

# **1. SYSTEMS VISION AND VALUE ADDED BY THE CENTER**

## **1.1 Systems Vision**

Engineered organic particulate systems are assemblies of multiple, predominantly organic constituents used for substance delivery applications. Such materials comprise a large segment of the US economy, spanning the pharmaceutical, nutraceutical, agrochemical, cosmetics, and consumer product industries. In most cases, the delivered substance is an organic compound solid at ambient conditions that is marginally soluble in water and yet must be delivered to a plant, animal, or human by transport to and across some cellular membrane.

Our ERC focuses primarily on particulate systems used by the pharmaceutical industry. As presented in previous site visits, our overall scientific goal is to take product development, process design and manufacturing science of organic particulate systems from its current empirical state, to the desired state in which, given an active substance and its administration/dosing requirements, the design of the multicomponent particle-based structure and its associated manufacturing process occurs in an integrated fashion via predictive models supported by a minimum of key experiments. In this desired state, the effects of materials variability and processing uncertainties are mitigated by optimizing design operating variables. Product quality is assured by using on-line measurements to determine the state of critical variables of each operation, on-line monitoring and predictive models to detect and project the impact of departures from normal operation, and advanced control methods to correct deviations from specifications. The product design and manufacturing space are expanded with innovative composite particle synthesis and processing methods that provide real alternatives to the traditional unit operations.

Consistent with this goal, **the Systems Vision of our ERC is to develop a model-predictive integrated framework for systematically designing materials, structures, and processes used to manufacture substance delivery systems (Integrated System Approach)**. The main barriers that need to be overcome to accomplish this vision, updated to reflect one year of progress, are as follows (Table 1-1):

<b>Barrier</b>	<b>Effect of the barrier</b>	<b>Action (taken/ongoing/planned)</b>
Adherence to legacy methods regarding product and process design practices	Delays adoption of new technologies Weakens support of intended adopters	Taken: Organized major symposia, developed short courses, enabled dialogue with representatives of regulatory agency to highlight value of predictive methodology Taken: Develop plan for commercialization of continuous manufacturing technology, obtained funding, currently negotiating license Ongoing: Series of publications and enable websites to facilitate access to new methodologies
Lack of effective analytical methods for characterizing	Hinders development of structure-function-performance	Taken: Established partnerships with Pharmalaser, Malvern Technologies, and VTT.

micro-structural characteristics of organic particulate systems	relationships Hinders/threatens feasibility of test beds 2 and 3	Implemented CT-Scan methods for structure characterization Launched molecular phenomena and materials properties working groups
Incomplete understanding of effect of properties of raw and intermediate material on process performance and on finished product properties Lack of predictive models for process components	Hinder development of predictive methods Hinder control of finished product properties Hinder ability to design and scale-up processes	Taken: Focusing on three relevant test beds, identified critical material properties and process parameters that need to be modeled Taken: Developed detailed research plan focusing on multiscale approach for understanding particle ensemble properties Taken: Launched major multivariate study examining the effect of raw material properties and processing history on the properties in intermediate and finished products Success: Identified nanosmearing as key operating mechanism of glidants and lubricants causing dissolution and hardness quality issues in tablets
Adherence to “largest possible batch” manufacturing approach	Hinders implementation of manufacturing approaches for personalized medicine Limits implementation of approaches for quality improvement	Taken: Emphasized alternative manufacturing platforms (test beds 2 and 3) that enable effective manufacturing of personalized dose forms Taken: in collaboration with Pfizer, launched new project for microdosing into capsules Ongoing: Actively pursuing conceptual development of new test beds that will further facilitate point of need micromanufacturing
Lack of demonstrated technology for closed loop control of particle-based manufacturing processes	Hinders implementation of continuous manufacturing methods	Taken: launched multiple project components seeking to establish control policies for test bed 1 Taken: Acquired control system and PAT software from Emerson and implemented it at Purdue, UPRM, and Rutgers Taken: established partnership with VTT for the development of multipoint sensor technology.

The ERC systems vision was enthusiastically supported by the site visit panel in the first two site visits. In the third site visit, we proposed a major reorganization of the research plan, seeking to streamline the Thrusts and make them more coherent, reduce overlap between projects, initiate activities that had been previously overlooked, etc. The reorganization was approved by the SVT, and was implemented on July 1. During the six months following the reorganization, significant effort was needed to launch six new projects, re-allocate mentors to project teams, streamline faculty and student components of project teams, etc. This implementation was largely completed during September-October 2009, and was “road tested” during the IAB meeting in late November, 2009. We are extremely pleased to report that the IAB, which sent >80 representatives to the meeting, thoroughly approved of the level of implementation of the reorganized research program.

## 1.2 Value added by the ERC and Broader Impacts

As mentioned in our previous presentations to the Site Visit Team, and as discussed in our previous annual report, Industry currently lacks a predictive framework for structured organic product and process design. Product formulation and process design and scale-up are performed largely by trial and error practices involving extensive testing. In spite of a growing interest in Process Analytical Technologies, end of process “inspection sampling” of product batches, a practice discontinued in many other industries in the ‘50s, constitute the main quality assurance tool in manufacturing of pharmaceuticals. The consequences of this “state of the art” are well known: long and expensive product development cycles, frequent product failures, and hindered adoption of modern design, manufacturing and quality control approaches.

At the present time, there is enormous interest in the Pharmaceutical Industry in moving beyond this situation and incorporating predictive design, optimization, and control methodologies. Increasingly, “quality by design” is becoming the prevailing language at industry workshops and in trade publications where the importance of this new paradigm is emphasized. The ERC has become a valuable asset to industry by focusing on guiding, facilitating, and enabling this transition while emphasizing scientific and technological value, across the entire research and educational program

In fact, the ERC’s definition of Quality by Design, which is *to understand and control effect of raw materials and processing conditions on product structure and performance*, has become a central focal point for the entire research program. Every major component of the center is selected and designed for the value it delivers toward this goal. In Table 1-3, we offer the site review panel an expanded table of examples of center components and their value statement, revised since last year:

As these center components are fully enabled, impact and value added of our ERC is becoming apparent. The center currently has 21 major research projects and three test beds, fully functional and highly productive and two working groups in an advanced state of implementation. Projects are generating scientific output at an increasing pace. In addition to the 52 papers reported in the first two years during the third year our efforts have generated 36 peer-reviewed publications and over 50 presentations at major technical conferences. This output is substantial given the short time elapsed since center inception, especially considering that associated projects yielded 32 additional peer reviewed publications.

