Route selection

Route selection is at the foundation of developing new products and processes. Selecting the optimal route to make your molecules can have a major impact on both the environmental impact of your route as well as the cost of goods.

Learning Objectives:

By the end of this module you should:

- Be aware of practical techniques used within route selection;
- Be able to balance a range of criteria to make a decision on which is the 'best' route.

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Recap of the SELECT criteria

The biggest impact a chemist can have on the economic and environmental performance of a manufacturing process is in selecting the optimum synthetic route using the best available techniques/technologies at that moment in time. Route selection is a complex process, and synthetic routes can change during the development pipeline of an API, and post launch as part of life cycle management activity. In their paper 'Critical Assessment of Pharmaceutical Processes; A Rationale for Changing the Synthetic Route' [1] Butters et al. published their work on the 'SELECT' criteria which have since been widely adopted . A manufacturing route could be improved/ changed to meet any or all of the SELECT criteria.

- S – Safety – removal/minimisation of reactive hazards and toxicity and hazardous reagents/solvents.
- E – Environmental – removal/minimisation of reagents/solvents harmful to the environment; volume and nature of waste.
- L – Legal – no infringement of existing intellectual property.
- E – Economics – minimise cost of goods/meeting cost of goods target.
- C – Control – meeting quality specifications; process must be under control, validated, consistent impurity profile.
- T – Throughput – availability of raw materials; manufacturing time; maximised space time yield.

The SELECT criteria are covered in more detail in Introduction to Process Chemistry in the Foundation topic.

1. M. Butters, D. Catterick, A. Craig, A. Curzons, D. Dale, A. Gillmore, S. P. Green, I. Marziano, J. - P. Sherlock and W. White, Critical Assessment of Pharmaceutical ProcessesA Rationale for Changing the Synthetic Route, *Chem. Rev.*, 2006, **106**, 3002-3027.

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Issues on a small scale

Within medicinal chemistry, the need to synthesise small amounts of a large number of analogues in a short time period can often lead to preference for tried and tested methodologies. This can be to the detriment of efficiency and often using reagents that would not be suitable for use on a larger scale due to, for example, safety issues. However green chemistry and medicinal chemistry are not mutually exclusive and adoption of green methodologies at an early stage in drug design provides the opportunity not only to reduce the environmental impact of small scale discovery research, but also to facilitate a smoother transition when promising candidates are scaled-up. To put this into context, it has been estimated that the drug discovery stage of the pharmaceutical industry as a whole produces between 200,000 and 2 million kg of waste on a yearly basis (based on annual worldwide production of active pharmaceutical ingredient and typical mass intensities from the ACS GCI Pharmaceutical Roundtable (ACS GCIPR) companies and taking into consideration annual new drug applications (NDAs), candidate survival rates and the ranges of weights of APIs produced for each R&D stage).[1]

1. B. W. Cue, Green Chemistry Strategies for Medicinal Chemists, in *Green Techniques for Organic Synthesis and Medicinal Chemistry*, John Wiley & Sons, Ltd, 2012, pp. 551-572.

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Application to API synthesis

In this video, Andy Wells explains the application of route design to selecting the best route for API synthesis, including what makes a 'good' or 'bad' route and the need to seek a balance between all the SELECT criteria at the currrent state of knowledge.

» View on YouTube
» Download

Transcript

What is route selection? There are usually many synthetic pathways, or routes, to construct a given structure There is almost always more than one route and each group will have given starting materials and intermediates, but also a choice of reagents, reaction types and solvents to construct the products.

Sometimes route selection can be relatively simple, as we can see from this molecule here, the choice is fairly straightforward.

Essentially four building blocks, all of these building blocks are commercially available at scale and the key task is really order of connection and it's a convergent, not linear, process.

And we can see the four building blocks being highlighted here.

And in practice this is the disconnection, this is how the molecule was made.

Reaction 1, reaction 2, reaction 3.

But sometimes route selection can be much more challenging.

If we look at this molecule, Ticagrelor, it's altogether more thought provoking.

It has a number of challenging synthons: highly functionalized cyclopentane ring a novel heterocyclic core and an amino cyclopropyl benzene fragment.

It also has the complexity of six chiral centers that have to be controlled and at the start

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

of the project, none of these main synthons were commercially available.

So a much more challenging structure.

Selecting the optimum route for a given API is often an iterative task.

There may be several, or many, paper routes and these need to be evaluated on paper the short ones tested in the lab.

This may lead to several rounds of test/evaluate/refine before the best route is chosen.

It should always be borne in mind, however, that the route selected reflects the best science and technology available at that point in time.

And advances in the development of new catalysts, bio catalysts, synthetic methodology and so may enable in the future a route that was discarded as unfeasible or economic at the time of selection.

