Scaling Up Biotechnological Chemical Processes: A Better Alternative to the Traditional Develop-Then-Scale Model

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Introduction

Industrial biotechnologies often rely on chemistry that is developed in the lab. The typical timeline of a biotechnological innovation, much like other chemical innovation typically looks like *Fig. 1*. Unfortunately, many biotechnologies that look promising after their initial laboratory development fail to cross the barrier to industrial scale, or do so at conditions that do not make economic sense.

Process scaling is an art form that requires forethought, time, and experience. A thoroughly conducted scale-up phase is essential to the long-term success of a factory process. Unfortunately, it is a step that is too often neglected by developers of new technologies and project promoters alike as they underestimate the complexity, time, and expertise needed in the fast-moving world of business development. The pilot or scaling-up phase is often seen as a metaphorical roadblock to be overcome as fast as possible on the road to production and sales, rather than a very necessary and worthwhile step to ensure long-term viability, safety, and performance of the process. Putting more emphasis on this step would save time and money and give a better understanding of the safest ways to control the process. To have a successful scaling-up process, collaboration between laboratory scientists and process engineers is crucial. It is also necessary to prepare the migration of a process from lab to plant scale not once you're ready to do said scale-up, but right from the conception of the synthesis at the lab scale. It will be important to evaluate and analyze the parameters which, on a small scale, seem irrelevant but become very important and greatly influence the process on a large scale.

The main problem with the implementation of the process scaling is that typical academic training does not prepare researchers that develop new chemistry for the challenges of scale-up. Also, the budget and time needed are often underestimated which limits the scope and extent of the study of the possible process problems and particularities. Also, the commercial pressure under which scale-up typically happens often leaves little room for an adequate and realistic schedule. In fact, an emphasis must be given to the study of the reproducibility of the process. Conducting a large-scale synthesis successfully once or twice does not guarantee the success of all subsequent productions runs. Finally, process scaling is not a linear endeavour. Several factors, including thermodynamics and fluid dynamics, make the transition from the laboratory to the factory extremely complex.

Team

During the entire length of the process development, from the lab scale to the plant scale, scale-up should be kept in mind. The scaling process itself requires a multidisciplinary team. This team should be composed of chemists, laboratory technicians, engineers and operators who will be able to communicate all their observations of synthesis done at different scales. Chemists and laboratory technicians will be able to evaluate the process from a mechanistical perspective. They will be able to fully study the reaction mechanism at a molecular level and to determine which parameters are essential to the tracking of the process. Engineers and operators have a better understanding of processes at a macroscopic level. Engineers will be able to choose equipment composing the processes, to transpose the procedures from the laboratory to the plant as well as to evaluate all the important aspects of the process. Operators are a key to the success of the implementation of the process. Because they control and maintain all equipment used in the process, their advice will help design a more efficient and safe process. Everyone on the team is critical to the success of the scaling step. This process requires good communication between all parties as well as good team cohesion. Every tiny detail could save valuable time and resources while optimizing scale-up steps. Steps made in the laboratory should not be dealt separately from the plant work. These two stages are closely related and are of equal importance. Thus, the involvement of engineers and operators from the beginning of the laboratory work as well as the involvement of chemists and laboratory technicians in the stage of the plant scaling are two aspects that are essential to the success of the process.

Equipment Selection

Choosing equipment and designing the process when going from the lab to the pilot scale can be a perilous step. All laboratory glassware must be replaced by functional industrial equipment and most of the time, a directly equivalent option simply does not exist. The overall process must then be redesigned while keeping in mind the best suitable industrial equipment.

