De Dietrich
PROCESS SYSTEMS

Addressing Process Scale-up Concerns in Chemical and Pharmaceutical Manufacturing

Introduction

With any successful manufacturing endeavor, eventually demand will exceed manufacturing capabilities. When this happens, scaling up from a laboratory or pilot plant is critical for meeting increased production demands. However, there are many changing variables that need to be considered when you are looking to scale-up a process. This paper is to provide a high-level overview of potential solutions to the issues that arise when scaling up and highlight some common processing concerns related to chemical/pharmaceutical processing. The data is very general and is not intended to be a full guideline. Formal scale-up should be done with involvement of chemists, engineers, and other personnel knowledgeable in the current manufacturing technology. Economic considerations are also touched on at the end.

For this discussion, we will use the example of a batch chemical process involving scale-up from a laboratory glass reactor arrangement (20-liter to 50-liter) up to a commercial glass-lined steel (GLS) reactor (100-gallon to 2000+ gallons) - figure 1.

Figure 1. Commercial glass-lined steel (GLS) reactor

Process Considerations

Lab to pilot plant to production… where you are at with your process will affect process scale-up. Is the process validated? Changes in the process due to not considering them in development could send you back to the beginning.

Again, for this exercise we are using a batch reactor system as the example. A partial list at the end of the section will raise other issues not covered and is not all encompassing (chemistry and processes do evolve). In our example, common differences between laboratory glass reactors and glass-lined steel reactors are as follows:

Vessel Configuration:

The two reactors can differ greatly in geometry. In the drawings below of typical reactors the length to diameter (L/D) ratio of the lab reactor is much larger than that of a GLS reactor (figure 2). Reasons for this are typically economics and restraints on agitator design. Most GLS reactors will have a length (straight side dimension) to inner vessel diameter ratio of 1:1 to 2:1. Also note that the bottom head is hemispherical on the glass unit vs. the dished GLS unit (figure 3).

From a process perspective, these differences will impact the ratio of heat transfer area to volume; in this case it will decrease, meaning slower heating and cooling, or larger temperature differences between utilities and product (and resulting higher wall temperature) to make up the difference.

