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Route design, the foundation of successful chemical development

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ABSTRACT

Route Design is the first step in the strategic development process for manufacture of a new active pharmaceutical ingredient (API). Numerous benefits can be realised for the project and the broader performance of the company. We present an appreciation of some of the potential challenges and describe the principles and practices that have shaped the Route Design culture within AstraZeneca. This is exemplified with case histories and we describe some of the activities that have supported our scientists and the simple messages used to educate the broader organisation.

1. Introduction

The manufacturing process has a significant impact in determining the viability of a product in its intended applications. In a research environment, any process might be considered acceptable if it rapidly provides sufficient material to support initial testing or structural confirmation. In contrast, a high volume, low cost commercial product mandates greater efficiency in areas where cost pressures are more apparent. In the pharmaceutical industry this can be exemplified by the contrast between life-threatening applications and those served by over the counter medications for minor indications such as headache relief. It should be realized however that application of the optimal process offers the most sustainable situation for a viable commercial product in any application.

The starting point for any chemical manufacturing process is the synthetic route.[1] Within AstraZeneca, our experience is that identifying the most effective route and delivering further development improvements can reduce the cost of manufacturing by orders of magnitude during development. By extension, introduction of the most effective chemical route to a compound should be viewed as a significant milestone during development for commercial use.

It can be seen therefore that the attributes of the most effective route are defined by the intended application. A casual observer attending a process chemistry conference might conclude that it is customary to open a talk by identifying every undesirable aspect of the medicinal chemistry route. Issues for scale up such as energetic reagents, environmentally detrimental solvents, handling operations and synthetic inefficiency are explicitly flagged as challenges to be overcome. Subsequently, the development chemist will share a masterclass in organic synthesis followed by the unveiling of the commercial, synthetic route in all its glory. Whilst an interesting if polarized view, this analysis misses the point that the context defines the most effective route. From the perspective of the medicinal chemist, the most effective route allows programmed diversity to be introduced efficiently since *de novo* synthesis of every candidate is too wasteful of resource for practical application. The development chemist already knows the target molecule, that it is accessible, a confirmed route and various physical properties. It should come as no surprise that a more efficient approach to the target molecule can be delivered from this starting position since it is invariably easier to reach your destination when you know where you are going.

In this report we will share our experiences in delivering a culture that directs focus on identifying the most effective synthetic route to each individual compound, a process which we refer to as Route Design.

2. Discussion

Within AstraZeneca we define Route Design as the identification of the synthetic bond formation strategy and this is viewed as the beginning of strategic development activities for drug substance. Our interpretation of this activity may differ to others since we discount the materials selection i.e. within AstraZeneca, Route Design leads to the selection of intermediates but does not define the underlying chemistry. Materials selection (reagents, solvents etc) is delivered along with appropriate manufacturing technologies in a subsequent activity termed Process Design. Route Design is viewed as the most value adding activity within Chemical Development, not so much due to the absolute

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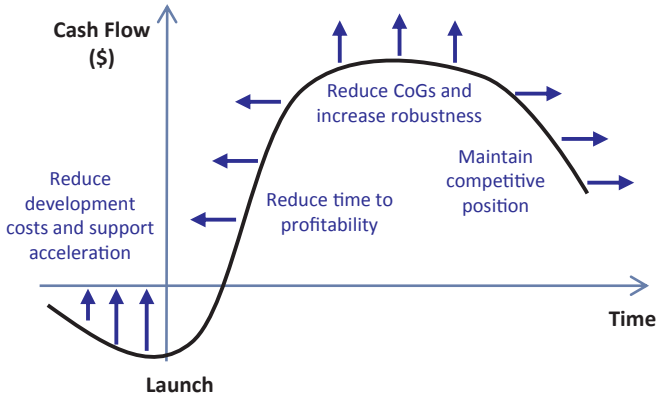

Fig. 1. Value Curve.

value released during Route Design itself but because it provides the optimum foundation for all strategic development activities and validation for undertaking them with confidence.

During the development phase, all projects can be viewed as costs to be borne and hopefully reduced. In the commercial phase, the Cost of Goods (CoGs) for a project drives the economic returns. This recognition of what we are trying to achieve underpins our approach to Route Design and all our development activities. It can be summarised by the Value Curve (Fig. 1) which has been a familiar feature to scientists in Chemical Development at AstraZeneca for over 10 years. It highlights that the synthetic route can have a profound impact on the performance of a project and the benefits of defining the most appropriate route with introduction at the earliest opportunity. While the value curve explicitly presents the economics, our experience in working with this model supports the consensus that costs and sustainability are coupled and improving performance of one invariably raises performance in the other.[2] Route Design is, therefore, also the first step in introducing sustainability into our API portfolio.