First, construction material is rarely a concern at lab scale. Glass is a material that is compatible with a very wide range of chemicals, is stable over a wide temperature range, and allows a good visual assessment of what's going on inside. In addition, glassware is affordable and widely available at small scale. On the other side, construction material for large vessel have a huge effect on its pricing. Glass is impossible to get at large scale, except by using glass lined steel. This, however, is expensive

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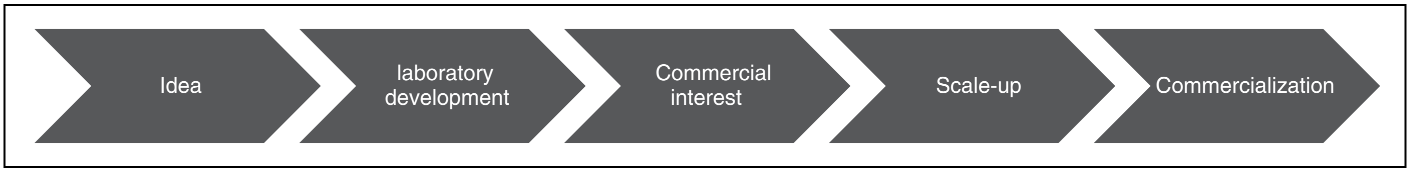

Fig. 1. Typical process development model.

and glass is fragile. The combination of materials limits the heating ramp, so glass lined steel is only used when there is no other choice available. The engineer will have to validate which available material is compatible with the specific conditions of the process. The evaluation must include temperature, pressure, pH, chemical compatibility, and so on. A wide variety of materials is available in the market, including high-density polyethylene (HDPE), carbon steel, stainless steel, and speciality alloys like Inconel or Hastelloy, to name a few examples. Obviously, this change of vessel material makes the process quite difficult to keep track of visually. Sight glass can be added to the vessel design but are quite limited in their usefulness. The engineer will have to push its study not only to vessel construction material itself, but also to all other components that are not used at laboratory scale. For example, material of valve seats, flanges and their gaskets, cover or manhole and others must be selected. All need to be compatible with the process. Adding to that, compressibility will be an important factor for sealing purpose, and resistance to friction will be important for any moving parts like valve components. For any stirred vessel, the way the shaft is sealed is a major point. Different technologies built from different materials are available and all have pros and cons. The most common technologies encountered are mechanical seals (simple or double) and packing. The team will have to add to the parameters the rotation speed to select the best component for the specific application.

Keeping mixing quality while scaling a process is a major concern. Mixing is a key factor in terms of kinetic, mass transfer and heat exchange. Some basic numbers can be obtained by calculation to get a rough evaluation of mixing but won't represent what happens at every single point of the vessel. So, this method doesn't allow the engineer to identify dead zones or actual exchange surface between two phases. Sometimes, it can be wise to resort to simulation by Computational Fluid Dynamic (CFD) when mixing is critical. It is possible in this way to optimize turbine type, geometry, position, quantity, and rotation speed. The engineer can also optimize the vessel geometry like the type of bottom (flat, conical, hemispherical) and the height to diameter ratio, the presence or not of baffles, its number and dimensions.

Most of the time, heating is involved in the process. Engineers must design a way to reproduce the same type of temperature gradient without being too harsh on the raw materials. Again, different systems are available and shall be selected considering the process needs and constraints. Laboratory hotplates or mantles are substituted with systems that use mostly recirculating hot water, steam, or oil. The team will have to choose between double wall jacket, half pipe coiled jacket, internal coil, or external heat exchangers. The team shall consider necessary heat flow, surface of exchange needed to reach this value, and sensitivity to temperature of the vessel content. Economics almost steer the final choice. Cost of acquisition is one thing, but efficiency, energy input (electrical, natural gas, propane, etc.), frequency of inspection and maintenance, and certification requirements are some of the aspects to consider when evaluating the overall economy of the final choice.

Everything that is used with an industrial vessel is very different than what is used at laboratory scale. For example, sampling is so quick and easy in a round-bottom flask using a disposable pipette, directly dipped into the medium. But it's quite different at industrial scale. The engineer may need to envision the use of a specialized apparatus designed specifically for this purpose if they need to take multiple samples along the process. Otherwise, it is very difficult, labor-intensive, and sometimes may represent safety issues to get a representative sample that is not contaminated with a certain amount of the last sample. Bad sampling can infer that a reaction is incomplete while in fact, it is already done. So, a bad sampling method could result in a huge waste of time and formation of side product unnecessarily.

