Learn Chemistry

Chemistry: Idea to Market

Scale Up and Manufacture

Developed by Dr. Samantha Pugh, Dr. Stephen Maw and Dr. Patrick McGowan, University of Leeds

This resource was produced as part of the National HE STEM Programme

National HE STEM Programme

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www.rsc.org/learn-chemistry

Registered Charity Number 207890

Scale up and Manufacture

This handout is based on information presented by Lyn Powell (AstraZeneca) and Nigel Corns (Vivimed) at the University of Leeds on 24 January 2012 and 17 April 2012 respectively

The straightforward message from this session is that you cannot simply multiply up what you've done in the lab and repeat on an industrial scale. There are unavoidable consequences of an increase in scale (e.g. reduction in surface area to volume ratio) and what may seem insignificant in the lab (e.g. a bit of foam) may be significant at scale (the bit of foam now has its own structure and impedes the addition of other materials). This handout aims to give you a brief summary of some of the major considerations when moving from the lab to a larger scale. Given the vastness of the topic (e.g. you can do an MSc in Fine Chemical and Pharmaceutical Synthesis, i.e. there is sufficient depth and complexity with this topic that you can do a higher degree in part of it) this can only be a brief introduction.

What are you looking for in a process synthesis?

1. Cheap, readily available, stable, non-hazardous raw materials

Catalogue Chemicals alone are no use for an industrial scale reaction. You need materials that are available in bulk, are stable enough to be easily transported and/or remain in the reaction mixture until the desired reaction temperature. Given that on an industrial scale reactions take longer to heat you need to ensure any raw materials are sufficiently heat stable. As with any business cost is an issue. Another question that needs asking is 'Are the Chemicals registered with REACH?' If not then further expense will ensue

'Non-hazardous' covers a range of potential difficulties.

If toxic then there is the additional cost of safe handling and use:

- appropriate storage facilities and security measures when not in use
- plant design to ensure containment of material whether used as desired or if spilled – have contingency plans to deal with any spillages
- monitoring of atmosphere and health of operators.
- operator training to handle equipment and materials safely.
- pro-active testing of equipment to ensure operating safely.
- record keeping.
- decontamination procedures

For the pharmaceutical processes Potential Genotoxic Impurities (PGIs) take on an additional importance (and cost) as the end product is designed to be ingested, often daily by people. So there is a duty not only to production staff but also the end user. PGIs are dealt with under 'Minimise impurities' in the next session.

Avoid flammable liquids. A Flammable Liquid is a liquid with a flashpoint of 55°C or less - or a liquid with a flashpoint >55°C that is handled above its flashpoint temp. If you use a flammable liquid on greater than lab scale, by law all your plant has to 'flameproof'. Everything from plug sockets, lighting through to stirrer motors and reactors must be intrinsically safe, i.e. not generate sparks or too much heat so as not to become an ignition

source. This even goes as far as process operators wearing anti-static footwear and clothing. Needless to say all this is expensive, as is potential disposal of flammable solvents.

2. Minimise impurities

Impurities in the lab may be useful as they give information about possible mechanisms for the reaction. In an industrial setting impurities present a problem as the contaminant may render the product unusable/unacceptable — generally the aim is to reduce impurities as to do so usually means improved yields and a better product. Given that total removal of every impurity is likely to be impractical or prohibitively expensive the question is generally which impurities to remove and which to control. Unsurprisingly the pharmaceutical industry has strict guidelines regarding the acceptable level of impurities

- Residual Solvents are regarded as impurities — International Conference on Harmonisation (ICH) guidelines for Residual Solvents (Step 4 version,1997, revised Feb 2009)
- Heavy Metals and other 'Inorganics' are impurities — 10ppm is typical for heavy metals, less for recognised toxics such as Pb, Cd, Hg etc. There is some leeway based on drug dose, nature of metal etc.
- Reagent/Raw material impurities
    - Diethylamine in triethylamine
    - Halogen impurities in halo-aromatics/aliphatics

Potential **G**enotoxic **I**mpurities (PGIs) deserve special attention. Genotoxic substances are known to be potential mutagens or carcinogens and are capable of causing genetic mutations and contribute to the formation of tumours. There are many PGIs including **some** but **not all** of the following classes

- Simple aromatics – benzene, PAH's
- Alkyl halides, mesylates, tosylates, triflates, sulphates
- Isocyanates
- Ureas – carbamates
- Aromatic amines – some anilines
- Aldehydes – formaldehyde
- Epoxides
- Nitroso compounds – nitrosobenzene
- Azo compounds - azobenzenes
- Nitro compounds
- Some sulphonates - chlorosulphonates
- Phosphorus compounds - HMPA

US Fedral Drug Administration/European Medicines Agency Guidelines are no more than 1.5ug of genotoxic per patient, per day for treatments > 1 year. However it is recognised there is the need to balance treatment benefits vs medium to long term risk e.g. *tiny quantities of carcinogen given to a patient already with cancer.*

Guidelines vary slightly depending on type and length of treatment, but as a rough guide

Duration of Clinical Trial/Development (days)						
	<14	14-30	31-90	91-180	181-365	>365
Threshold ug/day	120	60	20	10	5	1.5

3. Telescoping

Telescoping is the procedure whereby the product of a chemical reaction is not isolated but is used directly in the next stage of synthesis, often as a solution of the product.

