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PICKING THE RIGHT CDMO PARTNER FOR INTEGRATED AND ACCELERATED PEPTIDE THERAPEUTIC DEVELOPMENT

Protein therapeutics have played an important role in medicine since the advent of insulin therapy to treat diabetes in the 1920s.[1] More recently, peptides have emerged as valuable therapeutics with attractive drug properties.

Due to peptide therapeutics' potency, selectivity, and low toxicity, researchers are exploring them for a wide range of human ailments, including cancer, pain, and metabolic disorders.[2] In fact, the peptide therapeutics market is expanding rapidly. Peptides in the US are a $28 billion industry that's expected to grow 9% annually over the next 5 years.[3] As of February 2021, there were about 80 peptide therapeutics available globally. Many new therapeutic peptides are in the pipeline, with at least 150 in clinical development worldwide and over 400 in preclinical studies.[2]

Despite the safety, selectivity, and success of established peptide therapeutics, the full potential of these treatments has yet to be realized. Notably, the manufacturing pipeline presents many hurdles that can result in failure.[3] Thoughtful consideration of the best development strategy can give peptide therapeutics the momentum they need to hit the market and make an impact in the clinic.

CHALLENGES AND HURDLES DURING PEPTIDE DEVELOPMENT

The first challenge for therapeutic peptide innovators, particularly for smaller biotech companies, is managing all aspects of development and production from discovery to phase I clinical trials. Due to the complex nature of peptide drugs, many smaller companies need to outsource at least one part of the development process, such as non-natural amino acid production, peptide library production for screening, peptide lead synthesis (especially of complex peptides and conjugates), the development and application of analytical methods, and peptide formulation development, among other processes.

Then when a novel peptide proves effective in phase I clinical trials, scale-up to late phase clinical trials and eventual commercialization requires large-batch manufacturing. This has proven to be a barrier to development and production of peptide therapeutics even for larger innovators.

"Clinical trials lead to upscaling of the manufacturing process, and everything comes down to the scaling up process," says Garry Laverty, senior lecturer at Queen's University in Belfast, UK. "It may be easy to make something on a laboratory scale, but once you start scaling it up for clinical or commercial use, the process can be very expensive and complicated."

Laverty says the material needed for preclinical studies can typically be produced in-house. But clinical studies require much larger quantities of material that must meet strict regulatory requirements for quality to ensure safety and efficacy in humans.

In addition, many peptide therapeutics require complex synthesis processes or recombinant systems to manufacture, which can be intensive in terms of capacities and labor. Throughout, producers need to adhere to good manufacturing practice (GMP) regulations aimed at ensuring safety and quality. Laverty says that due to the high monetary and labor costs, the scale-up process from preclinical to clinical or commercial use is associated with a significant risk of timeline delays and failure.

Conjugating a peptide therapeutic can improve its stability and efficacy, but synthesizing and attaching the conjugate adds a layer of complexity during manufacturing. "The conjugated part of a peptide therapeutic also has to be developed, which involves a different kind of discovery process," says Yen-Huei Lin, executive director of biopharmaceutical development and manufacturing at Neuraly.

Unnatural amino acids or cyclic peptides may also require more troubleshooting during the scale-up process because of their complicated chemistries.

Many biotechnology companies lack the appropriate resources to increase peptide therapeutic production to the level and quality needed for clinical studies. Outsourcing part of or all the development and scale-up processes can help companies get their therapeutic to patients faster.

HOW PARTNERING CAN HELP OVERCOME BARRIERS

Partnering with specialists, including contract development and manufacturing organization (CDMOs), can provide the capability, capacity, and expertise to facilitate the development and manufacturing of peptide therapeutics for clinical studies and, ultimately, introduction to the market.

"Peptide specialist manufacturers have the equipment to purify and analyze therapeutic peptides at large scale and to quality requirements of drug regulators," Laverty says.

WuXi STA integrated R&D and manufacturing site in Changzhou, China

Source: WuXi STA

This expertise can help biotech companies achieve the output they need to move their therapeutic forward without building an in-house system from the ground up, which would slow development or be cost prohibitive.

