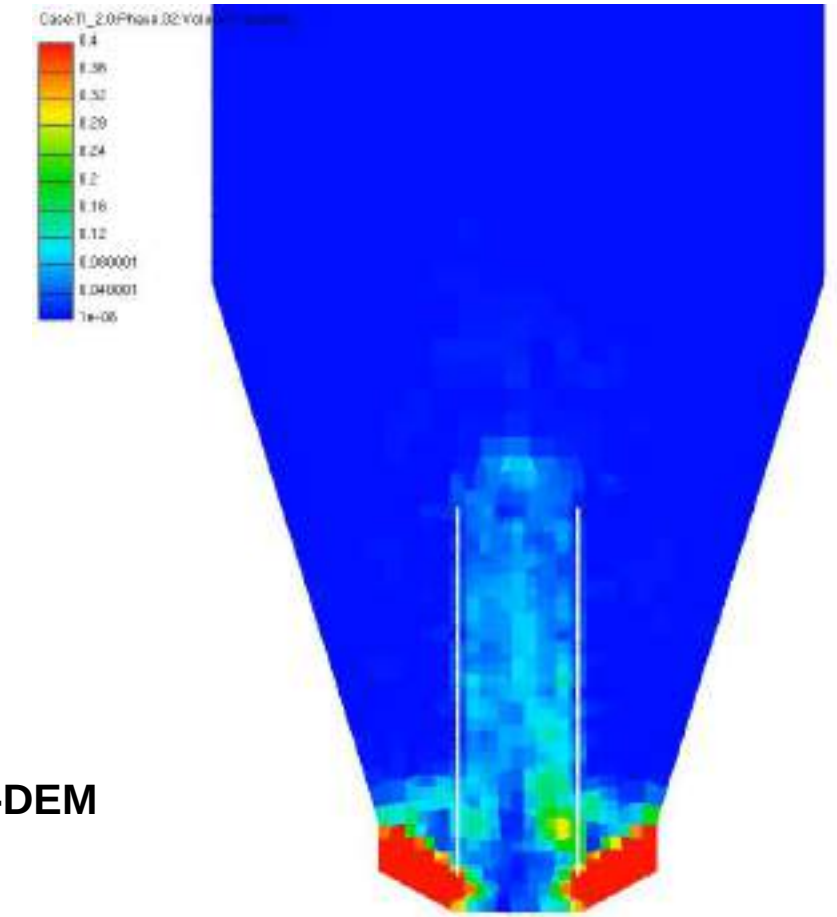
Fluid Bed Coater



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

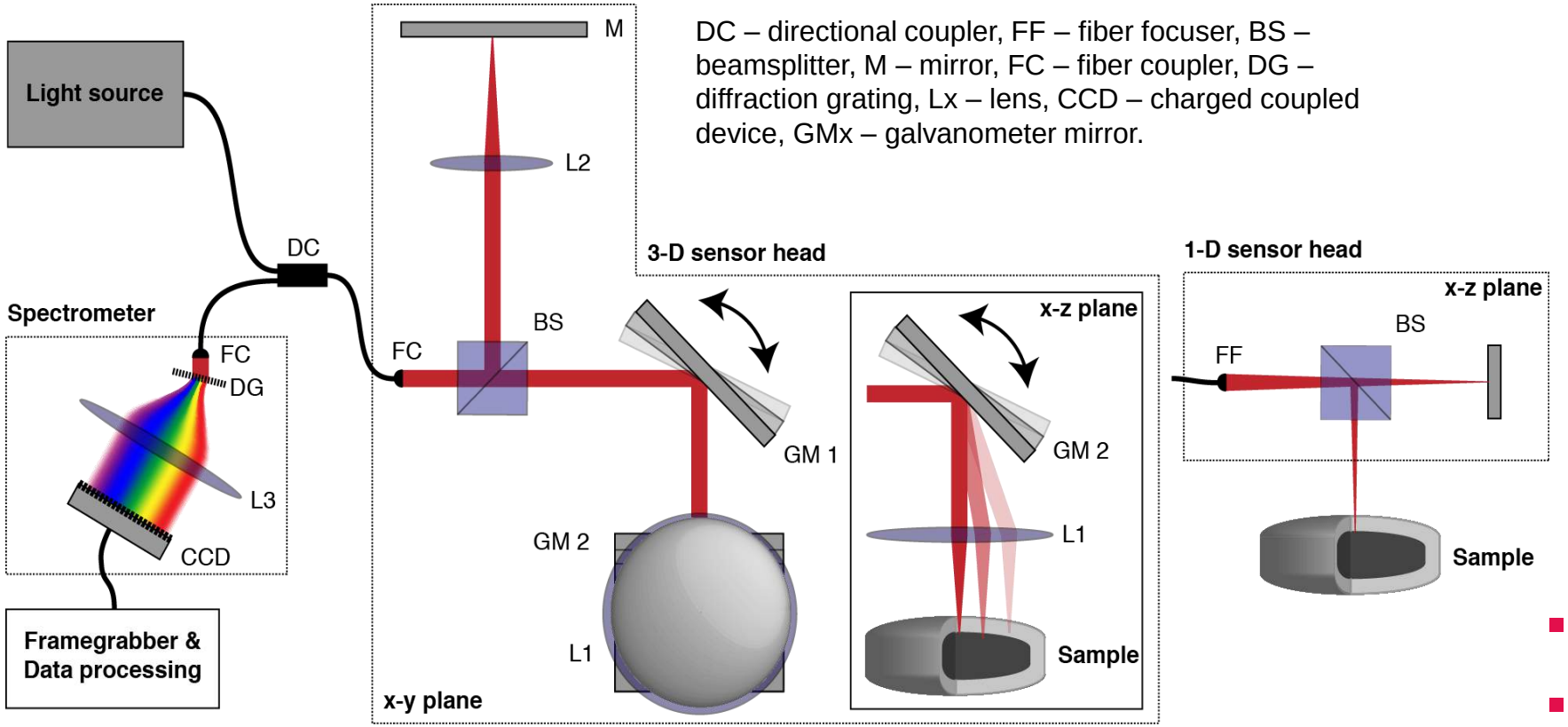
- Time, temperature, weight, pressure, conductivity, pH, pO2, outgas O_2 / CO_2, stirrer speed, power, foam level, etc.

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



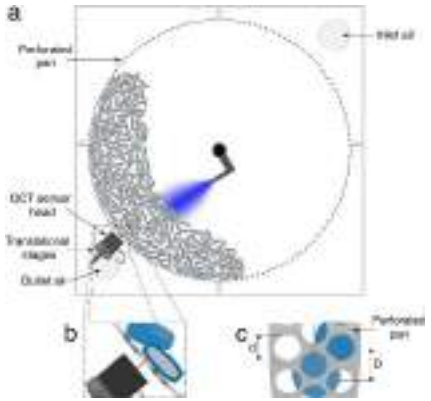
