# 21

# SCALE-UP DOS AND DON'TS

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## 21.1 INTRODUCTION

One of the chemical engineer's primary responsibilities in the pharmaceutical industry is to assist in scaling up laboratory or development-stage processes for commercialization. An unfortunate fact is that so much of the practical information that can make scale-up more efficient and ultimately more successful is generally acquired in the workplace only through years of on-the-job training. Most university engineering curricula are simply not geared toward teaching students about the many real-world issues that can complicate scale-up or lead to unexpected results, unsuccessful campaigns, and potentially dangerous situations.

## 21.2 LEARNING THE HARD WAY

I learned many of the important things about technology transfer and process scale-up on the floor of the pilot plant long after I left school. Suffice it to say that some of these lessons were hard won, sometimes at the cost of out-of-spec batches, close calls, and unnecessary delays. Lucky is the new graduate in a position to be mentored by someone who has learned about scale-up through experience by putting time in "in the trenches."

It sometimes seems that scale-up is simply a lesson in learning to expect the unexpected. But over time, one realizes that many of the surprises encountered during scale-up could have been anticipated and often prevented by paying attention to the appropriate details, conducting some relatively simple laboratory studies, or collecting the right quantitative data during early process development. That is why I have always been a strong proponent of appropriate process engineering studies early on in new process design. There are countless simple laboratory measurements that allow the process chemist or engineer to characterize and quantify the behavior of the reactants and other materials used in the process, and this can go a long way toward streamlining scale-up.

## 21.3 TYPICAL SCALE-UP ISSUES

One of the most common effects of scale-up is a change in reaction selectivity, especially in semi-batch reactions. This results mainly from differences in mixing between the laboratory or kilo-lab scale and the commercial scale. This is discussed in more detail in Chapter 14. Changes in selectivity can lead to lower yields and higher levels of impurities in the final product, or changes in the impurity profile that in turn can alter the physical form or polymorph of crystalline products. The appearance of previously unseen polymorphs of pharmaceutical solids upon scale-up is all too common, and this change in impurity profile is one of the major underlying reasons.

Product isolation can also lead to unexpected results upon scale-up. Despite the industry's best efforts to design better and more efficient filters and centrifuges for the recovery of solid products, the fact remains that the removal of impurities in the cake washing step is often not as complete or as efficient at large scale as in the laboratory. This is, in part, simply due to the difficulty of ensuring even distribution of the cake and cake wash at large scale.

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Other unexpected consequences of scale-up result from the very long times required to complete many processing steps at large scale. Operations as fundamental as charging raw materials can take many hours; likewise for transfers, distillations, and product isolations. It is critical to conduct the necessary laboratory stability studies to ensure that the various process streams do not undergo degradation during these prolonged processing times.

Sometimes, problems result from poor communication at the technology transfer stage. One of my more uncomfortable memories involves an API process being transferred to the 8000 L scale at a foreign CMO. It was only upon arrival at the manufacturing site that our team learned that the designated reactor train was not equipped for vacuum distillation—all stripping operations were to be conducted at atmospheric pressure. However, all previous development work for this process had utilized vacuum distillation. We somewhat unwisely proceeded with the campaign based on the results of a quick laboratory test, and wound up cooking our final product stream until it was dark brown and failed spec, because of the very elevated temperature and the many hours that the distillation took at that scale.

## 21.4 PURPOSE OF THIS CHAPTER

Throughout the long years as a process engineer and working in kilo labs and pilot plants, I came to develop a list of things that should be followed—things that made pilot operations more efficient and safer—and a list of things that should be avoided, or operations that could not be scaled up effectively. At times, I worked with scientists with little scale-up experience, and often used these lists to help educate them about the types of procedures that might work well in a plant setting and those that would probably not. These lists evolved into a set of scale-up "dos and don't" for professionals involved in technology transfer, operating pilot plants, or laboratory personnel developing processes for eventual scale-up that I first published in 2002 [1] and that I expand upon in this chapter. This is a very subjective list, representing my own personal take on scale-up. Many of the activities or approaches I recommend are considered *de rigor* for companies involved in the GMP manufacture of pharmaceutical materials to comply with ICH guidelines, but even for small companies and start-ups, these practices often just make good sense and can be beneficial for long term safety and success.

## 21.5 THINGS TO DO DURING SCALE-UP

### 21.5.1 Make It a Team Effort

One thing that has helped me greatly in my career is establishing strong channels of communication with the many process development chemists with whom I have worked. I feel strongly about the important role that process engineering plays in process development. There have been those few inexperienced chemists who tended to practice "over the wall" chemistry—that is they would develop a new process and then toss it "over the wall" to the engineering/pilot plant group and expect to never see it again.

