SAFC®
Pharma & Biopharma Raw Material Solutions

Complete Single-Use ADC Technology from Development through Scale-up

A Case Study

Introduction

The global antibody-drug conjugate (ADC) market is growing rapidly. From 2017 to 2022, it is projected to expand at a compound annual growth rate (CAGR) of 22%. This growth will be driven by the large number of ADC drugs in the pipeline, the rising number of cancer patients and the wider therapeutic window offered by ADCs. Given this avalanche of new ADC projects, any way to simplify development and manufacturing will benefit the pharmaceutical industry and bring new therapies to patients sooner.

Background

Typically, ADCs are manufactured using either glass or stainless steel reactors, depending upon the scale and phase of development. Elsewhere in the process, many single-use components – filters, disposable flow paths, etc. – have been used successfully for years. The correlation between small-scale glass reactors in the development-space to large-scale glass or stainless steel reactors in the GMP space has been well established. However, transitioning from a small, developmental–scale glass reactor to a large, GMP-scale complete single-use system, including the processing equipment and reaction vessel, is still a new but attractive concept. The numerous benefits of using complete single-use systems under GMP include operator safety, decreased risk of contamination, scalability and reproducibility, flexibility, small footprint, lower cost, and saved time through efficiencies such as easy setup and cleanup with no need for cleaning validation.

While there are many advantages to using single-use systems, there are several perceived challenges and risks. MilliporeSigma has found ways to mitigate these risks through careful design and extensive testing. Here, we study a case in which MilliporeSigma succeeded in scaling up an ADC process from a small-scale glass reactor to a fairly large-scale clinical batch under GMP controls.

Challenge

As a contract development and manufacturing organization (CDMO), MilliporeSigma was commissioned to perform the technology transfer and optimization of bioprocess chemistry and associated analytical methods for the production of antibody-drug conjugate ADC-X. This therapeutic agent's construct featured a novel IgG1 isotype antibody conjugated to a new drug linker; it was to be used as an active pharmaceutical ingredient (API) for human Phase I clinical trials. The client needed a clinical batch produced from 1,000 grams of antibody, under cGMP.

Production featured longer processing at a higher temperature than is typical of ADC manufacture, placing the process at higher than normal risk for bioburden growth. It was up to the team to develop consistent and scalable bioprocess chemistry that reliably afforded a high yield of functional ADC-X with the desired final product specifications.

MilliporeSigma

Solution

To achieve the objective, MilliporeSigma initiated an evidence-driven development campaign to produce a demonstration batch and a pilot batch, to be followed by technology transfer to cGMP production (Figure 1). While ADC processes are most often scaled up to glass or stainless steel reactors, the team decided single-use technology would be the best option in this case because it minimizes the risk of contamination and also offers numerous efficiencies (Table 1).

While the customer's team saw the immediate benefit of single-use systems in relation to lengthy processing and associated risk of contamination, they were unfamiliar with the use of this technology for production scale-up. They needed more information to mitigate the risk of failure during GMP before moving ahead with single-use systems for their entire ADC project.

Figure 1:

Conjugation vessels used in demonstration batch (left, glass vessel), pilot batch (middle, single-use vessel) and GMP batch (right, single-use vessel)

Table 1:

The benefits of single-use technologies for ADC manufacturing

Single-Use Technology: The Benefits	
Safe	• Minimizes operator exposure to potent materials
Integral	• Decreased risk of contamination • Validation, quality and regulatory compliance support
Novel	• Process automation enables reproducible commercial-scale quantities • Highly customized solutions from our expansive component library
Greater Flexibility	• Closed, sterile sampling system enables representative samples • Compact footprint and mobile carrier construction for enhanced flexibility
Lower Cost	• Single-use flow paths provide maximum adaptability to your changing operational needs • Eliminates cleaning validation
Efficient	• Easy setup and use • Reduced downtime for cleaning • Broad working volumes

