

How to Bridge the Gap Between Medicinal Chemistry and Chemical Development to Improve Drug Discovery

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Executive Summary

When medicinal chemistry hands over molecules of interest to chemical development, the quality of that handover can have a big impact on the speed of subsequent progress.

Early stage chemistry is often focussed on inventing molecules and finding routes to produce them. But the first route may not be the most suitable for later stages when large batches are needed. Nonetheless, once molecules progress to scale up, substandard chemistry is often accepted as it is viewed as the quickest option.

Inefficient chemistry can cost a project many months of delay and even if those occur early on, they will have an effect of the filing time and thus affect the NPV of the project. A delay of 18 months can impact the product value by up to 30%. It is generally quicker, and always cheaper, to solve chemistry problems in the lab than “firefight” in the plant.

A close working relationship between medicinal chemistry and chemical development, where they aim to understand challenges around material sourcing and chemical production, can significantly improve that early stage chemistry, in ways that improve the availability of material down the line, and so reduce timescales throughout the drug development process.

This paper discusses shifting thinking around early stage research to deliver that benefit when outsourcing to contract research organisation (CRO).

Introduction

The overlooked intersection of medicinal chemistry and chemical development

Medicinal chemistry invents molecules that could have a beneficial effect against a disease target. Chemical development develops a process for producing these molecules in batch sizes suitable for toxicological studies and clinical trials. This is the active pharmaceutical ingredient (API) – the fuel for the subsequent stages of development.

The quality of the process dictates how easy it is to produce this ‘fuel’ in ever-larger batches as the compound progress through clinical trials. The quicker they are to produce, the faster things can progress, since they can’t go faster than API supply.

The relationship between medicinal chemistry and chemical development can therefore have a big influence on the speed of subsequent progress, and in some cases, even the success of the molecule. Many years ago, these two divisions worked quite closely together. As the industry has evolved, different phases have become siloed, with a focus on making each stage as efficient as possible. There are advantages of a siloed approach in terms of specialisation, certainly and cost management. But in doing so, walls have often been erected between functions which should be collaborative.

Many Big Pharma companies have taken steps to bridge this gap, but many small companies don't have an internal chemical development capability and use CROs, often for both discovery and early development activities. This approach risks recreating these barriers.

Medicinal chemistry needs to chase the best molecule they can, but there are many hurdles that need to be overcome to get to the market. There are a wide number of other issues which medicinal chemistry do not always appreciate – from solubility, stability/physical form, to availability of raw materials used in synthesis – that determine how quickly a candidate can move or whether a molecule will make it to clinical trial and beyond. If these were addressed earlier, the whole process could be made much smoother and sometimes can also lead to a change in candidate.

Chemical development can be presented with a molecule of interest without a proper understanding of its chemistry. Under pressure to deliver quickly, they then pursue sub-optimal approaches. This may involve pauses whilst they source materials that they didn't know that they would need. These issues can normally be addressed, but they can take time which hasn't been accounted for.

By closer collaboration with medicinal chemistry, chemical development gains better understanding of the challenge that they are taking on, and can plan for issues like supply of adequate starting materials; and in turn medicinal chemistry can understand the issues that chemical development will face and can consider routes that will make their colleagues lives easier.

For these reasons, there is a strong case for more attention being paid to early chemistry, with a view to producing routes that are likely to run more smoothly through the Development process. Both areas are staffed with synthetic organic chemists, so they can easily communicate and learn from each other. A closer working relationship between the two, where they communicate and aim to identify the best outcome rather than simply passing the buck, would go a long way to delivering this benefit.

The move to specialisation has created a gap in understanding between functions. Medicinal chemists often have little real understanding of what goes on after candidate selection – their job is to simply invent new candidates.

However, promising changes are happening: as bits get squeezed out of the big pharma internal process, niches emerge at CROs, such as a combined medicinal chemistry and chemical development offer, that allow them to differentiate. There are good reasons for pharma and biotech companies to explore how these preclinical niches can produce better drugs.

How Medicinal Chemistry Benefits Chemical Development

Closer collaboration between medicinal chemistry and chemical development has the potential to create a number of advantages, which we discuss below

Keeps Chemical Development a phase ahead of other departments

Chemical Development needs to be a phase ahead of all other departments so that it has batches of the API ready when they are needed to fuel research. Collaboration ensures it has a good understanding of chemical routes, the required starting materials and time scales, so it can accurately plan ahead.

Reduced rework and failures and speed the process

It is often quicker, and always cheaper, to fix chemistry problems in the lab rather than struggle in the plant. A week in the plant can be 15 times more expensive than a week in the lab. Once molecules progress to scale up, substandard chemistry routes are often just accepted on the false assumption that it is quicker. In some cases the route is good enough to make a few kilograms, but later supplies become much harder due to the poor process. Neither will happen if the problem is addressed in the lab at an earlier stage. In some cases, Chemical Development may even spot molecules that will never be viable at scale, and so be able to abandon them before money is spent developing them.

