Perspective

Can Pharmaceutical Process Development Become High Tech?

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Introduction

While the pharmaceutical industry is well known for its innovation in developing drugs and therapies, and its ability to provide quality medicines to the public, its manufacturing efficiency lags behind that of most other industries. Batch processing with laboratory testing of samples to evaluate quality has been typical of pharmaceutical manufacturing. A recent article in the *Wall Street Journal* suggested that the pharmaceutical industry lags behind potato chip and laundry detergent makers in the use of modern manufacturing systems.[1] This article was motivated by new initiatives from the Food and Drug Administration (FDA), which, in a reversal of traditional roles, found itself pushing the industry it regulates to adopt more modern approaches to quality and manufacturing systems, to adopt "quality by design," and to develop more science-based, mechanistic understanding of its manufacturing processes. This is only one of several sources of pressure on the pharmaceutical industry, including scrutiny of drug costs and a decline in R&D productivity, which call for meaningful increases in productivity and manufacturing efficiency. Such changes must start in the arena of process development: processes must be developed rapidly, with fuller mechanistic understanding and manufacturing feasibility in mind. The commercialization team (process development and manufacturing colleagues) must partner to provide a meaningful database for implementation of statistical process control and a seamless transfer of technology.

It is not all bad news for the pharmaceutical industry. The investments in modern biotechnology are now paying dividends as novel targets are leading to more new drug candidates with reduced prospects for attrition. The challenge has become how to get these drugs to market in reduced timelines, and how to manufacture them efficiently using modern methods. The pharmaceutical industry is evaluating approaches from other industries to develop processes efficiently and to utilize modern manufacturing systems, such as lean thinking and Six Sigma. But developing processes for pharmaceutical products presents special challenges.[2] Each product presents unique synthetic and drug delivery challenges due to a unique molecular structure, physico-chemical properties and biological behavior. We do, however, have the opportunity to apply some basic principles of lean thinking, such as creating systems to avoid reinvention (R&D's key form of waste), harmonizing procedures, equipment and information systems, and linking directly the needs and vision of modern manufacturing to the activities in R&D.

This article proposes a new approach for process development based on the following four elements:

- The approaches proposed by the FDA, including Process Analytical Technology (i.e., on-line measurements) coupled to real time control; the principles of quality by design and risk-based analysis; the use of statistical, multivariate analysis; and providing mechanistic understanding through lab automation, miniaturization, using Design of Experiments (DoE), and an emphasis on physical organic chemistry and kinetics.[3]
- Shaping the science of process development by applying Instrument, Systems and Automation Society (ISA) S.88 standards[4] from development through commercialization, which provide a natural language for chemical and pharmaceutical processes, as well as analytical methods. This provides us with a vehicle for creating and systematizing process knowledge and is also a very effective basis on which harmonic interactions between R&D and manufacturing can be built. This leads to the use of a number of electronic tools for the laboratory, for process modeling, for execution of process recipes in labs, pilot plants and production facilities, and for managing data, linked seamlessly between R&D and manufacturing.
- The use of modeling tools to reduce the need for empirical experimentation, for verification of mechanistic understanding and for process control.
- The use of parallel experimentation using automated work streams for rapid probing of process options, exploring process operating windows ("design space"), and generally increasing productivity.

These four elements are discussed in the following sections.

21st Century Pharmaceutical cGMP

Among the many initiatives being championed by the FDA in recent years, none has the potential for a bigger impact on pharmaceutical process development than the "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the

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21st Century."[5] While the original intent of the agency may have been to modernize its regulatory approach and to utilize its resources more efficiently, adoption of the tools outlined in the guidance can result in a more rigorous scientific development effort. The regulatory framework summarized by the agency also promotes a quality system perspective to the design of the pharmaceutical manufacturing process. The following sections are a brief description of the key enabling tools that facilitate the efficiency gains.

Process analytical technology (PAT)

PAT has been a cornerstone of the agency's 21st Century initiative for the past few years through the issuance of the FDA guidance,[6] and the subsequent incorporation of key concepts into the International Conference on Harmonization (ICH) Q8[7] guidance. In essence, it is an umbrella collection of technologies that provide information on the chemical, physical, and (micro)-biological characteristics of the active pharmaceutical ingredient (API), and drug product during manufacturing. On-line process sensors, multivariate data acquisition and statistical analysis, predictive process modeling, and process control are all tools which fall under this initiative. The systematic implementation of such technologies will improve process understanding and will measure, control, and predict quality and performance.

