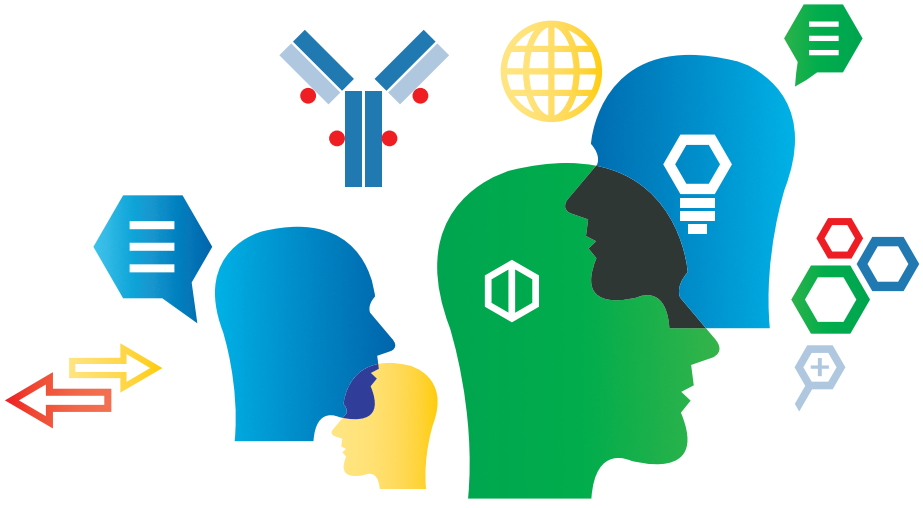
The Watershed Moment for ADCs has Arrived

Now, CDMO Selection is the Last Barrier

As far back as ten years ago, antibody drug conjugates (ADC's) were being talked about as the next big breakthrough in pharmaceuticals due to their highly targeted approach to therapies, especially in areas such as oncology. When Adcetris® became the second ADC approved by the U.S. Food and Drug Administration (FDA) in 2011, it was predicted to be a watershed moment when the floodgates would open for more approvals and novel ADC approaches. Despite that possibility, the approval of nine ADC therapeutics since 2011 has only occurred within the last two to three years. Alongside the increasing number of approvals, we have also seen an expansion in therapeutic uses for ADCs outside of oncology (including for inflammation and rheumatoid arthritis), new bioconjugate combinations and a larger number of payloads and linker alternatives. If we dig a little deeper, it is clear that the recent wave of approvals is no rarity, and our excitement for the future of ADCs is now justified. There are approximately 90 ADC candidates now in clinical development and well-over 200 candidates in preclinical development. Adding to this, we expect that there will be approximately 20-25 Investigational New Drug (IND) applications for ADCs by the end of 2020, which is in line with the last two years where there have been 18-20 applications each year. Part of the reason behind this surge in the antibody-drug conjugate space is that many of the new developers have learned from the difficulties encountered when developing first-generation ADCs, and the second- and third-generation targets are proving much more successful and well-tolerated in vivo.



WuXi Biologics is a global company with leading open-access biologics technology platforms. STA Pharmaceutical, a subsidiary of WuXi AppTec (WuXi STA), is a leading pharmaceutical development and manufacturing capability and technology platform.

Understandably then, we have seen some big moves from large pharmaceutical companies into the ADC arena. In the last month alone, two notable deals highlight this resurgent interest in ADCs by Big Pharma. Gilead Sciences acquired Immunomedics for approximately $21 billion and through this acquisition will be looking to build on the company's recent approval for Trodelvy™ (sacituzumab govitecan-hziy), a first-in-class Trop-2 directed ADC indicated for the treatment of adults with metastatic triple-negative breast cancer (mTNBC). Secondly,

"Despite the recent approvals, ADCs still, at times, come with significant development and manufacturing challenges."

Merck's $1.6 billion deal with Seattle Genetics for ladiratuzumab vedotin (LV) shows that we may see an increasing interest in ADCs combined with checkpoint inhibitors. With the abundance of ADCs in the drug pipeline and increasing interest from large pharmaceutical companies, it appears that we have arrived at the long-awaited watershed moment.

> *"Increasingly, innovators are looking to work with CDMOs that can handle at least two or more stages of production... between development phases and through the supply chain"*

Despite the recent approvals, ADCs occasionally come with significant development and manufacturing challenges. These obstacles require innovators to be specialists in both the development and manufacturing of biologics and small molecules, as well as bioconjugation. In fact, the manufacturing difficulties are such that a remarkable 70-80 percent of ADCs under development are outsourced. The contract service market has responded to this growing demand and the industry has made sizable investments to keep the pipeline of candidates advancing at a record pace. Yet with increasing difficulties to access capacity from the best contract development and manufacturing organizations (CDMOs) and with the complexity of the supply chain that comes with developing any ADC, innovators, particularly smaller biotechs, are faced with difficult choices about how best to advance candidates through chemistry, manufacturing and controls (CMC) development and into clinical trials quickly and efficiently while maintaining the requisite drug quality. Historically, the innovators were required to work with a minimum of three contract partners – one for the mAb, one for the payload (and potentially one more for the linker) and one for conjugation. With partners likely operating in different geographies, innovators were faced with complex global supply lines. With more molecules now advancing towards clinical trials and commercial production, and the need to advance these molecules more quickly, this multi-partner model is now evolving. Increasingly, innovators are looking to work with CDMOs that can handle at least two or more stages of production to help streamline the transition between development phases and through the supply chain.