We know this cannot happen in the real world. It is only through close cooperation between the various disciplines that a successful, scaleable process can be obtained. The best process chemists understand this. While the chemist has a deeper understanding of the effects of the various process variables on product quality, the engineer may have a better appreciation for the physical limitations of pilot equipment, or in short, what operations can or cannot be conducted safely in a pilot or commercial plant. Each has his or her own set of priorities, and they must be communicated clearly to each other, and the earlier in the development cycle, the better.

For example, the engineer can inform the chemist that his or her choice of solvents will not be acceptable in the plant, or that certain laboratory operations such as evaporating to dryness cannot be scaled up. Likewise, the chemist can communicate the need for tight temperature control during a certain critical step, or the need for a certain degree of agitation, and so on.

Engineers bring many valuable skills to the table to assess and improve the scalability of novel processes. Some of the areas in which process engineers can make important contributions to the development effort are as follows:

- Identify and determine limits for critical process parameters
- Identify process hazards and conduct the necessary hazards analysis, including isothermal and adiabatic calorimetry and explosivity studies.
- Compare projected commercial costs of alternate routes (COGS)
- Complete mixing and heat transfer calculations for scale-up and assist with "scale-down" experimental design
- Conduct reactor design calculations
- Size and specify equipment
- Complete material and energy balances
- Investigate opportunities for continuous or other alternate processing

However, as mentioned above, there are many simple experiments and measurements that fall under the category of process engineering that any laboratory scientist can carry out easily, such as solids drying studies; distillation stability studies; and simply measuring and recording operating pressures, temperatures, densities, and other physical

properties of the various process streams. This type of information will be a great aid in speeding scale-up.

### 21.5.2 Develop an Operating Philosophy

No matter how large or how small the facility is, it is very important to lay down some ground rules for the safe transfer and scale-up of laboratory processes to the kilo lab or pilot plant. For example, at one company, we made a key decision of not operating the new kilo-lab under cGMP. This eliminated the need for strict compliance to regulations imposed by outside agencies, streamlined scale-up, and allowed more operating flexibility. This did not mean, however, that we threw caution to the wind and worked haphazardly.

We established clear, strict requirements for all processes to be transferred to the kilo lab. With management support, we were able to adhere to these requirements even in the face of pressure to meet aggressive timelines. For example, we required a written batch record for all processes, and that the batch record be proven by using it to run a minimum of three laboratory-scale batches (see below). One of the three laboratory runs would typically serve as the raw material use test, conducted using the actual kilo-scale raw material lots.

We also called for strict cleaning and rinse-test protocols for all equipment to minimize the possibility of cross-contamination between batches. Another important requirement was the completion of a Haz-Op study, conducted by a team of at least three individuals representing the kilo-lab staff, process chemistry, and when possible a company safety officer.

Although it may appear that these requirements would hinder efficiency, it was not the case. Once it was clear that the rules would be strictly enforced, everyone on the development team adjusted his or her thinking accordingly with the end result that kilo lab experienced no serious accidents and virtually no failed batches over many years of operation.

### 21.5.3 Establish Use-and-Maintenance Files

Both good engineering practice and good common sense are required in a cGMP environment No matter how small the operation is, developing a sound recordkeeping system to capture how each piece of equipment in one's kilo lab or plant has been used and maintained, starting from the moment of installation, can pay big dividends in extending the life of the equipment, minimizing life cycle cost, and providing traceability for important clinical or preclinical materials.

Established companies will have detailed IQ–OQ (installation qualification and operational qualification) protocols and preventive maintenance (PM) systems. Smaller companies should, at a minimum, establish a logbook (a laboratory notebook works well) in which they can record manufacturer data and wiring and engineering diagrams, in addition to information about each batch of material processed, the results of cleaning operations or rinse tests, maintenance performed, calibrations or other measurements made such as heat transfer coefficients, volume calibrations, and so on. Such records should be kept over the life of each reactor or mixing vessel, each filter or centrifuge, and even reusable transfer hoses and other portable components.

### 21.5.4 Establish a Sample Database

Another recordkeeping practice that will prove invaluable is maintaining a sample database in the kilo-lab or pilot plant. Keep a permanent record of each and every sample or process stream that is collected for analysis or observation during your operations. That includes any in-process batch samples, distillates, wet cakes, final products, and waste streams. Every sample should be given a unique sample number and the batch, time, date, amount, reason for its collection and any other important observations should be recorded. Larger companies may have a fully integrated digital laboratory information management system (LIMS) but for kilo-scale operations, any kind of logbook is sufficient. Provide columns to make sure that all the pertinent data are recorded.

