A CAI E-Publication:

SPEED TO MARKET AND BEYOND

MANUFACTURING IN A CHANGING ENVIRONMENT

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EXECUTIVE SUMMARY

The competitive market demands rapid introduction of new GMP products. Manufacturing organizations configure their production systems to achieve the necessary agility and flexibility to rapidly develop and manufacture new GMP products at full-scale. But the market also demands reliable and inexpensive sources of existing GMP products. Many manufacturing organizations get caught in the speed (to market) trap and find themselves without robust management systems in place to achieve operational excellence at full-scale after initial market penetration. Management systems can help organizations control and improve their supply chain capabilities from end-to-end. Regulatory bodies recognize that organizations which have greater control over their entire manufacturing supply chain at full-scale have the ability to reliably produce quality product. Speed to market and operational excellence at full-scale both require a better focus on developing management systems across five organizational elements: project, people, process, facility, and quality.

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Speed to Market in a Changing Environment

With impending competition and regulatory uncertainty, it's no surprise that many manufacturers feel they need to get their new GMP products to market faster than ever before. Combine this with the advent of more advanced and complex therapeutic products, manufacturers find themselves in a very demanding market environment.

In response to this environment, manufacturers require tightly integrated product development and manufacturing functions with a focus on organizational agility, flexibility, and shortened product lead times to achieve a competitive advantage. [1]

But what happens when the market environment changes? What happens when product success is re-defined from *speed to market* to *market sustainability*? Manufacturing conversion costs, which were once dwarfed by the cost of clinical development, are now on the chopping block. Full-scale commercial production is not the same as developmental production. Product variation, once easily controlled at lab/bench scale or handled through wasteful rejection practices, becomes an increasingly large cost pressure on the product value chain. Will the manufacturing organization have the capability to change itself and adapt as reliability and cost reduction become the dominant drivers for long-term product success in the marketplace?

Priority:
Speed to Market

Market Capture

Priority:
Reliability and Cost

Market Sustainability

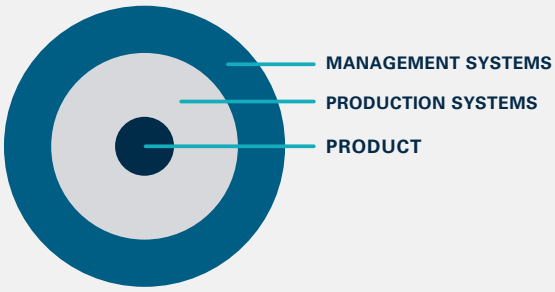
Commercialization Inflection Point

Manufacturing Organizations 101

Manufacturing organizations can be divided into two distinct layers: management systems and production systems. Management systems are the intangible business processes responsible for the development and operation of the production systems. Production systems are the tangible elements, such as the people, process, and facilities responsible for the physical creation of product. Weaving these two systems together properly is necessary to achieve the desired outcome of robust production capabilities.

The operating version of this paradigm begins with the design of an organization's management systems, which in large part determines the flexibility, agility, and reliability of its production systems. In turn, the configuration of an organization's production systems in large part determines the cost, quality, and lead time of its product. The reverse of this paradigm looks at how capabilities should be developed such that the needs of the product instruct the design and operation of the production systems, which in return instruct the design of its management systems.

For example, an organization may place a focus on having a healthy people management system to ensure that the people it hires, then trains, and finally qualifies have the correct knowledge, skills, and abilities to do the job of consistently producing quality output. The people management system creates the environment that drives people's behaviors to create the product.



Production Characteristics

RELIABILITY
Ability of the organization to consistently execute business functions with an expected repeatable outcome.

FLEXIBILITY
Ability of the organization to change in response to both intended and unintended, internal and external factors.

AGILITY
Ability of the organization to change with respect to time.

Production Performance

QUALITY
The collective characteristics of each product unit against predetermined specifications as it relates to its intended strength, identify, safety, purity, and quality.

COST
The total of all direct and indirect, fixed and variable costs related to the manufacture of each product unit.

TIME
The total time required to create each product unit across the entire value stream from raw material to delivered/ administered goods.

