PROCESS SYSTEMS ENGINEERING TOOLS IN THE PHARMACEUTICAL INDUSTRY

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Abstract

The purpose of this paper is to provide a summary of the current state of the application of process systems engineering tools in the pharmaceutical industry. In this paper, we present the compiled results of an industrial questionnaire submitted to pharmaceutical industry professionals. The topics covered in the questionnaire include process analytics, process monitoring, plant-wide information systems, unit operation modeling, quality control, and process optimization. A futuristic view of what process systems engineering tools will enable the pharmaceutical industry will be also be presented. While the industry is regularly using the traditional Design of Experiments approach to identify key parameters and to define control spaces, these approaches result in passive control strategies that do not attempt to compensate for disturbances. Special new approaches are needed for batch processes due to their essential dependence on time-varying conditions. Lastly, we briefly describe a novel data driven modeling approach, called Design of Dynamic Experiments that enables the optimization of batch processes with respect to time-varying conditions through an example of a simulated chemical reaction process. Many more approaches of this type are needed for the calculation of the Design and Control Spaces of the process, and the effective design of feedback systems.

Keywords

Process Systems Engineering, Process Analytical Technology, Plant Wide Information Technology Systems, Process Monitoring, Control, Optimization.

INTRODUCTION

Almost a decade has elapsed since the FDA publication "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" and almost eight years since "PAT – A Framework for innovative Pharmaceutical Manufacturing and Quality Assurance" were issued. Much progress and innovation in pharmaceutical manufacturing

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has occurred since the publication of these landmark documents. For example, pharmaceutical companies have readily adopted in-process measurements systems, such as near infrared spectroscopy for concentration, and focused beam reflectance measurements for estimation of particle size distribution. The application of multivariate process monitoring for real time fault detection and isolation has also found it's way into pharmaceutical manufacturing. The industry has moved away from quality control strategies based on uni-variate parameters specifications, and towards the multivariate design space approach. While, tremendous progress has been achieved in the decade, there is work to be done to realize the full potential of the process systems engineering (PSE) toolbox.

The purpose of the paper is to describe the current state of the art of the application of PSE tools in the pharmaceutical industry. The sub areas of PSE discussed in this work are process analytical technology (PAT) measurement systems, process monitoring, plant wide information technology systems, process control, modeling, and optimization methodologies. This paper focuses on PSE applications primarily related to active pharmaceutical ingredient (API), and solid oral dosage manufacturing. Details on the application of PAT measurement systems, and process control in biologics are out of scope of this work, for readers interested in biologics PSE applications we are listing a few relevant review papers[1, 2].

To augment information available in the open literature, we conducted an industrial benchmarking survey on the above-mentioned PSE sub areas that contained twenty-one questions in total[a]. The survey was submitted to current pharmaceutical industry professionals in all areas of the industry: active pharmaceutical ingredient, solid oral dosage, and biologics, in both development and manufacturing. The companies that submitted responses to the survey are listed in Table 1.

Table 1. Profile of Participating Companies (from Wikipedia): Number of employee and revenue data (US dollars)

Abbreviations: BPh is Biopharmaceutical, Pha is pharmaceutical, CR is contract research, B is billions, M is millions. Superscripts: a is data from 2010, b is data from 2009, c data from Oregon business.com

Company	Category	Employees, Revenue
Alkermes	**BPh**	**610, 178M[a]**
Johnson & Johnson	**Pha**	**114,00, 61.6B[a]**
Bend Research	**CR**	**159, ~30M[b,c]**
Bristol-Myers Squibb	**Pha**	**28,000, 18.8B[b]**
Merck	**Pha**	**94,000, 46.0B[a]**
Cephalon	**BPh**	**3700, 2.8B[a]**
Eli Lilly	**Pha**	**38,350, 23.1B[a]**
Pfizer	**Pha**	**110,600, 67.8B[a]**
Vertex	**Pha**	**1,800, 102M[b]**

The paper is organized as follows, for each of the sub areas of PSE covered; we provide a brief background on how PSE tools are currently used in the pharmaceutical industry. Where possible, literature references have been provided, with a preference towards papers published by pharmaceutical industry professionals. The questionnaire results pertaining to each PSE area are presented at the end of each section. We then discuss the impact of increased out-sourcing of product development and manufacturing and the prospect of continuous processes on the future utilization of PSE tools. Lastly, we present the application of a novel method for batch process optimization called dynamic design of experiments. A simulated API synthesis reaction process is used to explain the method.

THE CURRENT STATE OF PSE TOOLS IN PHARMA

We describe the current state of the utilization PSE tools in the pharmaceutical industry. The sub areas of PSE discussed are measurement systems, multivariate process monitoring, plant wide information systems, and process control and optimization methodologies. The results of this section are a combination of work documented in the literature by authors in the pharmaceutical industry, and the results of the industrial benchmarking survey.

[a] Blank questionnaires are available upon request from the authors, see author contact information on the title page.

Measurement Systems for Active Pharmaceutical Ingredients and Solid Oral Dosage Manufacturing

There is a rich and long tradition of the use of in-line, on-line, and at-line spectroscopic measurement systems in the pharmaceutical industry. In-line is defined by the measurement being made in the process stream. On-line systems are characterized by a sampling system that removes material from the process stream for analysis; the sample can be returned to the process or diverted to waste. At-line measurement systems have operators manually removing material from sampling ports and presenting the samples to analyzers located in the processing area. These spectroscopic techniques, and sampling schemes have been successfully implemented in API, solid oral dosage, and biologics manufacturing, and are used to augment the data provided by standard process instrumentation (temperature, pressure, flow rate, etc.) In the following sections we briefly describe how PAT measurement systems are used in common process unit operations in API, and solid oral dosage manufacturing.

Active Pharmaceutical Ingredient (API) Manufacturing

The most common uses of process analytical techniques applied in API manufacturing are for studying reaction kinetics, reaction monitoring, secondary drying, crystallization, and milling operations. The state of the art of application of PAT measurement systems for each unit operation will be briefly discussed.

Reaction Monitoring

The primary measurement system applied to reaction monitoring for API production is in-line Mid Infrared spectroscopy[3-5]. Other techniques such as in-line Raman spectroscopy[6], in-line NIR, and on-line HPLC[7] are also in use. During process development, the concentration profiles measured from the tools listed above are used to determine reaction mechanisms, identification of reaction intermediates, and kinetic rate parameters for modeling[3]. In a manufacturing deployment, reaction monitoring would be used for reaction end-point determination, and verification that the process is operating under safe conditions. While most of the published literature describes laboratory scale applications, some work on production scale equipment has been reported[8].

Crystallization

Process measurement systems for API crystallization operations include the use of in-line Mid Infrared, Raman, and NIR spectroscopy, in-line focused beam reflectance measurements (FBRM), and in-line imaging systems. Mid infra red spectroscopy[9-11] is most often used for measuring the level of supersaturation in the crystallization slurry. Raman[12] and to a lesser extent NIR[13] spectroscopy are implemented to monitoring API form conversion. Lastly, in-line FBRM, and in-line imaging are used to estimate particle size distribution, and to assess crystal habit respectively. These tools are extensively used in process development to study and optimize crystallization conditions. In theory, these methods are transferable into manufacturing operations, but factory deployment of these technologies is not widely reported. Review papers that discuss process control schemes utilizing these measurement systems have reported in the literature[14]. Robust method calibration and probe fouling are common concerns for routine factory deployment of the in-line spectroscopic measurement systems. The application of in-line imaging systems in control and manufacturing is limited due to the generally poor image quality achievable in crystallization slurries.

