OUTSOURCED PHARMA

Guest Column | April 24, 2020

Ensuring Quality In Ventilator Production Scale-Up For COVID-19

By Bikash Chatterjee, chief operating and science officer, Pharmatech Associates

Manufacturers around the world are scrambling to scale up ventilator manufacturing to meet the worldwide needs of COVID-19, and we find ourselves in uncharted territory. Ventilator manufacturers such as Medtronic have increased their manufacturing output, while recent joint initiatives between General Motors and Ventec and between Ford Motor Co. and GE Healthcare have auto manufacturers committing to retool their plants to manufacture 40,000 to 50,000 units in the next three months. In parallel, open source developers and entrepreneurs such as MIT and Dyson are innovating new ventilator technologies to respond to the forecasted shortfall in units. Xerox has teamed with ventilator developer Vortran to manufacture 11,000 new disposable single-use ventilators.

Underpinning these initiatives in the U.S. is the FDA-initiated Emergency Use Authorization (EUA) directive[1] and guidance.[2,] The Korean War-era statute can force certain American companies to produce materials that are in short supply in the face of the growing outbreak. The EUA template is intended to be interactive, as this is uncharted territory for the FDA, as well as allowing for a relaxation of the GMP quality management system (QMS) requirements as defined by 21 CFR 820. While the new FDA EUA guidance appears to relax the need for a formal design control framework, the FDA is relying on testing against recognized consensus standards to mitigate the risk of an expedited review. In the absence of a cGMP framework, it is still possible to control the sources of variation that can impact product quality and safety by addressing them as part of the manufacturing process design and scale-up exercise.

Building In Quality

While the urgency to move quickly is paramount, the reality is that expediency cannot be achieved at the sacrifice of quality. We expect that the units manufactured or developed by new ventilator manufacturers will be just as reliable, safe, and effective as the current units on the market that have gone through the design control framework and the corresponding FDA 510K review and clearance process. Discrete manufacturing differs from process manufacturing in that identical products are duplicated by way of an assembly line. The raw materials used to create these products are the same from the first job to the next. The advantage of discrete manufacturing is that it is possible to increase capacity incrementally by simply duplicating assembly lines. This sounds simpler than it really is, as in a normal manufacturing scale-up environment the design and assembly process have had the benefit of a GMP QMS and regulatory structure. The FDA's vision for quality is predicated on process understanding after decades of an inspection- and testing-based quality framework confirmed that you cannot test quality into the product. So, the FDA may be sending a mixed message to industry and innovators by structuring the EUA template to rely so heavily on demonstrating compliance with the applicable consensus standards.

Lean Manufacturing As A Quality Tool

Most people think of lean as an efficiency tool, designed to reduce the cost of goods and drive output. Lean manufacturing focuses on minimizing waste within manufacturing systems while simultaneously maximizing productivity. Waste is seen as anything that customers do not believe adds value and are not willing to pay for. However, the byproduct of lean initiatives is often process stabilization and increased predictability. Lean principles will allow existing manufacturers and innovators to move more quickly as they start up new operations.

The following tools can be universally beneficial to driving process and product performance predictability:

Value Stream Mapping (VSM)

VSM looks at a variety of aspects, including cycle time, bottlenecks, and intersystem dependencies that could develop with multiple parallel processes. A complexity analysis is an excellent way to identify any missing elements and ensure they are formally systemized. This data can be used to establish key performance metrics and a capacity plan, to clarify that the latent capability of the supporting process operations will meet the needs of the operation. For example, if the current review time for a batch record release is two days at 5,000 units/month, what does it have to be to accommodate a rate of 50,000 units/month? 15 hours? Less than 3 hours? Understanding these cycle times is the best way to avoid bottlenecks and in turn avoid cutting corners that affect the safety and efficacy of the system once manufacturing starts.

Standardized Work

Standardized work in essence consists of recording a process, effectively communicating that process, and then using the record as a basis for continuous improvement. It provides personnel with clear and detailed instructions on how to execute their job responsibilities. If done properly, this lays the foundation for continuous improvement, as each incremental improvement becomes the new basis for the standard work.