Management system and production system impact on product manufacturing

The Speed (to Market) Trap

Speed to market requires the rapid development of new production capabilities such as manufacturing processes, facilities, and people. The rapid development of new production capabilities requires an organization with management systems designed for agility and flexibility.

A well-designed organization will have a road-map to develop new production capabilities that fits into their existing business processes and management systems. Less mature organizations may find themselves in the position of building their management systems as they build their production systems.

A common mistake, due to the need for speed, is focusing on just building production systems. If marketing authorization is granted, a shell of an organization is left without the management systems in place to maintain, replace, and improve those production systems. Staff turnover causes gaps in vital process knowledge. Equipment becomes outdated and unreliable. This misstep is a recipe for product shortages, recalls, angry shareholders, and most concerning – helpless patients.

Owner's project managers and manufacturing management consultants (e.g. CMC consultants) can help fill this knowledge void by sharing and implementing best practices. Normally, organizational deficiencies would be sorted out via competition in the marketplace, but GMP products are unique in that barriers to entry are high (e.g. development costs, intellectual property rights) and the implications of falling short impacts public health, not just shareholders. Regulatory agencies throughout the world are redefining the gate to market authorization from proving process performance to proving organizational and operational performance.

Convergence of Operational Excellence and Regulatory Compliance

Once upon a time it was possible to obtain and maintain regulatory marketing authorization of therapeutic products with product quality and utilization of good manufacturing practices. Good manufacturing practices required controls around the production systems (personnel, facility and equipment, and process) used for creating product. [2][3] This proved insufficient, and regulators created the expectation of validating a specific process for a specific product (e.g. FDA Process Validation Guidance 1987). [4] The unintended consequence of this guidance which held manufacturing processes as specific and static as possible was that the principles of continuous improvement and greater operational excellence fell by the wayside. Continuous improvement in manufacturing is becoming less of an ambition and more of a necessity with the advent of new and complex products, drug shortages, cost pressures, patent cliffs, and other market stresses.

Regulators know that manufacturing GMP product at full-scale is more than just a product challenge or a process challenge, but an organizational challenge. The FDA Process Validation Guidance 2011 and the ICH tripartite of Q8, Q9, Q10, which were created from a global collaboration of regulators, stipulates the lifecycle management of a manufacturing process. [5][6][7][8] This requires a continuous cross-functional collaboration between different departments to design a manufacturing process around product needs, demonstrating that the process works, and then continuously verifying and improving the process in tandem with commercial production. The concept is centered around developing process and product knowledge as well as continuously learning throughout the lifecycle of the product. This effort ultimately requires cross-functional organizational management systems to be successful.

Operational excellence is about achieving higher levels of performance from an organization's full-scale operations. For manufacturing organizations, this means improving the quality of the product, reducing conversion costs, and reducing lead times. It can also mean increasing the flexibility, increasing the agility, and increasing the reliability of its production systems. Increasing product quality and production reliability are particularly attractive to regulators.

Regulators are being continuously stressed to do more with less as the industry globalizes and grows at an alarming rate recognize they need to take innovative and proactive approaches in protecting the public. [9] In recent developments, regulators are hoping to use manufacturing quality metrics based on risk to product quality, and therefore patient safety, as a way to reduce regulatory oversight. [10]

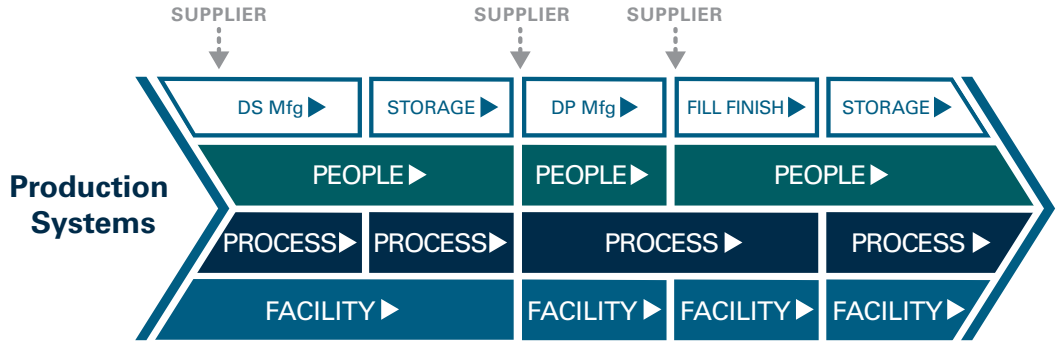
Manufacturers who can demonstrate production performance and the ability to organizationally learn through management sub-systems like CAPA programs will earn the good graces of regulators, and the prize will be more freedom and resources to spend on things other than compliance.

