CPhI Pharma Insights

UBM

Part 4.

The rise of the integrated CDMO and 'ADCs the intersection of small and large'

PANEL MEMBER
Vivek Sharma, CEO Piramal Pharma Solutions.

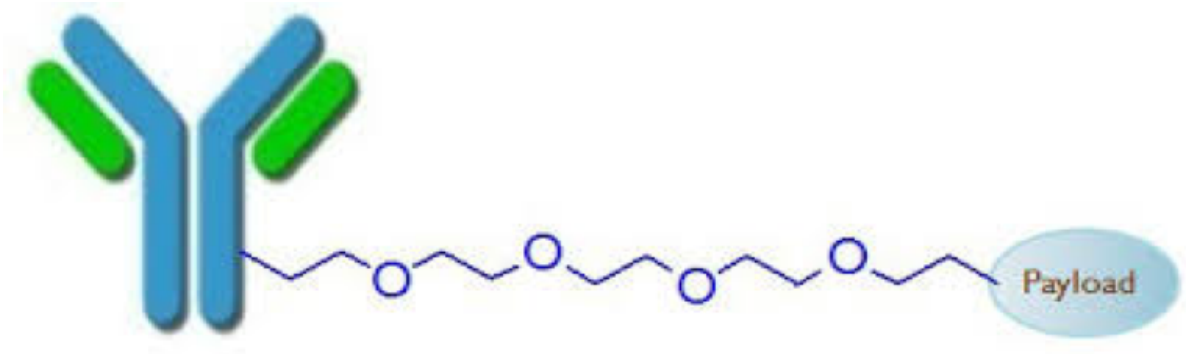
ADCs growth driven by lack of inhouse facilities, oncology and integrated CDMOs

Summary of trends forecast: the next 1-3 years

- Novel payloads that target tumour-initiating cells on third generation ADCs in phase iii will come to market in the next couple of years
- ADCs market forecast estimated to expand at nearly 20% CAGR until 2030 with 17 new drugs in late stage development, and double digit approvals of ADCs over next 3-years.
- Outsourcing of ADC manufacturing will continue to rise past 70% of overall manufacturing, with increased co-development – driven by increased biotechs and smaller companies in the pipeline needing specialist development expertise and facilities.
- Longer term (circa 5-years) the expansion of ADCs into therapeutic areas other than oncology will be the next evolution – bioconjugation in infectious disease is one potential area

Abstract

The past decade has seen significant advances in new cancer treatments through the development of highly selective small molecules that target a specific abnormality responsible for the disease. Traditional cytotoxic agents were another approach to treat cancer; however, unlike target-specific approaches, they suffered from adverse effects stemming from nonspecific killing of both healthy and cancer cells. A strategy that combines the powerful cell-killing ability of potent cytotoxic agents with target specificity would represent a potentially new paradigm in cancer treatment. Antibody Drug Conjugate (ADC) is such an approach, wherein the antibody component provides specificity for a tumour target antigen and the drug confers the cytotoxicity.



An ideal ADC has:

A highly selective Monoclonal antibody (mAb) for a tumour-associated antigen to identify cancer cell

A linker that is stable in circulation, but releases the cytotoxic agent in target cells

A potent cytotoxic agent that induces target cell death after being internalized in the tumour cell and released

Evolution of Antibody Drug Conjugates (ADC)

The foundation of ADCs' was laid back 100 years ago by Paul Ehrlich, by postulating 'magic bullets' for selectively delivering a cytotoxic drug to a tumour via a targeting agent. Nearly 50 years later, Ehrlich's concept of targeted therapy was first epitomized when clinically approved drugs with well-established mechanisms of action, such as antimetabolites (Methotrexate and 5-fluorouracil), DNA cross linkers (mitomycin) and anti-microtubule agents (vinblastine) were used by linking to an antibody targeting leukemia cells. At this point of time, polyclonal antibodies were used which had higher potential for cross reactivity due to ability of recognizing multiple epitopes on target antigen. In 1975, mouse monoclonal antibodies (mAbs) were developed using hybridoma technology by Kohler and Milstein wherein the antibodies were highly specific towards a single epitope on an antigen. This greatly advanced the field of ADCs and eventually led to development of first-generation of ADCs. For example, ADC-doxorubicin conjugate 1 (BR96-DOX) was designed using a bifunctional linker, wherein the cytotoxic drug was appended via a hydrazone moiety , and the BR96 antibody was conjugated using maleimide moiety via cysteine residues. Although curative efficacy was observed in human tumour xenograft models, the relatively low potency of doxorubicin necessitated high Drug to Antibody ratio (DARs, 8 per antibody) and high doses of the ADC to achieve preclinical activity. In clinical trials, significant toxicity was observed due to nonspecific cleavage of the relatively labile hydrazone linker and expression of the antigen target in normal tissue.

