Overarching ADC platform control strategies and reducing repeated testing

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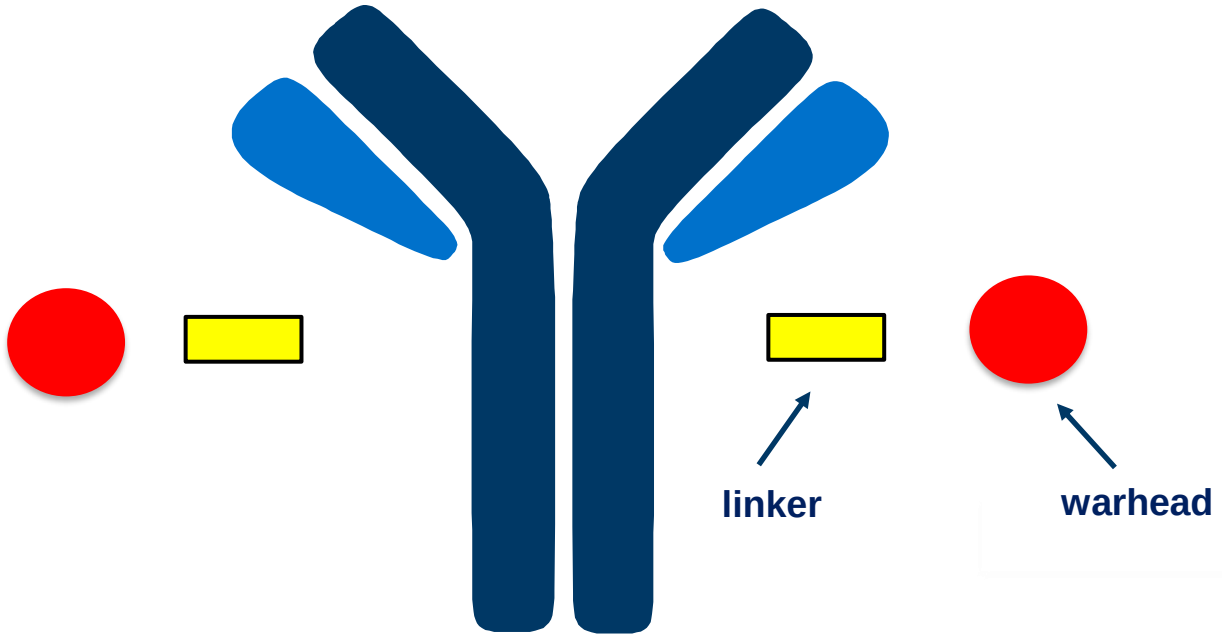
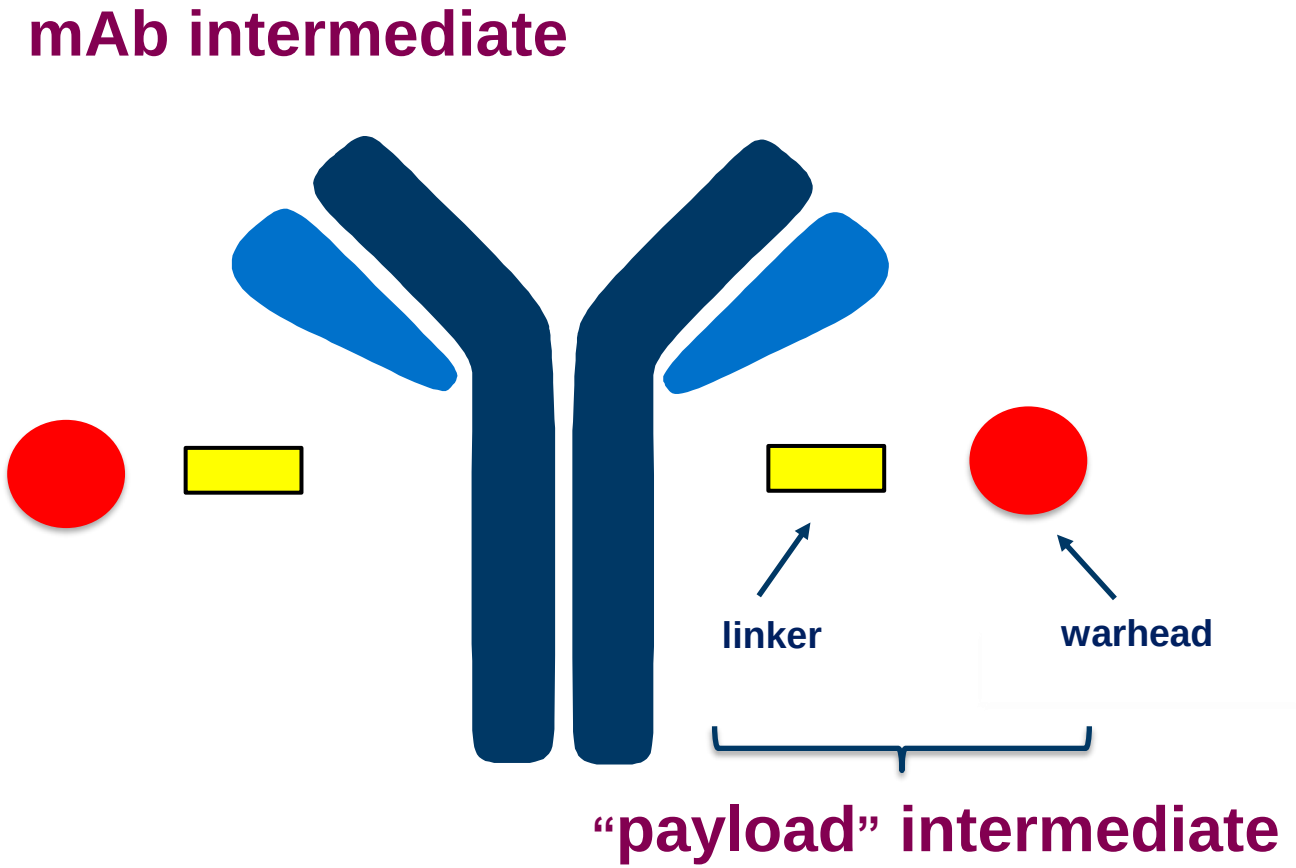
17 October 2023

