Scale Up Safety

Stanford Environmental Health & Safety

Scale-up is an iterative process in which the size, number, or extent of a procedure is increased. It is commonly applied to chemical synthesis, in which a researcher will increase the quantity of the reagents in order to run a larger reaction (or "batch"), typically for the purpose of synthesizing more chemical product or demonstrating the effectiveness of a technique.

However, due to the inherent risk involved in increasing the scale of a chemical reaction, scale-up reactions account for several incidents and injuries every year. In both industry and academia, scale-up incidents have included fires, explosions, injuries, and even deaths.

Summary of Hazards

- More reagent = More energy - And therefore a greater risk of thermal runaway or fire.
- More solvent = Greater splash risk - More liquid leads to more difficult pouring and transfers, increasing the risk of splash. Scale up reactions, work-ups, and purification mixtures are also heavy and can easily fall.
- Reactions can behave differently at large scale, often due to changes in heat transfer, reagent addition method, or stirring.
- Risks increase when specialized scale-up equipment is not available, such as appropriately sized flasks, glassware with compatible fittings, and specialty chemical fume hoods (e.g., floor to ceiling fume hoods). Larger equipment is more difficult to work with and may not fit in a standard fume hood.

The Scale Up Variables section describes these variables that constitute the primary hazards of scale up in more detail.

Summary of Safety Actions

- **Never scale a reaction greater than three times (3x) the previous run.** The only changes that are made should be the quantity of reagents and the size of the equipment. Any changes in reagents, solvents, molar ratios, temperature, etc. should be tested on a small scale first.
- Conduct a Risk Assessment prior to work and reassess after each increase in scale. Follow other general safety procedures for chemical reactions, including selecting the least hazardous reagents feasible.
- Discuss your plans with your PI and **receive PI-approval prior to starting scale-up work.**
- If there are unexpected observations, scale down the reaction and work with your PI to troubleshoot the reaction before proceeding with scaling.
- Plan for scale-up reactions to take longer.
- Carefully monitor the internal reaction temperature and have a method to quickly cool or stop heating. Temperature control is critical to safe scale-up.
- Scale up reactions need continuous monitoring and should not be run unattended.
- The flask volume must be at least twice the volume of all added substances.

The safety actions summarized here are described in more detail in the "Plan" and "Do" sections.

Scale Up Variables

There are several primary variables that can affect the safety, and the success, of a scale up reaction. Your ability to control the variables is crucial to ensuring safe work and achievement of the desired products and yield. Consider how sensitive your reaction is to each variable when completing a risk assessment prior to beginning the scale-up process. Please note that this is not intended as an exhaustive list of factors affecting scale-up, just some of the most common and significant. Be sure to consider all aspects of your specific procedure.

Scale

The scale of a chemical reaction refers to the quantity of all reactants, catalysts, and solvents in the mixture.

The qualitative descriptions of reaction scales as small, medium, or large is dependent on the hazards of the reaction. A 10g Fischer esterification can reasonably be considered as a moderate scale, but 10g of a highly hazardous reagent, like trimethylsilyldiazomethane, is excessively large. In all cases, work at Stanford University must be done on "lab-scale".

Some general guidelines for reaction scales are:

Small: Reactant and solvent amounts: <1 gram of substrate, solvent < 25 mL.

Moderate: Reactant and solvent amounts: 1-15 grams of substrate, solvent 25 – 500 mL.

Large: Reactant and solvent amounts: >15 grams of substrate, solvent > 500 mL.

Other factors to consider when determining the appropriate scale are the hazards of the reactants, intermediates, solvents, and products. Particular care and attention should be given to pyrophoric reagents, highly acutely toxic chemicals (e.g., cyanides, organomercuries, HF, toxic gases, methyl halides), peroxides, high-energy bonds/configurations (e.g., strained rings, carbon:nitrogen < 3).

Discuss the maximum scale acceptable to your PI and document their approval.

