Industrial Insights

What You Can Expect from a CDMO Partner to Reduce the Cost of CMC Activities

Nov 2020

PharmaBlock

Cost control is an important measure to the success of CMC development. Though it may not be the first thing to consider when selecting a suitable CDMO partner, a qualified CDMO should be able to fully weigh the influence on budget caused by every decision and action throughout the whole drug development lifecycle.

It is especially vital for small- to medium- sized biotech companies because of the constraints of financial resources. A good cost-control strategy will increase the chance of success for a biotech company, as the same level funding could allow to support more parallel projects simultaneously.

Even though that CMC activities cost during early phase is not that sensitive to big pharmaceutical companies, cost of goods (CoG) is also a major concern as the project moves close to commercialization.

Recently, Robin Feldman, author of the book "Drugs, Money and Secret Handshakes" mentioned CDMO's role in reducing drug costs. In fact, the CDMO market came into being for the purpose of lowering process development and manufacturing cost, and of course, emerging biotech companies are now relying more on CDMO partners' specialized capabilities. In this article, we will discuss several tactics that a CDMO partner could do to help clients reduce the cost of CMC activities.

1. Begin with an optimal route

Speed is essential; however, if a CDMO can quickly develop an optimal route, it will be an added bonus. It is always expensive and time consuming to troubleshoot at the later stage of development. Actually, many problems could be avoided at the early stage of development if the following questions are addressed:

1) Is the route scalable?
2) Can the number of steps be shortened or telescoped?
3) Can chromatography be eliminated?
4) Is there any safety or environmental risk?
5) Are the materials or catalysts used easily accessible without too much fluctuation of price?
6) Are the impurities especially GTIs controlled?

You may not achieve a perfect route at the beginning of development but going through all these questions could help you be more prepared.

To address these challenges, the CDMO partner is required to have very strong

chemistry capabilities. At PharmaBlock, with many years' experience in synthesizing and scaling up over 60 categories of building blocks, we have developed a strong database which helps chemists quickly understand the chemical properties and related reactions, and inspire them to design more innovative routes. In many cases, we help clients greatly reduce the scale-up cost by shortening the route and avoiding the materials which are very expensive, not easily accessed, or with potential EHS risks.

CASE 1-Intermediate

- Challenge: An intermediate with an 11 step synthesis and several chromatography purification steps.
- Advantages: Starting material is a PharmaBlock catalog compound, broad experience and expertise in this chemical series.

Previous Route		Our Route
11	*Steps*	**3**
23k USD/kg	*Cost*	**3k** USD/kg
15 weeks	*Timeline*	**4** weeks
1632	*Green chemistry (PMI)*	**132**

CASE 2-API

- Challenges: 1) Expensive Pd and Borane Reagent; 2) Heavy metal in late stage
- Improvement: Heavy metal free route with fewer steps

Original Route		Optimized Route
8 steps	*Steps*	**5** steps
~8k USD/kg	*Cost*	**~3k** USD/kg
280	*Green chemistry (PMI)*	**90**

2. Phase appropriate development plan

Incorporation of phase appropriate development strategies is becoming increasingly essential to manage the balance between speed, cost, and regulatory compliance during development. Thoroughly planning a phase-appropriate

approach is essential to avoid filing an incorrect amount of information, at an inappropriate point in the process. FDA defines the requirements for submission of CMC regulatory information in Title 21 CFR Parts 312 and 314.

CMC activities are varied, and can include the establishment of product characteristics and manufacturing processes, as well as identifying product testing methods to confirm product effectiveness, safety, and consistency between batches, phase-appropriate analytical methods, and a number of other issues should be considered, particularly those that relate to safety assessment, the drug substance's solid state (salt and polymorph form), transition from early-phase to late-phase clinical and commercial dosage forms, and transition from small scale manufacturing process trains to multi-product process trains. In order to minimize any risks of later-stage failure, a number of vital CMC areas should be explored in early development.

At PharmaBlock, we have a group of veterans in the industry of innovative drug R&D, with many years of experience covering the essential areas of process R&D, analytical development, pre-formulation and formulation R&D, chemistry & engineering technologies, and manufacturing. Some of them even have firsthand experience to lead the CMC projects and advance several drug candidates from preclinical stage all the way to the market within an average timeline of 3-5 years. These experts can help our partners to develop, optimize and execute the phase appropriate development strategy and reach the balance between cost, timeline, and regulatory compliance.

3. Innovative chemistry and engineering technologies

Applying new chemistry and engineering technologies to improve green, safe, and effective process development and manufacturing is the key to overcome the scale-up challenges and lower the long-term cost. A famous case is the application of biocatalysis in the manufacturing process of Sitagliptin (Januvia), which Merck was awarded the 2010 Presidential Green Chemistry Challenge Award. Before that, Merck had received the same award in 2006 for asymmetric hydrogenation of the unprotected enamine, which avoided protection and deprotection steps in Sitagliptin manufacturing. Through two generation of improvements, the manufacturing cost of Sitagliptin dramatically decreased along with the impact to the environment.