Another example is regards handling of materials. Pumps and piping must be selected by the engineer for handling of liquids keeping in mind compatibility, operational parameters, and cost. Handling of liquids is probably the easiest part. Loading a vessel of solids can be a real challenge, especially when liquid is already loaded, and worst if the liquid has to be heated before getting the solid in. Opening a vessel containing a significant amount of liquid that is either toxic or flammable is unthinkable industrially from a safety point of view. The chemist who develops a molecule should keep in mind that addition order is an issue at larger scale. Screw conveyors are available industrially, but they are subject to clumping. From a scaling-up perspective, it could be preferable to inert the vessel atmosphere and load the solid first, melting it if possible, and then introduce the liquid, preheated if needed to ensure that stirrer will not get stuck.

Filtration is a fairly simple step at laboratory scale using an Erlenmeyer flask under vacuum combined with a Buchner funnel and a filter paper. Industrially, this filtration step often constitutes a bottleneck. The engineer will have to perform some testing to characterize the solid itself, the cake permeability and compressibility. He will also have to trace the washing curve. Afterward, the engineer will be able to select the better adapted technology, size and filter material and porosity to ensure that filtration will keep pace. Acquisition cost, expected maintenance, energy consumption, and waste treatment or recycling will also have to make part of the equation.

Drying is another concern at large scale. Rotary evaporator is typically used at the laboratory but doesn't exist at large scale. Again, engineers will have to characterize the solid, temperature needed, if vacuum is desirable, if the cake has to keep moving, and so on.

These are just a few examples of situations that need consideration and are part of the art of scaling-up. One strategy that can be used to help with this is the application of a scale-down model of the process. This method generally requires the miniaturization of existing equipment with similar proportions and geometries to what is expected to be used at full scale. For example, a 10-L glass reactor can be setup with the same geometrical proportions and impeller type as the 1,000-L reactor that is expected to be used for piloting. In this setup, you can also artificially slow heating and cooling operations to simulate full-scale conditions. It facilitates the development and optimization of a larger scale process since the results can be applied directly without any intermediate study. The scale-down method is very popular in the biopharmaceutical industry due to the complexity of the processes. With this model, it is possible to obtain important experimental data quickly and at low cost.

Raw Material Variability

Raw materials are usually chosen based on a few different criteria. While it could be mainly based on the monetary considerations, quality of the product, ease and reliability of supply, or simply the quality of the customer service could end up being the main determining factor influencing the selection of a specific supplier. However, an aspect that is widely neglected is the variability in raw materials. In fact, this factor alone can make the manufacturing process very cumbersome. The inconsistent composition of the raw material or the varying chemical/physical characteristics from lot to lot can lead to unexpected effects that may have consequences on the quality of the final product. These unanticipated situations are rarely fully investigated during lab-scale development because typical synthesis development is made with lab-quality materials obtained from suppliers that cater to the laboratory market. If the raw materials variability impact is not thoroughly investigated during the scale-up process, scientists could end up with a final product that does not correspond to their expected parameters or with productions that are inconsistent from batch to batch. These situations often require some investigation to find a way to save the product batch which can require a tremendous effort when done in a production setting.

Scientists must adapt the process to make it more reproducible and less susceptible to raw material variability. To better control the influence of the variability of raw materials, it is first necessary to test different lots of raw materials. It will be important to analyze every technical certificate in detail and identify characteristics that could vary considerably from batch to batch. If deemed useful, chemical characterization not included in the supplier-provided certificates should be done as well. Laboratory tests will therefore be important to analyze the influence of each characteristic on the overall process. A very common mistake in the industry lies in the absence of tests conducted before a change of raw materials supplier. This type of modification can lead to productions that do not comply with the required specifications. In the case of a chemical synthesis, a change of raw material can also be the origin of a lower reaction yield that could be avoided with an adjustment of the reagents, hence the importance of testing new materials at the lab scale before approving certain raw materials for production. This can be especially true of biobased raw materials as they are, by nature, more subject to variations in composition and quality. Anticipating which characteristics needs to be monitored upon delivery can save a lot of headaches and a well-crafted process can mitigate the effects of those variations.