<b>Table 1-3: Value added by Center Components</b>	
<b>Center Component</b>	<b>Value Contributed</b>
Systems approach for process design based on predictive modeling	<p>Promotes conceptual transformation of the entire domain, providing a major vehicle for the use of engineering methodologies for product and process optimization and performance control</p> <p>Facilitates design and optimization of existing and new manufacturing methods</p> <p>Provides scientific foundation for FDA’s “quality by design” initiative, supports science-based regulatory decision making</p>
Focus on product structure	<p>Missing link in traditional pharmaceutical product development, promotes incorporation of materials science into product design.</p> <p>Facilitates increased product functionality, increased product safety, faster product development, enhanced product performance</p>

	Promotes development of “science of formulation”
Research Thrusts	Promote the development of particle-based product science and engineering Identify major scientific challenges and barriers and organize and integrate efforts to overcome them Facilitate development of generic science that transcends the target industries
Center projects	Contribute to the development of particle science and engineering Contribute to enhanced fundamental understanding of effects of material properties and processing components on structure and performance of particle-based products Enable test beds Drive formation of cross-functional project teams involving ERC personnel, industry mentors, and critical technology partners
Test Bed 1: Continuous tablet manufacturing	Provides industry and the regulatory agency a relatively “safe” scenario for adoption of new manufacturing technology Promotes development of in-line sensing methods, implementation of closed loop control strategies for granular systems, and model-based optimization of processes used to manufacture 80% of products by the target industry Facilitates large savings in equipment and operating cost Facilitates process scale up Reduces variability and improves product quality
Test Bed 2: Strip films	Manufacturing platform that facilitates flexible dosing (films can be easily subdivided), enabling personalized medicine efforts. Provides a novel platform for delivering engineered micro-structured particles Ideal platform for pediatric administration (“fun, sweet, cool” medications) Promotes development of product form amenable to 100% inspection Drug substances handled in suspension/solution form, never as a dry powder, decreasing exposure to manufacturing personnel
Test Bed 3: Drop-on-demand multilayer structures	Manufacturing platform that facilitates flexible dosing (product units can be individually “printed”), enabling personalized medicine efforts. Promotes development of product form amenable to 100% inspection Drug substances handled in suspension/solution form, never as a dry powder, decreasing exposure to manufacturing personnel Allows small lot production for clinical trials
Working Groups	Facilitate Thrust integration along cross-cutting scientific themes Allow creating of focused teams addressing “grand challenge” problems
Matrix Organization of Research program	Organization of research program suited for dual functionality or ERC efforts: Promote fundamental science (thrusts) while emphasizing outcomes-driven planning, tangible technology deliverables and interconnectivity (test beds)
Industrial mentors program	Promote a <b>culture of relevant scholarship</b> that prepares graduates for success in academia and industry Facilitate creation of multidisciplinary, cross-functional teams for addressing problems in context and using all necessary resources Leverage intellectual and material resources from industry Facilitate industrial adoption of center technology and science Help attract industry members

Major evidence of impact is the fact that topics and approaches traditionally advocated by center faculty have been the focus of a number of workshops and sessions at major scientific conferences. In the last two years, there have been multiple Chemical Engineering conferences devoted to pharmaceutical product and process design. At the present time, at least three major textbooks are being written on this topic, all of them involving center staff as chapter authors. The last year, many center senior staff (Muzzio, Reklaitis, Dave, Cuitiño, Venkatasubramanian)

have given major keynote or invited lectures at major forums describing center approaches to pharmaceutical process and product design, indicating that Pharmaceutical Engineering is rapidly becoming a major sub-discipline within Chemical Engineering. Finally, and perhaps most significantly, the center Director, Prof. Muzzio, has been appointed a member of the FDA committee on Pharmaceutical Science and Clinical Pharmacology (one of the FDA committee that makes recommendations on approvals of new drugs and new manufacturing and quality assessment methods).

Additional evidence of the center recognition is the fact that center faculty received several major awards and recognitions. They are not listed here in the interest of brevity, but a partial list can be found in center quarterly newsletters for 2009.

The number of people involved in center activities has reached a stable number, reflecting the maturity of our programs. Between Faculty, Students, Staff, and Industrial Participants, the center has involved over 350 participants, while maintaining a high degree of diversity, reflected in the large percentage of minorities and women participants. We continue to be very active in the National Institute of Pharmaceutical Technology and Education (NIPTE), a coalition of 11 universities that is chaired by Professor Reklaitis, the ERC's Deputy Director.

The Education and outreach program was further strengthened in spite of the fact that our Diversity Coordinator, Zulma Marrero, had to quit her position due to a family issue (we are currently seeking for a replacement). Focused on increasing diversity in the center, we asked Dr. Michael Harris to be the Diversity Director. His addition to the education committee has been valuable as well as his knowledge in minority programming. This year one of the ways we emphasized and unified education across the center institutions, as well as the community, was to brand our education programs. The education brand we have designed is **EXPLORE. EMPOWER. ENGAGE.** This brand is evident in the highlights described below, we partnered with Rutgers Graduate School – New Brunswick and RISE (Research in Science and Engineering) on the Winter Science and Engineering Forum. We had two main goals with this program. The first goal was to excite undergraduates at New Jersey colleges about research and careers in the STEM fields. The second goal was to use graduate students as ambassadors and get them involved in recruiting new talent for the university and the center. It also introduced us to diverse groups of students. Two other highlighted efforts, which embody our brand, are the Undergraduate Competition and K12 outreach in the labs at UPRM. In both cases the undergrads were EMPOWERED as facilitators of the engineering projects while the K12 students EXPLORED the projects presented to them.

Our vision has also proven exciting to industry. In our three years of operation, we have signed membership agreements with 29 companies, have verbal agreements with 3 and are negotiating with an additional 6 companies. We have attracted \$4.00 million dollars in cash membership funds and almost \$2 million in equipment and software (based on the actual cost of purchasing the goods and services obtained from members). Due to the poor economy, changes in strategic focus and reshaping of the pharmaceutical industry, 2 members (CAMP, Allergan) have dropped out, 2 members have been merged with other members (Wyeth, Schering-Plough), and 1 member has rejoined at a lower level (Johnson and Johnson). The overall number of

members has grown, however, with the addition this year of Pharmalaser, Malvern, Freeman, AIS, and ATS.

Of great significance is the increased, active participation of industrial members, which is a key component of our efforts to develop a **culture of relevant scholarship** among faculty, students and postdocs. Our mentor program continues to grow both in number (115) and breadth of participation (now including test beds). Technology transfer from the ERC to the industrial community has intensified; member companies have early access to Center technology and continue to put it into practice. We have had 3 new patents either applied for or issued. Most exciting, is the commercialization grant received, which will speed the implementation of Continuous Manufacturing Technology into pharmaceutical production practice.

As in the previous year, our efforts to build an effective research and education organization have been successful by many other measures. In our first three years, we applied for, and obtained, almost every major funding supplement available. Coordination of research activities with our IGERT in Nanopharmaceutical Engineering allowed us to significantly increase support for students. This type of concomitant support grew significant this year, since center faculty won two GAANN awards, one at Rutgers (PI Chiew) and one at Purdue (PI Beaudoin), which will provide an additional \$1.5 million in fellowship funding for students working on center projects. Collectively, during 2009, Center faculty have also attracted government and industrial support in excess of \$1.0 million/yr for Associated Projects that further strengthen research activities related to the ERC mission. Abstracts of associated projects are provided in Volume II.

These accomplishments have relied in no small measure on the diverse disciplinary make-up of our faculty. As further discussed in Section 5.2, and graphically displayed in the pie chart at the end of Section 2.1, the research program currently involves researchers from eight major disciplines. Chemical and Mechanical engineering still comprise 60% of the research team, with Chemistry and Pharmacy accounting for the largest share of the balance. This composition has promoted a rich multidisciplinary dialogue among faculty and students, allowing for systematic application of engineering methods to the pharmaceutical product design area traditionally dominated by pharmaceuticals and material science. Moreover, as fully described in Section 5.2, our faculty and student body are diverse across the board. Above in some cases and right on track in majority with the National Engineering Averages, women comprise 20% of the faculty, 33% of the leadership team, and 40% of the graduate student body. Underrepresented minorities and Latinos, if counted together, comprise 37% of the faculty, 34% of the leadership team, and 27% of the graduate student body (not counting foreign students).

In summary, in the current year, center activities have become more solidly established, and we have continued to improve execution and to grow in spite of the economic crisis. All major areas of center activity are established solidly, and most are growing rapidly.

