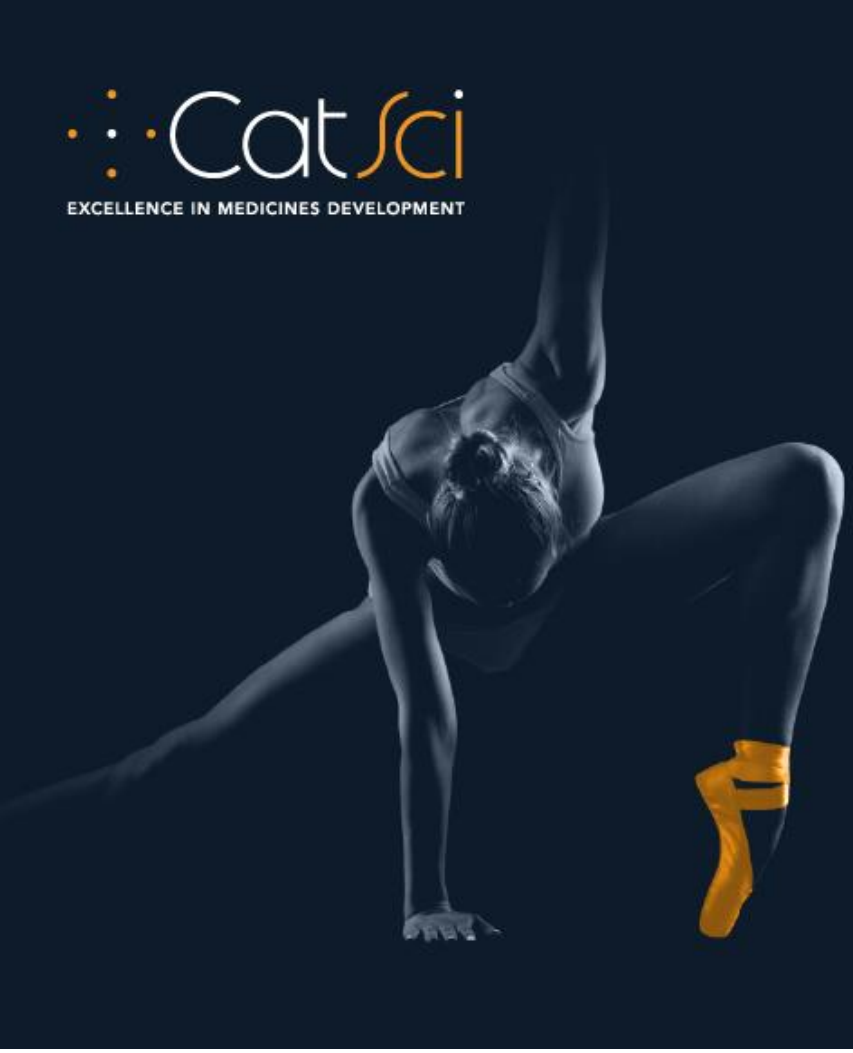
CatSci

EXCELLENCE IN MEDICINES DEVELOPMENT



WHITEPAPER

How a New Synthetic Route Could Save You Time & Money

The benefits of choosing a new synthetic chemistry route for your API

Introduction

In the ever-evolving landscape of drug development, it is often essential to explore opportunities to improve your synthetic chemistry route. A new optimised route has the potential to reduce cost, minimise environmental impact, and streamline your process. Deciding whether to investigate a new route involves assessing a variety of factors that can significantly influence the success of a molecule's development, commercialisation and lifecycle.

This whitepaper will explore the factors that need to be evaluated to drive this decision. We will examine how these considerations shape the decision-making process and what elements to assess when choosing to identify a new route. Additionally, we will highlight the cost and waste saving benefits that selecting the right route brings across both the development and commercial phases.

Why a New Route Could be Necessary

There are two main considerations that could necessitate the need to identify a new route:

1. **Safety Concerns:** The current route may be unsuitable for scale up or advancement past a certain scale due to safety concerns. These concerns could be driven by the reagents or chemicals involved the types of reaction or reaction conditions employed, or the thermal instability of intermediates within the process. Any of these factors would necessitate exploring an alternative route.
2. **Robustness of Chemistry:** Another key consideration is the robustness of the existing chemistry. If the current route, even after laboratory investigation, cannot run consistently, it can result in variable yields and low quality of products. As the scale increases, robustness becomes even more critical and an inability to find conditions which give consistent quality and yield makes campaign planning impossible.

If your need to change is driven by either of these two factors, it is an easy decision to invest time, resource and money into the search for a new route.

Why a New Route Could be Advantageous

There are also three additional factors to consider when deciding whether to investigate alternative approaches to produce your molecule.

