Could One Size Fit All- Why not?

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Outline

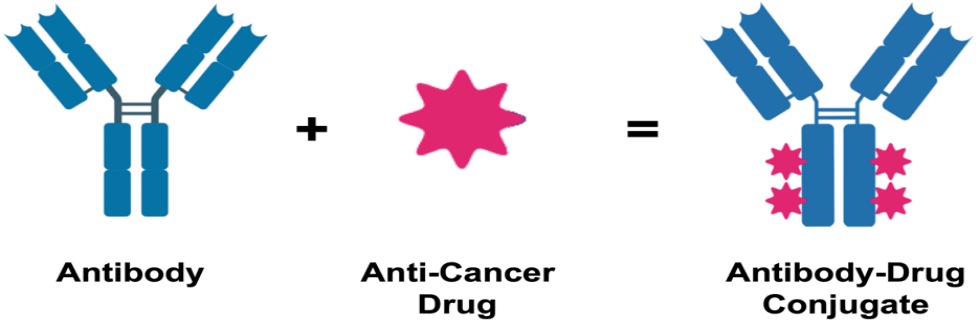
- Applying risk-based and modular approaches for demonstrating comparability for ADCs
- Case studies- introduction of drug linker and mAB intermediates new manufacturing site
- Proposal for future considerations

PREVENTING DRUG SHORTAGES!

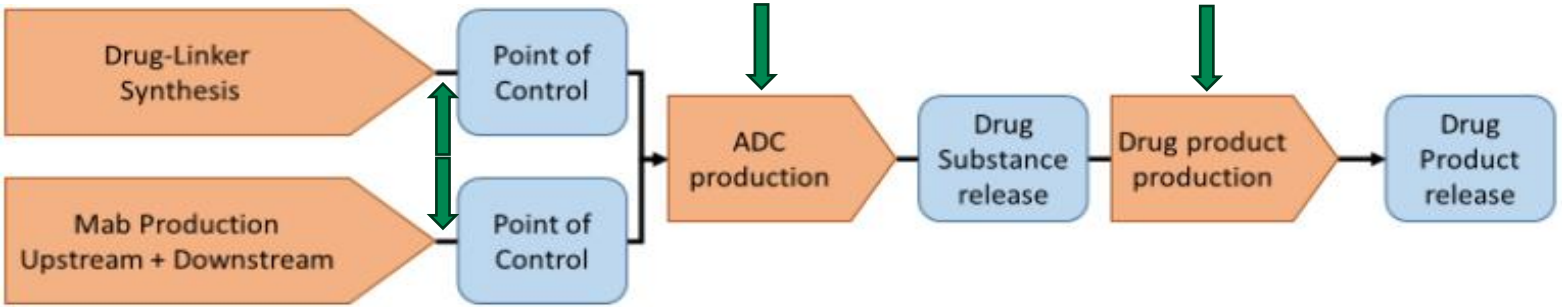
Focusing on the Patient

- Ensure supply continuity
- Scientific risk-based approach
- Build post-approval predictability
- Build regulatory agility (regulators and industry)
- Enhance global efficiency and effectiveness

Risk-based Comparability Is A Key Enabler To Product Lifecycle and Speed to Market



Where do you draw the line?



Current State/ Problem Statement

- Comparability study design does not commensurate with the level of risk
- Differing HA expectations for a change common across ADC products
- Diversity in global regulatory expectations results in divergent regulatory data packages

Case Study 1

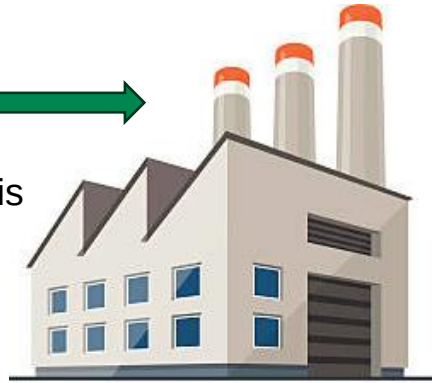
- **Differing HA expectations for a change common across ADC products**
  - Case Study- Addition of new Drug Linker (DL) intermediate manufacturing site

Case Study 1: Addition of New Drug Linker (DL) Intermediate Manufacturing Site

- Comparison between the existing and the new site- scale-up and facility fit changes

Risk Assessment

- Equipment- same operating principles
- Manufacturing process- same route of synthesis
- Raw materials, reagents- similar
- Analytical Methods- similar
- Purity/ Impurity profile- similar
- Specification- same