A representative lab group in the Stanford Chemistry department uses the following triggers to identify reactions that require extra scrutiny, safety controls, and PI approval:

1. Pressures > 1.1 atm in a glass apparatus; > 100 psi in a custom metal reactor
2. Volumes > 1L
3. > 500mL of a Flammable 3 or 4 material
4. > 1L of a Flammable 2 material
5. > 0.1g of a Physical Hazard 4 material
6. > 0.5g of a Physical Hazard 3 material
7. > 0.1g of a Health Hazard 4 material
8. > 50mL or > 50g of any Health Hazard 3 material

Time

The bigger the reaction, the longer the setup, run, and workup of the reaction will take. Allot extra time for the experiment, and do not try to rush the reaction. Cooling or warming a reaction will take longer. Quenching or passivation of reactive or energetic reagents will take longer.

Temperature

Temperature control is critical for safely performing scale-up reactions. Remember reaction kinetics: as the temperature increases, so will the reaction rate and therefore produce more heat (if it is an exothermic reaction). This additional heat can cause a positive feedback loop and cause a reaction to spiral out of control, often referred to as a "runaway reaction". Loss of temperature control can have devastating results. Additionally, loss of temperature control can alter the thermodynamics and cause side-products to form, which may be unstable. Importantly, heat dissipation is not linear because the surface area of the container increases by r^2 but volume, and therefore thermal energy, increases by r^3.

- Use a thermocouple probe or thermometer to monitor the internal reaction temperature, which can differ significantly from the temperature of the oil bath outside of the reaction vessel.
- If heat generated from reaction is not controllable using standard methods, do not scale up further.
- Determine if the heating or cooling method you have chosen is sufficient for the scale you will be working with. Have a backup plan in case it fails.

Personnel

The personnel running and monitoring a reaction are often one of the most important variables. Consider the following when considering the risk of a scale-up reaction:

- Training / experience
- Multiple people monitoring / adjusting one reaction (careful note taking, communication).
- Anthropomorphic factors (size, strength, fit of the equipment to the researcher)

Environmental/Utilities Factors

Stanford's facilities are exceptionally well-maintained, but unpredictable events can occur at any time. Earthquakes, power outages, exhaust fan outages, and process cooling water outages have all occurred at Stanford and their timing is unpredictable. While these factors can influence any scientific experiment, the risks of these events during a scale up reaction are significantly greater than in small scale work. Therefore, scale up reactions should be continuously monitored by trained and knowledgeable researchers. Do not leave scale up reactions unattended unless there is an emergency that requires evacuation of the building.

Stirring

As reaction mixtures get larger, the amount of solvent and reagents gets heavier and harder to stir, particularly with a magnetic stir bar. Consistent stirring is crucial to heat dissipation and preventing hot spots, which in turn can prevent the formation of energetic or hazardous intermediates/side products.

Use overhead stirrers for consistent stirring of larger reactions to prevent hot spots. Magnetic stir bars do not mix large, thick mixtures well, and overhead stirring is more consistent when scaling up from one level to the next.

Equipment

With increased reaction scale, the type and set-up of your equipment will need to evolve. Choosing the right equipment for reaction scale-up can make a major impact on the efficiency and safety of the reaction to be performed. Common equipment considerations include:

Glassware

- The volume of the vessel should be ***at least*** **twice the volume of all added substances** (including quenching material). Leave enough headspace in the event the reaction gets out of control.
- Practice with the glassware and non-hazardous reagents (e.g., water, compressed air, table salt). Large glassware is more difficult to manipulate, transfers take longer, they are heavier, more awkward, and may need additional clamps (i.e., > 1 clamp per apparatus). They also need more room in the fume hood and hood housekeeping is even more important. Consequently, the risks of splash, spill, and ergonomic injuries are increased.
- Use wide mouth glassware to facilitate entry and removal of materials along with good venting if emergency arises (massive gas evolution).
- Purchase the appropriate glassware and equipment and avoid jury-rigged set-ups with repurposed glassware.