Advantages include:

- Saves time, manpower and effluent concerns
- Can be used to handle non-crystalline oily products, e.g. dissolve them in the solvent for the next stage of the process.
- Can be used to avoid intermediates that are toxic, irritant, odorous or of unknown toxicological properties.
- Can be used to reduce effluent streams
- Saves time and effort in isolating a product that requires further processing
- Use of telescoping avoids 'production' as chemical is not isolated so REACH (see last section) does not apply – potentially saves large amounts of money and time as safety dossier preparation is avoided

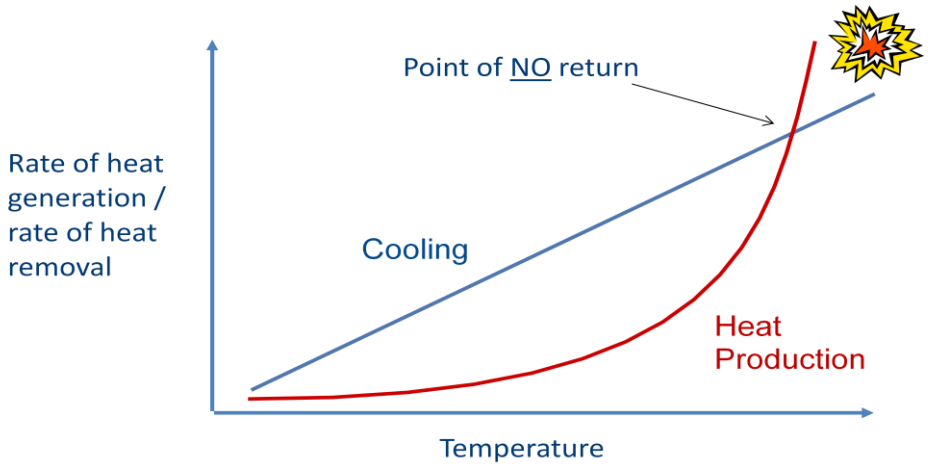
4. Crystalline products

Crystallisation has the potential to be a useful purification technique and many (though of course by no means all) crystal structures are stable. You still need to ensure you can actually get the crystals out of the vessel and that they are not too fine and block any filters. Variation in cooling times, agitation and perhaps surfactants can all be employed to alter crystal size

5. Not too exothermic

Heating a reaction incurs a cost and so does cooling; given that most chemical reactions give out heat then the focus tends to be on cooling. There are a number of aspects to bear in mind. Firstly the bigger your reactor the smaller your surface area: volume ratio and this has implications for the maximum rate of cooling. For any chemical reaction you need to consider the thermodynamics (magnitude of heat energy given off) and kinetics (the rate of heat release). Often you need to control the rate of addition of the raw materials to ensure you are in control of the reaction.

Always ensure that the heat evolved from a reaction mass never exceeds the capacity of the vessel's cooling system



REACH

REACH (**R**egistration, **E**valuation and **A**uthorisation of **Ch**emicals) is the European Community Regulation on chemicals and their safe use. All raw materials used and substances imported or produced in **>1tonne** quantities in the EU must be registered with appropriate safety dossiers - otherwise you cannot manufacture or market. REACH **does not** apply to all chemical categories, e.g. pharmaceutical & polymers are exempt.

Each manufacturer/importer in the EU provides a technical dossier for each substance to the European Chemical Ageny (ECHA) in Finland. The Technical dossier is not a trivial document (up to 300 pages) and must include:

- substance identifier
- company
- physical-chemical data set
- toxicological data set
- eco-toxicological data set
- uses
- chemical safety report

How much does it cost?

Tonnage band	Duty to register expected until	Estimated Costs
≥1000 t/yr or CMR* etc	01.12.2010	up to ~ 1.000.000 €
≥100 ... <1000 t/yr	01.06.2013	up to ~ 600.000 €
≥10 ... <100 t/yr	01.06.2019	up to ~ 250.000 €
1 ... <10 t/yr	01.06.2019	~ 50.000 €

*CMR etc. = substances of high concern: carcinogenic, mutagenic, reprotoxic (each Cat. 1,2) or persistent hazard to the environment

http://ec.europa.eu/environment/chemicals/reach/pdf/2007_02_reach_in_brief.pdf