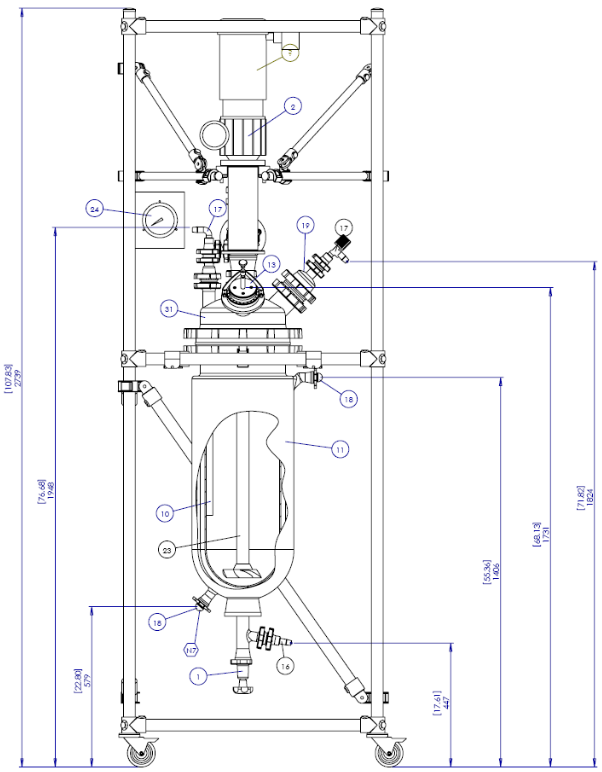

Figure 2. 50 liter (13 gallon) glass reactor

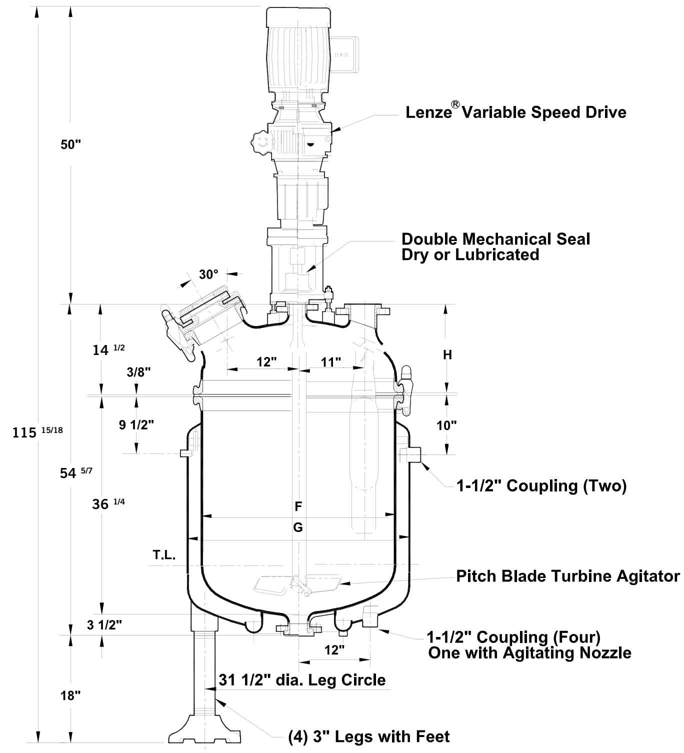

Figure 3. 100 gallon (378 liter) glass-lined steel reactor.

Heating/Cooling Arrangement:

In lab reactors, heating can be accomplished with several arrangements. The vessel diagrams on page 3 feature conventional jackets, but often a lab reactor will have a partial jacket (only on the bottom head), giving visibility to the cylindrical section above (figure 4) or an electric heating mantle (figure 5) without cooling.

The process implications with this during scale-up are typically improved heat transfer and faster ramp rates, so some adjustment of jacket temperatures may be required if this is adverse to the process. One potential negative is that the larger jacket area on the cylindrical portion of the vessel could "bake" materials onto the wall, again dependent upon the chemistry.

Figure 4. Partial jacket shows visible cylindrical section

Figure 5. Electric heating mantle on a spherical tank

Mixing:

Fluid mixing is different due to both impeller and vessel geometry, covered previously. With the smaller diameters of the lab reactors, the vessels are typically under-baffled, in that fluid flow patterns are "swirling" with minimal turbulence and batch turnover. With the higher L/D ratios, lab reactors will also have more stratification of suspensions. These issues are often addressed by adding additional flights of impellers or employing large anchor ("gate") style impellers. (figures 6,7,8).

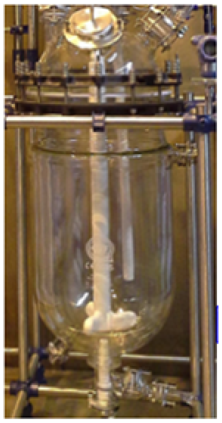

Figure 6. Glass Reactor (GLS) with single flight RBI Impeller

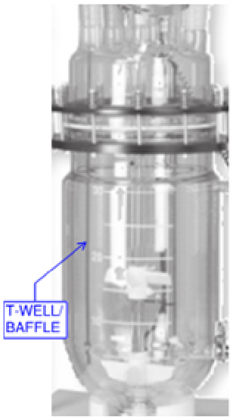

Figure 7. Glass Reactor (GLS) with dual flight PBT & VBT/ GATE Impeller

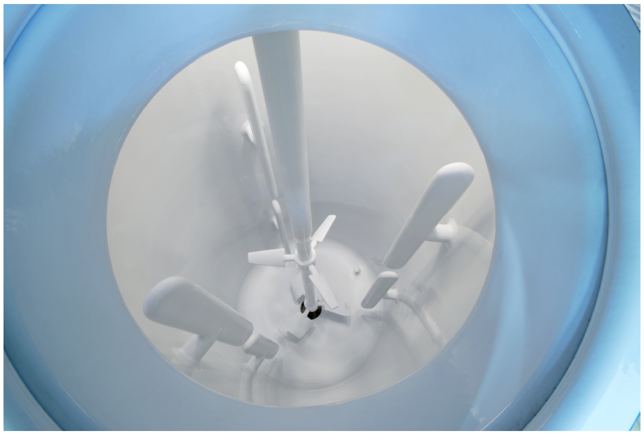

Figure 8. OptiMix GLS side wall baffles with dual flight hydrofoil & optifoil impeller

In the GLS reactor (figure 9), the turbulence / turnover of product is higher due to the additional baffles (insertion). This produces a more uniform suspension / mixing pattern for the entire volume of the vessel. The image and agitation simulation below illustrate this baffling difference, with the reactor containing a single insert baffle (thermowell) on the left, and reactor with three side-wall baffles on the right.

