Evolutionary vs. Revolutionary: a Snap Shot of the Current Tendencies in Pharmaceutical Industry and the Impact of Process Analytical Technology and Continuous Manufacturing Processes

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Abstract *— Food and Drug Administration (FDA) challenges the pharmaceutical industry to innovate itself and introduce ever higher quality standards through the use of technology. Development of continuous manufacturing systems and integration of Process Analytical Technology (PAT) applications are poised to introduce revolutionary innovation to the pharmaceutical industry with joint collaborations from equipment manufactures and the academia.*

Key Terms *— Chemometric Models, Mechanistic Model, Quality by Design, Statistical Process Control.*

INTRODUCTION

In the words of Dr. Janet Woodcock at the AAPS meeting October 2011; "Right now manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing [1]." From this we can easily understand that this industry unlike most has remained stagnant in development of new manufacturing techniques. Innovation has been a slow process mostly related to automation and instrumentation improvements, more related to the evolutionary nature of equipment development. Up to now Small Molecule Pharma products has been developed in technologies that have their roots in the 1950s and 1960s. This includes several of the highest sales volume products manufactured around the world. Most of this related leverage gained from formulators for pharmaceutical products used widely known material or those they had personal experience with basic equipment and little or no instrumentation [2] as well as companies looking for the ever prominent "block-buster" drugs in which high volumes and product flow characteristics far outweighed potential benefits brought forward by innovative manufacturing. This has changed, in this days the development of this "block-buster" drugs are less likely and being replaced with what eventually be lower volume more customizable drugs.

In the past few years the pharmaceutical industry is undergoing a paradigm shift in the development of new products and the way they are manufactured. This is especially true in the manufacturing of small molecules where companies such as Pfizer, J&J, Novartis and GlaxoSmithKline among others, are pursuing development activities for commercial scale manufacturing using continuous processing equipment. The FDA is at the forefront of this change by challenging the industry to invest in new manufacturing techniques that will introduce the use of Process Analytical Technology and Statistical Process Controls leading to improvements in quality and reductions in cost.

The FDA has been an important advocate of continued development of analytical techniques as well as processing equipment. Examples of this have been initiatives such as the development of the Center for Process Analytical Chemistry, CPAC, at the University of Washington which has been founded by the FDA. The Goal of the CPAC New Sampling /Sensor Initiative (NESSI) project is to enhance the understanding of continuous manufacturing and microreactions. Leading to the

developing a drug substance synthesis using microreactors following QbD paradigm, effective implementation of sampling and online analytics and leveraging data from analytical tools to design integrated control strategy. Other initiative developed by the FDA has been the Safe Harbor Exemption concept that addresses the industries general hesitation to introduce innovative systems to the manufacturing sector.

On 2012 as part of the IFPAC Annual Meeting the FDA made a presentation called FDA Perspective on Continuous Manufacturing. This presentation was focused in the advantages of continuous manufacturing over conventional batch process. Among the topics is the impact to cost; Integrated processing with fewer steps leads to increased safety due to no manual handling, shorter processing time and increased efficiency. The smaller equipment and facilities leads to more flexibility, reduced inventory lower capital and operational costs and smaller ecological footprint therefore reducing environmental impact of manufacturing [2]. Other elements addressed in the presentation were the perceived regulatory hurdles. They were addressed by the statements that no specific regulations or guidance for continuous manufacturing, other than the definition of "lot", clarifications that there is nothing within regulations or guidance prohibiting continuous manufacturing and that The FDA sees continuous manufacturing consistent with Quality by Design efforts.

This aligns with other initiatives and statements from the FDA that continuous processing improves product quality by: [1]

- Implementation of analytical tools pursue in-line monitoring of Critical Quality Attributes at higher sampling frequencies that will be possible in batch processing
- The development of non-destructive in-line techniques will further drive manufacturers to their implementation based on potential benefits of data gathered such as Real Time Release
- Feed forward mechanisms developed by equipment manufacturers will allow the system to respond to predictable impact of variations from raw materials (e.g.. such as respond to viscosity, particle size or even assay variations)

In addition the implementation of continuous processing by pharmaceutical companies will simplify product development, transfer and scale-up activities since:

- The use of modeling tools and scale factors allows developers to easily test the response of raw materials to the physical, chemical, thermodynamic conditions and resilience time distribution of large scale manufacturing based on testing at development scale equipment
- Fast response time to Process Parameters modification allow for increased data collection of their impact in the product attributes with reduced waste (improved design space modeling)
- Larger batches just mean longer running time by basic replication of processing within steady state conditions

For pharmaceutical companies the benefit of implementing continues processing along with implementation of PAT tolls aligns with the FDA beliefs that their supporting continuous processing equipment will promote the implementation of continuous monitoring instrumentation along with development of process modeling tools. Also improved data acquisition and analysis through integrated communication protocols and development of Chemometric Modeling through Multivariate Statistics, Applied Mathematics and Computer Science in order to address and respond potential chemical or biochemical problems (mimicking the use of psychometrics for determining the thermodynamic conditions of a process).

