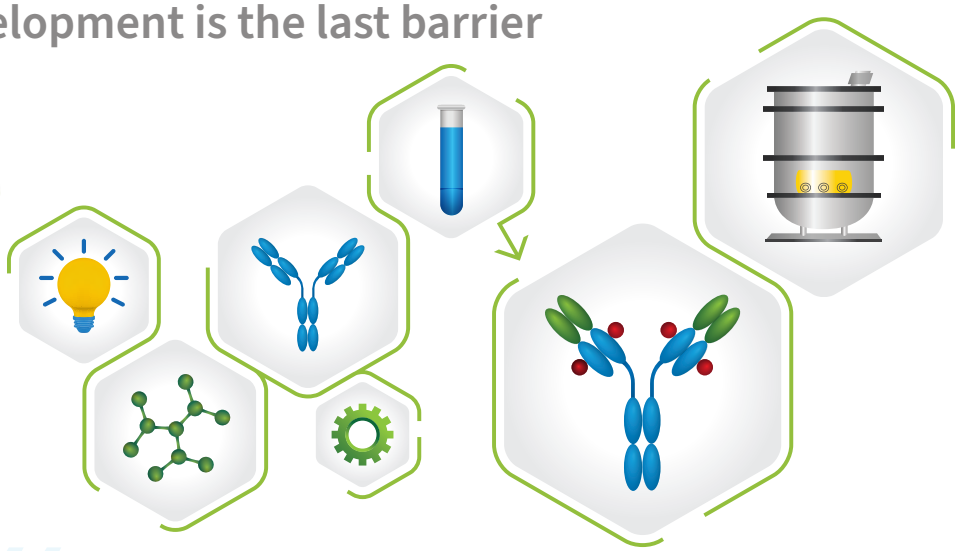
The Watershed Moment for ADCs has Arrived -

More efficient CMC development is the last barrier



WuXi XDC, a WuXi Biologics subsidary, provides end-to-end Contract Research, Development and Manufacturing (CRDMO) services for companies developing ADCs and other bioconjugates.

Ten years ago, antibody-drug conjugates (ADCs) were being talked about as the next big breakthrough in pharmaceuticals due to their highly targeted approach, 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 novel ADC approvals. Despite that possibility, the approval of 11 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 (e.g., 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 100 ADC candidates now in clinical development and well-over 150 candidates in preclinical development.

Adding to this, we expect that there will be approximately 20 Investigational New Drug (IND) applications for ADCs in 2021, 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 drug developers have learned from the difficulties encountered in those first-generation ADCs, and thus, the second- and third-generation ADCs are proving much more successful and well-tolerated in vivo.

With this level of ADC activity in clinical trials, it is understandable then, that we have seen some big moves from large pharmaceutical companies into the ADC arena. For example, in 2019, AstraZeneca prepaid US$1.35 billion and a milestone of up to US$5.55 billion to obtain a license for Daichii Sankyo's ADC, trastuzumab deruxtecan. Then, in 2020, two notable deals helped 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 govitecanhziy), a first-in-class Trop-2 directed ADC indicated for the treatment of metastatic triple-negative breast cancer (mTNBC).

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

Merck's $1.6 billion deal with Seagen's ADC ladiratuzumab vedotin (LIV-1) 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.

Despite the recent approvals, ADCs can 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.

