PEER REVIEWED

Challenges of Small Molecule Production

Over the last 10 years (2008–2017), the United States FDA approved a total of 320 new drugs. Of these, 249 were new chemical entities (NCE) or small molecules, about 78 % of the market share. In the same period, the average number of biologics doubled to seven biologic license applications (BLA) per year. Biologics are indeed on the rise. However, the average number of NCEs has not decreased either. The average number of NCEs approved by the FDA has increased slightly from 22 compounds a year in the late 1990s to 24 in this decade. This article evaluates the opportunities for small molecules, and how they can stay relevant in this ever-changing landscape. The challenges in production are discussed, including process scale-up, optimisation, analytical methods, supply chain, technology and knowledge transfer issues, and keeping up with regulations.

Challenges in Drug Production

The goal of any drug development is to scale up the laboratory process to production scale, that is, from milligram to ton scale. Simultaneously, a robust process that yields high-quality API consistently at the lowest possible cost must be maintained. Once a molecule reaches Phase III, a critical milestone in drug development, the synthetic route is re-evaluated to determine if the current process is adequate. Industry is moving towards building quality from the ground up. This has resulted in process chemists and engineers pre-investing in understanding various factors to match laboratory conditions at plant scale. These factors include reaction kinetics, process cycle time, mixing, filtration, and drying.

Once the process is finalised, it is necessary to develop a suitable in-process sampling procedure that is accurate, reliable, and reproducible. For consistent batch analysis, the method must be robust and preferably orthogonal. This is to address any mass balance-related issues if the process generates an unknown impurity. Another factor for successful scale-up is technology transfer. Often, the final API production is performed at a remote site. Hence, it is important to maintain good documentation practice, to keep records of parameters that can adversely affect the outcome of a product. Sharing this implicit knowledge about a process, sample handling, and other such information will ultimately minimise technology transfer failure. This will result in fewer out-of-specification (OOS) or out-of-trend (OOT) events.

During API development, one of the biggest challenges is to ensure consistent supply of high-quality raw material. Manufacturers find themselves increasingly dependent on suppliers to consistently supply good quality material. Even a small disruption in service will have a dramatic effect on the critical path of a project. Variability in starting material can occur due to the presence of trace level impurities such as heavy metals, potentially toxic by-products, or even biologic contamination. Starting material may be incorrect, not just in being the wrong chemical but also in having undesirable physical characteristics such as particle size or polymorph (desired form). Changing the particle size may potentially influence flow properties, which could in turn affect the blending behaviour, resulting in poor content uniformity. Therefore, using incorrect starting material will result in undesired product and time-consuming investigation.

Identification and release testing of raw material is an essential step in verifying if the correct starting material is being used and if it meets the minimum specification requirement. Typically, starting material can be identified by comparing the infrared (IR) spectrum of a sample in question with a reference standard. An alternative is to use chromatographic techniques (such as high performance liquid chromatography (HPLC), gas chromatography (GC) systems), or titration.

More recently, molecular and vibration spectroscopy (such as Raman and near-infrared (NIR)) have facilitated raw material identification testing. In particular, portable spectrometers have enabled the onsite analysis. Additionally, these methods are non-destructive, require minimal or no sample preparation, and enable faster turnaround time of analysis. Chemical imaging (CI) is another emerging technique that combines spatial and spectral information, enabling further interrogation of ingredient concentration and distribution in a given formulation. Process and product understanding leads to better control and reproducibility, resulting in improved efficiency, sustained quality, and lower regulatory burden.

In May 2016, the FDA issued new guidance for industry regarding "Contract Manufacturing Arrangement for Drugs: Quality Agreements". This was to ensure that both drug companies and contract manufacturing organisations do not introduce adulterants. It also assures that all steps in manufacturing, testing, and any supporting operations are carried out in a compliant manner. Raw materials for manufacturing drug substances or products often come from many suppliers. Many of these suppliers offer multiple products and may have suppliers of their own. This in turn greatly increases the risk of cross-contamination, making it increasingly hard to identify the source of contamination. As a result, in 2013, the FDA passed the "Drug Supply Chain Security Act" (DSCSA) with a deadline for implementation in 2023. Under these regulations, manufacturers, wholesalers, drug distributors, repackagers, or anyone else who is part of the drug supply chain, must keep and disclose all information about products sold in the US market. In a similar effort, for prescription drugs, the EU passed the Falsified Medicines Directive (FMD) in 2011 to be implemented by a deadline of February 2019. This challenge has posed a logistical nightmare for manufacturers everywhere attempting to map out the supply chain distribution system, which is often a complex conglomerate of partners. The opportunity here is to minimise

or eliminate the circulation of harmful or fake medicines in the supply chain.

