Mini Case Studies Session 2 - Could ADCs be the drug equivalent of Lego®?

WCBP 2024

11:00 AM, Thursday, January 25

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Agenda

Introduction to ADCs

- Anatomy of an ADC
- ADC Manufacturing
- ADC CQAs
- ADC Control Strategies
- CMC Strategy White Papers

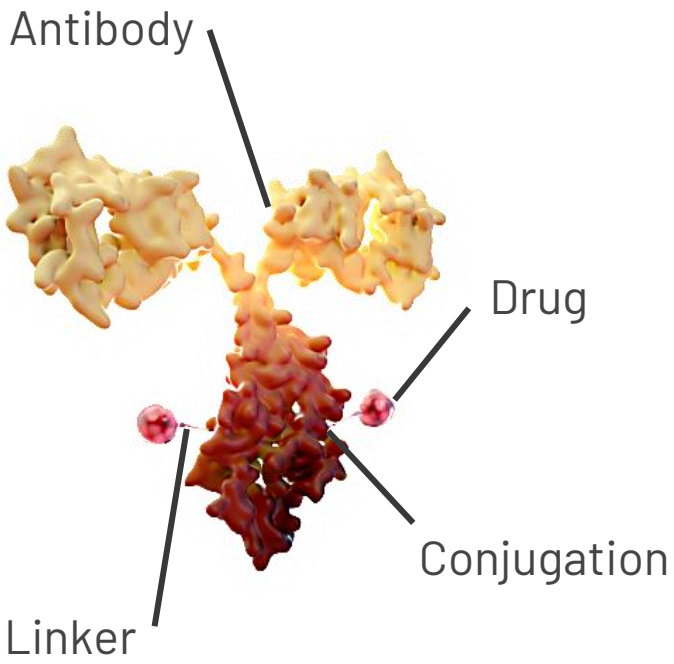
Three Mini Case Studies

- Post-Approval Changes

Group Discussion

Anatomy of an ADC

The whole is greater than the sum of its parts



Antibody • Targets tumor antigen • IgG, biospecific, other variants • Wild type or engineered • Known or novel	**Drug** • Drives primary mechanism of action • Cytotoxics • Immune modulators • Antibiotics • Oligonucleotides • Other drug classes
Linker • Cleavable • Non-cleavable • Physicochemical property modifiers	**Conjugation** • Controls drug-to-antibody ratio (DAR) • Lysine • Cysteine • Enzymatic • Stochastic • Site specific

ADC Manufacturing – Hybrid Processes

Intermediate Processes

- mAb process
- Drug-linker process

Biologic Manufacturing

Cell Line → Cell Culture → Purification → mAb Intermediate

Small Molecule Manufacturing

Raw Materials → Starting Materials → Drug-Linker Intermediate

Drug Substance/Drug Product Processes

- DS conjugation process
- DP fill/finish process

Bioconjugation

DS

Fill/Finish

DP

ADC Critical Quality Attributes: Focus on the Drug Substance

Drug Substance

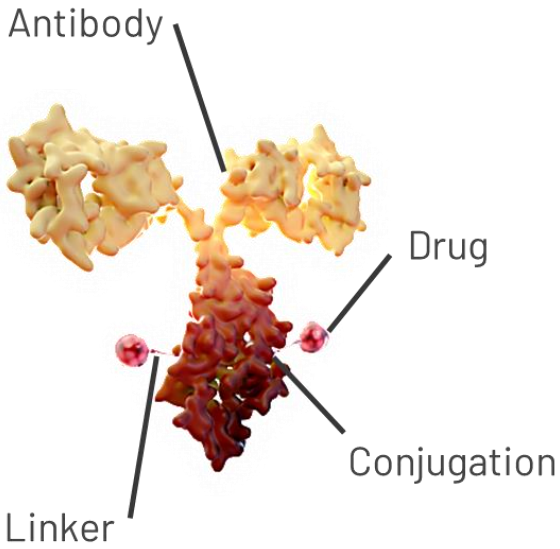
- Product-related attributes
  - MOA (Potency)
  - **Structure**
  - **Amino Acid Modifications**
  - Sequence Variants
  - Size/charge Variants
- Process-related Impurities and contaminants
  - DNA, HCP, Side Product, etc.

