

***SUMMARY REPORT ON THE
CPAC SUMMER INSTITUTE 2009
TOPICS IN PROCESS ANALYSIS AND CONTROL***

***Product and Process Optimization using Micro-
Instrumentation and Process Intensification: with an Emphasis
on Improvements in Bio-Processing (particularly Bio-Process
Intensification)***

***A Valuable Tool for Achieving Quality by Design (QbD)
using Process Analytical Technology (PAT)***

JULY 21-23, 2009 Seattle, Washington

The 2009 CPAC Summer Institute was held in an informal format, with technical presentations, and time allotted for open discussion and brainstorming on topics that arose from this interaction. The informal environment created a successful format for bringing together chemists, biologists, measurement scientists, and process related engineers from industry and academic institutions drawn from both CPAC and non-CPAC sponsors.

The multi-disciplinary program was structured to include plenary talks on broad topics such as climate change, needs in bio-processing, green chemistry, bio-energy, and water. Case studies highlighted the selected topics and demonstrated the results of implementation of quality by design (QbD). There were then talks that presented advances in technologies that will enable future process analytical technology (PAT) developments. These included areas like sensors, micro-reactors, micro-fluidics, and sampling. Advances in process operations such as separations and purification were also presented and discussed.

CONFERENCE SITE

The Summer Institute was held in two locations. Tuesday and Wednesday, July 21 and 22, at the University of Washington, Seattle, WA, and Thursday, July 23, at a Club House in the nearby Cascade Mountains.

OBJECTIVES AND SCOPE

CPAC has an established track record in fostering academic/industrial/national laboratory interactions, which aims at bridging the gap between basic research and full-scale process/product development. CPAC's Summer Institute (SI) provides continuing education opportunities in the areas of advances in measurement science linked to process control and process intensification.

The theme of miniaturization, initiated at the first Summer Institute in 1996, emphasized the futuristic concept of the versatile micro-analytical system (VMAS) and the feasibility of developing VMAS for process control. The Summer Institute objectives are to explore the needs of the end-users for new micro-measurement technologies and the potential impact of these technologies on product discovery and process control. Since 1996 the Summer Institute discussions have progressed through various concepts related to the miniaturization of measurement instrumentation, while refining user needs and process control impacts. Past participants have helped guide the direction of the Summer Institute toward this meeting's topic: **Micro-Instrumentation supporting High Throughput Experimentation (being used in many phases of product development and process optimization) and Process Intensification.**

Process Intensification, an increasingly important area utilizing miniaturization, involves approaches for drastic reductions in capital expenditure, resource use and waste generation per unit mass of product. This is achieved by reducing the footprint of the production unit operations often by employing micro-reactor concepts and/or combining unit operations such as reactive distillation. CPAC is now developing measurement strategies that enable these more efficient though more complex processing concepts. In support of these efforts the New Sampling/Sensor Initiative (NeSSI™) is being deployed for implementing new measurement tools, including various CPAC technologies. A key part of the outcome of the Summer Institutes is in the new approaches to education and training in these various related processing fields.

To explore this year's theme, **Product and Process Optimization using Micro-Instrumentation and Process Intensification: with an Emphasis on Improvements in Bio-Processing (particularly Bio-Process Intensification)** the CPAC Summer Institute (July 21-23, 2009) opened with an emphasis on historical approaches in the chemical and pharmaceutical industries with an indication of the needs for similar improvements in Bio-processing. A series of presentations addressed the challenges in Bio-processing, which involves optimization needs within the Bio-technology, Bio-energy, and Bio-sustainability industries. Jim Thomas of Amgen talked about **Needs in the Bio-processing Industry**. Kurt VandenBussche of UOP presented **Diversification of the World's Energy Sources and its Challenges for the Technical Professions**. John Gardner of the development office of Washington State University described the **The Third Wave of U.S. Bioproducts**. Ray Chrisman of Atodyne Technologies, and Affiliate Faculty, Forest Resources, UW, talked about **Challenges in Global Warming**, incorporating comments from a recent presentation by Woodrow W. Clark II of the Milken Institute. In addition, two important topics of global interest today (**Green Chemistry**, by Jim Ciszewski, EPA, and **Water Quality**, by Keith Pauley, MATRIC) were also covered in the plenary session.

