ExpertTalk



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Advanced Manufacturing

An answer to supply chain woes?

Advanced Manufacturing technologies (AMTs) in the pharmaceutical industry have increasingly gained attention in the last decade. Amongst the AMTs, continuous manufacturing (CM) has had the most prominent impact so far. International efforts to define manufacturing approaches, terms, regulatory expectations in a harmonised manner have been made. In many cases, manufacturers have benefited due to early adoption of CM. As the interest grows in the areas of API and drug product as well as biologics, it is important to understand the barriers and challenges for a broader worldwide adoption. USP has been working in different ways to lower some of these barriers. These include facilitating open dialog, supporting and advancing research, advocacy at various forums and contributing to the development of standards and guidelines.

How is automation impacting advanced manufacturing, and what benefits does it bring to businesses?

The general trend in manufacturing has been to eliminate intermediate stops between processing steps as much as possible to reduce the overall processing time. To accompany these advanced processing techniques, new process analytical technology (PAT) tools have been developed to allow quick sampling, automated processing/recording of data into computers that can talk to control systems. This has dual benefits — it reduces the chances of human error, and helps economies where human capital is scarce. Furthermore, faster automated analysis, even when not as deep as a manual, offline one, can preemptively alert the operator if the process is veering towards the outer limits of safe performance.

How can contract manufacturers maintain flexibility to adapt to changing requirements from their clients?

One approach is to modularise the manufacturing set-up as much as possible. This can involve individual unit operations, such as, reactive crystallisation mounted on skids that can be rolled in and out of the process train. New equipment is being designed with interoperability and flexibility in mind. Furthermore, the manufacturers can plan ahead and schedule campaigns for products requiring similar unit operations together. This can reduce time and effort required in switchover and intermediate cleaning.

On the personnel front, the big challenge for contract manufacturers is to keep abreast of the latest technologies, methodologies and procure equipment that can maximise flexibility to meet diverse customer requirements. USP has created the USP CM Knowledge Center as a free resource to share open-source knowledge and get the community to engage.

One strategy that could help would be to ensure that their staff is in a continuous learning mode, and that they are able to devote some time to self-development as opposed to being fully absorbed into customer projects. They can aim to find common elements in their projects and use time and material saving techniques such as validated models. Learnings from one customer project can be applied to speed up another.

Can you discuss the role of real-time release testing (RTRT) in advanced manufacturing, and how it is changing traditional testing approaches?

RTRT refers to use of (a combination of) measurements and calculations based on science- based validated models and PAT tools to determine the product quality. This determination can be an alternative to traditional release testing. RTR can be used for both batch and continuous manufacturing processes. In a fast-moving continuous manufacturing scenario, especially in a small footprint-high usage facility, RTR can help manufacturers maintain the production schedule flexibility. Being able to finish the manufacturing sooner can help improve the plant efficiency, workforce schedules, reduce laboratory waste, and enhance regulatory compliance.

However, achieving RTR requires additional experimentation which can lead to a significant added cost. It is not necessary to file for RTR along with a CM application. There are examples of manufacturers filing for it a few years later, after receiving the regulatory approval for the main CM process.

> Advanced manufacturing technologies associated with modalities like continuous manufacturing and 3D printing are evolving quickly.

What are the current trends in advanced manufacturing, and how are they shaping the industry?

The industry is responding to a deepening supply chain crisis. Many supply routes are now disrupted or are in danger of being so. With the uncertainty in demand and availability of key raw materials, the industry is looking to boost efficiency in operations.

Advanced manufacturing is an umbrella term that includes other modalities as well, in addition to CM. For example, a process can be an advanced-batch process, or a semi-continuous process with additive manufacturing (3D printing) as the final step. While this is not an exhaustive list, here are some trends we are observing:

- Finding new synthesis routes and techniques such as flow chemistry for small molecule APIs to build efficiency as well as flexibility to use raw materials that are more readily available
- New techniques in drug product manufacturing such as melt granulation to reduce complexity and risk. Aiming for direct compression whenever possible
- Near-shoring or on-shoring of manufacturing facilities which require higher automation, smaller footprint, deeper process insight and greater environment friendliness
- Semi-continuous manufacturing in biologics and biosimilars
- Increasing role and reliability of process models
- Advanced-batch and mini-batch manufacturing for lower risk
- Distributed manufacturing i.e. producing medicines closer to the patient.

In the era of digital transformation, how are pharmaceutical companies ensuring data integrity and traceability in advanced manufacturing processes?

This is best answered by the industry. However, we note that there is an FDA guidance on available on this topic ▶

(Data Integrity and Compliance With Drug CGMP: Questions and Answers | FDA) which should help the readers familiarise themselves with the regulatory expectations. There are a variety of vendors and platforms available for manufacturers for acquiring, processing, storing and retrieving data (for example, from secure cloud storage).

Can you share examples of successful implementation of robotics in advanced manufacturing?

There has been an increase in the use of robotics and automation in all types of manufacturing industries. This is done with the aim of increasing productivity as well as reducing error, and hence, the risk.

This can include simple pick-and-place types of robotic arms, used in operations such as packaging, transport, and inspection. These operations, however, may not be regarded as a part of the manufacturing process. Many modern quality control laboratories deploy robots for tasks such as sample preparation and automated syringe filling. In the early stages of drug discovery, many companies use high-throughput screening, which utilizes robots for sample preparation, dosing, cell seeding, etc.

In the pharmaceutical advanced manufacturing context, however, I would focus more on the automation aspect. For example, in a continuous process for producing drug products, loss-in-weight feeders are deployed. These are sophisticated devices that measure the weight of powder in their hopper with high sensitivity and precision. The weight measurement is relayed to a computer, and data is continuously recorded during the process. This ensures precise control over the formulation. In case of any unacceptable deviation from the set feed rate, an alarm is raised immediately. This is an example of increasing automation on the manufacturing line.

