

NSF Engineering Research
Center for **S**tructured **O**rganic **P**articulate **S**ystems (C-SOPS)



RUTGERS
THE STATE UNIVERSITY
OF NEW JERSEY

PURDUE
UNIVERSITY

NJIT
New Jersey's Science &
Technology University



Overview

1. Update on C-SOPS progress in the last 12 months
2. New Members
3. C-SOPS way forward
4. Agenda



C-SOPS' Expanding Impact

- Large increases in FDA support:
 - largest funding award in recent history from FDA; to develop regulatory science and train the agency
 - 20 people from FDA trained during week of 9/19 @ RU
- Receiving attention from prominent government players:
 - BARDA Referrals
 - Presidential Report
- Commercialization and CDO type activities:
 - ERC methodologies increasingly used in process development, filings and regulatory interactions
 - FDA approval of Prezista®
 - Pipeline for Janssen product dev.
- Building on Success:
 - Continuous Manufacturing Convergence Consortia
 - FDA/BARDA
 - 21st Century Cures → NJ-based consortium
 - USP partnership



Recent News

January 2016 - C-SOPS receives largest funding award in recent history from FDA to develop regulatory science and train the agency

March 2016 - Presidential Report listed C-SOPS as top example of successful government invention in critical emerging technology area of advance pharmaceutical manufacturing

April 2016 – FDA approval of Prezista® continuous direct compression process, which was partially developed at Rutgers

June 2016 – USP and C-SOPS launch partnership and hold roundtable meeting on continuous API and drug product manufacturing standards

June 2016 – C-SOPS two week hands on training course launches

June 2016 - Submitted \$16.4 Million proposal to FDA/BARDA on enabling rapid development and technology adoption of solid dose CM; 2016 budget issue due to Zika and allocations, asked to resubmit for 2017

July 2016 – CSOPS submits proposed draft guidance to FDA

September 2016 – C-SOPS one week hands-on training course for 20 people from FDA

September 2016 – Mforesight Gamechangers seminar by Futran and Muzzio

December 2016 – 21st Century Cures Act



Regulatory Interactions

- FDA is an ERC member
- F.J. Muzzio is a consulting member of Pharm. Sci. Committee
- M. Ierapetritou voting member of Pharm. Sci. Committee
- We teach courses for FDA, and have presented seminars at FDA (10 times since 2010).
- Training for FDA personnel in CM (20 participants for one week)
- *Coordinated an FDA invited proposed draft guidance document on Continuous Manufacturing of Solid Oral Dose (under review)*
- Currently funded by FDA:
 - *To develop modeling tools for risk based assessment of continuous processes (500K)*
 - *To do detailed investigations of integrated systems; exploring system robustness and control, RTR, and the links to material and process characterization and risk assessment (4 Million)*
 - *To explore oral strip film technology (900K)*



Summary of C-SOPS Technical Accomplishments in CM

- Promoted FDA support for CM
- Demonstrated feasibility – implemented first integrated line (2008) and built first closed-loop control line (Inspire, 2011)
- Developed approach to minimize feeder variability during refill
- Developed RTD framework for design of continuous mixers and for traceability of materials in integrated line
- Developed integrated flowsheet modeling methodology
- Demonstrated integrated closed loop control of feeders, RC, mixers, TP
- Integrated PAT approach for continuously moving powder
- Demonstrated arrested segregation in DC CM
- Created Integrated Product/Process Development Paradigm

Note: C-SOPS includes both academic and industrial participants

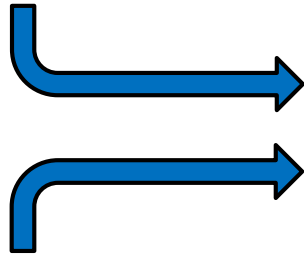
Advanced Pharmaceutical Development

The goal is to model pharmaceutical processes *in silico* and use these tools for optimization

