Synthetic Route Selection for APIs: It Pays to Get it Right the First Time

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- PCI Synthesis

Process chemists developing Active Pharmaceutical Ingredients (APIs) for clinical trials today face a challenging array of business and regulatory hurdles.

The pressures to reduce costs while meeting more complex regulatory mandates, create a difficult challenge: how to develop a commercial process for a drug candidate more efficiently and within a much shorter timeframe?

Because of these challenges, it pays to carefully plan synthetic route selection in API development so that you can shorten the time from synthesis to regulatory approval.

Planning a synthetic route for a compound is the job of a process chemist. The chemist typically first looks at the required compound, and works backwards through a logical sequence of reactions until the suitable starting materials can be found. During this process, there may be many intermediate compounds that have to be separated and purified from the other compounds. These are the necessary steps and the key process during drug development.

The Complexity of Synthetic Route Selection

Although drug candidates range from relatively simple structures to highly complex ones, nearly all drug candidates present significant challenges to the process chemist. Every API requires new chemistry never before attempted, with all the pitfalls that it entails.

Initially, as the chemistry is developed, you may be working on a small scale and everything seems easy – or so you think. Although the hypothesis being tested in a clinical trial may seem straightforward, the complexity resulting from the large number of variables involved creates a high-risk business with the highest failure rate for new product candidates of any industry.

So how do you ensure you get it right the first time when it comes to synthetic route selection?

Choose the route to greatest efficiency. You should not pay too much attention to yields as long as the conversion is relatively decent. Additionally, before you start doing experiments, focus first on things like which reagents to use and how to make the process as efficient as possible. The more efficient the chemistry, the easier to purify and to meet ICH guidelines.

Take the starting point: The medicinal route. The starting point for most process development programs is the medicinal chemistry route. This route is typically designed to be divergent to allow access to a variety of targets. But it is only a starting point. The medicinal chemistry route is not usually designed for further scale-up into a commercial process. Consequently it is likely that the process chemist will need to change the synthetic route at least once during the course of the development program. And the performance of a process on an even larger scale leading up to commercial production can be difficult to predict. Serious issues with the process may not come to light until the process is taken to pilot plant scale.

Understand how the synthetic route changes as development progresses. As the life cycle of drug development unfolds, the demands on the synthetic process will change. In early development, the emphasis is very much on timely delivery of bulk supplies of the API using a safe process. Thus, most of the SELECT criteria can usually be satisfied when preparing the first few kilograms of the API or New Chemical entity (NCE) in bulk.

In the early clinical trial stages, the most frequent issue encountered involves patient safety. However, we are also focusing our efforts on attaining the highest yield, the lowest number of impurities, the easiest purification process, the least amount of pressure and most moderate temperature. In other words – the most efficient process.

Prepare for Scale-Up. Until the first few kilograms of API are made available, little can be done to progress these clinical and toxicology studies. Given the complexity of the processes involved in scale-up, a key best practice is to include at least three kilo scale-up trials of the process while still in the lab, before heading into a far more costly cGMP manufacturing facility for commercial processing.

Developing Sound Synthetic Route Processes

While there are many things to consider and multiple steps to undertake in selecting a synthetic process for your drug candidate, best practices CMOs focus on the following five key factors:

- Chemical yield
- Cycle time
- Number of chemical steps and convergence
- Use of higher molecular weight protecting group and reagents
- Number of energy-consuming operations

Implementing this approach is key to reducing API development time as complexity grows and budgets shrink. As with any risk management plan, the goal is to be proactive in finding and mitigating sources of risk. This is accomplished by removing unwanted variability in each stage of a process.

When a drug enters clinical trials, the key is to identify, reduce, and monitor risks to patient safety, data integrity, regulatory and protocol compliance, and project scope. Paying close attention to the five key factors outlined above, not only ensure the most advantageous synthetic route, but safe, effective drugs for patients.

CMO based in Newburyport, MA and the largest small molecule drug substance manufacturer in New England. PCI Synthesis is also a commercial manufacturer of NCEs, generic active pharmaceutical ingredients (APIs), and other specialty chemical products for the medical device industryAs a CMO, PCI Synthesis provides emerging and mid-sized pharmaceutical companies access to the expertise needed to develop and manufacture complex small molecules.