DC – directional coupler, FF – fiber focuser, BS – beamsplitter, M – mirror, FC – fiber coupler, DG – diffraction grating, Lx – lens, CCD – charged coupled device, GMx – galvanometer mirror.

- System is modularly designed
- Light source: SLD Broadlighter
  - Central wavelength: 832 nm
  - FWHM spectra bandwidth: 75 nm

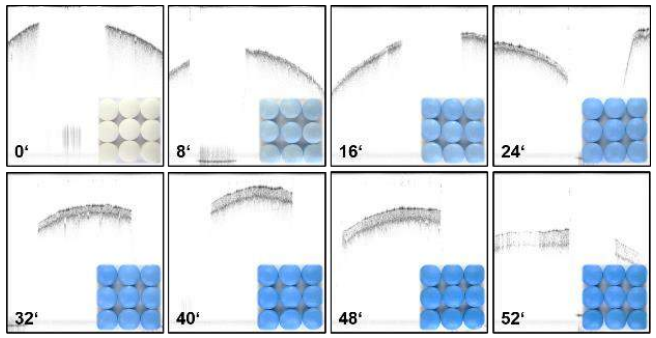
- Lateral resolution: ~14 µm
- Axial resolution: ~4 µm
- Acquisition rate: ~62 kHz (~ 62 fps)

