



Process Development

A CMO talks about scale-up issues

THE EMERGING DRIVER OF THE drug pipeline are virtual pharma companies. One bottleneck they face is developing a process to scale up a bench product for clinical use. Virtual pharma companies are repeating some of the same mistakes that pharma companies made in the 1980s. One such mistake is the force-fitting of what works in the lab to process development. **Richard Pariza, Ph.D.**, chief scientific officer of Cedarburg Pharmaceuticals, a Grafton, WI-based provider of clinical and commercial APIs, talked with us about best practices for how virtual pharma companies and contract service providers can work together, especially on process development.

Contract Pharma: How prevalent are scale-up issues in the industry?

Richard Pariza: Discovery chemists in every company, large or small, design syntheses to be versatile, so many analogs can be made using the same strategy or from common intermediates. That is their job. However, once the target is identified, the best way to make the one desired compound may be very different from the discovery route. Few medicinal chemists realize how difficult it is to scale up certain kinds of reactions or processes, such as chromatography. As the scale increases, safety and environmental issues quickly mount. The medicinal chemist is looking for the one reaction that can make all his analogs, while the process chemist is looking for all the various reactions that can make his one analog.

CP: For virtual pharma companies that insist on doing things their way, what's keeping them from trying out a new process?

RP: Part of it is inertia. The pharma company has a proven route and they don't want to take the risk that further labora-

tory work will cause delays and still not result in a better process. They are proud of the results of all their work, and rightly so. They no doubt had many obstacles to overcome, and found some very clever solutions to tricky problems. They are also in a big hurry. The impatience in getting the first few kilos of a candidate drug for preclinical and clinical studies is understandable when you consider what is at stake. Each day the final marketing approval is delayed can be worth several million dollars in revenue. However, each inefficient, hazardous or expensive step that is used in the early production of clinical and safety assessment drug can end up "locking in" enormous headaches for the future.

CP: How does a CMO encourage the virtual pharma company to try out a new process?

RP: The only way it can be done is by explaining the consequences and giving examples of projects that have been delayed by poor decisions regarding early process research compromises. Time is the major concern to any pharma company, and they need to know as soon as possible if they have a viable candidate drug. This is especially the case for a virtual pharma company that may need hard data to convince its investors to release additional funding. We have to point out what the real costs are to simply making early supplies by brute force, and the high likelihood that delays will result. Even if a drug does not make it all the way to market, the decision to stop the development should be made as early as possible. Such a decision is often dependent on obtaining enough of the drug so the necessary toxicology, safety, stability, and clinical studies can be completed.

CP: How does a CMO take an existing process and make it better?

RP: The CMO has to find the best scientists, synthetic and analytical chemists and engineers, and provide them with modern laboratory equipment to quickly evaluate potential processes. New ideas are generated by brainstorming sessions and use of all the available literature searching tools. There is enormous knowledge stored in the long history of published chemistry, and we need to find the scientists with the insights to imagine what approaches are worth trying. Ultimately, synthetic chemistry is an experimental science, but, as the old joke goes, "a month in the lab will beat a day in the library every time." With modern search engines, at least a few hours in a virtual library has to be your starting point. Once ideas are formulated, the chemist must go into the lab and try them, so the chemist with "good hands" becomes indispensable. Something as seemingly simply as the filtration of a fine precipitate can turn a great process on paper into a nightmare in the pilot

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IPS Launches "Lunch and Learn"

INTEGRATED PROJECT SERVICES (IPS) has launched a series of Lunch and Learn programs. Lunch and Learn programs are a powerful way to enhance knowledge and technical understanding within clients' organizations. Andrew A. Signore, PE, chief executive officer of IPS, commented, "These sessions are highly interactive and are a cost-effective opportunity to deliver in-house training and development opportunities that introduce and discuss current technical know-how and industry best practices."

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plant. And a chemist who can find the right conditions to avoid this problem, by empirically trying many tricks he has learned from experience, can save the day.

CP: *Have there been successful cases where an existing process can be scaled up, or does there always need to be tweaks?*

RP: Only the simplest of reactions behave the same way on both small and large scale. There are always some engineering problems. However, an experienced medicinal chemist will have seen enough processes go to larger scale to design the chemistry, from the start, to avoid many issues. There is no substitute for the wisdom that comes from experience!

CP: *What's the best way during process development to mitigate misunderstanding with the client?*

RP: Communication — early, often, and honest — is the only way to deal with these complex programs. The CMO should provide a knowledgeable contact person from their project management system, and be ready and able to answer all questions quickly and accurately. Weekly reports by e-mail and scheduled conference calls are also essential to keeping the relationship satisfied. The customer and CMO must realize that they are partners in the success or failure of the project, and learn to trust each other with bad news as well as good. The result of their mutual success will be a new treatment for a disease that can be manufactured safely, efficiently, and reliably — something that will benefit us all. ■

Baxter Facilities Win Shingo Prize

TWO BAXTER INTERNATIONAL manufacturing facilities will be recognized with the 2007 Shingo Prize for Excellence in Manufacturing at an awards presentation in March. Baxter's North Cove facility in Marion, NC and Cuernavaca facility in Morelos, Mexico are the two sites that will be honored for their achievements in "driving higher quality and improvements in productivity, manufacturing cycle time and customer lead time," according to a Baxter statement.

The Shingo Prize for Excellence in Manufacturing recognizes businesses and researchers that have demonstrated outstanding achievements in manufacturing and the supporting business processes that lead to outstanding quality, cost, delivery and business results. Named in honor of Dr. Shigeo Shingo, the renowned engineer who helped create the Toyota Production System, the annual Shingo Prize for Excellence in Manufacturing is administered by the College of Business, Utah State University.

The North Cove site was awarded the Shingo in 2000, and will be the first two-time winner. "Through our disciplined approach, we have remained the market leader and have continued to improve product quality and delivery and reduce manufacturing cycle time, year after year, for more than 34 consecutive years," said Tony Johnson, plant manager of Baxter's North Cove facility.