Heating

- Larger chemical volumes take longer to heat.
- Oil baths have limited volume capacity and can lead to spills. Consider using heating mantles that are appropriately sized for the glassware.
- The temperature of the heating apparatus may not be the same temperature as inside the reaction. Insert a thermometer or thermocouple into the reaction milieu.
- Larger chemical volumes also carry more total heat and larger/longer reflux condensers are necessary.
- Use lab jacks to elevate vessel heat sources so that they can be removed quickly if thermal runaway occurs.

Cooling

- Larger volumes of chemicals can take longer to cool and can rapidly consume the cooling agent (e.g., ice, dry ice, liquid nitrogen). Carefully monitor the temperature inside the reaction and monitor the rate of consumption of the cooling agent.
- Ensure that a cooling bath large enough to accommodate the glassware is available. It should be easy to add more cooling agent without moving or otherwise manipulating the reaction setup.

Adapters

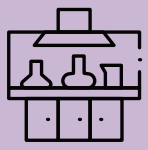
Avoid using adapters to make incompatible glassware connect to incompatible glassware fittings, which make equipment taller and may serve as another point of failure. Instead purchase glassware with compatible fittings.

Gas inlet / outlet

Avoid needle use for gas in-letting/out-letting on scale up reactions. This leads to excessive pressure increases. Rather, utilize gas inlet (or vacuum) adapters for gas lines. Adapters allow for better gas flow and venting if gas evolution increases rapidly.

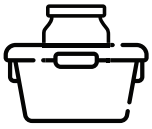
Weight of equipment

- Larger equipment and chemical quantities can significantly increase the weight.
- Practice pouring and other operations (e.g., shaking a separatory funnel) with water first to ensure that you're able to control the heavier glassware.
- Use additional clamps and cork rings (as appropriate) to keep glassware in place.



Fit inside of chemical fume hood

- A lab jack, heating or cooling bath, large flask, and a reflux condenser used for scale up can easily reach the top of the chemical fume hood, which can impair your ability to manipulate glassware or affect airflow.
- Practice assembling empty glassware first to determine if it fits well in the hood.
- Seek out alternative chemical fume hoods for large apparatus, including floor-mounted (also called "walk-in") fume hoods.
  - Never walk into a fume hood!



Secondary containment

- Even with careful planning, unexpected mishaps can occur. By planning ahead and installing secondary containment around scale-up reactions, the impact of a spill can be minimized.
- Ensure secondary containers are compatible with the chemicals used in the reaction and with the heating/cooling equipment and the temperatures they operate at.

PLAN

Risk Assessment

Carefully plan your scale-up reaction before beginning, even if the reaction has been performed on a smaller scale. A vital first step is to conduct a Risk Assessment, in which you gather information on the hazards of the chemicals and reaction parameters, determine a procedure, select appropriate personal protective equipment (PPE), consider what can go wrong, and discuss the plans with co-workers and your PI/lab supervisor.

The risk assessment needs to consider how sensitive the reaction is to key variables, and also the sensitivity of equipment used to monitor the variables. Use the Risk Assessment Tool to identify the hazards, determine appropriate PPE, plan the experiment, and consider the risk of the work. Key variables are discussed in detail below - review and understand the variables before performing the risk assessment.

Review the literature to plan the reaction. If the reaction you're planning has not been published, consider "reaction analogy" in which the same functional group change is made in the presence of similar functional groups. This strategy can identify several methods and allow a researcher to find the best method based on successes and challenges reported in the literature.

A key step in risk assessment is also to consider alternative methods. If a large quantity of product is needed, consider working with a Contract Research Organization (CRO) to perform the scale-up, either of the whole reaction scheme or of initial steps with the largest quantities.

PPE

As the scale of your experiment increases, your personal protective equipment (PPE) may also need to "scale-up" as well. Splashes and spills may be more likely or have a higher severity. Upgraded PPE may include a face shield with goggles, a chemical splash apron, and thicker chemical-resistant gloves. Review your lab's PPE Assessment Tool for further information on PPE selection.