### **1.3 ERC Highlights for 2009**

The 2009 year has been an important period of change for the Center. With the NSF's renewal of the Center for the next five year period, the Center has aggressively reorganized its research programs into four refocused thrusts and 21 projects, as proposed in the renewal proposal (for

summary see Section 2). The project research teams have been reconstituted consistent with that plan. Working with the Industrial Advisory Board, the reassignment of industrial mentors to both the new and restructured projects has been completed. Additionally, industrial mentors have been assigned to test beds. Under the new structure, significant progress has been made towards achieving project scientific and test bed deliverables (see volume II for details). Several particularly notable developments are highlighted in this section. Furthermore, as part of the center renewal process a strategic plan for education and outreach was developed, presented and approved. Under that plan the contributions of each partner institution has been clarified, deliverables assigned and assessment processes for evaluating past and current contributions instituted and carried out. As shown in the highlights reported in this section, particular attention has been directed at K-12 and undergraduate outreach in order to strengthen the pipeline and increase the diversity of STEM students. On the infrastructure front, the Center faculty team has been augmented with three well prepared assistant professors with expertise in core center technologies: solid processing operations, powder processing, process modeling and process control. A significant step forward has been made in Test Bed realization with the acquisition through donation to the Center of a film processing pilot facility. Additionally, the NSF has awarded CSOPS a unique three year supplemental grant targeted to speed the commercialization of Test Bed 1 developments in partnership with industry.

While the severe economic contraction and industry merger activities have had an impact on CSOPS industrial membership, the Center has sustained a robust and diverse membership, spanning 13 finished goods suppliers, 7 equipment suppliers, 3 instrument suppliers, 2 software companies, 1 raw material company, 1 consulting company plus the FDA. Thus the Center industry membership now consists of 27 companies – a net change in membership of only one since the last year. Several potential new memberships are under active discussion so as to grow the membership to 30 over the next year. The Industrial Advisory Council has been very active, with two multi-day meetings convened in June and Dec of this year. The Science Advisory Council has likewise been actively engaged in two meetings and has been expanded with two new members over the past year. In short, as demonstrated through the following highlights, CSOPS is aggressively moving forward on all fronts and making substantive contributions in education, outreach, fundamental research as well as technology transfer.

### 1.3.1 Advances in Learning

***Winter Science and Engineering Forum:*** This forum was a partnership between the Rutgers Graduate School – New Brunswick, RISE (Research in Science and Engineering), and ERC-SOPS; with participation and funding from Alliances for Graduate Education and the Professoriate (AGEP), Innovation through Institutional Integration (I3), and WIRED-Bio 1 NJ. We had two main goals: to excite



**Figure 1-1:** RISE-ERC-AGEP Partnership

undergraduates at New Jersey colleges about research and careers in the STEM fields, and to use graduate students as ambassadors, to Predominantly Undergraduate Institutions (PUIs) in New Jersey that have been feeders for RISE, and get them involved in recruiting new talent for the university and the center. We expect that as a result we will increase the pool of applicants to our science and engineering PhD programs and to the RISE 2010 undergraduate summer research program. Each graduate student team member was paired with a RISE alumnus/and used that relationship as a springboard to connect with a larger cohort of science/engineering majors and faculty at the school. The graduate student will visit one or more colleges to give a presentation, highlighting the scope and vibrancy of research at Rutgers and advising on preparing for and applying to graduate school. These connections have culminated into our Winter Forum on campus. We invited undergraduates and their faculty advisors from the target schools in NJ for a day of posters and workshops.

***Undergraduate Competition for K12:*** The ERC-SOPS announced a competition to promote engineering education in K-12 schools for 2009-2010. The pilot program at Rutgers paired teams

**Figure 1-2:** JP Stevens HS student Kelly begins chemical mixing process before recrystallization.



of engineering student chapters and an area K-12 school to work together to develop a hands-on learning activity that addresses curricular needs using different engineering concepts. Each student group developed a hands-on demonstration or experiment that illustrates an important concept in engineering, while also contributing to the K-12 curriculum learning objectives. The group, working in conjunction with an area school, submitted a proposal that describes the specific activity in enough detail so that it could be judged by a group of chemical engineers and educators as to its effectiveness. An assessment component was an important required element of the project. The student group completed a report of the project; including instructions on how to construct the demonstration/ experiment, the curricular goals and outcomes, and the success of the first

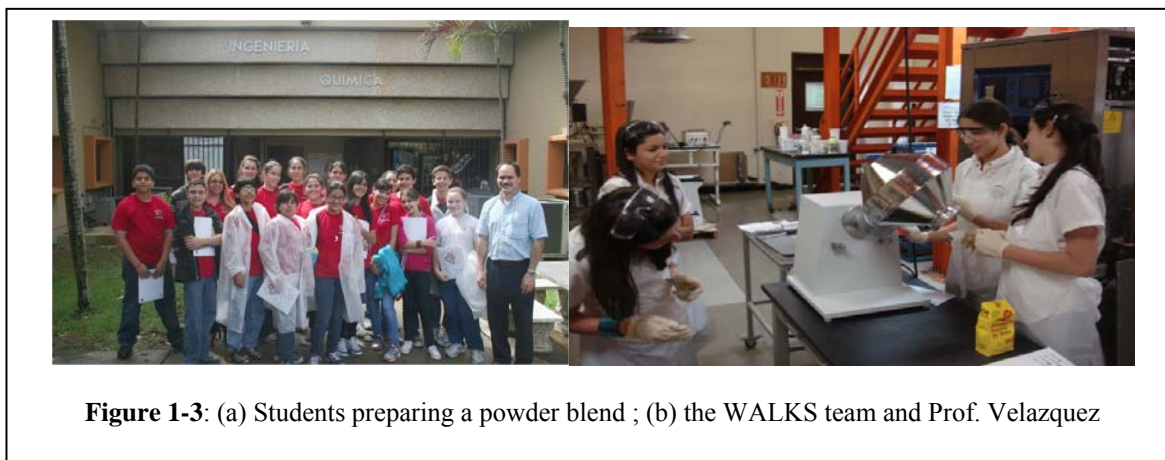
implementation of the project. The report will be included on the ERC web page for public access and dissemination to a broader audience. Feedback from the teachers was extremely positive; they were impressed with the proposals and experiment procedures written by the Rutgers undergraduate students.

Awards of \$1,000 will be provided to each student chapter/ organization. Many engineering student chapters/ organizations submitted proposals by only 3 were chosen:

- **MEET/NSBE** – *Minority Engineering Education Taskforce/ National Society of Black Engineers*
  - 2 Proposal/Engineering projects: **Boeing Flight Gliders**, a technical project in which MS and HS students designed gliders made of balsa wood.
- **AIChE** – *American Institute of Chemical Engineers*

- 1<sup>st</sup> Proposal/Engineering project: **Cure Your Own Headache: Acetaminophen from Lab to Plant**, HS students synthesized Acetaminophen, the active pharmaceutical ingredient in Tylenol and Vicodin.
- 2<sup>nd</sup> Proposal/Engineering projects: **From Bag to Batch: “The Engineering Behind the Scale Up of Ice Cream”**, MS students learned the fundamental chemistry behind ice cream.
- **Phi Sigma Ro - National Social Sorority for Women in Engineering and Engineering Technology**
  - 1<sup>st</sup> Proposal/Engineering project: **Dry Ice Boat**, educated MS students on different types of energy and how they can be applied to simple projects.
  - 2<sup>nd</sup> Proposal/Engineering projects: **Make Your Own Cleaning Products**, HS students tested the communication skills between engineers and marketers.