1. **Cost of Synthesis:** If the cost of making your molecule is not viable or is unattractive, new route work will be required to assess how far the cost of synthesis can be reduced. Even if a molecule can be manufactured for an acceptable cost, it may still be worthwhile to investigate whether a significant cost reduction is achievable.
2. **Environmental Impact:** A well-designed route should consider many factors, with environmental impact being a strong priority. Reducing the length of a synthetic route is likely to reduce the impact

on the environment. There are many methods used to assess how environmentally friendly processes are, but for the purpose of this whitepaper we will use PMI (Process Mass Intensity) or kg waste per kg of product as the measure, as this is still the most widely used metric across the pharmaceutical industry.

3. **Reduction in Supply Chain Complexity:** Introduction of a new, well-executed route can significantly impact the complexity of the supply chain and reduce lead times for delivering the required API. Identifying the route that is shortest, and which utilises simple, readily available starting materials will help to address supply chain complexities.

Assumptions and Limitations

Given the variety of different APIs, there is no single 'typical' molecule that represents all processes. For this analysis, we will need to make several assumptions. These assumptions mean it is important to consider trends and magnitudes of improvement, rather than looking at specific numbers.

1. The alpha raw starting material for the synthesis has a cost of $100.
2. The first starting material has a molecular weight (MW) of 200 and the API has a mass of 500. Mass is added throughout the synthesis (in a real-world synthesis, there is likely to be more fluctuation of mass due to the use of protecting groups or high MW leaving groups, but this variation does not alter the macro-outcome of this analysis).
3. Two yields will be compared, with each step of the synthesis yielding 80% and 90% in the two examples.
4. Processing costs are assumed to be a simple $100, $300 or $500 per kg per step. This number includes plant time, reagents, solvents, waste disposal, and analytical clearance.
5. For route length, we will examine routes with a starting point of 16, 12 and 10 steps, with improvements reducing the step count by either 4 or 2 steps.
6. For the green chemistry analysis, waste generation is assumed to be 20 or 30 kg of waste per kg of product per step. A waste level of 20 kg per step would be a reasonable outcome for a complex commercial process.

Impact of Step Number Reduction on Cost and Waste Generated

Figure 1 and Figure 2 illustrate the impact of reducing the number of steps on the cost of a process and the amount of waste generated:

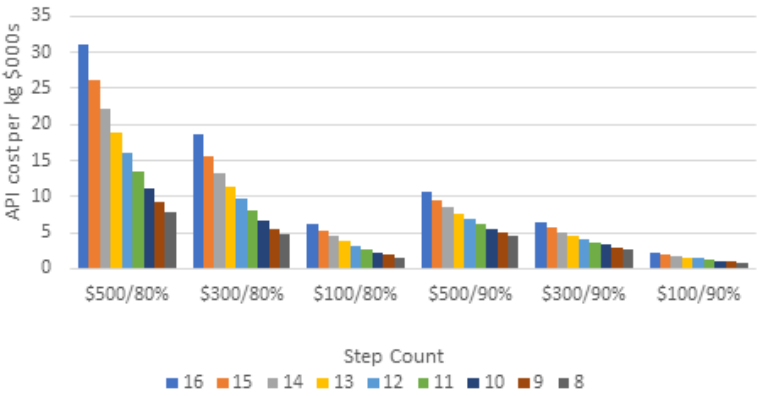


Figure 1 – Impact of reducing number of steps on API cost

As would be expected, significant cost improvements can be achieved in all scenarios. For example, removing 4 steps from a 16-step synthesis results in a 50% reduction in API cost, irrespective of other factors. Even starting from a shorter route and making smaller reductions in steps will have a significant impact; For example, shortening a route by 2 steps (10 to 8, or 8 to 6) leads to a cost reduction of approx. 33%.

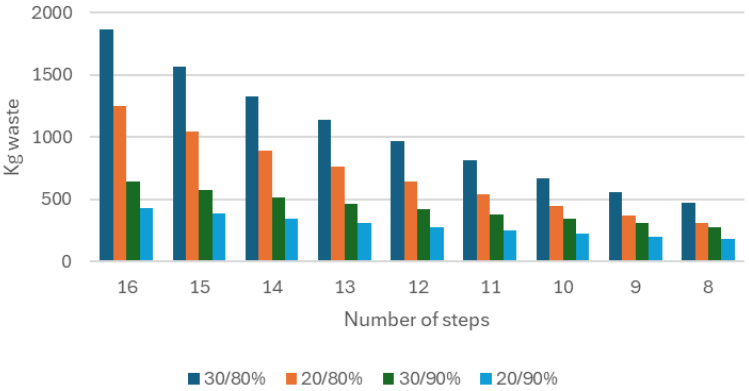


Figure 2 – Kg waste per kg API

In the case of waste, reducing a 16-step synthesis to 12 steps decreases the waste generated for the whole synthesis by approx. 45%. While a reduction of 2 steps for a shorter synthesis has a more moderate effect, it can still reduce the waste generated by between 25% and 30%.

