Successful Strategies in the Development and Technology Transfer of Antibody-Drug Conjugates

Received April 24, 2014 | Accepted May 1, 2014 | Published online May 2, 2014

Abstract: Effective introduction of a monoclonal antibody or antibody-drug conjugate into clinical trials and final commercialization requires a defined path toward an efficient, robust manufacturing process with suitable quality parameters. In this process, efficient technology transfer between the drug-developing technology originator and an approved and authorized third party or parties is crucial. In this article, Cynthia Wooge, Ph.D., discusses the requirements of a properly designed technology transfer process and how to ensure a successful transfer and reproducible conjugation process with solid analytics, appropriate engineering design, process (quality) controls and quality assurance. She emphasizes the need to understand which details are critical and how they get effectively communicated between the various parties involved in the transfer process.

Keywords: ADC Antibody-drug Conjugates, Technology Transfer, Biotechnology, Monoclonal Antibody, Antibody, FDA, NCI, TTC, Technology Transfer Center, CMO, Contract Manufacturing Organization

1.0 Introduction

Within the biotech and pharmaceutical industry, technology transfer refers to a systematic procedure that is followed in order to pass the documented knowledge and experience to an appropriate, responsible and authorized party. It is required to successfully progress from initial preclinical drug discovery to product development to clinical trials and, finally, to full-scale commercialization and distribution of a pharmaceutical drug or biologic. [1]

Technology transfer happens in many situations. A company might be addressing intra- or intercompany transfers of technology, expansion or relocation of operations, consolidations and mergers, or working with a third party like a government research institute or university. Alternatively, a company might be near market-ready with a pharmaceutical product, but not have commercial manufacturing capabilities, so they require support from one, or multiple, commercial contract manufacturing organizations (CMOs). There can also be the case of startup pharmaceutical or small biotechnology companies having a fully developed product and regulatory approval, but no functioning distribution channel.

In general, technology transfer—whether government-directed or between commercial parties—helps form alliances between development partners, create the framework for ongoing development of the technology, manufacturing, commercial development and distribution. Within this process, drug developers need to make their (proprietary) technology available to commercial partners that are part of the agreed-upon development path.

Overall, the process of technology transfer is complex. This complexity is primarily caused by a multitude of stakeholders involved in the development of pharmaceuticals. It is, however, a critical process.

2.0 Government and Academia

In the development of pharmaceuticals and biologics, technology transfer is quite common. For example, the National Cancer Institute, which is part of the U.S. National Institutes of Health (NIH), recognizes the importance of technology transfer in order to help translate basic science into direct benefits for public health. To facilitate the process, the institute has set up the Technology...
Transfer Center, which establishes formal relations and collaborative agreements between the pharmaceutical industry, academia and nonprofits, making co-development through technology transfer possible. The center's main objective is to support the NIH's mission. [2]

This work includes recommendations made to the NIH’s Office of Technology Transfer concerning the filing of domestic and foreign patent applications as well as working closely with NIH investigators and outside parties to facilitate commercialization efforts to benefit public health. All these activities are guided by the Federal Technology Transfer Act of 1986 and other federal laws (including the Stevenson-Wydler Technology Innovation Act and the Bayh-Dole Act) that use patents as incentives for commercial development of technologies and are designed to establish collaboration between academia, federal laboratories and the biopharmaceutical industry. [3]

In this case, the transfer of technology of federal funded research to the private sector is intended to bring pharmaceutical drugs and biologics to the marketplace sooner and more efficiently than is possible if a federal agency would have acted alone. [4] Similar organizations around the globe, including government as well as academic and commercial entities, are aiding and managing the technology transfer between various partners.

3.0 CMO Challenges For CMOs, there are a number of challenges involved in technology transfer, including varied production, development status, timing requirements, and communication flows. [5] This is particularly true in the transfer of complex technology, such as in immunoconjugates or antibody-drug conjugates (ADCs). In any situation, successful technology transfer depends on robust communication between originator and CMO.

From an organizational perspective, analytical method development and process development are key in successful technology transfer. It is important that the technology transfer covers all the key analytics, as well as enabling process chemistry and ensuring raw or source-material release in advance of manufacturing. In these cases, analytical method development and process development are concurrently managed to allow rapid communication and coordination of both activities. Yet this requires a balancing act because a “product” is needed to develop the analytical methods, while, on the other hand, the “right product” does not exist until the appropriate analytical methods are in place. [5] [6]

4.0 Quality by Design A successful technology transfer process incorporates Quality by Design (QbD) principles: a systematic, streamlined approach that begins with a predetermined objective and emphasizes project execution based on accurate product and process understanding, robust process control, complete and accurate communication. Based on the guidelines from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Q8), this approach is based on sound science and quality risk management methods. [Figure 3: Application of Analytical Methods]

To comply with the ICH Q8 definition, the first step in effective technology transfer is the development of a
transfer plan detailing all steps and criteria of the process, outlining—if applicable—the flow of the excising process and critical process parameters. In this plan, the expected results should be included.