Secondary Drying and Milling

Process analytical techniques for API secondary drying include the use of off-line and on-line NIR for water concentration and on-line mass spectroscopy of the effluent for an estimation of residual solvent concentration in the drying cake. These tools can be used in development for drying end-point determination. API drying processes can be in excess of 48 hours; therefore, these tools are often deployed directly into manufacturing operations as a means to reduce cycle times. Additionally, during process development several dryer types and equipment scales are used, which serves to complicate on-line method development. The investment in on-line methods is often deferred to until the full-scale development. In milling operations, particle size distributions are typically characterized off-line with various equipments, such as diffraction instruments and imaging systems. The use of in-line NIR for particle size have been reported in the literature[15], but is not in common use for particle size determination.

Solid Oral Dosage Manufacturing

Common applications of process analytical techniques used in solid oral dosage manufacturing are for blend/lubrication uniformity, tablet content uniformity, and moisture content during fluid bed drying. In this section, we briefly describe the state of the art in process analytical techniques for the common pharmaceutical unit operations: blending, compression, roller compaction, high-shear wet granulation, fluid bed granulation/drying, film coating, hot melt extrusion, and spray drying.

Blending and Lubrication

On-line NIR spectroscopy is the industry standard for tote blending operations. Commercial systems are available that have a large spot size process NIR mounted on the lid of the blender tote that collect several spectra at each revolution. Both qualitative and quantitative methods can be developed to assess blend uniformity. Application of qualitative methods is the more common approach due to the simplicity. In qualitative methods, measure of spectral variability is tracked as a function of blender revolutions in a moving block fashion. Common measures are relative standard deviation, API peak height, and API peak area. Blend uniformity is achieved when the spectral variability measure reaches a sustained minimum[16]. Quantitative methods correlate blend composition to NIR spectra with PLS models. Other analytical techniques such as Raman[17] and Laser induced Fluorescence spectroscopy[18] have appeared in the literature and the market place, but have not gained wide industry acceptance. The same methodologies have been applied to blend and granule lubrication uniformity, although lubricant compositional uniformity determined by in-line NIR does not directly assess the extent of lubrication.

Roller Compaction

Roller compaction process analytics include the use of instrumented rolls[19] that measure the stress profile across the ribbon width. The instrumented rolls have stress sensors embedded in the roll, and measure the compaction stress, and the ribbon stress uniformity in real time. Additionally, at-line measurements of ribbon attributes such as density, porosity, and moisture content are also in use. Ribbon property estimation methods can be developed using NIR[20]. In these methods, partial least squares (PLS) is used to correlate NIR spectra to traditional density and porosity measurements (Geopyc for density, Mercury porosimetry for example). Off-line NIR chemical imaging is also in use for ribbon characterization[21], and in-line/at line FBRM for granule particle size[22] has been reported.

High Shear Wet Granulation

The common process analytical approaches to high shear wet granulation involve the use of in-line/at-line measurements of particle size distribution[23], in-line/at-line NIR[24] for granule moisture analysis, and impeller power draw[25] to estimate granulation endpoint. In manufacturing operations, the at-line methods are more routinely used and are more robust than there in-line counterparts. Development of in-line methods for high shear wet granulation processes is challenging due to probe fouling, and sample heterogeneity. Efforts have been made to combat probe fouling, such as air purging, solvent rinsing, and windshield wiping type devices. While these systems offer some improvement, no truly robust systems are currently available, and performance is very much formulation dependent. Another challenge to in-line measurements systems for wet granulation is the dynamic complexity of the process itself. The main problem is where to position in-line probes to obtain representative sampling. A secondary challenge is that the morphology of the sample changes dramatically during the granulation process, going from a fine powder to course granules, and then resulting in fine granules.

Fluid Bed Operations: Drying, Granulations, and Coating

Process analytical tools for fluid bed operations includes in-line NIR[26] for moisture content, and at-line/in-line measurements for granule particle size distribution[27, 28]. Fluid bed operations are also highly amenable to multi-variate process control charting techniques[29, 30]. In process development, in-line NIR measurement systems can provide drying curves (granule moisture vs. time) as a function of process conditions, but at-line loss on drying or off-line Karl-Fisher analysis are often used, as real time

high frequency measurements are not needed at this stage. In manufacturing, in-line NIR methods are used for drying end-point determination[31] and process optimization[32], in this scenario the real time measurement system is valuable. At-line method for drying end-point determination in manufacturing are time consuming, because sampling often requires collapsing the bed during at-line analysis to avoid over drying. Similar to drying equipment, scale up of fluid bed operations is challenging, therefore in-line method development is often deferred until full-scale operations where the method implementations have more impact.

Hot Melt Extrusion

In hot melt extrusion, the state of the art in process analytical tools includes the use of in-line spectroscopy such as NIR[33], and Raman[34] for multi-component compositional monitoring. In process development and scale up, the spectroscopic in-line compositional methods are used for determination of residence time distributions, process characterization, and system identification[35, 36]. In a manufacturing setting these tools are used for continuous verification that the process is producing material at the target composition, and for real time isolation of off specification product due to disturbances from the feeding systems. Commercial extruders come with melt temperature, die pressure, and torque sensors. These measurements combined with spectroscopic systems are amenable to multivariate control charting for fault detection[36]. Additionally, in-line/on-line visible spectroscopy has potential for monitoring of degradation[37] and extrudate color, if color matching is important for the product.

Spray Drying

Spray drying is a unit operation where off-line characterization tools are used extensively during development to develop process understanding, and then the knowledge is deployed in manufacturing. Spray dried intermediates are typically tested for particle morphology, chemical and physical stability, and bio performance. These attributes are difficult to measure, estimate, or correlate with data from in-line instrumentation. In-line measurement systems that could determine characteristics of the spray zone may be of value. There is also some potential for in-line/at-line particle size distribution measurement systems, depending on particle size. Traditional sensors, such as temperature, pressure, and spray rate, tell the story for spray drying processes, and additional instrumentation is often not applied during manufacturing operations.

Compression

For the tablet compression unit operation, a state of the art process analytical system would include an at-line tablet method[38, 39] for API concentration measurements. Ideally, this would be coupled with a simultaneous measurement of tablet mass, to provide tablet assay and API content uniformity information. In-line NIR measurements systems for real time segregation monitoring in the feed frame of a tablet press are also available and in use[40]. For many pharmaceutical products, compression is the last processing step, only to be followed by release testing and packaging.

Film Coating

Film coating is generally considered undesirable from a cost and cycle time perspective, and is only used when the product requires it. Film coating is applied to tablets to function as a taste-masking agent, to provide protection from light. Tablets are sprayed with a coating suspension until a desired weight gain has been achieved. The traditional quality metrics of the process are coating weight uniformity, and tablet elegance. In some cases, the API is in the coating of the tablet, and at-line API concentration and uniformity measurements can be made with spectroscopy techniques, such as NIR.

Process Analytical Technology Measurement System Questionnaire Results

The results of our industrial benchmarking survey indicate that all of the responding companies actively use the measurement systems described above, with an emphasis on spectroscopic tools such as NIR, Raman, MidIR, and particle size measurements with FBRM systems. The majority, 75%, of the responding companies indicated that these tools were primarily used in research and development and not deployed into routine manufacturing operations, with the remaining 25%, reporting routine use in manufacturing. Dedicated process analytical technology groups exist in 75% of the participated companies, with the mean group size of 8±6 people, with additional people fractionally

dedicated to the PAT effort. Figure 1, shows a breakdown of how the participating companies are applying PAT measurements systems. Process monitoring is the largest reported use, with 75% of and product release testing and process control are the least reported applications of the tools.

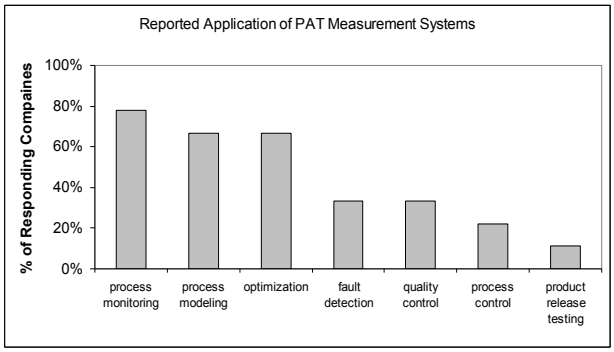

Figure 1: Summary of reported PAT measurement system applications.

