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BEYOND PROCESS CHEMISTRY

Technical Piece

SOME SCALE-UP CONSIDERATIONS

Some general points to consider

INTRODUCTION

The **scale-up** of chemical reactions is not simply a case of using a larger reaction vessel – many factors need to be considered just to keep reactive chemicals contained, let alone achieve successful scale-up for the desired product. Consequently, scale-up requires specially trained chemists, indeed often a whole department in larger companies.

This very brief technical piece seeks to highlight just a few of the important **initial factors** that need to be considered before embarking on the scale-up of any chemical reaction – factors such as **chemical** and **physical safety**; **availability of chemicals**; **analytical**, **chemical** and **engineering aspects**; **commercial considerations** (cost and time); **environmental and legal demands**, etc.

CHEMICAL CONSIDERATIONS

The initial chemical route to a potential new pharmaceutical is likely to have been designed for facile synthesis of multiple analogues by relying on late stage functionalisation (**Figure 1**, Step 7). However, once larger quantities are required, the route may no longer be viable if the starting materials are not available on sufficient scale, necessitating an extension to the route (**Figure 1**, Steps 1 and 2). A first priority therefore is to establish the **commercial availability** of materials on scale-up.

The initial route is also often not the most efficient to a chosen analogue. There may be the opportunity to develop a better shorter route using alternative starting materials, which are ideally cheaper and more readily available (**Figure 1**, Steps 1'-4'). This may also provide opportunities for further **patent protection** for the chosen compound. Thus, **route selection** is another early priority.

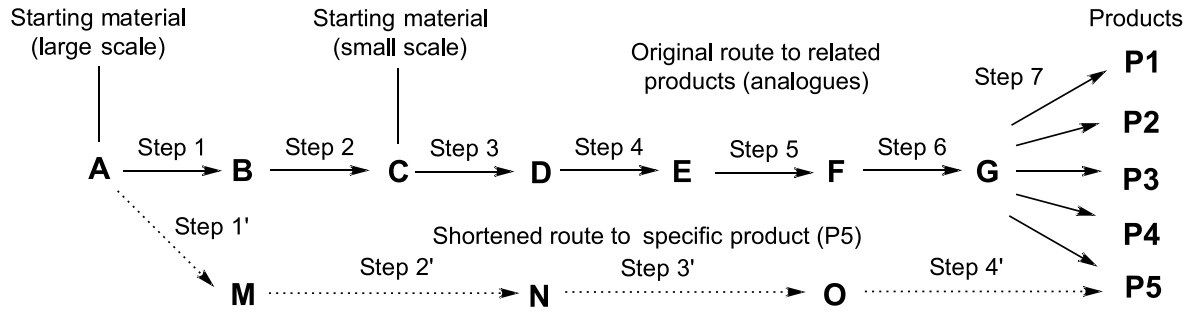

Figure 1: Schematic of route comparisons for standard discovery analogue synthesis (**top**) and bespoke synthesis for single selected drug candidate (e.g. P5) used for scale-up (**bottom**).

Chemical reagents also need to be chosen for **appropriateness**, **availability**, **cost** and **toxicity** – for example costs that might be tolerated on small scale, and toxicity that might be contained with specialist laboratory equipment, may become unacceptable or even impossible to manage on larger scales. Chemical hazards, especially from heat of reaction ("**exotherms**"), may also make some chemical routes, reagents or laboratory techniques impossible to use on larger scales – alternatives must be found.

Another factor valued on scale-up is **atom economy**, by which is meant the more efficient use of chemicals. Lower molecular weight reagents are preferred since they add less mass to the reaction vessel whilst achieving the desired transformation more efficiently. They are likely to require less processing and be much cheaper than heavier alternatives. Thus, for **redox reactions**, low-mass oxidants such as molecular oxygen (O_2), bleach (NaOCl) or hydrogen peroxide (H_2O_2) are preferred; and for hydrogenations, molecular hydrogen (H_2) and low mass hydride reagents such as $NaBH_4$ are desirable.

