The Drug Industry at a Crossroad: PAT's Role

The old paradigm must make way for the new; here's how it can happen.

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The drug industry is at a crossroad. Statistics of drug use indicate that more people are using more new medications to treat more conditions. While this benefits the public health, it is not without its challenges and costs for consumers and the government.

Major FDA reforms are underway to reduce drug-manufacturing costs. FDA plans to overhaul the pharmaceutical good manufacturing practices — current GMP policies have not been updated significantly in 25 years. Meanwhile, best practices in manufacturing technologies and methods have seen significant progress. The Agency's broad-based initiative intends to develop new GMP regulations based on the latest science of risk management and quality assurance. The new standards are being designed to encourage innovation in manufacturing and technology, coordinate submission review and inspection programs, and ensure consistent perspective by all FDA centers that regulate pharmaceutical products.

According to some experts, addressing, and reducing, the amount of downtime and discarded materials in the current pharmaceutical production process could reduce production costs by 25% or more. In a recent article, Dr. Janet Woodcock, the Acting Deputy Commissioner of the FDA, makes the point that U.S. consumers rely on a high level of quality of drug products. The reason, she states, is the strict, regulated environment within which the drug industry operates. This is, of course, a major expenditure for the Agency that regulates, as well as the industry that is being regulated.

Dr. Woodcock estimates that "expenditures on drug manufacture exceed most firms' research and development investment" [1]. Two years ago, FDA started its 21st Century cGMP initiative. This is part of a major FDA reform to reduce drug-manufacturing costs. The introduction of Process Analytical Technologies (PAT) into the pharmaceutical industry is part of this FDA broader initiative.

PAT catches on

PAT has become a very popular topic of discussion at pharmaceutical conferences and in industry publications [2-10]. Some major pharmaceutical companies are already heavily involved in the implementation of PAT in their manufacturing environment, and in their product development process. Many other organizations are contemplating, or are in the process of establishing dedicated groups to implement PAT in their settings. Why is there this sudden interest by the pharmaceutical industry in a technology that has been utilized for many years by other industries?

The time and the environment are right to introduce innovation into our relatively conservative industry. In the document entitled, “Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products”[11], FDA raises concerns that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients. The current medical product development path is becoming increasingly challenging, inefficient, and costly. Furthermore, because of rising costs, innovators often concentrate their efforts on products with potentially high market return.

“If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health,” the paper claims. FDA must modernize its regulatory tools under the Critical Path Initiative to keep pace with advances in drug development. FDA is working on a series of new policies constituting a “modern” approach to regulation. The Agency is taking steps that call for better science in its programs, to ensure that it is capable of evaluating the new sophisticated medical products.

Recently, FDA and 11 universities have joined together to form the National Institute for Pharmaceutical Technology & Education (NIPTE), an initiative aimed at identifying ways to improve drug product design, pharmaceutical manufacturing and regulatory science [12]. The institute will operate as a research partnership between the universities and FDA. Under a bill drafted by NIPTE representatives, Congress would appropriate FDA $25 million annually over a five-year period to fund the collaboration. Other aspects of FDA's drug regulation modernization strategy include hiring new engineers to improve manufacturing technologies and allowing electronic NDA submissions.

