

Establishing Commercial Manufacturing Services for Antibody-Drug Conjugates

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Antibody-drug conjugates (ADCs) are complex, potent biologics that offer significant potential to address serious diseases including cancer. The clinical potential of these therapeutics is attributed to their ability to effectively target disease-associated cells while minimizing off-target toxicity. Nine ADCs are currently on the market and hundreds are in development; it is estimated that the global market for ADCs could reach nearly \$10 billion by 2025. A significant portion of ADC projects are outsourced to contract development and manufacturing organizations (CDMOs) and with continued expansion of pipelines, this trend is likely to endure¹.

As more commercial products reach the market, there is an acute need for CDMOs that understand how to execute late-stage studies to support a filing strategy. CDMOs with plans to support commercial-scale ADC manufacturing are setting up processes to handle challenging supply chains and investing in facilities and processes to ensure efficiency, quality and security.

In this white paper, we describe how our organization built upon 12+ years of experience in clinical-scale supply of ADCs, commercial-scale production of linker payloads, small molecules and bio-organics, and an extensive knowledge base of biologics manufacturing to establish commercial-scale ADC manufacturing capabilities. Our experience with ADCs includes more than 65 unique

development projects and more than 600 development batches spanning many ADC technologies from conventional, to bispecific and antibody fragments, as well as a range of cleavable and non-cleavable linkers and many types of cytotoxic payloads. In 2015, we opened our commercial facility and since that time, have produced more than 160 GMP batches which included more than 20 commercial batches. These batches have enabled more than 30 investigational new drugs (INDs).

Our journey to commercialization started with determining what was required and expected for commercial ADC manufacturing including control strategies, risk assessment, process characterization and validation. Our extensive preparation lead to getting the approval to manufacture commercial batches. Several of these critical success factors are described below.

Establishing Microbial Control

Manufacturing a biologic requires a well-defined control strategy for endotoxins and bioburden. Our approach involves setting in-process endotoxin acceptance criteria based on the worst-case raw material input and historical process data. As the process advances into commercialization, continuous process verification (CPV) is leveraged; acceptance criteria which had been defined based on data gathered during qualification are monitored on an ongoing basis.

¹ <https://www.grandviewresearch.com/press-release/global-antibody-drug-conjugates-market>

Selecting Parameters to Ensure CQAs

Once downstream conjugation and purification are optimized and scaled, quality by design (QbD) is used to gain a deep understanding of the inputs and outputs of the process and establish controls to ensure critical quality attributes (CQAs). A step attribute matrix (SAM) is the first formal step in understanding how material inputs and unit operations of the process may affect product quality attributes.

The SAM is a detailed list of every quality attribute and how it could be affected at each step of the process.

Table 1A provides an example of a SAM created for assessing the impact of different unit operations on impurity levels, considered to be a CQA. In this example, the matrix was based on previous development and manufacturing data and scientific understanding of the process and the unit operations.

Table 1:

SAM (A) and PAM (B) used to assess the impact of different unit operations on impurity levels.

SAM				
Unit Operation				
Attribute	Step 1	Step 2	Step 3	Step 4
A1	Low	N/A	Low	N/A
A2	N/A	N/A	High	N/A
A3	N/A	Medium	N/A	N/A

PAM			
Process Step	Step Parameter	Potential Effect Severity	Attribute Affected
Step 1	Parameter 1	High	A2
	Parameter 2	N/A	N/A
	Parameter 3	N/A	N/A
	Parameter 4	Low	A1
Step 2	Parameter 1	Medium	A3
	Parameter 2	N/A	N/A

Once there is an understanding of which steps may have an impact on quality attributes, a parameter attribute map (PAM) is created to identify how variation within the process parameters could affect these quality attributes (Table 1B). This exercise helps select parameters that are critical to maintaining the product quality and

anticipates the impact of variation of those parameters on product quality. For example, the SAM/PAM exercise can help answer questions such as the degree to which variation in the operating parameters of tangential flow filtration can affect impurity levels.

Ensuring Process Characterization

The knowledge gained from these risk-based assessments provides guidance on areas for investigation at development scale in order to characterize the process and provide a design space. A key aspect of process characterization is qualifying the scale-down model. Qualifying the scale-down model ensures that the bench-scale model is predictive of the GMP scale; if it isn't, the full-scale process can't be scientifically supported with data generated at the small scale.

To qualify the scale-down model, a scientifically sound protocol is needed to provide evidence that the model is predictive. This qualification may include utilization of equivalent raw materials, various mixing studies and use of reference standards and controls where appropriate. We also apply a range of experiments to understand how the process parameters, both independent and dependent of one another, affect quality attributes of the process. These experiments can include design of experiments (DoE) and one factor at a time (OFAT) experiments, among others.