On-line process sensors provide continuous monitoring of parameters to measure variations in feed and/or process conditions. Process analyzers generate large amounts of data which have multifactorial relationships. Multivariate mathematical approaches allow pulling the relevant information from such a data set as well as understanding the significance of deviations for a given process. Such approaches include statistical design of experiments, response surface methodologies, process simulation and pattern recognition tools.

Quality by design (QbD)

In the new development and manufacturing paradigm, the FDA has repeatedly emphasized that a drug manufacturer cannot test in, but rather needs to build quality into, its pharmaceutical products. The concept of quality by design (QbD) has two components—the science underlying the design and the science of manufacturing. It calls for a liberal use of PAT to allow the creation of a process model, based on intrinsic process knowledge generated during the development phase. The subsequent scale-up to manufacturing demonstrates and validates the model, and is followed by process improvement through the use of statistical process control tools. The ultimate outcome of quality by design would be[8]:

- The product is designed to meet intended use.
- The process is designed to consistently meet product critical quality attributes.
- The impact of starting materials and process parameters on product quality is understood.
- Critical sources of process variability (raw materials, process) are identified and controlled.
- The process is continually monitored and updated to allow for consistent quality over time.

Intrinsic process knowledge

The foundation of quality by design is the availability of intrinsic (kinetic and mechanistic) process knowledge collected through the use of the various tools discussed in this article. A mechanistic understanding allows the identification and scientific justification of causal chemical or physical relationships between pharmaceutical materials and/or process factors. Such understanding improves confidence in the designation of the critical variables and their control strategy. Ultimately, a state of statistical process control can be achieved that provides an effective means for continuous process improvement within a company's quality system.

Applying the S.88 Standard to Development and Commercialization

In a systems-based approach, there are three main components to the release decision for a pharmaceutical batch, namely: business, production and analytical information. The business information consists of topics such as equipment/facility maintenance, change management (process and facility/equipment), training records, materials inventory, etc. The production information consists of a record of batch activities with their associated executed information. Analytical information consists of an executed sample plan which details what samples were taken and for each individual sample, what equipment was utilized, the method used and the acceptance criteria for the sample.

Over the last 5–10 years, the pharmaceutical industry has made significant investments in all three areas (business, production and analytical) as companies look to improve their supply chain, customer service and manufacturing efficiency. The industry has been working diligently to redefine the plant floor. The pharmaceutical industry operates predominately in batch mode, and has approached batch processing as a manual, paper-driven exercise. This manual approach is not sustainable for the industry, since it does not provide a robust supply chain due to deviations resulting from manual operations, which significantly extend cycle times for review and release, and require a significant infrastructure and investment in standard operating procedures and training.

An outcome of the industry's examination of its manufacturing efficiency was uniform adoption of the ISA S.88 standard. Lynn Craig, one of the original members of the S.88 committee, summarized recently that the "ISA S.88 standard provides a standard terminology and intuitive models that help in closing the communications gap between control professionals, process specialists, IT specialists and production management."[9] In Chemical engineering vocabulary, S.88 is basically a unit operations approach to batch processing. For any given process, the activities can be broken down into discrete, manageable unit operations that are predefined with a number of parameters and typically precoded in a control system, and thus executed in a standard manner every time.

We think that S.88 has only just begun to reach its full potential.[10] It is well established in the small molecule and biologics arenas, and is making slow but steady progress on the drug product plant floor. In all arenas, unfortunately, it has been an effort championed and recognized only by the process automation and production personnel in manufacturing. There are several more areas where S.88 thinking could benefit the industry, namely: (a) Lab to plant (i.e., shaping process development and linking it directly to technology transfer and commercial manufacturing), (b) coordination of plant floor with analytical laboratory, and (c) data analysis.

Lab to plant

Examination of paper notebooks of well respected organic chemists will show them thinking and operating in a unit operations manner as they approach their synthetic work. However, to date, S.88 has been slow to be adopted by the development segment of the industry, thereby creating a gap in technology transfer to manufacturing. The S.88 approach, if utilized properly, can provide a common vocabulary for both development and commercial activities. Once a synthetic route or formulation is selected, the S.88 process recipe with its associated parameters can quickly become the repository of the design space ranges, and the development history for a given process. A key portion of technology transfer would then become a recipe being sent electronically from a R&D scale-up facility to a production facility. The recipe could replace the manufacturing description of the common technical document for a regulatory filing and facilitate annual report updates. This recipe can be created utilizing a scientist's desktop which automatically requires collecting the basic data associated with the operation, and which also doubles as an electronic notebook. This tool also manages parallel experimentation and DoE, and executes portions of the recipe in automated equipment. The resulting S.88 recipe transfers directly into an S.88-based modeling tool which provides unit operations modeling, and is then used for mass balances, time cycle analysis, environmental impact analysis and examination of "what if" scenarios for manufacturing. The modeling tool then adjusts the S.88 recipe as needed and transfers it to the execution environment in the glass plant or pilot plant (Figure 1).