What are some of the key criteria we think about when we're selecting the route? So choosing the synthetic route can be a complex task with many important criteria to consider.

A key publication, Chemical Reviews, 2006, describe the SELECT criteria; so that's Safety, Environmental, Legal, Economics, Control and Throughput.

So we can see some the sub-sections here.

In safety: so thermal reactive hazards, use of toxic materials.

Environmental impact: the volume and nature of waste.

Legal: ensuring intellectual property rights; we don't want to breach anyone's patents.

Economics: we've got to make the cost of goods for the target molecule.

Control: We've got to meet the quality specifications.

And Throughput: so that looks at the availability of raw materials, manufacturing time; can we make enough material to satisfy commercial demand? A route that can make a hundred kilos of a product per year may be suitable for a low volume material, but this may not be suitable for 100 tons per year.

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

So if we think about the environmental impact of a process, the biggest impact we can have as chemists is in the R&D route selection process.

Here we can design processes that minimise the use of resources, use recycling etc.

Minimise our generation of waste.

By the time we get down here, to the manufacturing, where the process is established and validated, in a manufacturing plant all we can really do with the waste is rendered it harmless.

So the likelihood of success in generating a good, environmentally friendly route to an API increases we move back up this chain here.

And, as I said, the biggest impact we can have really as chemists is in this point here.

Ok, so to get a really good, efficient process, choosing the route is the foundation really.

Most processes can be improved in terms of efficiency, cost, throughputs, but choosing a good route; convergent, low number of steps, fewer isolations, minimum unit operations makes for easier optimization than a long and inefficient route that has, you know, a high number of steps, many isolations, issues in in processing.

Good route design is the foundation on which to build.

So we can we can use good green chemistry & engineering & optimization and these can all improve the selected routes.

But if we have fundamental flaws this can be very difficult to salvage.

What is the 'best' route? Well, a route which offers the best balance between operational, environmental, legal and economic factors at the current state of knowledge.

And, of course, the 'best' is a given point in time and this may change in the future.

So it's always important to evaluate all costs when designing a route to an API, to ensure that the product is produced for an economically attractive price.

For this simple molecule shown at the top the plant labour and equipment costs tend to dominate the full product costs.

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

If we look at some of these solvent costs and solvent treatment costs these are relatively small.

Whatever, if we consider just the raw materials to make this product the solvent and disposal costs are now the biggest contributors as we can see here, so in terms of minimizing the environmental impact of the process it's vital to think about which solvents we use and reduce the amount of solvent we use, but in some cases, this can also be a major contributor towards the cost of the product.

So if we look at the revenue stream of an API product, and so here we have time and money, because in the R&D phase we're spending money to develop products and launch it onto the market so it costs us money, it's negative.

When we get onto the market, hopefully the product will start to sell and we will make money and it will eventually go off-patent and sales will start to drop.

Where can a good route help us? Well it can reduce development costs, you can lower cost to launch, it can give us increase returns once on the market and designing and introducing better, more economical, more sustainable routes later can generate and defends patent life.

So if we look at some examples, Project 1 here, we can't show the structures, but these are real projects.

The initial cost of materials was around £1.5 million per kg and this is a considerable amount of money to spend and thinking here about new, more efficient and cheaper routes could save a considerable amount of money in the development phase.

Product 2, this had sales volumes at launch around 30 tons thinking and designing a good rate here saved around $30 million in the first year and if you ramp up to peak sales, that's up here, and, you know, this is a high-volume product and the savings in designing a good route were quite considerable.

Project number 3, and this was a compound with a very long multi-step route and failure to fix that inefficient route would double the company's annual hazardous waste generation.

Ok, so here we look at some of the positive metrics gain by changing the synthetic route.

The data displayed here are from 4 routes used to make the API Lotrafiban, shown on the

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

right, and we'll see more of this molecule throughout the rest of the training package.

So routes A to D are shown here and what you can see is the E Factors, this is the kilogram of materials used to make one kilo of product, and if we look across the four routes, and these four routes were really aligned with the development phases of this compound, we can see dramatic falls in the use of process water, solvents and input materials across the four routes.

This has 2 important consequences.

The environment of the processes is dramatically improved, of course, but the cost of the product, the API, also falls dramatically as we refine the processes and they have much better throughput.

The impact of good route selection can be vital to the commercial viability of a product.

In this case, Route A, which was used at the Med Chem stage will be far too costly and will result in a product too expensive for the market.

In developing better, more cost-efficient, low cost routes across B, C and D we now have a manufacturing cost that's acceptable and we can sell that product and it can be dosed to patients at an acceptable price.

