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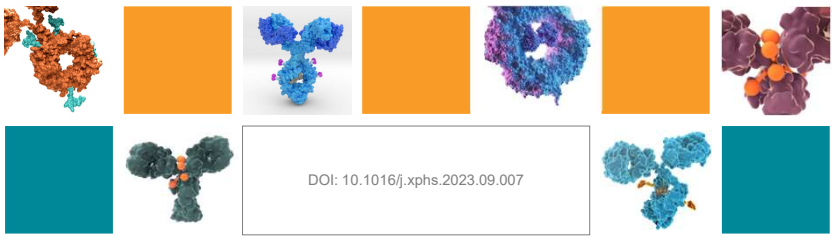
European Federation of Pharmaceutical Industries and Associations

CMC Regulatory Considerations for Antibody-Drug Conjugates



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1

EFPIA BIOMANUFACTURING WORKING GROUP

CMC Regulatory Considerations for ADCs A collaborative white paper

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efpia 2

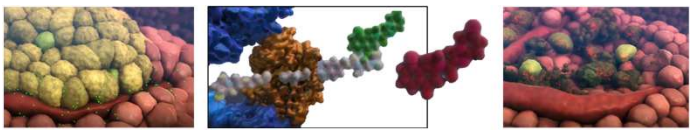
2

ANTIBODY DRUG CONJUGATES

From the promise of a magic bullet ….

Built from an Antibody and a Drug-Linker

To deliver specificity, safe circulation in the bloodstream and high potency upon internalization in tumor cells and activation of the drug



efpia 3

3

ANTIBODY DRUG CONJUGATES

To Building and maintaining dossiers

- Combination of chemical small molecules and large molecule biologicals
- Dossier structure
- Developing process understanding across moieties
- Each moiety delivering on its intended use
- Assuring appropriate controls across manufacturing
- Manufacturing Changes
- Comparability
- Multiple production locations

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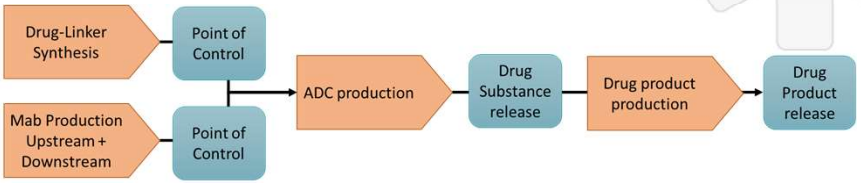
4

Generating understanding towards Control



Quality attribute considerations

- Origin of attribute: e.g. intermediate or during conjugation
- Risks resulting from impurities or contaminants
- Understanding conjugation technology
- Build data and control appropriately

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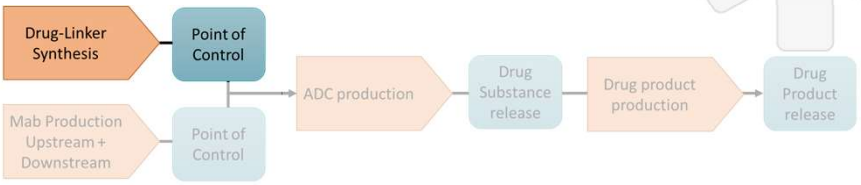
5

Quality Attributes from source to DP



Intended use of the Drug-Linker

- React to form covalent bond in ADC
- Toxicity of the activated drug
- Lack of harmful impurities and contaminants

Quality attribute examples for Drug Linker Intermediate

- Conjugatable impurities
- Free drug related impurities
- Chiral purity (if applicable)

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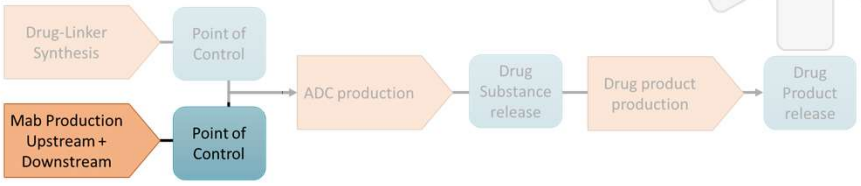
6

Quality Attributes from source to DP



Intended use of the Antibody

- Specificity in binding to target molecule
- Lack of harmful impurities and contaminants

Quality attribute examples for Antibody Intermediate

- Desired antibody sequence (consider further if conjugation sites)
- Adventitious viral agents
- Glycosylation (consider further if conjugation site)
- Host cell proteins

