



WHITEPAPER

Route Selection Excellence:

Discover our industry-leading process and assessment tools



Introduction

When developing your life-changing medicine, it is crucial that you select the right route to manufacture your API. The wrong decision can lead to a multitude of risks down the line, including increased costs, lost time, and missed milestones.

At CatSci, we have developed a suite of perfect-for-purpose route assessment tools to enable the selection of the best route for the right phase of development. We work with you to fully understand your objectives and with this understanding, we design and develop the most appropriate synthesis for your drug candidate.

Explore this whitepaper to learn more about our approach and tools that we leverage for route selection.

Our Route Selection Process & Assessment Tools

1. The Importance of “Why”

The first question we need to ask is: why do you need a new route? This need can be driven by several things. Your current route may be unscalable, due to safety or cost of goods, or supply chain length may be an issue. By understanding **why** you are looking for a new route, we can scope out the areas that require the most attention.

It is also important to consider the stage of development you are in. Are you looking for a route which will be used for long term commercial supply? Or are you in early development seeking a route that will enable rapid access to API to support early clinical studies and get you past key attrition hurdles? Whichever phase of development you are in, CatSci will fully support you in your goals and produce

options which will help you achieve your objectives.

2. Idea Generation

It is imperative to generate a wide range of ideas when designing a new synthesis. We follow three streams to ensure all ideas have been explored:

1. Utilise the chemistry experience of our team, with a variety of technical backgrounds, to generate a multitude of ideas on paper.
2. Create additional ideas through the exploitation of industry leading retrosynthesis software tools.
3. Partner with the customer to gain a full understanding of their ideas and incorporate these into our thinking.

With a full range of ideas, it is important to then generate a prioritised plan. To do this, we assess several areas: cost, chance of technical success, environmental impact, and effort required to reduce the ideas to practice.

3. Route Costing Tool

At the on-paper route ideation stage, it is not possible to ascertain an exact cost for the synthesis of a molecule. This is because not all the required information is available, such as reagents, yields, throughput, reaction times, and manufacturing location.

However, an accurate cost is not required at this stage. We only need to be able to fully understand two aspects:

- If this is a commercial route development, whether the cost of the route will meet the cost target at this stage.
- The relative costs between different routes to help make decisions on which routes to pursue.

To complete this assessment, we developed a simple costing tool. This allows us to build relative and indicative costs for each route. The tool considers route length, likely costs of some key reagents and starting materials, yields, and preferred manufacturing strategy (manufacturing costs). Although not 100% accurate, it provides the likely cost of different routes (Table 1). If we understand more about where the customer may want to manufacture material and commercial volumes, we are able to adjust some parameters to give a closer estimate.

Route	Steps	Predicted Cost (Low) USD/Kg	Predicted Cost (Mid) USD/Kg	Predicted Cost (High) USD/Kg	Key Cost Factor
1	10	11,265	29,868	48,472	Late resolution
2	8	5,369	10,505	15,641	PGM catalyst costs
3	10	5,852	14,686	23,520	Length
4	10	10,252	20,127	30,002	Enzyme costs
5	9	6,188	14,571	22,955	Length
6	8	4,743	7,427	10,201	Enzyme costs
7	7	2,018	5,741	9,464	Length
8	10	5,845	12,565	19,284	Enzyme costs
9	9	20,253	26,338	32,422	PGM catalyst costs

Table 1. Output of a cost assessment performed for one of our customers utilising our costing tool.

4. Measuring Chance of Technical Success (COTS)

The most critical part of any new route selection is predicting the Chance of Technical Success (COTS). To effectively attain the best prediction of COTS, it is important to rigorously assess all routes against a range of criteria, including literature precedent, alongside a number of other considerations, as well as utilising computational predictions where appropriate.

To achieve this, we developed an internal tool which drives a rigorous, objective assessment of all routes and predicts a score for COTS of each route.

We can also visually display each route, identifying which steps we predict will have the greatest risks and will require the most attention (Figure 1).

