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CMC Regulatory Considerations for Antibody-Drug Conjugates

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Perspective

CMC Regulatory Considerations for Antibody-Drug Conjugates

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Disclaimer

The views in this presentation are those of the presenter as an author of the EFPIA paper and do not necessarily represent the views of Denali Therapeutics Inc.

TALK OUTLINE

Control System

Key Points from the EFPIA paper

- Control of Quality Attributes
- Process Characterization
- PPQ and Stability
- Free Drug Related Impurities
- Comparability

CONTROL SYSTEM (1 OF 3)

In designing and implementing a control strategy, there are two key questions

1. What needs to be controlled and at what level?
2. How to control the necessary aspects?

For question 1, critical quality attributes are assessed.

For question 2, there multiple elements and points of control including raw materials, process parameters and understanding (CPP, PC, PV), in process controls and action limits and QC tests for release and stability.

CONTROL STRATEGY (2 OF 3)

CQAs are assessed across all process steps (end to end control strategy)

Analytical Testing Strategy (ATS):

determine which assays are required for release and which are in the extended characterization toolkit

Release tests must cover identity, purity, potency, quality and strength.

A specification, is defined as *a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described* (ICH Q6B).

CONTROL STRATEGY (3 OF 3)

Evolution of the Control System:

some QAs demonstrated to be sufficiently controlled (data acquired during development) are not tested at release in the commercial phase

Importantly for significant process changes the control strategy should be reassessed and the ATS may change. The ATS can also be streamlined over time as new data or sufficient data is acquired (wrt to manufacturing or clinical experience)

EFPIA BIOMANUFACTURING WORKING GROUP

What is EFPIA?

European Federation of Pharmaceutical Industries and Associations (EFPIA)

EFPIA's goal is to "create a collaborative environment that enables our members to innovate, discover, develop and deliver new therapies and vaccines for people"

A consensus position paper representing multiple companies was developed to provide clear recommendations, based on advanced scientific understanding of ADCs, lived experiences with development and manufacturing, and regulatory interactions across multiple technologies and regions

CMC Regulatory Considerations for ADCs was published in September 2023

DOI: 10.1016/j.xphs.2023.09.007

KEY RECOMMENDATIONS FROM THE POSITION PAPER

- **Points of Control for Quality Attributes**
  - Antibody and drug linker are intermediates, to be released for forward processing
  - Attributes should be assessed based on their relevance to forward processing, drug substance ("conjugate") or drug product
  - By combining scientific understanding of production processes with risk-based approaches, quality can be demonstrated at the relevant point of control and avoid redundant analyses
  - Advancing scientific understanding provides opportunities to streamline control strategies

- **Reaffirms strategy for establishing limits on small molecule impurities**
  - Calculate based on wt % of the impurity relative to mass of the intact therapeutic ADC

- Efficient strategies for process validation
- Outlines an approach for assessing comparability after process changes
- Recommends a structure for regulatory submission documents*

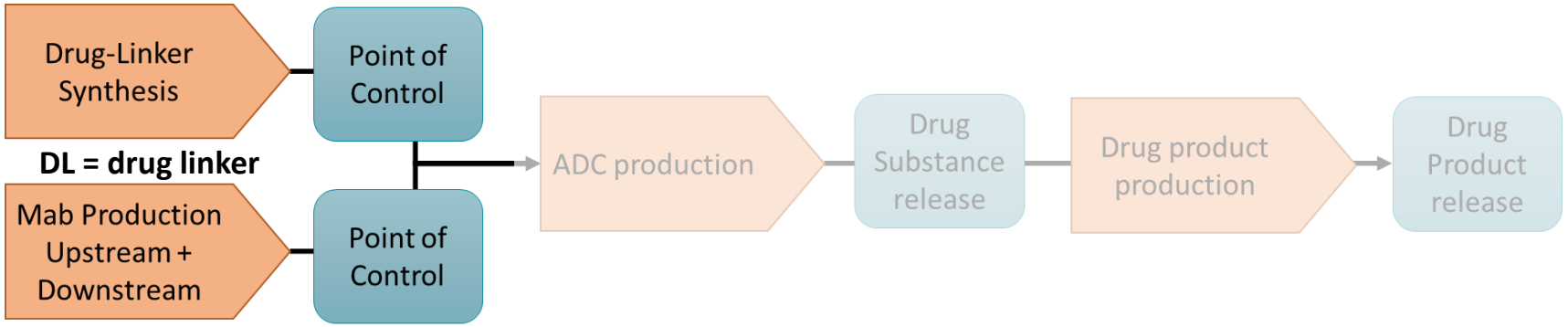
* Refer to appendix
Refer to appendix for additional publications relating to best practices

Quality Attributes Controlled in the DL

Concept

for Quality Attributes (QAs) that are set/determined during DL production and there is a low risk for them to change in downstream steps,
a single point of control after completion of DL production is appropriate.

Control of critical QAs is often at QC Release for the DL intermediate.
Other QAs are characterized / monitored as appropriate.



