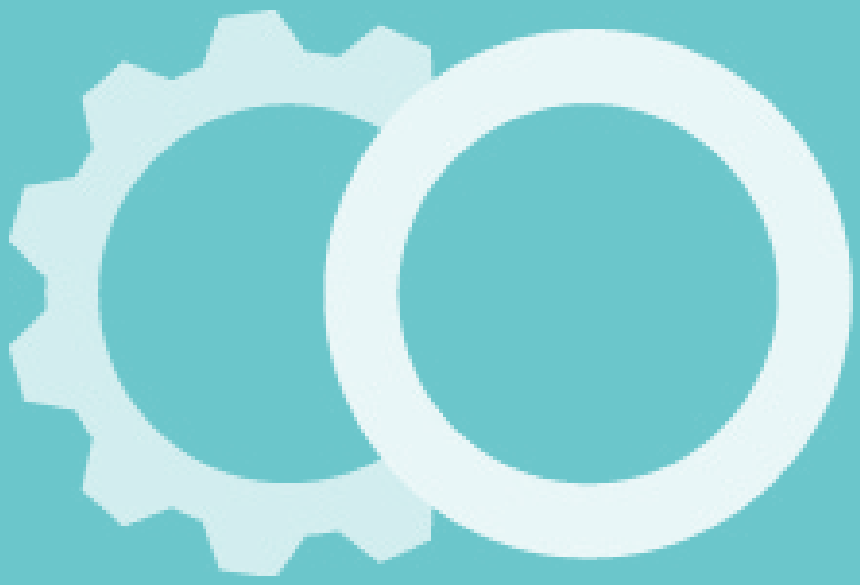
ALTHEA

THE POWER TO MAKE®

5 ADC MANUFACTURING CHALLENGES YOU NEED TO KNOW

The unique targeting capabilities and promising clinical trial results of antibody-drug conjugates (ADCs) have made them an exciting and promising treatment in the fight against cancer. According to recent analysis, experts anticipate the ADC market to be worth $10 billion annually by 2025. However, despite this tremendous growth, drugmakers still face a number of challenges in the manufacturing process for ADCs. Below are five key areas where pharmaceutical manufacturers may face the biggest uphill battles.



1. ANALYTICAL METHOD TRANSFERS

As with any pharmaceutical, a drug manufactured under cGMP has to meet certain specifications. Ensuring the product can be manufactured and tested to meet those specifications is necessary to initiate clinical studies. With ADCs specifically, there can be challenges in method transfer to the manufacturing and testing sites. For example, the product must meet the drug-to-antibody (DAR) ratio. With DAR, for some conjugation chemistries and assay methods, both the conjugation reaction and the assay may each have some variability. Minimizing these ensures the drug will fall within the necessary specifications. DAR is important as it impacts the potency of the drug.

In addition, the FDA recommends cell-based potency assays used for ADCs in Phase I clinical trials. With other classes of biologics, these types of assays are not needed until later in development. However, because cell-killing is part of the mechanism of action of an ADC, a cell-based assay is used to demonstrate the drug's ability to do this. These types of assays have more inherent variability than non-cell-based assays. Cell-based assays require significant time to develop and transfer, as well the appropriate capabilities in equipment and personnel, which are not typically found at all testing sites. In addition, if fully developed methods are transferred by the client, they must be able to be implemented in a quality control environment using the CMO's instrumentation. Frequently, the client and CMO have different views on what a "developed method" is, which must be addressed if additional work is put into method development.

To complete a successful analytical method transfer for an ADC, both the client and the CMO must produce comparable test results from the same sample. In some instances, an in-person method transfer and appropriate training is needed to ensure success. In any case, having a project team with analytical experts from both organizations who are in frequent communication is the key to resolving any potential technical issues.

2. CONJUGATION TECH TRANSFERS

An ADC is a combination of an antibody and a small molecule toxin. This means, on one hand, a manufacturer is faced with the typical challenges associated with the biologic itself, such as maintaining the activity and physical state of the molecule, keeping endotoxins low, and maintaining sterility/low bioburden. On the other hand, handling highly potent molecules that require high containment, as well as carrying out chemical conjugation, frequently in mixed aqueous/organic solvents, presents its own unique considerations. Any company that plans to work with ADCs must have specialized containment equipment, such as isolators, as well as access to experts who are trained in conjugation chemistry and biologics processing, and safety procedures for working with highly potent compounds.

Multiple conjugation chemistries are employed to make ADCs, and some methods may be more susceptible to

raw material and process variations than others. This can be true for non-site-specific conjugation methods that typically result in a distribution of species that must be consistent from batch to batch. These variations are less problematic for site-specific conjugations in which the reaction is driven to completion by using an excess of reagent (linker/payload). In any case, the process must be able to produce the same product profile every time. Ideally, during process tech transfer, the ADC produced by the CMO at small scale or during an engineering run is analyzed by both the client's QC lab as well as by the QC testing lab that will be doing the release testing. Both labs must be able to verify that both the transferred process and transferred analytical methods are comparable. Verification runs should also be carried out with the same raw materials to be used for GMP manufacturing in order to eliminate any impact of differences in raw material quality.

As with analytical method transfers, having a project team with bioconjugation experts from both organizations who are in frequent communication is key to resolving any potential technical issues. Frequently, the client sends a person-in-plant (PIP) for the first few manufacturing campaigns to ensure a successful tech transfer. In-person training may also be required.