In one kilo-lab, we used a laboratory notebook for the purpose, and simply assigned unique sequential numbers to all process and retain samples. We frequently needed to go back and reconfirm the identity of past samples for research or regulatory purposes, for conducting mass balances and the like, and the information we needed was readily available.

### 21.5.5 Collect Retain Samples

Along with a sample database, it is important to institute a retain sample system. Samples of all dried isolated intermediates and final products should be kept in appropriate sealed containers stored in a cool, dry, dark place, well organized, and readily accessible should the need arise. The exact sample size, storage container, and conditions will of course depend on the specifics of the material being stored, but the important things are that the containers be clearly, permanently labeled and that the storage system be carefully thought out and enable easy retrieval of samples when needed.

### 21.5.6 Fix the Process Before Scaling

This point goes hand in hand with developing a consistent operating philosophy. Last minute changes to a process being scaled up can lead to serious unexpected consequences, and possibly unsafe situations. It is important to minimize last minute changes by fixing the process well in advance of scale-up and ensure that laboratory demonstration runs of the actual final process have been conducted prior to scale-up.

The cases of processes that have failed due to on-the-fly changes in the plant are legion. One example that comes to

mind is a failed selective diastereomer crystallization that was "bumped" into a 12,000 L stainless steel reactor because the usual glass-lined reactor was occupied by another process. The expected enantiomeric enrichment did not occur and the batch failed miserably, most likely due to material surface effects or differences in the nature of mixing in the two reactors. This was a harmless enough—albeit tremendously expensive—lesson but last minute changes can, and often have led to the creation of very serious hazards.

### 21.5.7 Conduct a Haz-Op Review

There are two terms commonly heard in the chemical process industries, "Haz-An" (for hazards analysis) and "Haz-Op" (for hazards and operability study). The former is a detailed examination of a particular hazard, such as a potential decomposition reaction, in which one might conduct calorimetry studies to determine onset temperature, time to maximum rate, maximum adiabatic temperature rise, and so on. The Haz-Op, on the other hand, is a more general study conducted by a team in an attempt to identify all the potential hazards of a process prior to scale-up.

Most companies insist on some level of Haz-Op study before scaling up new processes, even to the kilo-scale, and of course a detailed study should be absolutely required for larger scale operations. The first step is assembling the team, which should consist of chemists and process and safety experts from within the company who are most familiar with the process and the plant. This team approach eliminates potential oversights by individuals working in isolation. The next step is the preparatory work and assembling the necessary documentation (batch record, plant P&ID's, process flow diagrams, etc.) to facilitate the study. And then finally there are the Haz-Op meetings themselves, wherein the team leader should encourage free expression of ideas and uninhibited "what-if" thinking in an effort to develop a list of potential dangers and "mal-operations" for each and every process step. Clearly documenting the findings and proceedings of the meetings is also a very important part of the exercise.

There is much excellent information on including Haz-Ops as part of a safety management program, and the reader is encouraged to take advantage of these and other resources [2, 3].

### 21.5.8 Quantify Reaction Energetics

Underestimating or failing to recognize the potential hazards of exothermic reactions is perhaps the single most common cause of harmful and destructive process industry accidents. One of the reasons for this is a failure to understand the very limited heat transfer (cooling) available in large chemical reactors, a consequence of the low surface area per unit volume.

Thus, an important part of safe reaction scale up should be calorimetry or similar studies designed to quantify the exotherm, identify the potential maximum rate of reaction, predict the adiabatic temperature rise, and so on. For companies that cannot conduct such studies in house, many safety laboratories offer these services on a contract basis. A number of innovative reaction classification systems have been proposed to help categorize the potential hazards of chemical reactions based on calorimetric parameters and to better ensure safe scale up [4, 5].

The same can be said for determining the explosion potential of dusts and powders, along with minimum ignition energy (MIE), limiting oxygen concentration (LOC) for ignition, maximum attainable pressure, shock sensitivity, and so on. Standard test methods exist for conducting and interpreting all these characteristics, and the information from these studies can help design safer procedures to prevent explosions and to engineer improved mitigative equipment [6].

Of course, engineering judgment and chemical wisdom must be applied to interpretation and use of the data obtained from such studies, as the data often do not tell the whole story. Gustin [7] reports the case of a nitration reaction that counterintuitively exploded after the reaction was completed and the reactor was being cooled. The reason appears to have been the crystallization of a highly nitrated shock-sensitive sodium salt that came out of solution upon cooling. A piece of this material may have collected on the impeller shaft, broken free and impacted the impeller or baffle resulting in the explosion. Calorimetry or other studies might not have predicted this event, but an examination of the chemistry by someone experienced with these compounds might have identified the potential for this compound to form. Then more exacting safety studies could have been conducted to determine the risk and potential consequences of this happening.