Examples

- Conjugatable Impurities
- Free Drug Related Impurities*
- Chiral Purity (if applicable)

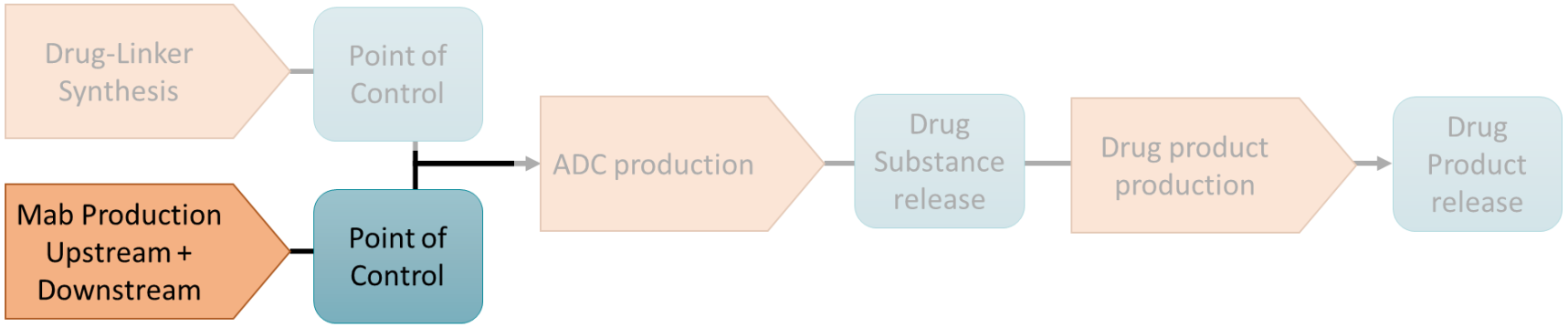
* Free drug, free DL, free DL impurities or any other forms of free cytotoxic drug that are not conjugated to the mAb are defined as “FDRIs”; as such these process-related impurities or degradants can be form either during the manufacturing process or over time during storage.

Quality Attributes Controlled in the mAb

Concept

for Quality Attributes (QAs) that are set/determined during mAb production and there is a low risk for them to change in the downstream process steps, a single point of control after completion of mAb production is appropriate.

Control of critical QAs is often at QC Release for the mAb intermediate.
Other QAs are characterized / monitored as appropriate.



Examples

- Adventitious Viral Agents
- Glycosylation*
- Host Cell Proteins

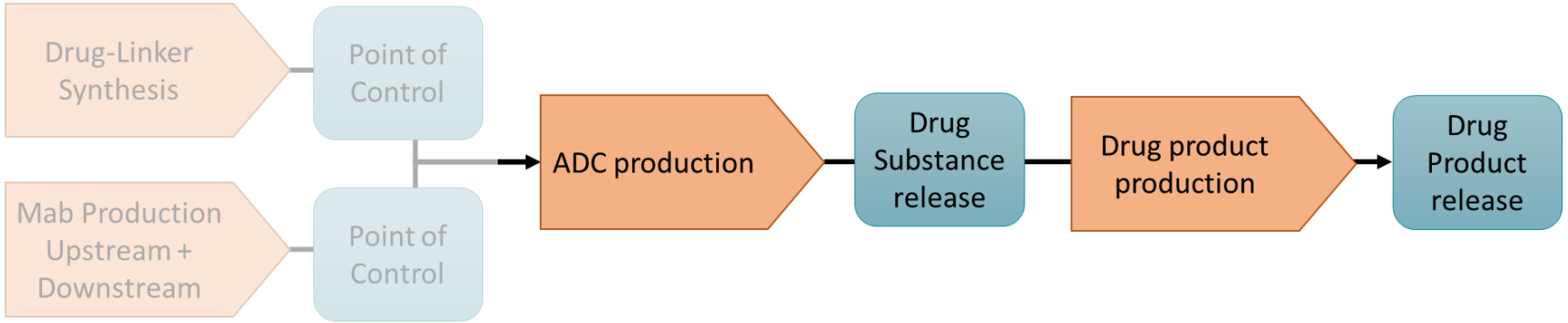
Quality Attributes Controlled in DS/DP

Considerations for Quality Attributes

- ❑ Origin e.g. incoming via intermediate(s) or generated during conjugation
- ❑ Risks resulting from impurities or contaminants
- ❑ Understanding conjugation technology and process performance
- ❑ Build data and control appropriately

Intended Product Profile (some examples)

- ❑ Consistent distribution profile of the drug on the antibody
- ❑ Sufficient control of DAR0, DL, FDRI etc