Process Monitoring

Process monitoring in manufacturing operations is commonplace in the pharmaceutical industry. Traditional approaches include univariate statistical process control charting, with the application of Western Electric rules for common cause variation. Univariate control charting is applied to critical process parameters and product quality attributes. Additionally, classical descriptive statistics are applied to historical data for entire process trains, on a batch-to-batch, and a campaign-to-campaign basis. Process monitoring is conducted primarily for two reasons: as a means of verification, that the process is running within the parameter space allowed by the regulatory filing, and for the development of process knowledge/understanding. Additional motivations for process monitoring include preventative actions such as fault detection, and for process control, such as end point determination.

Within approximately the last ten years, the use of multivariate statistical process control charting has emerged within the industry. Several commercial real time multivariate process monitoring software packages that are also suitable for batch processes are currently available. Table 2 presents some examples of commercially available run time multivariate process monitoring technology products. Most of these products listed utilize latent variable methods (PCA, PLS), and descriptive statistics, but other types of analysis are possible, such as neural networks, cluster analysis, and tree methods.

Table 2. Example Real Time Multivariate Process Monitoring and Predictive Analytics Software Packages

Company	Product Name
Umetrics	**SIMCA4000, SIMCA Batch On-line**
ProSensus	**ProSensus Online**
Unscrambler	**Process Pulse**
Ge-Fanuc	**Proficy Cause+ ,Troubleshooter**
Stat Soft	**Statistica Data Miner**

Multivariate process monitoring is conducted in real time on the individual unit operations level, and models for successive process steps are easily strung together. The data for the entire process is typically analyzed after batch completion. In addition to the primary process equipment, data from supporting equipment systems (feed tanks, steam generation, etc.) can also be included in monitoring schemes. Aggregated data from all systems, over multiple production campaigns are holistically analyzed off-line to detect trends, process drifts, and to develop correlations. This holistic process analysis can be automated with the use of plant wide information technology systems. Real time multivariate process monitoring is applicable to both continuous and batch processes, with the latter being the more common application in the pharmaceutical industry. These tools are applied to batch processes in the pharmaceutical industry such as high shear wet granulation, fluid bed drying[30, 41], and batch and fed batch fermentation process[42, 43]. These tools are often deployed only for process monitoring and fault detection, but they also enable run time predictive analytics capabilities.

Process Monitoring Questionnaire Results

Not surprisingly, 100% of the responding companies indicated that univariate process monitoring was conducted in manufacturing, and

that descriptive statistical analysis of plant historical data was practiced. Most, 67% of the industrial responders reported using a real time multivariate process monitoring technology product. A breakdown of the products reported to be in use are shown in Figure 2. The same percentage, 67%, indicated that multivariate analysis tools (principle components analysis and partial least squares) are used to analyze historical process and plant data.

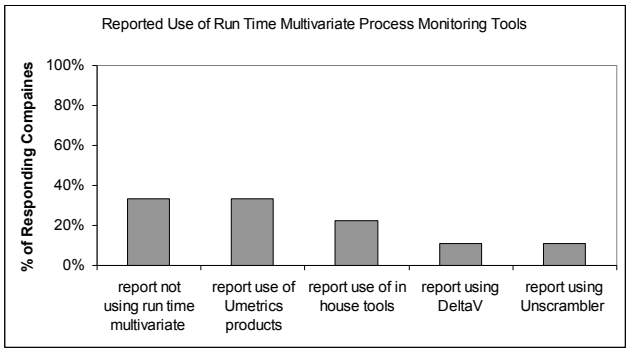

Figure 2: Breakdown of reported use of run time multivariate process monitoring tools.

PLANT WIDE INFORMATION TECHNOLOGY SYSTEMS

Historically plant wide information technology systems had the role of process historian and recipe automation. New applications for information systems include real time multivariate process monitoring, run time predictive analytics, and integration of PAT measurement systems. These new roles have given rise to PAT specific plant wide information technology systems. In the sections that follow we describe the complexities of these systems, and review the questionnaire results for this topic.

Multivariate Process Monitoring and PAT Measurement Systems

The incorporation of real time multivariate process monitoring, and predictive analytics has changed the quantity, and the type of data being handled by process engineers during manufacturing operations. In addition to the real time data coming from standard instrumentation on the process equipment, engineers are now incorporating state data from the automation system, raw material data (quality attributes, genealogy, meta data, etc., and off line laboratory quality testing into process models. Data driven models are constructed for fault detection, but in some cases can developed for the real time prediction of product quality attributes. Figure 3, shows a block diagram of the data streams and information flows handled by plant wide information systems with real time multivariate process monitoring and predictive analytics. To handle process data streams shown in Figure 3, a plant wide information systems must be able to accept a variety of data types (scalar, vector, text, continuous, discrete), and coming at a variety of frequencies. The data needs to be formatted for analysis. Before predictive analytics computations can be preformed, the data must be cleaned and pre processed. Finally, to close the loop, process set points must be passed back to the distributed control system. The software packages listed in Table 2 are capable of serving as the analytics engine, and in most cases can also serve to aggregate data for the analysis.

Company	Product	Functionality
Siemens	**SIPAT**	**PAT specific**
Optimal	**SynTQ**	**PAT specific**
Ge-Fanuc	**Proficy**	**Predictive Analytics**
Emerson	**Plant Web**	**Predictive Analytics**
Aegis	**Nexus**	**Predictive Analytics**

Table 3. Example PAT specific Plant Wide Information Technology Systems

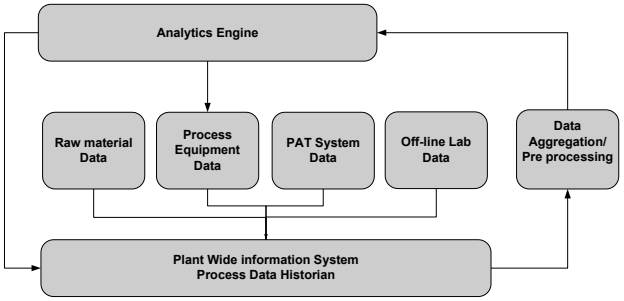

Figure 3: Plant wide information technology systems require connectivity to many data sources.

PAT measurement systems add another layer of complexity to plant wide information technology systems. The large and multivariate nature of spectral data is not convenient to archive and manipulate in traditional process historian systems. A spectral measurement could include on the order of ~10,000 absorbance values, spectral outlier diagnostics data, method information (version, validation state,…), and

predicted outputs. This information can be acquired on the per minute or even the per second frequency in some cases. In addition to the spectral data, the PAT measurement system state data, such as instrument qualification, performance qualification, and preventative maintenance status need to be tracked and associated with the spectral and method measurements. PAT measurement system data is often used for process control and for product release testing. In these applications, the management of the system, the data it generates, and the methods used are critical to ensuring quality. Additionally, PAT systems are often mobile cart based units used in multiple unit operations at different times and locations, therefore these plant wide systems need to be flexible and easily reconfigured by user companies.

These complexities have spurred the development of PAT specific information technology systems. Table 3 lists some examples of commercially available plant wide IT systems that enable multivariate monitoring, predictive analytics, and systems with specific capabilities for PAT system control, method management.

Plant Wide Information Technology Systems Questionnaire Results

Not surprisingly, 100% of the questionnaire respondents indicated that process data historians and automation/control systems are installed in all manufacturing facilities. Of the participating companies, 56% have indicated that they have standardized on a particular plant wide information technology products (historians, and automation systems). Another 22% indicated that they are in the process of, or planning on standardizing in the near future.