Figure 9. Glass Reactor (GLS) with single flight RBI Impeller

The forementioned type and size of impeller can be replicated in the scale-up due to fabrication differences with various materials of construction, but some impellers (primarily the gate style) are not realistic due to the manufacturing cost (larger access ports for insertion as well as a larger shaft and drive for high torque, i.e., mechanical strength). Ultimately, the flow and turnover will be the basis for the scale-up, and selection of impeller based upon specific

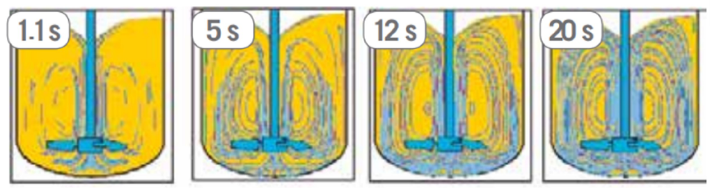

Figure 10. Mixing simulation for single insert baffle

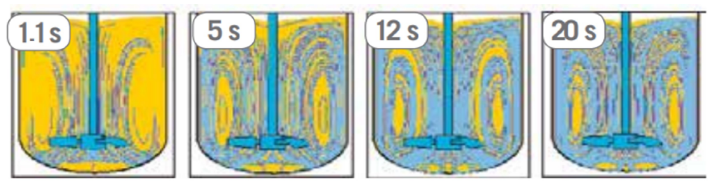

Figure 11. Mixing simulation for three (3) OptiMix (sidewall) baffles

process parameters (e.g., vertical / high shear blades for emulsion-gas dispersion, contoured blades for low level, multiple flights for higher flows - figures).

The process implications impacted by these differences are changes in reaction kinetics (good or bad!) and energy requirements. The decrease in L/D ratio on scale-up could decrease absorption rates.

Materials of Construction

The borosilicate glass lab reactor in our example is very common and useful to the process development, providing excellent visibility of the process, and a wide range of corrosion resistance to both high and low pH materials. Borosilicate glass is also a common material because components can be modified via a local glass blower to fit process modifications. However, it may bring limitations when replicating to the scale of larger GLS reactors.

The materials themselves, borosilicate glass and the glass for lining carbon steel (e.g., De Dietrich's 3009 glass), provide very similar corrosion resistance properties, which is good. However, noting any hazing of laboratory glass may be an indication that some corrosion has occurred, and for a scale-up with a long-expected campaign, it may be worth performing further corrosion testing.

Remember to not overlook the materials of the total reactor system. For example, a lab reactor's simple PTFE lip seals will be upsized to mechanical seals with ceramic seat, PTFE / Kalrez™ / graphite wear components. Special laboratory equipment may not be available in materials of construction for continuous installation / service, introducing new wetted materials to the process.

For our case, and even cases involving scaling up to alloy reactors, a big difference is the thermal conductivity of the glass and glass-lined steel. While both are "glass" with similar k values, the all-glass design is significantly thicker than the glass-lined steel reactor, impacting the overall heat transfer rate (overall heat transfer coefficient, U value).

Another issue impacting the heat transfer rate is the jacket film coefficient (another component of the U value). The glass constructed vessel with a glass jacket is restricted to very low-pressure rating and results in a very low flow rate, effectively laminar flow. Whereas in the GLS vessel, the jacket is commonly rated to 100+ psig, and available in several different configurations (half pipe, divided, conventional), allowing for a much higher fluid pressure and turbulent flow. The resulting U value is two to three times that of glass.

The general process implications are that scale-up will produce faster heating, cooling, and response. But remember, from the geometry section, the area to volume ratio will drop.

Material Handling & Containment

Much of the development work is done in contained lab hoods or downflow booths, with quantities of materials manually handled. Even a relatively small scale-up to a 50-gallon reactor located in a common production area greatly changes the perspective of these two issues.

The larger quantities of material also introduce issues downstream, including spill containment, waste handling (treatment / disposal), and emergency venting, containment and treatment.

It is your company's process, and its safe evaluation and plan are your company's responsibilities.