It is estimated that up to 30% of drugs in circulation are counterfeit and have resulted in millions of deaths annually worldwide. Medicine counterfeiting can occur in any class of compounds or formulation, whether these are branded or generic drug products. There are numerous analytical techniques to detect the presence of specific chemicals within a drug product. Chromatographic techniques such as LC/MS and GC/MS are specific, accurate, and reliable. However, the limitation of this technology is its portability, as it may require performing a quick analysis either in a warehouse or in a port, where drugs may be quarantined. Vibrational spectroscopy also finds a use here, especially NIR and Raman spectroscopy with their ability to discriminate between genuine and counterfeit products. Raman spectroscopy is easy to implement into the existing workflow, being non-destructive and providing information-rich data such as component identification, coating, and manufacturing sites of products. NIR, much like Raman, is non-destructive, requires no sample preparation, and can identify and distinguish the physical and chemical fingerprint difference between genuine and fake products.

Companies have adopted a scientific and risk-based approach to develop manufacturing processes that are reliable and robust, enabling the delivery of products of high quality in a cost-effective manner. This shift didn't happen overnight. It has been a culmination of events such as the FDA initiative in 2002 to use innovation in manufacturing technology and quality systems. This gave way to the formation of the process analytical technology (PAT) team in 2004, which recommended moving towards continuous real-time monitoring of critical quality attributes. PAT is defined by the FDA as a system to design, analyse, and control pharmaceutical manufacturing processes through the measure of critical process parameters (CPP). In turn, these affect critical quality attributes (CQA). Understanding and monitoring CPP in a timely manner, especially if this can be done either inline or online, is invaluable during process development. It enables manufacturers to create products with consistent quality, reduce waste, and develop cost-efficient processes. The challenge for manufacturers is knowing how and where to start. Factors to consider include reaction kinetics, which factors influence crystallisation, which polymorphic forms are produced, homogeneity of blending, drying, and potency. When scaling up, it is necessary to strictly control such parameters to ensure consistent product quality and yield.

In the manufacturing process, thermocouples and pressure sensors are used routinely. Chromatographic separations have been successfully implemented for real-time monitoring, as these techniques provide specificity, sensitivity to detect low-level impurities, and resolution. More recently, spectroscopic techniques such as Raman, mid-IR (MIR), or NIR have been utilised due to the specificity of various functional groups found in starting material, intermediates, and final products. Raman spectroscopy has been successfully utilised for understanding polymorphs, *in-situ* crystallisation monitoring, content uniformity, and many process-induced transformations. NIR spectroscopy can identify and distinguish the spectral homogeneity within a blend, content uniformity, and water content. These enabling technologies are complementary to each other and have successfully been used for quantitative determination of a component of interest. Continuous manufacturing of an API or drug product has the potential to provide benefits such as developing robust processes, reduced cost, and consistent quality. PAT data must be visualised with appropriate automation to minimise human intervention and enable real-time decision-making. As more PAT systems become integrated into the workstream, this will increase the knowledge of a process or its product, further enabling feedforward and feedback loops. This will reduce variability in the process and improve consistent output of product with higher quality.

The opportunities are vast as enabling technologies provide the pharma industry with a 360° view of its current processes and approaches. Communication between these systems will be fundamental to enable real-time monitoring and decision-making. Keeping up with regulatory trends and how to apply them will be of paramount importance. Automation of data acquisition and processing will control trends as these techniques become a common occurrence in routine testing. The US and EU regulatory agencies are focusing their efforts to establish a system for identifying and tracing drugs through the global supply chain. However, this will require applying smart technologies to analyse big data, cloud computation, and the internet of things (IoTs). Because of these regulations, manufacturers are making drugs that are safer, utilising technologies to enable them to manufacture drugs that are cost- and process-efficient. Regulations have indeed lengthened the process of bringing new drugs to market, but more importantly, they have ushered in a new paradigm in compliance. They will aid in supply chain transparency, identify any dependencies that may create compliance-related issues, and ultimately protect the consumer from exposure to drugs that may be harmful, contaminated, or counterfeit.

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