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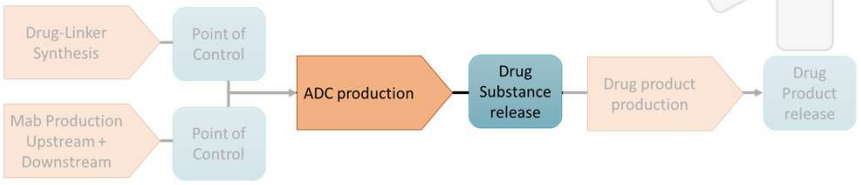
7

Quality Attributes from source to DP



Generating the Antibody Drug Conjugate

- Consistent profile of drug linked to antibody achieved
- Lack of unlinked drug, linker or antibody

Quality attribute examples for Antibody Intermediate

- Potency
- DAR profile
- DAL0 (antibody without drug) levels
- Free drug related impurities (FDRIs)
- Conjugatable impurities

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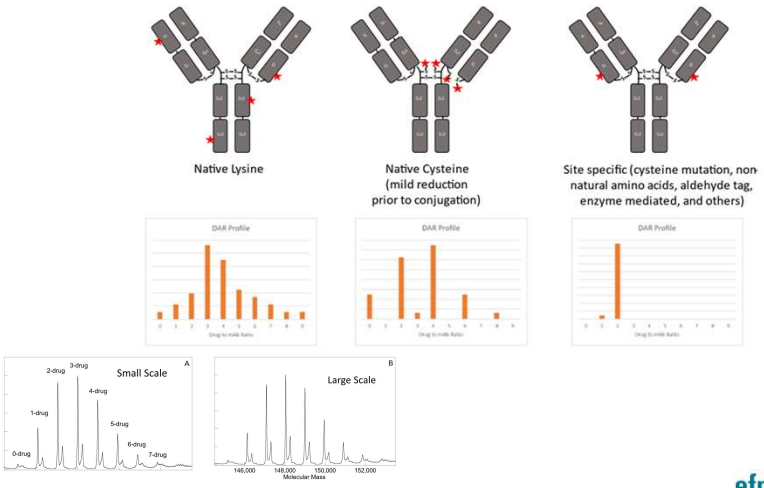
8

Conjugation variability depends on technology used consistency can be achieved by all



trastuzumab emtansine, Lys conjugation

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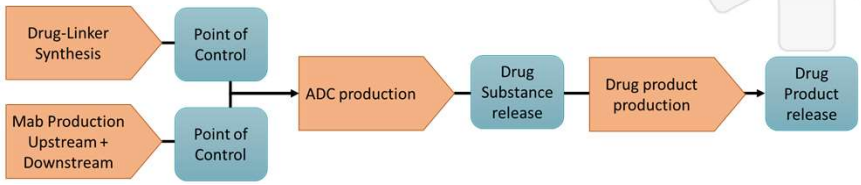
9

Examples of Control based on understanding

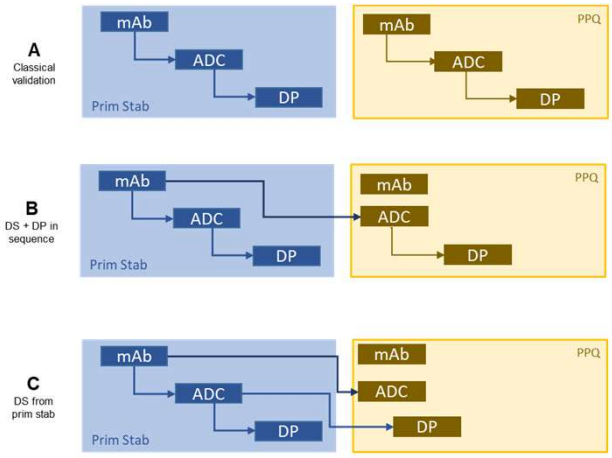


Quality attribute	mAb DI	Drug-Linker DI	DS	DP
Appearance and description (colour, clarity)	Commercial	Commercial	Commercial	Commercial
Bioburden	Commercial		Commercial	
Sterility				Commercial
Res ProtA	Clinical			
Conjugatable impurities		Commercial	Clinical	
DAR			Commercial	
DAL profile			Characterize	
DAL0			Characterize	

