

PAT, NeSSI, and Sample Conditioning Systems: State of the Technologies and Future Directions

This article reviews the development of FDA's PAT Initiative along with CPAC's ANSI/ISA-76.00.02 (2002) (NeSSI) development. The intent is to show how the NeSSI components could contribute to the PAT philosophy and physical requirements.

Robert E. Sherman

The early 1980s saw a group of researchers at University of Washington (UW) recognize that declining costs and increasing capabilities of microprocessors presented an opportunity to alter forever the relationship of the analytical and the control functions of the process industries. These functions could be combined, using the near-instantaneous computing speed and ever-increasing capability of the microprocessor, to provide near-real-time process chemical analyses and control functions in feedback (or, with the increasing capability and usage of chemometrics, feedforward) control of the process at hand.

Bruce Kowalski, an analytical chemist at UW, had the foresight to engage process industry support and used this consortium approach to gain support from the National Science Foundation. Alvin L. Kwiram, chairman of the chemistry department, used his network throughout the Council for Chemical Research to get industry participants to "risk their airfare" to hear the initial proposal for an industry consortium the professors called the Center for Process Analytical Chemistry (CPAC). The resulting industry participants' enthusiasm formed one of the first industry-university cooperative research centers in 1984, which evolved into CPAC. The original corporate sponsors were Dow Chemical, Eastman-Kodak, Exxon, and E. I. DuPont deNemours. Today, 21 years later, this list has expanded to 24 industry organizations and three government organizations (National Institute of Standards and Technology, Pacific Northwest National Labs [Battelle], and Westinghouse Savannah River Co.).

Early Technology Initiatives

The opportunities of CPAC were pursued diligently by the chemical and petrochemical companies with CPAC research scientists keeping continuous contact with their industrial



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sponsors. This assured a focus to the research and a short-term, if not immediate, transfer of the research methodology to industrial practice. A major benefit of the CPAC organization to its sponsors (both industrial and government) is cross-industry technology transfer. Techniques used in the petrochemical process industry would almost never be applied in pharmaceutical process manufacturing but, with the academic contribution as a catalyst, analytical technologies migrated across industrial fences for mutual benefit.

The CPAC organizational model essentially remained as founded from 1986 through 1996 when current director Mel Koch established new strategic objectives to further benefit the multi-industry membership of CPAC. A major long-term

objective was established to integrate process analysis and process control. This versatile micro-analytical systems (VMAS) initiative has resulted in microreactor technologies, new sampling-sensor initiatives (NeSSI), high throughput instrumentation (in miniature physical packages) and process intensification. This latter component of the VMAS initiative "... combines or reduces unit operations and/or often utilizes miniaturization which results in maintaining productivity and quality while achieving drastic reductions in resource use and waste generation."

The Systems Approach Becomes Formalized

It was becoming apparent from the multidisciplinary research projects that in every industry a systems approach made the most effective tool for process analysis and process control. This "system" would include sampling, sample conditioning, analysis, data generation, control signal dispersion from a "system management device," and data transmission to the enterprise control system to realize the financial benefit which pays for all the aforementioned hardware and brainpower.

This "system" approach was formalized after an initiative similar to that which founded CPAC in 1984. This initiative was a meeting held in late 1999 by Don Mayeaux of A+ Corporation, currently located in Gonzales, LA, USA. Don, the inventor of the process industry-standard Genie membrane (water discrimination) filter, invited several process chemical and refining industry technical and managerial personnel to his manufacturing facility. He proposed a modular sample conditioning system technology platform where all typical sample conditioning system components would have a common physical footprint and common flow patterns and be mounted on a common repetitive substrate. Industry leaders saw so much potential in this concept that they took the concept from this meeting and achieved a national standard within the unheard timeframe of approximately three years. The result is the current design basis for Modular Sample Conditioning Systems ANSI/ISA-

76.00.02 (2002). The drive behind this breakthrough technology for the petroleum and petrochemical industry was sample conditioning system cost reduction and, more importantly, total life-cycle installed-cost reductions.