OCT Capabilities: Coating Thickness, Variability & Defect Detection

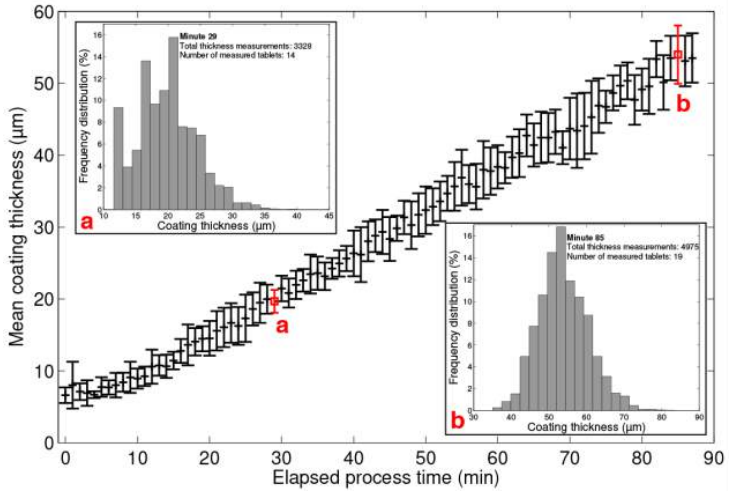
Online Integration



Online Measurements



Real-time Coating Distribution



Defect Detection

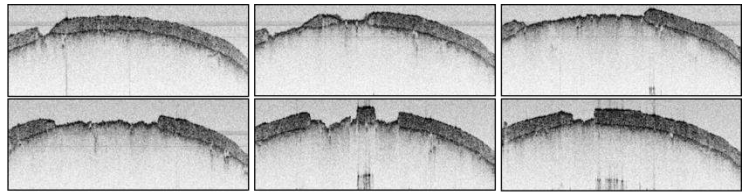
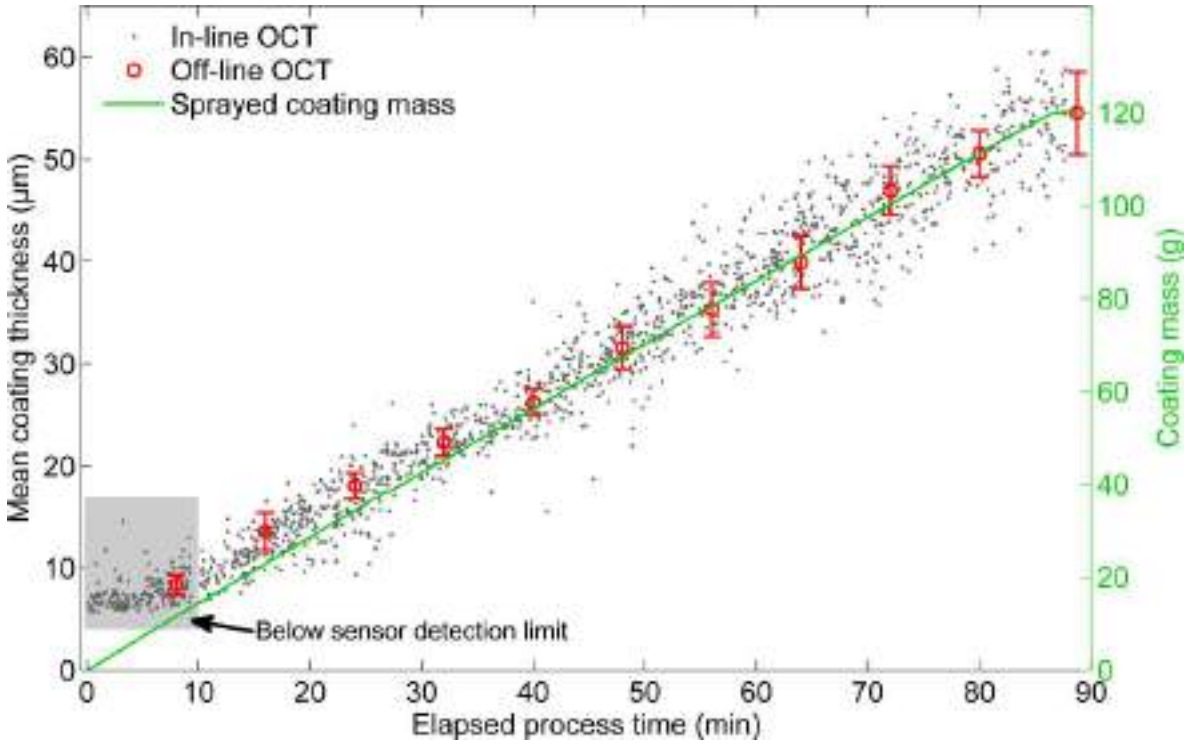
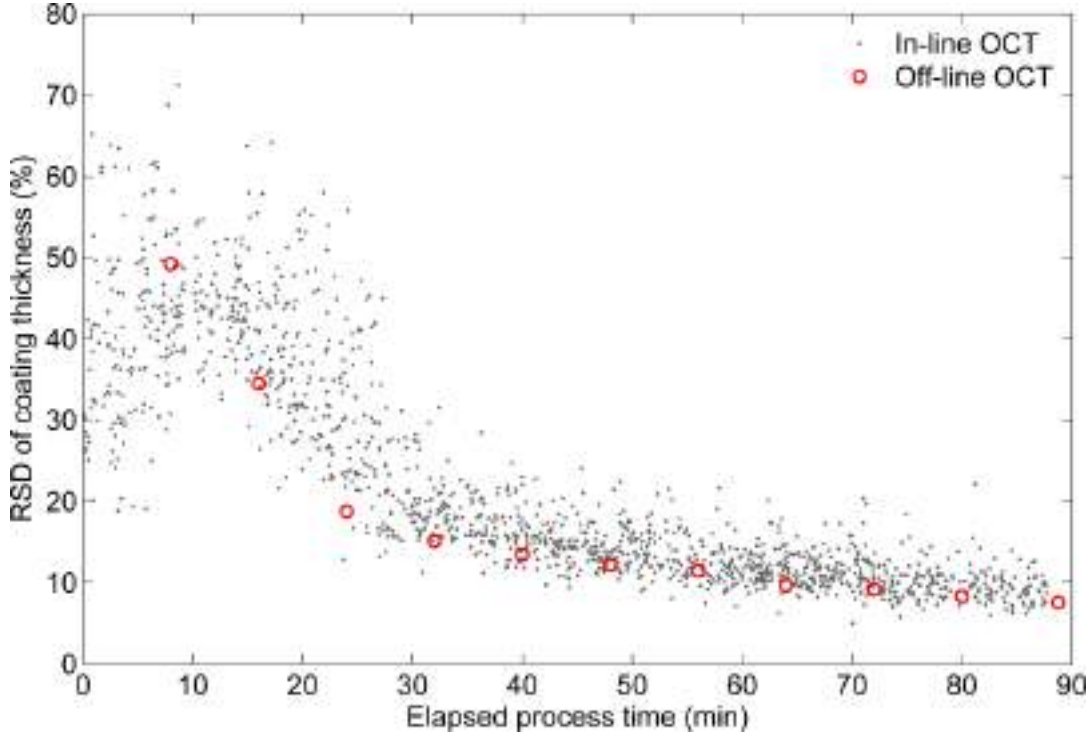