For PAT specific IT systems, 22% of the respondents indicated the use of these systems in their companies. This result is not unexpected as these products are relatively new to the market place, and are designed for routine PAT measurement systems use in manufacturing. It is not practical to deploy such systems only in development facilities. This result is consistent with the PAT application questionnaire results shown in Figure 1, which show that PAT tools are primarily used in process development.

Process Modeling, Quality Control, and Optimization

In this section, we discuss modeling of individual process unit operations, closed loop control, and process optimization methodologies utilized in the pharmaceutical industry.

Process modeling is used where applicable in the pharmaceutical industry for process design, and scale up. Fundamental modeling of reaction processes and kinetics is common in API process development, and scale up. In solid oral dosage manufacturing, the application of fundamental modeling is more limited by the complexity of the raw materials and processes. The same is largely true for biological processes. Although, theoretically based scale up principles do apply to some unit operations, and papers have been published for modeling of fluid bed drying (Kannan et al., 1994), and roller compaction (Hilden et at., 2011) processes. In most cases, fundamental models are not applicable to commercial scale processes. This leaves engineers and scientists with empirical modeling (response surface, regression, latent variable) as the only tractable option for mathematically describing process unit operations.

Process Modeling Questionnaire Results

All of the participating companies indicated that response surface models were routinely developed to describe individual unit operations. Additionally, all of the companies reported the use of fundamental models where applicable, but indicated that model development was limited. When asked what percentage of unit operations had fundamental models developed, 44% of the companies indicated that models were developed for greater than 10% of process unit operations. Secondary drying and spraying (film coating and spray drying) unit operations were cited as examples of process unit operations that has fundamental models developed for them. Figure 4 shows a summary of company responses for the development of fundamental models for individual process unit operations.

When asked about the advantages of fundamental models, the responding companies cited that the flexibility in the incorporation of product physical properties, and that the models are often applicable for multiple products as major

advantages. Additionally, the overwhelming response was that fundamental models offered increased process understanding, were robust, and allowed extrapolation in many cases. The disadvantages of fundamental models reported were that the effort and time to develop them is prohibitive, they require modeling expertise, model validation is resource extensive, and that model assumptions are often not consistent with full scale process operating conditions.

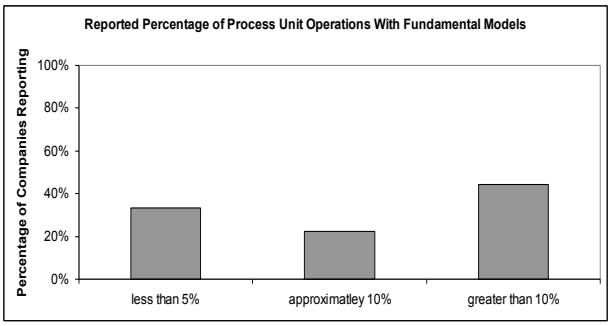

Figure 4 Breakdown of reported deployment of fundamental models on process unit operations, listed as percentage of process unit operations modeled.

Figure 5 shows the fraction of individual process unit operations that have data driven models developed for them. One third of the companies reported developing empirical models for 80%-100% of process unit operations, and another third report 40-%60% of all unit operations modeled empirically. Over half of the respondents, 56%, report routine use of latent variable modeling techniques, such as PCA and PLS, to describe process unit operations. The advantages of data driven models were reported to be that the models require a minimum of basic fundamental information to develop, and they can be developed relatively quickly. The models work even when the science is not fully understood or too complex to model via scientific theory. Junior scientists and engineers can be successful with these approaches, and the results can be easily understood by a broad audience with diverse backgrounds. Data driven models capture the physics and all of the variability in the data set, and assist in the identification and prediction of processes up-sets. Lastly, data driven models are reliable within their validated ranges, and in some cases be developed from only historical operation data.

The disadvantages of data driven models described by the questionnaire respondents were that the models are not fully transferrable between sites and scale of unit operations. Model development takes a lot of effort in sample generation, data aggregation, and analytical testing. Data-driven models cannot be extrapolated beyond their validated limits. Additionally, data-driven models have to be coupled with physical observations of the process and products. Instrument sensitivity and data acquisition noise need to be understood to develop robust models. No mechanistic understanding is obtained, and it is difficult to physically or chemically explain second, and higher order interactions.

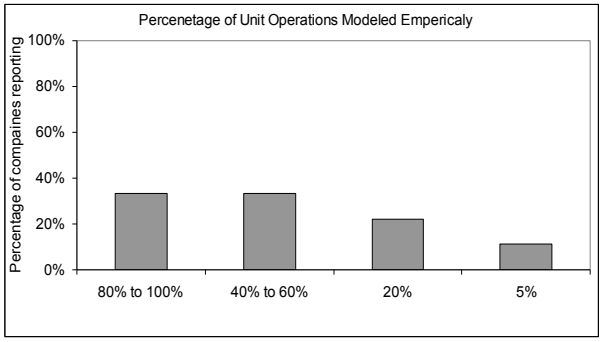

Figure 5 Breakdown of companies deployment of empirical models on process unit operations, listed as percentage of process unit operations modeled.

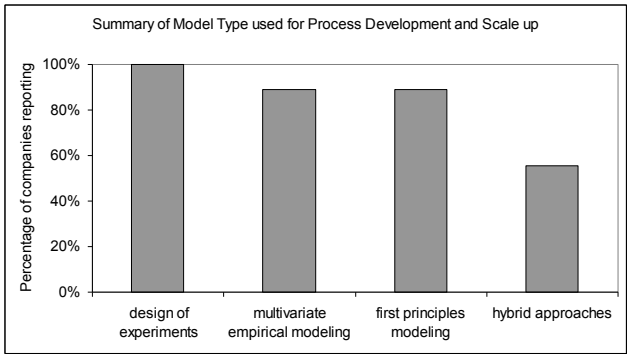

Figure 6: Breakdown of reported modeling approached utilized for process development and scale up. The results show that all of the participating companies have a balanced approach to modeling.

Figure 6 shows a summary of the type of modeling approaches practiced in the pharmaceutical industry. From inspection of Figures 4-6, it is clear that the industry has a balanced approach to modeling techniques, but favor empirical approaches for reduction of complexity and broad applicability to process unit operations. All of the responding companies

reported applying the modeling approaches shown in Figure 6 on the individual unit operation level, while 33% reported modeling on the plant wide/entire process train level.

Quality Control: From Univariate Specifications to the Multivariate Design Space Concept

Historically, in the pharmaceutical industry the approach to process control was defining univariate raw material attributes ranges and process equipment parameters ranges. The process was validated by executing three batches. They were at one-tenth commercial batch scale, with extensive analytical testing at each process step. If the results of the three batches were within the pre defined acceptable ranges, then the process was considered validated. A validated process could be run with only end-product release testing. If raw material attributes or process changes were introduced, the entire process would often need to be re-validated by the same protocol as described above. Process optimization activities were largely completed in development, before process validation. This mode of quality control was the norm in the pharmaceutical industry for decades.

While this approach to process control has been demonstrated to be both feasible and capable of producing/ensuring quality pharmaceutical products, it created an environment where the communication of technical process/product knowledge between drug producers and the regulatory agencies was reduced. (i.e., if the processes were truly robust, this information was not conveyed to the regulatory agencies in a systematic and understandable way). This was perceived as an obstacle to initiating post-approval process changes, and potentiality limiting process improvements. The FDA's PAT/QbD initiatives promoted the use of risk analysis tools and the process design/control space approach. The Design/Control Space concept is similar to the Feasible Region Concept in the classical process optimization literature. A related but more appropriate concept is that of process operability[44-54]. This concept, initially developed for continuous processes, starts from an estimated range of the process disturbances and calculates the desired ranges of the control variables so that a control strategy can ensure that the product qualities are within the acceptable range. Although, an actual optimal run condition is not typically computed, only the feasible region is defined. Additionally, in the pharmaceutical industry the objective functions are usually solely based on product quality attributes, and not economic considerations.