Further advancements including higher drug potency and careful selection of targets, ultimately led to the first ADC Mylotarg1-, i.e. Gemtuzumab ozogamicin to gain accelerated US Food and Drug Administration (FDA) approval in 2000 for Acute Myeloid Leukemia (AML). Despite initial encouraging clinical results, Mylotarg1 was withdrawn from the market a decade later owing to a lack of improvement in overall survival and higher rate of fatal toxicity compared to chemotherapy. Lessons learned from these failures were:

- Instability of the linker that attached the drug to the mAb
- Insufficient potency of ADC
- Immunogenicity issues observed with murine mAbs
- High antigen expression on normal cells leading to toxicity

Second-generation ADCs

The limitations and failures of first-generation ADCs were eliminated in second-generation ADCs. The premature release of drugs because of the unstable hydrazone linker in Mylotarg® had been avoided in second-generation FDA approved ADCs, by using different linkers such as:

1. Cleavable linkers: -E.g. Valine-citrulline (cathepsin cleavable) linker in Adcetris® for Hodgkin lymphoma
2. Non-Cleavable linkers: - E.g. Thioester linker in Kadcyla ® for Breast Cancer

The cytotoxic payloads used in second-generation ADCs were also more potent than in first-generation ADCs. For example, tubulin-targeting agents, such as MonoMethyl Auristatin (MMAE) used in Adcetris® is approximately 100–1000-fold stronger than DNA-intercalating doxorubicin of BR96 Dox.

Despite the improvement in cytotoxic payloads and the introduction of stable linkers, second-generation ADCs had significant limitations in terms of their heterogeneous DAR, resulting from stochastic coupling strategies between the antibody and drug. Typically, chemical conjugation between the drug and antibody occurs via the lysine or cysteine residue of the mAb, which generates DAR (range 0–8) with an average value of 3–4. Therefore, heterogeneous ADCs can contain a mixture of un-conjugated, partially conjugated, and over-conjugated antibodies leading to competition between unconjugated antibodies and drug-conjugated species for antigen binding that diminishes the activity of the ADC. By contrast, over-conjugation (DAR>4) results in antibody aggregation, a decrease in stability leading to incremental increases in nonspecific toxicity, and a reduction in the half-life of ADCs in the circulation. Overall, heterogeneous ADCs have a limited therapeutic index and tumor penetration abilities, resulting in induction of drug resistant in the tumour microenvironment. Apart from this, sometimes the ADC is poorly internalized; in such cases the cytotoxic drug does not reach the target as it is attached to antibody via a Non-cleavable linker.

Flaws from 2nd generation could be summarised as:

- Heterogeneous nature leading to limited conjugated ADC amounts with nonspecific toxicity and efficacy
- Eventually only DNA alkylating agents and tubulin polymerization inhibitors with subnanomolar activities proved to be useful for targeted delivery through ADC technology, due to limited delivered amount of ADC available in the tumour. Such drug could be used in monotherapy due to high cytotoxicity which creates resistance and narrow the therapeutic window
- Conjugation site on mAb which affects potency, stability and PK properties of the ADC
- Limitations due to nature of the linker and delivery mechanism: Only cleavable linkers have a broader efficacy as they can be active even when they are poorly internalized

Third-generation ADCs

The evolution continues and aforementioned concerns regarding the heterogeneous DARs of second-generation ADCs are been addressed in third-generation ADCs. Site-specific conjugation has been introduced to produce homogenous ADCs with well-characterized DARs and desired cytotoxicity. The site-specific conjugation of the drug to antibody provides a single isomer ADC with a uniform DAR value. Such ADCs can be made using bioengineered antibodies containing site-specific amino acids, such as cysteine, glycan, or peptide tags. For example, precise site-specific conjugation of MMAE to human IgG was developed by replacing the Ala114 amino acid of the CH1 domain of the IgG with cysteine to create a selectively engineered antibody, called THIOMAB. This ADCs had a DAR of 2 with an improved safety profile and maintenance of efficacy, compared with traditionally

conjugated ADCs with higher DARs. Alternative approaches to site-specific drug conjugation include:

(i) A thio-bridge approach : Interchain disulfides (four per mAb) are reduced and re-bridged with the drug generating a near homogenous ADC with DAR 4 and increased stability