Redox reactions provide a good example of energetic reactions that require careful control of potential exotherms – although an even better solution to their use is to avoid changes in oxidation state completely; and of course, **catalytic reactions** are to be favoured over stoichiometric reactions wherever possible for all transformations.

PHYSICAL CONSIDERATIONS

The most important physical factor affecting scale-up results from the square-cube law, which proves that the ratio of surface area:volume reduces as volume increases (**Table 1**). So, for reaction vessels of similar shape, a 1000 L vessel has proportionately a 10-fold lower surface area:volume ratio than a 1 L

vessel. This factor affects the rate at which heat can be put into, and more importantly, removed from a reaction vessel, for example during an exothermic event. Once heat is generated faster than it can be removed, a **"runaway reaction"** occurs, often with disastrous consequences. For this reason, scale-up is typically limited to maximum increments of 10-fold scale-up, and thorough **reaction calorimetry** (measurement of heat flow) is conducted as scale increases to ensure process safety.

	Reactor Volume (L)	Surface Area (m^2)	SA/V Ratio (m^2/L)	SA/V Ratio (to 1 L reactor)
Tube-scale	0.001	0.0004	0.407	9.3
Laboratory	1.0	0.044	0.044	1.00
Kilo-lab	10	0.209	0.021	0.48
Pilot plant	1000	4.75	0.0048	0.11
Production	10000	22.6	0.0026	0.05

Table 1 – Comparison of surface area:volume ratio with reactor vessel scale.

Figure 2: 1 L reactor vessel.

Physical agitation also unavoidably changes on scale-up. Whilst rarely a problem on small laboratory scale, magnetic stirring can actually be helpful by grinding undissolved inorganic materials in heterogeneous reactions into finer particles, increasing their surface area and thus reaction rate (although conversely grinding may degrade bio-catalysts). However, **magnetic stirring** is often ineffective well below 1 L scale in the concentrated reactions more typical of scale-up, in which solids are more likely to be present due to reduced solvent volume; **mechanical stirrers** must be used instead (**Figure 2**). Even so, these may not be fully effective as scale increases, and baffles may be required in the vessel to increase turbulence on mixing. This is difficult to achieve at intermediate scale-up levels, as is modelling agitation at any scale in the laboratory.

SOLVENTS

Almost without exception, **solvent** will be the largest single component in any reaction. This raises a number of possibilities and challenges. Reducing the solvent volume will increase the reaction rate; reduce the time required for engineering **unit operations** such as heating, cooling and removal of solvent by distillation; and reduce solvent recycling time or waste disposal volume. All these changes are beneficial on larger scale for which time, energy and waste disposal costs become significant due to the increased volumes involved.

Only a limited number of solvents are cheaply available on truly large scale, mostly petrochemical derived; others are by-products of other industrial processes for which **cost** and **supply** may be dependent on the state of those industries (e.g. acetonitrile shortage in 2008 due to recession in the car industry). **Environmental concerns** and **increasing regulation** mean that fewer solvents are available for use, and restrictions are getting tighter. Many chlorinated solvents are now banned at full manufacturing scale, including dichloromethane in some countries; so although laboratory studies are possible, scale-up options may be limited. Therefore, early choice of the preferred long-term solvent is highly desirable.

ISOLATION

Small scale reactions are typically purified by column chromatography, which is disproportionately difficult and expensive on larger scale and almost always avoided. **Crystallisation** is the preferred means of isolation for solid products on large scale (and **distillation** for volatile products), although aqueous **drown-outs** are also used. For crystallisation to be successful however, reactions must be essentially complete using a minimum of excess reagents and ideally with few impurities formed. Consequently, more than half the time spent on optimising a chemical reaction will typically be spent on devising a robust and efficient isolation and purification process for which, see later editions!

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