Using Statistical Engineering in Solving Pharmaceutical and Biotech Problems

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Statistical engineering can be applied in a wide diversity of areas. This case study shows how statistical engineering is used to solve a large, complex biopharmaceutical supply chain problem. This major undertaking has been discussed previously (McGurk 2004). This article shows how the project has all the characteristics of a statistical engineering project. The project story complete with steps and results is presented to illustrate how a statistical engineering project is conducted.

Statistical Engineering can help solve big problems. Since the emergence of Six Sigma around 1987 (Six Sigma, Wikipedia), there has been a growing awareness that some problems are too large, complex and unstructured to be solved with traditional problem-solving methods, including Lean Six Sigma. The case study to be discussed in the article is different than from those that can be solved through routine problem solving, or even through the use of Lean Six Sigma. Some attributes of these types of problems are:

- Large
- Complex
- Unstructured
- Data Challenges
- Lack of a single "correct" solution
- Need for a strategy

Statistical engineering (Hoerl and Snee 2017) was developed as an overall approach to developing a strategy to attack such problems. The International Statistical Engineering Association (ISEA) defines Statistical Engineering as: "The study of systematic integration of statistical concepts, methods, and tools, often with other relevant disciplines, to solve important problems sustainably" Note that statistical engineering is not a problem-solving methodology per se, such as Lean Six Sigma, but rather a discipline. A generic statistical engineering framework to attack large, complex unstructured problems is discussed in Snee and Hoerl (2018) and in the International Statistical Engineering Association (ISEA) website (www.isea-change.org).

The phases of a statistical engineering framework are shown in Figure 1 along with the purpose and critical work elements in each phase. We see that there are six phases, not "seven easy steps". It is not a "linear process"; recycles and iterations are required as the project progresses and learnings accumulate. Each phase needs to be tailored, depending on the problem structure and context. Several projects and data-based studies are often required.

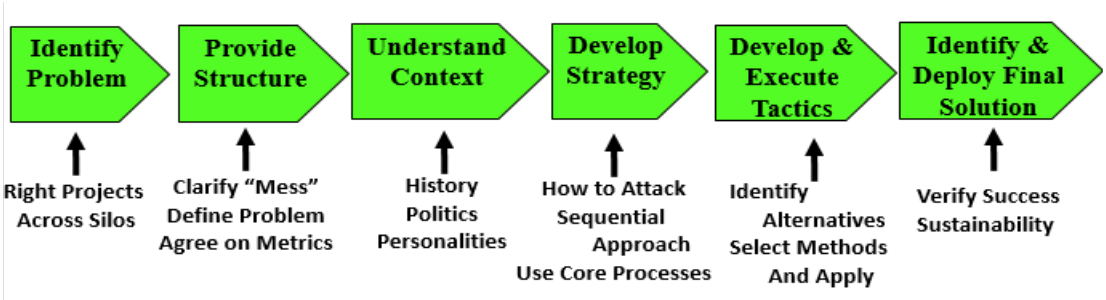

Figure 1. Phases of Statistical Engineering Projects

This framework will be used to describe a major biopharmaceutical supply chain improvement project including the problem solving process and results. As we will see the statistical engineering aspects of this project should come as no surprise. Talented problem solvers have been using the fundamentals of statistical engineering for a very long time. The problem has been that each project has been treated as a new event requiring that an approach be built from scratch. All the learnings from previous major projects were not recorded, lost or ignored. Statistical Engineering codifies the problem solving process giving the project team a head start including guidance on the work to be conducted, the sequence in which the various phases should be done and problems and issues that might be encountered along the way.

Phase 1: Identify the Problem

A major global pharmaceutical company faced supply challenges with two of its major biopharmaceutical products and decided to take systematic action to ensure a reliable supply of patient-critical products; a blockbuster drug and a monoclonal antibody. These two drugs were produced by different biopharmaceutical processes. This Company knew that one of the products was certain to be a blockbuster. A review of production and released product levels convinced the Vice President in charge of the two products that market demand for the blockbuster product could not be met. The monoclonal antibody product, had already encountered supply problems. The company was determined to establish predictable manufacturing capability for both products and meet the challenge of enormous market demands, all while ensuring sustainable Good Manufacturing Practices (GMP) compliance.

Management was also concerned that the organization may not have the experience and skills to identify and implement the needed changes. Clearly a major comprehensive review and improvement of these products and process that produced them was needed. The organization realized that this was a major problem that crossed organizational lines. A consulting firm was engaged to undertake this initiative as the firm had the needed capability and capacity to do the work.