Image size: 5 x 0.6 mm²

In-line Monitoring of a Pan Coating Process



- Mean coating thickness of each analysed tablet.

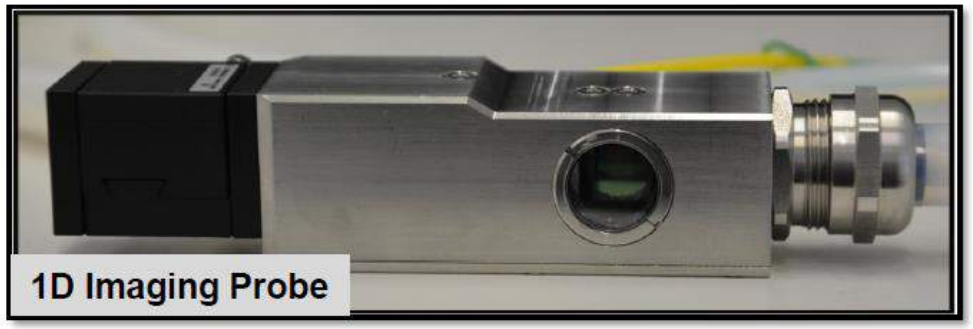


- Relative standard deviation (RSD) of coating thickness for each analysed tablet
- Corresponds to intra-tablet coating variability

OCT Technology is GMP Ready

- The systems includes
  - **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)