### 21.5.9 Create a Written Batch Record

Variously called a batch log sheet, batch ticket, or batch record, this is an approved document (either paper or electronic) to be filled out by the operating staff as the batch is conducted. The batch record is based on a detailed process description prepared by the project chemist or process engineer and formally approved by his or her direct supervisors or others as necessary. It is a step-by-step recipe sheet, if you will, with spaces for recording pertinent data such as raw materials charges, processing times, and temperatures, and so on, and with spaces for the initials or signatures of the individuals completing each task and checkers where necessary.

The batch record should be a controlled document. There is no need to point out the importance of ensuring that most current version of the record is in use, and that it is as free of errors as possible. The tremendous convenience and speed of

modern word processing has led to more than one pilot plant mishap due to careless cut-and-paste errors and poor proofreading. That is why a laboratory shake-down run is so important in ensuring the correctness of the batch record.

### 21.5.10 Understand the Raw Material Grades

Many common raw materials and chemical reagents are available from a variety of sources and in a variety of qualities, purities, or grades. By convention, some terminology has arisen around these various grades, such as reagent grade, technical grade, but the precise meaning of these terms is anything but consistent from manufacturer to manufacturer, and the global supply chain creates even more confusion.

What one company may call spectrophotometric grade, another may call reagent grade and vice versa. Many supply companies have devised their own systems of nomenclature and provide various proprietary grades or purity levels that are impossible to directly compare to those of other suppliers. That is why it is important to understand the critical quality attributes of the raw materials used in a process and ensure that the chosen supplier can consistently provide the quality needed. If there a particular impurity in a raw material that can adversely affect a reaction, then its effects must be quantified and the specification for that impurity must be set based on the resulting data.

Much laboratory work uses reagent grade solvents and materials, but beware that the commercial grades available at large-scale may not match the purity of many of these substances. It is wise to work with commercial grade materials as early in development as practical to better anticipate the results upon scale-up. This is also why it is so critical to conduct the laboratory-scale raw material use test prior to the first scale-up batch (see below).

Chemical purity is not the only characteristic to be concerned about. The physical form, such as particle size in the case of solids, can have a major effect on results of the process. A well-known example of this is the use of $K_2CO_3$ as an acid-sequestering agent in many alkylations and in other organic reactions. Moseley [8] tells a tale of woe about their experiences in scaling up just such a process, due to the fact that a granular form of the carbonate with relatively low specific surface area was used during some large-scale runs. Their problems were exacerbated by the fact the mixing conditions in the large-scale vessel were insufficient to suspend these granular solids and so the carbonate lay unmoving and inaccessible on the bottom of the reactor, a very common phenomenon in large vessels.

### 21.5.11 Conduct a Raw Material Use Test

It should be considered an absolute requirement that a laboratory-scale experiment be conducted, ideally following the written batch record, that uses the very same raw material lots or batches of intermediates that will be used in the scale-up campaign. This demonstration batch should be carried to completion; the product should be isolated and analyzed in full just as the pilot batch would be. The pilot batch should not proceed until all analytical results are reported and it has been demonstrated that the batch passes all specifications. In this manner, if and when there are quality or processing issues in the scale-up batch, the raw materials can for the most part be eliminated as a cause. This can save a great amount of work and head-scratching and can prevent an investigation of a problem from being focused in the wrong area.

### 21.5.12 Make the Most of the Opportunity

A tremendous amount of time, effort and money is expended in preparing for and conducting pilot-scale batches. These batches can consume alarming amounts of precious raw materials and labor. Consequently, in most cases only a limited number of pilot-scale batches can be conducted. That is why it is important to try to learn as much as possible from each batch. For example, a well planned sampling and analytical plan will allow you to complete a mass balance, identify unexpected side products and otherwise troubleshoot batches that have not gone as expected. Basically every process stream, including wasted streams, should be weighed and sampled. There may never be another opportunity to collect many of the samples generated in a pilot batch.

All observations should be carefully noted and retain samples of isolated intermediates and final products should be saved for future reference if necessary. Putting in a nutshell, one should make the best use of the opportunity to gather as much scale-up data as possible and clearly document the results of the batch in a comprehensive campaign report.

## 21.6 THINGS TO AVOID DURING SCALE-UP

### 21.6.1 Avoid Complexity

We have no doubt heard of the famous "KISS" principle. There is certainly much to be said for keeping it simple, particularly in chemical process development and scale-up. The less complexity, the less opportunity for processing errors, operator slips and unforeseen complications.