- PPQ batches manufactured verified successful transfer of manufacturing procedures, equipment, material requirements, control systems and process knowledge
- Stability studies conducted on DL from new manufacturing site (post change)
- HA feedback recommended to demonstrate comparability beyond point of change (DL) to include drug substance (DS) and/ or drug product (DP)

Differing HA Expectations For Same DL Change Common Across Products- Divergent Comparability and Stability Data Requirements

Differing Feedback from FDA

Data	Product A* (Type C)	Product B (Type C)	Product C (No HA Consultation)
DL	3 PPQ batches: release data, long term and accelerated stability data **Modular approach- Consistent DL data package submitted across multiple products**		
DS	**Comparability- 3 by 3 batches** • Release data • Comparative batch analysis • Comparative thermal stress studies		
	Stability- 1 batch (*Sponsor's* conservative approach- *3 batches*) • Commitment for long term conditions	**Stability- 1 batch (*HA Feedback*)** • Commitment for long term and accelerated conditions	**Stability- 1 batch** • Commitment for long term conditions
DP	None	**Stability- 1 batch** (*HA Feedback*) • Commitment for long term and accelerated conditions	None
Outcome	Approved	Approved	Approved

*Product A, HA feedback recommended to provide comparability for DS and DP. 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

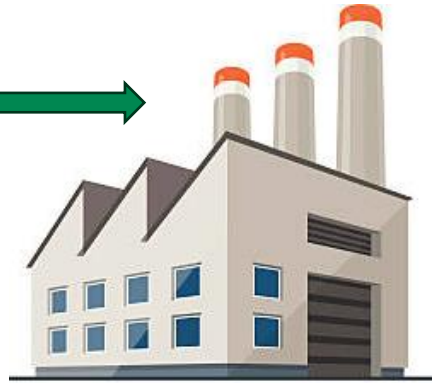
- **Comparability study design needs to commensurate with the level of risk**
  - Case Study- Addition of new mAb intermediate manufacturing site
  - Case Study- Addition of new Drug Linker (DL) intermediate manufacturing site

Case Study: Addition of New mAB Intermediate Manufacturing Site for ADC Product B

- Comparison between the existing and the new site- scale-up and facility fit changes

Risk Assessment

- Equipment- same operating principles
- Manufacturing process- same
- Raw materials, reagents- similar
- Analytical Methods- similar
- Purity/ Impurity profile- similar
- Specification- same



- PPQ batches manufactured verified successful transfer of manufacturing procedures, equipment, material requirements, control systems and process knowledge
- Comparability and stability studies conducted on mAb from new manufacturing site
- HA feedback recommended to demonstrate comparability beyond point of change (mAB) to include drug product (DP)

Comparability Study Design Needs To Commensurate With Level Of Risk Of The Change

Case Study: Addition of new mAb intermediate manufacturing site for Product B

<table>
<tr><th>Stage</th><th>FDA (PAS)</th><th>EMA (Type II) and MOW</th><th>Health Canada (sNDS)</th></tr>
<tr><td>mAb</td><td colspan="3">3 PPQ batches: release data, comparative batch analysis, extended characterization, thermal stress studies, long term and accelerated stability data
Modular approach- Consistent mAb data package submitted across HAs</td></tr>
<tr><td>DS</td><td colspan="3">Stability- 3 batches
• Commitment for long term and accelerated conditions</td></tr>
<tr><td rowspan="2">DP</td><td colspan="3">Comparability- 3 by 3 batches (FDA Feedback, EMA- sponsor approach, HC- NOC guidance)
• Release data • Comparative batch analysis • Comparative thermal stress studies</td></tr>
<tr><td>Stability- 1 batch (FDA Feedback)
• Commitment for long term and accelerated conditions</td><td colspan="2">Stability- 1 batch (Conservative approach from sponsor)
• Data from long term and accelerated conditions provided</td></tr>
<tr><td>Outcome</td><td>Approved</td><td>Approved</td><td>Approved</td></tr>
</table>

Desired state- Assess comparability at point of change. Confirm downstream performance based on risk using a qualified scale down model

Comparability Study Design Needs To Commensurate With Level Of Risk Of The Change

Case Study: Addition of new DL intermediate manufacturing site for Product B

Data	Product A* (Type C)	Product B (Type C)	Product C (No HA Consultation)
DL	3 PPQ batches: release data, long term and accelerated stability data **Modular approach- Consistent DL data package submitted across multiple products**		
DS	**Comparability- 3 by 3 batches** • Release data • Comparative batch analysis • Comparative thermal stress studies		
	Stability- 1 batch (*Sponsor's* conservative approach- *3 batches*) • Commitment for long term conditions	**Stability- 1 batch (*HA Feedback*)** • Commitment for long term and accelerated conditions	**Stability- 1 batch** • Commitment for long term conditions
DP	None	**Stability- 1 batch (HA Feedback)** • Commitment for long term and accelerated conditions	None
Outcome	Approved	Approved	Approved

*Product A, HA feedback recommended to provide comparability for DS and DP. Sponsor successfully rationalized to conduct stress studies on DS and place 1 batch on stability. This was not successful for Product B.