Drug Product (DP obligatory CQA)

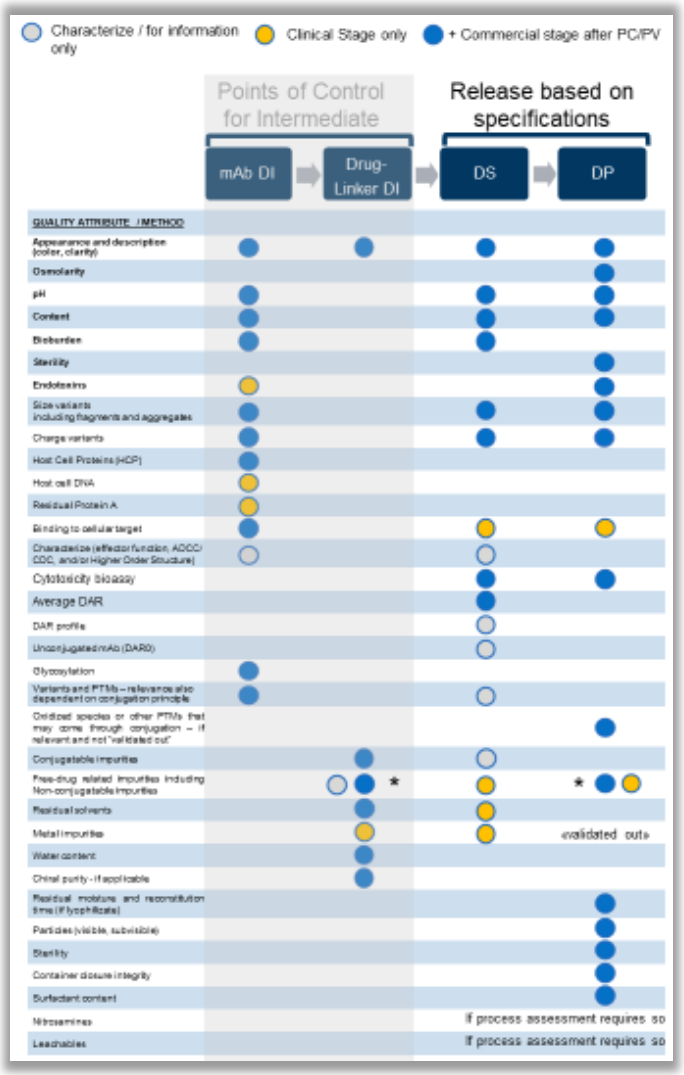
- Visible/sub-visible particles, pH, osmolality, excipient, etc.

Primary
Secondary
Tertiary

Oxidation Met
Oxidation Trp
Oxidation Lys
Deamidation Asn
Deamidation Gln
Glycation Lys



Rationalizing Points of Control and Specifications - Example



Attribute	mAb DI	Drug-Linker DI	DS	DP	
pH	●		●	●	Redundant Controls Expected
Content	●		●	●	
Size Variants	●		●	●	
Charge Variants*	●		●	●	
Effector Functions	◎		◎		
Host cell protein	●				Single Point of Control
Host cell DNA	◉				
Purity/Assay		●			

*Strategy regarding effector functions depends on mechanism of action

● - Controls through commercial

◉ - Clinical Controls

◎ - Characterization and/or comparability

Reference: Bechtold-Peters, *et al.*, Journal of Pharmaceutical Sciences 112 (2023) 2965–2980

Proposal: Comparability assessment at the Point of Change could be sufficient

Assumptions:

DL and mAb intermediates are well characterized and critical quality attributes (CQAs) are identified as intermediates for conjugation and as part of the final product

DL and mAb processes have been rigorously characterized, the parameters and controls are well understood, and prior knowledge could be applied.

DL and mAb meet the CQAs and demonstrated to be comparable to pre-change DL and mAb respectively

Comparability assessment is based on the risk assessment between intermediate sources and meets HA expectations in different markets

DS process has been rigorously characterized, intermediate attributes are well defined, and no DS processes changes are in scope.

Confirm similarity of DS process performance and product quality using qualified small-scale model.

Case Study 1: FDA feedback on addition of a new Drug-Linker intermediate supply for 3 platform ADCs

Critical quality attributes for the DL intermediate are well defined for:

- Manufacturing using platform conjugation process linking to platform mAbs
- quality target product profile in the resulting ADC

Risk assessed as LOW based on:

- Same specifications; similar purity/impurity profiles at release and on stability
- Same routes of chemical synthesis; 1.2 times larger scale
- Similar raw materials and reagents
- Similar analytical methods
- DL Process Performance Qualification successfully completed
- Facility GMP inspected and in good standing
- Meets incoming requirements for DS manufacturing

Case Study 1 - Evolution of HA feedback and Sponsor approaches

Example	Product A (FDA Consultation)	Product B (FDA Consultation)	Product C (No Consultation)
DL	**Same DL data package**: 3 PPQ DL batches, release data, long-term and accelerated stability data		
DS (-60°C)	**Comparability:** 3 x 3 DS batches, comparative batch analysis and thermal stress data		
	Stability: 1 batch Commitment for long-term conditions Sponsor's conservative approach - 3 batches	**Stability: 1 batch** (*HA Feedback*) Commitment for long-term and accelerated conditions	**Stability: 1 batch** Commitment for long-term conditions
DP (Lyo)	**None***	**Stability: 1 batch** (*HA Feedback*) Commitment for long-term and accelerated conditions	**None**
Outcome	PAS Approved	PAS Approved	PAS Approved

*Product A, HA feedback was to provide comparability for both DS and DP but Sponsor successfully rationalized to conduct stress studies on DS and place 1 batch on stability. The same approach was not accepted by HA for Product B.