Commercial processes are carried out by a chemical operations staff who are well trained, but often not educated as chemists or engineers, and certainly not as familiar with the idiosyncrasies and hazards of new processes as their developers are. These operators will carry out their jobs only as well as their training, experience, and operating instructions allow them. A clearly written batch record is supremely important, and this is much more difficult to achieve if

a process is overly complex. A simple example would be making an extra effort in development to find a single solvent or mixture of solvents that can be used throughout the reaction, workup, and crystallization steps so as to eliminate the need for time-consuming and wasteful solvent switches between each operation.

Of course, most development chemists understand the importance of simplicity, not only for improved safety and efficiency but also for minimizing processing time, minimizing waste, and so on. However, it is not always possible to keep things simple when the process involves chemistry that requires sophisticated controls or specialized equipment such as hydrogenation reactions, nitrations, aminations, or other types of reactions that could potentially be hazardous. It is always an option to contract out these particular steps to manufacturers who have expertise in those types of reaction and the equipment to carry them out.

### 21.6.2 Avoid "All-in-and-Heat" Reactions

One of the most dangerous practices in chemical processing, and one that is frowned upon at all scales, is to charge all reactants to a batch vessel and then begin heating it up. The danger is that once the mixture reaches the onset temperature of reaction, and the reaction starts, there will be no way of controlling it. Many reactions are highly exothermic, and once they "kick-off" they will continue to heat themselves to higher and higher temperatures, possibly exceeding the boiling point of the mixture and erupting. The mixture could also begin to decompose at higher temperatures. Many times, the decomposition itself is self-accelerating and more exothermic than the process reaction. Explosive gases can be evolved and a highly energetic explosion could ensue.

Of course, when the chemistry is well understood and known to be safe, this type of all-in operation may be acceptable. But when scaling up new processes for the first time, it should be forbidden.

A number of factors make carrying out exothermic reactions at large scale much more dangerous than at laboratory scale. Of course, the consequences of a large explosion are more devastating than a small one, but the key difference at large scale is the limited heat transfer area characteristic of large reactors, and the long response time if cooling is suddenly required. It can take many hours to cool a very large chemical reactor, by which point it may be too late.

The recommended approach for scaling up exothermic reactions is to maintain some degree of control. The most common approach for this is to use a "controlled addition" scheme in which the nonreactive components of the batch are charged to the reactor, and then the reactive (controlling) reagent is slowly added with agitation, allowing the reaction to proceed at a controllable pace. In the event of a temperature excursion, addition of the reagent can quickly be stopped, halting the reaction.

It is important in this method to ensure that the reaction is in fact proceeding and that the reactive agent is being consumed as it is added. If, for some reason, this is not happening, the reaction "stalls" for instance, then the reagent will accumulate in the reactor and may suddenly react all at once, putting us back where we started. Many methods are available for monitoring the progress of a reaction, but the simplest is to monitor the batch temperature and ensure that the anticipated rise is observed.

### 21.6.3 Do Not Apply Heat Without Agitation

A former colleague of mine would attest to the practical nature of this advice. He was performing a toluene/aqueous extraction experiment at about 70°C in a round-bottom flask with a heating mantle. He stopped the agitator briefly to let the phases separate, collected his sample, and then restarted the agitator. The entire contents of the flask instantly erupted out the top of the reflux condenser. Luckily no one was hurt. We surmised that while the agitator was stopped, the glass surface must have exceeded the 85°C boiling point of the toluene–water azeotrope. As soon as the agitator was restarted, the mixture boiled violently.

In my opinion it is never acceptable to apply heat to a reactor without agitation. Heat transfer is severely limited in large reactors to begin with, and what little heat transfer does occur is highly dependent on the degree of agitation in the vessel and the convection that it creates.

In addition to the incidents such as the one described above, countless other undesirable effects can also result. Without agitation, there can be no accurate reading of the internal reactor temperature. Because the reactor wall temperature is quite often much hotter than the bulk batch temperature, product can easily become overheated and "baked" against the side of the vessel, which can lower yield and lead to dangerous degradation reactions. Temperature gradients created by insufficient agitation can result in poor reaction selectivity and out-of-spec products.

Countless cases of violent reactions and explosions have been attributed to "agitation issues" of one kind or another. For example, one incident occurred during a highly exothermic reaction between the sulfuric acid and an organic amine. This biphasic reaction was normally carried out by slow addition of the amine to the hot acid with vigorous agitation. One fateful day, at shift change, the agitator was inadvertently left off when amine addition was started. The amine pooled in the bottom of the reactor but did not react. Much later, the second shift noted that the agitator was off and proceeded to turn it on, at which point the reactor exploded as all materials reacted instantaneously. A neighborhood in Frankfurt, Germany was dusted with a yellow coating of *o*-nitroanisole in a similar incident that eventually resulted in the company going out of business.