Comparability Study Design Needs To Commensurate With Level Of Risk And Standardization of Global HA Requirements

- DL and mAb are well characterized molecules
- Confidence in DL and mAb intermediates performance in DS manufacturing can be gained if all critical quality attributes (CQAs) including those meaningful for conjugation are met
  - Considerable knowledge of the DL and mAb process parameters and controls
  - DL and mAb manufacturing process, packaging, and storage conditions remain unchanged
  - DL and mAb meet the CQAs and demonstrated to be comparable to pre-change DL and mAb respectively
  - No change to mAb or DL intermediate inputs for each of the respective change and conjugation process at DS remains unchanged

Comparability Assessment at the Point of Change is Adequate as long as Pre and Post Change mAb and DL are Comparable

Case Study 3

- **Diversity in global regulatory expectations resulted in divergent regulatory data packages**
  - Case Study- Addition of new Drug Linker (DL) intermediate manufacturing site

Diversity In Global Regulatory Expectations and Sponsor's Risk Appetite Resulted In Divergent Regulatory Data Packages

Case Study: Addition of new Drug Linker (DL) intermediate manufacturing site for Product B

Data	FDA (PAS)	EMA (Type II) and MOW	Health Canada (sNDS)
DL	3 PPQ batches: release data, long term and accelerated stability data **Modular approach- Consistent DL data package submitted across HAs**		
DS	**Comparability- 3 by 3**		
	• Release data	• Comparati	tive thermal stress studies
	Stability- 1 batch (*FDA feedb*		**Stability- 3 batches (***HC NOC guidance*) Data from long term and accelerated conditions
	• Commitment for long accelerated conditio	ated	
DP	**No comparability asse**	**Comparability- 3 by 3 batches** (*Sponsor decision*) • Comparative batch analysis	**No comparability assessment**
	Stability- 1 batch (*FDA feedback*) • Commitment for long term and accelerated conditions	None	None (*HC guidance suggests to place 1DP batch on stability*)
Outcome	Approved	Approved	Approved

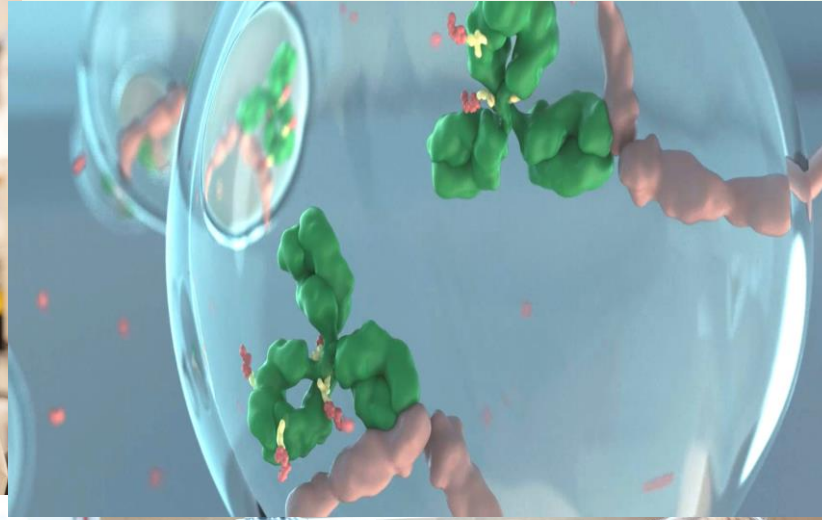
Additional data and documentation- Did it impact the product quality supplied to patients? Brings forth the question could the requirements be standardized?

Reflections And Desired State

- **What went well with the submissions?**
  - Global HA acceptance of modular approach across multiple products
  - Some level of consistency for comparability data packages across multiple products and global HAs for the same change
  - Supplements approved without additional data requests

- **Impact Of Varying HA Expectations**
  - Inconsistencies in data packages for same change across products from a major HA sets the precedent for global submissions
  - Diversity in global regulatory expectations resulting in divergent regulatory data packages impacts speed of access of life saving therapies for patients

- **Desired State**
  - Comparability study design to commensurate with risk level of change
  - Standardize data requirements across global HAs for the same change
  - Reference DL dossier across multiple products after submission to one product



Thank You