Case Study 2: Comparison of submission content by market for addition of a new Drug-Linker intermediate supplier

Example	FDA (Consultation)	EMA and ROW (No Consultation)	Health Canada (No Consultation)
DL	**Same DL data package**: 3 DL PPQ batches, release data, long-term and accelerated stability data		
DS (-60°C)	**Comparability:** 3 x 3 DS batches, comparative batch analysis and thermal stress stability data		
	Stability: 1 batch (*HA feedback*) Commitment for long-term and accelerated conditions	**Stability: 3 batches** (*Sponsor decision*) Long-term and accelerated conditions data	**Stability: 3 batches** (*HC NOC guidance*) Long-term and accelerated conditions data
DP (Lyo)	**No comparability assessment**	**Comparability: 3 x 3 batches** (*Sponsor decision*) Comparative batch analysis	**No comparability assessment**
	Stability- 1 batch (*FDA feedback*) Commitment for long term and accelerated conditions	**No stability data in submission**	**No stability data in submission** (*HC guidance suggests to place 1 DP batch on stability*)
Outcome	PAS Approved	Type II Variation Approved	sNDS Approved

Discussion Questions

1. What would you have done differently?
2. What submission strategies have you successfully used to add DL 2nd sources?
3. What submission strategies have you used to mix and match different mAbs with different DLs?
4. What datasets should be provided for DS and DP following changes to the DL if it meets incoming specifications and has been shown small scale to be fit for purpose?
5. What about following changes to the mAb if pre- and post-change mAb is analytically comparable?
6. What other mix and match strategies might be justified?

Case Study 3: Addition of new mAb intermediate manufacturing site

Critical quality attributes for the intermediate well defined for:

- platform conjugation process linking to drug-linker
- quality target product profile

Risk assessed as LOW based on:

- Same specifications; similar purity/impurity profiles at release and on stability
- Similar process modified for facility fit
- Similar raw materials and reagents
- Similar analytical methods
- Similar preliminary tech transfer process performance and product comparability data
- Process Performance Qualification successfully completed
- Clinical facility to be licensed as a commercial facility

Case Study 3: Comparison of submission content by market for addition of a new mAb intermediate manufacturing site

Examples	FDA (Consultation)	EMA (No Consultation) and ROW	Health Canada (No Consultation)
mAb	**Same mAb data package**: 3 mAb PPQ batches, release data, comparative batch analysis, extended characterization, thermal stress studies, long-term and accelerated stability data		
DS (-60°C)	**No comparability assessment**		
	Same stability package: 3 batches Commitment for long term and accelerated conditions		
DP (Lyo)	**Comparability: 3 x 3 batches** *(FDA Feedback)* Comparative batch analysis and thermal stress data	**Comparability: 3 x 3 batches** (*Sponsor decision*) Comparative batch analysis and thermal stress data	**Comparability: 3 x 3 batches** *(HC NOC guidance)* Comparative batch analysis and thermal stress data
	Stability: 1 batch *(FDA Feedback)* Commitment for long-term and accelerated conditions	**Stability: 1 batch** (*Sponsor decision*) Long-term and accelerated conditions data	**Stability: 1 batch** (*Sponsor decision*) Long-term and accelerated conditions data
Outcome	PAS Approved	Type II Variation Approved	sNDS Approved

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5. What about following changes to the mAb if pre- and post-change mAb is analytically comparable?
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Recent White Papers Presenting CMC Strategies for ADCs

- Control Strategy for Small Molecule Impurities in Antibody-Drug Conjugates
  Gong, *et al.*, AAPS PharmSciTech 19, 971–977 (2018).

- Drug-Linkers in Antibody–Drug Conjugates: Perspective on Current Industry Practices
  Bulger, *et al.*, Organic Process Research & Development 27 (7), 1248-1257 (2023).

- Strategies for UF/DF-Based Impurity Removal in the Post-conjugation Purification of Antibody–Drug Conjugates
  Fernandez-Cerezo, *et al.*, Organic Process Research & Development 27 (7), 1258-1268 (2023).

- Considerations for Starting Material Designation for Drug-Linkers in Antibody–Drug Conjugates
  Jones, *et al.*, Organic Process Research & Development 27 (7), 1269-1275 (2023).

- CMC Regulatory Considerations for Antibody-Drug Conjugates
  Bechtold-Peters, *et al.*, Journal of Pharmaceutical Sciences 112 (2023) 2965–2980.