Lifecycle Value of a Route Change

When assessing the potential value of a route change, it is important to consider its impact across the lifecycle of a project. Figure 3 assesses the cumulative benefits that can be achieved across a 12-year commercial lifecycle of a small molecule drug.

Three scenarios have been analysed:

- A low volume niche medicine (1MT per annum)
- A more typical average volume product (10MT API per annum)
- A high-volume product (100MT per annum)

For the high-volume product, market forces will significantly drive down costs and this is reflected in the $ savings achieved, but potential value is still extremely high. Even for low volume products, over the lifecycle significant cost savings and waste reduction can be realised.

Figure 3 shows cumulative savings in dollars ($) and waste reduction over the commercial lifetime of the product, demonstrating the long-term potential of route optimisation.

Cumulative Commercial 12-Year Lifecycle Cost & Waste Savings (at 80% yield per step, $100/kg/step processing costs and 20 kg/kg waste)

Step Reduction	$/kg saving	kg/kg waste reduction	Low Volume Product (12 MT)		Typical Volume Product (120 MT)		High Volume Product (1200 MT, at these volumes, scale will drive down cost)	
			Total Cost saving ($)	Total Waste saving	Total Cost saving ($)	Total Waste saving	Total Cost saving ($)	Total Waste saving
4 steps (16 to 12)	3100	603	37.2M	7236M	372M	72360MT	1000M	723600MT
2 steps (12 to 10)	983	135	11.8M	1620MT	117.8M	16200MT	350M	162000MT
2 steps (10 to 8)	670	108	8M	1296MT	80M	12960MT	240M	129600M

Figure 3 – Cumulative Commercial 12-Year Lifecycle Cost & Waste Savings

Lifecycle Value of a Route Change

Reducing the synthetic route length does not just deliver positive impact in the commercial phase, it can also provide

significant impact in the later phases of development.

Figure 4 illustrates the financial and environmental impact than can be achieved during development. To demonstrate this and to maintain consistency, we have used the same waste generation per step recognising that with lesser developed processes, the opportunity for impact may be higher. We have assumed a cost of $500/kg/step manufacturing cost to reflect, how typically, costs in the development phases are significantly higher due to shorter campaigns, less developed processes, and less developed supply chains.

To demonstrate this, we present two example programmes where 500 kg and 1000 kg (1 MT) of API are required and manufactured during Phase II and Phase III clinical studies.

Figure 4 shows cumulative savings in $ and waste reduction possible during the mid-to-late development phase of a product.

Development Phase Savings (at 80% yield per step, and $500/kg/step processing costs)						
Step Reduction	$/kg saving	kg/kg waste reduction	500 kg development API, cost & waste reduction		1 MT development API, cost & waste reduction	
			Total Cost saving ($)	Total Waste saving	Total Cost saving ($)	Total Waste saving
4 steps (16 to 12)	23,250	603	11.625M	301.5MT	23.25M	603MT
2 steps (12 to 10)	7372	135	3.69M	67.5MT	7.38M	135MT
2 steps (10 to 8)	5025	108	2.51M	54MT	5.02M	108MT

Figure 4– Development Phase Savings

Conclusion

For every API, it is crucial to evaluate the potential benefits that a route change could achieve. In the majority of cases, the introduction of a new route will have a positive benefit by reducing the API manufacturing cost as well as decreasing the environmental impact. In all cases, the savings are evident across the commercial lifecycle of a product. In many cases, and especially for high-volume products, significant cost benefits can be achieved during the development phase. **In simple terms, any investment in a new route will pay for itself.**

Explore CatSci's Expert Route Scouting Capabilities Here.

If you are considering a route change, look at our whitepaper above, which outlines the expert approach that we take to route selection at CatSci.

You can also **explore our page here**, where we demonstrate how our industry-leading approach to route selection enables environmentally and economically sustainable process development.

If you would like to discuss your specific challenges, please reach out to **Rob Crook**, **Charlotte Dalton** or **contact us via our website.**

About CatSci

CatSci Ltd is an award-winning innovation partner, dedicated to developing economically and environmentally sustainable pharmaceutical manufacturing processes. We proudly serve customers across the globe with projects, meeting their needs from candidate selection to product launch and beyond.

Our tailored services include route scouting and selection, initial scale-up and risk management for early development. For later development, we provide process design, assessment and optimisation, scale-up for clinical and commercial manufacture, tech transfer and post-approval improvements. We possess specialist facilities in Process R&D, catalysis, high pressure reactions, crystallisation, preformulation, analytical development, HPAPI development, and non-GMP supply, and recently launched our oligonucleotides capability. Through our partnership with AGC Pharma Chemicals, we offer scalable small molecule API manufacturing, from grams to tonnes, with complete accountability of tech transfer.

Recent recognition includes the highly esteemed Queen's Award for Enterprise: International Trade 2022, Wales STEM Awards 2022: STEM Company of the Year and the UK Fast Growth 50 Index 2023: Innovative Growth.

Contact us to learn more about how CatSci can support your project: enquiries@catsci.com