Mixing

Mixing is an operation that requires a lot of attention when scaling up a process. This operation depends on several parameters and can be very difficult to scale up. In fact, a large number of processes are unsuccessful due to an inefficient or improper agitation. This is often caused by the fact that the notion of mixing is not frequently analyzed and optimized at a lab scale. We often use different types of impellers or agitators that are chosen more for their availability than for their suitability. Since they are not optimized for a specific application, researchers usually end up simply cranking up the agitation speed to make sure enough turbulence is created. However, at a plant scale, things are not that simple. The type of impellers to use must be carefully studied depending on the raw materials in the tank. Also, the geometry of the vessel, the need for baffles or even the power of the motor are all characteristics that need to be taken into consideration when scaling up a process.

The analysis of an adequate agitation system is a job that requires a lot of experimental data. It is possible to indicate the efficiency of the mixture using the Reynolds number (NRe), which incorporates, among other things, the viscosity and the density of the mixture as well as the speed and the diameter of the impeller. The Power number (NP) is also another factor that may be considered to relate the resistance force to the inertia force. These non-dimensional numbers define which type of mixer is the most appropriate and whether the presence of baffles is optimal. Also, the study of the energy dissipation transferred from the impeller to the fluid can help compare the efficacy of mixing between different scales. On the other hand, all these mathematical studies cannot define a mixing system adequately on their own. These approaches generally serve as a starting point to the analysis. Several empirical relationships make it possible to get a starting point with respect to several factors such as the positioning or the number of stirrers to be used. However, these relationships are not infallible. Another method to optimize the efficacy of mixing is to use software that could model the flow patterns. However, these computer programs are expensive and have a steep learning curve. Everything considered, whatever theoretical methods are being used to predict mixing, validation and adjustments will more than likely have to be made experimentally.

Reaction Scale-Up

Many processes consist in the production of a material through one or more chemical reactions. These syntheses require an exercise in scale-up adapted to the evaluation of all facets of the process. In fact, the evaluation of process parameters at a laboratory scale is very limited. Many side reactions only occur at intermediate scales where the main reaction can take longer and allow for those slower side reactions to play a larger role than at lab scale. These reactions may be at the origin of poor yield, contamination, or even dangerous side products. Also, another aspect that must not be neglected is the reaction thermodynamic aspect. An exothermic reaction is not always perceptible in the laboratory since it may seem negligible at lower volume where the system can transfer most of the energy to the environment easily. However, energy dissipation becomes worse with increasing scale. If the scaling process did not properly account for thermodynamic elements and no measures for controlling the exothermic reaction are taken, accidents of high severity are more likely to occur due to a runaway reaction that could have catastrophic results. This situation could also result in the creation of toxic and dangerous products and might cause the destruction of expensive equipment.

The success of a chemical reaction depends on several conditions and parameters that must be meticulously controlled. For example, according to Le Chatelier's principle, the temperature, the pressure or the concentration of a chemical are aspects that could influence the behavior of a reaction. Also, chemical reactions are frequently carried out in a biphasic environment. In these cases, mixing becomes even more important as the limiting factor becomes mass transfer between phases and a well-dispersed suspension will ensure faster reaction time. These are a few situations that illustrate the importance for chemical scientists to know which fundamental parameters to prioritize to ensure the success of the reaction.

Additionally, it will be important to determine the specifications that will be used to confirm that the reaction is complete. In fact, it will be useful to determine an optimal time frame of the different tests to be carried over the course of the reaction to be able to follow its evolution. Most reactions can be characterized by conducting a certain analytical test at different moments of the process. In some cases, it is also possible to monitor the progress of the reaction in real time with sensors (pH, viscosity, pressure, spectrophotometry, etc.) or even visual characteristics such as a change of color of the product.