An example approach to design/control space development and definition could include a risk analysis tool to indentify material and process variables that potentially could affect quality for the specific product, then some initial screening DOEs to verify main effects and interactions of the candidate variables. Followed by response surface DOEs, such as Box-Behnken, and Central Composite designs for example, conducted on key variables and attributes for optimization and determination of the design spaces for the individual unit operations. It is theoretically possible to extend response surface methodology to an entire process train. The choice of risk management tools and design space definition are left to drug producers to decide.

Process Modeling Questionnaire Results

Of the companies surveyed, 67% reported using the multivariate design space approach to quality control for all new products. The design spaces include raw materials and process parameters. These companies report the use of design space strategies to identify a robust area of operation with respect to all major disturbances to the process. Augmented, with empirical models to relate input and process variables to end-product performance, manufacturability and stability. Individual parameter specification or control is used to maintain operation in a robust space to ensure end-product quality. The process can only operate under known and measured input conditions. One potential shortcoming in most companies' application of the design space approach is that it results in passive and potentially restrictive quality control policy. Disturbances are not compensated for by manipulated variable moves, and the process is operated in a smaller control space then it is capable of operating. The idea that there is an optimal pairing of process parameters to respond to different process inputs is not leveraged to reduce product variability and to enable a larger operating space[55]. Most companies are currently seeking to find one set of process conditions that can ensure product quality over a

pre-defined range of process inputs (process operability).

When asked about the potential benefits of dynamic control strategies (advanced process control) that actively seek to control end-product quality, by reducing variability, and enabling larger operating space, responding companies indicated that these approaches would be beneficial and consistent with ICH quality guidelines. Figure 7 shows a summary of the reported barriers to advanced process control implementations. The overwhelming response is that engineers and scientists at pharmaceutical companies are not familiar with APC techniques, and the potential benefits are not clear. Lastly, 50% of the questionnaire respondents reported at lack of predictive models to predict end of batch quality attributes from in-process measurements.

THE FUTURE OF PHARMACEUTICAL MANUFACTURING AND PSE TOOLS

In this section, we briefly discuss the future trends of contract manufacturing and continuous processing in the pharmaceutical industry and their impact on the utilization and advancement of PSE tools.

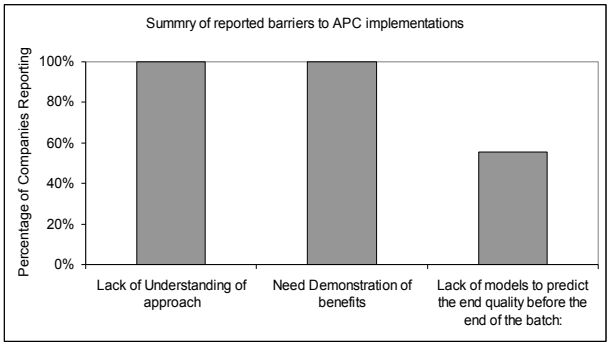

Figure 7: Summary of reported barriers to advanced process control implementations.

Contract Manufacturing

The services of contract manufacturing organizations have been utilized by the pharmaceutical industry for many years. It is expected that pharmaceutical companies will continue to utilize CMO, and that the fraction of product development and manufacturing work being outsourced will only increase in the coming years. This increase in outsourcing will slow down the rate of utilization of PSE tools, as financial pressures pull manufacturing to lower cost, and in most cases lower technology facilities. This outsourcing trend is both a set back and an opportunity for PSE tools. In the short term, products that are developed and manufactured outside of innovator companies will not have PSE tools applied to them or even be developed and manufactured in a true Quality by Design fashion. A future speculation would be that this would eventually be considered unacceptable to regulatory agencies. It is reasonable to expect that eventually CMO will need to invest in PSE tools to meet customer and regulatory requirements, and that competency in their use will be a significant differentiator in the CMO market place.

Continuous Processing

Continuous processing for API manufacturing is not economically feasible for most compounds. This is due to the complexity of the chemistries and the number of synthesis and purification steps involved in most processes. It is very common to have in excess of ten synthesis steps in an API manufacturing process. Additionally, the long secondary drying times associated with most processes are a serious obstacle to fully continuous API production. The idea of continuous processing for solid oral dosages is not a novel concept, but currently is it not widely practiced within the pharmaceutical industry. Many individual solid oral dosage manufacturing process unit operations are already continuous/semi-continuous, like roller compaction and compression for example. With the addition of powder feeders and continuous blending equipment, direct compression and roller compaction processes could be made fully continuous. Not all products are expected to amenable to continuous processing, such as products with low drug loads ($\leq$ ~5wt%), and products that have extremely poor flowing API. Additionally, appropriately scaled continuous film coating equipment is not currently commercially available, but batch sequencing this unit operation with continuous process train seems feasible. Adoption of continuous processing for solid oral dosages would enable the application of traditional PSE tools for system identification and process control. This would give the benefits of more rigorous design space development through multivariable system identification techniques. For example, process models could be identified using generalized binary noise test protocols that allow up to ten simultaneous manipulated variable moves per test condition. The biggest advantage

for design space development would be that the amount of material "in-process" at any instant, even at full scale would be greatly reduced compared to the batch process train equivalent. Therefore, it would free up valuable API for more robustness studies. An added benefit would be that full scale evaluations of alternate raw material supplies would be less costly to conduct.

Increase in the routine deployment of PAT measurement systems in manufacturing

The results of our questionnaire and the numerous publications indicate that pharmaceutical companies are using routinely using PAT measurement systems. While currently most companies appear to be using these tools in process development, it is reasonable to expect that in the future most companies will be routinely deploying these tools in to manufacturing operations.

Continued growth in multivariate process monitoring and real time prediction analytics

The availability of commercial software packages and the synergies of chemometrics with PAT measurement systems, it is expected that real time multivariate process monitoring will become an industry standard. The results of our questionnaire indicate that it is already quite common, with 67% of participating companies reported using real time multivariate process monitoring tools).

Growth in plant wide PAT information technology systems: both in-house, and in CMO

The combination of continued increases in the use of contract manufacturing for both product development and manufacturing, with the projection of increased expectations of regulatory agencies for demonstration of process control and robustness, we expect that contract manufactures will have to implement plant wide information systems. These IT systems will need to allow remote process monitoring, remote PAT method management and remote process control capabilities to client companies. Client companies would own the analytics, PAT methods, modeling expertise, advanced process control formulations, and most importantly the product data.

Real Time Process Control and Optimization

The summation of the all of the technological advancement above, will lead eventually lead to advanced process control and on-line process optimization implementations. As more of the remaining pharmaceutical companies implement enterprise based and plant wide information technology systems, the application of advanced analytics and optimization methodologies will evolve into scheduling, capacity, raw material supply chain management, and enterprise wide real time optimization.

The key to such advances is the availability of the appropriate models, mostly data-driven models. Several data-driven approaches, such as PCA and PLS, have been very useful indeed. However new ones are needed that will enable the development of explicitly dynamic and nonlinear models. The Design of Dynamic Experiments (DoDE) methodology described in the next section might be one of the new avenues that might become very useful.

THE NEED FOR DATA-DRIVEN MODELS

The inner workings of the majority of batch pharmaceutical processes are *not* well understood for a fundamental or knowledge-driven (KD) model to be developed. An additional roadblock in the development of such models is the small production rates of the majority of pharmaceutical products compared to the production rate of bulk chemical and petrochemicals for which a plethora of knowledge-driven models has found extensive use over the last four to six decades. Because, such KD models provide a much more detailed and insightful view of the process their development should be pursued, and is indeed pursued, for selective critical parts of the process.