Phyllon
pharmaceutical technology

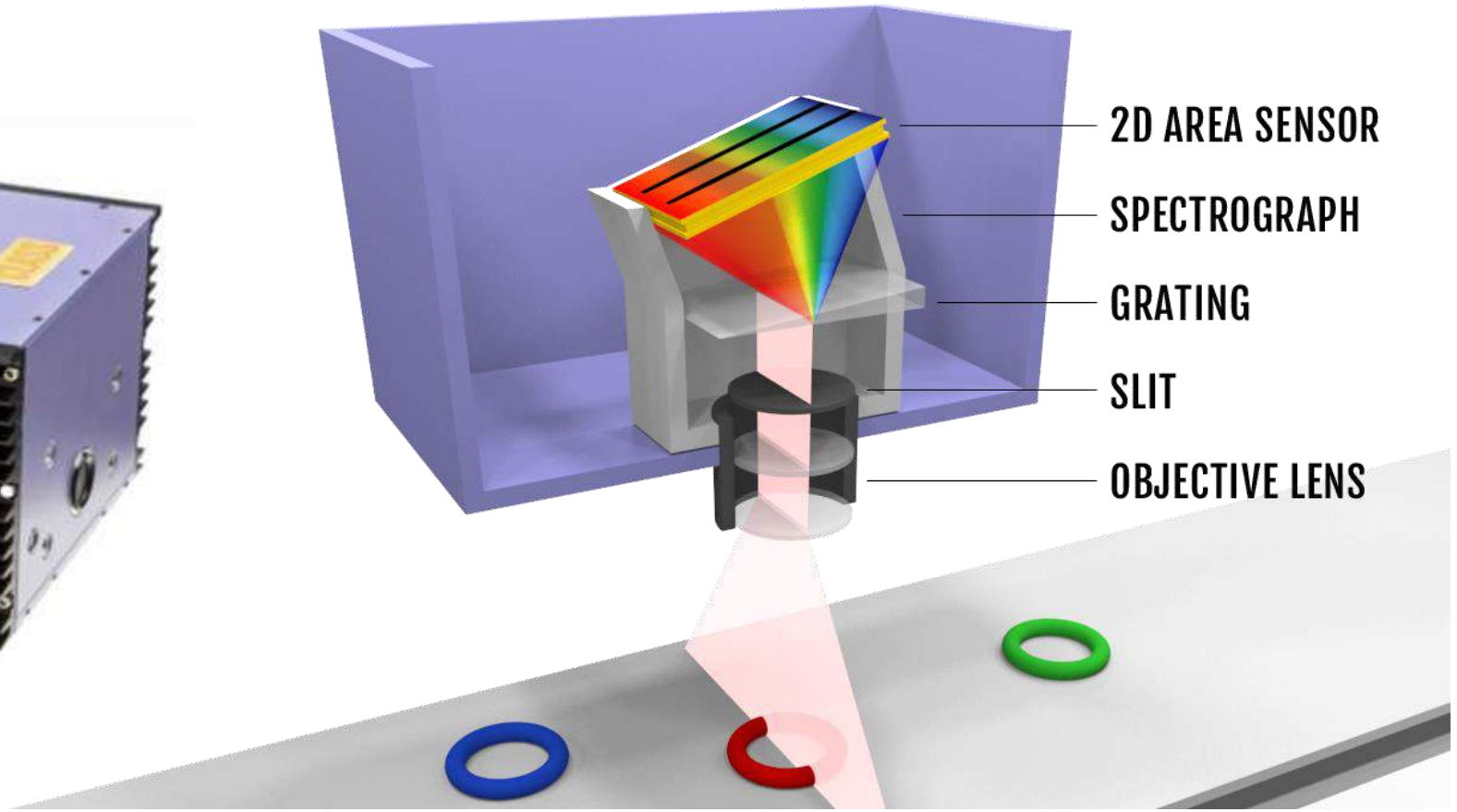


OCT Pharma 1D probe in hygienic design

Base Unit

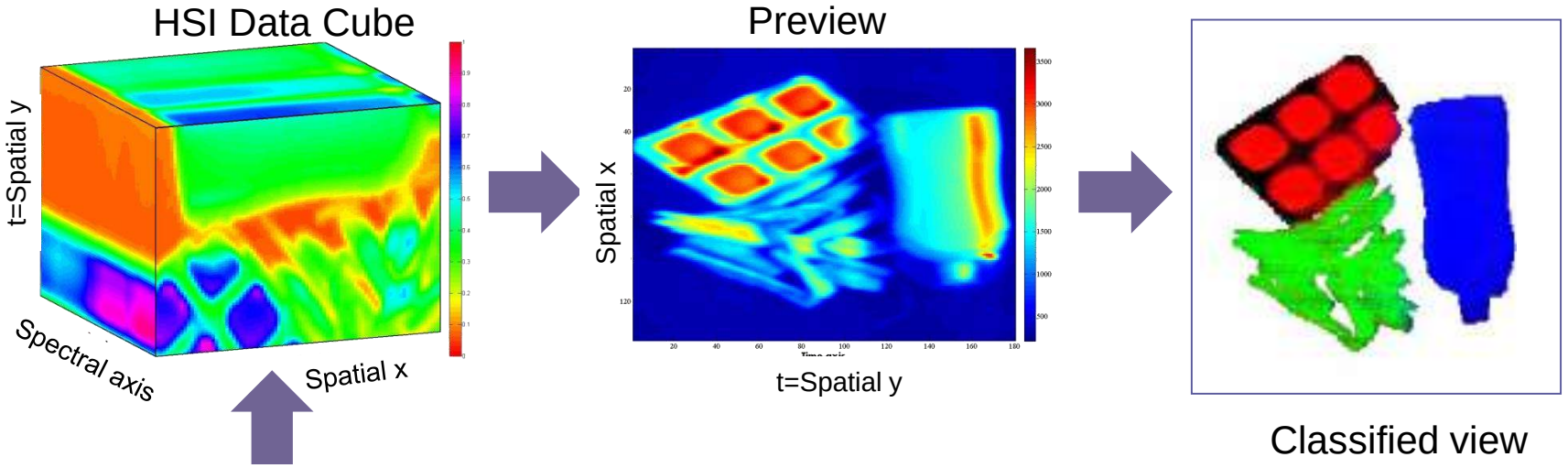
NIR Hyperspectral Imaging – How does it work

HELIOS G2 NIR



NIR Hyperspectral Imaging – How does it work

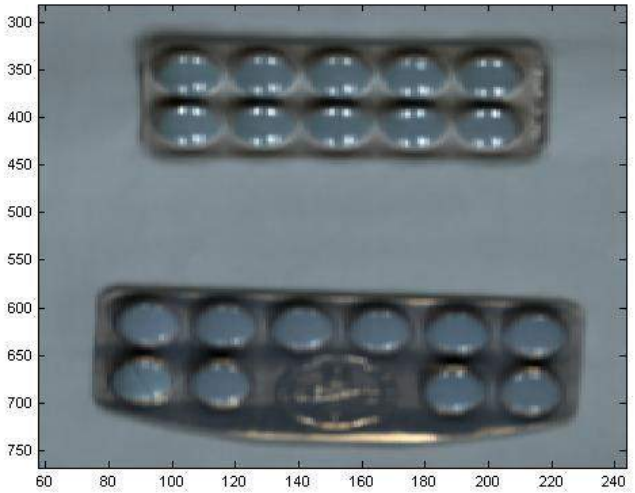
- Spatially resolved spectroscopic data is converted in real-time to „chemical colors“.
- Concentrations of chemical constituents can be measured non-invasevly at high product speeds



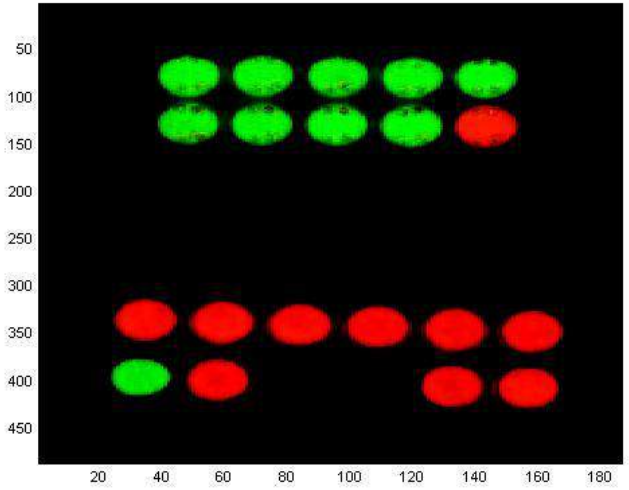
Camera internal classification and RGB visualization (chemical color representation) **of chemical differences for real-time analysis**

HELIOS Chemical Color Image (CCI)

Original (VIS)



