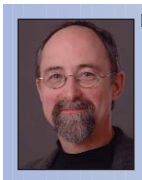
The Do's and Don'ts of Scale Up



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What are the most important things to keep in mind when scaling up a new batch chemical process?

Some of the most valuable advice about process scale-up consists of information not found in engineering course curricula or textbooks, but rather comes from experiences learned on the job. Unfortunately, this situation can result in some costly, time-consuming and potentially hazardous lessons.

Several years ago, I compiled the following list of things I considered important to a safe and successful scale-up in the kilo-lab or pilot plant. I call it my list of "12 things to do and to avoid" in process scale-up. Many are just common sense, and many are expected practice in the fine-chemical and pharmaceutical industries, but all of them can help save time, avoid mistakes, streamline the development cycle, and allow you to reap the maximum benefit from the scale-up experience.

12 things to do

1. *Operating philosophy*

Develop an overall pilot-plant operating philosophy and guidelines for the minimum documentation required before a new process can be run in plant equipment — for example, a detailed laboratory process description, process safety information package, etc. Get management buy-in and support, so that you can enforce these requirements.

2. *Equipment logbooks*

Set up operating and maintenance log books for each major piece of equipment in the plant (*e.g.,* reactors, filters, dryers, pumps, hoses, etc.). In them, document all batches, cleaning operations, test results, and any maintenance performed, beginning with the date of installation and qualification. Laboratory notebooks work well for this.

3. *Sample database*

Set up a sample log book or database. Using any reasonable numbering system, list in it every single sample collected in the plant for testing or retention. Include batch number, step number, time collected, purpose, test results, etc. This will become an invaluable archive for future reference, and will help ensure that important data are not lost. There may never be another opportunity to generate many of the samples collected during scale-up batches.

4. *Retain samples*

Keep samples of all isolated products or intermediates produced in the kilo-lab or pilot plant. Store them in a cool, dark, dry place, or as appropriate for the particular material.

5. *Collaboration*

Encourage engineers and chemists to communicate early in process development and route selection. The most successful processes result from a collaboration between those who best understand the chemistry and those who best understand the physical and mechanical limitations of the pilot equipment and the operations that may or may not be considered acceptable.

6. *Fix the process*

Try to solve any problems and finalize the process well in advance of scale-up so that there is time to focus on ensuring that the batch can be scaled up safely. Making changes on the fly or "experimenting" at scale can create unforeseen hazards.

7. *HAZOP*

Perform a hazard and operability review (HAZOP) each time you bring a new process into the plant. This should be conducted by a team of in-house experts from various departments and should include a process walk-through and a detailed review of process safety information, contingency plans and emergency preparedness.

8. *Energetics*

Insist on calorimetric testing to determine the stability of components, heats of reaction, potential for decomposition and potential magnitude of thermal runaways. Most adverse events in chemical processing occur because of poorly understood chemical reactivity or insufficient heat removal.

9. *Batch record*

Create a written batch record (batch log sheet) for each batch you conduct, even at kilo-scale. Master records should be reviewed and signed by representatives of the departments involved (R&D, Engineering, etc.). Document change control is particularly important to track revisions and ensure that the most recent version is in use.

10. *Raw material grade*

Conduct development experiments using technical-grade raw materials, or materials obtained directly from proposed large-scale suppliers. They will be more representative of future manufacturing sources.

11. *Raw-material use test*

Always perform a lab-scale use test using the actual lots of all raw materials and in-house intermediates earmarked for the pilot batch. Ensure that the product made meets specifications before proceeding with the scale-up. If a pilot batch

later gives unexpected results, you'll be able to eliminate raw materials as a source of the problem.

12. *Seize the opportunity*

Make the maximum use of each batch. Take as many in-process samples as practical and retain them for later troubleshooting. This includes key effluent streams. Use the opportunity to collect mass balance data, to test your energy balance relationships, and to verify analytical methods. Document all significant details in a campaign or batch report to make the information readily accessible at a later date.

12 things to avoid

1. *Keep it simple*

Avoid reactions that require highly specialized equipment, or that are known to be hazardous and require special safety facilities, such as nitration reactions. At a minimum, obtain full calorimetric data and compare them to the maximum heat removal rate of the reactor. If necessary, consider outsourcing (tolling) such reactions to companies that specialize in them.

2. *Heating*

Never heat a reactor without agitation. It can create hot spots that can erupt into violent boiling when the mixer is turned on or initiate unexpected decomposition. Never stop the agitator until a reaction mixture has cooled to a safe temperature.

3. *Decomposition*

Do not operate a reactor at a temperature within 50°C of the known onset temperature of an exothermic decomposition reaction that might run out of control.

4. *Solids addition*

Avoid having to add solid reagents to a reacting mixture. Manual addition can be extremely dangerous, and while screws, conveyors and other apparatus for contained large-scale solids addition are available, they are often unreliable and expensive. Similarly, do not add solids to a hot or refluxing mixture.

5. *Evaporation*

Do not develop a process that relies on the common laboratory technique of evaporating to dryness or to very low volumes. Most large-scale reactors have a minimum stir volume of about 20% of their capacity.

6. *Exotherms*

Try to avoid "all in and heat" operation (adding all reagents to the vessel and then heating up). Because of diminished heat-removal capacity at large scale, exothermic reactions can cause a thermal runaway. Exothermic decomposition reactions may follow, putting the reaction beyond any chance of operator control. Rapid gas evolution can compound the problem. It is better to design reactions so they can be controlled by slow addition of a limiting reagent at a rate that matches the equipment's cooling capacity. As a corollary to this rule, never add a catalyst to a reaction mixture last.

7. *Timing*

Avoid reactions that must be worked up or isolated "immediately," such as the kinetic resolution of some enantiomers. At commercial scale, many operations can take orders of magnitude longer than in the lab. Solid product isolation alone can take 24 hours or longer. For this reason, try to ensure that the product slurry or the stream of interest is stable for a sufficient length of time.

8. *Solvents*

Avoid using solvents that are considered environmental hazards or that may not be permitted in human pharmaceuticals, etc., such as methylene chloride or other halogenated compounds. Beyond permitting difficulties, waste treatment or removal costs at manufacturing scale can often make a process uneconomical.

9. *Filtration*

Avoid hot filtrations or polish filtrations of highly saturated solutions. Solids can crash out quickly in pipes or lines and clog the filter or other equipment. To prevent this in the plant, lines often have to be steam-traced or preheated.

10. *Extractions*

Try to avoid reverse phase splits (where the upper phase goes to waste). Such operations require the addition of another vessel to the equipment train, a considerable expense at the manufacturing scale, and add time to the process cycle. Likewise, when quenching reactions with water, remember that at large scale, it is most common to add the quench to the batch and not the other way around.

11. *Chromatography*

Try to avoid using flash chromatography for purification. While useful in the lab, it is used commercially only for very-high-value products or where there is no other choice. Even then, chromatography requires very large amounts of solvents and support material. It is better to develop a salt or other crystalline form.

12. *Play it safe*

Don't risk all of your limited raw materials or intermediates on one batch! Be prepared for the possibility that the batch, especially in a new process, may still hold surprises in spite of your careful preparations. Operator errors or errors in the batch record are also more likely the first time through a new process.

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