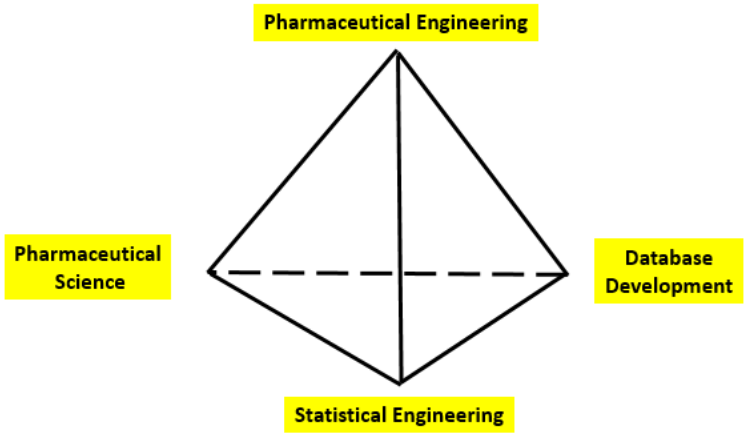

Figure 2. Required Project Team Skills

The consulting firm and the company worked collaboratively throughout the project. One of the first steps was to form a team that had the required experience, knowledge and skills. The personnel involved pharmaceutical science, process engineering, data base development and management and statistical engineering (Figure 2). Such a broad skilled team was needed to ensure that all the relevant knowledge was available to carefully collect the relevant data, perform the appropriate analyses and develop solutions that were workable and would be sustainable over time. Such diversity of skills is characteristic of statistical engineering projects. It is rare that the broad range of skills and knowledge required to successfully complete these projects reside one or two persons. Thus, a multi-skilled team is needed. Separate sub-teams were created for each product.

Phase 2: Provide Structure – Clean up the Mess

The scope and project goals were very clear at the beginning. The focus was on meeting the launch date for the new product and obtaining a major increase of the yield of the monoclonal antibody product. The two sub-teams were managed by a common project leader. The timing for the project was approximately one year. It was also clear that a considerable of data collection and analysis would be involved.

Such a major undertaking requires a well-defined structure to guide and prioritize the work. Large, complex and unstructured problems are typically very messy at the beginning. Creating structure for the problem and work helps, as we fondly say, “clean up the mess”. This was done by first conducting a process and organizational assessment. Conducting such assessments is a very effective tool to identify the needed information to properly structure the problem, identify opportunities for improvement and conduct the improvement work.

As shown in Figure 3 the assessment team looked at seven (7) focus areas using a mixture of tools including document review, interviews of critical personnel at all levels in the organization, surveys and process observation Four (4) areas of opportunity were identified: throughput and quality, leadership and management, process and equipment reliability and compliance and organization and behavior.

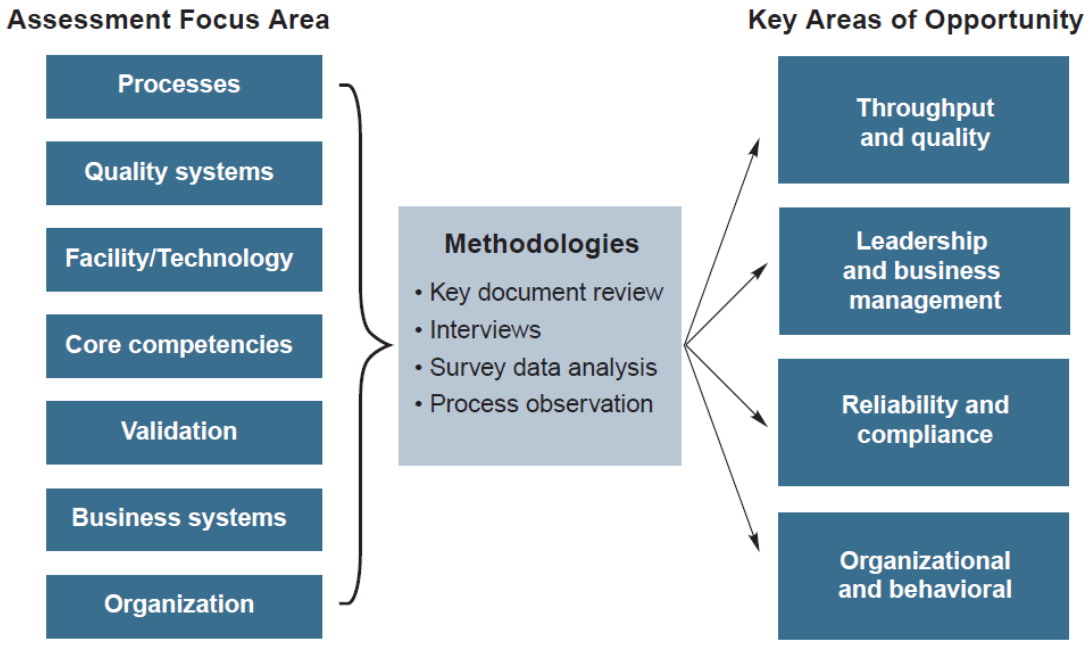

Figure 3. Elements of a Comprehensive Assessment (Source: McGurk 2004)

