Review of Existing In-Process Imaging Techniques with an Eye Toward the Future: A Multi-Dimensional Particle Size and Shape Analysis Tool

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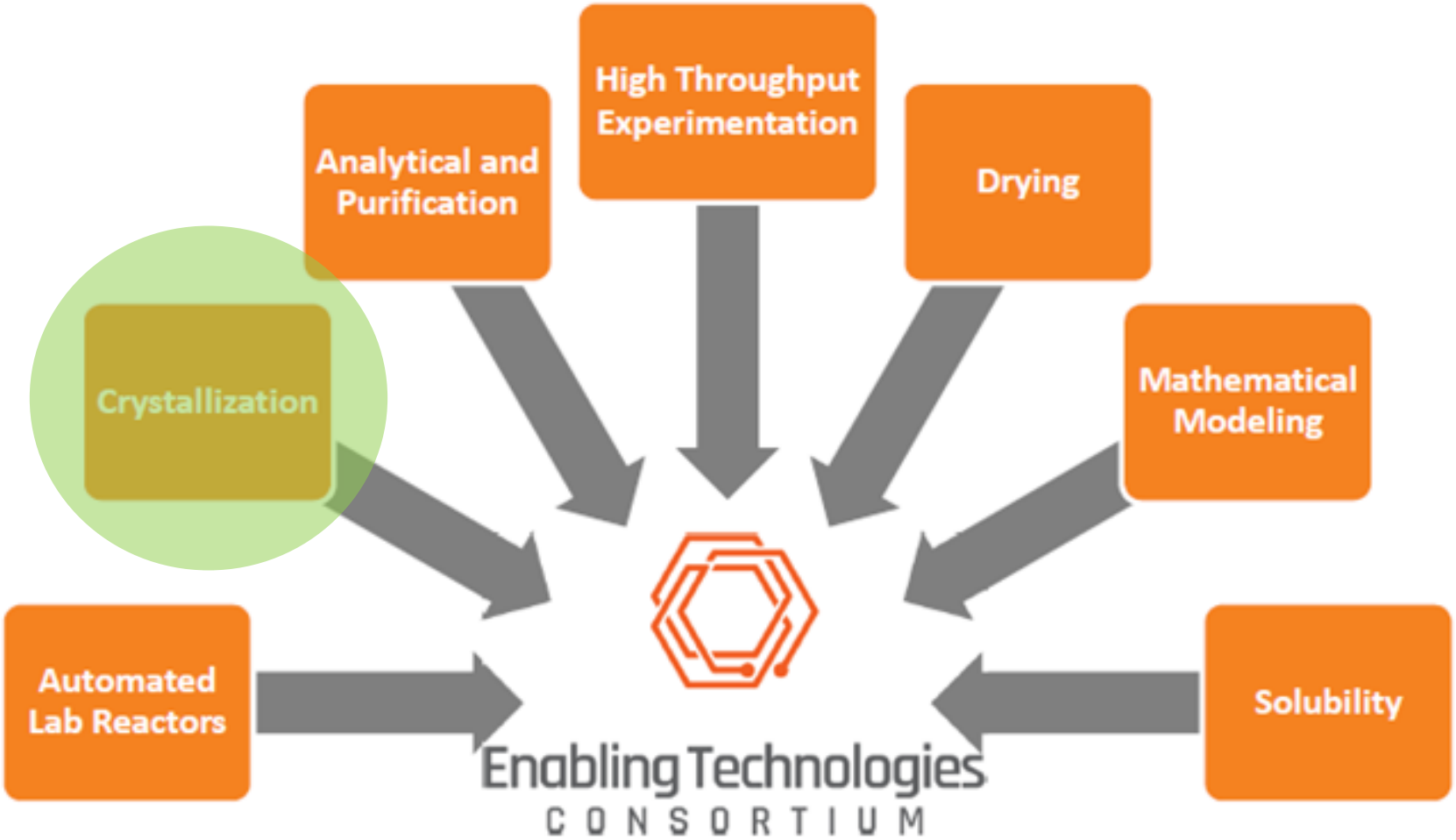
On Behalf of ETC Crystallization
Working Group
1-Mar-2018

Overview

- What/Who/How Crystallization working group
- PSS Tool – evolution of proposal
- Analysis of existing tools/Gap analysis
- Proposal for “what we want”
- Evaluation protocol
- Next steps
- Other Cryst WG activity

L’uomo dagli occhi e re nel paese dei ciechi
— Desiderius Erasmus

Current ETC Working Groups



Who is the ETC Crystallization Working Group?