Examples

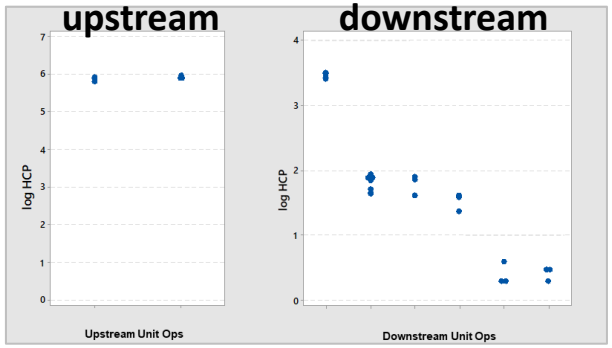
- ➢ DAR profile incl. DAR0
- ➢ FDRIs
- ➢ Potency
- ➢ Conjugatable impurities

Process Characterization (1)

Build data sets to demonstrate how quality attributes are impacted across the process steps and unit operations

- **mAB specific**
  e.g. Host Cell Proteins (HCP)

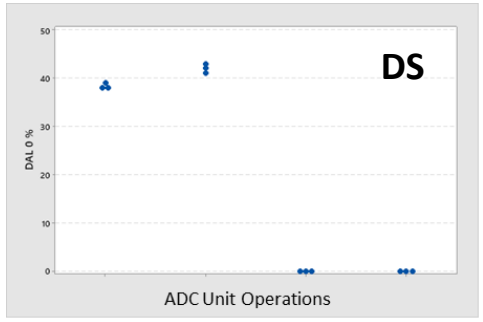
  Data set measuring HCP for upstream (cell culture) and downstream (chrom) steps across multiple batches and production scale (as needed)

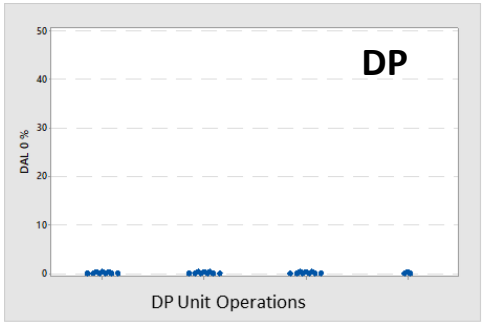


Process characterization and knowledge about the relevance and robustness of steps to clear HCP

- **ADC specific**
  e.g. DAR0

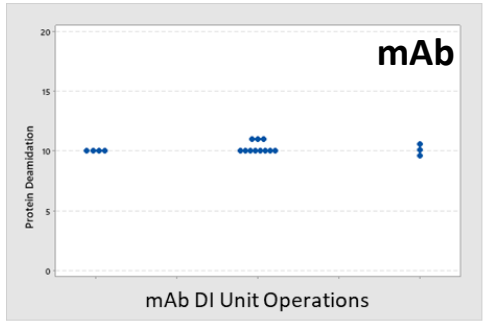
  Data set measuring DAR0 across DS and DP steps across multiple batches and production scale (as needed)

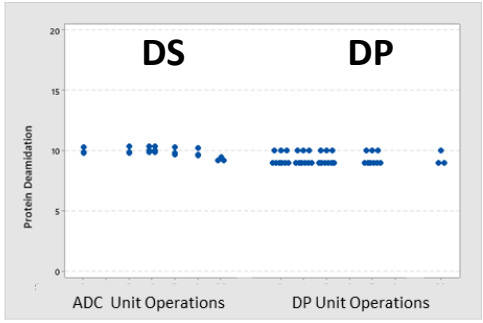




- **End to end process**
  e.g deamidation
  (if impacting binding/potency)

  Example of a quality attribute that needs to be measured across mAb and conjugate and multiple DS and DP steps





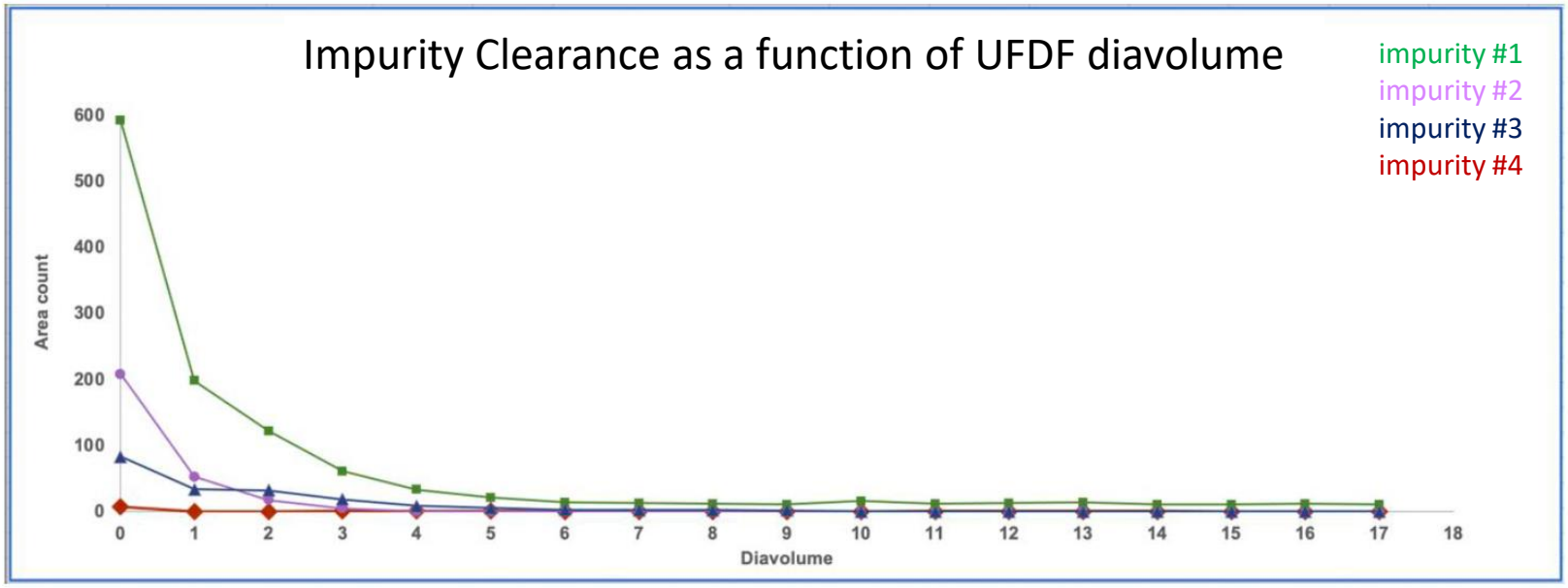
Thanks to Nienke Vriezen for these examples