### 21.6.4 Do Not Ignore Potential Decomposition Reactions

This recommendation goes hand in hand with Section 21.6.3. Not only must the necessary calorimetry be conducted on exothermic reactions but also the possibility of self-heating decomposition reactions must be considered. This may require additional testing, such as adiabatic reaction calorimetry (ARC). Such testing should be considered for all process streams if it is believed that the particular chemistry involved has the potential to create unstable decomposition products.

One of the difficulties is that these self-heating decomposition reactions may happen very slowly that they may not be identified in routine testing. Even below the onset temperature, exothermic reactions are still happening at some finite rate. In one case, a reactor exploded many hours after the reaction was completed, the services shut off and the reactor left to cool on its own. A previously unknown decomposition reaction was occurring so slowly that no one noticed the temperature rising in the reactor. Eventually the temperature reached the onset temperature and the self-accelerating reaction kicked in, resulting in an explosion (it is generally safer to cool a reactor to a safe temperature using the jacket rather than allow it to simply cool down on its own). Waste stills have been known to explode days after being charged with a waste stream that underwent a slow decomposition and unanticipated increase in temperature.

### 21.6.5 Avoid Adding Solid Reactants to Reacting Mixtures

Another common laboratory technique that is not easy to scale (without some advance planning) is the portion-wise addition of solid reagents to a reacting mixture. Laboratory scientists routinely use this technique to avoid the "all-in-and-heat" approach, but in the laboratory it is a simple matter to remove a glass stopper from the flask in a fume hood and add a small spatula full of the solid and close it back. This is repeated until the addition is complete.

There are a number of reasons that this becomes much more difficult at scale. First, it is most inadvisable to open the manway of a large reactor containing flammable solvents because an ignitable atmosphere may form as vapors exit the vessel or air enters it. This is especially true if the contents of the reactor are being heated. Second, it is quite possible that the reagent may react quickly, causing the eruption or ejection of material out of the manway, endangering the personnel (sadly, operators have died because of this very thing). Therefore, the solids addition must somehow be accomplished with the reactor sealed.

One possibility is to reconsider the order of addition. It is always much easier to charge solids to a reactor first, and then the solvents and liquid ingredients. Of course, changing the order of the addition may change the selectivity of the reaction, or worse, may remove an important component of exothermic control. Another possibility is to make a solution of the solid, which can be conveniently charged by pump or other methods, or even a slurry, although charging slurries at a consistent rate is somewhat more difficult than charging a solution.

Where modifying the process is not possible, number of solids charging apparati do exist that enable the controlled addition of solids to a reacting mixture. An excellent review of available options was recently published, which discusses the advantages and weaknesses of each approach for a number of given situations [9]. Many of these devices are also very helpful for improving the dissolution of hard-to-wet solids or solids that tend to float or form large lumps, which can become major processing issues in commercial-scale operations.

### 21.6.6 Avoid Evaporating to Dryness

Generally speaking, the common laboratory technique of evaporating a process stream to dryness by removing all solvent on a rotary evaporator or similar piece of equipment simply will not fly in pilot-scale equipment. First, toward the end of distillation, the liquid level will fall below the agitator (minimum stir volume) in most standard reactors. As discussed above, it is inadvisable to continue applying heat without adequate agitation.

One of the consequences of heating without agitation, or stripping to dryness, could be the decomposition of the product in contact with the hot reactor walls. This presents not only quality but also safety issues. When complete removal of the solvent is necessary so that a different solvent can be introduced for the next processing step, the standard approach is to conduct a "solvent exchange." In this operation, the solvent is first partially distilled down to a safe (but mixable) level; then the second solvent is added and distillation is continued. This process is repeated until the concentration of the first solvent is as low as required. Of course, the specifics of the operation and its success depend on the relative volatilities of the solvents and whether or not they form an azeotrope. It is also well known that the so-called constant volume solvent exchanges are much more efficient than the add-and-distill approach [10, 11].

### 21.6.7 Do Not Underestimate Processing Times at Scale

I have often said that one of the biggest surprises that an R&D chemist experiences when bringing a new process to the pilot plant for the first time is how long everything takes. My first scale-up campaign at a CMO was no exception.

I remember arriving early on the first day eager to get the process underway. Step 1, charging a major raw material, a solid, took the entire 8 h first shift. This included time for

completing the release paperwork, transporting the material from the warehouse, the operators suiting up, the laborious act of charging the material manually, and coffee breaks. Later in the process, a distillation step that we routinely accomplished in about 30 min in our kilo-lab took over 12 h, including heating up and cooling down the reactor. The final product isolation, which used a product centrifuge, required seven or eight separate centrifuge loads; the entire recovery operation took over 24 h. Again, this was something I was used to completing in 1 h, even at the pilot scale, where one filter load could accommodate the entire batch.