Inefficient chemistry can cost a project up to 18 months in time, negatively impacting product value by up to 30%. In our experience, taking an extra week or two to understand issues that will arise later in the process will often identify such an issue.

Creates molecules with the right properties and enables quicker transfer to scale-up CROs

If medicinal chemists have a wider appreciation of early development, they are better equipped to consider design and initial synthesis routes that improve the chances of later success. Too often, they don't consider things like physiochemical properties (solubility, stability, and physical form, etc), until it's too late, and therefore don't budget in terms of additional money, time, or materials.

This is 'bird in the hand syndrome'. Once they have a route that works, it is often assumed that one can just turn the handle, or use larger vessels. The biggest issues in process chemistry often come when early stage chemists were not brave enough – or were under too much pressure – to introduce early route changes (see Example on next page).

Once chemical development is finished, the process is scaled up to make larger kilogram quantities. If the early work lacks data, further lab work will have to be carried by scale teams before they commit their expensive facilities to a product that might cause problems once it scales, creating delays.

If chemical development understand the chemistry better, they can provide a more detailed hand over to the scale up CRO or in-house team. This avoids wasting time and money on work being redone. It also reduces the risk problems will appear at this stage – such as exorbitant cost of material – which will delay or sometimes kill the case for taking it forward.

By working together, both departments can better understand issues that determine whether that molecule will progress efficiently.



Example: Changing the route for better outcomes

In a real example, a major effort was made to prepare 200g of intermediate to support lead optimisation development. This took nearly two months, due to low yields, containment requirements for sensitive reagents, and poor chemical selectivity, necessitating extensive use of chromatographic purification.

Stepping back, the synthetic chemist recognised the opportunity to introduce the ethyl group in a one-step process, through a reaction with EtMgBr.

When tried in the chemical development laboratories, this gave a 90% yield of the desired product with remarkable selectivity. It subsequently took one day to repapre 500g of material.

The consequence was that candidate drug nomination happened several months earlier, kilo quantities could be manufactured faster, and fewer resources were needed.

Why wasn't this attempted sooner? With the pressure to progress and a lack of clear communication between divisions about the longer-term goals, people were happy to repeat what was done previously, rather than try something new.

Outsourcing Medicinal Chemistry and Process Development

How to get them to work together

This whitepaper has argued that there is often value in combining medicinal chemistry and chemical development expertise to product candidates that are easier to scale and more likely to succeed. In this final section we share advice on what to look for when working with companies – or indeed internal resources – to ensure you benefit from this collaborative approach.

1. Experience and curiosity

Accessing teams which contain people with experience of your challenges, along with an inquisitive nature, is critical. Once you move away from standardised approaches you need people who can think analytically and draw on their experience to spot opportunities and potential problems. And you need people with experience of collaborating across divisions who are used to speaking each other's language. Low staff turnover is also a good indicator that a company is performing well.

2. The right equipment

Look at how they are investing in technology. State-of-the-art equipment is always a good sign. But also look at whether they are investing strategically in equipment built around clear objectives and problem solving, or just buying shiny new kit.

3. Niche skills and relationships

The world of contract research is becoming more specialised, so organisations which are very clear about their expertise should inspire trust. But equally, an honesty about what they don't know, ideally combined with a knowledge of who to go to when there are gaps, should be reassuring.

4. Communication

A commitment to clear communication will improve the process. Having people around a table who all speak the same language (linguistically and scientifically) allows you to have detailed conversations about what reactions looked like and draw on collective knowledge and thinking to consider whether to investigate them further or consider alternatives.

Innovation comes from experimentation outside of prescriptive plans which allow chemists to spot things they would have otherwise missed. A classic example is the HIV drug Crixivan, where a key step was unlocked by an internal decision to follow up a reaction most people didn't think would work.

Conclusion

Closer collaboration between medicinal chemistry and chemical development brings a number of advantages. It is not always true, but there are times when it can improve early stage work in ways that improve success rates and reduce delays down the line. It should always be discussed, then acted upon when there is clear value in doing so.

There are no universal solutions, but it is valuable to think through the long-term impacts, before you start. Ask whether additional effort at this stage will speed up lead optimization or not. If it does then that this is a job for Medicinal Chemistry with help from Chemical Development.

The common theme is doing good chemistry early. Getting a molecule's chemical development off to a good start is one of the best investments R&D can make. Time spent working on the interface between Medicinal Chemistry and Chemical Development will be hugely beneficial to this.



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