It should also be kept in mind that a larger-scale reaction usually takes a longer time than at laboratory scale. This time constraint can also cause the reaction to require more than a workday. Therefore, it will be important to analyze in advance if it is possible to pause the reaction at certain moments without causing detriment to the process or if extended work shifts need to be planned.

Safety Concerns

Safety in the development of a process is *the* foremost aspect to prioritize. It is important, in a scale-up development, to anticipate all potentially dangerous situations and develop solutions in the event of an accident. However, the study of all potentially dangerous situations takes a lot of time and thinking. Lab-scale experimentations help determine a few dangerous elements in a process. However, a number of these critical situations are not visible at a small scale.

For example, the handling of hazardous raw materials in a plant is an aspect that needs a lot of planning and care. In a laboratory, since these materials are used in terms of grams or millilitres, safety measures are easier to handle by using, for example, a laboratory fume hood or other similar equipment. The same step needs more attention in a plant. The right equipment must be considered with all the safety equipment that could limit any exposure to the hazardous material. It will be important to select the appropriate material for each equipment to avoid any operational hazards.

One of the most frequent causes of accidents is the presence of exothermic reaction for which the proper mitigation measures were not in place. In the case of a reaction to be transposed to a large scale, it will be important to study the kinetic and thermal behavior of the process using a calorimeter. The calorimetric analysis will measure the energy produced or absorbed during the reaction under the actual conditions of the process. This study is mainly used for safety purpose because it allows adapting the equipment to the temperature regime of the reaction. It will therefore be possible to apply procedures that will ensure adequate control of the process which will avoid any disasters related to a runaway reaction. Calorimetric analysis also makes it possible to determine several other factors such as the presence of flammable gas or the amount of pressure generated during the reaction.

It will be essential to identify any safety issues preceding the scale-up. Every possible situation will have to be analyzed by a safety committee that will first make a preliminary assessment of the risks. Then, this study will be pushed further with a more advanced risk analysis (HAZOP, what if, etc.) that will assess all possible precarious situations. It will be possible to evaluate all the possible consequences and make a list of safeguards already installed and recommendations if necessary.

Quebec Bioeconomy

The province of Quebec is rich with natural resources to valorize: forests, minerals, aquatic resources, and fertile land. With the shift of the economy from traditional resources exploitation toward more sustainable models, many initiatives emerge. May it be for exploitation of lithium for electric cars, the development of new sustainable sources of energy like wind turbines, or the slowdown on the production of wood pulp for paper, each change toward the new economy provides its own set of opportunities for the province.

To help harness these opportunities, different tools putting emphasis on innovation are available to Quebec entrepreneurs. Several research and technology transfer organizations are available to support companies in their technological innovation project, such as College Centers for Technology Transfer (CCTTs), which are organizations linked to colleges and Cegeps. They aim to support companies in their technological development while providing them with technical support. Approximately fifty centers are in operation and each one of them has its own area of expertise, and many of them incorporate expertise relevant to biotechnologies. Several other research centers as well as Quebec universities are available to bring their touch of innovation. All these organizations are grouped under the banner of Quebecinnov, a network recognized by the Quebec government, which prioritizes access to innovation for various companies.