As articulated by Janet Woodcock, Director of FDA CDER, the realization of this vision would result in:

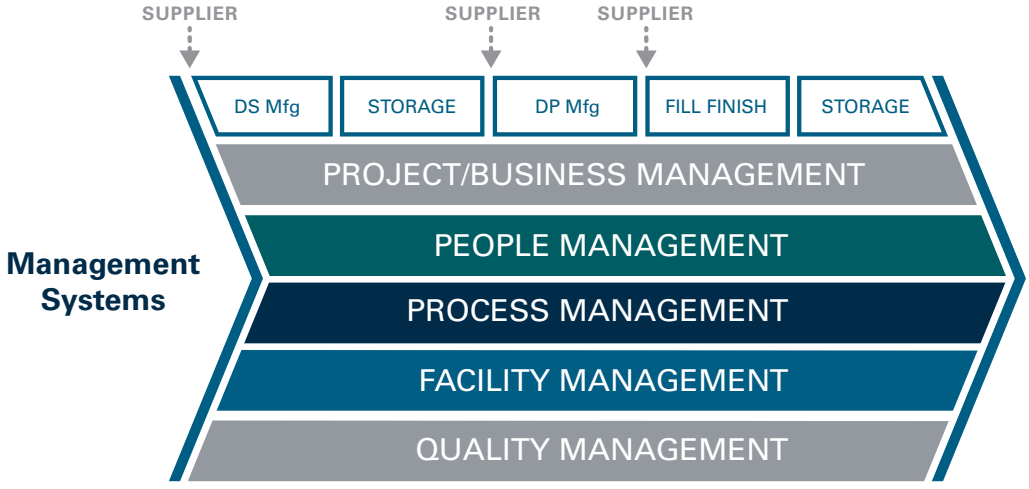
> "A maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight." [11]

End-to-End Responsibility

Manufacturing at full-scale and supplying GMP products to market often require a chain of production systems working together. There may be a variety of facilities and personnel working across multiple organizations (in-house and outsourced) to execute portions of the process. Manufacturers (who hold market authorizations) must take responsibility for their entire supply chain from end-to-end, from raw material supply to patient delivery. Management systems can be used to provide unity across all production systems increasing control of their supply chain to ensure that the chain of production works together to not only create the product, but also create knowledge of the process and product. Increased control can lead to operational excellence with significant benefits such as increased security against counterfeiting and reduced product variability.



How do you handle variability with different resources/capabilities across the supply chain?



Robust management systems which reduce variability and ensure business, effective production.

Comparison of production and management systems across entire supply chain

The FSO Model as the Framework

CAI has developed an organizational model called The Chemistry of Full-Scale Operations™ (FSO) to help managers and leaders who are rapidly developing new production capabilities and optimizing existing operations see through all of the linkages needed to achieve excellence. The FSO model focuses on the use of management systems centered around the organizational elements of project, people, process, facility, and quality.

There are five management systems every manufacturing organizations must focus on:

Project

The Project, Program, and Business Management System is responsible for managing and preserving the interests of the business. Whether it's a small project or a large capital program, success will be defined within the bounds of scope, schedule, and budget. These dimensions must be actively managed from beginning to end. In an operating context the cost, quality, and lead time must be actively managed and improved upon.

People

The People Management System is responsible for developing, maintaining, and continuously improving the necessary collective human function required for manufacturing operations. The process and facility will require qualified people with the appropriate knowledge, skills, and abilities in order to consistently create quality product.

