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LEAN STRATEGIES

Lean Manufacturing

The role of continuous processing in the pharmaceutical industry

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One of the fundamental tenants of lean manufacturing relates to the use of continuous processing as a game changing methodology to replace more traditional batch processing.

At the heart of this philosophy is the basic concept that to reduce individual break points in the manufacturing process reduces the non-added value work components of the process. In reducing these manufacturing breakpoints, many of the seven forms of waste can be eliminated which ultimately has a significant impact on the efficiency of the overall pharmaceutical production process.

Typically in operating a continuous process system rather than a traditional batch process one would eliminate several things including: repetitive set up times, changeover processes, cleaning operations, start up and shut down operations, uneven flow, certain maintenance requirements and inefficient use of labor. So the drive towards a continuous processing methodology from a process engineering standpoint appears to be extremely attractive although the future potential of such systems is not merely based upon process considerations alone. Another significant factor that needs to be considered for the successful implementation of a continuous processing strategy is the need to fulfill the various requirements imposed by international regulatory authorities, particularly in relation to regulatory compliance manufacturing issues.

HOW THE PHARMA INDUSTRY COMPARES

By comparison to other process industries like microelectronics, the pharmaceutical industry is extremely conservative. In many respects, it is this conservatism that has stunted the implementation of more progressive ideas that have found their way into these other industrial sectors. However, while this may be true the changes made by the various international regulatory authorities during the last 5 to 10 years have provided a foundation upon which the adoption of continuous processing becomes more attractive and more likely.

In particular, with the adoption of the FDA initiatives on cGMP's for the 21st-century and PAT, the groundwork has been laid to enable progressive approaches to continuous processing to become possible and more likely.

Today the possibility of fully integrated systems based on continuous processing is more likely to occur as the industry embraces the Quality by Design (QbD), philosophy. With the adoption of this type of approach which is in stark contrast to the Quality by Analysis (QbA), philosophy of the previous 30 years, there is a greater understanding of the processes involved in the manufacture of a product. In turn, this has led to the development of numerous new development tools including: simulation models, specific process analytical technology and sophisticated process control capabilities which all play important roles in the adoption of continuous processing.

So what is forcing the change towards implementation now?

1. Inevitably the cost of manufacture in a global market where the downward pressure is significant and is a leading factor driving change.
2. Increasing regulations that require more control over the process and product specifications to assure quality.
3. A greater focus on the use of physical plant and labor resources. Continuous processing offers the possibility of smaller sized plants and smaller sized equipment.
4. Increased development times for new products due to the complexities of scale up from bench scale through pilot production to commercial production. Continuous processing offers the possibility of no scale up and the potential for longer runtimes without a break.

In reviewing batch processes, one is immediately struck by the cumbersome practices which often involve repetitious quality checks and assessments to be made throughout each phase and/or unit operations of the manufacturing process for a particular pharmaceutical product. In many cases these checks are occurring because the processes involved are open-ended and require off-line analytical procedures to assure correct weights or some other specification. In these cases this is compounded by the next unit operation which is completely freestanding and not connected to the preceding operation in terms of flow. All of these factors add to the overall cost of production in addition to contributing to the length of the process in terms of its overall cycle time.

CURRENT CONTINUOUS PROCESSING TRENDS

In terms of current trends, there are a number of initiatives ongoing by various pharmaceutical companies to bring along innovative methodologies that will permit the use of a continuous processing approach. Notable among these is the MIT collaboration with Novartis which aims to identify numerous technology opportunities.

Others include GEA Pharma Systems which is pioneering continuous processing from a systems perspective.

Currently there are a number of areas that appear to be benefiting from modern process philosophies towards continuous processing. In particular the areas of wet granulation and drying line up very nicely with continuous processing due to the inherent plug flow characteristics/conditions.

In the case of the GEA Pharma Systems high shear granulation system; this system is based on three modules:

1. a wet granulation module
2. a drying module
3. an analytical module

Other areas where continuous processing is having some impact include weighing, mixing, compressing and coating, particularly connected with tablets and capsules. In all these areas there is a requirement for cheaper, faster and more flexible online methods of analysis and with these addressed, the advantages of continuous processing can be realized. This is an area of more significant growth in relation to the implementation of continuous processing in pharmaceutical manufacturing.

On-line functionalities will be a significant contributor to enable continuous processing to fulfill its potential, so new sensor technology will ultimately be at the forefront of new advances and may well prove to be an important key in the realization of this is an approach. An example of this is TeraView's terahertz imaging system that uses a series of spectroscopic sensors to accurately measure the coating thickness of tablets as they are produced. The advantages of such systems is obvious in the reduction of invasive sampling techniques, off-line analysis and cumbersome documentation which can lead to a whole host of non-added value issues associated with poor cGMP documentation practices. With an on-line approach, this issue goes away!

BIOTECH OPPORTUNITIES

In relation to processes made in the biotech industry, some of the opportunities are less obvious and may be more complicated because of the nature of the living process that defines the product specifications. That said, opportunities are being realized for lean manufacturing gains especially connected with modular approaches to bioprocessing through single use and disposable technologies. Here through the use of run on systems, particularly at the downstream processing end of operations, opportunities are being realized through the use of fluidized bed technologies to continuously capture and separate cellular material from product material in a single step. An example of this is DSM's second-generation expanded bed absorption unit which clarifies, concentrates and catches products in one step. This both embraces the idea of a modular continuous processing philosophy as well as fulfilling lean manufacturing principles through the reduction of non-added value steps and through the leveling of process flow.

In conclusion, the future for continuous processing in pharmaceutical manufacturing appears to be bright. The march forward will inevitably be influenced by several factors that will include the regulatory process that continues to evolve and this will occur in concert with the development of online analytical capabilities that will be necessary to assure the consistency of product specifications. ■