In today's pharmaceutical manufacturing industry, there are several technologies that have attracted much attention, and PharmaBlock has accumulated experience:

- **Flow chemistry**

At PharmaBlock, continuous flow chemistry has been routinely applied to multiple projects. In addition to compounds from clients, PharmaBlock has a number of building blocks that have been synthesized and scaled up via flow technology. PharmaBlock also has a professional team specialized in mechanical, electronic and automation engineering that designs and assembles flow reactors of high flexibility.

Silicon Carbide Tubular Reactor

Dynamic Tubular Reactor

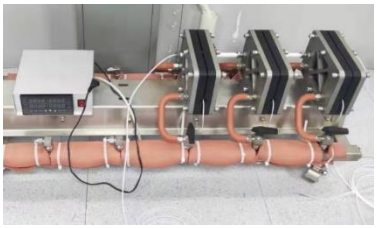


Plate Carbide Tubular Reactor

- **Micropacked bed technology**

Application of continuous flow process in hydrogenation with micro-packed bed reactor is a viable and promising option to overcome the barriers of conventional batch reactors. At PharmaBlock, micropacked bed has been successfully used in different reaction types. Most applications of micropacked bed reactors in pharmaceutical industry nowadays are still limited to from lab-scale to kilogram. However, PharmaBlock has designed and assembled manufacturing-scale equipment which has the capacity of delivering hundred metric ton output annually.

Micropacked Bed (mfg. scale)

- **Heterogeneous catalysis**

Heterogeneous catalysts harboring transition metals can finely tune reaction selectivity and accelerate reaction rates. They also feature the great advantages of easy separation and reusability, boosting the efficiency and greenness of the chemical process. On top of PharmaBlock's constantly growing in-house catalyst inventory, we continue to research, design, develop, and manufacture different catalysts to support our projects.

- **Biocatalysis**

Biocatalysis with enzymes has already proved to be a valuable alternative to traditional chemical methodologies, with advantages like higher enantio-selectivity, mild reaction conditions and lower energy and equipment requirements. The team has been developing capabilities of enzyme screening and route design, chemoenzymatic process development, and manufacturing.

- **Solid state and crystallization research**

Solid-state research is an essential part of the innovative drug development process and can reduce the time to filing an IND application. It is also a key patent tool for innovative pharmaceutical companies to protect their product profit cycle.

The solid-state chemistry research team at PharmaBlock has professional crystallographic skill that combines the best-in-class synthesis technology, crystalline engineering capabilities, formulation technology to provide systematic solid-state chemistry research and pre-formulation services.

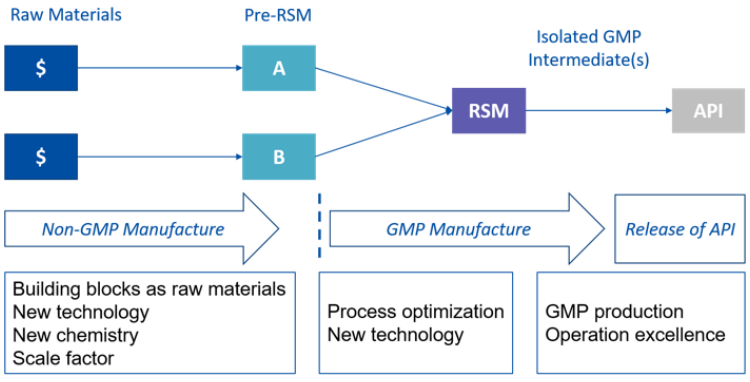
For crystallization technology, in addition to the laboratory-level crystallization process development capabilities, PharmaBlock is also equipped with commercialization, engineering, and equipment design capabilities.

4. Supply chain

It is very important for a CDMO partner to have a reliable and sustainable supply chain. Material purchasing in many cases takes up a key part in cost. Especially for the campaign with large demand of APIs, even a small percentage difference could greatly influence the CoG. Of course, not to mention the lag in raw materials supply will cause the costly delay of clinical material delivery which is even worse.

A CDMO partner should always have a plan B once the supply of raw materials becomes problematic. At PharmaBlock, our experience in building blocks synthesis and scale-up helps us by having abundant raw material supplier resources and capability plus capacity to produce the raw materials by ourselves as many of our building blocks are the key fragments in the clinical candidate structures.

Moreover, upon their consent, we always help our partners cut down the cost by continuously optimizing the scale-up process of building blocks as the raw materials. As they are usually not registered in the filing document, there's less constraints for the process improvements.



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[2] Merck & Co., Inc. & Codexis, Inc, "Presidential Green Chemistry Challenge: 2010 Greener Reaction Conditions Award | US EPA," US EPA, 2010. Available: https://www.epa.gov/greenchemistry/presidential-green-chemistry-challenge-2010-greener-reaction-conditions-award

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