PEER REVIEWED

Strategies for Developing a Cost-Efficient Pharmaceutical Manufacturing Process

The last two decades of the twentieth century gave us medicines that were products of our innovation and technological advancement. Devastating epidemics such as HIV infections could be treated as well as widespread illnesses like high cholesterol, hypertension and diabetes. Cancer survival rates were improved and life expectancy increased by nearly five years worldwide between 1980 and 2000.[1]

Plavix, Prevacid and Seroquel, just to name a few therapeutics that were approved for marketing between 1990 and 1999, affected lives of millions and earned the highly-sought blockbuster status. Notably, Pfizer's Lipitor, approved for marketing in 1997, was on *TIME* magazine's "Top 10 best-selling product list" in 2014, second only to Sony's PlayStation and followed by Toyota's Corolla, America's sweetheart and the best-selling car ever.[2]

We continued to witness a steady number of marketing approvals in the first decade of the twenty-first century. While blockbuster drugs from previous decades continued to account for more than half of the total pharmaceuticals sales in the mid-2000s,[3] the newly-marketed medicines ranged from blockbuster-potential to ones more focused on narrow indications and not expected to offset the sales generated by blockbusters as their brand name patent protections expired. The 2005 *New York Times* article "Blockbuster drugs are so last century" forecasted that the pharmaceutical industry will focus on the development of medicines that are aimed at smaller patient populations and could be rapidly advanced through clinical development, incurring lesser costs and possibly having fewer side-effects.[4] While this is certainly true to some extent, the first decade of the twenty-first century gave us a number of blockbuster medicines that continued to have a significant impact on our lives, for instance, Nexium®, Advair®, Abilify®, Crestor® and Neulasta®, all approved for marketing between 2000 and 2009.

Today's pharmaceutical business is far more complex than in the past when fewer marketed products, stable drug demand, and high profit margins were the norm. Pharmaceutical business is rapidly becoming global with about half of the industry growth in emerging markets.[5] Thus, a pharmaceutical company's objective is to build a sustainable and cost-efficient supply chain that meets global regulatory requirements.

There are three key factors in pharmaceutical development: (1) quality of clinical trial material administered to patients, (2) time to develop processes and controls, produce and distribute clinical trial material, and conduct trials, and (3) money to fund ongoing development programmes. Time controls quality: given enough time we will develop robust processes with adequate controls to reproducibly deliver high-quality clinical trial material. In turn, quality controls the cost – in other words, the ease of achieving quality will dictate cost. The industry remains committed to patient safety, thus no supply chain cost reduction could be derived from reducing quality oversight.

As an increasing number of drug candidates enjoy accelerated clinical development timelines, the traditional development of *phase-appropriate* manufacturing process and controls may not be an optimal approach to chemistry, manufacturing and controls (CMC). There simply may not be enough time to redevelop process and controls as clinical studies rapidly advance through phases. The pharmaceutical company, who is a programme sponsor, should assess early on whether the focus should be on development of commercialisation-ready CMC, regardless of the clinical development phase. The supply of clinical trial materials for both high-volume therapeutics, such as high-dose and large clinical trial patients' population anti-microbials, and low-volume and small patient population orphan-designated drugs, which typically are on an accelerated clinical development timeline, present challenges to sponsors. This article discusses the three factors of the manufacturing process throughput: (1) materials yield, (2) volumetric efficiency and uniformity, and (3) production cycle time, and provides examples of how the manufacturing process can be optimised utilising process throughput concept.

As successful clinical programmes rapidly advance through the development phases and near the marketing application submission, the related CMC programmes should not fall far behind but rather be ready to transition from clinical to commercial supply chain. There are numerous examples of accelerated development programmes. For instance, marketed Imbruvica (ibrutinib), the Bruton's tyrosine kinase inhibitor, administered as an oral dose capsule for treatment of mantle cell lymphoma, chronic lymphocytic leukemia and small lymphocytic lymphoma, was developed within four and a half years by Pharmacyclics LLC, an AbbVie Company, in collaboration with Janssen Biotech, Inc., a Johnson & Johnson Company. Notably, the first human was treated with ibrutinib in 2009, followed by Phase II studies and convincing efficacy and safety data in 2012. Three Breakthrough Therapy Designations by the US FDA were granted in 2013. Following the submission of the new drug application (NDA), the drug received approval in November 2013.