**Visit to UPRM Pharmaceutical Engineering Center Facilities:** A group of 18 seventh and



eighth-grade students and their teacher from Winnie’s Active Learning Kids School (WALKS), Mayagüez, Puerto Rico visited our Pharmaceutical Engineering Center Facilities and participated in three hands-on interactive modules developed in collaboration with the Science on Wheels (SONW) Educational Center. The survey completed by 11 girls and 7 boys displayed very positive results. 90% of the students gave the facilities, projects in the lab, and research personnel an excellent score on a scale from poor to excellent.

The modules included:

- Dissolution of a Tablet in Different Solution Media
- Compression and Friability Test for tablets
- Microcrystalline cellulose suspensions

### 1.3.2 Advances in Discovery

#### **Particle Formation and Stabilization:**

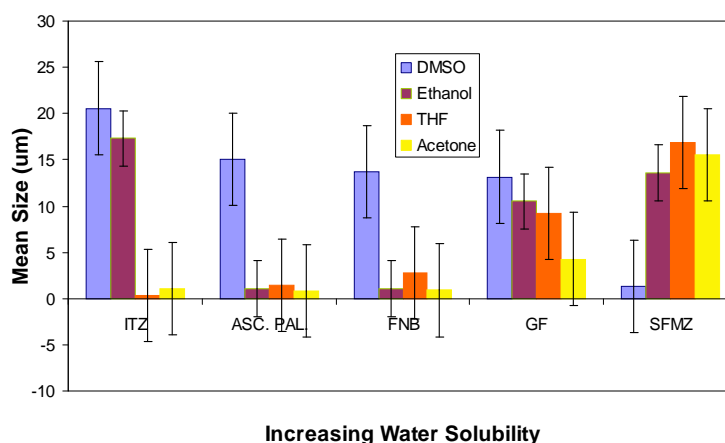
Several particle formation techniques as well as size reduction methods have been investigated. The use of an ultrasonically driven T-shaped mixing device, which is inherently scalable by parallelization, is highlighted here and was shown to significantly improve the mixing of solution and antisolvent streams for precipitation of ultra-fine particles in a continuous operation mode. It is shown that uniform mixing conditions, one of two important steps in liquid antisolvent (LAS) process, ensures rapid and uniform supersaturation making it a precipitation controlled process where the particle size is not further affected by the mixing conditions and results in the precipitation of ultrafine particles with narrow particle size distribution (PSD). Multiple APIs are considered and LAS precipitation in the size range

of 100 nm – 10 µm has been carried out from their organic solutions in acetone, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and ethanol (EtOH). Classical theory of homogeneous nucleation has been used to analyze the result which suggests that higher nucleation rate results in finer particle size. The most interesting outcome of this work is that experimental determination of degree of supersaturation indicates that higher supersaturation does not necessarily result in higher nucleation rate and nucleation rates can be correlated to the solvent polarity. Table T-A-2 lists the properties of the APIs investigated, while Figure T-A-3 shows how the solubility in water as well as solvent polarity impact particle size. For example, with THF, as the API water solubility increases, the particle size also increases, which is as per the conventional understanding. However, when higher polarity solvent such as DMSO is used, that trend is completely reversed.

**Simultaneous Surface Modification and Size Reduction: Improved Dissolution and AFM Characterization:** Scalable, continuous operation is employed using a fluid energy mill (FEM) to size reduce API powders which are pre-mixed with surface modifiers such as nano-silica,

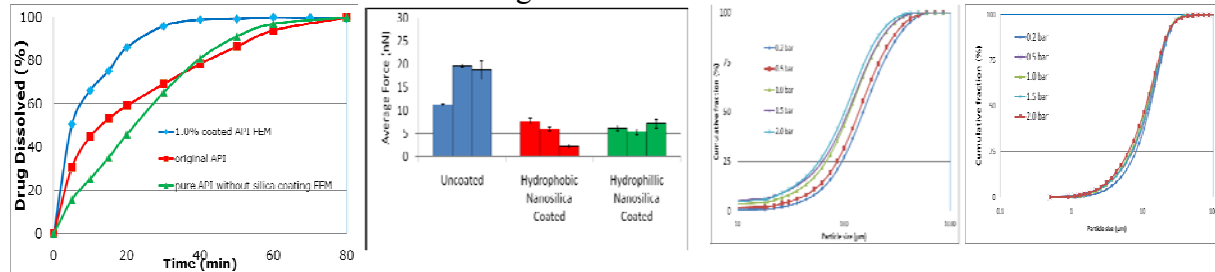
API	MW	MP (°C)	MP(°K)	Sol(mg/L)	Log P
Itraconazole	705.6	166	439.35	4.72 x 10(-3)	6.5
Ascorbyl Palmitate	414.5	167	440.15	0.34	5.66
Fenofibrate	360.8	80.5	353.65	0.50	5.3
Griseofulvin	352.8	220	493.15	8.64	2.18
Azodicarbonamide	116.1	225	498.15	35.0	1.52
Sulfamethoxazole	253.1	167	440.15	610	0.7

**Table 1-1:** Physico-Chemical Properties and Solubilities APIs.



**Figure 1-4.** Effect of Solvent Polarity On Mean Sizes of the six APIs, depicting a strong influence of solvent polarity (decreasing order, DMSO, ethanol, acetone, and THF).

amino-acids or waxes for improved flow and dispersion. When coated with hydrophobic or hydrophilic nano-silica, the method provides freely flowing API powders (less than 20 microns, down to 5 microns) that could be used in direct blend and compression tableting and exhibit improved dissolution (with hydrophilic silica). As shown in Fig.1-5, while size reduction is expected to provide improved dissolution, the agglomeration of fine powders cause poorer dissolution. On the other hand, when surface coating is employed, the size reduction yields the improved dissolution as expected. Direct AFM measurements were carried out for uncoated and coated fine powders, indicating reduction in inter-particle force down to one third the original value as shown in Figure 3.



**Figure 1-5.** Dissolution of original (~100 µm) API, size reduced API without silica (~15 µm) and size reduced (~15 µm) but with coating of silica.

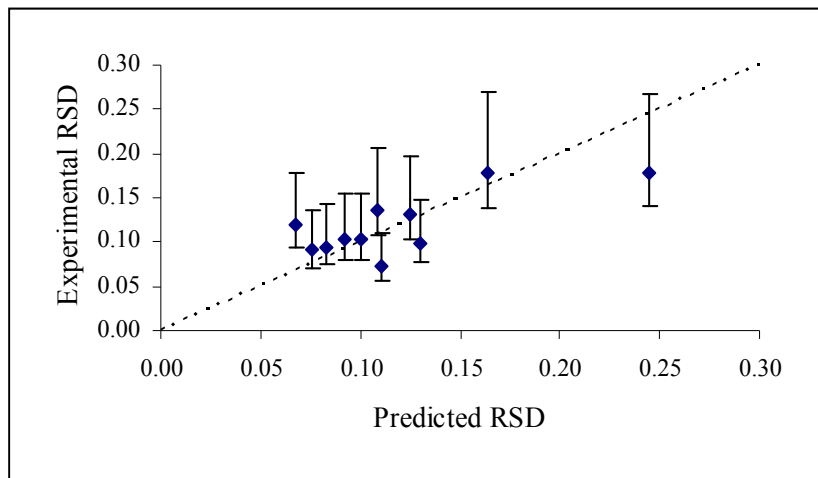
**Figure 1-6.** PSD as a function of Rodos dispersion pressure. Left, Direct AFM measurements of uncoated and coated ~10 µm powders. Middle, original (~100 µm) API, with a wide divergence of values at D<sub>50</sub>, implying significant agglomeration. Right, size reduced API with silica surface modification (~15 µm). Even for very fine size, divergence at D<sub>50</sub> after surface modification is negligible, implying almost lack of agglomeration and low cohesion.

used API powders also disperse very well as shown in Fig. 1-6 using Rodos/Helos, a particle-sizer from Sympatec, where the spread in the PSD as a function of dispersion pressure indicates poorer dispersibility or higher agglomeration tendency of powders. As shown in Fig.1-6, the dispersion of very fine, surface modified powder is significantly better than the original 7 times larger non-surface-modified powder. These results indicate the ability to create highly dispersible, non-agglomerated fine API powders, allowing for improved dissolution and lack of agglomeration.