Implementing QbD principles further involves risk assessment of potential areas of failure, small-scale model qualification, design and execution of experiments, definition of operating parameter ranges and process validation acceptance criteria followed by manufacturing-scale implementation and process validation. The impact of operating parameters on product quality attributes and process-performance parameters is established in statistical experimental designs and applied to the execution of process characterization studies.

Process characterization experiments are then used to define the proven and acceptable range and classification of operating parameters, leading to a consistent product and optimized process. [Figure 3: Application of Analytical Methods]

Finally, successful implementation and validation of the process in the manufacturing facility, and subsequent commercialized manufacturing, verify that the approach taken is suitable for the development, scale-up and operation of the manufacturing process. [7]

The implementation of the QbD principles will almost always be completed during the phase II clinical process. Process standards for manufacturing and validation tests will then be established during phase III clinical trials, including product testing and audits to guarantee that the product manufactured after the technology transfer meets all predetermined standards and requirements.

Furthermore, implementing QbD principles in the technology transfer process facilitates the robustness of the final manufacturing process. It also aids continued improvements and offers consistency in the process across multiple facilities. [8]

5.0 Emphasis on Communication Communication between transferring parties is one of the most significant elements of successful technology transfer. As part of a robust communication approach, members of each of the transferring parties need to be confident and keenly aware of their roles, scope and responsibilities. Failure to properly develop a robust communication strategy may cripple the entire transfer process, ultimately wasting millions of dollars.

6.0 Growth of the ADC Market The recent approval of two ADCs—ado-trastuzumab emtansine (Kadcyla®; Genentech/Roche) and brentuximab vedotin (Adcetris®; Seattle Genetics)—and more than 30 clinical trials programs is making the market for ADCs especially interesting for CMOs seeking to expand their business. [9][10] Currently, large oncology-focused pharmaceutical and biopharmaceutical companies are heavily investing in this market. Experts believe the market for ADCs will grow exponentially. According to a new report published in March 2014, the ADC market is anticipated to reach US$3.45 billion by 2018. [11]

One reason for the expected growth is that companies are able to turn existing antibody therapies into ADCs, thus extending patent life to make the original antibody more profitable. Another scenario involves drug developers “resurrecting” ineffective antibodies and turning them into successful ADCs. Yet because of their complexity, the manufacturing and production of ADCs offers unique challenges for CMOs as well
as government/academic and biopharmaceutical companies seeking CMO partners to help them in the manufacturing of their ADCs. Meeting the challenges of this process is no easy path. To take the process from the bench to the clinic requires a dedicated and robust approach to technology transfer.

7.0 Complexity of ADCs

ADCs are composed of a cytotoxic drug conjugate linked to a monoclonal antibody or antibody fragment, and are designed to combine better tumor penetration and killing properties with fewer side effects for cancer patients. They show high efficacy as cancer therapeutics. [Figure 4: Antibody-drug Conjugates: A Variety of Chemistries]

Conventional chemotherapy is designed to eliminate fast-growing tumor cells. It can, however, also harm healthy proliferating cells, which causes undesirable side effects. [12] In contrast, ADCs are designed to increase the efficacy of therapy and reduce systemic toxicity, often seen with small-molecule drugs.

The concept of ADCs is not new. Since the late 1970s, drug developers have been working on the realization of targeting drugs. The development of monoclonal antibody technology by Köhler and Milstein in 1975 was an important step, steering the way to develop highly selective antitumor therapeutics that ultimately resulted in the development of immune-conjugates or antibody-drug conjugates. [13]

The unique targeting properties of monoclonal antibodies have made it possible to conjugate or link them to radionuclides, cytotoxic agents and enzymes, and use them in therapeutic and imaging applications.

8.0 Overcoming Clinical Barriers

ADCs are generally more effective in the treatment of hematological or liquid cancers. To be successful as a therapeutic treatment in solid tumors, ADCs overcome the barriers to penetration within tumor masses, antigen heterogeneity, conjugated drug potency and efficient drug release from the antibody inside tumor cells. [14]

Unfortunately, early trials with, for example, cBR96-doxorubicin (also known as SGN 15; Seattle Genetics), a tumor-specific monoclonal antibody linked to doxorubicin (Adriamycin; Pfizer), showed little clinical efficacy, poor pharmacological parameters and problems with toxicity. [15] cBR96-doxorubicin showed limited clinical antitumor activity in metastatic breast cancer as well as glioma.