The supply capability of an organization depends on its ability to plan and execute not just the manufacture of product, but also wider operations including process reliability, Good Manufacturing Practices (GMP) compliance, effective leadership, clear communications, and operational metrics. To generate a targeted list of improvement opportunities in all these areas, the company first assessed a range of operational expertise including manufacturing and quality assurance (QA) knowledge, operational metric design, organizational development, and statistical process control (SPC).

The initial target list was broad, ensuring no significant opportunities were missed (Figure 3). As Linus Pauling points out, "The best way to have a good idea, is to have a lot of ideas". By uncovering causes common to the problems on the initial list, the project team was able to consolidate improvement opportunities into categories and further characterize them, aligning them with the overall goals and strategy of the organization and calculating the potential return on investment.

Phase 3: Understand Context - History, Politics and Personalities

Stock outages of pharmaceutical and biological products occur with disappointing regularity. Even newly launched products have not been immune, particularly biopharmaceuticals, which take longer to manufacture and require production operations that are more difficult to control. These shortages result in Industry and regulatory issues and bad perception by the public. As a result not meeting demand is both a financial and political issue.

The two products involved were of critical importance to the health of the company and were highly visible to senior management. The Vice President in charge of these products was concerned that the launch date and yield improvement goals would not be met. There was much risk involved.

The organizational and process assessment was very useful in understanding the context of the problem. In particular the interviews with leaders in all levels and functions provided critical information regarding the history, politics and personalities of the organization and the people working in it.

The interviews made it clear that the staff had little manufacturing experience as manufacturing was staffed by several employees who developed the drugs in R&D. Operating manufacturing requires a mindset change from developing new and innovative products and processes to operating processes to consistent and compliant manufacture. Development of skills for manufacturing excellence will have to be developed. Thus an enabling objective was to get the staff at ALL levels to a new level of performance. A significant amount of training and one-on-one mentoring would be required.

Phase 4: Develop Strategy – How to Attack the Problem

The assessment uncovered a number of gaps that impeded both the production ramp-up for the blockbuster drug and the consistent supply of the monoclonal antibody. Knowledge of these gaps greatly facilitated the development of strategies regarding how to attack the problem and the subsequent creation of tactics for implementing the strategies.

The gaps identified included:

- Need for 100% more manufacturing capacity to meet demand for the blockbuster drug
- Suboptimal manufacturing reliability for the monoclonal antibody, which stood at only 80% ‘right first time”.
- Inefficient processes for review of batch records, including review periods more than twice as long as necessary
- Inadequate measurement system for monitoring operational performance

- Insufficient leadership and interpersonal skills for cross-functional teamwork
- Inadequate training for production operators.

These gaps identified four critical focus area: Manufacturing Capability, Batch Record Review, Create Metrics and Training and Leadership. Tactics were developed to address each of the four (4) critical focus areas. The team compiled a list of specific projects and formed cross-functional teams to address them. As the projects crossed functional lines, the teams employed were also cross-functional. The plan called for the four focus areas to be worked on simultaneously. The project was of critical importance so management made the resources available. While these focus areas were part of the same project, improvement could be made in the areas independent of each other.

