The Challenges of Increased Complexity in API Development and Manufacture

There is no getting away from it: the small molecule drugs now entering and travelling through the clinical pipeline are becoming more complex. This increasing complexity poses a variety of challenges that pharmaceutical and biotech companies will need to overcome.

First, there is the molecule itself. It may be that, as an integral part of the way it is designed to hit the target, it includes features and moieties that are difficult to make. Chiral molecules, for example, nowadays are unlikely to be progressed unless they are single enantiomers, and this requires chirally selective chemistry or separation processes to make them. The more chiral centres it contains, the greater the complexity of the synthesis is likely to be.

Complexity in the chemical structure might also result from functional groups that are difficult to handle or insert, or perhaps the molecule has one or more quaternary centres, which can be particularly challenging. Moreover, if the final molecule or intermediates are highly potent, their development and manufacture will require special handling procedures, including dedicated equipment with high containment, and trained personnel.

The chemistry required to make it might also be complex. While skilled process chemists will do their best to find alternatives, there are times when it is unavoidable. Some reactions require very low temperatures or high pressure. Or they might involve reagents that are particularly hazardous, perhaps because they are extremely toxic, or even explosive.

As an example, a client engaged us to make an API for Phase 1 studies where the synthesis involved an unstable intermediate within the synthetic route. This intermediate required very low temperatures to prevent degradation, and new equipment would be needed. The installation and qualification of this equipment had a long lead-time, and added to the cost. Moreover, the work-up and purification of the molecule were particularly laborious. The low stability of the intermediate and the related low purity (about 80%) had a knock-on effect on the subsequent step, which gave a yield of just 58%. The crude API also had low purity, which therefore also required a tedious purification.

An obvious change to make seemed to be to try switching to a different, more stable intermediate. This was successful, and the increased stability of the new intermediate meant that 97% purity could be achieved with a simple aqueous work-up followed by crystallisation. This increased purity improved the subsequent step, too, with an improved yield of 77%. A re-slurrying was all that was required to achieve the desired purity of the final API.

This change also removed the need for cryogenic conditions, and therefore the many months of delays that would have been caused by upgrading the kilolab could be avoided. In all, 5kg of the API ready for clinical trials was produced in just four months, thanks to the optimised route and process, with improved yield and product quality.

More Steps, More Complexity

Synthetic routes are getting longer, too, an increase in the number of steps clearly increases the complexity of the overall process. A good example that we worked on for a client involved the process development and kilo-scale manufacture of an API for Phase 1 clinical trials. The synthetic route involved eight chemical steps, and the overall yield was just 14%. The client required the Phase 1 batch to be completed in six months, and this timeline posed a significant challenge in the light of the overall low yield.

We took advantage of the skills and capabilities of scientists at several of our sites to solve the multitude of problems within the synthesis. Each of the eight steps was optimised at our facility in Nansha, China, including a mass balance study to aid in the optimisation of the overall yield. As an example, in one step the sequence in which the material was charged was changed, cutting the amount of an impurity formed in the reaction from 10% to just 1.6%, with a consequent increase in yield. In the final step, slurrying the crude product rather than washing with acid and extracting proved effective, too.

Downstream particle engineering and encapsulation took place at our sites in Switzerland and Florida. This spread of talents enabled us to deliver the supplies within the required timeline, making about 3kg of API in a scalable process that had an overall yield of 29%. This was more than double that of the original process and represents an average 86% yield per step.

Another source of complexity comes with purification. However efficient the synthetic route to an API might be, if it cannot reach the required purity effectively then changes will have to be made, either to the synthetic steps or to the process by which it is being purified.

An example here comes in the form of a project for making a building block for an ADC linker for Phase 1 clinical supply. In the original process that came from the client, this could only be made as an oil, making purification and further processing distinctly challenging. Our first thoughts were to use a chromatographic technique for the final purification, but as the molecule was acid labile, it decomposed on the silica column, even though it had already been neutralised by base. This made it very difficult to improve the purity in this way.

The answer lay in developing a new workup procedure using heptane. This time, the pure product formed as an insoluble dispersed gel, and the impurities were extremely soluble. It could then be adsorbed onto celite, and this filtered off. A demo campaign in the kilolab scaled this celite-based process up, producing 600g of the oil at much higher purity than had previously been possible. Even better, it turned out that, with a purity in excess of 99%, the oil tended to crystallise. This could then be used to seed a larger scale crystallisation, and once this was implemented in the pilot plant, 8kg of crystalline product that was

99% pure was made – a far cry from the impure oil that had been made previously.

Complexity in Physical Properties

But the increasing complexity does not stop with the molecular structure and the synthesis – the molecule's physical properties have an impact, too. There has been a noticeable trend in recent years towards molecules in the development pipeline being insoluble, sometimes to the extent that they resemble brick dust, being incredibly insoluble in water and organic solvents alike. If a molecule does not dissolve in water, it will not dissolve when the patient takes it, and therefore it will not be efficacious as its bioavailability will be negligible.

While solubility is an inherent property of the molecule, there are technical solutions that can be employed to improve it, such as using spray drying to transform it into an amorphous dispersion. It is also possible to use a mechanical method to enhance its dissolution properties, simply making the particle smaller via micronisation or milling.

Alternatively, changing its crystal form in some way may work. Sometimes, finding a different polymorph will suffice if it dissolves better. If the molecule has ionisable groups, then it is definitely worth checking to see if a salt form can be found that is more soluble. In the absence of ionisable groups, the answer may lie in forming a cocrystal instead.

Identifying the optimal physical form early in drug development is important if changes in later phases are to be avoided. Our team worked on a product that was initially developed as a free base for Phase 1 trials and, during the manufacturing campaign for Phase 2 supply, the customer decided to shift to a hydrochloride salt. This added complexity to the overall process, as the production campaign was already under way. Clearly, this switch required the process for the final API to be redesigned, and then optimised once more. There were two possible polymorphs of the HCl salt, and it was unclear which would be the best option.

The change was made at such a late stage that the penultimate step of the synthesis was already under way at a 100kg scale in the GMP facility, and the client wanted 10kg of the HCl salt at extremely short notice. The free base process was rapidly redeveloped to accommodate the formation of the HCl salt, alongside processes to create each of the two polymorphs of the salt. This enabled the physicochemical properties and stability of the two polymorphs to be assessed, allowing the client to make the final decision about which would be best to take forward into the clinic.

The required 10kg of salt form was delivered within two weeks – before the final API step was initiated in the GMP production plant. This highlights the importance of flexibility and agility in meeting the changing requirements during product development. Being able to change the kilolab plan immediately was key to the ability to meet the deadline for formulation development: the first batch of free base from the GMP plant was released rapidly and diverted back to the kilolab for the salt formation step.

Regardless of the strategy employed to address complexity in all its forms, a skilled CDMO partner can be instrumental in success. They will have significant experience in working across a wide range of different molecules, and employing a range of techniques to solve problems ranging from chemistry challenges to solubility problems. This expertise can be critical in keeping to development timelines, and transforming a complex molecule into a successful medicine.

Giovanna Libralon

Giovanna Libralon serves as the Senior Director of Commercial Development in Europe and APAC for Early-Stage Small Molecules across Drug Substance, Particle Engineering and Drug Product. She received her bachelor's degree in Pharmaceutical Chemistry and Technology from the University of Padova (Italy). Giovanna brings 20 years of pharmaceutical experience in process chemistry, manufacturing, and different commercial roles for both pharmaceutical and CDMO companies.

Email: giovanna.libralon@lonza.com