



## Avoiding safety problems when scaling up a process from the laboratory to manufacturing-scale reactors

Many chemists and engineers face the challenge of establishing effective safety and process envelopes for manufacturing, based solely on information derived from the laboratory.

This critical transition demands both a broad perspective of the entire process and rigorous attention to detail. Getting it wrong can have significant penalties in terms of safety, time, cost and quality.

I recently experienced just such a problem, which typified the potential impact on safety and time that can occur during scale-up from the laboratory to manufacturing.

We transferred a 6-step process from the laboratory. The process had already successfully run at one litre scale, and was to be scaled-up to 1000 litres in the manufacturing facility.

All was well until step four, when the key reagent was added. This had a reaction heat of 250 Kj/mol, a molecular weight of 85 Kj/mol and a density of 0.8 Kg/litre. Based on the literature, the development team knew that the process could evolve hydrogen during the reagent addition phase (2 litres/mol of reagent) but this had not been observed under lab conditions.

The process was duly released to manufacturing and the addition of the reagent was carried out under a standard scale-up calculation method. This method defined that, for the given scale, the laboratory addition rate should be reduced by a factor of three resulting in an addition time on plant of 90 minutes which should ensure that the resulting exotherm could be controlled and that the reaction would perform correctly.

However, the team observed significant hydrogen evolution during the addition and the nitrogen inertisation was increased to the maximum rate of 800 litres/minute. Shortly thereafter, an alarm was received from the bulk nitrogen storage tank and the chemical engineering team went to investigate.

The team identified that the nitrogen volume for the remainder of the manufacturing facility was falling rapidly. They quickly reviewed the processes that were running at the time in manufacturing, identified this particular reaction as the source of excessive nitrogen consumption and shut the process down immediately. They subsequently calculated that the reaction was evolving over 1000 litres of hydrogen during the period of addition.

A detailed review of the process indicated that the required 1% maximum safety level for hydrogen in the headspace of the vessel would require that the hydrogen evolution remain below 8 litres/minute. This low rate would ensure compliance with the Lower Explosive Limit (LEL) and mandated safety factor of 25%. The LEL for hydrogen is 4%. In the 1,000-litre reactor at the given addition rate the reaction evolved over 11 litres/minute of hydrogen.

To enable the reaction to be performed safely and successfully, the reactor size was scaled down, so that the correct addition rate could be achieved (based upon inertisation). Six batches had to be run in a 160-litre reactor to ensure that the maximum hydrogen evolution would not exceed the critical capacity of the nitrogen plant. The total hydrogen evolution on the scaled down process was 160 litres per batch and this resulted in an addition time of 25 minutes to keep below LEL of 8 litres/minute of hydrogen evolution.

In the end, the solution to this problem resulted in a significantly longer total campaign time and subsequent commercial penalties due to late delivery of the finished product. However, the lessons we learned were invaluable:

1. It is generally true that for large campaigns, larger vessels have less overall addition times, but only if they are limited by heat transfer.
2. This experience greatly improved our understanding of the impact of gas evolution as scale increases. Following this situation, we incorporated gas measurement equipment in the reaction vent of our reaction calorimeter to actually measure real flammable gas evolution from reactions prior to scale up. Today, modern techniques such as micro reactors coupled with in-silico modelling programmes can very quickly enable scale-up effects to be quantified and understood at very low risk.
3. We experienced firsthand the value of a concept we call right-to-left thinking (downstream-to-upstream and vice versa). In this case, the process would have improved exponentially had both the manufacturing team and the laboratory development team possessed an in-depth understanding of the manufacturing plant's capabilities. However, neither the lab chemists nor the operational team in the manufacturing facility had understood the true envelope of the inertisation system, which led to the difficulties described above.

In the transition from laboratory to manufacturing, the ability to understand and characterize potential problems - before they become problems - ensures superior safety as well as realistic and achievable commercial commitments. Benefits can be immense.

For example, consider the benefit achieved when the collective team consider ways to shorten the time needed to scale up a process and also provide greater assurance of safety and quality through:

- Cooling and inertisation capacity;
- Surface-to-volume ratios as the reactor scale increases; and
- Techniques like reaction simulation.

Many processes will perform differently if all technical staff involved in developing, scaling up and manufacturing processes possess a comprehensive understanding of manufacturing plant operational parameters. This broad perspective from team members at both ends of the process can tremendously alleviate the potential for safety, time, cost and quality penalties. In my experience, the time to develop this broad understanding is a highly worthwhile investment.

Remember, very rarely do things improve on scale-up.

## About This Article

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He has worked for a number of Engineering Design Organisations and latterly in his career has held senior positions within a number of Fine Chemical and Pharmaceutical Organisations including SmithKline Beecham and Sigma-Aldrich.

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