3. SCALE-UP

One of the most notable challenges of scaling up ADCs is the process variation caused by changes in equipment, scale, and raw materials. Like the scale-up of many biologics, a process carried out at a milligram scale multiple times with consistent results does not necessarily mean the same outcome will occur at larger scales. There may be instances when the reasons for scale variations are not clear; however, the expert team should be able to identify what changes are needed to make the results consistent. Identifying these changes can be especially challenging with ADCs due to variations in processing equipment and materials of construction, addition rates/mixing, and even dissolved oxygen in the conjugation reaction with some chemistries.

FREQUENT COMMUNICATION IS KEY TO RESOLVING ANY POTENTIAL TECHNICAL ISSUES

This is why it is ideal to have an established scaled-down model (typically 0.1g to several grams) that mimics as closely as possible the unit operations for clinical scale manufacturing. This applies to both conjugation as well as subsequent purification by ultrafiltration diafiltration and chromatography. An example of a process that is difficult to mimic at milligram scale is ultrafiltration/diafiltration, which is used to remove small molecule impurities from the product.

4. COMMUNICATION

As with any project, all teams involved must have clear lines of communication established from the beginning. Any issues need to be resolved in a timely fashion and in a collaborative manner. Good communication is essential to achieving a successful manufacturing campaign, especially for transferring complex processes that produce lifesaving medications.

There are ways to determine whether a potential partner

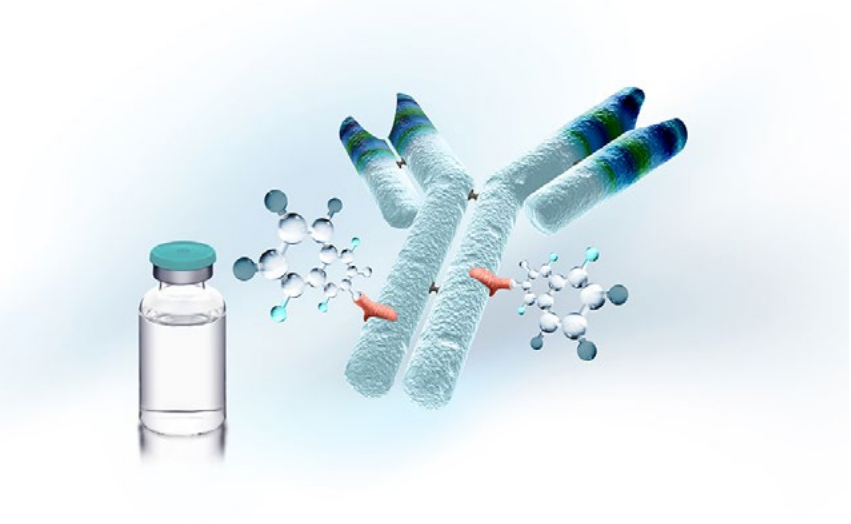
can communicate effectively. For example, when vetting a CMO for your project, it is highly recommended to speak with references who are the CMO's previous or existing clients. In addition, it is important a CMO is willing to agree to the way the client wants their project executed in terms of the frequency of communication between the client and the CMO. For example, the CMO should indicate if they allow the sponsor to assist with troubleshooting analytical issues or process issues or if the sponsor is able to have someone present at their facility for the initial manufacturing campaigns. This information as well as details on the CMO's experience, staff, available equipment, safety program, and more can be collected through the use of a questionnaire.

5. CMO FACILITY

For ADCs, a CMO must have a facility designed with the proper engineering controls to provide product and personnel protection from the highly potent compounds. This includes isolators for highly potent powder handling for ADC conjugation, and, for ADC fill-finish, a fill line with lyophilization capability enclosed in an isolator. Containment at the level required for handling ADC toxins and ADCs 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/formulation/QC and stability testing, and fill finish. The more of these the CMO can offer at a single site, the better for the client.

Single-source CMOs offer multiple advantages. First, they eliminate the considerable risks often present in the supply chain for an ADC. If the "parts" of an ADC (antibody, linker, cytotoxin) are made at different sites, each has to be manufactured and shipped safely and on time. This poses a risk to not just the timeline but also potential damage to the product. Second, a single-source CMO offers flexibility. For example, a client using multiple suppliers reserves facility space for an ADC's antibody, drug/linker, conjugation, and then fill finish. Unexpectedly, the site making the antibody falls a month behind schedule. Now the client has to coordinate this change in schedule with multiple sites as opposed to coping with the delay at one organization. Finally, utilizing a single-source CMO reduces an ADC's time to market. For example, if the client can perform both the conjugation to produce the ADC drug substance and the fill finish of the drug product, this saves a considerable amount of time in scheduling, testing, and release if those processes are well integrated, which ultimately helps



get your product into the clinic faster. As a single-source CMO for ADCs, Althea has made significant investment into its new ADC high containment facility, technical staff, and manufacturing equipment. The goal is to deliver both high quality ADC conjugation and fill finish contract manufacturing services to developers pursuing the ADC market.

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.

UTILIZE SINGLE-SOURCING TO MANAGE THESE ADC MANUFACTURING CHALLENGES

1. ANALYTICAL METHOD TRANSFERS
2. CONJUGATION TECH TRANSFERS
3. SCALE-UP
4. COMMUNICATION
5. CMO FACILITY

ALTHEA | THE POWER TO MAKE®

A MEMBER OF THE AJINOMOTO GROUP

Ajinomoto Althea, Inc | 11040 Roselle Street, San Diego, CA 92121 | 1.888.425.8432 | 858.882.0123

www.altheacmo.com