Large-volume pharmaceuticals present challenges, requiring drug

supply for thousands of patients in late-phase clinical trials.

Furthermore, in the same timeframe, the sponsor needs to fulfill regulatory requirements to position for a successful process validation as part of the transition from clinical to commercial supply chain. An example of a steep increase in clinical trial material demand to supply another successful and rapidly advancing clinical development programme is captured in Figure 1. Startlingly, within three years, clinical trial material demand increased from 10 kg to more than 6 metric tons.

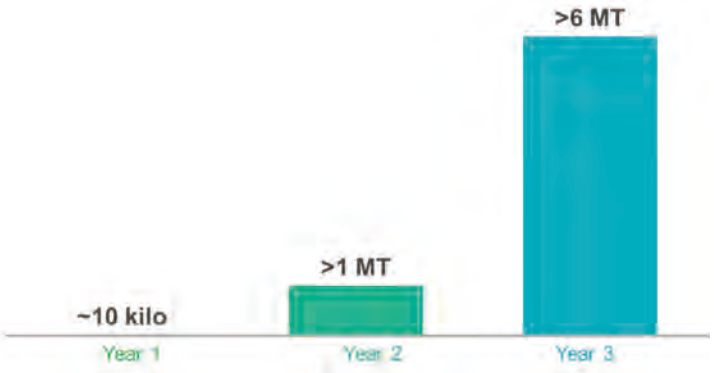

Figure 1. Example of evolution of clinical trial material demand over three-year period

The combination of high daily dose, large clinical trials and rapid advancement from the start of a Phase II study to marketing application submission present challenges to manufacturing process development teams which have two major objectives: supply clinical trial material and meet regulatory milestones to enable successful commercial launch and supply chain. There are four components to achieve readiness to transition from clinical to commercial supply chain: (1) lock of the manufacturing processes for drug substance and product, and evidence of adequate stability for each segment of supply chain; twelve months' stability data is expected, according to guidelines ICH Q11, (2) determination of critical quality attributes for API and formulated drug, (3) agreements with regulatory agencies worldwide about regulatory starting materials (RSMs) designation, and (4) assessment of manufacturing process parameters, establishment of their acceptable operating ranges and determination of whether any process parameters are critical, i.e. variability in parameter's range would have a direct impact on critical quality attributes of API or formulated drug. The companies that fully or partially outsource process development and manufacturing activities should identify and engage contract development and manufacturing organisations (CDMOs) that have sufficient *critical mass*, i.e. expertise, resources and capacity, to respond to ever-changing manufacturing trends and achieve these four objectives within a limited time.

The labour and utilities (natural gas and electricity) costs are the major contributors to production cost and should be considered when identifying opportunities for optimisation of manufacturing process. Traditionally, pharmaceutical process development teams tend to focus on materials yield, and while it is an important indicator of process efficiency, other contributors to process throughput, such as production cycle time and volumetric efficiency, should be assessed and optimised to achieve full manufacturing process potential. The following is an analysis of how process throughput controls manufacturing efficiency.

There are three key factors that affect process throughput: (1) materials yield, (2) volumetric efficiency and uniformity, and (3) production cycle time. The yields are increased by optimising the efficiency of chemical reactions and minimising losses in isolation operations. This is typically achieved by studying reaction mechanism and influencing reaction course by choosing the right reagents' stoichiometry, solvents, temperatures, addition rates, etc. The benefit of increasing materials yields is obvious: larger quantities of intermediates and final products are produced per batch, thus fewer batches are required to achieve inventory objectives. The volumetric efficiency is achieved by identifying the highest possible batch concentration, allowing for the largest quantities of starting materials and products in each production train. The volumetric uniformity across all operations further simplifies processing by employing the same size equipment for multiple manufacturing steps. The optimal production cycle time is achieved by assessing the purpose and efficiency of each operation, eliminating all unnecessary ones and shortening the duration of remaining operations.