A variety of case studies were presented and discussed. These case studies began with the new pharmaceutical production concept which was discussed in two presentations **Quality by Design (QbD)** - by Carl Longfellow, Wyeth and **Formulation Optimization of Transdermal Drugs Using Quality by Design**, by Barry Gujral, Noven. The utilization of micro-scale processing equipment was described in two presentations, **the effective use of micro-reactors** - by Céline Guermeur, Corning, and **Improved Chemical Synthesis Using Automated Microfluidic Platforms**: Jonathan McMullen of Klavs Jensen's group at MIT. The advantages of the coupling of microreactors with real-time measurements were described by Brian Marquardt, UW

CPAC / Applied Physics Lab, in **Preparation of Active Pharmaceutical Ingredients (API) by Continuous Processing**: and by Seth Rogers, Seahorse Bioscience, in **High Throughput Bioprocess Characterization and Optimization**. In addition there were two case studies presented describing issues in the bioenergy field – **Bio-Energy**: Greg Crabb, Syngenta and **Impact of Process Economics for Green Energy**: Tom Maliszewski, MATRIC.

The focus of the presentations then shifted to the description of the significant advances in measurement strategies that compliment micro-unit operations developments and new sampling approaches. These advances were elucidated in selected talks on technology advances in both unit operations (reactions, mixing, separations, and fluidics) and in measurement sciences, with a focus on improvements in miniaturization and related process intensification efforts. The technology advancement presentations included:

- **Gas Chromatographic Technologies for Bioprocess Analysis**: Rob Synovec, Chemistry, UW
- **The Need for Multidimensionality in Analytical Thinking, Chromatographic Developments as an Example**: Hernan Cortes, HJ Cortes Consulting, LLC
- **Advances in Micro-Fluidics**: Bahram Fathollahi, Caliper Life Sciences
- **Exploring the Need for Distributed Miniaturized Sensors for Accurate Monitoring of Inhomogeneities and Nutrient Gradients in Bioreactors**: Scott Gilbert, Crystal Vision-Microsystems SA and CPAC Visiting Scholar
- **Portable Surface Plasmon Resonance Instrumentation for Rapid, Versatile Biodetection**: Clement E. Furlong and Scott Soelberg, Department of Medical Genetics, UW
- **Development and In-Situ Reaction Monitoring**: Paul Scholl, Mettler Toledo
- **Monitoring Dynamic Processes in Micro Fluidic Streams**: Lloyd Burgess, CPAC, University of Washington
- **Selected Micro-Sensor Developments**: Joe Stetter, KWJ Engineering
- **Self-Assembled Micro-analytical Systems with an Emphasis on Wireless Connectivity**: Brian Otis, Electrical Engineering, UW
- **Multi-Channel Instrumentation for Fringing Electric Field (FEF) Sensors**: Alexander V. Mamihev, Electrical Engineering, UW
- **Optical Characterization of Random Nano Non-Uniformities**: Anatol Brodsky, Lloyd Burgess, and Gordon Mitchell, CPAC, UW
- **Characterization and Reproducibility of Vapochromic Sensors**: Kent Mann, University of Minnesota
- **The Chemometrics Role in Process GC**: Brian Rohrback, InfoMetrix Inc.
- **Rethinking Process GC**: John Crandall, Falcon Analytical Systems & Technology

The impact of these technology advances on the challenges within the Bio-processing industries and other industrial segments was discussed and action plans developed. Past action plans from CPAC Summer Institutes have resulted in successful collaborations between participants, including a multi-author book (*Micro-Instrumentation for High Throughput Experimentation and Process Intensification – a Tool for PAT*) published by John Wiley Publishing in 2007 and a successful series (2006-2009) of Satellite Workshops held in Rome, Italy.