Process Characterization (2)

- **Small Molecule Impurities Are Typically Cleared Effectively in a UF/DF step**

FDRI (incl. residual DL, “free drug” and other DL degradants, non conjugatable impurities present DL, other DS impurities, incl. reactants, byproducts, organic solvents, elemental impurities

From a safety standpoint, demonstrating clearance can justify a streamlined ATS



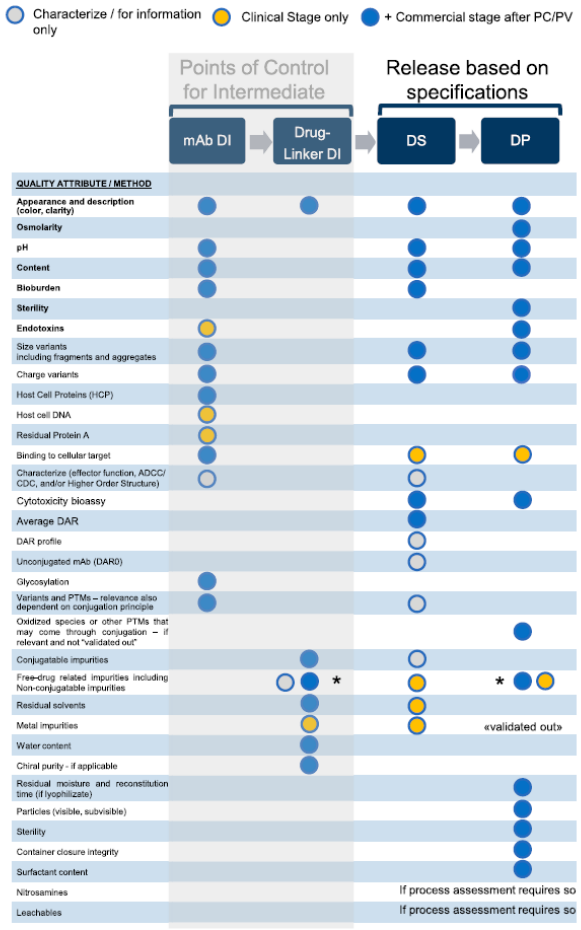
Thanks to Nathan Ihle for this example

Mapping and Rationalizing Points of Control for ADC Attributes

Map CQAs across the production processes

Rationalization ensures control strategy contains sufficient control

Design an efficient analytical strategy in which analytics are correctly validated/ qualified for their intended use (release or characterization of product or process)