Extended processing times are a fact of life in plant-scale operations, but for the unprepared, it will be a test of their patience. More importantly, serious quality and safety issues might arise if the question of process stream stability has not been considered prior to the scale-up. As a case in point, Dunn [12] describes a deprotection step involving trofluoroacetic acid (TFA) that was subsequently distilled off. This technique was quite successful in the laboratory, but in the very first scale-up batch, that distillation step took many hours, and when it was completed only about 5% of the product remained! No one had recognized that the product was not stable in the presence of TFA at elevated temperature because the stripping only took a few minutes in a laboratory rotovap.

A simple stability experiment in which the product stream is cooked at distillation temperature for a time would have given the researchers a heads-up that there could be a problem. Every step of a new process should be considered from this perspective since even under the best of conditions, not withstanding equipment failures or scheduling delays, every operation will take much longer in the plant than in the laboratory or kilo-lab.

### 21.6.8 Do Not Ignore Plant-Scale Solvent Issues

Chemists often develop processes using their favorite solvents, those that provide solubility for a wide range of substances, or those that are most easily removed in distillation and drying. Unfortunately, some of these very solvents may need to be avoided in pilot or commercial operations due to safety concerns or environmental issues.

Hexane comes to mind as an excellent organic solvent for running many types of reactions and for crystallizing a broad range of organic compounds. However, with a flash point of only $-23^{\circ}C$, a relatively low enthalpy of vaporization, and very low conductivity (making it prone to electrostatic buildup), many processing plants will simply not allow it as a production solvent. It is also toxic, as are a number of other common organic solvents.

Ethyl ether, methylene chloride, chloroform, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), *n*-methyl pyrrolidone (NMP) are but a few of the solvents that have been widely used in industry for decades, but which suffer from either flammability and safety issues, high water solubility and the accompanying environmental concerns, toxicity or other reasons that make their large-scale use unfavorable, or in many cases prevented by law. There are also those solvents that, because of health concerns are not allowed by the FDA and other regulatory bodies to be present in the final formulation of human drug products, and this list of solvents is constantly evolving. Finally, there may be waste-disposal concerns for certain solvents in particular locales.

Thus, it is important for those working in process development to understand as early as possible what limitations on solvents they will have to deal with in their companies, or the plants or countries they will be operating in. Sometimes, it is not easy to find replacement solvents with a better safety profile, and the process may need to be entirely redesigned, but the earlier this is recognized the better.

### 21.6.9 Avoid Hot Filtration Operations

A common processing step is the "polish filtration," in which a final product solution is filtered through a small-pore cartridge filter or a filter coated with celite or other filter aid to remove any particulates or undissolved contaminants as a final polishing step. This is usually carried out just prior to isolation of a final product by crystallization.

At laboratory scale, this step is often ignored, but plant operators know that small amount of dust and dirt and other undissolved solids often wind up in a product batch after multiple processing steps, and that this material needs to be removed prior to crystallization. Unfortunately, the way many crystallization processes are designed, the product solution is supersaturated to help maximize crystal yield. Thus, the polish filtration step must be carried out at elevated temperatures to ensure that no product crystallizes out in the filter or the pipes connecting it.

This can present some difficulties and potentially unsafe situations on scale-up. In order to prevent material crystallizing in the filter, the filter and all lines leading to it must be heated, perhaps by steam tracing, which complicates the operation. If the temperature of the pipes falls too low, the lines and filter may become plugged with solids. Also the handling and transferring of heated flammable solvents is not a particularly safe practice.

For these reasons, it is best to avoid filtering heated, supersaturated solutions. The most obvious way to do this is to dilute the product stream so that it is not supersaturated at ambient temperature and then distill off the solvent prior to crystallization. This, of course, can be time-consuming and could potentially affect product quality in other ways, illustrating again that process scale-up always involves compromises and trade-offs, and that processing decisions must be made while keeping the whole process in mind.

### 21.6.10 Do Not Underestimate the Quench/Extraction Step

Most reactions carried out in organic solvents are conveniently "quenched" by adding an aqueous solution of an acid, base, buffer, or other quenching agent. This rapidly stops the reaction by neutralizing the reactive species, and via the phase separation step that follows, provides a convenient way to extract and remove unreacted starting materials, side products and other impurities from the reaction mixture. However, often this important step is taken for granted and simply tacked on at the end of a clever new synthesis with the attitude of "work up as usual." This is unfortunate because the quench and extraction (or "work-up") step is a source of countless problems during scale-up and as much care should go into the design of this step as goes into the chemistry that precedes it.