Team Members

Abbvie: Jie Chen, Manish Kelkar, Laurie Mlinar, Nandu Nere

Amgen: Mike Lovette

Astra-Zeneca: Simon Black

BI: Huayu Li, Bing-Shiou Yang

Biogen: Daniel Patience

BMS: Nathan Domagalski, Deniz Erdemir, Li Tan

GSK: Rahn McKeown

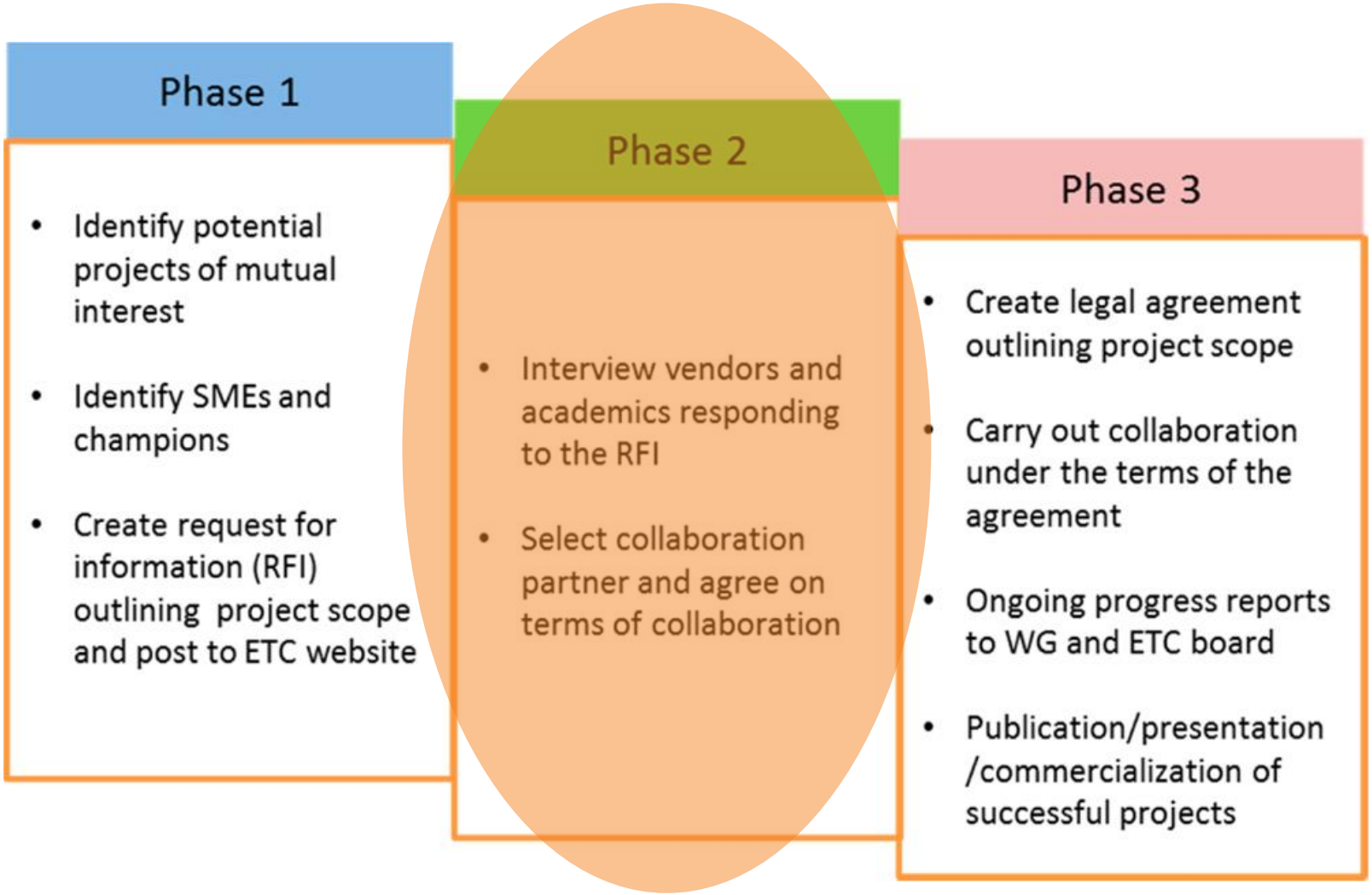
Lilly: Chris Burcham, Jeremy Merritt, Chris Poster,

Merck: Aaron Cote, Eric Sirota

Pfizer: Kevin Girard, Samir Kulkarni

Takeda: Justin Quon, Yihui Yang

Process for ETC Project Collaboration



Org. Process Res. Dev. 2017, 21, 414−419

If there is one tool that is absolutely vital to crystallization troubleshooting, it is Light Microscopy