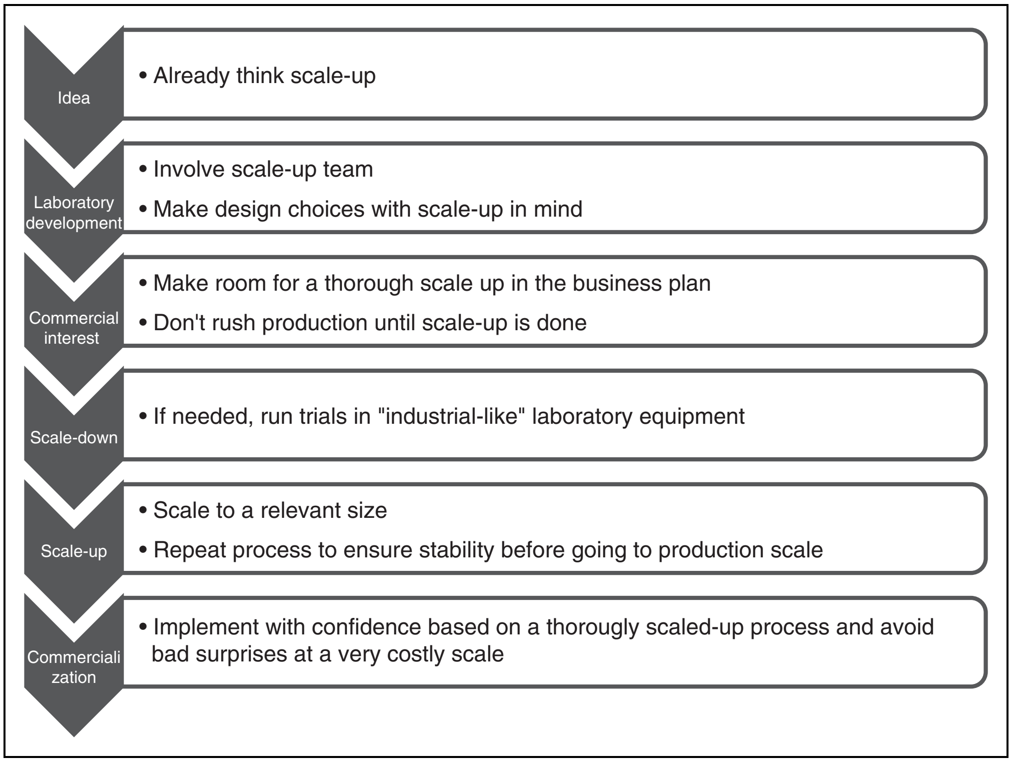

Fig. 2. Proposed process development model.

Innovation projects in Quebec can benefit from several types of funding depending on the nature of the project. The Ministry of Economy, Science and Innovation (MESI) reserves funding for any project prioritizing performance optimization and innovation within a company. The CRIBIQ (Quebec Consortium for industrial bioprocess research and innovation) provides financial support for all research projects in the field of bioprocesses as well as biosourced products. Finally, coming more specifically from the federal government, Natural Sciences and Engineering Research Council of Canada (NSERC) presents several funding options for different R&D projects that can be very advantageous for companies wishing to do a project in partnership with a college or university.

All in all, with its vast biomass availability and the multitude of technological development partners covering the whole spectrum from ideation to scale up regrouped within QuebecInnov, the province of Quebec is in a very welcoming place to develop the bioeconomy at the industrial scale.

Conclusion

Process scaling is an unavoidable step to move from the lab scale to the factory scale. It is essential that this step be thoroughly conducted but is too often neglected. This step requires close collaboration from engineers, chemists, lab technicians and operators to ensure a global understanding of the process both at the molecule level and at a much larger scale.

However, several obstacles occur when scaling. The choice of equipment is an arduous task that will define the basis of all processes. It will then be possible to take a critical look and evaluate any parameters that could be the source of difficult situations. The variability of the raw materials and the optimization of mixing are some examples of concepts that could be the reason behind a nonconforming production. Also, the safety of the process will have to be emphasized to avoid any dangerous situation especially if there is the presence of chemical reactions in the process, which can be, among other things, hazardously exothermic.

So, knowing the complexity of scaling up chemical processes, and knowing how crucial it is in the commercial success of industrial biotechnologies, is there a better model than the traditional ''develop-then-scale?'' We think that yes, there is, and it is very similar to what the field is already doing, with one fundamental difference, as shown in Fig. 2.

By thinking ahead, planning for, and conducting a thorough process scale-up, more biotechnologies will make it to market safely and become commercial successes, paving the way for the new bioeconomy.

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