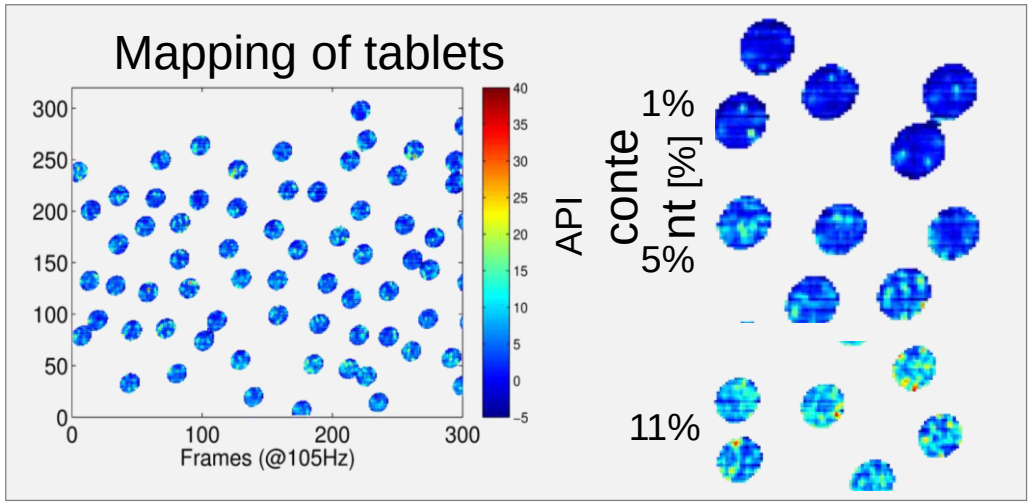
HSI preview
(mean intensity)