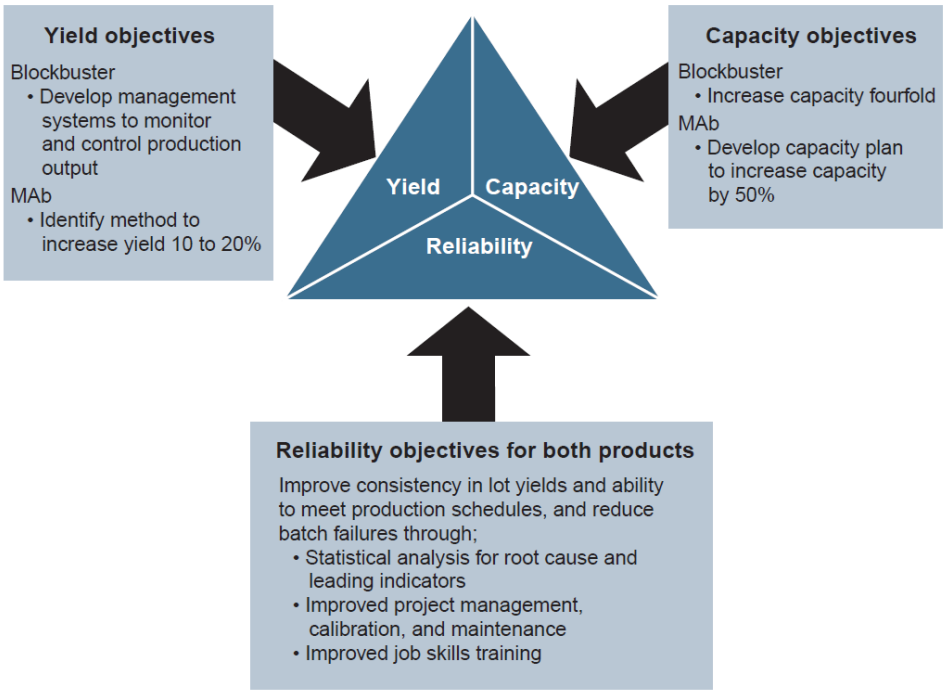

Figure 4. Manufacturing Capability Model (Source: McGurk 2004)

Phase 5: Develop and Execute Tactics

Manufacturing capability depends on the interaction of three components — capacity, yield, and reliability (Figure 4). Understanding their interaction was critical to prioritizing improvement activities. Two manufacturing product teams, one for the blockbuster drug and one for the monoclonal antibody, were formed. To address capacity, the teams conducted a bottleneck analysis of equipment, people, and training constraints.

To improve yield, the team applied statistical process control and multivariate analysis to historical production data. This method provides knowledge that cannot be derived from a few pilot, demonstration, or even validation runs (Hoerl and Snee 2020). For example, after the

monoclonal antibody production team identified process shifts in fermentation yields, they formed a cause-and-effect team that included fermentation experts and a statistician.

It is critical when analyzing production data to assess the quality of the data. The critical question is are the data "fit for use" in the problem solving venture being pursued. This is accomplished by understanding the "data pedigree". Do we know the origin of the data and the route it has taken prior to be considered for analysis? Data pedigree is defined as "documentation of the origins and history of a data set, including its technical meaning, background on the process that produced it, the original collection of samples, measurement processes used, and the subsequent handling of the data, including any modifications or deletions made, through the present." (Hoerl and Snee 2019)

Assessing data quality is particularly important in analyzing production data because the data are "observational data" collected without the aid of a planned protocol such as a statistically designed experiment (Montgomery 2019). Observational data are of lower quality for many reasons including missing variables, recording errors and poor measurement technique (Hoerl and Snee 2020). In this case the data were transcribed from batch records. Great care was taken to get the transcription done correctly and involving subject matter experts to check the validity of the data. It was concluded that the available production data were adequate for studying the production process behavior.

To improve reliability, the teams analyzed historical process variances. Variances are instances of "things that went wrong", which are referred to as "special causes" in the quality improvement world. These can include process control parameters that were not in control, changes to procedures, or any other variation from normal practice. Without process reliability, accurate and precise supply predictability remains impossible. Of course companies compensate for this unpredictability by adding manufacturing capacity— and incur additional costs. In the pharmaceutical industry, production variances and the resulting investigations pose a great threat to reliability and, in turn, supply capability.

Batch Record Review can greatly affect supply chain performance which depends as critically on the flow of required documentation as it does on the flow of product. A Lean Six Sigma approach was used to analyze the batch record review process (Snee and Hoerl 2005). A cross-functional team of production and quality personnel constructed a process map of the batch record review process, detailing bottlenecks such as excessive time spent in the queue, an overly complicated flow of records, and a lack of clarity in the company's expectations of reviewers. The team collected baseline batch release data for both products and used fishbone diagram analysis to organize the variables that would impact defects of the batch record review process. They then used Pareto analysis to prioritize the correction of defects and control charts to

measure the progress and impact of changes to the process. The use of a large collection of quality tools in the problem solving process is characteristic of statistical engineering projects.

Process Metrics are central to the effective monitoring, control and improvement of manufacturing processes. Complicated operations require clear operational definitions and accurate and timely flow of information among shop floor, planning, and operations management personnel. For example, inconsistency concerning when a particular operation is considered complete can cause enormous confusion. A batch could be deemed "done" in a number of ways: when an operator finishes making the batch, when the documentation is reviewed, when Quality releases the batch, or when it is in inventory, ready for shipment. A month or more could elapse from the time something is *believed* to be done to when it *is actually* done.