Impact on Equipment Manufactures

Most of the original efforts for major pharmaceutical companies were focused in the development of custom manufacturing trains developed from Food Industry applications or modifications to existing equipment that included some equipment vendors. A lot of these efforts were

related to maintaining intellectual property of these new manufacturing applications or the potential impact of patent extension to marketed products. This approach although innovative lack the benefit to be gained from collaboration with major equipment vendors and their knowledge of years of research and development activities related to equipment performance and controls system integration.

On other end of the spectrum were some efforts from equipment manufactures that developed what they perceived as single platform systems that will be capable to support multiple functionalities required by the pharmaceutical industry. In both cases there were substantial failures in the development of these new manufacturing platforms.

The paradigm shift comes from these failed efforts from both sides into integrated approach by Pharma and Equipment Manufacturing Industry that has led to major developments of manufacturing platforms that have fully integrated controls and PAT platforms and can be easily modified by equipment manufacturers to tailor for the needs of individual companies without the complexity of having to develop a custom control system schema for each application. This has been enhanced further by inclusion of academia into the development efforts. Integrated efforts between pharmaceutical industry, equipment manufacturers and academia has led to major developments in chemometric modeling, SPC, process modeling and understanding the influence of the Residence Time Distribution for individual equipment as well as characterization of disturbances and changes through the system during startup and as it reaches steady state.

Other area impacted by the joint efforts of Pharma, equipment manufactures and academia is the development of measuring devices and their applications. Major equipment manufacturer have worked with academia to develop the knowledge to understand the impact of sample frequency, material flow over the optics in the data collection probe as well as the "blind" times encountered in some steps of the process. This has improved response time of rejection devices, accuracy in data collection process and increased data collection rates. Some of the new devices have been developed to allow for cleanability of the optics in process as well as capacity for implementation of purging and CIP process of the instrumentation.

One such example is the GEA Lighthouse probe (Figure 1) that has the capacity to clean the observation window automatically in an integrated wash chamber. This probe can be used for multiple optical analysis methods such as FT-NIR, NIR, and RAMAN among others in processes such as granulation, drying, blending, milling and coating. The probe in equipped with a pneumatic actuator that offers four positions

- Measurement. Probe deployed in product stream
- Window Wash. Probe retracted with optical element directly in front of Wash Connections to be cleaned by vacuum
- Cleanness Check & Calibration. Probe retracted further to reference element in front of optical element
- Clean in Place. Probe fully retracted that allows clean ports to be pressurized with connection to CIP distribution system

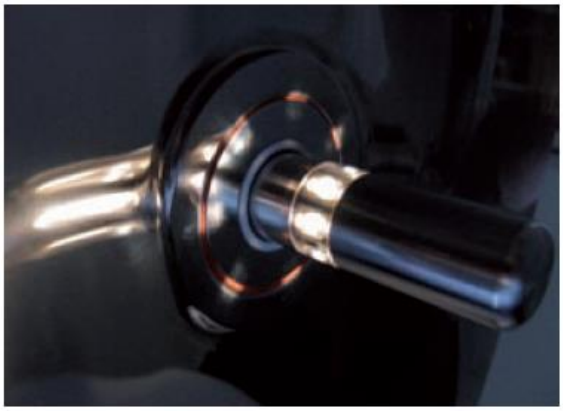

Figure 1
GEA Pharma Systems LHP-A-2"SP Probe Installed in Process Equipment

Other manufacturers have also incorporated cleaning devices or data collection chambers to optimize the performance of their optics and presentation of sample material as is the case of the Mettler Toledo Focused Beam Reflectance

Measurement (FBRM) where the scattering Laser probe (Figure 2) has been design for installation in multiple applications ranging from liquids to solids with sample chambers optimized for the applications.