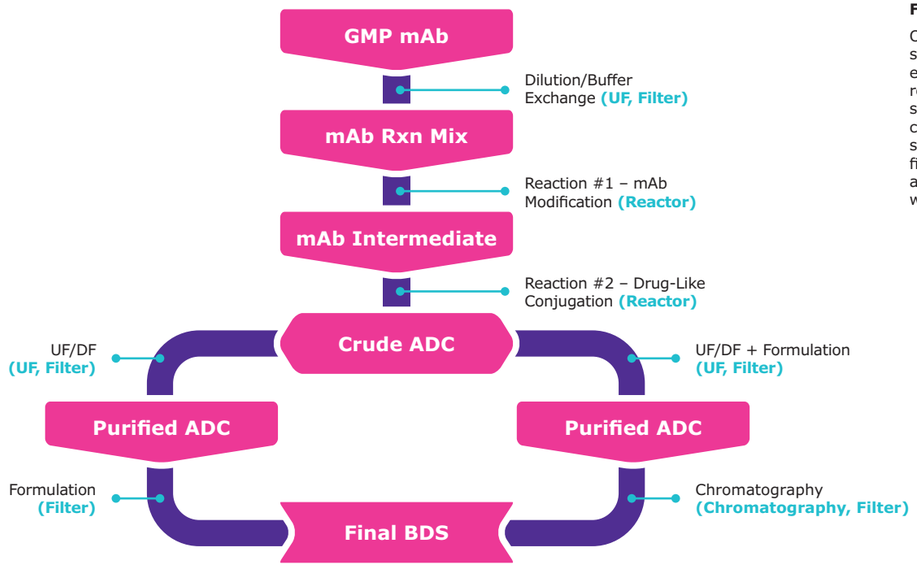


Figure 2:

Opportunities for single-use equipment – such as reactors, ultrafiltration systems, chromatography systems, and filters – within a standard ADC workflow

In fact, as shown in Figure 2, typical ADC production workflows offer ample opportunities for single-use equipment, and a variety of single-use, custom-designed systems are available to meet the needs of ADC production. Nonetheless, because these systems are relatively new to the market, customers often wonder how well they will work. Typical concerns – and relevant facts – are listed in Table 2. Mixing correlations for these systems are shown in Table 3.

Customer Questions	Our Answers
Is there a good model existing for scale-down?	A pilot-scale single-use reactor can be used as a scale-down model for the GMP single-use reactor. Existing mixing correlations and blend-time studies show how to scale glass reactor mixing and pilot-scale single-use reactor mixing up to the GMP single-use reactor.
Will the system leak?	The GOLD Mobius® certification ensures factory integrity testing for each bag assembly.
Do components from the plastics leach into my product?	Single-use systems are USP Class VI certified – per the U.S. Pharmacopeia extractables standard.
Will the SU film be compatible with my solvents?	We have performed our own compatibility/extractable studies and have confirmed that our systems do stand up to typical solvents used in ADC processing, for typical process durations and temperature conditions.
Are extractable and leachable testing a concern?	Extractable and leachable data has been generated with aqueous solutions of ADC solvents. We can generate product specific extractable and leachable data internally as a validation service.

Table 2:

Addressed challenges regarding single-use assemblies for ADC production and scale-up

Table 3:

Example of mixing scale-up based on turnover time for a 1 L glass reactor, a 10 L single-use reactor and a 100 L single-use container

Volume (L)	0.8	8	80
Reactor	1 L Glass	10 L single-use	100 L single-use
Mixer Speed (rpm)	Turnover Time (min)	Turnover Time (min)	Turnover Time (min)
75	0.25	0.45	1.16
135	0.14	0.25	0.65
350	0.05	0.10	0.25

The customer agreed to a trial application of single-use systems. The crude ADC was prepared by conjugating the mAb with the drug linker at X°C for Y hours. The resulting crude ADC was purified by preparative chromatography using linear gradient elution. The column pool was buffer exchanged and formulated into the final bulk drug substance (BDS). The in-process samples and the final product were characterized.

With single-use equipment, the optimized process was then scaled up to a pilot batch. The goal was not only to assess the scalability of unit operations and overall process consistency, but also to form the basis for setting the criteria for GMP processing. Comparative analysis of the intermediate in-process samples and the final formulated pilot batch was performed.

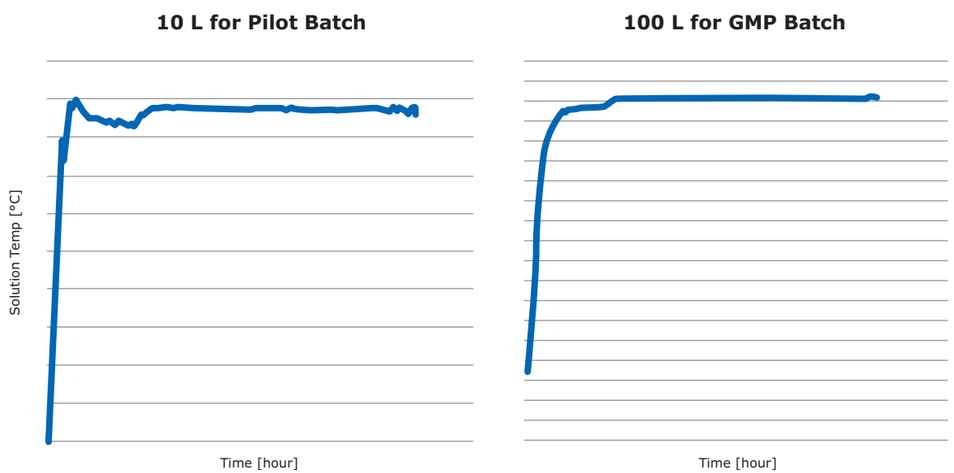
Based on the positive outcome of the pilot batch, it was decided to proceed with the GMP batch.