For the majority of pharmaceutical processes or their processing steps, one needs to rely substantially on the development of data-driven (DD) models. The availability on an ever-increasing set of off-line and on-line process measurements (spectroscopic or otherwise) avails the engineer with substantial data as the starting point of developing a DD model and, through it, attaining a certain understanding of the process. Such measurements are highly correlated with each other and techniques like principal

component analysis (PCA) and Partial Least Squares or Projection to Latent Structures (PLS) have been extensively used. They reduce the dimensionality of the available data and help distinguish the informative from the non-informative data segments or variables. They have been used in a variety of situations, as several of the references given above demonstrate. Even though they are statistically sound, such tools have two major limitations. They are linear and they are not explicitly dynamic. Contrast this with the nonlinear and dynamic character of the majority of pharmaceutical processes that are auto-correlated in time. Both batch and continuous pharmaceutical processes can be approximated by linear models if they do not depart substantially from a nominal operating mode. However, recent FDA regulatory guidelines allow the substantial enlargement of the operating window as long we understand the consequences on the product quality and we have a reliable approach ensuring that quality attributes will remain within their acceptable limits. Enlargement of the operating window necessitates the development of nonlinear DD models. This is often achieved by the development of mostly quadratic Response Surface Models (RSMs) related to the methodology of Design of Experiments (DoE)[56, 57].

RSM models with higher than quadratic nonlinearities (including cubic, quartic, or higher terms) are definitely possible. However, the number of experiments that need to be performed to estimate the increased number of model constants is often prohibitive. For example, in a process unit with five input variables (factors in the DoE terminology) that need to be varied, a quadratic RSM model requires a minimum of 21 experiments for the estimation of all of its parameters while a cubic and a quartic RSM model require 56 and 126 experiments, respectively. To these experiments one needs to add 3-5 replicated runs for the estimation of the inherent variability of the process and another 3-5 runs to assess the lack-of-fit statistic. This last statistic is often neglected, but it is very useful in providing an assessment whether the estimated RSM is able to represent the majority of variability in the data that is not due to inherent experimental error. The number of experiments increases very rapidly as the number of input variables or factors increases. This happens when either the process unit is more complex or we consider a larger number of interconnected process units, aiming to develop a plant-wide DD model. For example, if the factors are increased to 10, the quadratic RSM model requires 66 (plus 6-10) runs and the cubic RSM 286 (plus 6-10) runs. Consequently, one needs to perform a substantial number of experiments in such a limited time window available for the development of a process to manufacture a product that might or might not be successful in clinical trials and might or might not be approved by the FDA. To remedy such shortcomings, one tries to utilize historical data and experience that, with a much-reduced number of additional experiments, might provide the needed coverage of the operating region.

Another type of DD nonlinear model that people have explored is that of neural network models. Such models can represent a richer set of nonlinearities than the RSM type of models. However, they require a similar large number of experiments. Despite their substantial promise, no systematic statistical analysis tool is available to assess the accuracy of the developed model in a similar fashion that the Analysis of Variance does for RSM models[b].

A further restriction of the above-mentioned models is that they do not account explicitly for the dynamic character of the pharmaceutical process unless they are coupled to parameterized dynamic linear models. In the case the process is a batch or semi-batch one, as in happens in the majority of cases, the dynamic character is a critical one. The same is true when the manufacturing process is a continuous one as it has started to happen and will happen more frequently in the near future. Without the use of the most rudimentary data driven (DD) dynamic models the systematic design of feedback controllers will be difficult. These feedback controllers are our main mechanism for compensating, using on-line measurements, the variability on the input feedstock and the variability on the operating conditions in order to ensure the desired tight product quality specifications.

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[b] *A search in the Web of Science database with "Neural networks" and "Analysis of Variance" and "Pharmaceutical process" at the three topics yielded no entry. A search with the first and last of the above three topics yielded only 3 publications.*

We organize the discussion that follows in three topics, monitoring, optimization, and control. We focused on the models used for the achievement of each of the tasks. We discuss the types of models that are available and the ones that need to be developed to serve these tasks well. We primarily focus on data-driven models, as they offer the quickest return on the invested effort. On the other hand, we welcome all efforts to develop knowledge-driven models as they offer the largest return on the invested effort since they greatly enhance our understanding of the process. Their only drawback is that they require a much larger investment in effort and time for their development.

Monitoring Models

Monitoring is a frequently encountered application of data-driven models. Its aim is mostly to monitor if the process proceeds as expected (normal operation). Otherwise, an abnormal effect has taken place and corrective action might need to be taken. Several publications address this issue with respect to pharmaceutical processes[58-61]. By designing univariate or preferable multivariate control charts, the variability of the new online data is plotted and compared to the expected variability from prior good batches and always with reference to the profile of a normal operation. In the majority of cases, the models are linear and static using Principal Component Analysis (PCA) or Partial Least Squares[c] (PLS) tools. Even though the data are auto-correlated and a dynamic PCA methodology has been proposed[62] and used in several applications, its use in pharmaceutical processes is not very prevalent, possibly because it introduces an additional complexity, that of modeling the autocorrelation characteristics of the measured variable that might not significantly enhance the fault detection ability of current approaches.

Models for Optimization

The Optimization of batch processes is a long-standing problem of interest. See for example the 1983 comprehensive review by Rippin[63]. The number of publications that address pharmaceutical processes is much smaller; see for example[64-66]. The longstanding methodology of batch optimization in the unit as well in the overall process level is certainly applicable to pharmaceutical processes if a model of the unit or overall process is available. However, the most prevalent case in pharmaceutical applications is that a fundamental model is not easily at hand. Consequently, optimization is achieved mostly via data-driven models or intuitively via *ad hoc* approaches. The most frequently used technique is the Design of Experiments (DoE)[67, 68]. The appropriately selected factors that could affect the product of the pharmaceutical process are varied in a full or, most frequently, a fractional design. Many special designs are of interest here such as Plackett-Burman, Taguchi, Central Composite, Box-Behnken or optimal designs such as D- or G-optimal designs. A limitation of such traditional designs is that they only design for time-invariant conditions. It is quite possible than many operating conditions can offer an more optimal process if they are varied with time. Such operating conditions, whose change with time might be beneficial, include the reactor temperature, the co-reactant feed rate, or the cooling rate in crystallizations, binder addition during wet granulation, among many others. A new methodology, called Design of Dynamic Experiments (DoDE), which removes this limitation, will be discussed below.

Models for Feed-forward and Feedback Control

The implementation of feed-forward and, most importantly, feedback controllers in the manufacturing plants has not been widely practiced in industry even though its importance is increasingly appreciated. Feed-forward control can be implemented by use of eth RSM model derived through DoE experiments as well as the DoDE ones described in the next section. However the use of feedback controllers, utilizing real-time data and changing in real-time the operation of the unit to achieve the tightest product quality, is not extensively practiced. This is despite the fact that feedback is the perfect tool to compensate for your lack of perfect knowledge of the different pharmaceutical unit operations. This might be partially due to the lack of wide understanding among non-experts of the power of feedback.

[c] *Alternatively called Projection to Latent Structures (PLS)*

However, the true major limitation might be due to the nonlinear character of batch processes and the lack of modeling approach for the development of simple nonlinear dynamic models to be used in the design of these controllers. Here we focus our attention on the task of controlling the end-product quality and for this task the Model Predictive Controller (MPC) would be the most appropriate approach but in conjunction of a simplified modeling methodology to lessen the developmental costs. If attention is not focused on directly controlling the characteristics of the product, a substitute strategy might be implemented by controlling a surrogate variable, such as temperature, cooling rate, or super-saturation. This is much easier to affect with simpler (P, PI or PID) controllers. Their success is dependent on how close the surrogate variable(s) is(are) related to the product qualities.