* Scenario depends on chemistry of ADC, example of a general situation

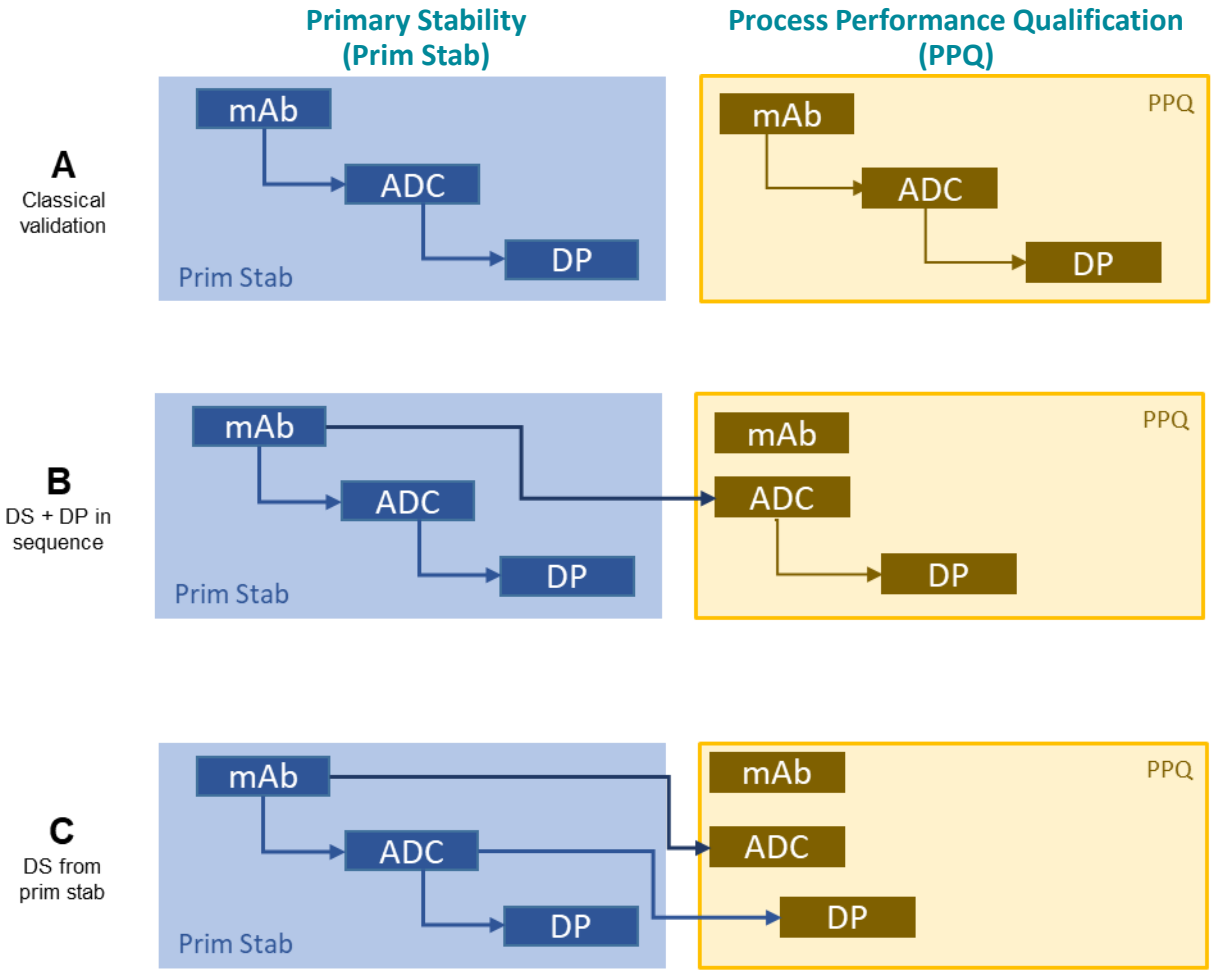
Attribute	mAb DI	Drug-Linker DI	DS	DP
Average DAR			●	
DAR Distribution‡			◎	
Unconjugated mAb‡			◎	
Conjugatable Impurities		●	◎	
Non-conjugatable Impurities or FDRI*†		◎	◎	●

‡Some conjugation technologies may require alternative control strategy
*FDRI limits applied to DS and DP only
† FDRI for DP only applies to degradation products

● - Controls through commercial
◎ - Clinical Controls
◎ - Characterization and/or comparability

Demonstration of control

Strategy and selection of batches for primary stability and PPQ



Traditional approach to PPQ, linear and sequential, takes the most time

Options to streamline and go faster.

For example, a primary stability batch of mAb which is pivotal clinical material and pre-PPQ could be justified if sufficiently representative

FREE-DRUG-RELATED IMPURITIES (FRDI)
DEEPER DIVE

Level of control should be based on a number of factors:

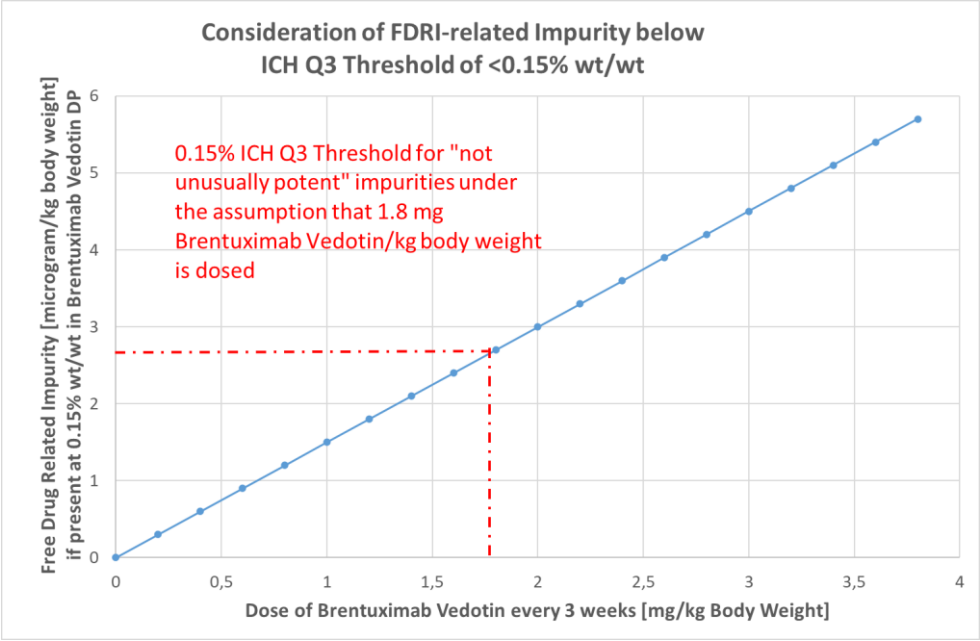
- *Patient Risk:* review impact to safety and efficacy.
  Impurities may be less cytotoxic than the drug itself and understanding their biology may justify higher impurity levels.
- *Process and Product Characterization:*
  understand where in the process FDRIs are created.
- *Stability Data:* understand how FDRIs levels change over time, incl. stress studies (DS and DP). If data consistently demonstrates high degree of stability, rationale to remove FDRIs tests in stability protocols.
- *Consistent performance* across scales, manufacturing processes and batches may justify removing tests for FDRIs from specifications.
  Analogous to approach for mAb and residual DNA.

ICH Q3A APPROACH FOR FDRI

For marketed ADCs, ICH Q3A could be used to revise specifications and beneficial to reduce a historically high burden of testing & controls to a science-based approach that does not impact either safety or efficacy of the marketed drug. A threshold of 0.15% FDRIs as impurity is acceptable, if the impurity is not “unusually toxic”.

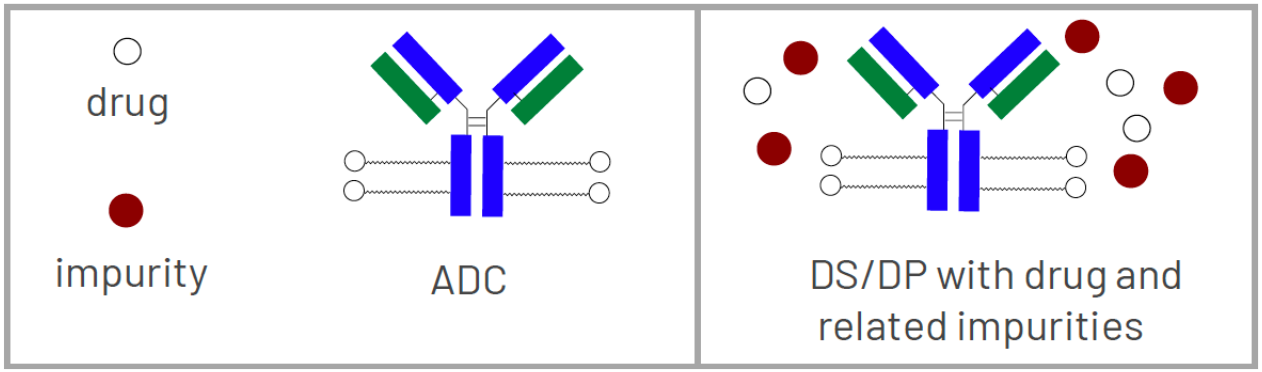
Case Study: brentuximab vedotin

Confirmed at time of registration that the drug (MMAE) was not pharmacologically active at doses up to 2.7 microgram/kg (equivalent to 0.15% at 1.8 mg/kg every 3 weeks). Thus free MMAE should be categorized as “not unusually potent”.



ORGANIC IMPURITIES IN ADC DRUG SUBSTANCE AND DRUG PRODUCT

How should we report FDRI?



Report as wt %, comparing mass of impurity to total mass of the intact ADC

$$Wt\ \%_{\ imp} = \frac{Wt_{\ imp}}{Wt_{\ ADC}} \times 100$$

In the absence of specific safety concerns, adoption of ICH Q3 limits is scientifically justifiable

Thanks to Nathan Ihle for this example

Refer to appendix for the tables of threshold values in ICH Q3A and Q3B

CONJUGATABLE IMPURITIES IN THE ADC

Conjugation processes may also link some small molecule impurities to reaction positions on the mAb and could lower the ADC potency or a pose a safety risk. As such conjugatable impurities are typically controlled at the DL stage.