As this year's focus was on improving the efficiency of chemical processing steps in material manufacturing, much of the discussion dealt with measurements in the dynamic and changing environment of a process stream. Thus sampling, measurement speed and more importantly precision and accuracy and long term reliability were key issues. The addition of bio-processing to the processes under discussion added new complexity to these basic measurement concepts.

An additional aspect of the discussion was the need in the pharmaceutical manufacturing world to determine the design space as part of the program of Quality by Design, QbD. This was seen as a very important and useful direction as it implies the need to fully characterize a process during the development stage. The need for process understanding required by the QbD approach was considered applicable across a broad range of processing industries and offers the potential to dramatically lower production costs by improving process efficiencies.

The need for better process understanding in bio-processing as well as traditional processing suggests that more work will be required in the early stages of process development. While deemed valuable, this requirement also will add additional conditions to real time analysis such as working with smaller sample sizes, higher probability of unknown components present and the additional complexity of sample preparation with small quantities of bio-samples. It also will require even more flexible reaction equipment availability as processes will need to be evaluated through a broad range of process variables.

In general the growth in micro-reactor capabilities is seen as a key factor in helping with process understanding. First, the process conditions in micro-reactors tend to be better understood and more uniform, and can be modeled with higher accuracy. Second, the processing conditions can be safely and rapidly varied over wide ranges for reaction characterization. Third, except for very large scale, they can be numbered up to insure production scale is as well understood as lab scale. Finally, due to the better understanding of their performance the derived information can be much more efficiently applied to operation in other types and scales of processing equipment.

Based on these understandings the group suggested 6 areas for additional discussion to better shape technology for utilization in the processing industries;

- The first concept is to help develop a needs list to drive the development of the remote analysis capabilities based on RFID sensing. More discussion is needed on what could be done and this then should be coupled with what needs to be done. There was also discussion about whether spatial information was needed if the devices were dispersed throughout a bioreactor or do they just need to detect the presence of inhomogeneities.

- With projected water quality concerns along with water shortages in the world, there will be a need to use purified recycled water. There was a general discussion on quality and a particular focus on the need to do more in the field of trace analysis of metals, endocrine disruptors and other contaminants.
- There was general consensus that there is a need for more focused discussion about measurement needs in the bio-processing field. This discussion is hampered by concerns about confidentiality concerning the various processes under development, such as protein therapeutics, and the reluctance of the bio-fuel manufacturers to describe manufacturing issues.
- The concept of Green Chemistry needs to be pursued based on its potential for reducing the environmental impact and improving energy utilization of processes. In addition, the use of improved unit operations for reaction, separations, mixing, etc. (often significantly reduced in size) offer new opportunities and challenges to the manufacturing community.
- The NeSSI standard and the current level of its development for on-line sampling systems was described. Given its high level of commercial implementation in the chemical and refining industries, it was felt that the technology should be rapidly expanded into the bio-processing field. Thus it was felt that more discussion of new tools for the bio-processing industry should occur.
- Finally, the concept of data alignment where variation in complex data sets can be removed to allow long term comparisons was viewed to be an area where more rapid deployment would be quite useful. It is projected that this concept will improve evaluation of analytical quality and enable diagnosis of sensor vs process deviations, leading to more rugged and reliable sensor operation.

The final outcome of the meeting, while not fully documented, was an extremely active discussion of new concepts to be explored which drew on the strengths of the multiple backgrounds present at the meeting. These include new sensing concepts, the coupling of sensors to various unit operations to enable new processing approaches and new utilization of new data analysis tools to enhance process understanding.

For further information, please contact: Nan Holmes, CPAC Administrative Manager,
 +1 206 685 4323, nan@cpac.washington.edu, Box 351700, University of Washington
 Seattle, WA 98195-1700