

## Ramping Up From Pilot: Three Keys to Success

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Process knowledge,  
good decision-  
making, and  
communication are  
crucial to the  
bottom line.

**T**he FDA's recent Quality by Design (QbD) initiative emphasizes the need for greater diligence by sponsor companies in understanding the sources of variation in their processes that may affect the quality of their product. Concomitant with the development of a good scientific knowledge base is the need for excellent and detailed documentation, which is vital to the technology transfer process often involved in ramping up from pilot scale.

Pharmaceutical and biotechnology-derived products are like people; they evolve during their life cycle to larger and more complex stages—from the baby steps of the laboratory, to adolescent pilot plant stage, and finally maturing into full-scale production. With this progression come the inevitable growing pains that a company must deal with. The problems frequently associated with ramping up processes from the pilot plant stage into full-scale production may, however, be tempered by foresight and planning. Several elements need to be considered from both the technical and business perspectives. Three keys to success should guide the ramp up process.

- Advanced Knowledge of Your Product and Process
- Informed and Timely Business Decision-Making
- Effective Communication across a Balanced Team

### KNOWLEDGE OF PROCESSES

The first commandment for ramping up a process from pilot scale is "Thou shalt know your product and process well." Scale-up processes are often nonlinear. Therefore, a detailed understanding of the nature of the product and the variables that factor into its manufacturing process are crucial. Determined at an early stage of drug development, or even before the pilot plant stage, that understanding can help a company anticipate and avoid problems that may arise during the ramping-up process. The more you get to know your product at the early stages, the better off you will be later in the game.

The following two case studies illustrate this point.

*A company producing a protein-based biological at pilot scale planned to scale up to full scale production. The company failed to anticipate the non-linearity of the scale-up process in the lyophilization step, however. Resulting full scale production lots had different water content from pilot scale lots, which affected product stability. With proper process development due diligence, the company could have avoided the problem altogether, saving valuable time and much aggravation.*

*Another company used a size-exclusion chromatographic process for the purification of its oligosaccharide drug product. This worked well on the small laboratory scale and even pilot-plant scale, producing a drug product of greater than 99 percent purity. When the process was simply scaled up lin-*

early, increasing the ion-exchange column dimensions proportionally, the product was isolated at only a 94 percent purity level, and had a different impurity profile. A detailed technical investigation retrospectively identified problems with column overloading and regeneration of the column matrix from production run-to-run. Those had not been factored in. The entire manufacturing set-up had to be modified and reconstructed. The product solution had to run in parallel through multiple smaller chromatographic columns that were not subject to overload and had easily replaceable and reconditionable column cartridges. These modifications, which were costly and time consuming, could have been averted altogether by a good understanding of the process variables during the process development phase.



A "let's just cross that bridge when we come to it" approach often leads to delays and increased costs.

## R&D can contribute greatly in identifying potential problem areas that may arise during full production scale manufacturing.

### INFORMED DECISION-MAKING

A company must make a number of business decisions during the process of ramping up from pilot-plant scale. Biotechnology company executives must make informed decisions based on documented facts and a thorough understanding of the product and processes. The decision-making process should be initiated early in the game. Although plans do change over time, too often company (and particularly biotechnology start-up company) executives take a "Let's just cross that bridge when we come to it" approach, failing to plan for fiscal contingencies well in advance. This often causes delay and increased costs down the road. It must be realized that ramping up from pilot is a giant leap that requires foresight and good fiscal planning. Adequate financial outlay needs to be in place, together with good advance strategic decision-making. If the decision is made to build full production facilities on site, the allocation of capital for operating costs of the facility and growth in personnel

strength to staff the facility must also be carefully figured into the equation. You invariably pay now, or pay later.

*A biotechnology company that developed an immunomodulator polypeptide drug was faced with the decision of whether to outsource the full-scale*

*production of the product, or develop the resources for manufacture in-house. Although it is often more cost-effective to outsource, in this case the informed decision was made early to relocate to a larger facility and build an in-house production facility. The manufacturing process was not a standard biofermenter process that could be outsourced easily to a CMO with a facile technology transfer. The process needed specialized and specifically designed equipment for manufacture, which would in turn have required substantial modifications of a CMO facility at considerable cost and investiture of time. Rather, early fiscal planning allowed the company's man-*

### COMMON PROBLEMS IN RAMPING UP FROM PILOT AND THEIR SOLUTIONS

PROBLEM ENCOUNTERED	SOLUTION
Temperature control	More efficient cooling/heating systems
Mixing	More efficient stirrer systems
Shearing of cells in bioreactors	Control of stirring/agitation rates
Overloading of large chromatography columns	Pass product through parallel sets of smaller columns
Lyophilization efficiency	Process R&D to optimize lyophilization conditions
Maintenance of sterility in product	Map heat sterilizer unit, consider sterile filtration
Removal of residual solvents	Longer drying times, rotary evaporation/drying steps
Non-uniformity of raw material/process materials batches	Establish strict vendor qualifications/specifications
Efficiency of viral removal	Precipitation/column removal. Test by viral spiking studies

agement to seek and raise the venture capital funding to help build its own in-house production plant, and hire trained personnel as production staff, which proved more cost-effective in the long run.

### EFFECTIVE TEAM COMMUNICATION

The key to success in any business sector ultimately hinges on good communication. Successfully ramping up from pilot plant to full scale-production is no exception. There must be good, open lines of communication between R&D staff, production staff, and management from the get-go. There is often a disconnect between management and technical

staff that can result in delays; delays invariably cost a company money. Active dialogue among all involved must be encouraged by biotechnology executives early in the game.