The gastrointestinal toxicities, on the other hand, were considered to be the result of binding of the agent to normal tissues expressing the target antigen, compromising the delivery of the immune-conjugate to the tumor sites. [16] [17]

Since the early failures, better antibody engineering and production combined with improved target selection, cytotoxic synthesis and a deeper understanding of conjugation chemistry have led to a number of successful drug candidates entering clinical trials.

The first ADCs contained well-known cancer therapeutics including doxorubicin and methotrexate. But today most ADCs include vastly more potent and highly toxic cytotoxins, including monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF), or microtubule-depolymerizing maytansinoid derivatives
such as DM1 or DM4, or calicheamicins, a class of enediyne antibiotics and duocarmycin analogs. Other (experimental) cytotoxins in trial drugs can include derivatives of pyrrolobenzodiazepines antibiotics or PBDs.

The first ADC to receive market approval was gemtuzumab ozogamicin (Mylotarg®, Wyeth/Pfizer). The drug, a monoclonal antibody to CD33 linked to a cytotoxic agent from the class of calicheamicins, was approved in 2000. [18] However, due to unacceptable adverse events, Pfizer withdrew the drug from the market in 2010.

9.0 Production of ADCs

The complexity of the production and manufacturing as well as the technology transfer between the development partners is enhanced by the complexity of the product itself and the required processes involved in production.

The production of ADCs is based on a mix of biotechnology and synthetic chemistry. [FIG 4: Antibody-drug Conjugates: A Variety of Chemistries] Hence, manufacturing requires both biologics and small-molecule manufacturing capabilities. Mammalian cell cultures are used to develop the monoclonal antibodies, and synthetic chemistry is used for the manufacturing of linker and the cytotoxic component.

While the general objective in the manufacturing of biologics is to have a simple supply chain—making technology transfer easier—this may not always be possible in the manufacturing of ADCs. One reason is that the manufacturing of ADCs may involve multiple players in multiple locations. For example, while one company may manufacture antibodies and the highly potent cytotoxin, it may depend on a second company to provide the linker technology (offering a variety of technologies including non-cleavable, peptide-cleavable, disulfide-cleavable and acid-cleavable). A third company may be asked to manage the conjugation. While today many CMOs are able to offer most parts of the production and manufacturing of ADCs, no one is able to offer a single-source solution.

10.0 Managing the Process

From a production and manufacturing perspective, managing the various steps of building an ADC is complex. The safe production and manufacturing of ADCs is technically challenging because it involves the coupling of a biologic to a chemical in which both need to retain their original activity. In addition to the standard impurity and stability tests, CMOs need to be able to show that the actual conjugation process has worked.

While conjugation of biological molecules to nonhighly potent active pharmaceutical ingredients is an established technology in anything ranging from the delivery of vaccines to in vivo diagnostics, conjugation with highly potent molecules is much more complex. One of the main reasons for this complexity is the requirement of containment when dealing with cytotoxic molecules—an environment decidedly different from that for biomolecules. The handling of the cytotoxins, for example, necessitates manufacturing in a highly containment aseptic biological manufacturing facility to limit occupational exposure levels.

Furthermore, the complexity of the manufacturing of ADC involves mammalian expression systems as well as bioreactor systems. To be within the good manufacturing practice (GMP) guidelines, these production mechanisms require extensive upstream as well as downstream processes.

But the complexity does not only involve the production and manufacturing environment. [19] In practice, it has been very difficult to control the site of conjugation as well as the final stoichiometry. For example, the
currently approved ADCs are produced by conjugation to surface-exposed lysines (ado-trastuzumab) or partial disulfide reduction and conjugation to free cysteines (brentuximab vedotin). These stochastic modes of conjugation lack “control,” which leads to heterogeneous drug products with unpredictable and varied numbers of drugs conjugated across several possible sites.[9][10]

The proper coupling of the antibody and cytotoxin is crucial, since it significantly influences the ADCs’ efficacy, safety, stability and pharmacokinetics. All elements must function as intended (both for the separate biologic and cytotoxin as well as the final conjugated combination), a concern that has become an important focus for regulators as well as drug developers and their commercial (CMO) partners.