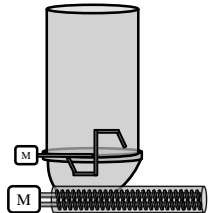
Material Properties



e.g., Flow, Bulk Density,
Angle of Repose



Unit Ops Models

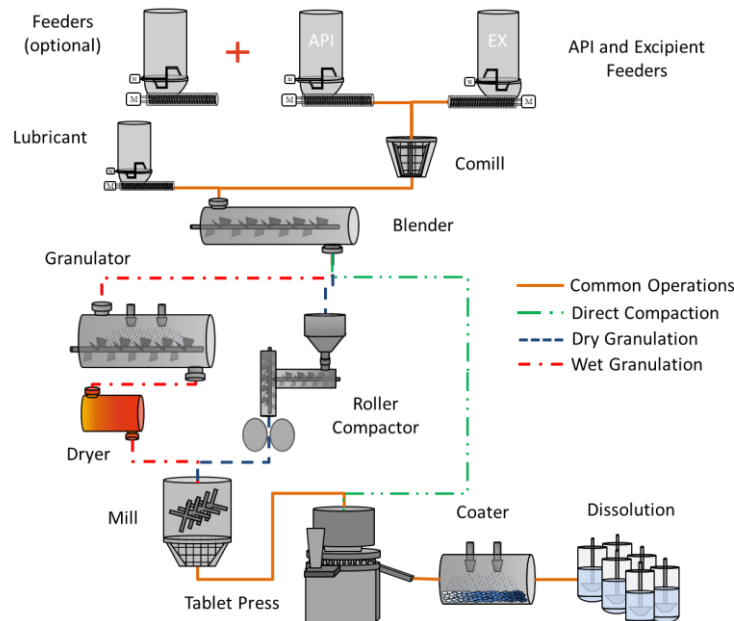


e.g., Feeders

$$y = f(x, a, t, m, n)$$

$$\frac{dy}{dt} = g(x, a, t, m, n)$$

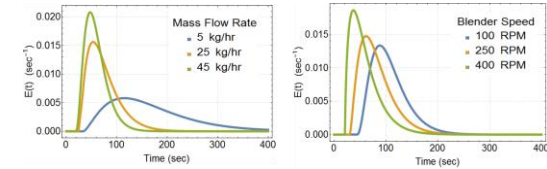
Integrated Process Model "Flowsheets"



Operating Parameters & Design

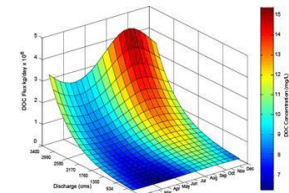


Predictive Modeling



Reduced Order Model

$$y = \beta_0 + \sum_{i=1}^k \beta_i x_i + \sum_{i=1}^k \beta_{ii} x_i^2 + \sum_{i < j} \beta_{ij} x_i x_j + \varepsilon$$



Optimization

$$\min f(x)$$

$$\text{st. } h(x) = 0$$

$$g(x) \leq 0$$

7

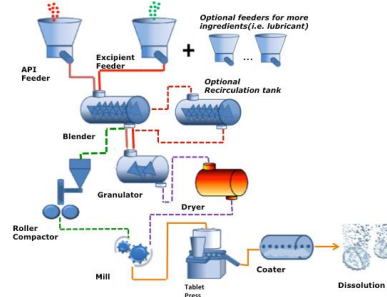
The Design Chain

How does the process create a structure?

How do material properties affect the structure?

How does the structure determine performance?

Bulk Ingredient



Process

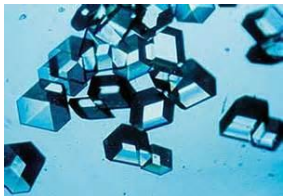


Product

In vitro
performance



In vivo
performance



Crystal

New Members

- Catalent
- The United States Pharmacopeia
- OSI Soft



Way forward

- Focus
- Membership
- Janssen
- Other companies
- FDA
- USP
- BARDA
- State of NJ EDA
- 21st Century Cures



Focus: Solid Dose Continuous Manufacturing

Strategic Technical Priorities:

1. Systematic methods for minimizing time and materials
2. Understanding material properties
3. Aligning on sensing, control, release criteria (RTR)
4. Improving API “processability”
5. Integrating product, process, and analytical development
6. Building community of practice, including industry, government, and academia



Membership

- Transition to cash-only, single tier (\$50K/y)
- Membership is strong and growing
- Many upcoming opportunities:
 - Technology Improvement
 - Technology Commercialization
 - Commercial Implementation
 - International Partnerships
 - Regulatory Interactions



Janssen Partnership

- Strong and growing
- Supporting pipeline
- Expanded toward fundamentals
- Open to collaborations



Other Activities and Interactions

- New consortium planned to support technical alignments among drug manufacturers
- Negotiating partnerships as development site for two other companies
- Rapidly growing opportunities in China
- Expanded focus toward workforce development



FDA

- Ongoing projects
- Targeting new projects by regular BAAs
- Will wait for opportunity to resubmit “platforms” proposal
- Pursuing enlarged collaboration via 21st century funding



USP

- Strong partnership, growing rapidly
 - Road mapping workshop
 - Expert panel
 - Collaboration/partnership agreement signed (2/27/17)
 - Negotiating multiple projects
 - Excellence center
 - CM Monograph
 - Training program
 - International interactions (Malta, India, China)