(ii) Bio-orthogonal chemistry : Introduction of unnatural amino acids, such as p-acetylphenylalanine, or non-canonical amino acids

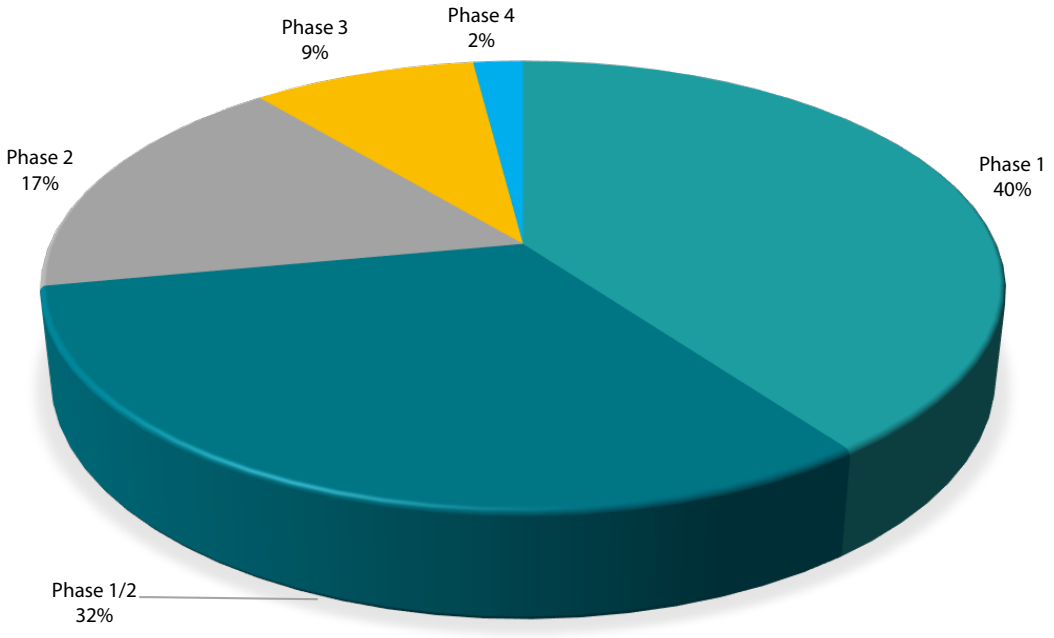
At the same time, efforts are continuing to expand on payloads with novel modes of action with a focus on agents having activity against non-proliferating cancer cells in order to widen the target area to include tumour-initiating cells (TICs) and to overcome resistance. Furthest in development are:

1. Pyrrolobenzodiazepines (PBDs):- Currently 4 molecules are in clinical phase with Rovalpituzumab tesirine moving through Phase 3
2. Topoisomerase inhibitors (Irinotecan metabolite) e.g.:- Sacituzumab govitecan has progressed significantly in Phase 3 with an average DAR of 7.6 and a relatively hydrolysable linker.
3. Cell cycle-independent activity comprise the duocarmycins E.g.;- trastuzumab-duocarmycin conjugates in Phase 3
4. Pseudomonas Exotoxins : E.g.: Oportuzumab monatox in Phase 3