Training and Leadership Development are always required for major organizational change. This need was especially acute given the preparation for launching a blockbuster product. Approximately 70 members of the quality and operations functions underwent training in such interpersonal skills as understanding people, expressing oneself, and resolving conflict —all critical for the smooth functioning of any organization with extremely complicated and highly interdependent processes.

Members of the leadership group participated in an assessment of leadership knowledge, the results of which were compared to an extensive database and used to create ongoing leadership development plans. A significant amount of individualized and group coaching and ongoing assessment of the program's effectiveness supplemented the organizational development work.

Operator Training was needed to increase production levels with the launch of the blockbuster product, the project team undertook a detailed analysis of the manufacturing operation and its operators. A digital video camera recorded the actions of trained operators using both existing and revised standard operating procedures (SOPs) and batch record instructions for the operations. The videotapes provided both a model of appropriate behavior for operators and a forum for them to work together to develop best practices.

Phase 6: Identify and Deploy Final Solution

As discussed in the section on "tactics" several critical process changes were deployed in each of the critical focus areas: manufacturing capability, batch record review, process metrics and training and development.

Manufacturing Capability. As a result of the bottleneck analysis, the team broke the bottlenecks by purchasing needed equipment such as additional storage vessels and refrigeration capacity, identifying the personnel required for production ramp up, and cataloguing skill deficiencies — especially those in biopharmaceutical production, such as batch weighing, batch

charging, chromatography, and GMPs. After identifying the needed skills, the team set up a training program to teach them how to effectively employ these new skills in their daily work.

Analysis of the monoclonal antibody production data using a control chart identified 30% shift in yields (Figure 5). The root cause of the shifts was the media lots used in the antibody production. On investigation it was learned that there were no specifications for the media lots. The explanation was that ‘we take what the supplier sends us”. Specifications were developed for the media lots along with associated measurement methods. Yield was significantly improved when the new specifications were instituted.

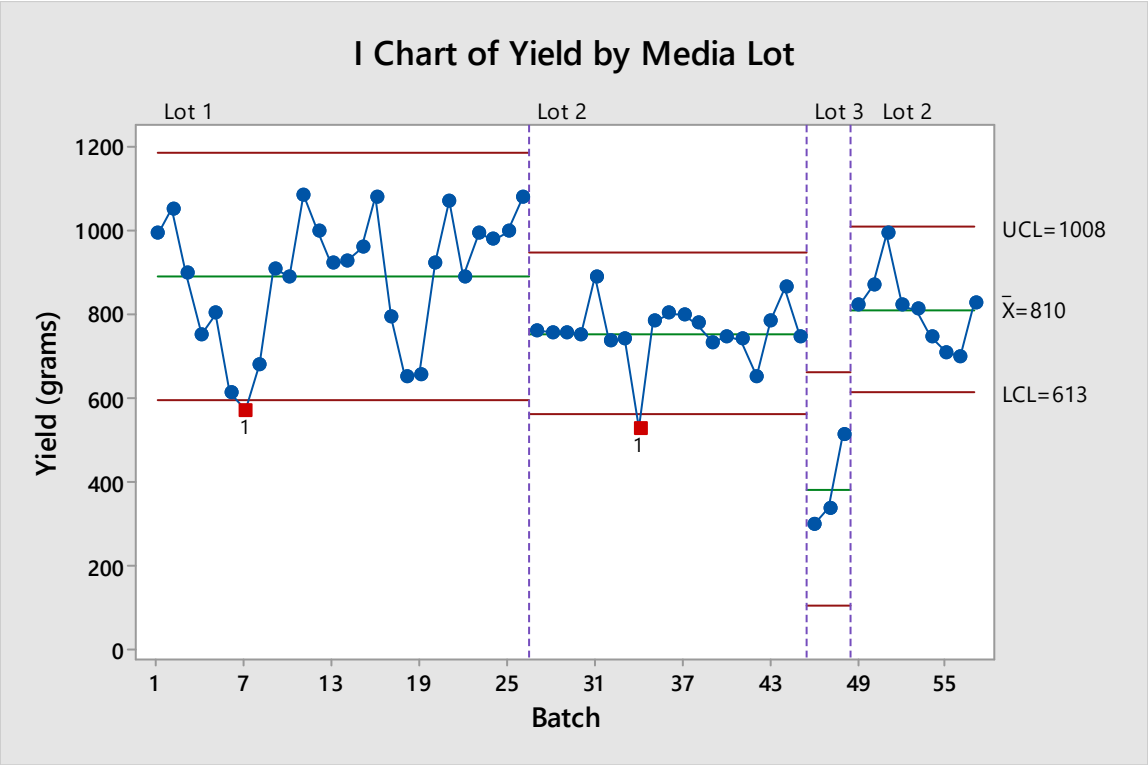

Figure 5. Control Chart of Process Yield for Production Batches

The application of similar statistical and analytical techniques to other areas, including column chromatography performance and optimum column loading, resulted in higher reliability and a 10% improvement in yield. By identifying causes and effects, these techniques focus sharply on particular problems, thereby saving time and maximizing return