Results

Data directly comparing the demonstration, pilot and GMP batches are shown in Figures 3-6.

Figure 3:

Temperature of the conjugation reaction in the 10 L (pilot) and 100 L (GMP) single-use containers over 24 hours



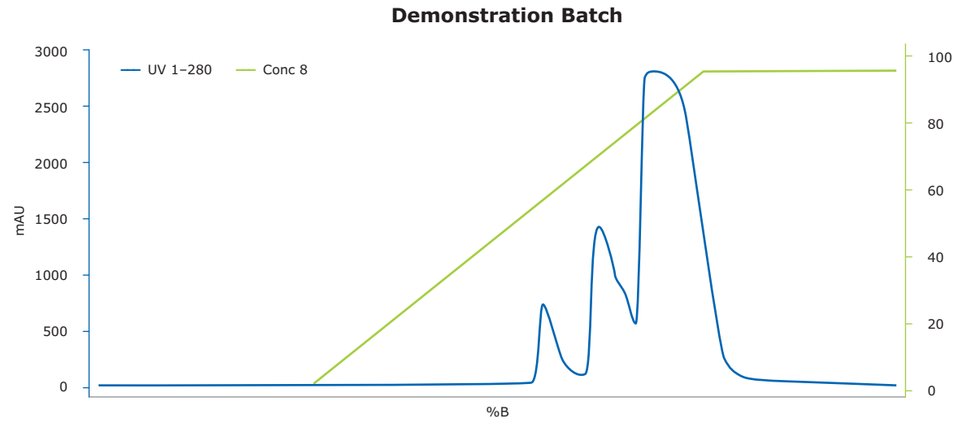
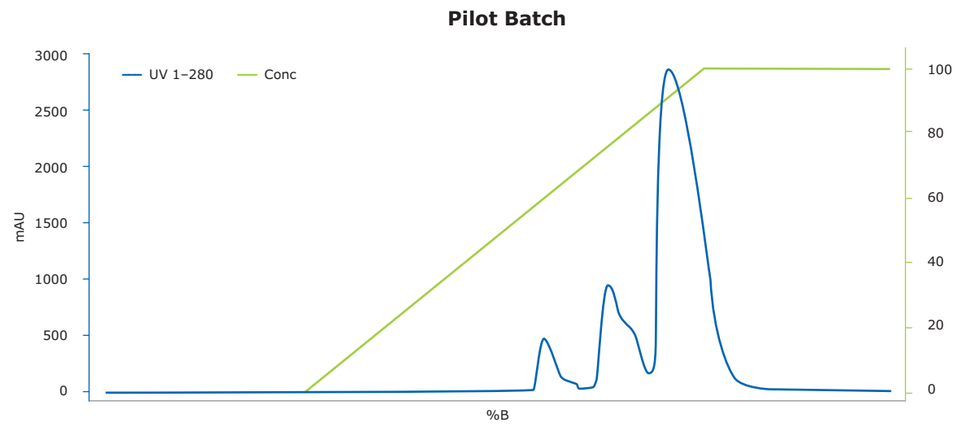
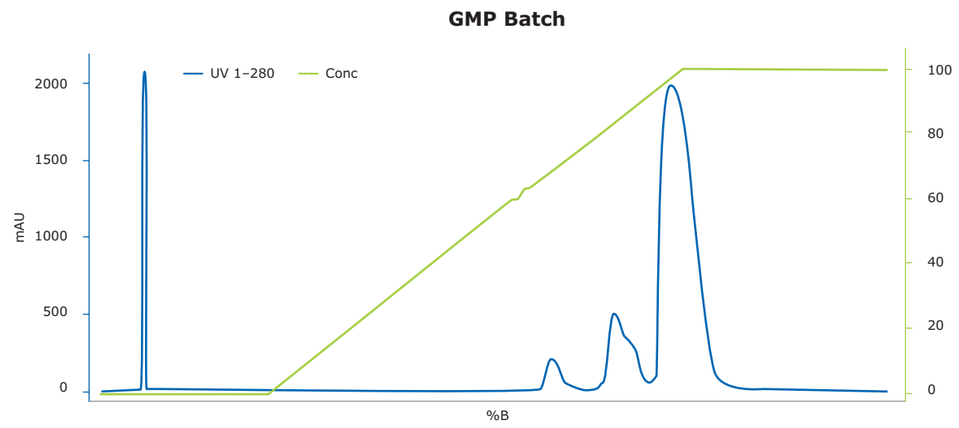


Figure 4:

Preparative chromatography elution profile of the demonstration batch, pilot batch and GMP batch





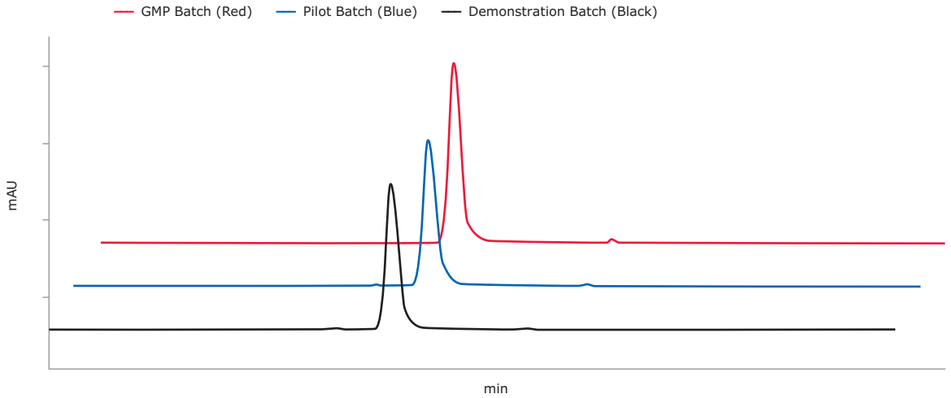


Figure 5:
SEC-HPLC chromatogram overlay of the final ADC from the demonstration (black), pilot (blue) and GMP (red) batches

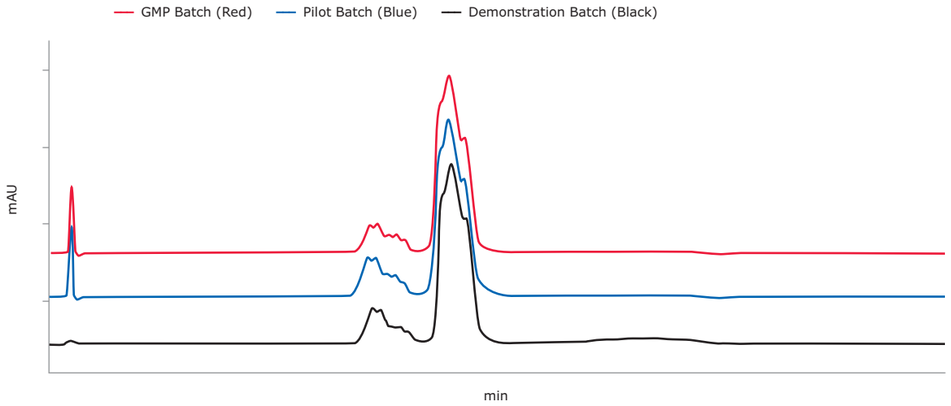


Figure 6:
HIC-HPLC chromatogram overlay of the final ADC from the demonstration (black), pilot (blue) and GMP (red) batches

Test	Demo Batch	Pilot Batch	GMP Batch
Appearance - Color	B6	not more intensly colored than B6	not more intensly colored than B6
Appearance - Clarity	9.5	10.4	10.1
Appearance - Particles	Essentially Free of Particulates	Essentially Free of Particulates	Essentially Free of Particulates
pH	with 0.1 unit difference		
Protein	with 1.0 mg/mL difference		
DAR	with 0.1 unit difference		
Monomer	comparable		
Aggregate	comparable		
Unconjugated mAb	comparable		
Fingerprint 1	comparable		
Fingerprint 2	comparable		
Fingerprint 3	comparable		
Osmolality	comparable		
Residual Free Drug Linker	comparable		
Endotoxin	0.011	0.007	0.006
Bioburden (TYMC, TAMC)	0 TYMC 0 TAMC	0 TYMC 0 TAMC	0 TYMC 0 TAMC

Table 4:
Comparison of product quality analyses of demonstration, pilot and final GMP ADC batches

Comparable analytical results were obtained for the products of the demonstration, pilot and GMP batches, and all test results met the target specifications. It was concluded that the client's ADC process had been successfully scaled up from demonstration batch to GMP production.

SAFC®
Pharma & Biopharma Raw Material Solutions

Summary

ADC processes can be proportionally scaled up to GMP production using readily available single-use equipment. By performing an evidence-driven development campaign, the team succeeded in producing a pilot batch, followed by technology transfer to cGMP production. Scale-up was aided by a broad range of single-use equipment designed to meet the challenging needs of ADC production, including scale-up to proportionally larger reactors. ADCs made with single-use equipment can achieve consistent and scalable bioprocess chemistry to produce functional ADCs with high yield that meet target quality attributes at GMP scale.

10/2018 Lit. No.: MS_WP2936EN