Process

The Process and Product Management System is responsible for capturing and developing process and product knowledge throughout the lifecycle of the product. This knowledge is utilized to develop, demonstrate, and continuously improve process controls.

Facility

The Facility, Systems, and Equipment Management System is responsible for developing, maintaining, and continuously improving the necessary, collective mechanical, electrical, and chemical functions required for manufacturing operations. The process will require an environment, utilities, and process systems and equipment with the appropriate critical aspects to consistently create quality product.

Quality

The Quality and Regulatory Management System is responsible for ensuring product quality and preserving the interests of the patients throughout the development and ongoing use of manufacturing capabilities. The quality management system ensures changes are conducted in a controlled manner, that information is recorded in a manner which ensures its integrity, and deviations from expected procedures/specifications are investigated. Regulatory functions communicate with global regulatory bodies to acquire and maintain marketing authorization for their products.

In addition, there are several key organizational principles which must permeate through all management systems and functional areas:

Organizational Culture

Organizations must organize and align in a way which enables a healthy culture that puts the highest priorities of the organization, such as patient safety, at the forefront of everything they do.

Knowledge Management

Organizations must embrace the ideals of continuous learning and capture of this knowledge in order to constantly improve and sustain manufacturing performance.

Risk Management

Organizations must appreciate that risk is evident in every decision and action taken throughout the organization, and that risk should be understood, managed, and controlled.

Change Management

Organizations must make changes in a controlled manner so that the outcome of the changes is continuous improvement and does not have unintended negative consequences.

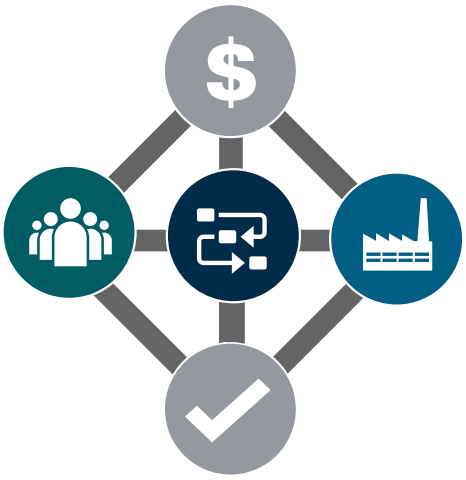
Asset Management

Organizations must realize that everything within the organization, such as people, equipment, and products, should be considered assets of value, and that value should be maximized through the life of the asset.

Automation/IT

Organizations must embrace a world of digitization in which automation and information technology systems help create efficiencies and increased productivity while reducing costs and risks.

Manufacturing organizations which focus on developing their management systems and embrace these key principles will find themselves in a position to achieve both speed to market and ongoing operational excellence.



The Chemistry of Full-Scale Operations™ (FSO) Model

Conclusion

The competitive marketplace requires GMP manufacturing organizations that can adapt to the dynamic business landscape of product realization. Successful organizations use management systems to help deliver new products to market fast and then achieve operational excellence in the form of increased reliability, agility, and flexibility. Organizations take control of their supply chains from end-to-end with management systems, which in return helps them reduce product lead times, reduce cost, and increase quality. Regulatory bodies are coming to expect operational excellence from GMP product manufacturers because they know it leads to better outcomes for the patients and consumers. The Chemistry of Full-Scale Operations™ (FSO) is a model for developing and improving GMP production capabilities through the use of robust management systems.

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R. J. Filannino

R. J. believes there are a significant amount of people throughout the world who aren't getting the life improving therapies they deserve because the industry isn't moving fast enough in developing advanced life science manufacturing capabilities.

R. J. is a project management and engineering professional with more than half a decade of experience in the biotechnology, pharmaceutical, and biomedical device industries. R. J. has owned responsibilities across process, product, and facility lifecycles such as new product development, construction and verification of facilities, and continuous improvement of established manufacturing lines.

R. J. is interested in helping organizations achieve speed to market and operational excellence with life science product manufacturing.