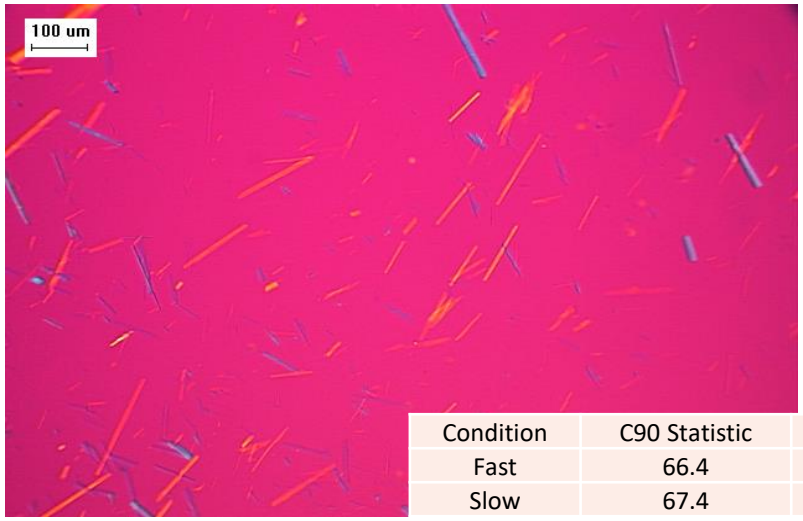
- **Light Microscopy is a simple and powerful technique for crystallization development**
  - Observe habit (and sometimes, polymorphs)
  - Track changes in size
  - Infer crystallization mechanism
  - It gives you intuitive ‘primary’ data, i.e. the result isn’t interpreted through another filter
  - Requires removing sample from vessel – temperature effects, etc.
  - Slide prep may impact interpretation and narrow window of view
- **In-situ tools offer real time interrogation and more frequent trending**
  - What do seeds do?
  - When does agglomeration start?
  - Is my system oiling?
  - What is FBRM® (Focused Beam Reflectance Measurement aka Particle Track™) measuring?
  - Is my NCE really dissolved when seeding?

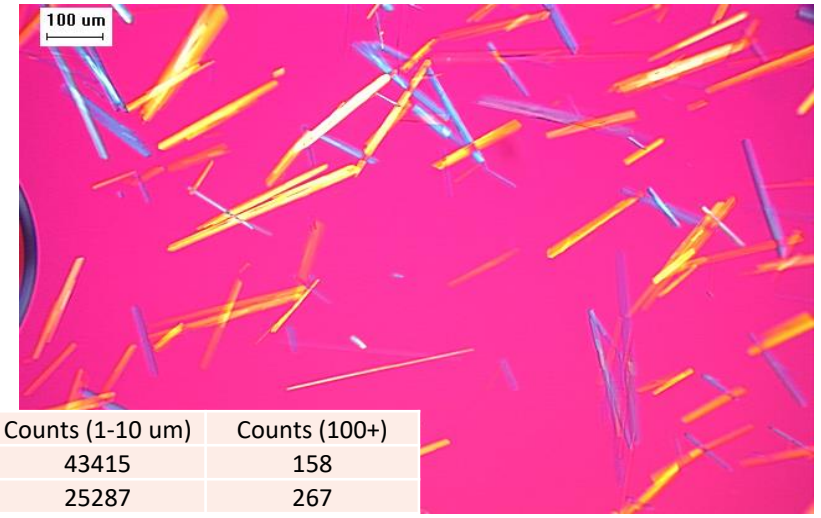
State of Play

- **Mettler FBRM® technology is ubiquitous in Big Pharma for crystallization development**
  - Provides simple, customizable, and easy to understand statistics
  - Samples at a high frequency
  - Excellent for fingerprinting and data trending
  - Portable and rugged
  - Frequently, statistics do not represent true size and no indication of shape/morphology
  - Transforming signal (Chord Length distribution) to interpret and model crystallization kinetics (as Particle Size distribution) has not been straightforward