So apart from the improved environmental metrics, so we're using far less solvent, we're generating far less waste; through good route selection we've reduced the cost of this API by around 85%.

Ok, route selection, some case strategies just to finish up.

We should minimise the number of steps in a synthetic route; 4 will be cheaper and greener than 10 steps.

We should look to get convergent, not linear, syntheses.

We should look to use catalytic reactions, identify risks and remove/minimise these hazardous materials.

As discussed previously, solvents are a major burden, we should choose and use wisely.

Gather and use appropriate metrics; we need to beware of 'green wash' solutions.

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

We should minimise unit operations and energy usage.

Avoid isolation and drying if we can.

We should think about Process Intensification, things like flow chemistry; can we use those to design cleaner and better routes? Consider where we can reuse and recycle.

And of course we'll never effectively remove all the waste, so we need to think about some effective abatement and waste treatment measures.

So how do we gather together the information needed to design synthetic routes? Well there are now quite a wide number of packages available to do this and there are some listed here.

And these are very commonly used by Medicinal and Process chemists to seek out information on compounds, intermediates, reactions and really now, helping to design 'in silico' new synthetic routes to APIs of choice..

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Summary and further reading

Route selection is at the foundation of designing a route that meets operational, environmental, legal and economic factors. The following are a selection of just some of the tools that are available to provide information and assistance with route selection:

- SciFinder
- Reaxys
- Science of Synthesis
  - *Information arranged according to structure*
- Prous Science Integrity
  - *Compounds which have entered clinical trials*
- Smartchem
  - *Database of bulk chemicals*
- Spresi
- Wiley ChemPlanner
- Google Scholar

These tools enable information to be sourced for route selection: ranging from searching for existing synthesis routes to an API; information and physical data on existing intermediate compounds; reagents and transformations; patents and even designing novel synthetic routes to a given target molecule.

Recommended reading:

There are also a wealth of journal articles and printed books on the subject. Here is a selection for further reading:

P. J. Dunn, The importance of Green Chemistry in Process Research and Development, *Chem. Soc. Rev.*, 2012, **41**, 1452-1461.

R. B. Leng, M. V. M. Emonds, C. T. Hamilton and J. W. Ringer, Holistic Route Selection, *Org. Process Res. Dev.*, 2012, **16**, 415-424.

R. Dach, J. J. Song, F. Roschangar, W. Samstag and C. H. Senanayake, The Eight Criteria

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Defining a Good Chemical Manufacturing Process, *Org. Process Res. Dev.*, 2012, **16**, 1697-1706.

M. Butters, D. Catterick, A. Craig, A. Curzons, D. Dale, A. Gillmore, S. P. Green, I. Marziano, J. - P. Sherlock and W. White, Critical Assessment of Pharmaceutical ProcessesA Rationale for Changing the Synthetic Route, *Chem. Rev.*, 2006, **106**, 3002-3027.

I. W. Davies and C. J. Welch, Looking Forward in Pharmaceutical Process Chemistry, *Science*, 2009, **325**, 701-704.

H. - J. Federsel, Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective, *Acc. Chem. Res.*, 2009, **42**, 671-680.

N. G. Anderson, Assessing the Benefits of Direct Isolation Processes, *Org. Process Res. Dev.*, 2004, 8, 260-265.

A. A. Desai, E. J. Molitor and J. E. Anderson, Process Intensification via Reaction Telescoping and a Preliminary Cost Model to Rapidly Establish Value, *Org. Process Res. Dev.*, 2012, **16**, 160-165.

G. Van der Vorst, W. Aelterman, B. De Witte, B. Heirman, H. Van Langenhove and J. Dewulf, Reduced resource consumption through three generations of Galantamine[middle dot]HBr synthesis, *Green Chem.*, 2013, **15**, 744-748.

C. A. Busacca, D. R. Fandrick, J. J. Song and C. H. Senanayake, The Growing Impact of Catalysis in the Pharmaceutical Industry, *Adv. Synth. Catal.*, 2011, **353**, 1825-1864.

T. Y. Zhang, Process Chemistry: The Science, Business, Logic, and Logistics, *Chem. Rev.*, 2006, **106**, 2583-2595.

C. - K. Chen and A. K. Singh, A “Bottom-Up” Approach to Process Development: Application of Physicochemical Properties of Reaction Products toward the Development of Direct-Drop Processes, *Org. Process Res. Dev.*, 2001, **5**, 508-513.

P. J. Dunn, Pharmaceutical Green Chemistry process changes - how long does it take to

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

obtain regulatory approval?, *Green Chem.*, 2013, **15**, 3099-3104.

K. D. Collins and F. Glorius, A robustness screen for the rapid

This resource has been created as part of the IMI funded CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries). CHEM21 has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.