A case study is presented below to illustrate the manufacturing process throughput optimisation. A schematic presentation of process consisting of three distinct manufacturing steps is shown in Figure 2.

Figure 2. Schematic presentation of the three-step manufacturing process

Below are the results of process throughput optimisation for each of the three manufacturing steps. All volumes, expressed as L/kg, are related to 1 kg of API.

Throughput factors	Initial process	Optimised process
Maximum batch volume	30 L/kg	12 L/kg
Intermediate product isolation	28 L/kg, initial solvent	6 L/kg, new solvent
Organic and aqueous waste	61 L/kg	28 L/kg
Molar yield	92%	92%
Batch size	49 kg input 76 kg output	86 kg input 133 kg output
Production cycle time	5 days	3 days

Table 1. Manufacturing step 1: process throughput optimisation results

As the yield of manufacturing step 1 was high (92%) for the first intermediate (Table 1), the process optimisation efforts were focused on improving the poor volumetric efficiency by decreasing maximum batch volume allowing for larger batch size. This objective was achieved primarily by identifying an optimal solvent for the isolation of the first intermediate. By design, the step 1 product had a low solubility in the new solvent, thus requiring much lower volume (12 L/kg) to obtain the same high yield, without any loss of the product's quality. The nearly threefold net increase in volumetric efficiency translated into a significantly increased input and output scales, affording 133 kg of first intermediate in the same size production train. Furthermore, careful assessment of purpose and duration of each operation provided an opportunity to shorten production cycle from five to three days.

Throughput factors	Initial process	Optimised process
Maximum batch volume	44 L/kg	21 L/kg
Organic and aqueous waste	172 L/kg	102 L/kg
Molar yield	40%	75%
Batch size	86 kg input 47 kg output	133 kg input 115 kg output
Production cycle time	8 days	5 days

Table 2. Manufacturing step 2: process throughput optimisation results

The low yield of second intermediate and poor volumetric efficiency were the focus of manufacturing step 2 optimisation (Table 2). The emphasis was on studying the chemical reaction mechanism and optimisation of related process parameters to positively influence the course of reaction and to suppress or eliminate unproductive pathways, which led to loss of second intermediate yield and demanded elaborate purification methods. The optimisation efforts resulted in nearly doubling the product yield (75%). Moreover, as the significant increase in yield was achieved by enhancing the desired reaction pathway, this simplified the purification, as it demanded lower quantities of solvents, fewer operations and shorter cycle time to achieve the required product quality. The more than two-fold net increase in volumetric efficiency translated into significantly increased input and output scales, affording 115 kg of second intermediate in the same size production train. Optimisation of process parameters and assessment of purpose and duration of each operation allowed for reduction of the production cycle from eight to five days.

The optimisation of volumetric efficiency, material yield and production cycle time resulted in a significantly increased product output (84 kg) in addition to nearly four-fold reduction in cycle time from fifteen to four days.

Throughput factors	Initial process	Optimised process
Maximum batch volume	81 L/kg	54 L/kg
Organic and aqueous waste	400 L/kg	255 L/kg
Molar yield	55%	80%
Batch size	100 kg input 64 kg output	115 kg input 84 kg output
Production cycle time	15 days	4 days

Table 3. Manufacturing step 3: process throughput optimisation results

The long production time, poor volumetric efficiency and modest product yield were at the centre of the manufacturing step 3 optimisation efforts (Table 3). As the main purpose of this step was the ultimate purification to yield the product which met acceptance criteria for all critical quality attributes, naturally this step employed large quantities of solvents and generated significant amount of waste. A study was conducted to assess the product stability in all media used in step 3 and optimise process parameters, such as acidity or alkalinity, temperature, rates of materials addition, residence time in each media, accordingly. The production equipment was also assessed with a particular focus on filtration and drying of the product. An *in-situ*, real time monitoring of the drying process was introduced which provided an opportunity to determine the earliest time point at which acceptance criterion was met and the product was ready for packaging.

The impact of overall process throughput improvements is summarised in Table 4. The increase in materials yield, decrease in solvent demand and reduction of waste, and shortening of the production time created a sustainable, more environmental-friendly and cost-efficient manufacturing process and had a direct impact on labour and utilities cost reduction.