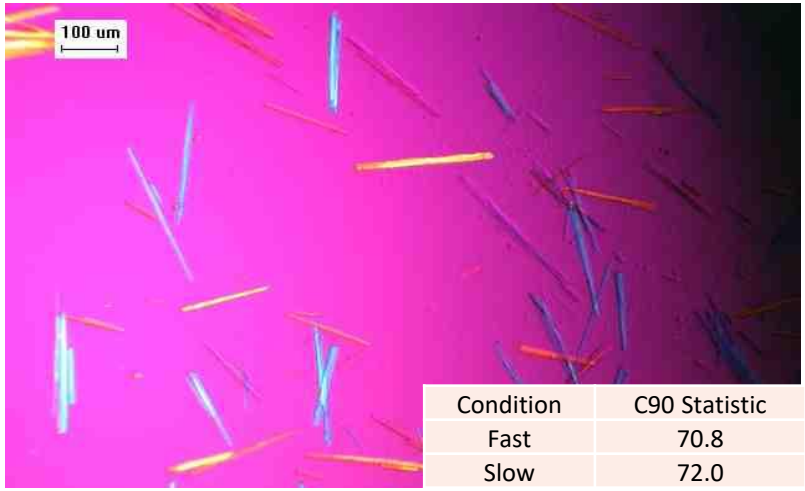
- **A wide variety of in-situ imaging probes exist within ETC members experience set**
  - Difficulty imaging in highly concentrated slurries
  - Image analysis techniques inadequate
  - Translating data stream into format appropriate for population