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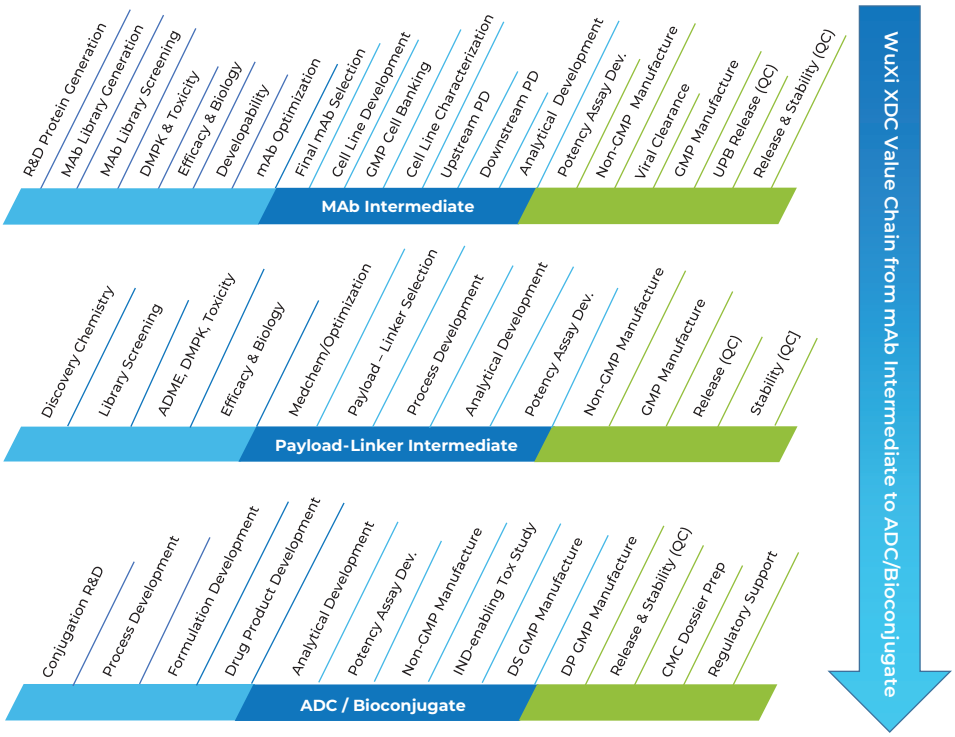


With partners likely operating in different geographies, innovators were faced with complex global supply lines. With more molecules now advancing towards clinical trials and commercial production, and the need to advance these molecules more quickly, this multi-partner model is now evolving. Increasingly, 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.


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

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.

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 afore-mentioned 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.

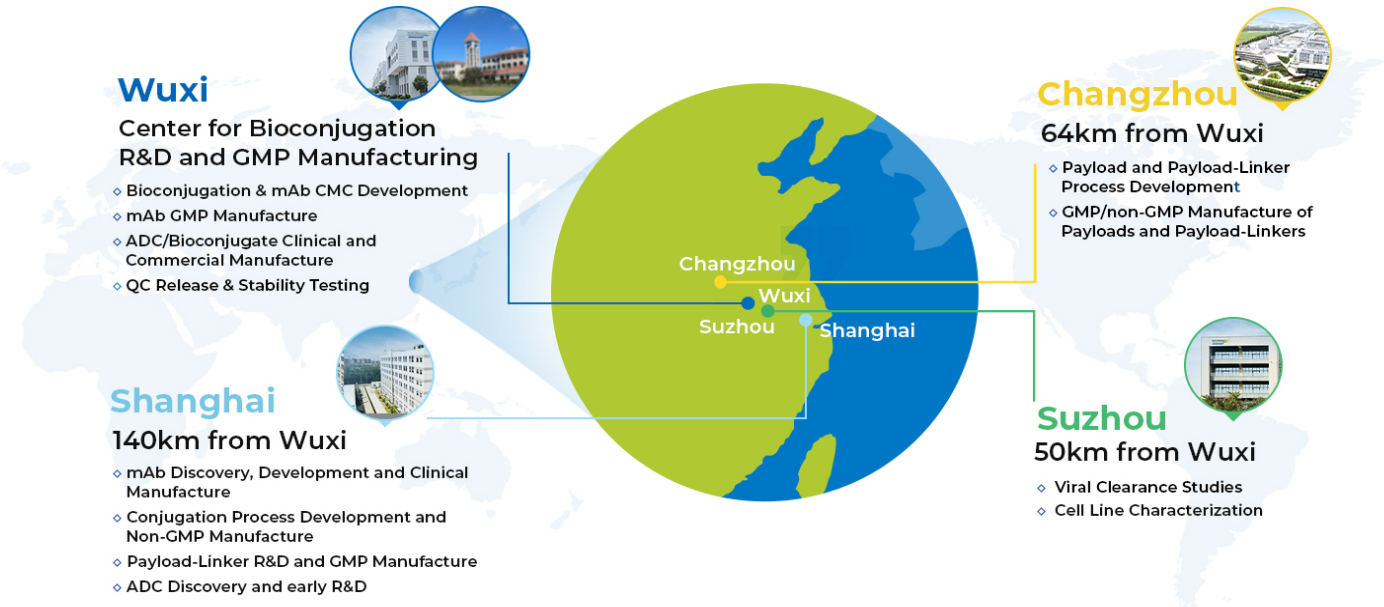
WuXi XDC site for integrated R&D and manufacturing of payloads and linkers (co-located within a site operated by WuXi STA, a WuXi AppTec Subsidiary