"Even large innovators may run into a capacity issue," says William Fang, executive director and head of the oligo and peptide business at WuXi STA. "Outsourcing to a CDMO with available capability and capacity could lessen the bottleneck."

Jean-Luc Poyet, research director at the French National Institute of Health and Medical Research, can attest to the utility of partnering with CDMOs. He founded the biotech company Jalon Therapeutics earlier this year with the goal of bringing to market peptide therapeutics that treat aggressive cancers. As a small start-up, Poyet says, partnering with CDMOs is often necessary to expand capacity and can provide additional benefits, such as toxicity analysis.

"CDMO partnership is very important in terms of processivity—on our own, we don't have the processivity to make GMP peptides," Poyet says. "We try to analyze as much as we can, but these partnerships are mandatory to expand our capacity." The need for expertise is even more pronounced in the case of peptide conjugates. Innovators of conjugates can benefit from finding one partner that can handle every component—the carrier, linker, and payload—from discovery to commercial scale rather than sourcing individually and possibly needing another provider for conjugation. Working with a partner that has experience in development and manufacture across all components of conjugates as well as experience with the conjugation process can save time and money, reduce risks, and simplify supply chain management.

In short, CDMOs can aid the peptide therapeutic discovery, development, and manufacturing process in the following key ways:

- *Providing expertise* CDMOs typically offer a range of development and manufacturing strategies, with large teams of chemists and knowledge gained from various projects, enabling faster development. Experience with the specific challenges associated with each development step may also help accelerate the project timeline, and having a dedicated analytical team responsible for developing and validating methods can also speed development.

● *Expanding capacity* CDMOs have significant resources, especially in terms of space, labor, and equipment. Once a candidate progresses, they will have the capacity to provide the product on a sufficient scale, which may not always be possible without a partnership.

● *Timeline adherence* A CDMO's expertise and capacity can ensure projects are moving quickly toward regulatory approval and clinical use. CDMOs with broad capabilities to handle all a project's components, including amino acid reagent, peptide production, various conjugations, and drug product formulation can also help prevent delays.

● *Risk management* CDMO's with a strong track record of regulatory agency inspection approvals can be critical to staying on track. Experience with the chemistry, manufacturing, and control (CMC) requirement of regulatory filings at major health regulators can help a CDMO evaluate risks in the development plan and identify contingencies.

WHAT TO CONSIDER WHEN CHOOSING A PARTNER

CDMOs offer a range of services and can provide expertise throughout the product development pipeline. When partnering with a CDMO, consider if their expertise sufficiently fits with the project needs, Laverty says. Beyond expertise, he says, there are other important factors to consider. The development process can be expensive and resource intensive, so understanding what a CDMO can offer at what price is important. Establishing clear guidelines surrounding intellectual property can also help ensure a smooth partnership. Finally,

This 1,000 L peptide synthesizer is at WuXi STA's Changzhou, China site.

Source: WuXi STA

ensuring the CDMO has a proven track record of complying with GMP and other regulations will help prevent delays.

When it comes to the challenge of metabolic stability of peptide therapeutics, the current approaches include unnatural amino acid incorporation, C- and N-terminal modification, backbone modifications, and various conjugates to extend the half-life and facilitate cellular uptake. These modifications require chemists with both peptide and small-molecule expertise. Few CROs or CDMOs have a deep bench of chemists able to tackle all these projects in the same place.

Even for early-stage innovators that can perform all the above steps in-house, preparing a drug candidate for an investigational new drug (IND) filing and clinical trials requires a skill set not found at many smaller innovator companies. The regulatory requirements can be daunting for GMP process development and production, analytical methods for development and validation, formulation development, stability testing, and CMC writing. A full-service CDMO can take bench chemistry to IND and beyond and can do all the steps in parallel.