balance modeling is not possible without significant manual effort

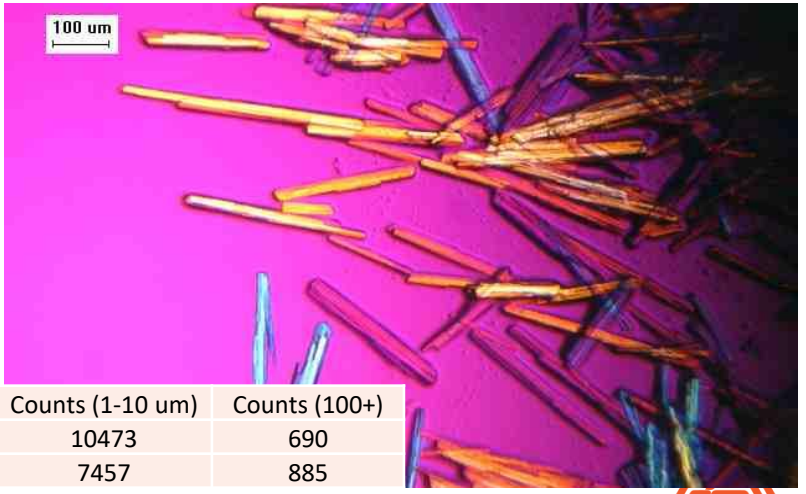
FBRM vs. OLM





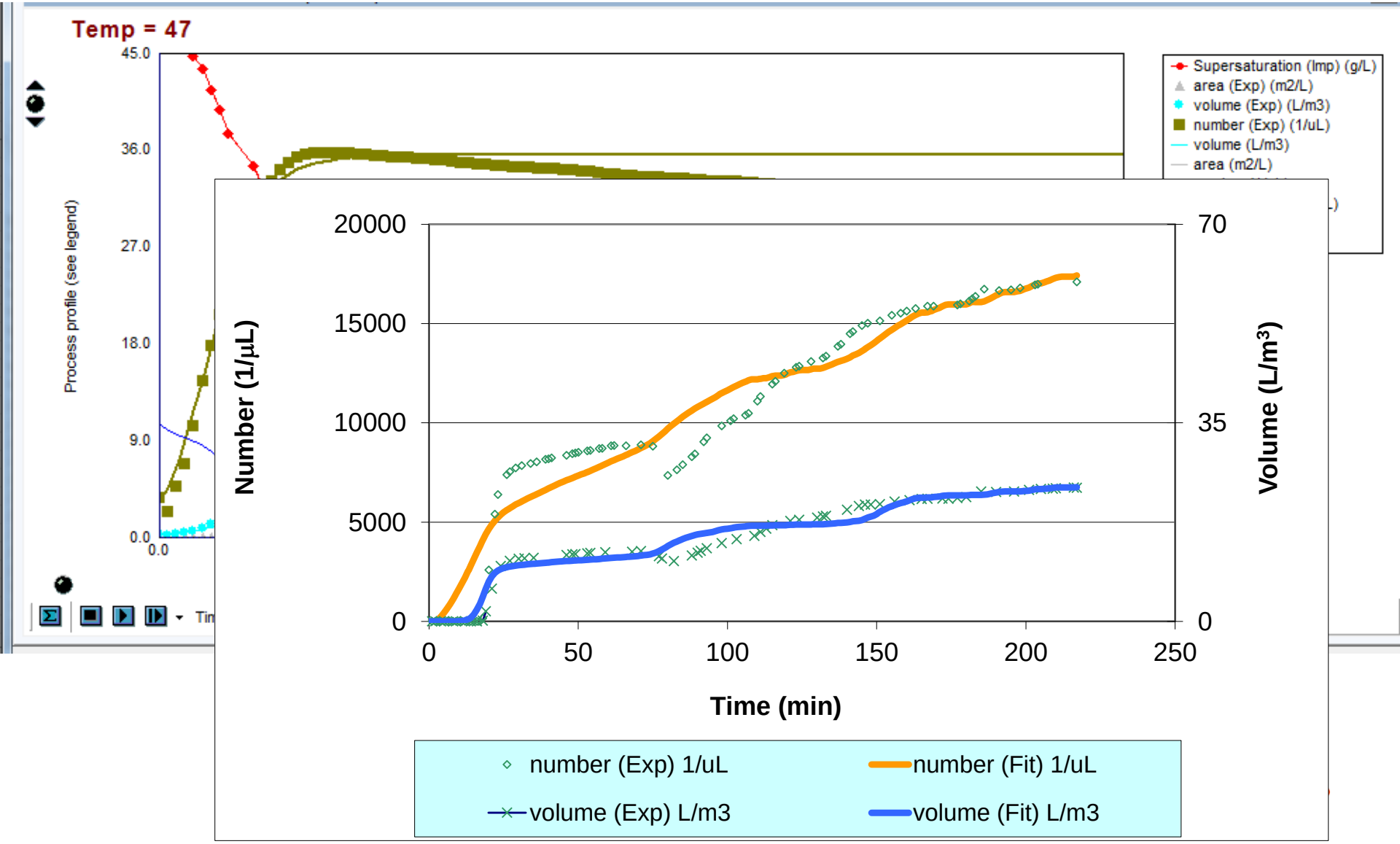
Condition	C90 Statistic	C50 Statistic	Counts (1-10 um)	Counts (100+)
Fast	66.4	5.3	43415	158
Slow	67.4	7.0	25287	267