For our example, it is common that the charging of solids and sampling present major changes from those in the development scale. All effort is made to eliminate the need to open the process equipment for these, but sometimes it is not avoidable.

Contained sampling loops which also can be augmented with fragile instrumentation (pH probes) are viable for this. Solids charging while maintaining containment is also difficult. Equipment, such as DDPS's Powder Pump (figure 12) can assist in this. Docking valves (figure 13) can also serve this purpose.

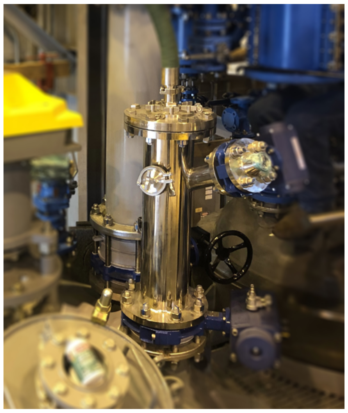

Figure 12. DDPS's Powder Pump

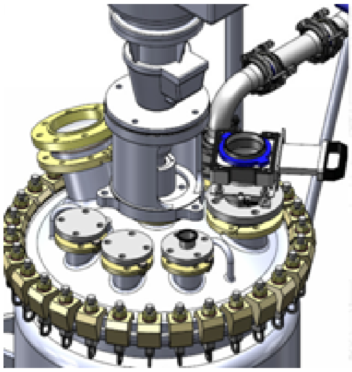

Figure 13. Docking valves

The process implications with these items are related to the question, "Does the sampling / measuring / monitoring method sufficiently replicate those in a lab hood set up?" An additional issue, somewhat more of a project management and engineering concern, is accounting for equipment typically omitted in the initial requirements as well as space requirement (relating the reactor top head / nozzle assignment).

Miscellaneous

The following items are issues to be considered, impacting physical / mechanical items, not directly related to process scaleup:

Electrical Rating

When moving from a lab hood or enclosed booth, and with larger quantities of volatile materials, it's likely that the electrical hazard classification for the area will change, impacting motors, instruments, and electrical devices. Laboratory analytical instruments may not be available with the required ratings, resulting in developing new control means.

Visibility

When it comes to vessel material of construction, glass is very nice for visual observation of the process, but per the items previously mentioned introduces some scale-up issues. But there are applications where visibility of the process is required for control (color / phase separation-detection). These can be potentially addressed with added instrumentation and through the incorporation of both glass and glass-lined steel components within the system (figure 14).

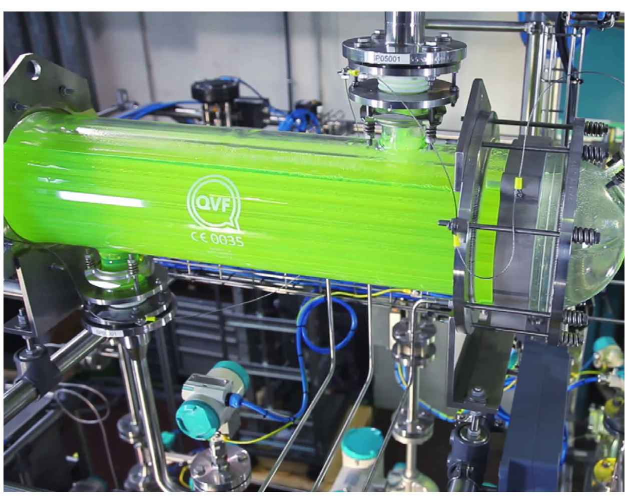

Figure 14. QVF borosilicate glass shell & tube condenser

Controls / Instrumentation

The complexity of the instrumentation, not only for analysis but for automation as well, may be required in scale-up due to manpower or access restrictions. The level of automation can be minor (involving a sub-portion of the process with some operator interaction required) to major (fully automated solutions - figure 15).

Figure 15. PLC control panel

Utilities

As the process scale increases, so will the utility requirements. Some of the items to keep in mind for evaluating economics / capabilities are:

- Does the existing utilities meet both the duty and parameter requirements (e.g., -60°C chilled fluids)
- Is there capacity for the existing needs and new / additional demand (subject to if units run concurrently or staggered)
- Does the new process require segregated utilities (e.g., independent vacuum system for recovery or incompatible adjacent processing for controlling)

Space Requirements

It is understood that scale-up means bigger, but this is not just related to key process equipment – everything gets bigger. This is hit upon briefly in the Material Handling section, related to difficulties in top head space for all the process and instrument connections. Scale-up piping is typically industrial ANSI flanged and insulated, with utility headers and emergency vent piping, which may have been relatively small and/or had different sizing requirements during the lab reactor phase.