The analysis of variances identified systems that were prone to problems — either mechanical problems, such as design and equipment suitability, or operational problems such as how the system was used. For example, repeated variances in the batch weighing process could reveal mechanical failures (such as inadequate scale design and installation suitability) as well as

operational failures (which can include unskilled or inadequately trained operators and poor operating documentation).

By uncovering root causes of variances, the team was able to strengthen both the mechanical and operational aspects of vulnerable systems. Most variance reduction programs fail because they do not uncover the root cause of variances, lack connection to a thorough system analysis, and poorly execute the corrective action. Given a poor definition of the problem and the lack of a system-level analysis, poor corrective action is inevitable.

Batch Record Review. As in most documentation processes, time for review is a major bottleneck. Through the use of a process map, the team established a framework for allocating the *who*, *what*, *when* and *where* of the review. The document review process which was embedded in the batch record process was divided into seven steps. The cycle time for each step was recorded for each process step associated with the review of 37 batches. The goal for cycle time was a 50% reduction which would be a major step forward and greatly increase the ability to release the product for distribution to customers

These cycle times were plotted on a Pareto chart. As we see in Figure 6 the 'big bar" on the chart is for the review time of the manufacturing organization. Several improvements were made including the following changes:

- Target cycle times and associated monitoring procedures were developed.
- Periodic retraining of process operators was instituted and backup personnel were identified for critical positions.
- The process tracking meeting was redesigned to focus on problem identification and solution rather than data reporting and review.
- O*ne-unit flow*, a lean manufacturing concept, was instituted to manage the document review process. Individual records were submitted for review when complete rather than waiting for all the records for a batch to be complete before submitting the "batch of records" for a given production batch.

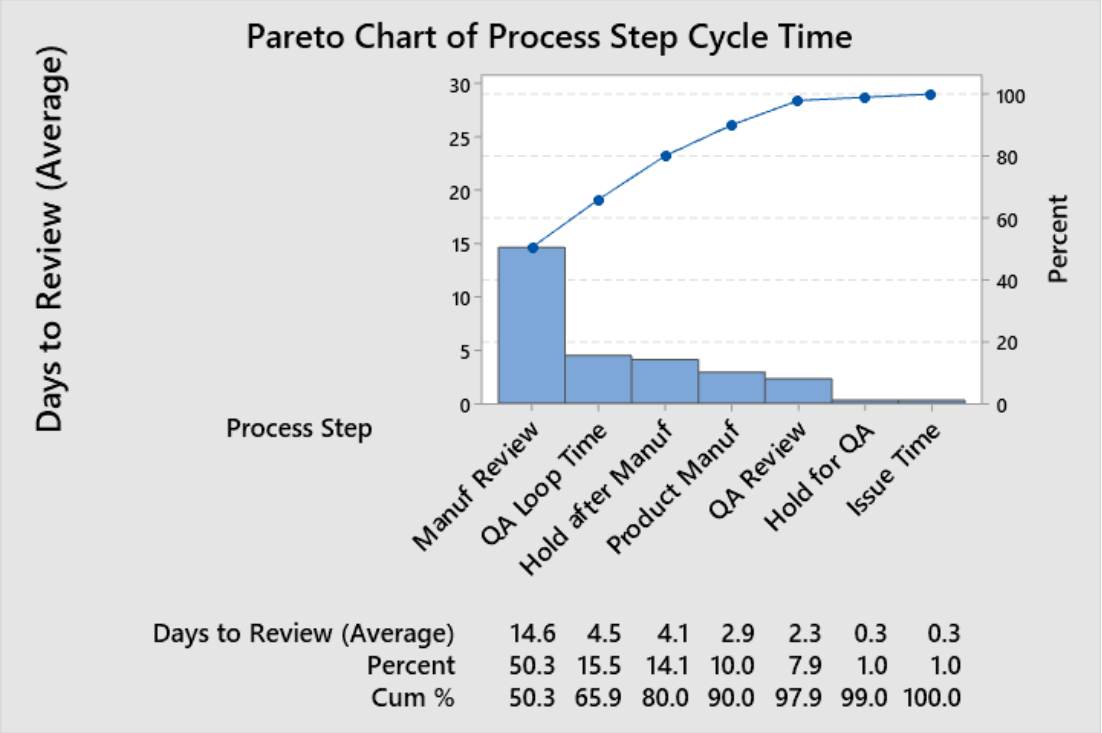

Figure 6. Pareto Chart of Process Step Cycle Time

In Figure 7 we see that when these and other improvements were made, a major drop review cycle time of 35% for one product and 55% for the other product. We also see in Figure 7 that the variation in cycle time also resulted as a result of the improvements.