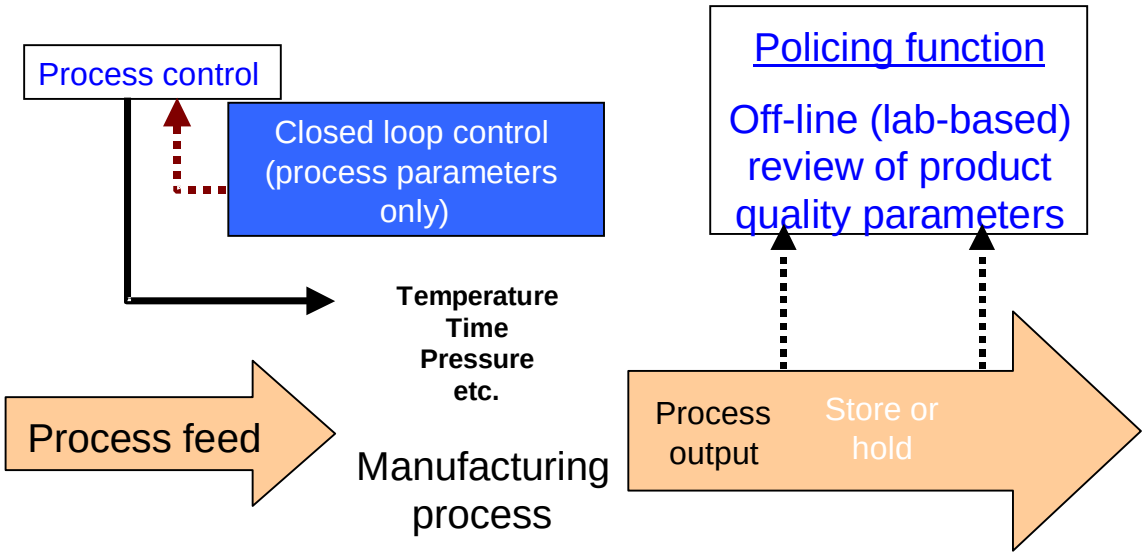
Other high-tech industries with essentially no tolerance for errors or impurities, such as the semiconductor industry, have achieved enormous productivity gains in manufacturing in the last 25 years. Can our industry achieve the same? PAT has been proposed to help us in this task.

Two paradigms

Scheme I (*below*) portrays the current pharmaceutical manufacturing control paradigm. The Active Pharmaceutical Ingredient (API) and the excipients are fed into the manufacturing process. Based on specific responses or tests (Process Output) — ideally established during product development—that have been validated, the process is determined to be completed. The batch is now stored, and sampling, according to a statistical algorithm, takes place. The samples are sent to a remote QC laboratory (Policing Function). This Policing Function determines if the batch is released for commercial use. Any unusual or out-of-specification test outcome results in rejection or delay of release of the batch.

Batch failure, of course, is costly to our industry and to society. Batch holdup — until the Control Function clarifies unusual test results — usually gives rise to an unusable inventory, which is also very costly. The assumption is that the validation process

Scheme I: Current Manufacturing Control Strategy

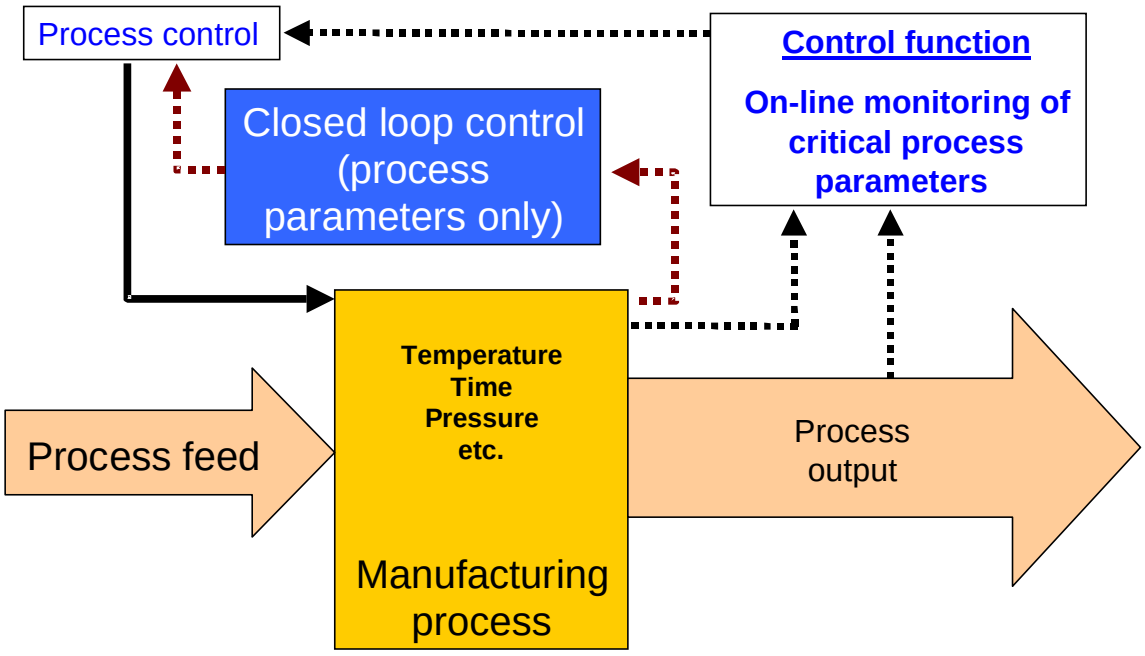


(consecutively three successful batches) should guarantee successful and consistent production. However, the reality is that changes in the formulation components, and uncontrollable manufacturing conditions, cause significant holdup times, and inventory that can not be delivered to the patients. Today, only manufacturing parameters such as temperature, pressure, and humidity to some extent are maintained and adjusted through a feedback mechanism. All other process parameter outcomes rely on off-line testing of samples that we hope represent the entire manufactured batch.