**Macroscopic models for continuous blender design:**

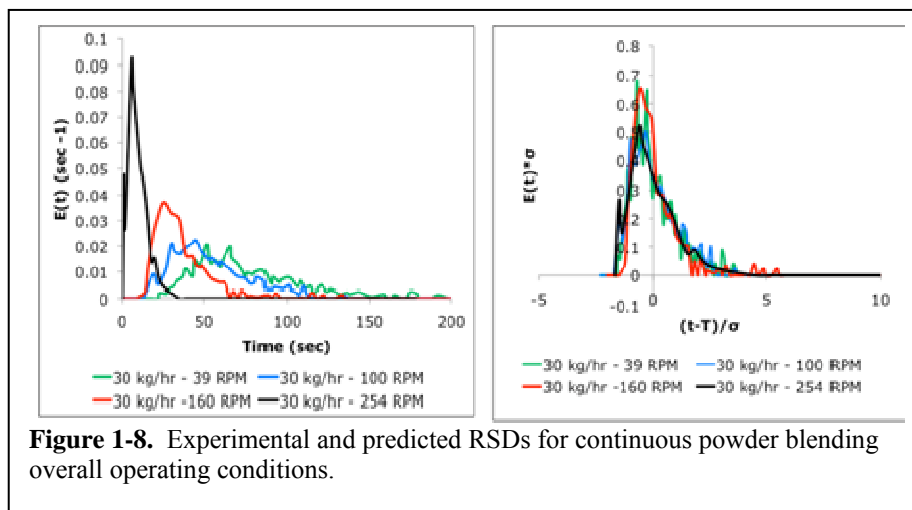
Continuous mixer performance has been experimentally characterized over a large range of operating conditions. The first set of experiments was performed using Acetaminophen (APAP) as the API and a second set is now being performed using Caffeine. Residence time

distributions have been shown



**Figure 1-7.** Dimensional and non-Dimensional RTDs for continuous powder blending.

to have similar shapes for all operating conditions (Fig 1-7) when made non-dimensional in terms of the mean residence time ( $\tau$ ) and mean centered variance ( $\sigma$ ). This simplification to a

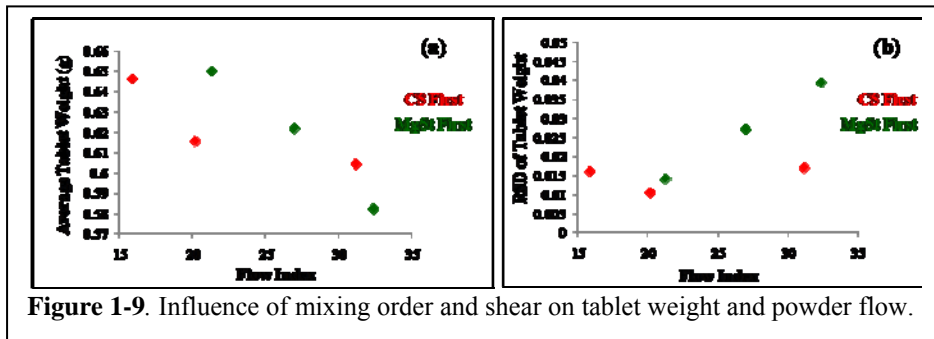


**Figure 1-8.** Experimental and predicted RSDs for continuous powder blending overall operating conditions.

characteristic non-dimensional residence time distribution allow for prediction of blender performance over a wide range of flow rates and impeller speeds with a single model parameter – the mean residence time. We have previously shown that the characteristic RTD can be modeled as a series of well mixed tanks.

With this approach, the residual standard deviation (RSD) in the blended powder exiting the mixer is successfully matched over a wide range of conditions (Fig 1-8).

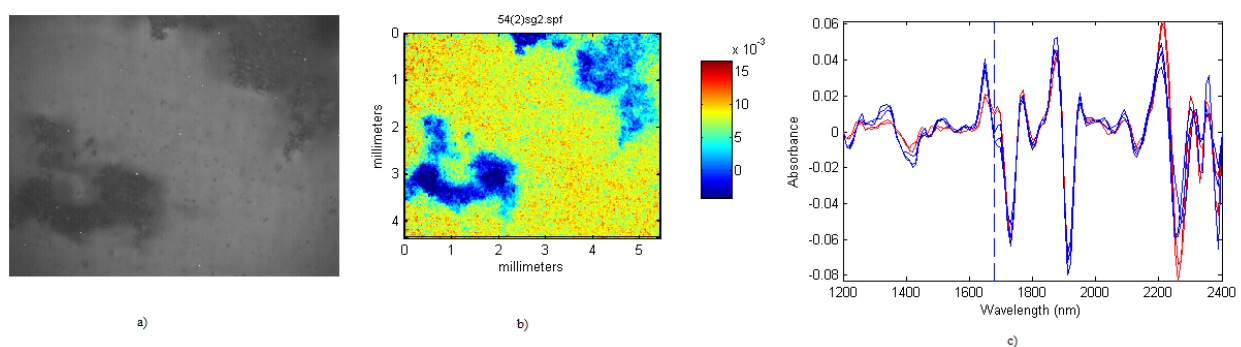
**Influence of Shear Stress and Strain on Flow, Tablet Weight and Hardness:** The relative impact on the final properties of tablets of shear, order in which blend ingredients are added and powder flow properties has been on occasion been observed in practice and the subject of various conjectures. To begin to understand these factors a systematic study has been initiated with some quite interesting preliminary results. Sheared powder blends (the formulation contains 49 % Pharmatose, 100  $\mu$ m, 49% Avicel, 90  $\mu$ m, 9% acetaminophen, 19  $\mu$ m, 1% MgSt and 1% Cab-O-Sil) were tested for powder flow, tablet weight and hardness. It was found that the mixing order was ineffective in changing the overall flow of powder blend at various shear conditions (first all ingredients low sheared in a v-blender without intensifier for 5 min at 15 rpm; followed by a high shear rate in a coquette cell for all the samples at 80 rpm, at three different shear strain of 40,



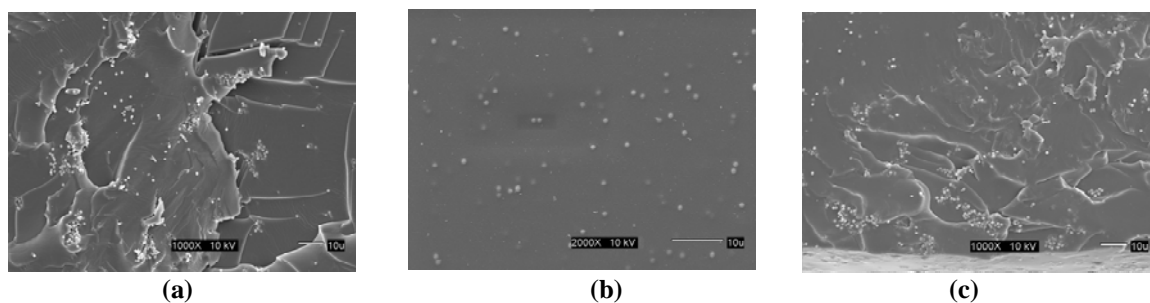
**Figure 1-9.** Influence of mixing order and shear on tablet weight and powder flow.