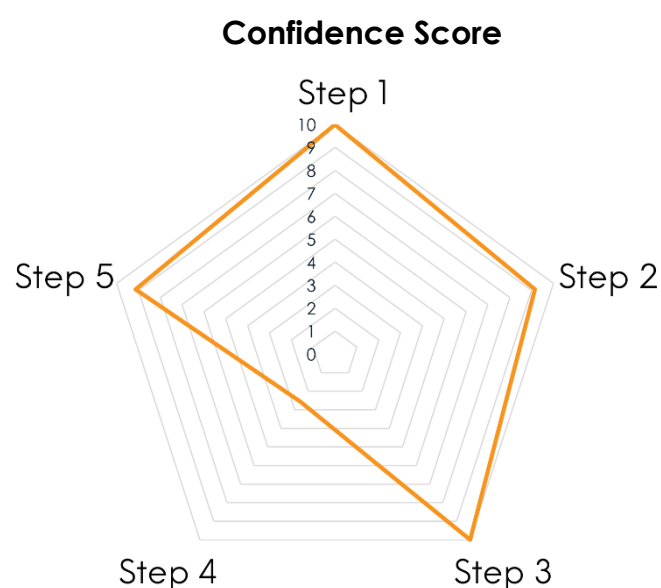


Figure 1. Output of a COTS assessment performed for one of our customers utilising our tool.

The tool we have developed provides an industry-leading assessment of each route, taking away individual scientist biases and displaying all routes in a visual, digestible manner.

5. Environmental Impact Assessment

Until a process has been developed, it is not possible to give an accurate figure for environmental impact. However, we can predict the PMI factor of each route by utilising a tool developed by the ACS Green Chemistry Round Table. This is based on a number of criteria, including literature assessments of reaction types and other factors. The tool has been shown to give a reasonable correlation between predictive and actual values. **Alongside any PMI predictions, our assessment highlights any reagents which could cause concern, such as heavy metal catalysts (Table 2).**

Route	Steps	Critical Step	Pros	Cons	Predicted PMI (kg waste/kg API) [95% C.I.]
1	10	Final resolution	Precedented, solids	Long, final resolution	1750 [1352,2201]
2	8	Chiral reduction	Chiral, solids	1x critical step, Rh	696 [543.7, 863.7]
3	10	Chiral reduction	Chiral, solids	1x critical step, long	1336 [1048,1676]
4	10	Chiral reduction	Chiral, solids	1x critical step, long	1336 [1048,1676]
5	9	Chiral reduction	Chiral, solids	Harsh step	1019 [790.5, 1279]
6	8	Chiral reduction	Chiral, short	1x critical step	601 [472.9, 748.5]
7	7	Relay cyclisation	Chiral, short, new IP, solids	Less precedented	406.8 [340.4, 478.5]
8	10	Resolution	Precedented, chiral	Long, resolution, oils	781.8 [616.5, 961.9]
9	9	Chiral reduction	Precedented, chiral	Rh, (TMSO) ₂ , oils	542.2 [429.9, 665.4]

Table 2. Output of an environmental impact assessment performed for one of our customers utilising our environmental impact tool.

6. Resource Requirements

We develop a plan based on the required resources, focusing on de-risking the project as rapidly as possible, which is then shared with the customer. This plan can be modified and altered depending on our customer's specific requirements, providing the flexibility they require.

7. Practical Execution

Once an agreed plan has been developed, the next step is to practically demonstrate the chemistry. This is done within our state-of-the-art laboratories, utilising a team of highly experienced chemists. Our expert chemists also have the support of a well-equipped analytical group with access to all necessary analytical equipment, including HPLC, GC, UPLC - all equipped with MS where necessary - as well as an NMR to support structure elucidation.

8. Tracking

We carry out regular reviews of progress whilst the work is ongoing. We provide regular updates to customers via meetings, presentations, or written reports.

As results emerge, we will either continue with the agreed plan or adapt it based upon the results. This will always be done in consultation with our customers, where we will impart our expertise and provide advice on where the results guide us for the best possibility of success.

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 material 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, the 2022 Bionow Awards (Export of the Year), the 2022 Inspire Business Awards (Business of the Year (25+ employees)), and the 2022 Wales Business Awards (Workplace Wellbeing).

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