Leader Standard Work

Leader standard work is a set of actions, tools, and behaviors that are incorporated into the daily activities of leaders at all levels. This is an essential activity when bringing two disparate organizations together to work to a common goal. This will drive down the potential for workarounds and uncontrolled processing steps, when coupled with tracking key performance indicators (KPIs).

Technical Considerations

Increasing output can be achieved by either decreasing cycle time or increasing the number of units per cycle. Both require the same considerations: minimizing the sources of variability in each unit operation, ensuring the resolution of the measurement tool is adequate to gauge what is meaningful within each process step, and making sure the product's critical quality attributes (CQAs) are meaningful in terms of product safety and efficacy. Some of the factors that could be considered in terms of stabilizing variation include:

Injection Molding

Many ventilators use a combination of machined and injection molded components. One consequence of increased demand is to move to additional duplicate injection tooling or move to a larger multi-cavity tool. High precision injection (HPI) molds are often machined using electrical discharge machining (EDM), which is more art than science in some cases. Tool designers must account for material shrinkage to ensure that each part in each cavity meets the design specifications. Taking the time to perform the first article inspection of the parts made from each cavity, in each new tool, is essential to making sure each ventilator assembly will work properly. Numbering each cavity helps in tracing manufacturing challenges back to the tool and the cavity as manufacturing proceeds.

Optimizing the injection parameters of a larger multi-cavity tool requires monitoring of parts as they age, to ensure molded-in stress will not create a problem after assembly.

Design For Assembly (DFA) and Manufacturing (DFM)

Together, DFA and DFM make up both pieces of a puzzle. DFA looks at simplifying the product structure, since the total number of parts in a product is a key indicator of design quality; fewer parts result in a more efficiently assembled product. DFA also examines the parts for ease of assembly, using keyed parts or things that can only go together in a correct orientation. For innovators bringing new designs to the FDA via the EUA process, a DFA exercise would help minimize the variability in the commercial manufacturing process, simplifying the overall production start-up and commercial debugging process. For manufacturing operations looking to automate the manufacturing, a DFA exercise focusing upon those operations that have the largest degrees of freedom to control could greatly reduce the need to inspect and test as part of the process control strategy.

DFM concentrates on minimizing the complexity of manufacturing operations. This can help reduce the amount of verification testing required in the overall process.

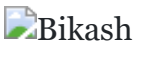
Conclusion

The adage that "adversity reveals character" has never been truer. While the FDA has relaxed cGMP requirements for the EUA program, the need to provide a safe and effective ventilator is urgent. We see the damage being done to our response to COVID-19 by overseas manufacturers providing antibody tests that are not capable under the FDA's latest decision to self-police and provide validation data after the fact. For organizations new to the device design and manufacturing paradigm, investing in structured systems such as DFA and standardized work and taking the time to ensure that the critical steps are engineered for consistency will go a long way toward meeting the critical demands of the COVID-19 pandemic.

References:

1. https://www.fda.gov/media/136423/download
2. Enforcement Policy for Ventilators and Accessories and Other Respiratory Devices During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency Guidance for Industry and Food and Drug Administration Staff, March 2020

About The Author:



Bikash Chatterjee is chief operating and science officer for Pharmatech Associates. He has over 30 years' experience in the design and development of pharmaceutical, biotech, medical device, and IVD products. His work has guided the successful approval and commercialization of over a dozen new products in the U.S. and Europe. Chatterjee is a member of the USP National Advisory Board and is the past chairman of the Golden Gate Chapter of the American Society of Quality. He is the author of Applying Lean Six Sigma in the Pharmaceutical Industry and is a keynote speaker at international conferences. Chatterjee holds a B.A. in biochemistry and a B.S. in chemical engineering from the University of California at San Diego.

Comments

Login

There are no comments posted yet. Be the first one!

Post a new comment

Enter text right here!

Comment as a Guest, or login:

Name

Displayed next to your comments.

Email

Not displayed publicly.

Website (optional)

If you have a website, link to it here.

Subscribe to None ▼

Submit Comment