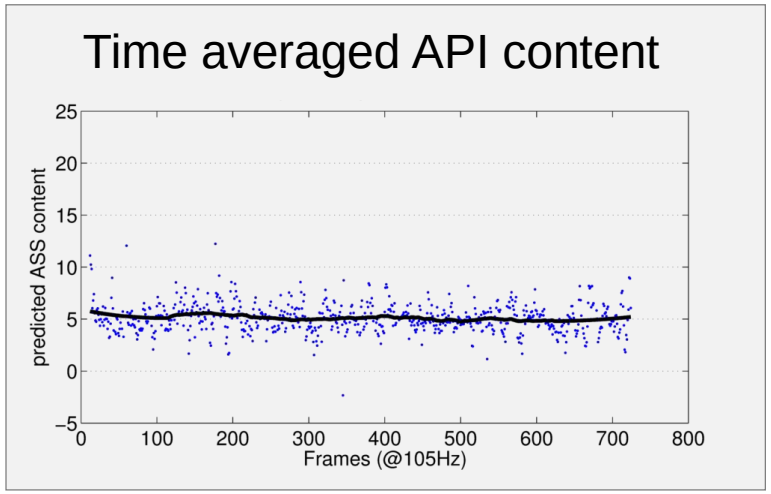


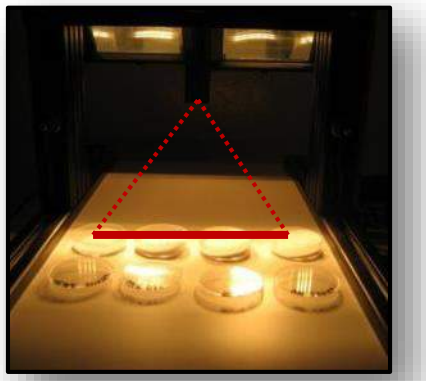
HELIOS CCI

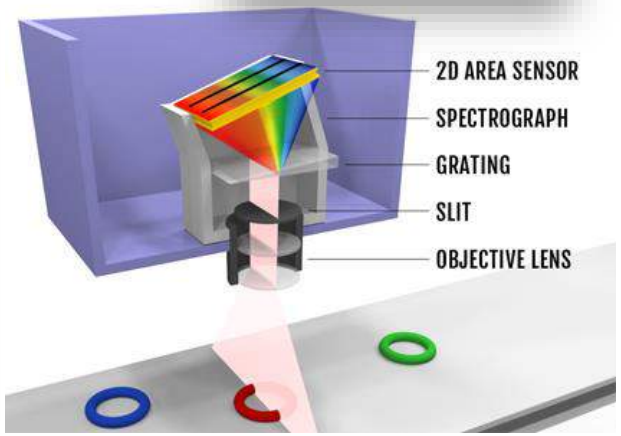
PAT for Continuous Manufacturing

100% Monitoring of Tablets with Chemical Imaging



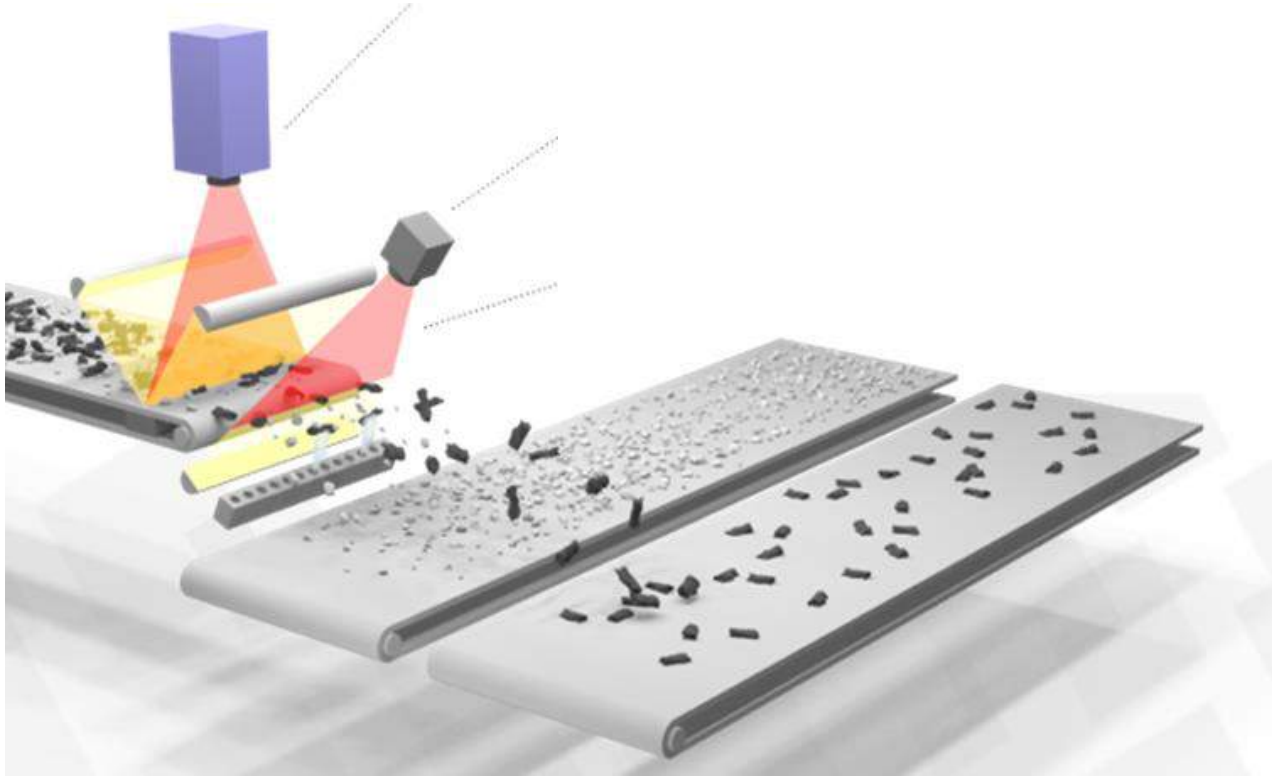


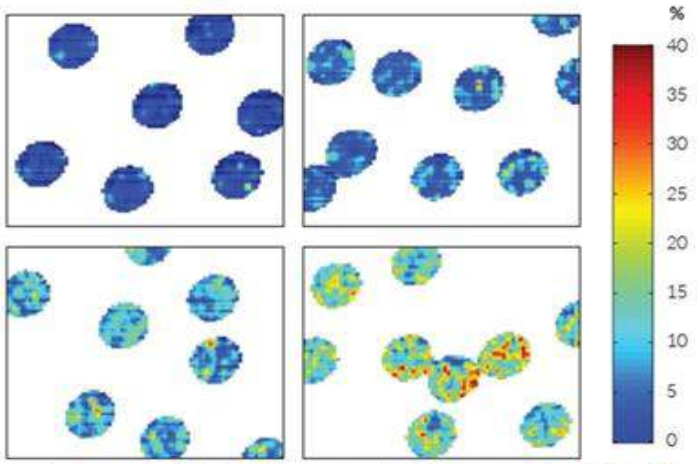




Sorting System

- 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.





Clockwise from top left: Chemical mapping of tablet API content for 1%, 5%, 11% and 15% nominal concentrations, as well as agglomerated API spots (by RCPE)

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