What role does additive manufacturing play in the advanced manufacturing landscape, and how is it transforming traditional production methods?

While there are only a few products approved for additive manufacturing (AM) or 3D printing (3DP), there is great potential. The techniques are still under development and may not be suitable for all types of formulations. However, they offer great flexibility in both manufacturing and personalisation. A few things required for AM:

- Selection of the right AM approach among the many that are under development. This selection can depend on the product and its formulation
- Selection of appropriate ingredients and understanding their behaviour when subjected to the 3D printer conditions
- Determination of operational procedures, cleaning routines, etc. to complete the control strategy
- Development of printers to be distributed to the manufacturing or compounding locations, ensuring favourable economics
- Monitoring of their performance, collecting data and analysing it continuously.

How is advanced manufacturing contributing to the integration of supply chains, and what advantages does this offer?

Advanced manufacturing allows for:

- More sources of raw materials to be used, since there are more process controls available that equip the manufacturer to handle deviations better, at times even proactively
- Smaller manufacturing facilities, which can make it easier to install plants in different geographies depending on market demand
- More transparency in process due to PAT, modelling, and control loops which can make it easier to transfer the process to a contract manufacturer. The same goes for scaling up or scaling down.
- All of these can help make more quality medicines in more places, which will strengthen supply chain resiliency

> Since a lot of equipment used in advanced manufacturing is different from batch equipment, and some designs are still evolving, there can be challenges in procuring it in a timely and cost-effective manner.

What efforts are being made in advanced manufacturing to promote sustainability and reduce environmental impact?

As an example, in our collaborative work with Medicines for All Institute, our scientists are developing new synthesis routes for essential APIs that are also at the risk of shortage. These methods prioritise the use of starting materials and reagents to reduce environmental burden significantly, using methods such as solvent recovery and recycling.

In the drug product side too, the increased use of in-line PAT aided by

process models reduces wastage. When developing a process, the sheer number of experiments in a design of experiments (DoE) can lead to tremendous amount of material usage. With AM, the process designer gains the capability to vary multiple parameters in a single continuous run, which can reduce the environmental burden significantly. The flexibility in production quantity (scaling up/down by time as opposed to equipment size) can also reduce environmental impact.

Are there challenges associated with supply chain integration in advanced manufacturing?

It depends on the type of advanced manufacturing being used. The materials for many continuous manufacturing operations are not significantly different from batch manufacturing. Hence, we don't expect any additional supply chain related challenges for them beyond those already present for batch manufacturing. For newer modalities such as 3D printing, the materials and ancillary requirements can differ depending on the product and the chosen printing platform. These can include special type of excipients, polymers, ancillary equipment, software, etc.

Since a lot of equipment used in advanced manufacturing is different from batch equipment, and some designs are still evolving, there can be challenges in procuring it in a timely and cost-effective manner. Ongoing global supply chain disruptions impact both raw material as well as equipment supplies.

11. What do you foresee as the next wave of advancements in manufacturing standards for the pharmaceutical industry?

Advanced manufacturing technologies associated with modalities like continuous manufacturing and 3D printing are evolving quickly. Creating a standard typically requires a certain level of technological maturity and widespread usage. Quite a number existing USP general chapters standards will continue to remain relevant for advanced manufacturing as well.

Given the fast-moving nature of technologies, we at USP have adopted a different approach to arrive at advanced manufacturing standards. In addition to our existing standards setting approaches, our series of Technical Guides on continuous manufacturing present detailed explanations of relevant topics such as development of control strategies, process models, dissolution modeling, and techniques such as residence time distribution. These are freely available for download.



AUTHOR BIO

Atul Dubey earned his Ph.D. in Mechanical Engineering from Rutgers University, NJ, USA. Dr. Dubey has carried out research in pharmaceutical manufacturing processes using modelling and simulation to optimise unit operations such as continuous mixing, granulation and pan coating. He has authored several journal articles and book chapters and is the editor of a recent book titled "Continuous Pharmaceutical Processing and Process Analytical Technology", Taylor & Francis.

In his current role as Senior Principal Scientist in the Global Science and Standards Division (GSSD), he is leading the development of new Technical Guides on PCM while also engaging with Expert Panels and Subcommittees of the Physical Analysis, Chemical Analysis, and Chemometrics. His more recent contributions are USP's first Technical Guide on Control Strategy and the USP CM Knowledge Center.

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In addition, our expert committees, consisting of volunteer experts from industry, regulatory bodies, nonprofits and academia, regularly publish thought-provoking publications known as stimuli articles. These are designed to illicit responses from the wider user community on specific topics. For example, the article New Approaches to Product Performance Testing describes new and upcoming methods for performance testing. The responses we get are very valuable and they play a crucial role in the direction that our expert committees take while creating a new standard.

Digital standards are another way in which process and material quality checks can be made quickly. USP is developing these standards such that they can be digitally delivered and be machine readable for quick, in-process decision making.

Several new advancements are being made by USP to help with the adoption of advanced manufacturing. Among these are:

- New general chapters on PAT for small molecules and biologics
- New and upcoming chapters on powder electrostatics property measurement, powder wettability, and tablet compaction simulation
- Technical Guides on Control Strategy (published), Process Modeling and Dissolution prediction (upcoming)

Any concluding remarks?

Significant amount of work is being carried out globally to reduce any perceived regulatory hurdles to the adoption of advanced manufacturing. Implementations such as continuous direct compression for oral solid dose drug products are considered mature and are no longer emerging methods. Technological challenges in other implementations are quickly being overcome. We are poised to see a significant shift in the use of technology in pharmaceutical manufacturing. ■