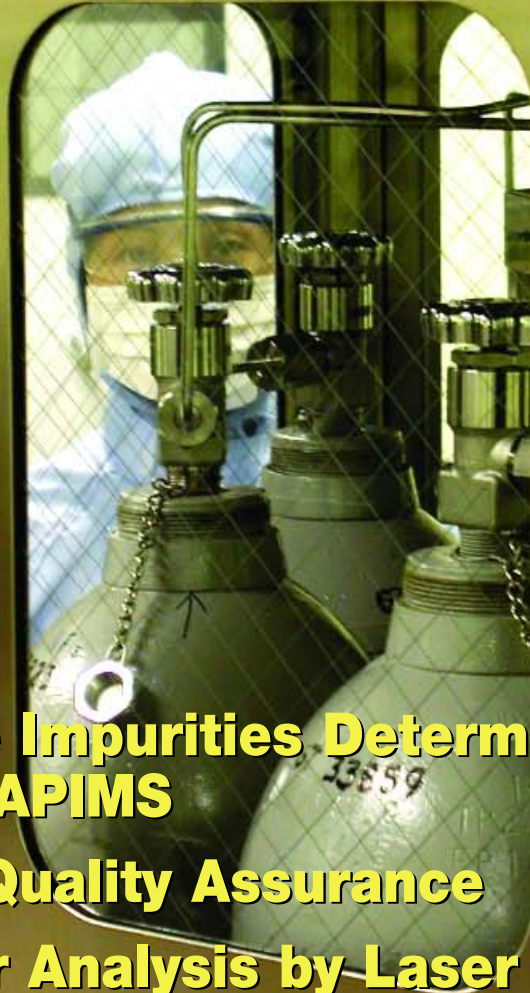


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PROCESS ANALYTICAL TECHNOLOGY – PRODUCTIVITY GAINS AND RISK MINIMIZATION VIA PROCESS INTIMACY

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Process manufacturing is impacted by global demands for higher yields and greater productivity driven by product sophistication, increased yield requirements, and tighter specifications on control, quality and safety. Higher manufacturing performance is directly dependent on real-time and online visibility into the process. Traditionally, process manufacturing has been managed by relatively basic measurements that rely on “touch and feel” instrumentation, e.g., pressure, temperature, flow rate. Process analytical information is typically provided by the “industrial lab” where manually collected samples are taken to certify a product (or intermediate) after the fact. Running samples to the lab requires that the continuous process is discretized to a batch process or that product is held in storage until certified. In either case, lack of quality implies loss of time and material (e.g., re-runs, slop or flaring). In addition to slowing down the process, the lack of process information increases uncertainty and risk, resulting in unnecessary alarming and lower yields as processes are run in safer regimes.

Process analytical technology provides real-time visibility into the process via instruments that measure presence of specific chemical species or physical state to determine indicative information, e.g., reaction state, kinetics, uniformity, and concentration. This level of process intimacy promises productivity gains resulting from our ability to manage quality early in the process to reduce risk and enhance yields. The need for process intimacy is being driven by: increasing demands for performance; increasing regulatory needs; and availability of online analytical technology.

The use of process analyzers as productivity enablers has been proven in the large throughput petrochemical process plant applications, where the continuous nature of the processes and relatively large profitability impact of small improvements in yield and throughput makes the use of online process analyzers financially attractive. For instance, process gas chromatographs and process mass spectrometer applications for certifying raw material feed, product quality and yield in the production of chemicals, e.g., Ethylene, Ethylene Oxide, Methanol,

Polyethylene and Polypropylene, have been successful.

On the regulatory front, the US Food and Drug Administration have reinforced the notion of process intimacy, via the FDA PAT Initiative. FDA's PAT initiative has tied risk management to the use of analytical technology vs. validated procedural methods in pharmaceutical manufacturing by allowing PAT as an inherent part of accepted GMP (Good Manufacturing Practice). PAT is holistically applicable to all aspects of risk minimization and covers worker safety, product integrity, consumer safety, medicinal efficacy, repeatability and environmental impact. Whereas, in the past “change” in pharmaceutical manufacturing was limited by regulation, FDA is encouraging change based on risk managed process intimacy. Clearly, the FDA believes that online and real-time access to process information will increase product quality / integrity and provide productivity gains in all aspects of pharmaceutical manufacturing.

In addition to the FDA, other regulatory initiatives require greater control of harmful chemicals, increasing the need for online process analyzers. For instance, the clean fuels initiative limiting sulfur content in gasoline, diesel and jet-fuel is driving the need for analyzers in refineries, blending and transmission applications. Refiners and transporters of fuels are managing their compliance to these regulations by increasing the use of online process analyzers that are able to detect parts per million and parts per billion of sulfur in fuels.

The third driver for process analytics is the maturity of technology and its availability outside of the laboratory, driven by miniaturization and robustness of hardware, software and firmware. Sophisticated laboratory instruments, such as the mass spectrometer, are now available in rugged form for online applications; IR and NIR spectrometers are now available as MEMS (Micro-Electro-Mechanical Systems) devices. Further increase in microprocessor capabilities provides greater capabilities for executing sophisticated mathematical models and

digital signal processing algorithms in smaller footprints. These advances are leading to better accuracy, diagnostics, robustness, and fault tolerant performance.

New analytical instrumentation applications for PAT require that technology be transferred for use online—this is not a trivial matter. This transfer requires a paradigm shift from designing a sophisticated instrument which measures many parameters with high accuracy to designing an instrument that measures one or few key parameters with high degree of reliability. In addition to making a rugged and

environmentally safe instrument, other details need to be carefully considered, e.g., data communications in a variety of legacy protocols, onboard diagnostics to assist the local maintenance technicians.

The successful use of process analytical technology, particularly for pharmaceutical manufacturing, depends on integrating sophisticated analytical instruments into existing operations—functionally and technically. Functional integration implies a full understanding of how an instrument impacts manufacturing (quality and throughput), information and knowledge man-

agement in the context of decision making. Technical integration requires the full consideration of online sampling systems, controls, human machine interface, alarm integration and diagnostics.

The future of process analytics in process manufacturing will depend on our ability to apply technology in the right place in the right form such that data becomes information helping us increase our knowledge of the process and enable effective decision making, leading to productivity gains and risk minimization in process manufacturing operations.