As many drug candidates rapidly advance through clinical studies and as producers of generics are in the rearview mirror of every marketed brand name therapeutic, pharmaceutical manufacturing plays a very important role in building a sustainable commercial supply chain. Manufacturing process throughput optimisation has become a necessity rather than an option. Having high product yield, volumetrically efficient process and shortest possible production cycle time will enable the sponsor to withstand future increase in labour and utilities costs and reduce the probability of complex, expensive and risky post-approval changes driven by the need to address the unacceptable cost of goods. As shown in the example above, the optimal process throughput will also minimise environmental impact through reduction of input materials, waste, natural resources and energy consumption.

Manufacturing process	Overall molar yield over three steps	Volumetric efficiency relative to 1 kg of API	Overall production time
Initial process	20%	633 L/kg	28 days
Optimised process	55%	385 L/kg	12 days
Throughput increase	2.75-fold	1.6-fold	2.3-fold

Table 4. Overall process throughout improvements

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Product News

Sartorius Stedim Biotech launches new versions of data analytics software solutions

SIMCA® and SIMCA®-online software updates in the UmetricsTM Suite help manufacturing industries make better business decisions and optimize process control

Sartorius Stedim Biotech (SSB), a leading international supplier for the biopharmaceutical industry, has introduced a new version of its SIMCA® and SIMCA®-online data analytical solutions, which are offered by its subsidiary Sartorius Stedim Data Analytics, formerly known as Umetrics.

Every day, businesses generate a vast array of data derived from a variety of different sources. This data holds the key to better performance. The challenge is to interpret this information in a meaningful way. However, with so many parameters and such vast system complexity to consider, it is hard to find a solution that is both powerful and smart enough. SIMCA®, an established advanced data analytics and visualization program as part of the company’s proven Umetrics™ Suite, makes it possible to combine and analyze data from all sources to isolate, understand and act on the hidden gems that hold the secret to better decision-making and greater business success.

SIMCA®’s multivariate data analysis engine enables companies to swiftly detect and analyze deviations from normal operating conditions by modeling an idealized process. Once this model is transferred into SIMCA®-online, it serves as a valuable reference for your current production. The newly enhanced software offers an intuitive graphical interface and the flexibility to handle complex data, such as reworking, splitting and merging, and more. SIMCA® projects can be uploaded directly to an available SIMCA®-online server for real-time visualization of the process from a data point of view.

The real-time monitoring and prediction system, SIMCA®-online, constantly monitors processes to provide a continuous snapshot of the users’ operations. It not only helps to identify when set parameters change, but also enables remedial action to be taken before production is affected, ensuring that product quality remains consistent. With this level of control, it is possible to maximize resource efficiency, minimize operational costs and benefit from increased confidence in end-product quality. Among the new features in SIMCA®-online is the self-service analytics capability, which allows anyone to create fundamental process models, regardless of their background. The new notification system, along with the new web client, gives the user peace of mind about the quality of production anywhere and anytime as this system provides an overview of the production processes on devices such as tablets or mobile phones. SIMCA® and SIMCA®-online have been developed according to GAMP5 and have been extensively tested and validated. These programs are also used by the EMA and FDA for Real-Time Release testing.

As leading experts for analyzing data, Sartorius Stedim Data Analytics helps companies in any industry, which include the pharma, chemical and food sectors, find the growth opportunities they need using the comprehensive Umetrics™ Suite. These solutions enable them to harness the wealth of data within an organization, identifying vital elements to improve the results of research, product development and manufacturing processes. With improved process understanding and more consistent product quality, users will be able to reduce risk, speed up time to market and accelerate business growth.

A complete solution encompasses software, training, support and project management. Also, as part of the Sartorius Group, a global company with approximately 7,500 employees, Sartorius Stedim Data Analytics provides the backup of an international network.

Find out how our solutions can help your business grow, whichever industry you are in. Visit www.umetrics.com to access a trial version of SIMCA® and view the details of our free SIMCA®-online simulation.

The real-time monitoring and prediction system, SIMCA®-online, constantly monitors processes to provide a continuous snapshot of the users’ operations.

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