Condition	C90 Statistic	C50 Statistic	Counts (1-10 um)	Counts (100+)
Fast	70.8	12.6	10473	690
Slow	72.0	15.1	7457	885

Translating to PBM



Summary of Imaging Solutions

Flow Cell Technology

Reactor wall

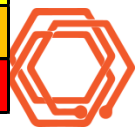
Probe based Technology

- Front lit (back scatter)
- Back lit (transmission)

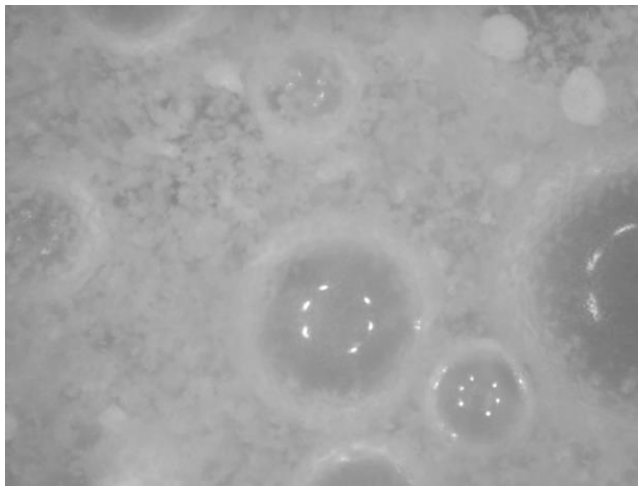
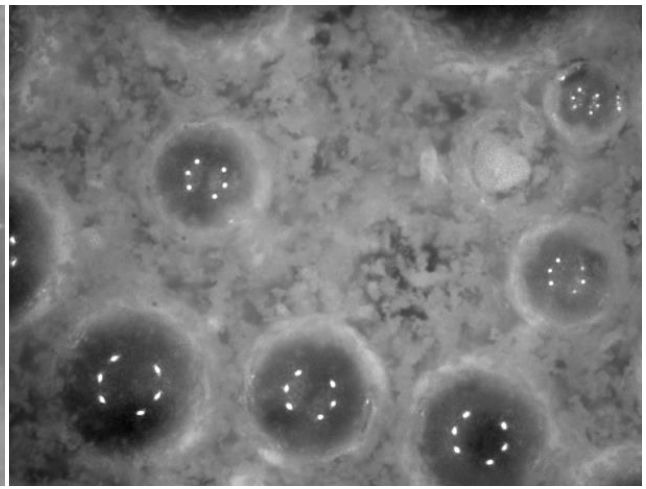
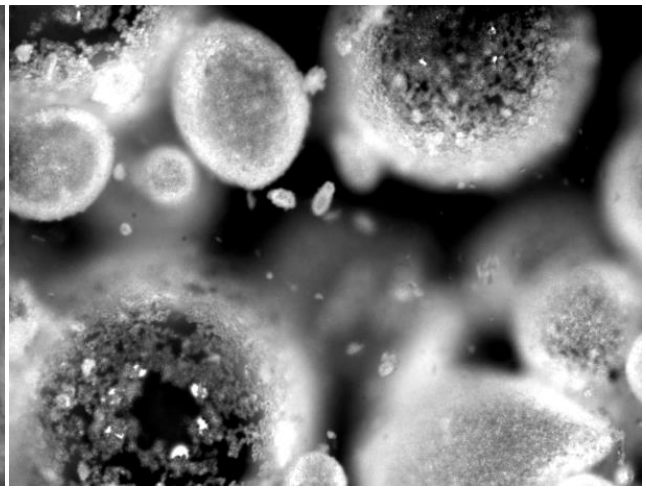
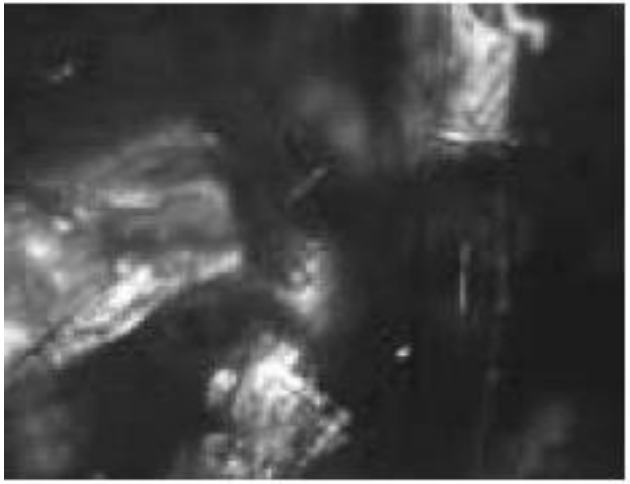
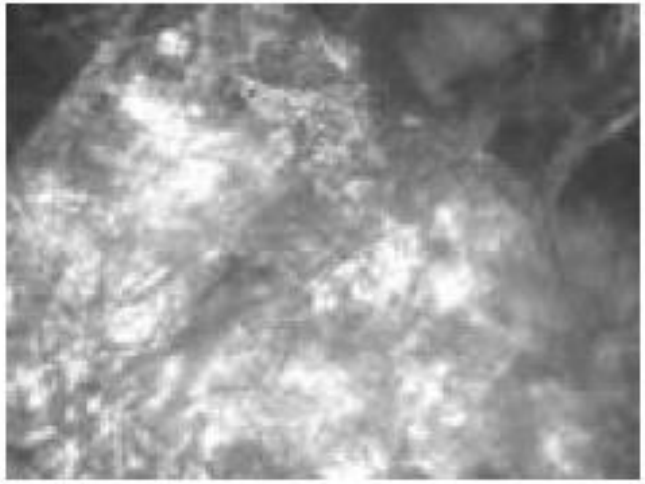
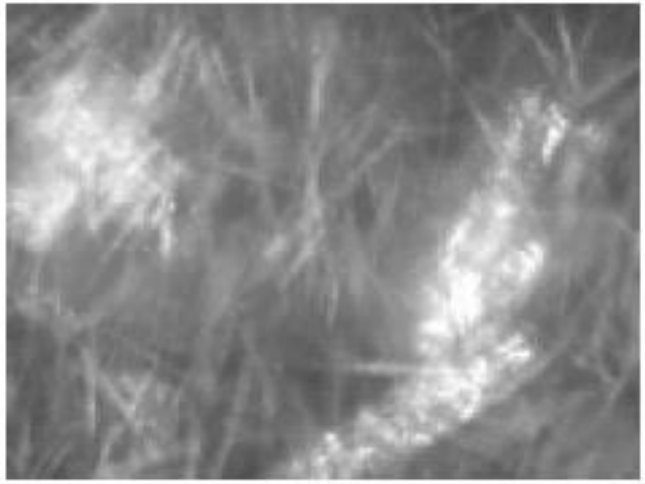
“3D” Microscopy