CPAC saw the development of the ANSI/ISA-76 standard and a concurrent semiconductor industry development ASIC (application-specific integrated circuit) as a springboard to develop more than a common footprint. CPAC termed this initiative "NeSSI" and set forth three generations with NeSSI being the first generation comprising a common small footprint high-performance substrate or platform. ConnI (connectivity initiative) is the second generation of NeSSI and it brings ASIC to the common footprint. ConnI allows one wire pair (or possible wireless technology) to carry all signals to operate valves, read differential pressure by pressure sensing and reporting devices set across system filters (to monitor sample flow across the filter element and to indicate or allow a forecast of the degree of clogging of the filter element and optimal time to change this element). The NeSSI third generation analyzer initiative (AnI) brings the analyzer out of its dedicated climate-controlled walk-in shelter, reduces its size (often times while increasing its performance due to microprocessor logic capabilities), and places it down onto the ANSI/ISA-76 footprint. The NeSSI Generation III (AnI) process analyzer has shrunk to the size of three decks of cards from its original size of a small refrigerator. This integration of Modular Substrate (ANSI/ISA-76), ConnI (NeSSI Gen II) and AnI (NeSSI Gen III) results in an industrial chemist's PAL, or Portable Analytical Laboratory.

Adoption by the Pharmaceutical Industry

This demonstrated success algorithm recently has been applied to pharmaceutical industry processes with the cooperation of FDA and its CDER organization. Ajaz Hussain of FDA (CDER) worked closely with Mel Koch of CPAC to define recommended guidelines for Process Analytical Technology (PAT)

which can take advantage of both NeSSI and ANSI/ISA-76 technologies. The PAT initiative will have a significant impact on optimization of pharmaceutical production processes while assuring quality of the final (drug) product. This optimization should result in price reductions for pharmaceutical products due in part to physical size reduction of the process equipment (modular manufacturing processes as well as modular process analytical systems) and in part to less inventory and record-keeping due to product quality being "designed into the product" and not "analyzed out from the product." The NeSSI devices generate real-time data about the pharmaceutical process and allow quality adjustments during the process, not analyses after the completion of the product.

FDA's PAT Initiative first was discussed at an FDA Advisory Committee for Pharmaceutical Science meeting in July of 2001 with a lofty goal of facilitating innovation in pharmaceutical manufacturing processes. These are the many processes where innovative young scientists entered the industry from academia with visions of improving their processes only to hear their manager comment, "Very nice work but it will never be accepted by FDA."

Within FDA's regulatory environs, PAT was defined as "...a system for designing, analyzing and controlling manufacturing through timely measurements (i.e., measurements during the process operation) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality." This terminology reflects a systems perspective and was preferred over singular terms such as process analyzers or process analytical chemistry. As such, it is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. This quote is the agreed upon view of Ajaz S.Hussain, D. Christopher Watts, Huiquan Wu (all of FDA/CDER/OPS Rockville, MD) and Ali M. Afnan (FDA/CDER/OPS/PAT team member) as stated in the foreword of Volume 1 Issue 1 of *The Journal of Process Analytical*

Chemistry by Russell Publishing LLC (www.patjournal.com). The authors also state in the foreword, "Timely, simultaneous measurements of both physical and chemical characteristics of pharmaceutical materials can provide an opportunity to improve our understanding of how these characteristics evolve during processing, and provide the prospect of quantitatively relating this understanding to product quality and performance." This plays directly to the ANSI/ISA-76 standard and its NeSSI Gen II and Gen III developments. NeSSI is a system, and its size dictates low internal volumes and small internal surface areas which, along with substrate-based analytical devices, gives near real-time analytical results "...to improve our understanding of how these characteristics evolve during processing..."

Guidance Is Published

FDA's "Draft Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" was developed from several public meetings incorporating commentary from corporate committees of pharmaceutical scientists and managers. This "PAT Guidance" was announced on September 3, 2003. The draft guidance is not a technological tour de force but it is an overview of the regulatory requirements needed to integrate future technological improvements into a PAT manufacturing process. A revised guidance will be published soon by FDA.