160 and 640 rev. However, the correlations of tablet weight to flow index (a flow parameter derived from the avalanching of powder in a rotating cylinder) in GDR shown in Fig. 1-9 (a) indicated that average tablet weights were different for two sets of blends mixed with CS (colloidal silica) and MgSt. Although the presence of CS and MgSt in both the sets of blends had acceptable powder flowability for direct compression done at 12 kN, the average tablet weights were slightly higher for the tablets of M.O-1. Such class of tablets also exhibited less weight variability as seen in Fig.1-9(b). From the present investigation, it is apparent that shear, mixing order and powder flow could indeed all have a significant impact on compaction of tablets.

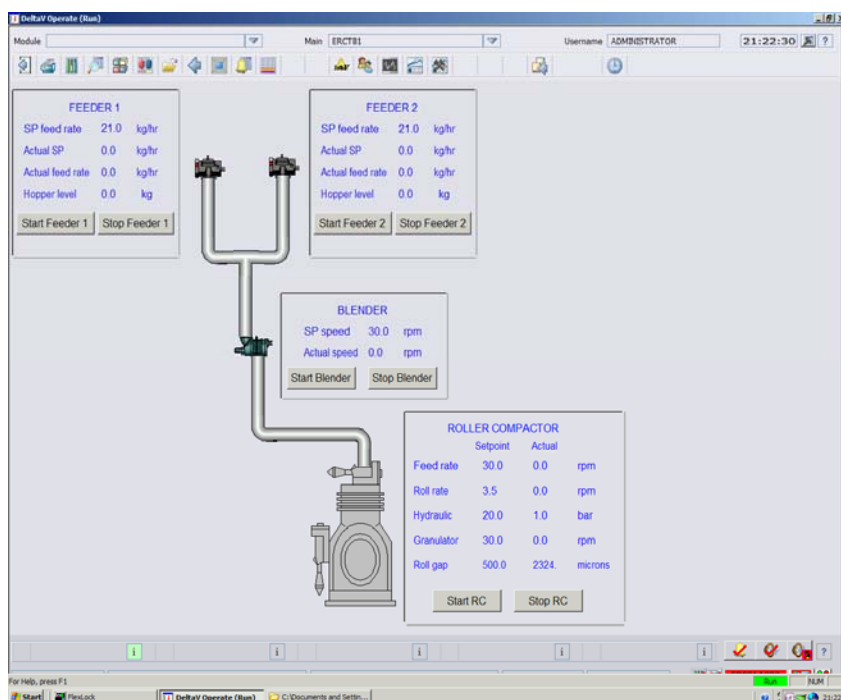
**Encapsulation of API Particles in Crosslinked Hydrogel Networks: Stability and Loading Optimization:** Particle encapsulation in polymer systems has been used in several industrial applications in the biomedical and pharmaceutical fields. This investigation focuses on the physicochemical interaction between particles and crosslinked hydrogel networks for the creation of homogenous dispersed membranes. Factors such as particle charge, size, concentration, and membrane charge were examined. For this purpose silica particles functionalized with various surface charges were employed as model particles and these were encapsulated in crosslinked hydrogel membranes of various compositions. Figs. 1-10 and 1-11 illustrate the qualitative (SEM imaging) and quantitative measurements (NIR imaging) performed. Particle aggregation appears to be a combined function of size, charge and concentration. Current work will focus on data analysis to quantitatively identify aggregation and rheological measurements to understand the mechanical effects of these particulate on such systems.



**Figure 1-10.** NIR imaging for positive membrane with 100  $\mu\text{m}$  negatively charged silica particles: (a) Microscopy image; (b) NIR image at 1680nm; (c) different areas spectrum, red for high concentration and blue for low concentration.



**Figure 1-11.** SEM imaging of 1  $\mu\text{m}$  sized silica particles with various polymer structures: (a) positive membrane and negative particles; (b) negative membrane and positive particles; (c) neutral membrane and negative particles.



**Figure 1-12:** TOPS-DeltaV User Interface for TB1

OPC. Fig. 1-12 displays a screenshot of the user interface. The functionalities provided include operator remote start, stop and set point changes as well as consistent, steady-state model based adjustment of all set-points in response to operator initiated changes in global variables such as throughput rate or composition changes. Both conventional PID and model predictive control strategies can be employed as required by process dynamics.

### 1.3.3 Advances in Research Infrastructure

**New Faculty Additions to CSOPS:** The ERC team has been strengthened by the addition of three new faculty members. **Dr. Ecevit Bilgili** whose research interests cover many aspects of the production and characterization of particulate materials has joined the NJIT Chemical, Biological and Pharmaceutical Engineering Department as an Assistant Professor. His expertise in nanoparticle production brings new depth to the project A1 team. With PhD studies at IIT in Chicago and industrial experience at Merck, he is well prepared to assist in CSOPS commercialization efforts. **Dr. Rafael Méndez Román**, who completed his PhD studies at UPRM, followed by a two year post doctoral appointment in Dr. Muzzio’s laboratory at Rutgers, has joined the Chemical Engineering Department of UPRM as an Assistant Professor of Chemical Engineering. He will continue his research in powder characterization, flow, and powder processing equipment especially in support of C-PEDaL. **Dr. Rohit Ramachandran** will bring his expertise in mathematical modeling, control, and



**Figure 1-13:** Professors Bilgili, Mendez, and Ramachandran

**Dry Granulation Embodiment of Test Bed 1 is under Integrated Operation:** The TOPS-based integrated framework has been implemented using the Emerson DeltaV process control system to operate the dry granulation embodiment of TB1. DeltaV provides communication with two Schenck AccuRate loss-in-weight feeders (for API and excipients), a Gericke blender, and an Alexanderwerk roller compactor with granulator. All process operating history is recorded in DeltaV’s continuous historian and the data made available for external applications through

optimization to the ERC through his position as an assistant professor in the Rutgers Chemical and Biochemical Engineering Department. A PhD graduate of Imperial College (UK), he has most recently been a postdoctoral associate at MIT. He will be contributing to several aspects of Test bed 1, especially modeling and process control.

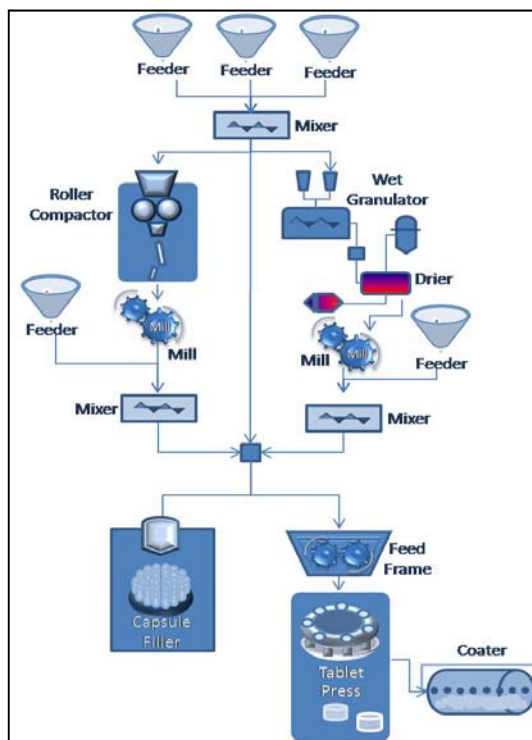
**Commercialization Project:** Building on the progress made in Test Bed 1, the Center has been awarded a supplemental grant by the NSF to advance the commercialization of continuous manufacturing technology. The three year project has three main goals:

Goal 1: To create viable, highly capable commercial sources of integrated continuous manufacturing technology in partnership with C-SOPS member companies.