On the very positive side, several academic publications have recently started to address the problem either with the use of simulated processes or experimentally through industrial collaborations. The purpose of the present section is not to present a comprehensive review of what is has been done. Rather we highlight a few notable examples. Since crystallization is a widely used unit operation one needs to mention the extensive work of Richard Braatz's group on this topic[69-72]. On the other hand, the group of John MacGregor has published a series of paper utilizing the PLS modeling approach[73-78]. The work of Fevotte[9, 10, 12, 13] and Nagy[79-84] at well as the important contributions of many other researchers should be mentioned. On particular, one should mention the utilization of a PLS model in the framework of a Model Predictive Controller[75, 76].

A NEW APPROACH: DESIGN OF DYNAMIC EXPERIMENTS

In an effort to develop a data-driven approach for the optimization of the end-result of a batch process unit with respect a time-evolving decision variable, Georgakis[85] generalized the classical Design of Experiments (DoE) with respect to time-varying decision variables. Examples of such time-varying decision variables are the temperature of a batch reactor, the cooling rate of a crystallizer, or the feeding rate of the nutrient in a fed-batch fermentation unit. A set of experiments is designed, each with a specific time-dependant function for the decision variable and the performance of the batch is measured at the end. The data from all the experiments are used to estimate a response surface model from which the best time-dependent operation is calculated. The detailed explanation of the methodology is given elsewhere[86]. This methodology was been applied successfully to a crystallization process[87, 88] and a pharmaceutical hydrogenation process[89]. Here we will present the main idea of this methodology through its application to the following simple but illustrative batch reactor problem.

We will simulate the following reaction network, assuming that the reactor temperature and volume of the reactor are kept constant.

$$\begin{aligned} &Rxn1: A + B \rightarrow C, \quad r_1 = k_1 C_A C_B \\ &\qquad with\ k_1 = 2\,lt \cdot gmol \cdot hr^{-1} \\ &Rxn2: 2B \rightarrow D, \quad r_2 = k_2 C_B^2 \\ &\qquad with\ k_2 = 1\,lt \cdot gmol \cdot hr^{-1} \\ &Rxn3: C \rightarrow E, \quad r_3 = k_3 C_C \\ &\qquad with\ k_3 = 1\,hr^{-1} \end{aligned} \tag{1}$$

We assume that the reactor volume is 10 *lt* and that the initial concentration of *A* is 1.0 *gmol*/*lt*. We want to maximize the production of C and for this reason, the reactant B should be fed in semi-batch (fed-batch) mode. The decision variables are the total amount of *B* that should be fed, the batch time and the dependence of the feeding profile with time. For the total amount of *B* fed, we set the value of 15 gmol as the reference value and we will consider a range between 10 and 20 *gmol* fed. Concerning the batch time, the nominal value is set to 1.0 *hr* and the range between 0.5 and 1.5 *hr*. The material balances that comprise the model and will be used to simulate the experiments are given in eq. (2).

$$\begin{aligned} &\frac{dC_A}{dt} = -k_1 C_A C_B; \\ &\frac{dC_B}{dt} = u(t)/V - k_1 C_A C_B - 2k_2 C_B^2; \\ &\frac{dC_C}{dt} = k_1 C_A C_B - 2k_3 C_C; \\ &\frac{dC_D}{dt} = 2k_2 C_B^2; \\ &\frac{dC_E}{dt} = 2k_3 C_C; \end{aligned} \tag{2}$$

with

$$C_A(0) = 1.0\, gmol \cdot lt^{-1}$$
$$C_B(0) = C_C(0) = 0\, gmol \cdot lt^{-1}$$
$$C_D(0) = C_E(0) = 0\ gmol \cdot lt^{-1}$$

We parameterize the batch time t_b with the first decision variable x_1 as follows: $t_b = 1 + 0.5x_1$. Here x_1 will be bound by the $-1 \le x_1 \le +1$ constraint. The total amount of B, B_T, is parameterized by the definition of the second decision variable x_0 as follows $B_T = 15 + 5x_0$ with $-1 \le x_0 \le +1$ as the corresponding constraint. The above two definition impose a constraint on the incoming flow rate $u(t)$ of B, as we have to make sure that the planned total amount of B, B_T, is indeed fed within the planned batch time, t_b.

$$B_T = \int_0^{t_b} u(t)dt \tag{3}$$

We now define a nominal feeding profile, $u_0(t)$, in the same spirit that we defined the nominal values of t_f and B_T. This profile should use the nominal amount of B, 15 *gmol*, and the nominal batch time of 1 *hr*. Then the above constraining equation is:

$$15 = \int_0^1 u_0(t)dt \tag{4}$$

Besides satisfying the above constraint, we have a lot of choices for the selection of $u_0(t)$ because of its time dependant character. Keeping in mind that B is a reactant, we here choose the simplest meaningful profile; a feeding flow of B that is linearly decreasing with time and with a value of zero at the end of the batch

$$u_0(t) = \frac{30}{t_b}(1-\tau), \quad with \quad \tau \equiv t / t_b \tag{5}$$

The base feeding profile will change with the value of the batch time and for the reference value of t_b=1 it is equal to $u_o = 30 - 30t$. Then the flow rate of *B* for the other experiments is parameterized as follows.

$$u(\tau) = u_0(\tau) + \delta u(\tau) w(\tau) \tag{6}$$

Here we define the range of the experimental region by

$$\delta u(\tau) \equiv \frac{20}{t_b}(1-\tau), \ -1 \le w(\tau) \le 1 \tag{7}$$

The parameterization of $w(t)$ needed to convert its infinite dimensional character to a tractable finite dimensional approximation is done using a polynomial expansion. Because of their convenient orthogonality property in the (0, 1) interval, we use the set of Shifted Legendre polynomials, instead of the simple (1, t, t^2, t^3, …) polynomial terms, to which they are equivalent. The expansion is done in the dimensionless time τ (=t/t_b). We expand the dynamic coded variable $w(\tau)$ in terms of the Legendre polynomials, $P_i(\tau)$, keeping only the first three terms so as to limit the need experiments.

$$w(\tau) = a_0 P_0(\tau) + a_1 P_1(\tau) + a_2 P_2(\tau) \quad with \ \ \tau = t / t_b \tag{8}$$

To satisfy that the $w(\tau)$ values are in the (-1, 1) interval, we require that:

$$-1 \le a_0 \pm a_1 \pm a_2 \le 1 \tag{9}$$

Because the experimental region shrinks to zero at the end of the batch, we will also impose the following constraint, $w(1)$=0, which yields:

$$a_0 + a_1 + a_2 = 0 \tag{10}$$

To ensure that the amount of reactant B fed is the desired one, we impose a constraint on the $u(\tau)$ (or $u(t)$) flow rate.

$$\begin{aligned} 15 + 5x_0 &= \int_0^{t_b} \{u_0(t) + \delta u(t) w(t)\} dt \\ &= t_b \int_0^1 \{u_0(\tau) + \delta u(\tau) w(\tau)\} d\tau \end{aligned} \tag{11}$$

This simplifies to

$$x_0 = -2\left(\frac{4a_1}{3} + a_2\right) \tag{12}$$

We let x_2 and x_3 be the two additional experimental variable equal to a_1 and a_2, and we observe that the x_0 factor is dependent on the values of x_1 and x_2. We need to design a set of experiments with the factors x_1, x_2, and x_3 that need to satisfy the following constraints.

$$-1 \le x_1 \le 1,\ -0.5 \le x_2 \le 0.5,$$
$$-0.5 \le x_3 \le 0.5, -0.5 \le x_2 + x_3 \le 0.5, \qquad (13)$$
$$and\ -1.5 \le 4x_2 + 3x_3 \le 1.5$$

A D-optimal design with the above constraints consists of a minimum of 10 experiments to estimate the 10 parameters of a quadratic model, three additional experiments to assess the Lack-of-Fit (LoF) statistic and three replicates to assess the inherent variability of the process. Table 4 describes the experiments simulated.