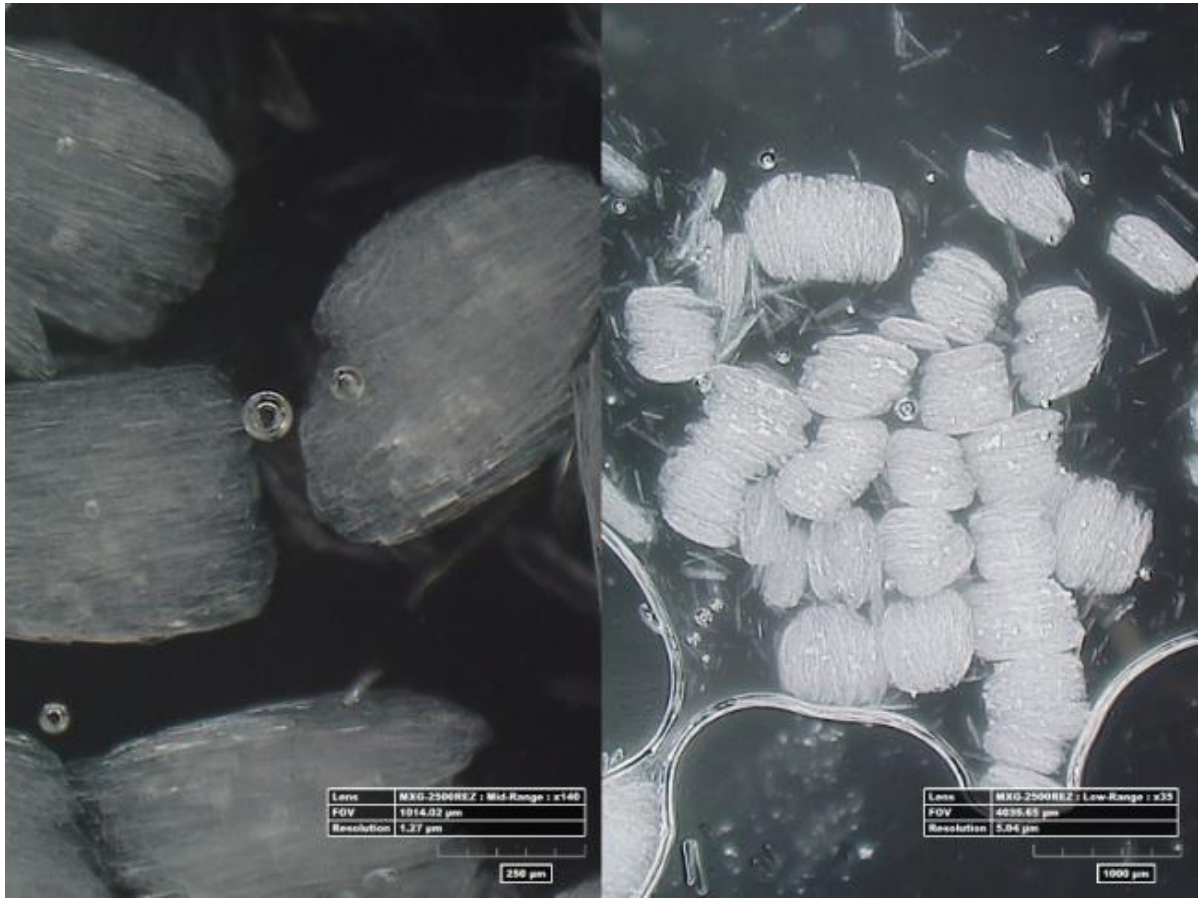
Note: Assessment done at GSK presented as scored and does not necessarily represent other ETC members

Criteria	Flow Cell Reactor Wall	Flow Cell External Loop	Probe Front Lit	Probe Back Lit	"3D" Imaging
Clarity of images	10	10	7	7	10
Ability to detect nucleation	10	10	4	10	1
Ability to generate clear images in concentrated slurries	4	1	10	1	1
Ease of use - hardware	4	4	10	10	4
Built-in particle sizing	7	7	4	7	7
Real-time imaging	10	4	10	10	1



PVM



movie001.wmv

movie005.wmv

RFI Problem Description

1. To improve our ability to model particle size and shape and predict downstream flow behaviors of powders, a novel tool is required to measure and provide meaningful descriptors of multidimensional particles as they form and grow.

2. The current state of the art equipment provides either a trending statistic (e.g. chord length) that is correlated to particle size and is a single dimension, an image analysis routine with limited multidimensional information and poor resolution, or off-line image analysis with slurry dilution due to inability to collect quality images in a concentrated suspension.