NEXT-GENERATION THERAPEUTICS

The increasing prevalence of chronic diseases and outbreaks of new diseases has spurred the need for new and more effective medications.[3] Peptide therapeutics are a promising class of treatments that is rapidly expanding to target a wide range of disorders.[3] Consideration of the peptide therapeutic development process, including careful selection of CDMO partners, can position peptide therapeutics to be key players in the pharmaceutical market for years to come.

CASE STUDY

Neuraly, a biotechnology subsidiary of D&D Pharmatech based in Maryland, developed a cyclic peptide conjugated with PEG called DD01 to target glucagon-like peptide-1 receptor (GLP1R), and glucagon-like glucagon receptor (GCGR). They observed it was effective at controlling blood glucose and at reducing body weight as well as liver fat in animal models.[4, 7]

CHALLENGES: Neuraly had two critical deadlines. First, deliver material on time for a scheduled GLP toxicity study in 4 months; then deliver GMP material, drug product formulation, and CMC dossier for an expected IND filing in 11 months.

"The timeline we were trying to target was short, and we knew the synthesis chemistry would be challenging because of the structure and conjugation of our peptide," says Yen-Huei Lin, executive director of biopharmaceutical development and manufacturing at Neuraly.

The research-grade benchtop process had very low yield that would have required extensive time and resources to produce at scale. Other challenges arose from limited supply of raw materials, with extra logistic complications due to the COVID-19 pandemic.

"Sometimes chemistry is easy on the benchtop, but when you scale it up you have to balance the yield with GMP process control," Lin says.

SOLUTION: Neuraly wanted to quickly enter human trials so decided to partner with a CDMO to help provide the capacity and expertise needed to achieve its timeline. They started by identifying organizations capable of peptide synthesis with conjugation and injectable formulation expertise; they then talked with each group to find the right balance of regulatory compliance, quality, capacity, price, and team mindset. In the end, Neuraly chose WuXi STA as its CDMO partner in part because it could offer active pharmaceutical ingredient (API) development and manufacturing, drug product formulation, and CMC writing within the same facility.

Culture match is another key decision point. "Neuraly is a small biotech company, so we needed not just a supplier but an extended team or partner that understands our scenario in terms of science, budget, and time frame," Lin says. "WuXi STA's transparency, capabilities, and partnership are what finalized them as our partner."

THE DD01 PROJECT REQUIRED SEVERAL KEY ACTIVITIES:

- Process development and manufacture for both the non-GMP toxicity material and the GMP material for the IND application, including developing and validating analytical methods.
- The 30 amino acid peptide with a cyclic section, containing a free cysteine for conjugation, required preparative high-performance liquid chromatography purification both before and after conjugation
- Injectable drug product formulation and manufacture of a demo batch
- Writing support for the CMC section of the IND for both the API and drug product

RISK MITIGATION STRATEGIES

The API project team conducted an extensive risk assessment—paying particular attention to supply chain issues magnified by the pandemic—to determine the path forward.

Risk 1 The best synthetic path to a molecule isn't always obvious at the beginning of a project, and choosing an inefficient route can waste time and other resources. WuXi STA's contingency plan for DD01's linear synthesis involved starting three work streams in parallel. One stream focused on the optimization of the original linear synthesis with on-resin cyclization, and a second stream aimed to scale up development of this same route. A third stream initiated design and feasibility of two new synthetic routes if the original synthesis approach didn't work out.

The team quickly concluded that the original linear approach was not suitable for scale-up, as only 5% peptide API purity was obtained even after process and condition optimization. The team found an alternative approach combining fragment and linear synthesis methods that improved purity to 15–20%. With that, over 20 batches of DD01 were produced in only 6 weeks.