DO

Risk Assessment

In addition to the procedural plan and risk reduction actions identified in the risk assessment, the following general checklist can be used to guide your scale up work:

Prepare

- Put on identified PPE (at minimum appropriate street clothes, lab coat, safety glasses, and chemical-resistant gloves).
- Select a day and time that allows you to attend the reaction at all times. If the reaction proceeds for a very long period of time, consult with your PI and co-workers to institute shifts to allow for continuous monitoring.
- Clean the fume hood and clear out any unnecessary chemicals, combustible materials, or equipment.

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- The rack (or “monkey bars”) may need to be reconfigured for larger glassware and equipment.
- Inspect all equipment and glassware. Ensure electrical cords are intact and glassware is free of defects and star-cracks.
- Select glassware that is at minimum twice the volume (2x) of all added substances, including quenching reagents.
- As needed, dry glassware, syringes, cannula, and solvents.
  - When anhydrous conditions are needed, consider using molecular sieves with new solvent containers or solvent column systems instead of distillation.
  - Dry glassware in an oven overnight rather than flame-drying.
- Pre-assemble all glassware and equipment in the hood to confirm the fit and security.
- Identify a buddy who will be present in the lab with you during your work. Inform them of the hazards and any emergency response instructions.
- Identify all the location and condition of all safety equipment that may be necessary. Ensure there is a clear path from the work area to the safety shower/eyewash. Consider temporarily bringing the appropriate fire extinguisher to the work area. Notify co-workers of any relocated equipment.

Run the Reaction

- Clear the fume hood of any unnecessary items, flammable liquids, and combustible materials.
- Post a sign on the fume hood sash with information about the reaction.
- Weigh and transfer chemicals in the hood. If a chemical cannot be weighed in the hood, use the tare method in which a vessel is weighed, filled in the hood and capped, and weighed again. Repeat until the desired amount of chemical is in the container.
- Carefully observe the rate of addition of chemicals, the internal temperature of the reaction, and the heating or cooling apparatus.
- Monitor the reaction to determine progress.
- TLC samples can be difficult to obtain from large flasks, two potential methods are:
  1. Use a long Pasteur pipette without a bulb to get a small aliquot. Add it to a vial and dilute with solvent, then spot the TLC plate as usual.
  2. For anhydrous reactions, use a dry long needle and syringe. Draw up a very small aliquot and add it to a small flask with solvent and quenching agent. Spot the TLC plate as usual from the organic layer.
- Allow the reaction to warm/cool to room temperature (as appropriate) prior to quenching. Add quenching agent slowly with good stirring.
- Allow extra time for the quenching process.
- Gather glassware for the work-up that is also twice the volume of all added substances.
- Check the clamps and rings are sturdy enough to hold the separation funnel or other equipment.
- Clear the fume hood of used glassware and other unnecessary items. You will need plenty of space for the large glassware for work-up and purification.
- Consider ways to simplify the purification process

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1. Continue washing the organic layer with aqueous solutions if that removes impurities.
2. Add activated carbon.
3. Recrystallize or distill.
4. Run a short column with a small amount of silica to reduce impurities that run well before the product or that stick to the silica. This can allow a shorter column for purification with less solvent use.

- Finally, clean all glassware and equipment and dispose of hazardous waste in appropriate containers marked with hazardous waste tags.

STUDY & ASSESS

Record your observations from all phases of the experiment, including the planning, equipment set-up, reagent addition, reaction progress, quench, purification, and clean-up. Note anything that was unexpected or required problem-solving in the moment. Discuss these observations with co-workers and your PI and determine if the reaction is safe and feasible to continue scaling up further or if the maximum scale has already been identified.

Acknowledgements & References

This document has been adapted from Scale-Up Reaction Safety with permission from the University of Illinois University Urbana-Champaign, Division of Research Safety.

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