WuXi XDC, a WuXi Biologics subsidiary, is a distinct example of a company that has answered the call. The organization is a joint venture between industry giants WuXi Biologics and WuXi AppTec's subsidiary, STA Pharmaceutical (WuXi STA). WuXi XDC offers the most comprehensive set of in-house capabilities to handle all stages of ADC drug discovery, research, development, and manufacturing. On top of the comprehensive capabilities, what makes this company so unique is the close geographic proximity of their facilities in China (all are within driving distance) across the entire discovery, development, and manufacturing spectrum – allowing them to reduce the complexity of working with numerous service partners across various stages of development. In addition, WuXi XDC's experienced R&D scientists offer unmatched expertise for certain critical aspects of the ADC engineering, preclinical candidate (PCC) evaluation, development, and manufacturing process.

WuXi XDC not only offers one-stop mAb discovery research, CMC development capabilities and manufacturing, but 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 formulation and fill site, which can safely handle a wide variety of highly potent or toxic payloads classified as OEB 5, have expanded to include 500 L conjugation reactors for drug substance (DS) production and a 20 square meter lyophilizer to handle the ADC industry's increasing commercial manufacturing needs. The annual conjugation batch capacity (DS) is over 100 batches and up to 200 kg per year. The annual drug product (DP) fill capacity is 1,800,000 20R vials for liquid formulation, and 300,000 20R vials for lyophilization formulations. The DP facility can handle 2R, 6R, 10R, 20R, and 50R container closure system (CCS) configurations. The facility has completed more than 40 projects and over 200 batches through December 2021 with 0 rejected lots. In addition, WuXi XDC is expanding its' bioconjugation manufacturing capability and capacity to meet the demand of current clients for large scale and commercial Drug Substance and Drug Product manufacturing.

Further, WuXi XDC continues to lead the industry in reducing the timelines required for ADC development. The CRDMO has 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. These shortened timelines are due to well-vetted development platforms and highly efficient and well-controlled project management and supply chain systems.

Although the industry has seen much success in expanding ADCs' therapeutic index and achieving market approvals, challenges remain, especially in the areas of controlling the number of payload molecules conjugat-