Goal 2: To transfer to the commercialization partners, on an ongoing basis, the knowledge required to design, specify, integrate, implement, and optimize continuous manufacturing systems for a growing variety of pharmaceutical products

Goal 3: To expand ongoing research efforts in order to develop methods for integrating additional operations and expanding the range of products that can be manufactured continuously.

As captured schematically in Fig.1-14, the project will span all three main routes to the manufacture of solid oral dosage form products (direct compression, dry granulation and wet granulation), will include the three unit operations required for wet granulation that are not within the current scope of Thrust B (fluid bed drying, granule milling and wet granulation) and additionally will address capsule filling and tablet coating operations. Working in partnership with an integrator company as well as with equipment and instrument manufacturers, we hope to be able to make available to pharmaceutical companies turn-key integrated continuous manufacturing systems. A number of the major center member companies have expressed interest in the adding such lines to their manufacturing sites when they become available.



**Figure 1-14:** Scope of Continuous manufacturing commercialization project

**Commercial scale facility for drug loaded polymer film formation:** During the past year, major progress has been made in terms of acquiring a commercial scale film-line from FMC Corporation, a significant addition to the ERC infrastructure. The donation made to ERC/NJIT is valued at over \$0.5M, and includes; (a) Pilot Casting line (by Sandvik), (b) Slot Die with Positioner (Premium Die Corp), (c) Multi-shaft Mixer (Premier Mill), (d) Water Heater/Chiller (AEC), (e) Metering/Dosing Pump (Moyno, Inc), and (f) Floor Scale (Mettler-Toledo). This line was designed for aqueous HPMC films, and could produce 1000's of "strip-films" units per hour; making is suitable as a pilot scale plant for manufacturing of engineered particle based active substance delivery for test-bed 2 applications. The main casting unit consists of film casting system and a bank of driers. Each drier is individually controlled for temperature as well as air flow rate and will be retrofitted to handle organic solvent drying and vapor collection. The film casting system will be integrated with other test-bed operations including suspension formation. The unit is depicted in Fig.1-14. This will jump start the commercialization activity



**Figure 1-15.** Two photographs of the FMC film-line. Left, the gel castor unit over the stainless steel belt. Right, three banks of oven through which the belt passes for drying the film.

based on test-bed 2 platform. In addition, several member companies have shown interest in use of this line for their development work for strip-film based products. Both FMC and Sandvik have expressed interest in helping the ERC in further development of this system.

### ***Response to Past Comments from 2009 NSF Site Visit Panel***

See Section 6 for a summary of responses to comments from the Site visit panel relevant to Section 1.

*Web Table 1: Quantifiable Output*

<b>Table 1: Quantifiable Outputs</b>					
<b>Outputs</b>	<b>Early Cumulative Total [1]</b>	<b>Jun 01, 2006 - Oct 31, 2007</b>	<b>Nov 01, 2007 - Dec 31, 2008</b>	<b>Jan 01, 2009 - Dec 31, 2009</b>	<b>All Years</b>
<b>Publications That Result from Center Support</b>					
In Peer-Reviewed Technical Journals	0	15	37	36	88
In Peer-Reviewed Conference Proceedings	0	3	17	53	73
In Trade Journals	0	0	0	0	0
With Multiple Authors:	0	0	0	33	33
Co-authored with ERC Students	0	0	0	32	32
Co-authored with Industry	0	0	0	4	4
With Authors from Multiple Engineering Disciplines	0	0	0	3	3
With Authors from Both Engineering and non-Engineering Fields	0	0	0	0	0
with authors from multiple institutions	0	0	0	1	1
<b>Publications That Result from Associated Projects in the Strategic Plan</b>					
In Peer-Reviewed Technical Journals	0	0	33	32	65
In Peer-Reviewed Conference Proceedings	0	0	68	6	74
<b>Publications Resulting From Sponsored Projects</b>					
In Peer Reviewed Technical Journals	N/A	0	33	0	33
In Peer Reviewed Conference Proceedings	N/A	0	3	0	3
<b>Participating Industrial and Practitioner Organizations</b>					
Members	0	21	23	25	69 [2]
Affiliates	0	0	0	0	0 [2]
Contributing Organizations	0	1	0	0	1 [2]
<b>ERC Technology Transfer</b>					
Inventions Disclosed (submitted to agencies by	0	2	1	1	4
Patent Applications Filed	0	0	3	0	3
Patents Awarded	0	0	0	3	3
Licenses Issued	0	0	0	0	0
Spin-off Companies Started	0	0	0	0	0
Estimated Number of Spin-off Company Employees	0	0	0	0	0
Building Codes Impacts	0	0	0	0	0
Technology Standards Impacts	0	0	0	0	0
New Surgical and other Medical Procedures Adopted	0	0	0	0	0
<b>Degrees to ERC Students</b>					
Bachelor's Degrees Granted	0	0	0	1	1
Master's Degrees Granted	0	0	0	3	3
Doctoral Degrees Granted	0	0	8	6	14
<b>ERC Graduates Hired by</b>					
Industry:	0	0	4	5	9
ERC Member Firms	0	0	1	0	1
Other U.S. Firms	0	0	3	4	7
Other Foreign Firms	0	0	0	1	1
Government	0	0	0	0	0
Academic Institutions	0	0	0	5	5
Other	0	0	1	0	1

Web Table 1: Quantifiable Output (continued)

Table 1: Quantifiable Outputs					
Outputs	Early Cumulative Total [1]	Jun 01, 2006 - Oct 31, 2007	Nov 01, 2007 - Dec 31, 2008	Jan 01, 2009 - Dec 31, 2009	All Years
<b>ERC Influence on Curriculum</b>					
New courses based on ERC research that have been approved by the curriculum committee and Currently offered, on-going courses with ERC content	0	7	9	20	36
New Textbook Chapter Based on ERC Research	0	0	0	3	3
New Textbooks Based on ERC Research	0	0	0	0	0
Free-Standing Course Modules or Instructional CDs	0	0	8	0	8
New full degree programs based on ERC research	0	0	1	0	1
New degree minors or minor emphases based on ERC research	0	1	0	0	1
New certificate programs based on ERC research	0	0	0	0	0
<b>Active Information Dissemination/Educational Outreach</b>					
Workshops, Short Courses, and Webinars [3]	0	2	12	3	17
Number of participants that attended activity	N/A	N/A	0	100	100
Seminars, Colloquia, Invited Talks, etc.	0	3	17	86	106
ERC Sponsored Educational Outreach Events for K-12 students	0	0	0	8	8
Number of students that attended activity	0	11	0	285	296
Number of teachers that attended activity	0	0	0	32	32
ERC Sponsored Educational Outreach Events for Community College or Undergraduate students	0	0	0	5	5
Number of students that attended activity	0	0	0	84	84
Number of faculty that attended activity	0	0	0	10	10
<b>Personnel Exchanges</b>					
Student Internships in Industry	0	6	3	7	16
Faculty Working at Member Firm	0	0	1	0	1
Member Firm Personnel Working at ERC	0	0	0	0	0

[1] For Centers in operation for more than five years.

[2] Cumulative count of Individual Firms/Organizations may not equal the sum across all years.