The example of gemtuzumab ozogamicin illustrates the importance. In a 2001 article published in Clinical Cancer Research, Peter Bross and Julie Beitz et al. note that approximately 50 percent of the antibodies were not linked to the cytotoxin calicheamicin derivative. [20] And because the relationships between the site of conjugation and the extent of drug loading has an important effect on efficacy, safety, pharmacokinetics and immunogenicity of the drug, the authors suggested that the reliability of gemtuzumab ozogamicin should be questioned.

11.0 Technology Moves Forward

Over the last decade, researchers have improved the conjugation chemistry process. As a result, site-specific conjugation, designed to create a more homogeneous product, is now among the novel technologies being adopted.

One team recently published their success in developing a robust platform for rapid production of ADCs with defined and uniform sites of drug conjugation. Their results showed an ADC that proved highly potent in in vitro cell cytotoxicity assays. [21]

For CMOs involved in the manufacturing and production of ADCs, it is important to truly understand the complex technology before getting involved. But with new cytotoxic compounds and ongoing development of linker chemistries, the possibilities will be virtually limitless.

While most drug developers are focusing on oncology, a growing number of researchers are exploring the opportunities of ADCs in other therapeutic areas, including autoimmune and inflammatory disease. One company, Intellect Neurosciences Inc. (New York, NY), for example, develops innovative approaches aimed at arresting or even preventing Alzheimer’s disease and other neurodegenerative diseases with ADCs targeting amyloidogenic proteins with additional neuroprotective properties by combining them chemically with a small molecule such as an antioxidant. [22]

12.0 Conclusion

Pharmaceutical development practices based on GMPs established by the FDA in 1978, and QbD principles established more recently, offer a robust mechanism to ensure that the equipment, processes and people in ADC development do what is expected and required to produce high-quality results. [23]

This includes a system for documenting expectations, as well as the results of testing to prove those expectations are satisfied. Furthermore, such a process provides the tools for investigating and correction if unanticipated deviations occur, as well as documenting them in a controlled and logical fashion. The focus is on excellence, and the same is true for technology transfer.

With the increasing complexity of pharmaceutical products and biologics, a properly structured, robust
technology transfer process is crucial. Furthermore, to succeed in this unique market, CMOs need to demonstrate a systematic, streamlined approach to the entire ADC project.

Today most CMOs have become actual partners of the technology originator and industry partners they work with. They are no longer considered just a vendor of specialized services. This has consequences for the process in which novel technology is transferred between parties, including a set of regulatory implications. [5]

Only a select number of established and experienced CMOs will be able to meet the criteria to aid in the flawless transfer of technology for complex projects such as the development, production and manufacturing process of ADC.

Given the involvement of multiple industry partners participating in the development and manufacturing of ADCs, each partner needs to understand the product and technology needs, and be able to clearly recognize how to translate this into appropriate specifications. Furthermore, all partners need to be able to identify the process and understand how to make it robust upon scale-up to deliver on time. This is especially the case when one drug-developing originator works with multiple industry and CMO partners.

Acknowledgment

The author would like to thank Mike Bienkowski, Ph.D., Sue Berlin, Ph.D., Latashuia Browning, Amy Knecht, Lisa McDermott and Mary Robinette for their meaningful contributions in developing this article.

References

APPENDIX: Figures 1-3 of article provided by SAFC

Figure 1: Process Development Approach

- DRAFT Final Product Specifications / Front Load Analytical Development
  - Define Success
- Technology Transfer and/or Process Development
  - Client Dependent
- Design of Experiment/Quality by Design (DoE/QbD)
  - Confirm/Establish Critical Process Boundaries
- Perform Demonstration Batches (2-3 at Small Scale)
  - Assess Scalability and Process Consistency
- Engineering (Toxicology) Batch (At or Within 10-Fold of GMP Scale)
  - Partnership with Engineering/Manufacturing
- Documentation & Technology Transfer to GMP Manufacturing & GMP QC

Figure 2: GMP Manufacturing Communication Flow

- Process Development
  - Analytical Development
    - Technology Transfer Or Development
  - GMP Manufacturing
  - Quality Control
    - Master Manufacturing Formula
    - Release Testing Data
    - Quality Assurance
      - Certificate of Analysis
  - GMP Drug Substance

Figure 3: Application of Analytical Methods

- Process Optimization
  - Analytical Platform
    - GMP Stability Testing (BDS/DP)
    - ADC Characterization
    - ADC Stability – Developmental
    - GMP Release Testing (RM/BDS)

Platform Analytical Methods Are Optimized For Each ADC Construct