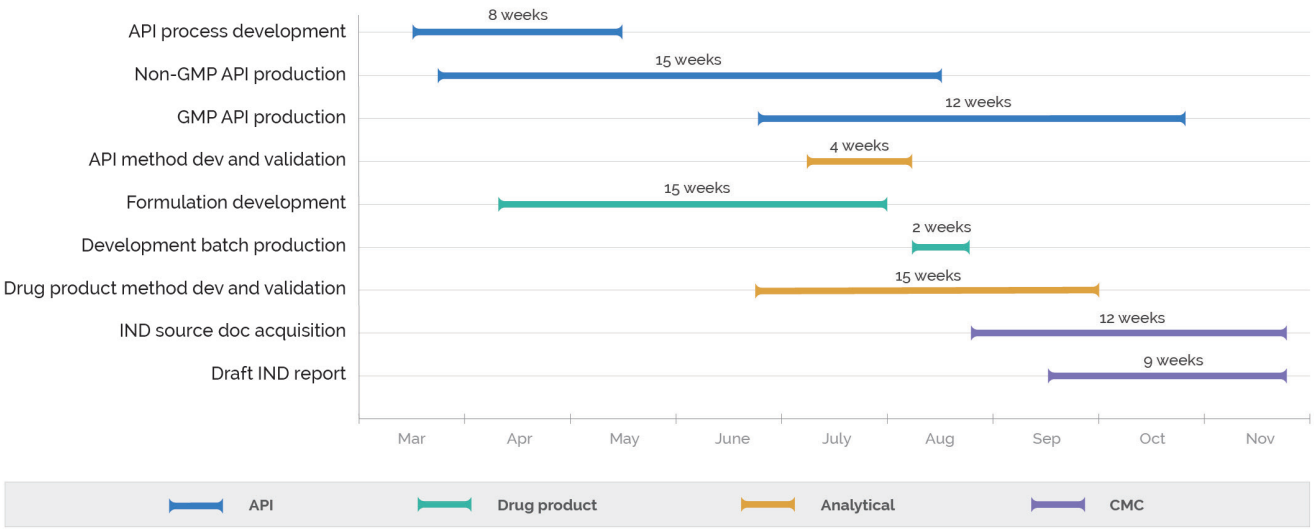
Risk 2 A special building block required for the conjugation had very limited stock and lead time up to 1 year.

To address the supply chain risk, another team screened various reaction conditions over 25 experiments and found an optimized conjunction process that improved the yield by four times, which significantly reduced this material requirement.

The teams were able to meet both deadlines by conducting many activities in parallel. A non-GMP batch enabled

toxicity studies within 4 months, and the entire project was completed in 10 months—a month ahead of the IND filing deadline. "WuXi had the capacity and resources to ensure timeline commitment and to troubleshoot any issues along the process," Lin says. "We wouldn't have been able to file [for regulatory approval] within 10 months otherwise."

Integrated peptide conjugate project in 10 months



Source: WuXi STA

SUMMARY

- The synthesis was completed using the new optimized linear + fragment approach, which improved the crude purity by 35% and overall API yield by four times compared with the initial route.
- The optimized conjugation conditions stretched the limited supply of the special building block.
- Developing and validating analytical methods as well as formulation work were expedited because teams work closely together.
- The entire CMC process was documented by the CMC writing team, who assembled the dossier in time for the IND filing deadline.

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ABOUT WUXI STA

WuXi STA, a subsidiary of WuXi AppTec, is a leading pharmaceutical CDMO capability and technology firm serving the life sciences industry, with global operations in China, the US, and Europe.

WuXi STA's comprehensive peptide platform provides customers worldwide a truly one-stop solution from drug discovery to commercial manufacturing for both API and drug product, with over 560 dedicated peptide scientists and staff from six peptide R&D and manufacturing sites.

The CDMO's vertically integrated peptide API capability covers unnatural amino acid catalog products (over 2,500 amino acids); custom peptide synthesis; peptide-based conjugation synthesis; and comprehensive analytical support, including unique enantiomeric purity analysis. WuXi STA's chemistry capability includes both solid- and liquid-phase synthesis.

WuXi STA's large-scale peptide production capacity enables multiple project simultaneously, with nine production lines at various scales up to 1,000 L synthesizers. Another three production lines, including synthesizers of up to 2,000 L, will be ready for operation by 2023.

The company's platform supports 1,000-plus clients worldwide, delivering on over 10,000 peptide compounds every year.

To learn more: peptide.wuxiapptec.com

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