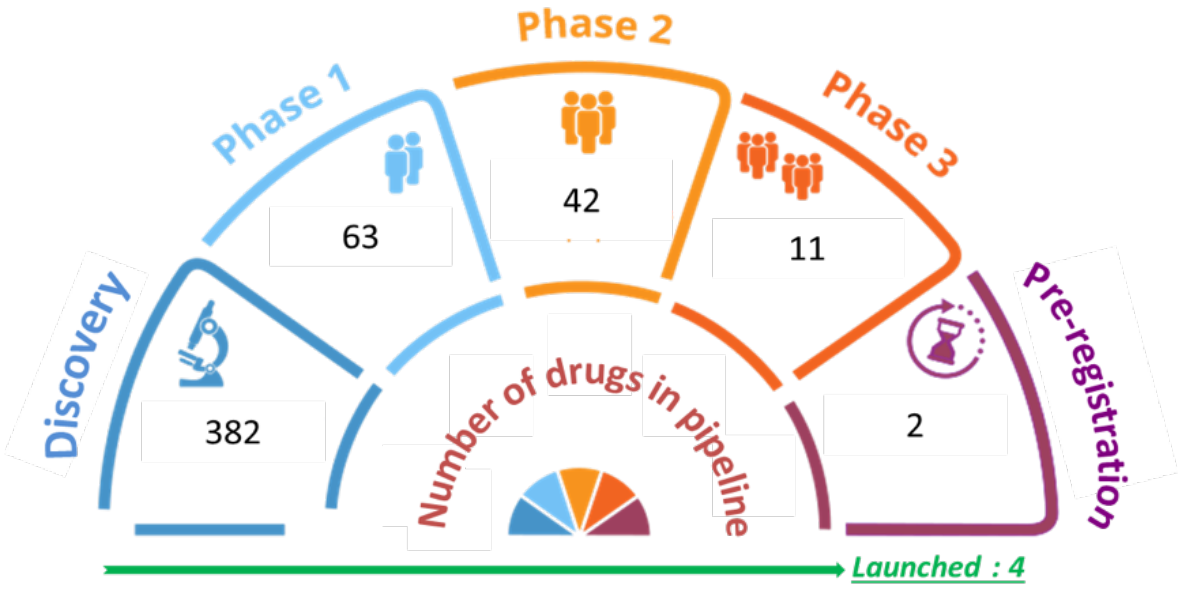
Market Outlook

Preclinical evaluation of the recent wave of third-generation site-specifically and homogenously conjugated ADCs has offered reasons for optimism in the ADC field. This understanding has speeded up the FDA approval rate of ADCs and has led to drastic increase in the number of clinical trials, especially in solid tumours. Currently 600+ clinical trials are been conducted worldwide on ADCs'.

ADC Clinical Trials



Nearly 202 ADCs have been entering into clinical trials out of which 116 are actively progressing. There are about 23 new ADCs in last 12 months increasing at a rate of 30%.



Around 70% of these drugs are in the preclinical / discovery stages. Of the clinical stage candidates, more than 12% are being developed for breast cancer, while around 10% are being developed for the treatment of Non-Hodgkin's Lymphoma. Candidates targeting AML and multiple myeloma together occupy 14% (7% each) of the clinical pipeline. More than half of the ADCs in the current clinical pipeline are being developed using the technologies provided by Seattle Genetics ; however, several small sized companies have emerged in last few years, offering novel technology platforms.

Some of the approaches that have been adopted for the development of third generation ADC conjugation platforms include:

- Limiting retro-Michael drug de-conjugation (Kyowa Hakko Kirin, MedImmune, Pfizer, ProLynx, Seattle Genetics, Syndivia),
- Cysteine re-bridging (Abzena, Igneica Biotherapeutics, University College London / ThioLogics),
- Enzyme-assisted ligation (Catalent / Redwood, Innate Pharma, LegoChem Biosciences, NBE Therapeutics, Pfizer, Sanofi, Tubulis Technologies, ProBioGen),
- Glycan re-modelling (Philogen, Seattle Genetics, Sanofi, Synaffix, University of Georgia, US National Cancer Institute), and
- Ligation at Fab nucleotide-binding site (Meditope Biosciences, University of California)

With close to 17 drugs, that are either approved or are in late stages of clinical development, the ADCs therapeutics market is anticipated to grow at a CAGR to 19.4% between 2017 and 2030 with an estimated value of $8 Billion in next 5 years.

The global market for antibody drug conjugates is expected to be driven by the advancement in medical technology, rising incidence of cancer, and an increasing demand for biologic therapies. In the quest for more targeted therapies and potentially more clinically efficacious drug, bio/Pharma companies are increasing their research and product development in biologics. Many players are investing huge capital in this space that justify the market potential of ADCs' namely Wuxi; invested $20 Million to start new facility located in China. Abzena has been investing nearly ~$17 Million in past 2 years to upgrade and expand its California site that is dedicated to bioconjugation. Seattle Genetics has invested $17.8 Million in antibody production to support its ADC pipeline and so on..

Unlike conventional chemotherapies that also damage normal tissue, ADCs target only cancer cells and

hence majority of the antibody drug conjugates under development are for oncological indications propelled by the availability of monoclonal antibodies targeting different types of cancer. Some market players are also looking outside the oncology domain to develop antibody drug conjugate, though, such drugs are limited in number are in preclinical stage of development. ADCs' that would fuel the market growth which are in late phase pipeline are Sacituzumab Govitecan by Immunomedics, Moxetumomab Pasudotox by Astra Zeneca, Rovalpituzumab Tesirine and Depatuxizumab Mafodotin by Abbvie, polatuzumab vedotin by Genentech