10

DEMONSTRATION OF CONTROL

Process Performance Qualification considerations

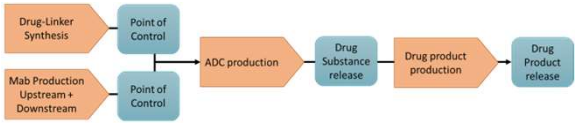


11

LIFE WITH A REGISTERED ADC DOSSIER

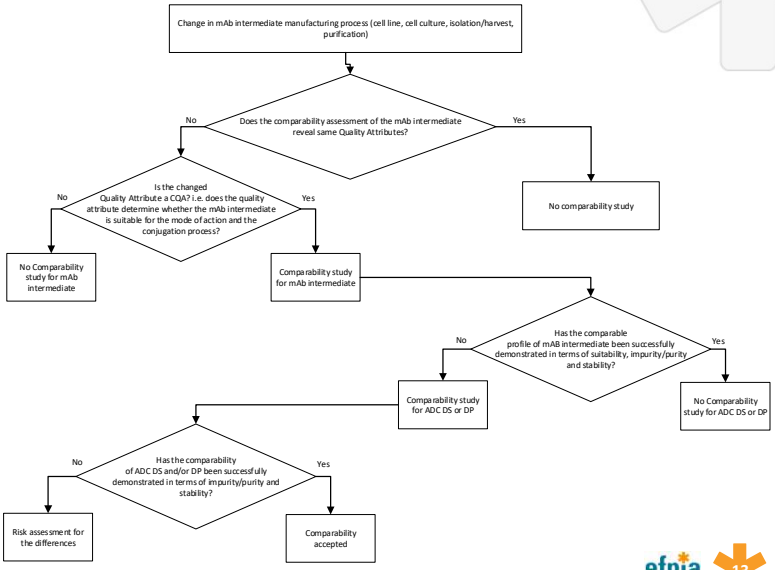
Process changes for mAb, DL, DS or DP

- Changes will happen
- Networked manufacturing, multiple locations
- Knowledge driven, risk-based assessments of potential impact leading to demonstration of intended use
- Comparability studies as/when indicated



12

Consideration for mAb intermediate process changes



13

Comparability

Comparability in general similar in approach as for biologicals, but beware of the mix

Specific attention to ensure that lots represent the variation to be demonstrated

- **e.g. a mAb change should compare sufficient different mAb lots**

GLP tox vs GMP clinical process

- **safety (impurities) and potency (DAR profile) in focus**
- **Generally no comparative stability, unless major process differences**

Late stage (clinical vs pivotal process)

- **CQAs speaking to safety, efficacy, quality and stability included; purity/impurity profiles, DAR, potency, primary and higher order structure**
- **Suitable lot selection should cover process variabilities**
- **Improvements in impurity profiles acceptable**
- **Stability data should be available to support comparability**

14

Formulation

Generational difference between ADCs

- Early ADCs linker was most unstable element, optimization of linker technologies has improved this
- Improved linker technologies that alter protein structure may impact stability
- Understanding of drug-linker-protein requirements allow for improved formulation strategies across all areas of the drug

Formulation for stability and the intended use of the component: formulating a mAb for a patient is different to formulating a mAb for conjugation

Improved understanding leading to liquid formulations in future

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15

Regulatory Dossier structure

Subdivision required

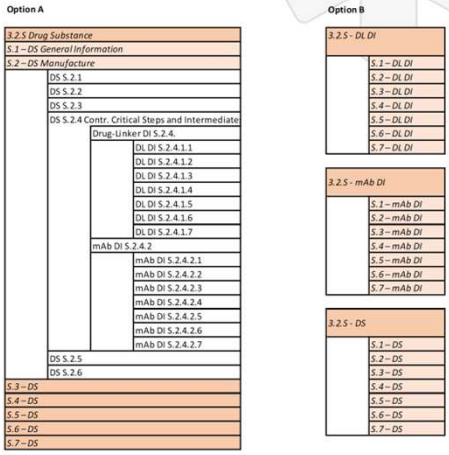
Guide the reader/reviewer

Consistent cross-linking in eCTD

DI should not be held to DS standards

Authors propose Option B preference

- DL-Intermediate may be use in multiple ADC products
- Opportunity for efficiencies in DMFs (currently USA and Canada only)
- Chemical/Biological separated, allows experts to find each section easily



efpia 16

16

In conclusion

Antibody drug conjugates

- Combination of chemical small molecules and large molecule biologicals
- Each moiety delivering on its intended use by appropriate controls across manufacturing
- (Prior) knowledge across moieties will guide through
  - Dossier structure
  - Manufacturing Changes and where needed comparability
  - Managing multiple production locations

17

18