To summarize, an extensive characterization supports subsequent risk assessments and control strategies, informs the design space and has the potential to reduce the time required to investigate deviations. It can also enable more rapid troubleshooting of any process-related issues that might arise. Ultimately a robust characterization can accelerate batch release, which is critical in getting the treatment to the patient.

Establishing Process Performance Qualification

ADCs combine the complexity of biologics manufacturing with the environmental controls required for highly potent compounds. This combination necessitates a holistic view of ADC manufacturing and controls to build a detailed roadmap for commercialization which includes:

- Validation master plan scoping
- Risk assessment and demonstration of process control
- Process performance qualification

The validation master plan should outline everything needed to move into process validation (Figure 1). While many of these items are completed as part of clinical ADC manufacturing, this is the opportunity to formally review all potential risks, aspects of control and commercial requirements, including:

- Equipment and facility qualification
- Analytical method validation
- Microbial method verification
- Cleaning validation for equipment
- Risk assessments
- A process specific control strategy
- Validation supporting studies (to validate particular attributes of the process such as solution hold times or homogeneity during filling)
- Characterization and risk assessment reports
- Shipping validation

As part of the validation master plan scoping, additional risk assessments needed for commercial manufacture should be identified, along with existing risk assessments which should be reviewed and updated to support additional controls for commercial manufacture (Table 2). Risk assessments must span all areas of the process including process risks, operational and equipment risks, raw material risks, and microbial risks. The purpose to outline any final studies or process changes that are needed before moving into validation, and to lock down critical process parameters.

Journey to PPQ

Validation Master Plan Scoping



Figure 1:
Holistic look at all aspects of the process.

Final review of all potential risks, controls, and requirements for commercial manufacture.

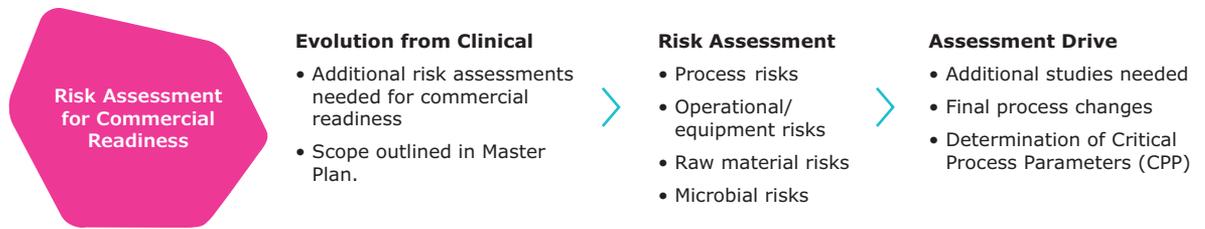
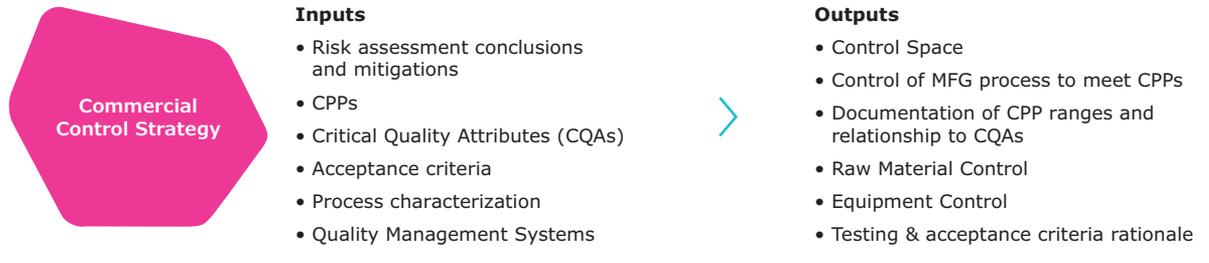


Table 2:

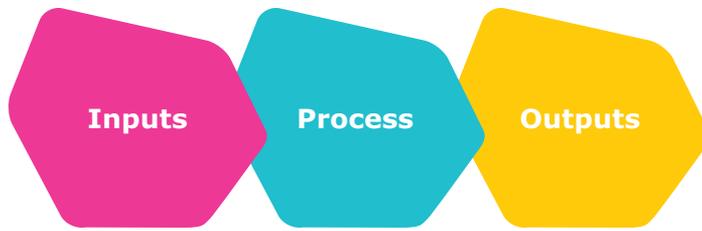
Summary of risk assessments for commercial readiness and the commercial control strategy.



