Achieving Agility When Facing Uncertainty -- Scaling Aseptic Pharmaceutical Production

By Samuel Chia, Jay Shukla, and Dr. Bryan Braxton

This past year has taught us that agile organizations will not only survive, but prosper, when faced with unexpected challenges. Case in point is the rapid development of COVID-19 vaccines. A long-standing clarion-call across the drug development community has been to speed-up the drug development process. Until recently, the industry had not made much progress, but the speed with which the COVID vaccine was approved is giving us hope.

The question many of us are now asking is: can we do it the next time something like this happens? What capabilities and organizational features must we possess to have the same level of success? In one word, its agility! Agility is not typically associated with the pharmaceutical industry, but at Pii we spend a good deal of time studying it, understanding what makes organizations agile, and applying those lessons to our own operations.

What is Agility and Why is it Important?

Speed is often used to describe agile organizations, but agility is not about speed alone. More accurately, it is the ability to adapt rapidly and easily to changing conditions, but why is agility important to the pharmaceutical industry?

Sometimes we tend to delink drug development from production, but the purpose for development is commercial production that delivers therapies to patients. Much of the testing that is done on drug candidates in early-stage research and development (R&D) is to determine if production can be scaled to commercial-size batches. It has a predictive outcome—determining how the formulation will behave when produced in larger quantities, but it is not perfect. Agility can help sustain the momentum of the drug development process when unexpected challenges arise.

Agile organizations are also more stable and reliable regardless of size or how long they have been in business. 1 The outcomes desired by pharmaceutical development require stability and reliability, any disruption to the process is costly and can place the drug product and patients at risk. Add in the complexity and inherent risks associated with aseptic processes, operational practices that deliver agility, stability, and reliability can be the difference between failure and success.

At Pii, part of our commitment to continuous improvement is striving to be more agile and the framework we use includes capabilities, organizational structure, quality systems, and standard procedures.

Capabilities

As a contract development and manufacturing organization (CDMO), we continuously examine our capabilities to deliver results to our clients with agility. This means having the right capabilities in our facilities, close strategic relationships with our suppliers and partners, and skilled, experienced professionals.

Scaling aseptic operations requires producing batches of drug product in ever-increasing sizes with quality. However, during preclinical and phase 1 development, the unknowns far outnumber the knowns. Will lyophilization be used to stabilize the drug product or what will the delivery mechanism be? Managing capabilities with agility as a feature will keep the drug development process moving forward without disruption.

There are many critical capabilities needed for scaling aseptic production operations, here are several. Aseptic formulations often require stabilization through freeze-drying and having in-house lyophilizers and scientists skilled in developing lyophilization cycles is critical. Another critical capability is fill-finish suites able to fill a variety of delivery devices: vials, pre-filled syringes, auto-injectors. A third is fill-finish suites that can produce varying batch sizes with adequate speed and under highly sterile conditions. Ideally these suites are automated, limiting operator contact with the filling process

Organizational Structure

Agility has less to do with organizational size and more with structure, with some structures better for enabling agility.2 Consider the hierarchical, line-and-block chart versus the flatter networked structure.

The traditional line-and-block structure facilitates the vertical flow of information, regardless of how many dotted coordinating-lines are included. This model inhibits the rapid flow of critical information because it flows up before it can be passed laterally and down to someone who can act.

Networked organizational structures encourage the multi-directional flow of information and they enable critical information sharing to teams and people who can best act in ways to keep projects advancing toward their intended outcomes.

Critically important information is abundant when scaling complex aseptic production operations and it requires extensive cross-functional coordination. A networked organization is better able to adapt rapidly and easily. For example, cross-functional

teams—quality, operations, regulatory, facilities, safety, project management—working closely together are ideal for fostering agility.

Quality

One component of our agility framework that cannot be uncertain is quality and the important role it serves in the drug development and manufacturing process. While quality is a special functional area within pharmaceutical organizations, making it an inherent component of all other functional areas and imbedding quality specialists throughout your organization is vital.

The head of quality must have direct lines of communication throughout the organization to include quality control in research and development laboratories as well as manufacturing spaces, and throughout the supplier supply chain. Quality specialists must have close integration with operations such as Change Control, Supplier Qualification, Product Complaints and Annual Product Reviews (APRs).

A robust Pharmaceutical Quality System (PQS) must be applied in the earliest stages of development and its integrity maintained through technology transfer and commercial scale-up. A strong PQS is the foundation for quality and continuous improvement.

Standard Procedures

Organizational structure can promote agility by having the right people working together, but they must also have procedures and ways of interacting that enable agility. Procedures important for scaling aseptic production include triggers to begin planning for the next phase, technical review meetings, and escalation criteria.

To eliminate wasted downtime between phases of development, the cross functional teams described earlier must be planning several steps ahead of where they are. Manufacturing process development and validation is a major undertaking, and it should begin when the drug candidate is in the preclinical stage. It is during pre-clinical research that formulations begin to take shape in a way that can inform the manufacturing process. While changes will occur during testing, adjusting a planned manufacturing process is faster than beginning the development when the R&D team has completed their work.

No one likes more meetings but assembling your entire cross-functional team for a technical review is important. Each technical review should be project specific, but they all should include--project overview and timeline, drug candidate critical quality attributes, regulatory issues, capacity review, facility readiness for scale-up, and limiting factors that might disrupt the project.

It is also vitally important to have a decision-maker in the technical review meeting. The decision-maker must be someone who can commit resources or re-set priorities across the organization. For example, if a capacity issue is raised as a limiting factor in advancing development, the decision-maker is there to redirect resources. Nothing robs an organization of agility more than disruptions caused by haphazard decision-making processes because the person needed to make the decision is not available.

Conclusion

Aseptic production and fill-finish operations are complex and unexpected challenges should be anticipated, but not disrupt the outcome of delivering needed pharmaceutical products to patients. Agility is the key to rapidly and easily adapting to changes. A framework that can be used to assure agility when scaling aseptic drug production should include capabilities, organizational structure, quality and standard procedures.

1. Agility, It Rhymes with Stability, McKinsey, Agility: It rhymes with stability | McKinsey

2. The Most Agile Companies Organize Themselves Themselves Like Bamboo, by Veronique Nguyen, HEC Paris, published by Forbes, The Most Agile Companies Organize Themselves Like A Bamboo (forbes.com)

ABOUT THE AUTHORS

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Bryan held roles of increasing responsibility in sterile products at both Unither, AMRI, Pfizer, Abbott, and Glaxo, in the areas of Formulation Development, Process Transfer, Quality by Design, Technical Services, Contract Services, and Project Management.

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Jay Shukla is the Director of Aseptic Process Quality at Pii. He joined Pii in 2006 and has over 27 years of experience in the pharmaceutical industry.

He has held multiple roles of increasing responsibility in Microbiology and QA while working at Torrent Pharmaceuticals and Cadila Pharmaceuticals. Jay has a thorough understanding of cGMP regulations for Sterile Pharmaceutical Manufacturing including Quality System elements including Investigations, Root Cause Analysis, CAPA, Change Control, SOP's, Equipment and Process Validations, Annual Product Quality Review, Microbiology, Batch Record Review/Release, Training and Audits.

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