Hurdles/ Challenges in ADC Manufacturing/ Importance of CMOs' in ADC Space

The ADC field is in a good space yet has been humbled by clinical failures due to great technical and manufacturing challenges. Technical challenges include development issues like:

1. Optimizing additional process steps in developing conventional mABs' from ADC perspective
2. Controls in conjugation chemistry to avoid aggregation of ADCs
3. Antibody binding activity after conjugation
4. Biological activity of cytotoxic drug after conjugation
5. Limited choices of highly effective linkers and few classes of highly potent cytotoxic agents
6. Production of components requiring both cell culture and synthetic chemistry capabilities
7. Limited and complex purification platforms

ADCs manufacturing requires a cGMP facility designed with the proper engineering controls to provide product and personnel protection from the highly potent compounds. This includes isolators being operated at containment Category 4 designated as Safebridge® for to cope with very low occupational exposure range (OEL). For ADC fill-finish, a fill line with lyophilization capability enclosed in a separate isolator is an additional requirement. Containment at this level is also required to maintain an aseptic biological manufacturing environment to avoid contamination which must be verified through surrogate testing, which can be challenging with the most potent toxins currently under development. An ADC manufacturing/fill finish facility is a substantial investment, which is why most ADCs are manufactured at CMOs. Most smaller companies, and even some larger companies, do not have enough of a pipeline to justify the level of facility investment needed for ADCs and/or cannot keep the facility fully utilized. In addition, the supply chain for manufacturing ADCs is complex, including linker/toxin manufacture, antibody manufacture, conjugation/ QC / stability testing, and fill finish. The more of these the CMO can offer as an integrated service, the better for the client which is backed up by multiple advantages:

1. CMOs offer technical expertise in conjugation and linker developments with robust platforms
2. Utilizing an integrated CMO reduces an ADC's time to market as they can perform all steps like conjugation , scale up , commercial manufacturing and the fill finish of ADC saving a considerable amount of time in scheduling and testing
3. Opportunity to eliminate penalties associated with rescheduling due to delays in a prior part of the supply chain
4. Reduced sponsor effort associated with management of inventory and logistics by the CDMO
5. Also, integrated CMOs' offer flexibility for any changes made during the process which are well co-ordinated by adept program managers at the site
6. Lower risk associated with transfers if the different units are co-located

As a result, most of the pharmaceutical companies have opted to outsource the manufacturing of their ADCs with approximately 70% of all ADC manufacturing activities conducted by CMOs'. Major players in ADCs' like Genentech, Sanofi, Takeda, Pfizer either rely on CMOs by outsourcing or follow a co-development model with them. ImmunoGen, recently shifted its ADC Manufacturing work to an outsourcing model mentioning its benefit to have increased access to the expertise which a CMO brings in, in turn saving about $20 Million!

While many of these challenges exist with other biologics, the complexity of ADCs can make the drug development process and tech transfer process even more difficult. However, through fruitful partnerships and the right expertise, these problems can be overcome and ADCs can continue to have an increased impact as targeted cancer therapies. Piramal Pharma Solutions is one of the global leaders in providing integrated ADC manufacturing solutions from development through clinical and commercial GMP batch manufacturing and ADC fill/finish. Our facility in Grangemouth, UK is dedicated to process development, scale up and manufacturing of bioconjugates which is forward integrated with our Lexington, US facility for Fill/Finish activities. Our Facility located in Riverview, US provides API for cytotoxic payloads and linkers. We are the pioneers in the field of GMP manufacturing of ADCs' and we have partnered with leading ADC technology companies for over past 10 years. Our experience counts in terms of:

- 850 ADC batches manufactured
- 440 GMP batches manufactured
- 118 Development programs completed
- 180 Different ADCs from over 110 antibodies
- 55 Different toxin/toxin-linker systems
- 20 ADCs and other antibody/protein conjugate projects
- 6 integrated programs for ADC across Piramal sites

A better ADC for future…

Expansion of ADCs' into therapeutic areas than than oncology can be the next thing in evolution. Opportunities for improved therapeutics made through bioconjugation exist in infectious disease, where an Antibody–Antibiotic Conjugate (AAC) was shown to be more effective than the free antibiotic payload for treating infections caused by drug-resistant bacteria. ADCs' can also help to improve treatment of chronic conditions e.g., autoimmune and cardiovascular diseases through reducing side effects by selective payload delivery. Wisely chosen target antigen, novel linker technology and original mode of drug action continue to be investigated to fully optimize ADC-based targeted therapy and holistic approach to the development of ADCs remains paramount!