An additional requirement for commercial ADC manufacturing readiness is development of a detailed and robust commercial control strategy. The control strategy incorporates risk assessment conclusions and mitigations, critical process parameters (CPPs), product CQAs, acceptance criteria, process characterization data and general quality management system controls. As an output, the commercial control strategy should provide a complete outline of the process control space and clearly identify how the manufacturing process is controlled to meet the CPPs. It should include documentation of CPP ranges and their relationship to the

product CQAs, an outline of additional components of control such as raw material, facility, and equipment control, as well as rationale for testing and acceptance criteria established.

Each risk assessment begins with inputs that are specific to the purpose of the assessment such as the manufacturing process, raw materials, equipment, process controls and quality management system controls (Figure 2). These inputs are used to drive the scoring of potential risks and failures identified.



- Scope of risk assessments defined in master plan
- MFG process
- Process controls
- Raw materials
- Equipment
- Quality Management System controls

- Determination of failure modes
- Severity:
 - Impact to the process?
 - Impact to Critical Quality Attributes (CQAs)?
- Occurrence
- Detection:
 - What controls are in place?
- Mitigation:
 - What additional controls are needed?

- Summary of process risks
- Detailed outline of inputs impact on product quality
- Additional mitigations needed
- Summary of current controls and risk mitigations

Figure 2:
Process for development of a detailed and robust risk assessment.

The inputs create the backbone of the assessment, to pave the way for determining the potential failures that need to be addressed. These may include equipment failures, failures to meet parameters required per the manufacturing process, or even failures related to the acceptance criteria for critical raw materials. The risk assessments we performed for validation followed a severity, occurrence and detection scoring pattern. The scoring starts with severity, answering questions including:

- What is the impact to the process should this failure occur?
- Is there any impact to overall CQAs as a result of this failure?

Using a deep knowledge of current controls as well as process history, one can then assess the likelihood of occurrence, followed by the detectability of a particular failure. To accurately score a failure's detectability, first assess how a failure would be caught should it occur, followed by reviewing the point in the process at which it would be caught (before the next unit operations, upon product release, etc.) Risk assessments allow for strong connections to be made regarding how specific inputs impact product quality and highlight any final mitigations that are needed. These mitigations may come in the form of additional controls, process improvements, or additional validation or characterization studies.

Through completing a holistic summary of all the process risks and current process controls, the risk assessment is also able to point out areas of strong control and low risk, that should be outlined in the control strategy. It is important that the risk assessments allow for clear conclusions to be made to support process control and knowledge, as this is critical for supporting approval and the preapproval inspection audit (PAI).

Once most of the validation master plan deliverables are completed, the process performance qualification (PPQ) protocol must be developed, to allow for execution of the PPQ batches. The PPQ protocol must outline the validation approach for the product, including components such as the number of consecutive batches, proposal for batch scale variability, incorporation of raw material variability, and additional requirements such as processing or solution hold times that will be challenged during validation. It is important that the validation approach, and any decisions made regarding components of the validation, be clearly documented and justified as this justification may be a point of review during the PAI audit.

The second component of the PPQ protocol is the acceptance criteria and test plans. PPQ batches may, for example, include additional, non-routine testing to validate attributes such as drug substance excipient levels or impurity clearance. In addition, the parameters to be monitored should be clearly outlined, including CPPs as well as any additional process parameters that are required to demonstrate successful execution. This may include process capability measurements that are not routinely captured during batch manufacture, such as process yield. Once the PPQ protocol is ready, completion of a formal review of the validation plan should deem the process ready for validation and PPQ batch execution. Once the batches are completed, a PPQ report is written to provide a summary of execution and adherence to acceptance criteria and make a conclusion regarding the successfully validated status of the process (I.e. successfully validated). A report should also be completed for any additional studies run to support validation that were not included within PPQ execution (ex: filling homogeneity). These reports are essential as they ultimately feed into the product file and can be a large component of the PAI inspection.