2.1. Why do route design?

The principles we follow for a better route are simple to understand since, in most cases, they offer a multitude of benefits with several contributing factors. Firstly, better constructed routes offer greater efficiency in using raw materials due to the impact of cumulative yields. A yield of 80–95% is a reasonable expectation for a single step but the overall yield rapidly decreases as the number of steps increases (Fig. 2). The impact of this is to require larger quantities of materials to be purchased, processed and disposed of.

Shorter routes also provide for reduced lead times and plant

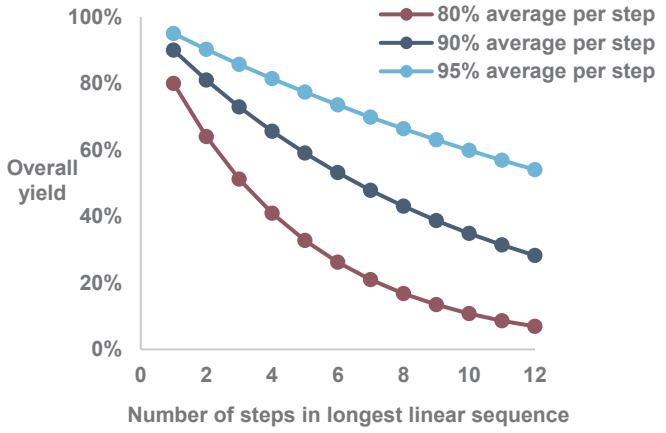

Fig. 2. Impact of linear sequence length on overall synthetic yield.

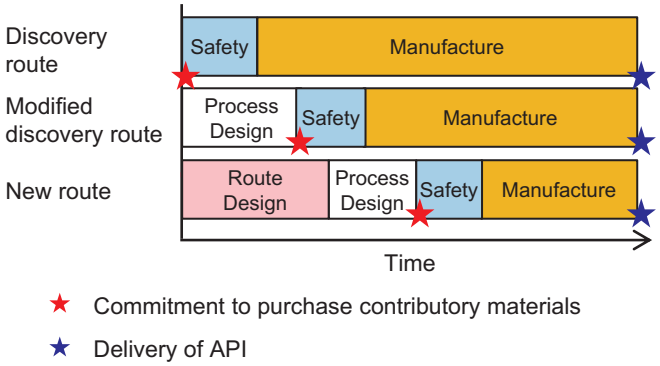

Fig. 3. Using a new route to delay spending commitments.

occupancy times in the supply chain. This allows for better management of financial risk across the project as the timings of major project decisions can be better exploited. These attrition points (eg clinical trial readouts and portfolio management decisions) might lead to project delays or even a project stop decision. A shorter manufacturing cycle therefore supports greater flexibility in scheduling manufactures to exploit the timing of such decisions reducing financial commitments at risk and allowing lower material inventories to be held (Fig. 3).

One additional advantage of this approach at any stage in the development cycle is that it exploits the order of magnitude difference in occupancy costs between the lab and those in a GMP facility. Time spent defining a route or developing a process is a good investment if it can mitigate potential plant issues where costly delays might be introduced. Such a view can present a challenge to the traditional idea that 'We need to start the manufacture as soon as possible'. We would suggest the correct approach should be to turn this around and focus on when there is a need for a manufacture to deliver API to match project requirements.

The second benefit is that shortening the sequence should require less resource to be engaged in process design. Alongside the obvious financial returns to the business, reduction in resource demand is a direct benefit for the Chemical Development group delivering such activities. The capacity of such groups to deliver activities is a function of how many chemical steps are present in the portfolio of supported projects. Fewer steps means that more projects can be supported or activities such as capability build can be progressed.

It should be recognised however that cost savings may not be realised immediately. The introduction of innovative technology or chemistry associated with a new route might even lead to increased short-term costs as unfamiliar techniques are learnt. These will represent a diminishing concern however, as understanding and control are gained and the process becomes more defined and robust. We would never challenge that less preferable synthetic routes could deliver the target material to an appropriate specification with scope for further optimisation. In an environment where corporate contraction has reduced resource levels over the years, our position is that it is unproductive to support prolonged periods of troubleshooting and tactical improvements. Even in the most highly optimised and well understood situations, increased numbers of operations or repetitions raise the likelihood of errors as anticipated by operational initiatives such as lean six sigma.[3]

A key differentiation between companies is the timing of when Route Design is seriously pursued, many models are pursued but not always with valid reason.[4] We seek to conduct Route Design as soon as possible during development but recognise that activities elsewhere in the portfolio also require resource. Ultimately some issues are just a higher priority than others and our view of the most effective route reflects a commercial environment. In many cases it is possible that we could do better but it may not be effective to do so, therefore our thoughts on best route may not always match academic views due to