For one thing, the quench usually represents the highest volume step, and to maximize volumetric productivity, the workup should be designed to minimize the use of extract phase while still accomplishing the necessary goals. This also minimizes waste disposal. Also, the settling and phase separation part of the operation can take much longer than in the laboratory due to a number of factors, including finer dispersions and more of a tendency to emulsify due to the higher tip speeds and higher shear associated with commercial-scale impellers. Inexperienced operators may operate agitators at speeds much higher than necessary during extraction steps and create emulsions that can take many hours to separate.

There is also the issue of phase continuity. Every dispersion consists of a continuous phase and a dispersed phase. Depending on the relative ratios of the solvents, their surface tensions, densities and other factors, the aqueous phase may be dispersed in the organic, or the organic phase may be dispersed in the aqueous. These two systems can often show drastically different behavior, sometimes creating an intractable emulsion in one case and readily separating into two phases in the other. These differences should be studied in the laboratory in order to minimize difficulties on scale-up. This phenomenon is described in better detail in Atherton [13].

Unfortunately, emulsions are sometimes unavoidable in batch chemical scale-up, but an awareness of how easily a mixture can become emulsified and a familiarity with the ways to minimize or deal with emulsions will make the scale-up less problematic.

### 21.6.11 Avoid Routine Reliance on Flash Chromatography

Chromatographic separation techniques are important tools in process development, and in certain sectors of the industry, biomolecule and protein production, for example, they play a major role in commercial production. Certain specialized types of chromatography such as simulated moving bed (SMB) are also used in full-scale production of small molecule products for the separation of chemical enantiomers.

But then there is so-called "flash" chromatography, the purification of a product stream by means of a single pass through a packed silica-gel column, and then eluting out the various bands with solvents. This is a favorite technique of many laboratory chemists, especially early in development where the goal is to simply isolate a small amount of product for analysis and characterization. Unfortunately, this technique is not very amenable to scale up for commercialization.

This type of chromatography can use very large amounts of solvent. Solvents are generally responsible for the majority of the environmental impact of chemical processes in the pharma industry, and chromatography utilizes a disproportionately large amount of solvent per unit product. This solvent needs to be disposed of or recovered and purified for reuse. It is also difficult to design, manufacture and pack very large chromatography columns so that they will operate without short-cutting and backmixing. There will be higher pressure drops through larger columns, necessitating larger pumps, and the temperature and flow control becomes more difficult for very large columns.

For these reasons, it is best for the process developer to recognize that flash chromatography is generally a method for the laboratory only, and that a reliable, scaleable purification process, such as crystallization, will be much better for commercialization. There are numerous ways to approach this, either by crystallizing the product directly from a solvent or mixture of solvents or, if necessary, by forming a crystalline salt form of the molecule with an appropriate anion or cation.

### 21.6.12 Play It Safe

While safety always has to be the number one priority, what I specifically refer to here is minimizing the risk of losing all of your valuable raw materials or intermediates in a single batch, especially when scaling up for the first time. Avoid the temptation to go for the home run and convert all of that hard-earned feedstock to final product at once. No matter how careful you are, and how much time you spend going over the details of the process, there will always be unexpected occurrences the first time a new process is scaled up.

An instruction might be misinterpreted by an operator, processing steps will take longer than expected possibly resulting in product degradation, a key piece of equipment may not operate as anticipated. Better to play it safe by running two or more smaller batches to ensure that the program is not stopped in its tracks because all key intermediate or custom raw material is used up.

Running smaller batches has other advantages. There is improved heat transfer area per unit volume, and there will be fewer issues with mixing and chemical transfers, and so on if the scale-up factor is smaller. One group described scaling up a hydrogen-generating reaction, and their plans to dilute the

hydrogen in the off gas with nitrogen to keep it below its lower flammability limit. Halfway through the first batch an unexpected alarm went off, indicating that the liquid nitrogen tank that supplied the whole building was empty. They had completely drained it; to complete the campaign they split the remaining work into a number of smaller batches to eliminate this from recurring.

## 21.7 CONCLUSIONS AND FINAL THOUGHTS

It should be clear from the above that experience plays a major role in the speed and success of any scale-up campaign. There is also a tremendous amount of valuable published information about scale-up and process safety available and the process engineer should certainly make an effort to access it and learn from it. Although it is impossible to anticipate every possible mishap during first-time scale-ups, I hope that the above list of dos and don'ts will provide food for thought and a better appreciation for the fact that making cross-disciplinary communication and cooperation high priorities (i.e., keep it a team effort) will maximize your chances for success.

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