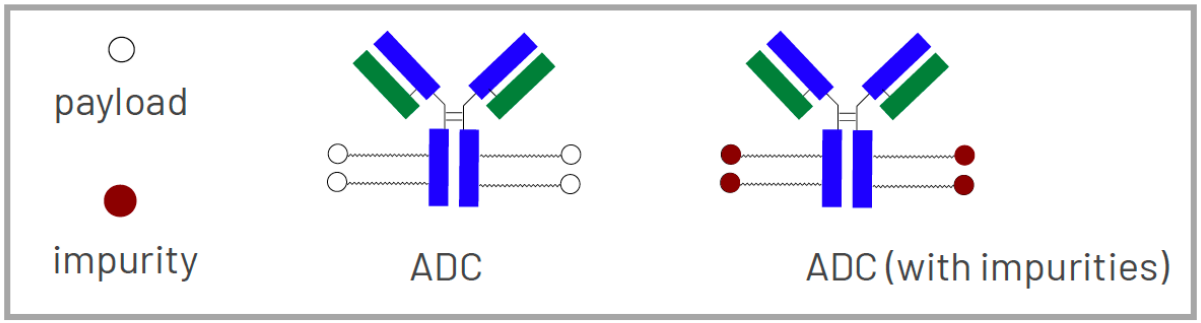
Testing for conjugated impurities after conjugation is technically challenging due to the low detectability of conjugated impurities in the ADC.

Level of control is based on a number of factors:

- Patient risk due to the conjugated impurities (both safety & efficacy impact should be reviewed).
- Process and product variability. A consistent impurity profile will help to demonstrate process control and will ensure consistent DS and DP quality.

ICH Q3A/Q3B THRESHOLDS FOR SMALL MOLECULE IMPURITIES APPLIED TO CONJUGATED IMPURITIES

Applying ICH Q3 principles to conjugated impurities



$$Wt\%_{imp,\,ADC} = Wt\%_{imp,\,DL} \times \frac{MW_{imp}}{MW_{ADC}} \times DAR$$

Example for 1% impurity in DL, DAR 4

$$Wt\%_{imp,\,ADC} = 1\% \times \frac{2{,}000\ Da}{150{,}000\ Da} \times 4 = 0.05\%$$

Higher levels of impurities in DL can be justified

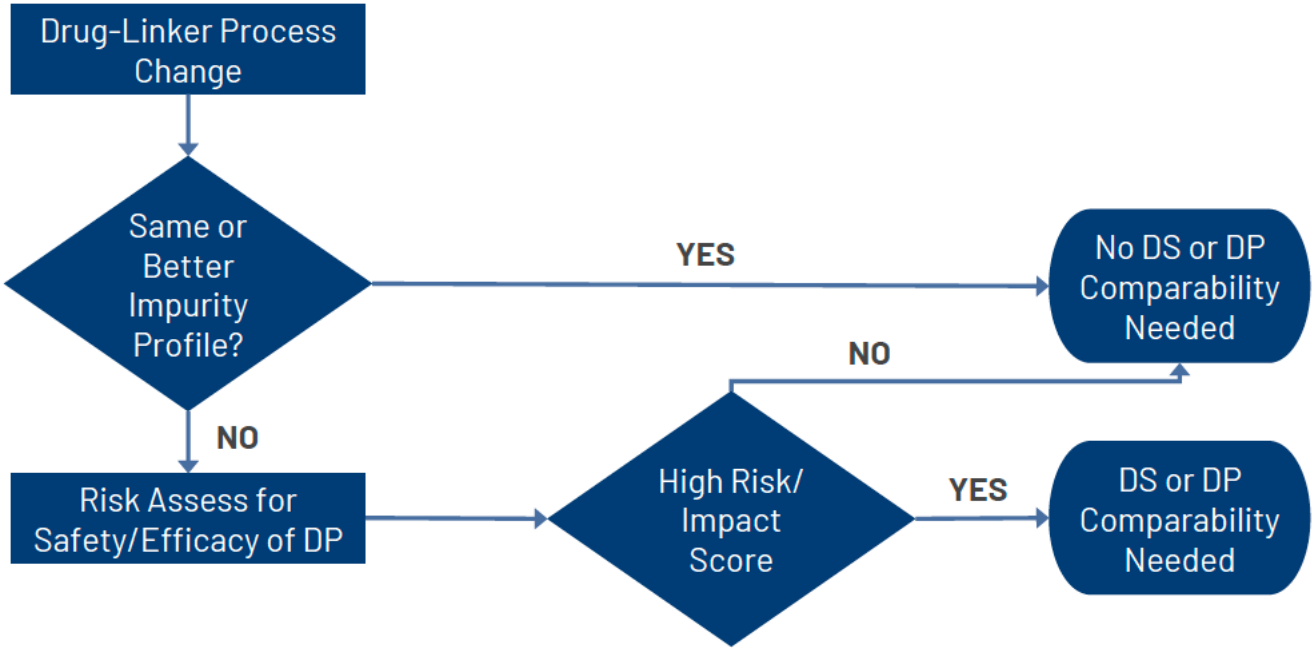
Thanks to Nathan Ihle for this example

Refer to appendix for the tables of threshold values in ICH Q3A and Q3B

Comparability Strategies

- Change happens!
- Risk assessments of the potential to impact product quality should be documented
- Apply critical thinking and knowledge

