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CASE STUDY

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The criticality of API CDMO selection: insights from a client

The global value of the oncology drug market is estimated to reach nearly $180 billion by 2025, making it a targeted area of opportunity for many pharmaceutical companies.[1] Yet, despite its promise, the complexity of cancer and the drugs used to treat it present several risks when it comes to the cost of development and the threat of failure.

Small and emerging companies entering this space already face significant challenges related to limited funding and resources, such as technical expertise and capacity, making it imperative they find a competent partner to support them. This requires not just a Contract Development & Manufacturing Organization (CDMO) that can fill these gaps but also one that values the relationship enough to maintain clear and open lines of communication at every stage of a project. Doing so helps avoid common pitfalls that can result from a lack of transparency, especially for a company taking on the exciting but challenging field of oncology.

Finding this type of partner as it began its journey was top of mind for 4SC AG, a clinical-stage biopharmaceutical company focusing on the development of small molecule drugs targeting key indications in cancer with high unmet medical needs. With less than 50 people in its company, 4SC sought a CDMO that could provide the know-how and mutual trust necessary for the small company to successfully develop its lead asset, resminostat. It found this partnership with Thermo Fisher Scientific Pharma Services, where an experienced team helped 4SC overcome active pharmaceutical ingredient (API) manufacturing hurdles, leading to a path toward commercial success.

The power of effective project management

Resminostat is an orally administered histone deacetylase inhibitor that could potentially be used for a wide range of oncology indications, both in monotherapy and in combination with other anti-cancer drugs.[2] Dr. Rolf Krauss, Director CMC at 4SC, says they ultimately selected Pharma Services based on positive interactions with the project management team. “Some factors we use to evaluate the capabilities of a potential partner, such as experience and cost, are fairly simple to measure. However, what is most important is how effective and empowered its project management team is, which can be determined by how openly and honestly they communicated from the start,” he explains. “With Pharma Services, we were given direct communication with the account manager, and his expertise gave us the confidence we could consult him and his team on any issue and they would be able to help.”

As with most project management teams in drug development, Pharma Services' consists of a project leader working on-site with the experts and a business manager overseeing the commercial side of the project. What makes the structure of Pharma Services' teams unique, though, is that the project leader and business manager positions are filled by chemists and project engineers with several years of experience in lab and production settings. "It is imperative that the technical experts can communicate directly with their counterparts while keeping the project leader on both sides in the loop," explains Dr. Hanno Wertal, Senior Project Manager, Thermo Fisher Scientific. "That way, information is not lost in translation, and the project leader can rely on his strong technical background to steer discussions in the most productive direction."

Pharma Services' project teams are small, including only a quality specialist, analytical chemist, chemist, process engineer and manager, so core members can communicate directly. This leads to faster response times, something smaller companies are often used to. If necessary, the composition of the teams can be adjusted to better fit the level of knowledge required for the project. "It is important to have a mix of young chemists who question things and have a certain drive and experienced experts who have a better overview and can draw from previous projects," says Wertal. "It is a key task for the project leader to 'feel' which approach best suits the customer."

He says the relationship should begin with a face-to-face discussion, where all team members from the customer's side and Pharma Services' internal team get to know each other and contacts can be established. Dr. Krauss agrees this is a vital part of CDMO/customer relationship. "Having direct communication with the people who will play a critical role in the project, such as developing the synthesis, is essential to breaking down the silos that so often exist in our industry," he explains. "If those people have expertise and experience with that task, they can understand our concerns and address them in real time." As challenges were encountered later in the project, this aspect of their partnership became a key factor in maintaining the timely delivery of 4SC's clinical materials.

Readying for the reality of API development

Drug development is an inherently costly and risky undertaking that will undoubtedly have setbacks and surprises along the way. Fundamental to the long-term success of a molecule, though, is the development and validation of the API manufacturing process. Working with a CDMO with the resources to seamlessly align the development and manufacture of an API and finished drug product will help speed a molecule through development and prepare a company for commercial success faster. This, combined with open lines of communication, can provide the tools necessary to overcome challenges that often find their way into the drug development process.

For example, due to tightened, process-immanent raw material specifications, an additional step had to be added at the beginning of the five-step synthesis for resminostat shortly before scheduled production. In addition, a challenging impurity control strategy required longer analytical and experimental development times on nearly all of the steps. Resminostat is an anti-cancer agent and a high-potency compound; thus, very high safety standards had to be applied. New results from API physicochemical characterization and drug product formulation made a near-real-time update of the accompanying GMP-documentation necessary. Specifically, over 500 pages of documentation had to be quickly but accurately revised, reviewed, and approved by both parties before validation could begin. This required not only fast action from Pharma Services but also seamless collaboration between both parties, facilitated by weekly teleconferences and several face-to-face meetings.

Although the issue could have caused serious and costly delays, the teams worked together and overcame the challenge, leading to a successful validation campaign with a substantial amount of material produced and ready for commercial use. "In our entire communication with Pharma Services, we always felt they possessed the capabilities and forward-thinking necessary to deeply understand our process, determine what we needed, and help us through any challenges," says Dr. Krauss. "Almost more importantly, we felt we were being given the same amount of attention as they would give a bigger company and that it meant just as much to them as it did to us that this project finished successfully."

Today, resminostat has shown to be well-tolerated in several clinical trials and is currently being investigated in a pivotal study in cutaneous T-cell lymphoma (CTCL) by 4SC.4 Looking forward, 4SC is eager to pursue the development of another candidate in its pipeline, domatinostat. This is another orally administered small molecule treatment for cancer, which is currently being tested in clinical trials. Once these trials are complete, 4SC plans to advance domatinostat into a pivotal case study, where it will look to Pharma Services for its API development. Dr. Krauss explains, "The relationship we developed with Pharma Services during the development of resminostat gives us confidence that we can entrust our company's future with their team, and they will offer us the expertise, effective problems olving, and attention we need to bring our drugs to the market safely, efficiently, and with the highest level of quality."

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