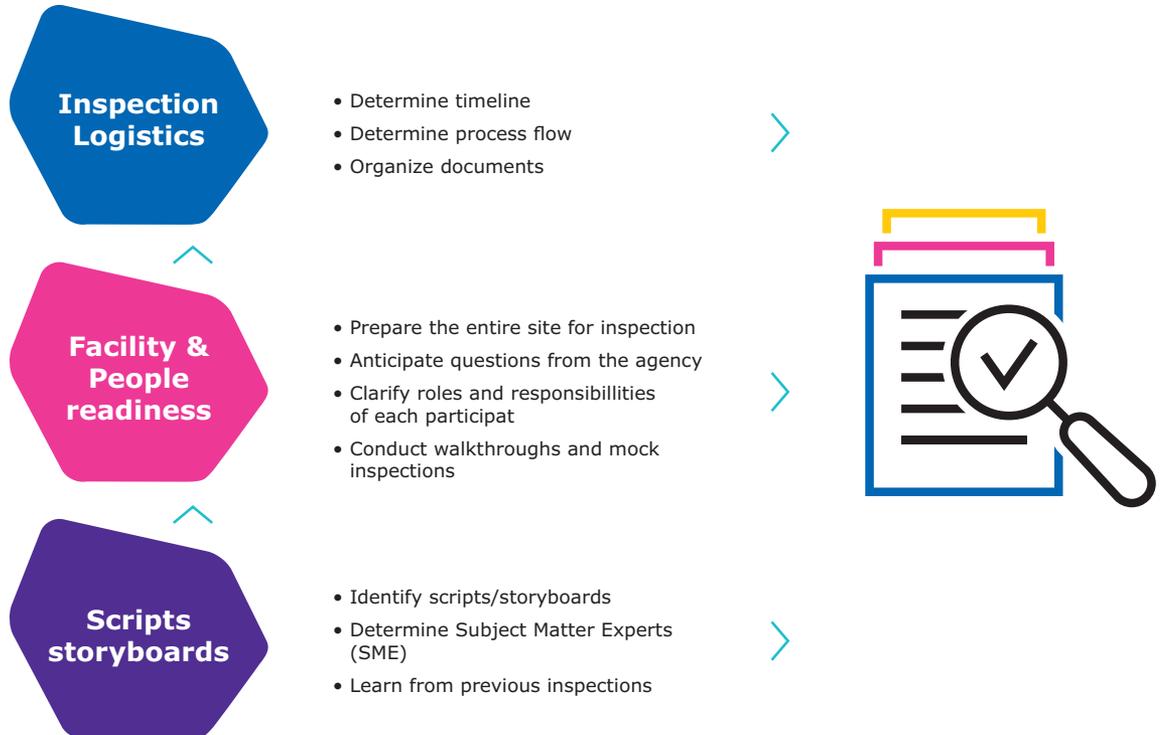
Preparing for Pre-Approval Inspection

The way we approached the PAI of our commercial ADC manufacturing facility differed from how we had traditionally hosted inspections for small molecules at the same site. For non-biologics, the inspection was driven by the quality assurance team, with support from subject matter experts as needed. For ADCs, our subject matter experts were the core of the inspection team, given that much of the audit was focused on control strategies as well the facility itself.

While the inspection was conducted according to Q7 guidelines, there are many different areas that the FDA focuses on in relation to biologics. Figure 3 summarizes the approach used to ensure inspection readiness.

Figure 3:

A structured approach was used to ensure inspection readiness



Scripts and storyboards, consisting of four to five slides, were used to describe complex processes. An example of a process that could benefit from a script is the raw material receipt process or any procedure at the site that would benefit from a very organized script to describe the workflow. Storyboards can also be used to describe complex gaps in the process, repeat deviations or the validation narrative to the inspector. This approach ensures the subject matter experts are comfortable with how they will relate the narrative of their department, their process or the deviation that they helped investigate.

We also ensured the readiness of both our facility and staff. This is essential as the inspectors may question staff members other than the subject matter experts when touring the facility; in many cases, the inspectors want to question the operators on the floor that are performing a particular action. Site-wide training reminded individuals how they may want to respond to inspectors and provided insight into the questions they may receive during the audit.

It is also very important to clarify roles and responsibilities of each participant in the audit well ahead of time. Walk-throughs and mock audits are invaluable for helping subject matter experts become comfortable with the audit process and know what to expect. Team members can be enlisted to play the role of inspectors and ask critical questions to ensure our experts could explain their process effectively and concisely.

Finally, inspection logistics were coordinated and included establishing a timeline for preparation as well as the process flow and organization of documents. During the inspection itself, it doesn't matter how much preparation has gone into it if there isn't a well-defined process flow. To ensure a robust and streamlined process flow, we had an audit team dedicated to each inspector or audit stream and a host who was well-versed in general quality systems at the site. The host answered general quality system questions and enlisted subject matter experts to speak to the individual process capabilities or any deviations.

The Journey to Commercialization

ADCs offer remarkable potential in the fight against cancer and other diseases. As more therapeutic candidates approach the approval finish line, the need for commercial-scale manufacturing will continue to grow. In this white paper, we have described the key elements that were central to the establishment of our commercial manufacturing services for ADCs. Building towards a robust control strategy starts early in the process development characterization and includes microbial control strategy, risk assessments and scale-down model qualification. From there, process validation requires a holistic assessment of your process, and includes master plan scoping, risk assessment completion, and PPQ execution; all leading up to preparation for a successful PAI, which requires advanced planning and orchestration of the team members.

The typical technical data above serve to generally characterize the excipient. These values are not meant as specifications and they do not have binding character. The product specification is available separately at: [MerckMillipore.com](https://www.MerckMillipore.com)

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