R.W. Miller started his first article of the series appearing in *American Pharmaceutical Review* with the following: "There is a change on the immediate horizon for our industry that will be a paradigm shift from the way we look and perform pharmaceutical manufacturing operations." (1) The PAT initiative is only a part of a much broader effort to create cGMPs for future quality improvement and cost reduction efforts. The PAT guidance relates a scientifically grounded yet risk-based envelope that contains all aspects of understanding the process at hand. Scientific principles and tools are provided that will support process innovation and a strategy for regulatory implementation is provided

that will accommodate the innovation earlier developed.

Under current FDA regulations and industry policies, product quality is verified by product testing before release to shipment. The goal of the PAT Initiative is to build quality into products by process measurements and understanding on a real-time basis, thus minimizing the end-of-line testing.

Perhaps the most important point to be recognized across the pharmaceutical industry is the signal of a changing relationship between FDA and the pharmaceutical producers. Scientific achievements and engineering practices are being accepted in daily operations.

Quality is being built into the manufacturing process by utilizing real-time results from on-line analyses to control the process during its operations. The resultant product has quality built into it.

The Role of ANSI/ISA Technologies

The small part of sample conditioning to get process samples to on-line (process) analyzers such that quality can be built into the pharmaceutical processes is enabled to a large measure by the ANSI/ISA-76 and NeSSI (Generations I, II and III) technologies.

ANSI/NeSSI sample conditioning systems have many advantages for the pharmaceutical industry over the classic tubed-or-piped-component sample conditioning systems.

The basic ANSI/ISA-76 element in the NeSSI Gen I sample conditioning system is a block that is 1.53 in. long (on the manifold axis) and 1.50 in. wide (90° to the manifold axis). It has three sample transfer passages, each with an inside diameter of 0.110 in. These passages might seem small but they easily pass 3 L/min of gas or liquids (up to the viscosity of diesel fuel).

Analysis elements currently commercially available on the ANSI/ISA-76 (NeSSI) format are limited to ppm oxygen and ppm moisture. NIR and Raman probes can be adapted readily to this format by threaded adapter plates. As soon as volume increases for the ANSI/ISA-76 (NeSSI) format one of the NIR or Raman probe manufacturers will machine a probe in this for-

mat. Complete spectrophotometers (UV/Vis) and gas chromatographs currently are under active development, which will be complete in a 1.5 × 3 × 3 in. format.

Control element selection commercially available on the ANSI/ISA-76 (NeSSI) format is quite varied. Valves (manual, pneumatic, or electronic actuation available) are available in most control formats: ball, diaphragm, metering, needle, solenoid. Control valves currently are not available but are in active development thru digital stepper motor control element activation. Some valves available in this format have an internal volume of 0.01–0.02 cc, with no dynamic o-rings, lubricants or springs in contact with the process fluid, and with expectations of more than one million cycles at process pressures and temperatures. Flow, pressure, and temperature sensors are available on the ANSI/ISA-76 format in classic-legacy types and in "advanced control" electronic configurations.

Control elements currently are connected via classic-legacy wiring for control and signal contacts. Availability of "Bus Connectivity" soon will be implemented as NeSSI Gen II. Unfortunately its implementation is somewhat fragmented between CANBus (IEEE 1451.6), PROFIBus PA, and Fieldbus, with wireless (IEEE 802.11b) circling around the outside edges of the discussions.

Summary

In this paper FDA's Process Analytical Technology (PAT) Initiative development was reviewed along with CPAC's ANSI/ISA-76.00.02(2002) (NeSSI) development. Detail was provided to show how the NeSSI components could contribute to the PAT philosophy and physical requirements.

Reference

1. R.W. Miller, "Process Analytical Technologies (PAT) – Part I," *American Pharmaceutical Review* 5(2) 25–29 (2002). ■

Robert E. Sherman is an ISA fellow and industry specialist–process analytical systems for CIRCOR Instrumentation Technologies (Joliet, IL). E-mail: rsherman@circortech.com.