Not surprisingly, this had a significantly favorable one-time impact of inventory levels and costs of approximately $5 million, especially for the monoclonal antibody with its longer cycle time. Annual operating costs were also decreased $200,000 per year.

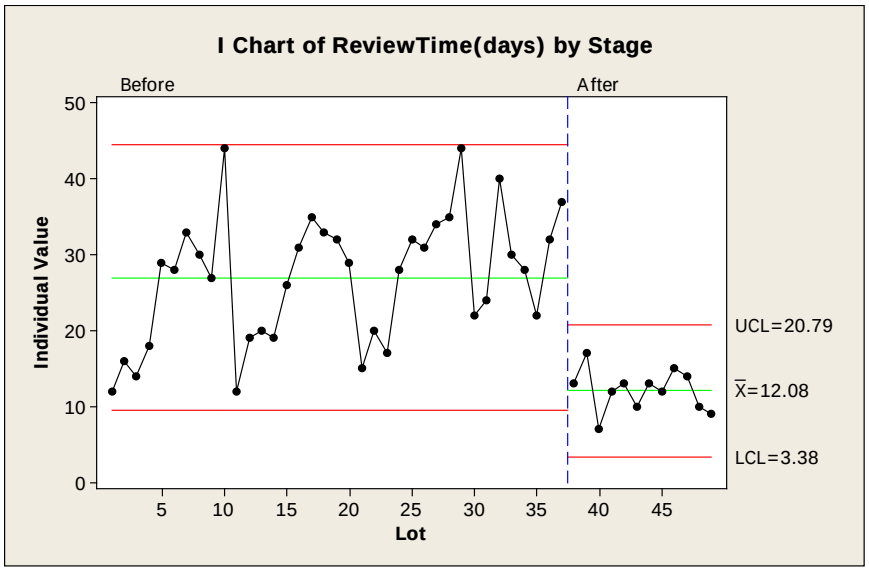

Figure 7. Cycle Time for Document Review for Product A

Better management of investigational reports for manufacturing variances and better design of the batch records themselves also improved cycle time. Further details on this document review process improvement project can be found in Snee and Hoerl (2005)

Process Metrics. To establish relevant metrics, the team first reviewed the management goals of the operational, quality, and compliance functions to align them with the goals of the entire organization. Each metric was defined to ensure clarity regarding what was being measured and to ensure that it contributed to the desired outcome (Table 1).

The measurement system consisted of both a broad set of metrics called the "dashboard" and a more detailed set called the "manager's metrics." The broader, summary-oriented dashboard serves site management. The more targeted manager's metrics enable functional managers to gauge improvements in their respective areas. For example, the dashboard metric for batch-record release time indicates release times for the entire operation. The manager's metric, however, encompasses only the release times for the batch records in that manager's area. The measurement system immediately established a common understanding and communication of performance. Moreover, it provided a platform for improvement in numerous areas.

Table 1. Critical Metrics for the Operational, Quality, and Compliance Functions
(Source: McGurk 2004)

Operational	Quality	Compliance and Documentation
Product cycle times	Batch record release cycle times	SOP revisions
Inventory levels	Root-cause tracking	Investigational reports
Product supply plans	Variance tracking	Commitment tracking
Costs: direct and assessed	Training schedules and execution	Revalidations
Overhead	Environmental monitoring actions	Training activities
Yields		

Regular Management Review of Metrics was instituted to ensure the solutions deployed were effective and sustainable over time. Executive and manager metrics dashboards were implemented and regularly reviewed monthly or weekly depending on the metric and the group (Executive or Manager) performing the review. More than 50 parameters including compliance, scheduling, training and costs were monitored at various levels in the organization. Regular management review is essential for a process to operate as desired over time.

Training and Leadership Development. Approximately 70 members of the quality and operations functions participated in the training and leadership development workshops. Approximately 95% of the participants reported they were "comfortable in applying the new skills." Forty people from that group received additional training in leadership, using case studies constructed from actual company experiences.