Another spatial issue with scale-up is multi-floor layouts due to larger or taller equipment. A small list of some additional items to evaluate with this are:

- Loading / unloading of materials
- Valves accessibility or automation
- Gauges readability or transmitters
- Clearance for mobile equipment/ containers
- Secondary emergency release treatment and containment
- Maintenance windows / lifts
- and many more…

Commercial Considerations

Defining production requirements (short term / immediate vs. long term) provides an internal starting point that allows for fair comparison of multiple solutions. As with most evaluations, this will have variables that will need to be weighted regarding importance.

Budgetary / Project Estimate

A rough order of magnitude (> +/- 50%) project estimate is an initial jumping in point for a preliminary economic evaluation. Even with this rough calculation, definition of scope of supply is required to determine what is to be included. For example, there is a major difference between a modification of an existing reactor system vs. a greenfield development, in both cost and timeline to develop cost.

The extent of detail and design efforts put into the development of the project estimate can vary from basic / preliminary estimates with equipment / module vendors to capture core equipment cost to factor upon, up to a thorough detailed front-end loading (FEL) engineering effort, which can proceed up to a formal estimate and detailed engineering packet. These can be developed with internal resources or through contact engineering, or a combination of both.

FEL Stages

It is common industry practice to divide front-end-loading activities into three stages: FEL-1, FEL-2, and FEL-3 (table 1). For each stage, typical deliverables are listed below:

FEL-1	FEL-2	FEL-3
• Material balance • Energy balance • Project scope	• Preliminary equipment design • Preliminary layout • Preliminary schedule • Preliminary estimate	• Purchase-ready major equipment specifications • Definitive estimate • Project execution plan • Preliminary 3-D model • Electrical equipment list

Table 1. Front-end-loading activities stages

The following are some issues that can impact the cost associated with scale-up, which may have not been major issues associated with the lab reactor:

Engineering and Design

With most of the items above, development of flow diagrams, process calculations, general arrangements drawings, equipment and control specifications will need to be developed, versus "making it work" with existing pilot plants.

Site Development / Preparation / Permitting

This is a very broad category, spanning minor architectural / structural engineering review of a support to land acquisition, permitting, development, construction and / or commissioning of a new plant.

Installation

More than likely, the scale-up will require external industrial trades: riggers, millwrights, electricians, etc. versus DIY.

Operations & Maintenance Staff

Does current staff have the knowledge, tools, and availability required with the scale-up and existing demands?

Timeline

The time from project approval to production of commercial product will be longer than that of the lab reactor, but how much will depend upon the scope and process system qualification / validation (remember this is about a process "scale-up").

In-house vs. External (Contract)

The contracting of the scale-up / manufacturing to an outside firm may be the best solution to all the above. The burden of the process work is transferred and potentially some of the capital cost, subject to each contact.

The evaluation of all the process and commercial issues raised still need to be addressed, but the new items to be evaluated with in-house vs. contract manufacturing are:

- Confidence – How confident are you in the contractor's ability to meet your product / production requirements, equal to what you require internally.
- Cost – The cost may not necessarily be higher, perhaps lower if the contract manufacturer has existing built-in infrastructure. However, this may be negative possibly limiting long-term growth of your firm ("If not now, then when?" scenario).
- Combinations – As with most solutions, the best one is often a combination of initial brainstormed ideas. You may employ contract manufacturing and / or research while you develop an internal expansion. This could be driven by product / market timelines and / or personnel or physical limitations.

Summary

The scale-up of a chemical process is impacted by the physical changes of primary process equipment (reactors / mixers in this case) but also the auxiliary / support equipment and facilities to support them.

Key areas impacting processing scale-up include:

- Vessel Geometry & Jacket Design
- Mixing System Parameters
- Different Materials of Construction & Resulting U Values
- Availability / Design of Industrial Auxiliary Equipment vs. Laboratory Arrangements

Proper evaluation of the difference in scale through basic or front-end loading engineering / design helps minimize the production / process startup problems and economic implications.

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