Here we see that experiments 3, 11, and 15 are replicates of experiments 2, 11 and 14. The value of y_s is the concentration of product C at the end of the batch obtained from the simulations. To this value we add a proportional measurement error of about 4% to obtain the values y_e given in the last column of the table. This calculation is necessary to simulate what happens when the physical experiment take place. It is described by the formula:

$$y_e = y_s(1 + \lambda N(0,1)),\ \lambda = 0.02 \qquad (14)$$

N(0,1) is a random number with zero mean and variance equal to 1. We observe that the resultant product C concentration has a minimum of 0.1633 and a maximum of 0.4252., a substantial range. In Figure 8 we plot the 13 different feeding profiles of the co-reactant B. A typical set of concentration profiles with time is given in Figure 9 corresponding to the first experiment (#1). A linear regression step yields the flowing relation of the response surface model:

$$y = +0.37 + 0.063x_1 - 0.06x_2$$
$$-0.05x_3 + 0.036x_1x_2 + 0.015x_1x_3 \qquad (15)$$
$$-0.037x_2x_3 - 0.079x_1^2 - 0.040x_2^2$$

The model has a favorable LoF statistic (p=0.18), implying that all the measured variability has been appropriately represented by the above equation. Optimizing this model so that we maximize the final concentration of product C, C_C, we find that the optimal conditions are those given in the row noted as Opt-1 in Table 5. On the other hand, if we wish to optimize the amount of C produced pet unit time of batch operation, C_C/t_b, the optimal conditions are given by the row noted as Opt-2 of the same table.

In Figure 10, the above two optimal feeding profiles are plotted. One can clearly observe that they are quite different from each other, yet there were determined by the same set of experiments.

Conclusions

In this paper, we summarized the state of the art of the utilization of PSE tools in the pharmaceutical industry and tried to glance a bit into the future. We have presented the results of an industrial benchmarking survey, and discussed the projected impacts of out-sourcing and the rise of continuous manufacturing on PSE tool advancement. We hope to have motivated the audience for the greater need of data-driven rather than knowledge-driven models, suitable for quick deployment in process optimization and on-line control tasks related to pharmaceutical processes. We have also presented a novel-data driven optimization methodology called Design of Dynamic Experiments.

The literature references provided in this paper, and the data from the questionnaire indicate that the pharmaceutical industry has embraced the use of PAT measurement systems such as spectroscopic tools (Mid-IR, NIR, Raman) and has adopted multivariate data analysis tools (PCA, PLS) for process monitoring and modeling. Some activities on closed-loop control are staring to appear. These PSE tools are currently mostly used in process development, but several companies are using them during manufacturing operations. The survey data also showed that fundamental models are sparingly applied to processes where they are feasible both technically and from a resource perspective. Data-driven models (response surface, latent variable) are widely used for scale up and design space development. All the participating companies reported that the risk management/design space approach is applied to product development. They also expressed interest in advanced process control approaches for reducing variability and enlarging the size of the control space. There are clearly many more opportunities for applying existing techniques to other processes as well as in postulating new methodologies such the nascent one on the Design of Dynamic Experiments. Pharmaceutical processes are similar enough to the general class of chemical and petrochemical processes to benefit a lot from the existing plethora of PSE tools. At the same time, they are substantially different in

many aspects to provide for a wide opportunity for innovative new approaches that have not been considered so far.

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Table 4: Details of the DoDE design for the batch Reactor

#	x_1	x_2 (=a_1)	x_3 (=a_2)	x_0	a_0	y_s	y_m
1	0.00	0.00	-0.50	1.000	0.50	0.4227	0.4252
2	-1.00	0.50	-0.50	-0.333	0.00	0.1973	0.1961
3	-1.00	0.50	-0.50	-0.333	0.00	0.1973	0.1958
4	1.00	0.50	-0.50	-0.333	0.00	0.3718	0.3670
5	1.00	-0.16	-0.28	0.987	0.44	0.3702	0.3679
6	0.00	0.45	-0.10	-1.000	-0.35	0.3011	0.2995
7	-1.00	0.00	-0.01	0.020	0.01	0.2268	0.2295
8	1.00	0.28	0.04	-0.827	-0.32	0.3386	0.3305
9	0.13	-0.10	0.10	0.067	0.00	0.3804	0.3895
10	-1.00	-0.50	0.17	0.993	0.33	0.2836	0.2790
11	-1.00	-0.50	0.17	0.993	0.33	0.2836	0.2785
12	1.00	-0.50	0.17	0.993	0.33	0.3583	0.3474
13	0.00	-0.50	0.50	0.333	0.00	0.3844	0.3769
14	-1.00	0.00	0.50	-1.000	-0.50	0.1653	0.1726
15	-1.00	0.00	0.50	-1.000	-0.50	0.1653	0.1633
16	1.00	0.00	0.50	-1.000	-0.50	0.3138	0.3199

Table 5: Details of the optimal Operations for the batch Reactor

#	x_1	x_2 (=a_1)	x_3 (=a_2)	x_0	a_0	y_s	y_s/t_b
Opt-1	0.31	0.00	-0.50	1.00	0.50	0.4314	0.3790
Opt-2	-1.00	-0.50	0.17	0.99	0.33	0.2787	0.5605

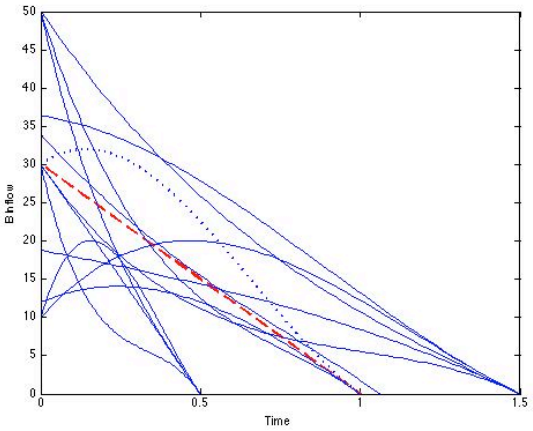

Figure 8: The 13 distinct feeding profiles of the co-reactant B in the DoDE set of experiments. Dashed line: Base Case, Dotted line: Best of 13 cases

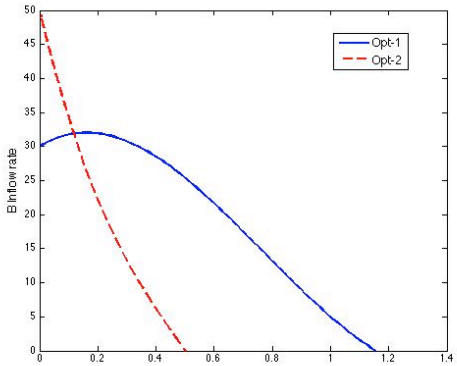

Figure 10: The feeding profiles of the coreactant B that correspond to Opt-1 and Opt-2 that maximize $C_C(t_b)$or $C_C(t_b)/t_b$, respectively.

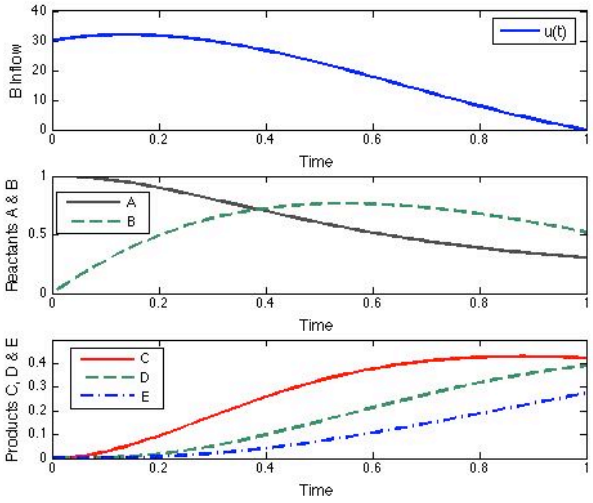

Figure 9: Concentration profiles for an example feeding profile corresponding to the first experiment (#1).

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