Coordination of plant floor with analytical laboratory

As manufacturing has examined its efficiencies, so have the analytical laboratories that provide both in-process, as well as final release testing. Unfortunately, these examinations amount to optimizing each individual department rather than the overall process. The coordination of the plant floor and the analytical laboratory could be significantly enhanced in the pharmaceutical industry. A common S.88 philosophy in both worlds would facilitate that. This desirable approach will require a significant change in the thinking of analytical equipment manufacturers, but this change is similar to the transformation that the control system vendors have undertaken as they adopt the S.88 standards into their products.

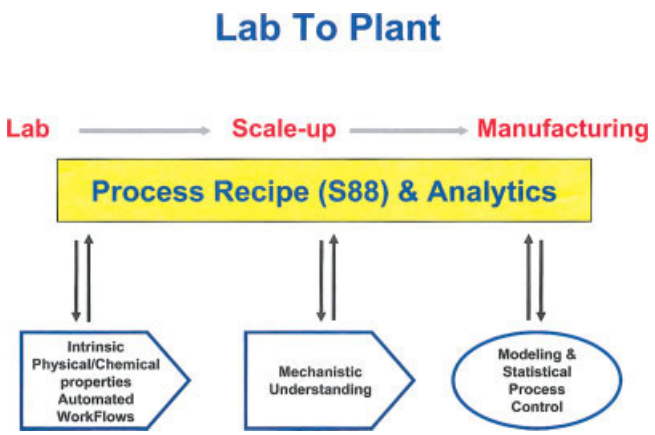

Figure 1. Lab-to-Plant.
Use of process recipes and analytics to connect process development from the laboratory through scaleup to the manufacturing floor.

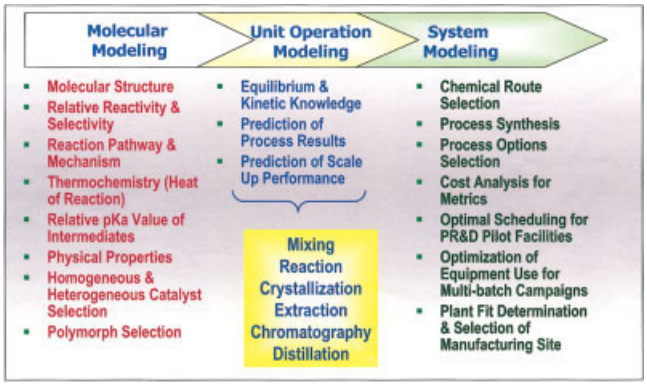

Figure 2. Potential applications of modeling in Bristol-Myers Squibb.

Data diving the S.88 way

S.88 enhances the capability of technical personnel to model. It organizes process and analytical data in the context of the specific process and unit operation. If utilized across the development continuum as discussed earlier it allows modeling to be a life cycle event from the first batches at small scale to the commercial manufacturing batches. S.88 eliminates the inertia for scientific personnel to access and review data.[11]

Modeling

Predictive modeling is a strategy to achieve both increased productivity and "quality by design." Modeling achieves this in two ways: better fundamental understanding of unit operations, and reduction of scale-up risks via prediction based on actual process design data. Based on time and length scale, models are categorized into molecular, process (unit operation) and systems level (Figure 2).

Molecular modeling focuses on physical property prediction. Examples include solubility, prediction of polymorphism, reactivity, selectivity, and thermochemistry prediction for reactions, and drug-excipient interactions to estimate physical properties for formulations. **Process modeling** focuses on the unit operations (reaction, mixing, extraction, distillation, crystallization, chromatography, drying, granulation, blending, and coating). It focuses on equilibrium and kinetic knowledge and allows for prediction of process results and scaleup performance. **Systems modeling** uses models to enable such activities as chemical route selection, process cost analysis, quality risk assessment, and scheduling of plant and equipment activities.

Many examples of such modeling exist and are in use in pharmaceutical development. Some recent examples include predictions of drug solubility in mixed solvents.[12] the use of computational fluid dynamics,[13] and numerical simulations to design crystallization processes,[14] and reaction modeling using commercial packages.[15] In all of these examples, a min-

imal experimental dataset provided sufficient information to develop a model (mechanistic or correlative), and to conduct virtual experiments with a resulting overall minimization of development time for process optimization.