Participants reported "a common language and a shared understanding of concepts" that could be used in their day-to-day activities. Most importantly, this training ensured the thorough integration of the operational and organizational elements designed into the entire project at its inception.

Operator Training. In the operator training group meetings the experienced operators and process experts discussed and analyzed the operators' actions. The training resulted in clearer SOPs and greater consistency of action from all operators without the interference of shop floor noise, production gowns, or the fast pace of production. The operators themselves confirmed its effectiveness in their feedback.

Reaping the Benefits - Process and Business Results

The project team's efforts produced dramatic improvements for both the blockbuster product and the monoclonal antibody. For the blockbuster, the breaking of bottlenecks increased capacity by more than 100%. Batch record review cycle time was reduced 35% resulting in a one-time inventory decrease of $5 million. Meanwhile, reliability improved in five manufacturing systems, including the maintenance system. SPC ensured the continued and accurate monitoring of critical process variables through the dashboard and manager's metrics.

For the monoclonal antibody, the company attained 50% more capacity through optimized production scheduling: the proper sequencing and usage of equipment and utilities and the flexibility of operating personnel who were now trained to handle a variety of tasks. Statistical tools helped improve yield by 20%, and reliability improved in weighing systems and two other manufacturing systems. As with the blockbuster, SPC ensured continued monitoring.

The overall batch review cycle time of both products was reduced 35-55% depending on the product. The improvements included enhanced document flow, improved operator training, a redesigned batch record, and streamlined investigations. These benefits were sustained, the process and structure were monitored and reinforced, ensuring the changes are taking root, operational and organizational improvements became more integrated, and the improvement program's momentum is sustained. Taking into account yield increases, a reduction in safety stock of 10%, material savings, and cost avoidance, the improvement of so many areas and systems produced a *tenfold return* on investment in the project.

The real return, however, was even more significant. After the project, a much improved operating group exists with the confidence of the company to deliver on other challenging opportunities. The measure of that confidence? Following the successful launch of the blockbuster product, the biopharmaceutical group was cited for a global corporate award for their crucial role in the supply of the blockbuster.

So What Have We Learned?

This exercise has highlighted a number of things regarding the value and deployment of Statistical Engineering including:

- A general framework such as that shown in Figure 1 is useful in solving large, complex unstructured problems
- An organizational and process assessment is a very useful tool for providing the needed structure and context for the project
- One or more multi-shilled teams are needed to be successful. It is very rare that one or two persons have all the experience, skills and knowledge to solve such problems
- Assessment of the data pedigree is essential to ensure that the data are trustworthy and fit for use.
- A variety of tools, technical and non-technical are needed in such projects

This case study affirms that Statistical Engineering is a very useful approach to solving large, complex and unstructured problems. The methodology provides the philosophy, concepts, methods and tools needed to bring the project team up the learning curve quickly and develop useful and timely solutions. As the approach is used in an organization it can be customized to the culture of the organization enabling the approach to be used broadly across the organization.

Opportunities for Pharma and Biotech to Use Statistical Engineering

Pharmaceuticals and biotech have many opportunities for improvement that involve large, complex problems that can utilize statistical engineering in their solution. These opportunities include both the building of new processes as well as the improvement of existing processes.

Major Enhancement of Legacy Processes, processes that have been in operation for a long time, have been often ignored as opportunities for improvement unless a major problem occurs. Even though these processes have been in compliance and producing in-spec product, these processes frequently become wasteful and inefficient over the years. A process and organizational assessment like the one discussed in this case study is a good way to identify the source and process and financial value of improvement opportunities. Experience has shown that the financial payoff can be large having a return on investment of 4:1 to 10:1 and more in many cases.

New Initiatives such as Quality by Design (ICH 2009, Snee 2019), Continued Process Verification (FDA 2011) and Continuous Manufacturing are major undertakings that can be classified as large, complex unstructured problems that can be addresses by statistical engineering. These initiatives typically involve multiple sites, multiple functions and multiple processes and products. The structure provided by statistical engineering framework (Figure 1) speeds up implementation as teams get off to a good start developing and implementing strategy and getting the initiative producing useful results quickly.

Predictive Analytics and Big Data Problems is another major opportunity. The literature contains several mentions of the use of this methodology in the Pharmaceuticals and Biotech industries. These projects typically involve multiple data sets, from different organizations with different management agendas as well as multiple sites, functions, processes and products. The result is a large, complex problem. These problems are typically messy and involve several organizational and political issues beyond those of the data analytics considerations.

These opportunities and other major initiatives resulting from customer, environmental and regulatory issues can be profitably addressed using the concepts, methods and tools of statistical engineering. The result is better outcomes being created in a timely fashion.

Acknowledgement

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