Building a Resilient Commercial Supply Chain for Antibody-Drug Conjugate Products: A Risk-Based Comparability Approach

- Navigating the complexities of multi-site manufacturing, comparability, and regulatory compliance

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Anatomy of ADC Complexity

Unlike traditional monoclonal antibodies (mAbs), Antibody Drug Conjugates (ADCs) have additional components that make comparability more complex. Changes may occur at any node and the impact assessment requires a granular, science-based approach depending on where the change occurs in this chain.

Drug Linker Intermediate

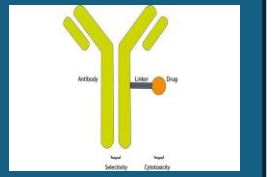
- Manufacturing Site/process
- Starting Materials
- Specifications

mAb Intermediate

- Manufacturing Site/process
- Raw materials/equipment
- Specifications
- Container

Drug Substance

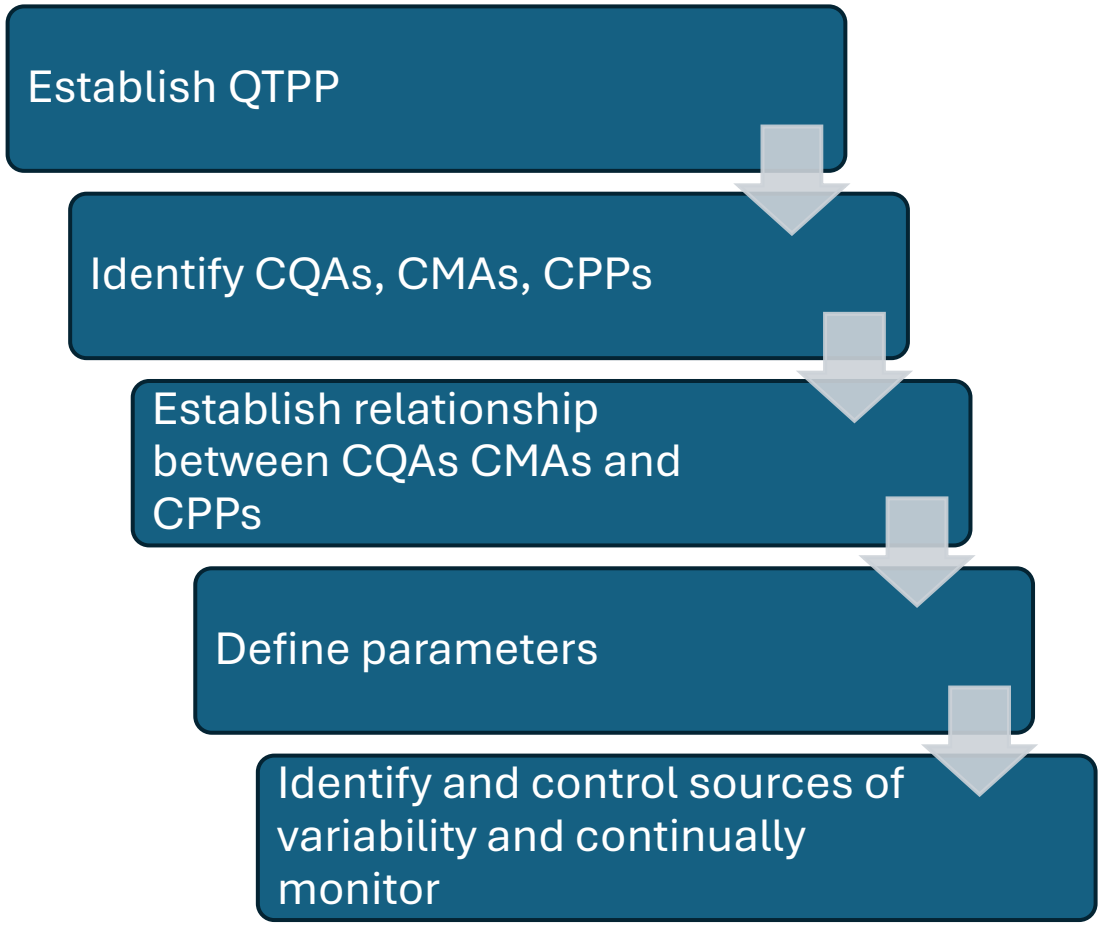
- Manufacturing Site/process
- Changes in intermediates
- Specifications
- Container



Drug Product

- Manufacturing Site/process
- Dosage form
- Specifications
- Container

Process Comparability: Building Quality In



Leverage of Control

Changes in the manufacturing process directly influence control strategies. By rigorously comparing process performance, sponsors can leverage existing knowledge to:

- Reduce the burden of characterization studies.
- Streamline validation requirements.
- Lower risks to physiochemical release and stability comparability.
- Ensure control over process “drift”

Regulatory Constraints

When introducing changes, regulatory guidance dictates strict boundaries (i.e. critical process parameters or established conditions), particularly for multi-facility operations.

EMA guidance (EMA/CHMP/BWP/187338/2014)

Process improvements are not allowed within the same Marketing Authorization.

Control Strategy Changes

A change in process steps may necessitate a revised control strategy.

- Need for revised process controls
- Need for re-classification of criticality of controls

Case Study 1: Building a Secondary Supply Chain Chain

Adding a Drug Linker Site

Increase in scale and facility-fit requirements.