Another challenge for innovators – and one that they will likely continue to face – is having the right skill set to bring their products through preclinical activities into clinical development. Although capacity is available, there is a shortage of experienced R&D scientists to manage all the various complexities of ADC development. What innovators need are partners with specialist teams to advance analytical, formulation and process development, and if possible, other development platforms and processes for common elements like the mAb and common payloads and linkers. One of the last big hurdles to overcome for ADC developers is getting into clinical trials as quickly as possible to help potentially deliver much needed therapeutics to patients faster.

Comprehensive bioconjugation CMC development and Drug Substance and Drug Product cGMP manufacturing (WuXi Biologics)

Integrated Drug Substance R&D and manufacturing site for small molecule, oligonucleotide and peptide (WuXi STA)

Typical DNA to IND timelines for ADCs are long, ranging between 24 to 30 months – a function of the complex development process and supply chain as well as management and coordination of multiple partners. Thus, innovators look to their CDMOs to dramatically reduce these timelines by offering more in-house services and platform processes that can be streamlined through efficient project management and expertise and quality systems that result in right-first-time execution. Taking each of the aforementioned challenges into account and looking ahead to an increasing number of smaller biotech companies with limited internal resources and expertise, the need for end-to-end partners – from discovery through to commercial production – has never been greater.

WuXi Biologics and STA Pharmaceuticals, a WuXi AppTec company (WuXi STA), are two distinct examples of companies that have answered the call over the past few years and now offer the most comprehensive set of in-house capabilities to handle all stages of ADC drug development and manufacturing. On top of the comprehensive capabilities, what makes these two companies so unique is the close geographic proximity of all of their facilities in the cities of Wuxi and Changzhou in China (within driving distance) across the entire development and manufacturing spectrum – allowing them to reduce the complexity of working with numerous service partners across various stages of development. In addition, WuXi Biologics and WuXi STA's experienced R&D scientists offer unmatched expertise for certain critical aspects of the development or manufacturing process.

WuXi Biologics not only offers one-stop mAb CMC development capabilities and extensive manufacturing capacities for antibody production, but last year it also established a dedicated state-of-the-art ADC GMP bioconjugation and drug product filling and lyophilization facility within driving distance of the mAb production sites. This bioconjugation and fill site, which can safely handle a wide variety of highly potent or toxic payloads classified as OEB 5, will further expand to include 500 L bioreactors and a 20 square meter lyophilizer in the next few years to handle the ADC industry's increasing commercial manufacturing needs. Further, WuXi Biologics continues to lead the industry in reducing the timelines required for ADC development. The CDMO has also been successful in bringing multiple ADC programs to the IND filing stage in 15 months or less, nearly cutting in half the traditional development timeline.

> ***"One of the last big hurdles... for ADC developers is getting into clinical trials as quickly as possible to help potentially gain a competitive advantage and reduce their burn rate"***

These shortened timelines are due to well-vetted development platforms and highly-efficient and well-controlled project management and supply chain systems. WuXi Biologics will also offer a global "dual source" supply chain by 2023 for their commercial partners.

Although ADC companies have learned from past setbacks connecting payloads to antibodies to improve the ADC's pharmacokinetic properties, challenges still remain, especially in the areas of controlling the number of payload molecules conjugated to the antibody. WuXi Biologics' ADC research team developed a novel technology platform – WuXiDAR4 – to help address the control of the drug to antibody ratio and further advance bioconjugates. The WuXiDAR4 platform greatly enhanced DAR4 (four payload molecules per mAb) percentage in the final ADC product and also improved conjugation efficiency. Through the WuXiDAR4

platform, the tightly controlled ADC product homogeneity enables more accurate assessment of clinical efficacy and most importantly helps ensure greater patient safety.

WuXi STA has built industry leading high potency API (HPAPI) handling capabilities from preclinical through commercial manufacturing with integrated analytical capabilities. The team can handle HPAPI with an occupational exposure limit (OEL) as low as 10 ng/m^3 for all common reactions at the drug substance sites in Jinshan and Changzhou. The manufacturing capabilities include HP labs, a kilogram-scale HP lab and a HP plant with more than 10 reactors ranging from 1 L-1,000 L. A large toxin/linker library is also available, which gives great flexibility for the evaluation of linker/payload combinations. WuXi STA offers popular payloads such as MMAE/F, DM1/DM4, Calicheamicin, Duocarmycin, Doxorubicin, SN-38 and PBD and helps develop and manufacture novel payloads and new conjugation modalities that include oligonucleotide- or peptide-based linkers. WuXi STA has developed an integrated oligonucleotide, peptide and payload platform that includes in-house analytical support from development to commercial manufacture. This platform results in much shorter timelines due to the close collaboration among the multi-discipline R&D and manufacturing teams. All WuXi STA sites have successfully passed multiple inspections from major regulatory agencies, thus meeting the highest quality and Environment, Health, and Safety (EHS) standards.

Both WuXi Biologics and WuXi STA have hundreds of dedicated and highly-trained scientists in each CMC discipline required for ADC development and throughout the entire ADC biologics, small molecule and bioconjugation supply chain. Since 2014, over 70 different companies have taken advantage of these extensive capabilities in one form or another – including 14 completed IND projects, and one program in phase III. The aforementioned projects all used WuXi Biologics and WuXi STA from concept through development and as supplier of all intermediates (mAb, payload and linker) and as the final drug product manufacturer. Currently, WuXi Biologics and WuXi STA are managing more than 30 integrated ADC programs in the preclinical to late stage clinical continuum. The existing expertise, robust communication and project management, combined with the geographic proximity of the manufacturing facilities and globally-approved quality systems establishes WuXi Biologics and WuXi STA as two of the few end-to-end partners of choice for pharmaceutical and biotech customers globally.