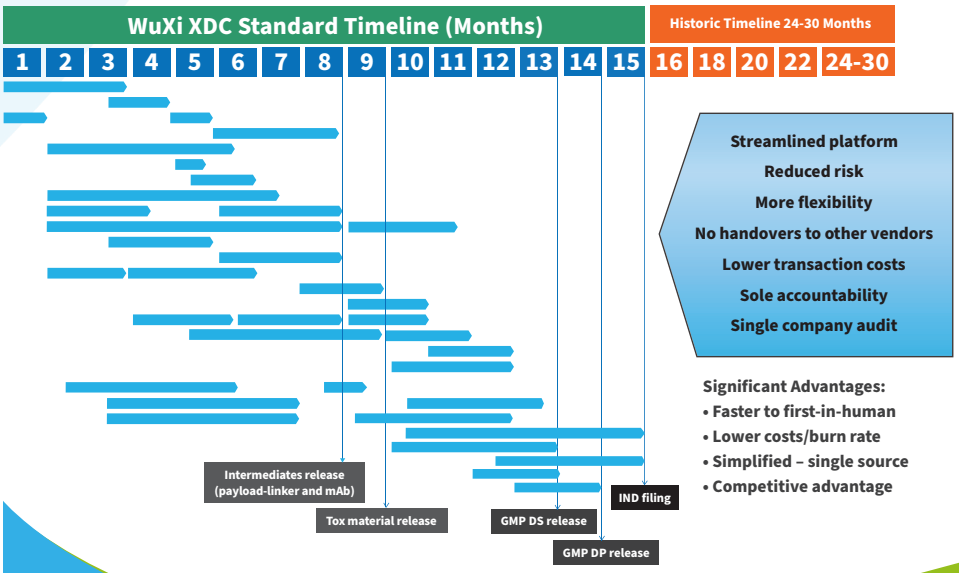
ed to the antibody. WuXi XDC's ADC research team developed a novel technology platform – WuXiDAR4™ – to help address the control of the drug to antibody ratio (DAR) and further advance bioconjugates. The WuXiDAR4 platform greatly enhanced the DAR4 (four payload molecules per mAb) percentage in the final ADC product and 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. The WuXiDAR4 technology has helped multiple companies advance their ADC program through IND filing and into the clinical trials.

The discovery services team also developed other tools and platforms that have supported >100 research projects each year, including high-throughput PCC screening, small scale ADC conjugate development, linker-payload combination testing, and PCC characterization or in-vitro testing of the various bioconjugate drug candidates. The team essentially serves as an extension of many clients' R&D arm and can deliver a one-stop discovery service.

WuXi XDC has maintained industry-leading high potency payload (HP compound) handling capabilities from preclinical through commercial manufacturing with integrated analytical capabilities. The team can handle HP compounds with an occupational exposure limit (OEL) as low as 10 ng/m3 for all common reactions at the manufacturing sites in Jinshan and Changzhou. The manufacturing capabilities include high potency (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 at the ADC discovery research stage. WuXi XDC offers popular payloads such as MMAE/MMAF, DM1/DM4, Calicheamicin, Duocarmycin, Doxorubicin, SN-38 and PBD and helps develop and manufacture novel payloads and new conjugation modalities that include peptide-based linker/payload combinations. WuXi XDC has developed an integrated payload-linker 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 XDC payload and linker manufacturing sites have successfully passed multiple inspections from major regulatory agencies, thus meeting the highest quality and Environment, Health, and Safety (EHS) standards.

WuXi XDC has 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 100 different companies have taken advantage of these extensive capabilities in one form or another. The WuXi XDC team has enabled 22 IND filings for its clients, and now six projects are in Phase II/III late-stage development supported by the company's vast development and GMP manufacturing capabilities. Most of the afore-mentioned projects used WuXi XDC from concept through development and as supplier of all intermediates (mAb, payload and linker) and as the final drug product manufacturer. Currently, WuXi XDC is managing more than 60 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 XDC as the rare end-to-end partner of choice for pharmaceutical and biotech customers globally.

WuXi XDC Expedited CMC Development and GMP Manufacturing Timeline



WuXi XDC, a joint venture between WuXi Biologics and WuXi STA, a WuXi AppTec subsidiary, is an end-to-end contract research, development and manufacturing organization (CRDMO) for bioconjugates including antibody drug conjugates (ADCs). The company's expert-driven, high-quality services include discovery R&D, CMC development and GMP manufacturing of antibodies or other biologics, chemical payloads and linkers, and the bioconjugated Drug Substance (DS) and Drug Product (DP).

The world's leading global single-source platform from concept to commercialization.

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