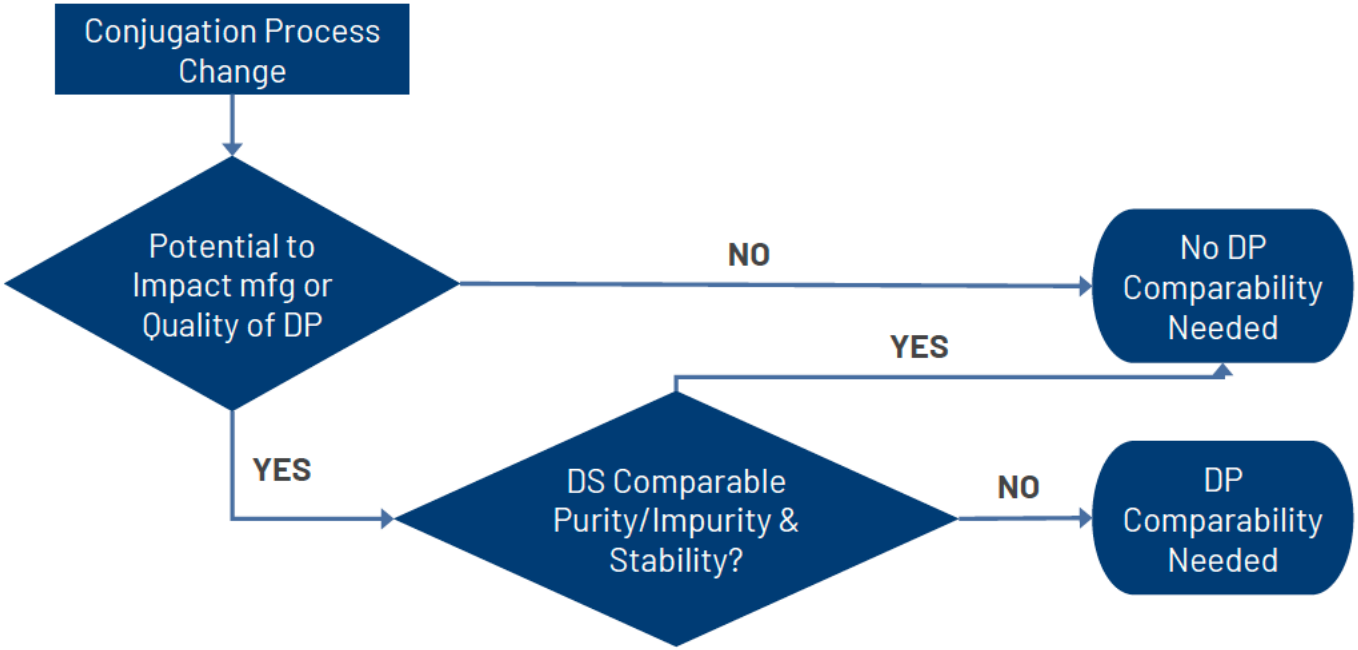
Decision Tree for a DL Process Change



Thanks to Nathan Ihle for this decision tree

Comparability Strategies

Decision Tree for a DS Process Change



Thanks to Nathan Ihle for this decision tree

Conclusions

Building a control strategy is both a technical exercise and a knowledge management effort

Context is everything

- Product use (indication, dose frequency, route)
- Design and product attributes (stability, impurities)

A science and risk based control strategy

- what is known with confidence
- what is known conceptually and will need experimental demonstration and confirmation

Just when it's set, it changes!

Appendix

ICH Q3A/Q3B THRESHOLDS FOR SMALL MOLECULE IMPURITIES

ICH Q3A (R2) applies to organic impurities in DS

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

ICH Q3B (R2) applies to organic degradation products in DP

Maximum daily dose	Threshold
Reporting thresholds	
≤1 g	0.1%
>1 g	0.05%
Identification thresholds	
<1 mg	1.0% or 5 µg TDI, whichever is lower
1–10 mg	0.5% or 20 µg TDI, whichever is lower
>10–2 g	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%
Qualification thresholds	
<10 mg	1.0% or 50 µg TDI, whichever is lower
10–100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

Additional References from IQ Consortium

- Control Strategy for Small Molecule Impurities in Antibody Drug Conjugates

  Gong, *et al*., AAPS PharmSciTech 19, 971-7 (2018).
- Drug Linkers in Antibody Drug Conjugates: Perspective on Current Industry Practices

  Bulger, et al., Organic Process Research & Development 27 (7), 1248-57 (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), 1258-68 (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)

Recommended Dossier Structure

Separate S sections for each component

3.2.S – Drug-Linker Intermediate	
	S.1 – DL DI
	S.2 – DL DI
	S.3 – DL DI
	S.4 – DL DI
	S.5 – DL DI
	S.6 – DL DI
	S.7 – DL DI

3.2.S – Antibody Intermediate	
	S.1 – mAb DI
	S.2 – mAb DI
	S.3 – mAb DI
	S.4 – mAb DI
	S.5 – mAb DI
	S.6 – mAb DI
	S.7 – mAb DI

3.2.S – Drug Substance	
	S.1 – DS
	S.2 – DS
	S.3 – DS
	S.4 – DS
	S.5 – DS
	S.6 – DS
	S.7 – DS