Technical Justification	Gap Analysis	Final Outcome
➢Same route of synthesis but different process conditions	➢Repeated impurity purging studies and provided DS comparability data (3 batches)	➢Commitment needed to place 1 DS and 1 DP batch on long-term stability from some markets

Case Study 2: Building a Secondary Supply Chain

Adding a mAb Intermediate Site

Site addition for mAb intermediate also involved scale-up and additional facility-fit changes

- Process Comparability package in addition to analytical comparability
- Limited Characterization Studies were needed
- Regulatory requests to provide stability comparability at DS and DP

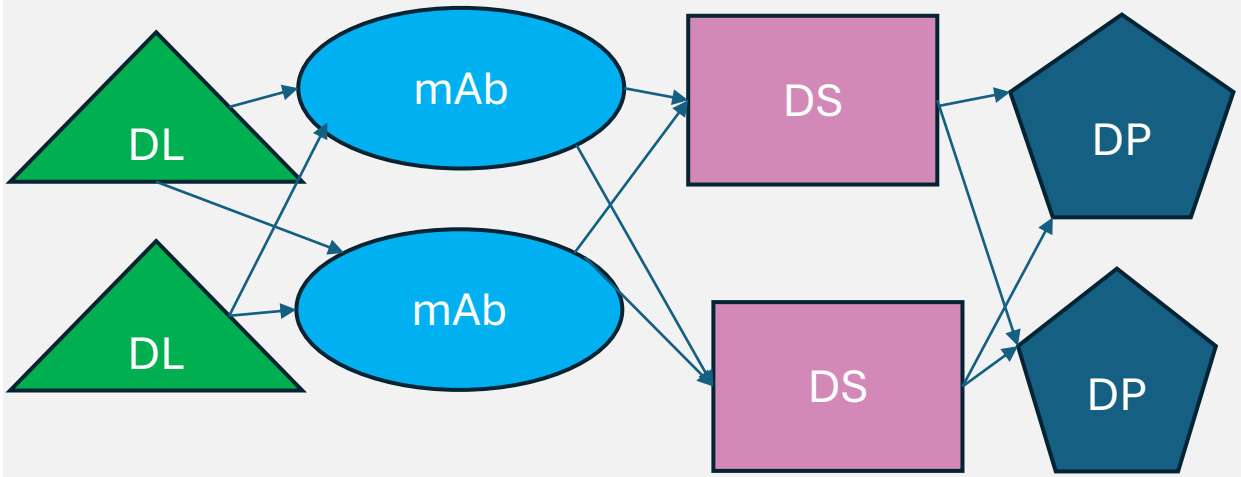
*example process comparison which fails to show process comparability

Case Study 3: Building a Secondary Supply Chain

Adding a DS and DP site

What would be the right approach?

2	2	4	12
DL Sites	mAb Sites	Distinct DS	Total Batches?



This is not sustainable.

Adding a Drug Substance (DS) site creates a combinatorial explosion.

- FDA guidance mandates factoring in "all sources of variability"
- EMA expects a minimum of 3 process validation batches.
- Relying solely on source comparability may result in a regulatory gap

Case Study 3: Solution

- **Defined Supply Route**

Limit scope by defining the supply route in the submission

- **Flexible Combinations**

Provide a process risk assessment to support interchangeability

Our strategy was to define the supply route in the submission for DS and DP site addition

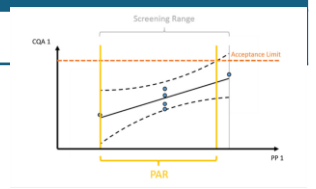
Executing the Process Risk Assessment

When justifying a reduction in validation batches, you must interrogate the process and product understanding. This type of assessment is also applicable to additions within a site (suite addition, line additions, equipment (i.e. lyophilizer) additions etc.)

Understanding Link between Process and CQAs

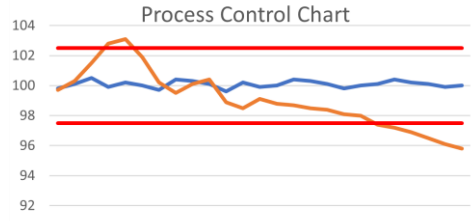
- Process Characterization
- Data from SDM or Engineering run

CQA	mAb thaw, pool, filter	Reduction	Conjugation	Quench	UF/DF	Formulation and fill
Aggregation		X	X			



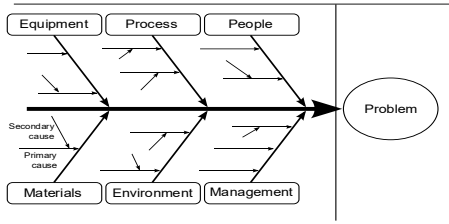
Understanding Process Capability

- Process knowledge
- Analytical capability



Evaluating Variables

- Differences that could potentially impact performance or product quality



Realizing Unknowns

- Knowledge gaps

Executing the Process Risk Assessment - Simplified

Process Risk Assessment may be broken down into 4 simple questions

Variable Steps?

Does the process have highly variable steps impacting quality?

Site Specifics?

Are there significant process changes?

Knowledge Gap?

Is there a significant lack of process history?

Downstream Impact?

Do differences in final containers or supply routes exist?

Closing Thoughts

The ADC landscape currently lacks specific global regulatory harmonization, creating a natural tendency toward "over-testing." However, this can be mitigated.

Through a robust comparability assessment that factors in process comparability, risks can be clearly presented to agencies, avoiding unnecessary data generation.

We recommend clear, transparent, and early discussion with regulatory agencies regarding your validation and comparability strategy.

The framework presented here can be used to justify your position in regulatory submissions