3. This project may include the development of hardware (e.g. optics and/or interfaces) as well as software (size/shape descriptors via image analysis)

Requirements

	Requirement
1	Measure crystals in situ real-time as they are produced from standard pharmaceutical processing (stirred tank reactors, at a minimum, with preference given to a tool that can also be used in a flow reactor)
2	Produce multidimensional statistics that can be easily understood, are relevant and meaningful to the actual size and shape of the crystals, and can be easily converted to the data required for population balance modeling.
3	Shape to be described by at least one parameter e.g. aspect ratio, and preferably two or more to give a 3D representation
4	Measure particle sizes, ideally within a range of 1 to 1000 um length in any given dimension (minimum range of 5-200 um)
5	Ability to provide a statistic related to the total number of particles per measurement volume and time
6	Make accurate measurements at realistic slurry concentrations, ideally 5-20 wt% solids
7	Be compatible with a broad range of operating environments including temperature (-20 to 120°C), pH, and organic solvents
8	Robust to fouling or self-cleaning
9	Measure particle populations at a frequency of at least once per minute.
10	Ability to detect and evaluate morphological differences, including primary particles versus agglomerates
11	Sort based on differentiating features to create statistical distributions of multiple morphologies, shapes, and sizes descriptors that are measured (e.g. differentiation of a population of oil droplets from acicular particles within the same system)
12	Versatile/portable tool that can be readily moved from one crystallizer confirmation to another
13	**Optional** - flexibility to be applied across scales (as low as 50 mL stirred reactor)
14	***Optional*** **-** measurement device shows minimal impact of system hydrodynamics (i.e., agitation intensity) on measured particle size and shape

Other Crystallization Workstream Projects

"*User-friendly Population Balance Model with Data Integration for Crystallization Development*"

- **Objective**
  - Develop a commercially available user-friendly and robust population balance model (PBM) based tool that seamlessly integrates with online PAT tools and experimental platforms for crystallization process development

- **Tool to be developed on two platforms in parallel in collaboration with Purdue University and PSE**
  - Purdue University to develop a new tool
    - Project execution commenced on February 1, 2018
    - Current project sponsors: AbbVie, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Eli Lilly, GSK, Merck, Pfizer, Takeda
    - Project execution commenced on February 1, 2018
  - PSE to enhance current tools with concerted input and guidance from ETC crystallization team
    - Project support companies: AbbVie, Amgen, AstraZeneca, Biogen, BMS, Boehringer Ingelheim, Eli Lilly, GSK, Merck, Pfizer, Takeda
    - Project execution commenced on February 1, 2018

Crystallization screening tools for impurity rejection and morphology modification

- Goal is to have small scale crystallization platform
  - Multiple reactors (<20 mL) with microscopy and ability to sample filtrate
- Development of RFI paused to first evaluate if project could leverage/piggyback onto Personal Parallel Reactor ETC project
- Attended ‘Personal Parallel Reactor’ meeting with Mettler Toledo in 3Q2017 to provide feedback on crystallization requirements
  - Similar design and functionality requirements (8-10 reactors, overhead stirring, etc)
  - Provided feedback to Mettler Toledo on desire for microscopy

Thank you!

http://www.etconsortium.org/crystallization

Backups

PBM Tool Development: Platform – I

- **Project partner: Professor Zoltan Nagy and his group at Purdue University**

- **Current project sponsors:**
  - AbbVie, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Eli Lilly, GSK, Merck, Pfizer, Takeda

- **Required deliverables**
  - Year 1:
    - Numerical Improvements on the existing software: CrySiv for efficient and accurate PBM solution
    - Development of the data input/communication module
    - Development of robust parameter estimation module
  - Year 2 and onwards
    - Enhancement of the tool with easier GUI, process optimization strategies, screening of various crystallization process relevant configurations, advanced model discrimination capability and ability to do automated and adaptive DOE
    - Ability to support multi-dimensional population balance models
    - Ability to account for system hydrodynamics by integrating computational fluid dynamics with the PBM

- Project execution commenced on February 1, 2018

PBM Tool Development: Platform – II

- **Project partner: PSE**

- **Current project sponsors:**
  - AbbVie, Amgen, AstraZeneca, Biogen, BMS, Boehringer Ingelheim, Eli Lilly, GSK, Merck, Pfizer, Takeda

- **Required deliverables (1 year project)**
  - Data import tool (currently ~10-15% of modelling time spent importing data)
    - Collation and alignment of data from disparate sources and types – HPLC, PSD, temperature, mixing etc.
    - Direct import from commonly used tools (MT, Crystalline)
  - Reduction in model validation efforts – automated reporting
  - Improved tool for solubility fitting
    - Project is in planning stage; defining user requirements (what does success look like).
- Project execution commenced on February 15, 2018