A key challenge for the pharmaceutical industry is learning how to integrate molecular, process and system modeling to enhance efficient process development. To enable this, a higher level of information technology infrastructure will be needed, along with changes and improvements to currently available commercial software packages.

Automated Parallel Experimentation and High-Throughput Workflows

In recent years, a number of research-supported technologies have been developed to advance productivity across the stages of pharmaceutical process R&D, from early exploratory process research and route selection through process definition, and knowledge generation surrounding control parameters, to process verification/parameter range setting.[16] Early efforts evolved from automation tools designed to support parallel synthesis activities in drug discovery. These efforts progressed into both commercial and home-grown parallel reaction systems that allowed automation of multiple common unit operations, including heating and cooling, agitating multiple reactions in parallel, the automatic addition of liquid reagents and withdrawal of reaction aliquots, and the analysis of samples by high-performance liquid chromatography (HPLC) and gas chromatography (GC). These systems have been used extensively for the optimization of organic processes through the application of statistical design of experiments.[17]

High-throughput workflows are typically highly differentiated to address specific needs and often include sophisticated combinations of robotics and software. For these reasons, these workflows are commonly operated by dedicated expert groups within an organization or outsourced to specialty contract research companies. Expert groups are generally able to spur innovation given their focus on the technology, and have been able to drive its application across many different facets of pharmaceutical development. Some of the most successful and high-impact applications of high-throughput technologies to pharmaceutical development activities have been screening for new and unexpected crystal forms (polymorphs) and salts of APIs,[18] development of solubility maps for APIs and process intermediates to aid in crystallization and reaction planning,[19] and transition metal catalyst screening for optimized chemical transformations.[20]

To advance the use of automated experimentation further will require progress toward software and hardware standardization. Integration of the technologies that make-up the workflows is crucial, such that (a) common hardware can be shared among workflows, (b) method development to adapt a specific hardware device to a new workflow is rapid and efficient, (c) learning curves for operating new equipment are easily climbed, and (d) data are stored centrally and in context, and can be mined from different locations by different people from within an electronic environment, such as an electronic lab notebook.

Conclusion

For a variety of reasons, including the regulatory environment under which it operates, manufacturing in the pharmaceutical industry has lagged behind other sectors in adopting modern systems for operations, process control and quality systems. A number of converging pressures have pushed the industry to address this issue forcefully, and it is now poised to adopt state-of-the-art approaches. In our opinion, this task starts in the process development arena, where the deliverables must include in-depth mechanistic understanding along with more rapid and efficient development. Adoption of the FDA's new cGMP initiative is one-key element needed to achieve this goal, and it must be complemented by a powerful set of modeling tools, automated experimentation tools, and an information technology backbone for gathering data in an organized way to generate knowledge more efficiently (Figure 3). We view the S.88 standard as the natural language to accomplish this, so that the process data and knowledge are recorded and represented as an executable recipe with all the relevant data associated with each unit operation. By extending this concept, developed for the plant floor, to both the process development laboratory and the analytical methods arenas, we can create a seamless environment for the various components of process development, for the transition from R&D to manufacturing, and for the manufacturing floor/process control/quality control environments.

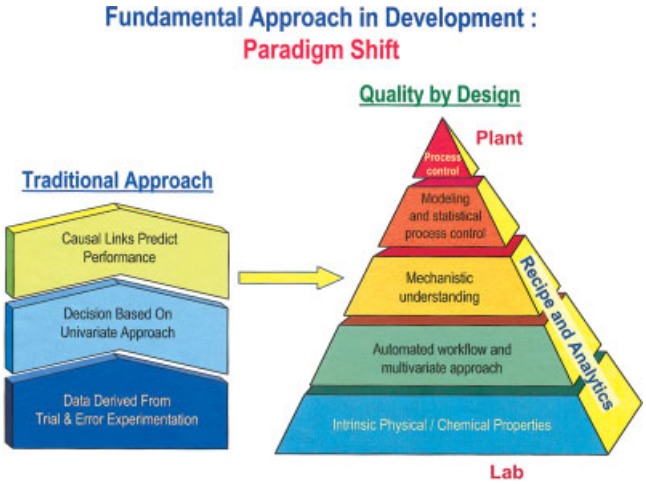

Figure 3. Fundamental approach in development: paradigm shift (adapted from presentations by Ajaz Hussain).

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