BARDA

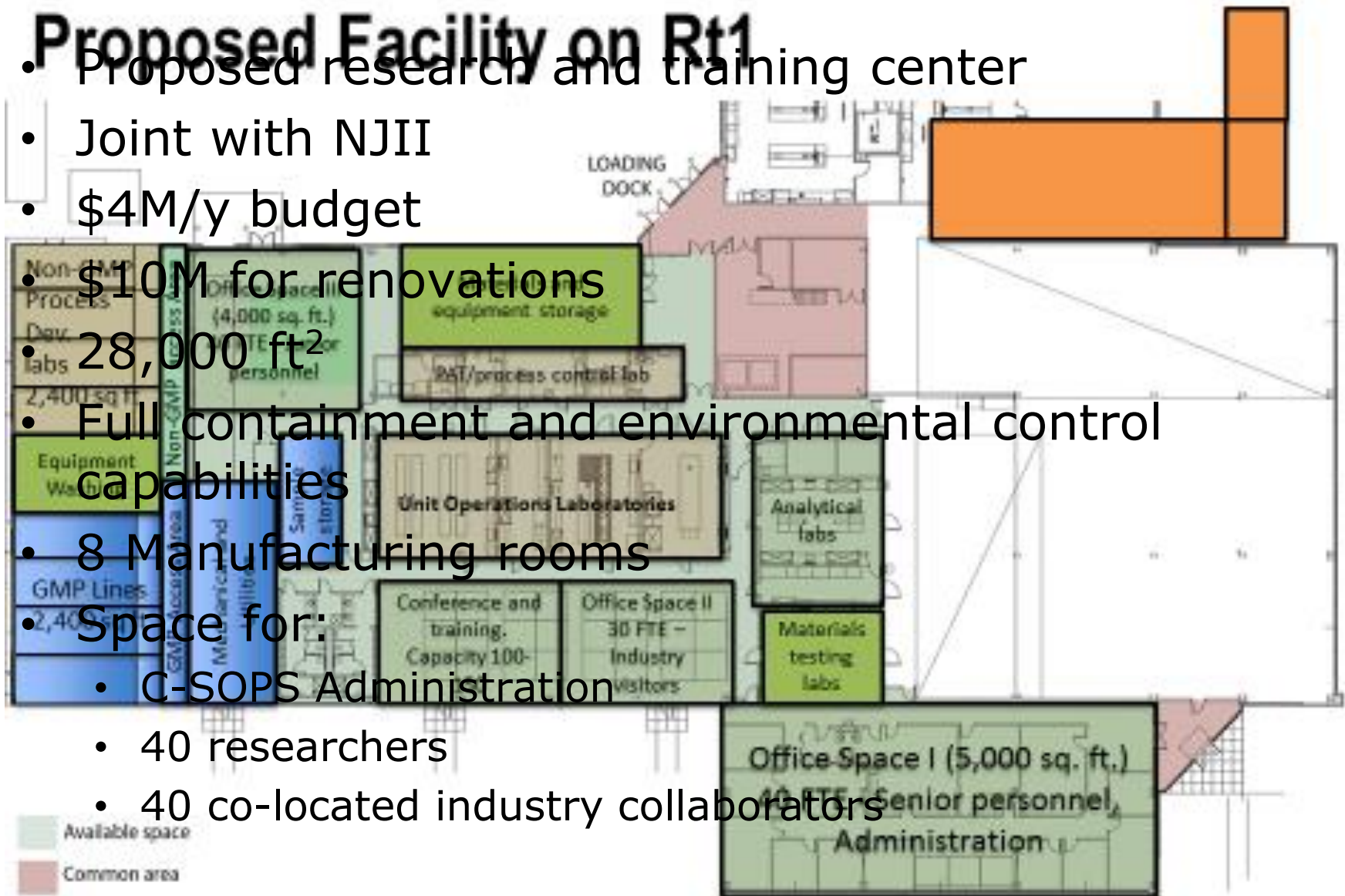
- CM is a strategic priority
- High level of interest in collaboration
- Negotiating collaboration project with BARDA contractor
- Waiting for new statement of technical priorities to re-engage



State of NJ EDA

Proposed Facility on Rt1

- Proposed research and training center
- Joint with NJII
- \$4M/y budget
- \$10M for renovations
- 28,000 ft²
- Full containment and environmental control capabilities
- 8 Manufacturing rooms
- Space for:
 - C-SOPS Administration
 - 40 researchers
 - 40 co-located industry collaborators



21st Century Cures

- Joint C-SOPS/NJII program
- Authorization in Dec 2016 law to create a CM center sponsored by HHS
- Seeking appropriation for FY18-FY22
- Request: \$10M/y
- API, solid dose, biologicals



Today's Agenda

9:00 AM Keynote: Jaap Venema, USP, CSO
Continuous Manufacturing as a Strategic Initiative for USP

9:30 AM Kickoff Talk: Fernando J. Muzzio, Director, C-SOPS, Rutgers University
Review of C-SOPS and Broader Advanced Pharmaceutical Manufacturing and Updated 2020 Vision

Break

10:15 AM Membership Program: Douglas B. Hausner, Associate Director, C-SOPS, Rutgers University

10:30 AM C-SOPS Technical Research Program for 2017:
Rex Reklatis, Deputy Director, C-SOPS, Purdue University

- 1. Predicting & managing API blend properties for batch and continuous manufacturing (Dave, Bilgili)**
- 2. Hot Melt Extrusion: Model Development (Ramachandran, Ierapetritou)**
- 3. Staged Powder Addition in Twin-Screw Granulation (Gonzalez, Wasgren)**
- 4. NIR evaluation of Low Drug Concentration Blends (Romanach, Mendez)**
- 5. Science-based statistical comparison of dissolution profiles (Drazer, Cuitino, Ierapetritou)**
- 6. Value of Information in Sensor Networks (Reklaitis, Nagy)**
- 7. A Comparative Assessment of Nanocomposites versus Amorphous Solid Dispersions for Dissolution Enhancement (Bilgili, Dave)**
- 8. Microwave-Based Fluid Bed Drying (Glasser, Ierapetritou)**