[3] For years prior to 2009, the values include 'Workshops and short courses to industry' and 'Workshops and short courses to non-industry groups'

[4] New courses currently offered and approved by the curriculum committee are only counted in the first year that they are

*Web Table 1a: Average Metrics Benchmarked Against All Active ERCs*

Table 1a: FY2008 Average Metrics Benchmarked Against All Active ERC's and the Center's Tech Sector					
Metric	Average All Active ERC's FY2008	Average Biotechnology Sector FY2008	Average for Class of 2006 - FY 2008	Engineering Research Center for Structured Organic Composites for	Engineering Research Center for Structured Organic
	(20 ERC's)	(7 ERC's)	(5 ERC's)	FY2008	FY2009
<b>Industrial Member Firms</b>	18	11	24	23	25
Small	38%	45%	54%	30%	36%
Medium	14%	8%	12%	4%	8%
Large	49%	47%	34%	65%	56%
<b>Non-Industry Sector Firms</b>	1	0	2	0	0
<b>Total Member Organizations</b>	19	11	26	23	25
<b>Affiliate Organizations</b>	1	2	1	0	0
<b>Contributing Organizations</b>	1	2	1	0	0
<b>Total Membership Fees Received</b>	\$				
<b>Direct Sources of Support [1]</b>	\$				
NSF	66%	67%	69%	61%	57%
Industry	8%	8%	12%	22%	25%
Other Federal	0%	0%	0%	0%	0%
Academic	23%	23%	17%	17%	18%
State	2%	0%	0%	0%	0%
Other	0%	1%	1%	0%	0%
<b>Associated Project Support</b>	\$				
<b>ERC Personnel &amp; Educational Participants[2] [3]</b>	687	753	2,053	506	326
Leadership Team [7]	13	13	12	13	15
Faculty [2] [4]	44	44	40	41	51
Graduate Students [2]	87	91	123	100	57
Undergraduate Students [2]	87	168	248	118	75
REU Students	11	13	26	54	20
K-12 Teachers [3]	111	22	15	16	39
K-12 Students [3]	1,437	457	1,537	126	285
Faculty that attended ERC Sponsored Educational Outreach Events [3]	2	6	0	0	10
Community College or Undergraduate students that attended ERC Sponsored Educational Outreach Events [3]	26	73	0	0	84
% Women [5] [6]	28%	35%	34%	38%	41%
% Underrepresented Racial Minorities [5] [6]	13%	12%	11%	7%	12%
% Hispanic [5] [6]	10%	9%	11%	28%	27%
<b>Publications</b>	<b>Average</b>	<b>Average</b>	<b>Average</b>	<b>Total</b>	<b>Total</b>
In Peer Reviewed Technical Journals	23	16	27	37	36
In Peer Reviewed Conference Proceedings	29	17	50	17	53
Multiple Authors: Co-Authored With ERC Students	32	18	40	0	32
Multiple Authors: Co-Authored With Industry	4	3	9	0	4
<b>Intellectual Property</b>	<b>Average</b>	<b>Average</b>	<b>Average</b>	<b>Total</b>	<b>Total</b>
Invention Disclosures	4	6	5	1	1
Patent Applications	4	6	4	3	0
Patents Awarded	2	4	0	0	3
Licenses (patents, software)	3	1	0	0	0
<b>Education and Outreach Outputs</b>	<b>Average</b>	<b>Average</b>	<b>Average</b>	<b>Total</b>	<b>Total</b>
New Courses Developed	1	2	4	9	20
Currently offered, on-going courses with ERC content	10	4	10	0	0
New Full Degree Programs	0	0	0	1	0
New degree minors or minor emphases	0	0	0	0	0
New certificate programs based on ERC research	0	0	0	0	0

[1] Includes new support (unrestricted cash, restricted cash, and in-kind donations) from table 9 only. Residual funds carried over from previous years are not included in benchmarking figures.

[2] Includes total ERC Personnel from table 7.

[3] Includes participant values from Table 1 Quantifiable Outputs.

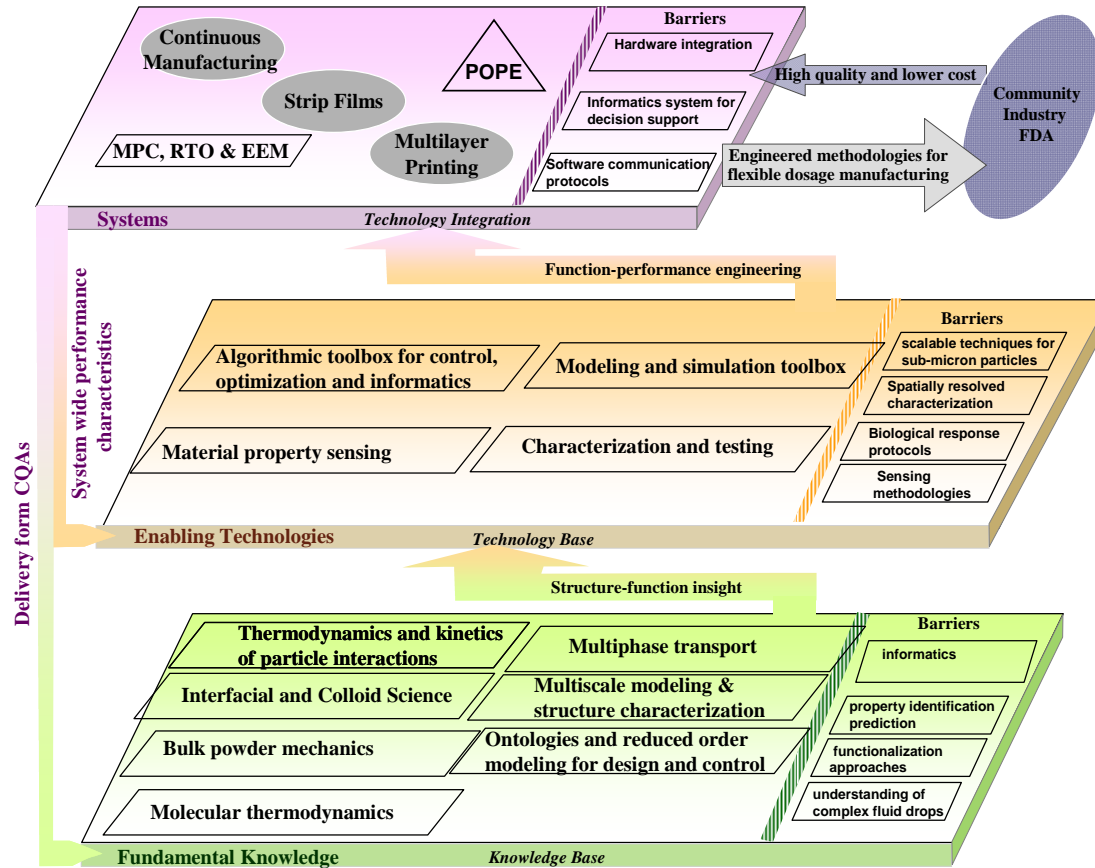
[4] Includes Directors, Education Program Leaders, Thrust Leaders, Senior Faculty, Junior Faculty, and Visiting Faculty from table 7.

[5] These data do not include K-12 Student or Teacher Participants in the percentage calculations. Demographic data are not collected for K-12 Student or Teacher Participant. We only collect the total number of K-12 Student and Teacher Participants.

[6] The percentage calculations are based on the following categories of Personnel only:  
Faculty, Graduate Students, Undergraduate Students, Directors, Thrust Leaders, Research Thrust Management & Strategic Planning, Administrative Director, and Industrial Liaison Officer.

[7] Includes Directors, Thrust Leaders, Education Program Leaders, Research Thrust Management & Strategic Planning, Administrative Director, and Industrial Liaison Office

## ERC Strategic Framework: Muzzio, SOPS, Rutgers



**Figure 2-3: ERC-SOPS three-plane strategic plan chart**