Figure 2
Mettler Toledo FBRM in-line Particle Track G600L unit

Collaboration with Academia

The roll of the academia has gained ever more leverage in the past few years with the emphasis of innovation brought forward by development of PAT techniques and new Continuous Manufacturing processes. Now more than ever before joint ventures between pharmaceutical companies and universities have brought forward the need to develop new resources with emphasis in chemometric, analytical, statistical and mathematical modeling of data and equipment performance. This has open new opportunities to disciplines not previously related to pharmaceutical R&D disciplines. One such instance is the advent of mechanistic modeling of process equipment. Others are chemometric models of PAT data collection. Both of them correlate to the measurable and predicted performance of a product when exposed to the conditions within the process equipment.

The importance of this modeling techniques and ultimately the resources can be seen in the ever expanding role of the Pharma-Academia and Equipment Manufacturers-Academia joint ventures in which grants from pharmaceutical or equipment manufacturer companies have allowed development of new continuous processing techniques, improvements in performance of the equipment and instrumentation and development of modeling techniques that can predict product performance under different thermodynamic and mechanical conditions.

A few of the examples between Pharma and academia are Novartis-MIT[2] continuous manufacturing system project (Figure 3), Rutgers University collaboration with Janssen in development of direct-compaction line using continuous manufacturing principles and exercises performed by Pfizer and University of Berlin and Rutgers University in development of continuous manufacturing systems.

Figure 3
Novartis-MIT Drug Manufacturing Prototype at MIT's Center for Continuous Manufacturing

In Puerto Rico the academia is playing a major role in the development of chemometric models and implementation of PAT in projects local and abroad. They have been involved in projects with Pfizer, Wyeth, J&J and Rutgers University among others as part of developmental activities.

Integration Equipment/Instrumentation

One of the major elements that have motivated the development of continuous manufacturing systems and the widespread acceptance by regulatory agencies and Pharma industry is the advances of Process Analytical Technology and the

integration to the systems controls. Continuous manufacturing systems are extremely efficient at replicating exacting conditions. This means that once the steady state has been reached it can be maintained for predetermined periods with minimal variability of the processing conditions. PAT allows in line data collection and process analysis.

Unlike the batch processing, where there are limited or in some cases no mechanism to influence the outcome of a process in response to variability of raw material, in the case of continuous manufacturing processes, proper implementation of PAT allows responding and potential implementation of feed-forward controls to the system based on the detected variations. The development of data management tools is at the cornerstone of the development of these controls. Equipment and instrumentation manufacturers have agreed upon implementation of open communication protocols such as OPC as the backbone in communications for these control systems.

The new process control applications being developed allow much simpler SCADA application (Figure 4). These applications do full integration of Engineering Systems, Operator System, Diagnostic and Maintenance, System Libraries, Automation Systems, Communication, Distributed I/O, Process Data Archiving and Reporting, Batch Automation, Safety Integration, Industrial Security and Process Device Management among other. This allows developers to use a single application for integrating the DCS structure within the same platform with common language and similar interfaces.