Quite often, the R&D team members who developed the drug at the small scale are left out of the process of ramping-up from pilot plant scale. That is a mistake, because they are often the most knowledgeable about the physicochemical characteristics of the drug, its stability, and its analyses. R&D can contribute greatly in identifying potential problem areas that may arise during full production scale manufacture. The technical staff and the business decision-makers must

communicate effectively to identify early what infrastructure or investment may be involved down the road to full scale production and why. The business executive should also be a good listener and pay heed to what the technical staff is saying. On occasion, management responds more to external stakeholders such as investors or venture capitalists, budgeting accordingly rather than relying on information from their in-house staff. To make correct forecasts of projected costs, it is important to listen to those with the most intimate knowledge of the product. Although development costs of other products may be used as a rough guide, ultimately each product is unique, with its own timelines and budget for ramping up from pilot to production scale.

When a company decides to proceed with the design and implementation of the infrastructure for full scale production of a biotechnology product, it should assemble a balanced project team. Team members should include persons from R&D who worked on the discovery and early development of the product, those involved with the pilot-plant production and testing of the product, staff involved in the full-scale production, and the business management staff. Such a multi-faceted planning team ensures that nothing falls between the cracks. Open lines of communication must be maintained throughout the process by all the team members. This ensures realistic expectations and timelines, early anticipation of potential problems, and more accurate budget allocations.

If manufacturing is to be outsourced to a CMO, the lines of communication must be extended early to the staff of that external company as well, so the transition to CMO can be achieved seamlessly. The CMO should function almost as an extension of the sponsor company. This is crucial to both the smooth technology transfer process and to the ongoing business partnership that will help take the product to the marketplace.

The importance of including R&D staff in the ramp-up to production dialogue is well-illustrated by the following case study.

## OUTSOURCING CONSIDERATIONS

Before deciding to implement the ramp-up process from pilot plant to full manufacturing scale, a biopharma executive has to decide whether to develop the resources in-house or to outsource the manufacturing function.

*The following considerations must be taken into account.*

### TECHNOLOGY TRANSFER

It is sometimes a difficult and time-consuming process to transfer technology to a CMO. The transfer process is more difficult and more time-consuming the more complex the manufacturing process is. Therefore, if the product manufacturing process uses standard fermentation, isolation, and purification methods that are readily adaptable to the CMO's existing equipment, outsourcing may be a good option. If, on the other hand, it involves specialized, nonstandard equipment or processes, in-house development may be a better option

### TIMELINES

Contracting manufacturing to a CMO may shorten or lengthen timelines, depending on the circumstances. In most cases, it would shorten the timeline, because building a cGMP manufacturing unit in-house requires construction time, personnel hiring, and possibly development of ancillary facilities such as a quality control laboratory. On the other

hand, for CMOs having specialized facilities and technologies, there may be a lag time for manufacture with clientele lined up in a long queue.

### ROOM TO GROW

The decision to build in-house manufacturing capability often requires a company to move to a larger facility, or to add a separate manufacturing facility at a different site. Use of two sites often separates R&D from production staff and leads to an unwanted disconnect in communications. A larger space may just not be a viable option if it wasn't planned for and budgeted well in advance; in that case outsourcing is a better option.

### ADAPTABILITY

If a production facility built in-house can be easily adapted to other products coming down a company's production pipeline, it may be cost-efficient for a company to consider building such a unit.

### FACILITY MAINTENANCE

There are fiscal and regulatory responsibilities inherent in maintaining an in-house cGMP manufacturing unit including utilities, operational costs, and personnel costs that are not associated with the outsourcing option

*A CMO ramping up a process for a biotechnology-derived drug product observed an impurity profile different from the pilot-scale. Although only minor impurities were involved, the substances had to be identified and characterized qualitatively to determine their source and means of removal. Because they were included in the technology transfer process, the sponsor company's R&D staff members were able to quickly identify the new impurities as the same ones they had seen early in the laboratory-scale process, where they had identified a number of process variables. They identified the cause as inadequate pH control during one of the manufacturing steps. The problem was resolved without delay because the lines of communication were open among all involved.*

#### **THE BOTTOM LINE**

The bottom line from the product standpoint is that companies should gain a good level of product and process knowledge early in the drug

development cycle. Potential problems likely to be encountered during scale-up can be anticipated and preempted or resolved quickly. This can save a great deal of time, aggravation, and costs during the transition from pilot-plant to full production.

From the financial bottom line perspective, ramping up from pilot means a concomitant ramping up of costs. The long-term costs associated with added infrastructure and personnel must be planned and budgeted well in advance. A decision has to be made whether full-scale production is most cost-effectively done in-house, or should be contracted out.

Finally, good, effective communication is crucial to the strategy and planning for full scale production of a biopharmaceutical product. This should involve all those who have worked on the development of the product through its various stages and incarnations. And, when a company is ready to implement the transition from pilot-plant to full-scale production, effective communication with

those who are actually involved in the technology transfer for manufacturing, whether in-house manufacturing staff or the staff from external CMOs, must be implemented as well.

Ramping up from pilot plant to full scale production is often a challenging process; it is product and process knowledge and good advanced planning that make all the difference in its success. Such foresight can clearly help a company's bottom lines. The real bottom line, of course is to get high quality new drug product to the patients who need it most, and can benefit from it, to mitigate their suffering and improve their quality of life.

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