PAT can change radically this paradigm. Scheme II (*below*) outlines the PAT manufacturing control strategy. There are two very significant changes to the present state described in Scheme I. First, the Policing Function is replaced by a Control Function that runs the manufacturing process through online monitoring of the critical process parameters. Second, the quarantine stage is eliminated. Since the process adjusts itself and is continuously monitored, independent of a sampling process, we should not have unusual or OOS test results when QC tests are performed. Elimination of this forced inventory is clearly a major manufacturing savings, and it provides better quality assurance for our products.

Adding efficiency is not the only benefit that PAT brings. It is essential that PAT is utilized during product development. A continuous monitoring of the process, as it is developed and scaled up, is essential to understand and define the critical process parameters. During the research and development phase it is extremely critical not to depend on sample testing to understand what is occurring in the manufacturing bowl. PAT presents opportunities to monitor, and with some new techniques even visualize the process — that is, we are opening the manufacturing “black box.” Therefore, PAT is a

Scheme II: Future Desired Manufacturing Control Strategy



powerful tool to add important knowledge and understanding of the manufacturing science utilized during product development.

The current manufacturing paradigm is directed toward testing to document quality, and rejecting unacceptable quality. This needs to be shifted toward a "right first time" paradigm. PAT can provide assurance that processes are always in control and result in consistent finished product of high quality. Furthermore, PAT can be considered as a continuous process validation. Ali Afnan of FDA has stated that the classical validation concept defined as a well-rehearsed demonstration that a manufacturing formula can work three successive times, "is out the window" [13]. The traditional three validation batches do *not* demonstrate that the process is validated. Validation is demonstrated by good science, and by continuous process improvement throughout the life cycle of the product [14].

Making PAT happen

To make PAT happen we need to create a culture of trust. We need to eliminate the industry fear that the initiative will lead to more regulation, or that FDA will dictate pharmaceutical development. The regulatory agencies need highly trained pharmaceutical inspectorate staff, and we must have a global, non-U.S.-centric change in regulations, as stated by Tobias Massa of the PhRMA organization [15].

PAT is a new way of thinking for a relatively conservative industry. It is critical to foresee the impact on our organizations. We need to understand the capacity for such a change, and it is extremely important to involve key stakeholders early in the process. PAT will require resources and commitment from the executive leadership of our organizations.

There are a few PAT areas in which regulatory agencies and the pharmaceutical industry need to cooperate. These include issues such as:

- Interpretation of specifications and their fundamental meaning
- The process of establishing specifications, handling them, and investigating OOS results
- The true underlying definition of batch in the world of PAT
- Uniformity of Dosage Units (UDU) acceptance criteria guidance for end product testing when PAT is utilized
- Multivariate Process Control: Can its implementation lead to real-time release?
- In-process measures: Can they accurately predict end-product parameters?

PAT has to overcome technical hurdles before its complete implementation. These include data acquisition, retention and storage concerns, documentation, electronic records and E-signature closure of decision points. Industry and the regulatory agencies must come to an absolute understanding of how to handle existing products for which the PAT application may reveal deficiencies.

Regardless of those issues, I do believe that in five to ten years PAT will monitor and control many production processes. I believe also that in 10 years automated continuous processing will become a reality. In summary, the desired control philosophy of pharmaceutical manufacturing is one in which an off-line policing function is replaced by an on-line control function. This should enable a continuous manufacturing process that controls itself.

PAT is the mechanism to implement such manufacturing strategy. In addition to manufacturing efficiency, PAT is a tool to study and understand the manufacturing process that is developed during drug product evolution. This can ensure that quality is being built into the product, rather than tested in. At the end of the day, effective use of PAT can improve our manufacturing efficiency, reduce costly inventory, and ensure consistent quality.

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