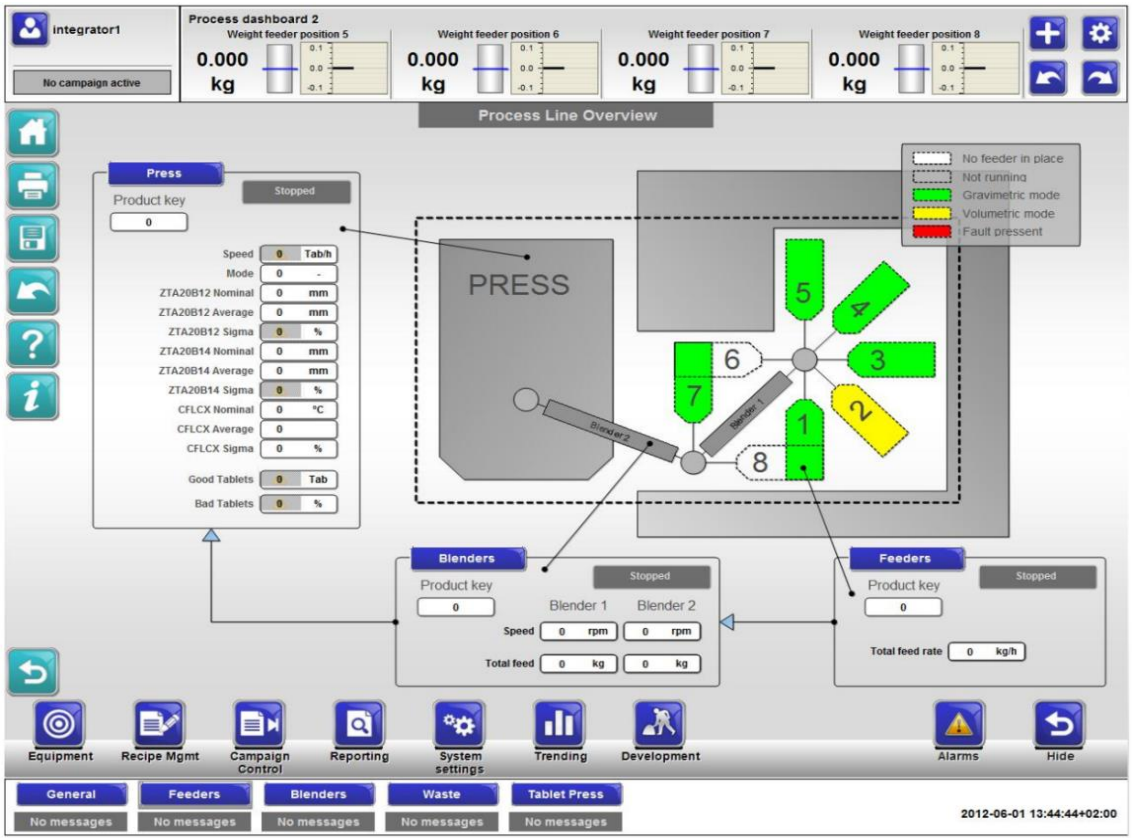

Figure 4

GEA ConsiGma Direct Compression Operational Interface Screen Developed with Siemens Simatic PCS 7 Software

These packages allow for development of operator interface terminal that can handle multiple functionalities ranging from operation and maintenance to batch recipe editing, data analysis and report as well as analysis of spectral data. In the past this could have require multiple terminals and applications in order to provide the functionality requirements to support such a complex DCS with the addition of the incorporated PAT tools.

The implementation of batch controllers within this applications have also allow equipment vendors to customize their applications to the individual needs of the client without requiring major modifications to platforms being developed. Functionality modules can be developed for product feeding devices, for roller compaction, continuous mixing module, twin screw extrusion units and others allowing the user to select application required for specific processes and ultimately allowing this modules to be activated or disabled based on something as simple as the selection of the individual product recipes or the identification of the equipment module installed.

One such application has been developed by GEA in their ConsiGma units (Figures 5 & 6). These units have been developed in a modular approach. This allow GEA to provide companies with process trains with multiple granulation process options that can be easily switched from one to the other based on recipe selection and activation of corresponding process module.

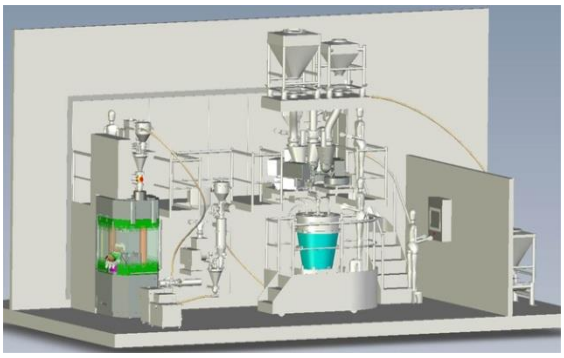

Figure 5
GEA ConsiGma Wet Granulation System

Figure 6
GEA ConsiGma Direct Compression Module

CONCLUSION

We are approaching an interesting period within the pharmaceutical industry. A period of adaptability to a change in the paradigm of scale and adapting to the ever changing environment where efficacy of drugs is correlated not only to the expected therapeutic effect but also to its cost and development time. Regulatory agencies are embracing new manufacturing technologies such as PAT and continuous manufacturing expecting that they will introduce revolutionary changes to the science of making drug products. With expectations of maintaining the Quality by Design paradigm and a balanced risk based approach to product manufacturing and development. This in turn should improve the efficacy, quality and cost for drug products. On the other side is the pharmaceutical industry embracing the benefits of continuous processing due to the substantial reductions of capital cost, plant footprint and resources consumption as well as flexibility and improvements in scale-up and reduction of in-process.

This new shift has introduced another benefit to the equation in the spirit of collaboration between the pharmaceutical industry, equipment manufactures and the academia. New fields of study are being developed base on the innovation of these technologies and the expectations of the regulatory agencies that the risk based approach is supported by understanding the operating principles being applied, introduction of statistical process control (SPC) and improvements in the modeling techniques

that will predict performance of products based on data analysis.

It is an exciting time especially with mayor pharmaceutical companies developing projects that will change the way we produce some of the biggest selling products in the world with the expectation of improving product quality and benefiting from the improvements in cost that can be obtained from the shift to continuous process.

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