ADC terminology alignment

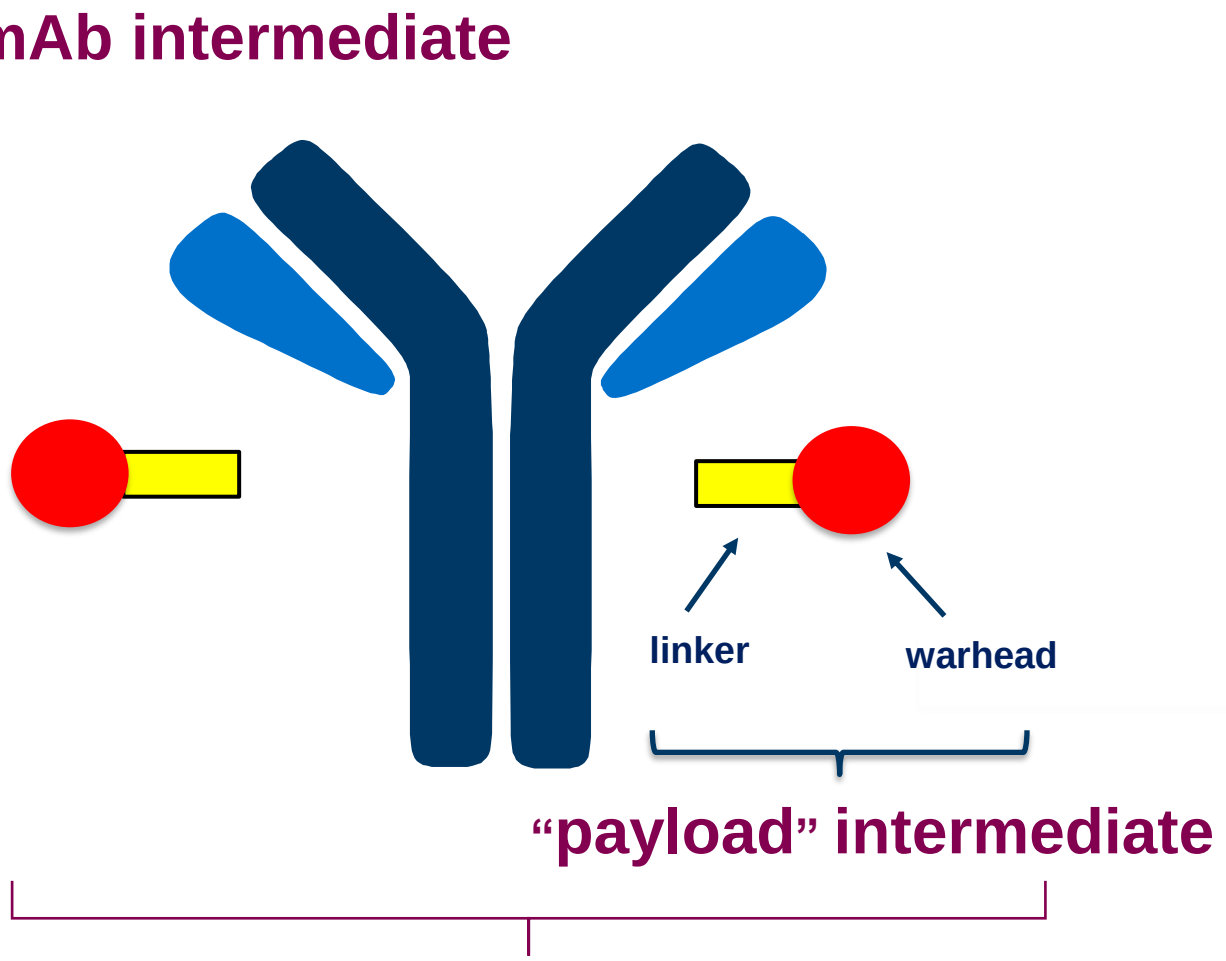
mAb intermediate



ADC terminology alignment



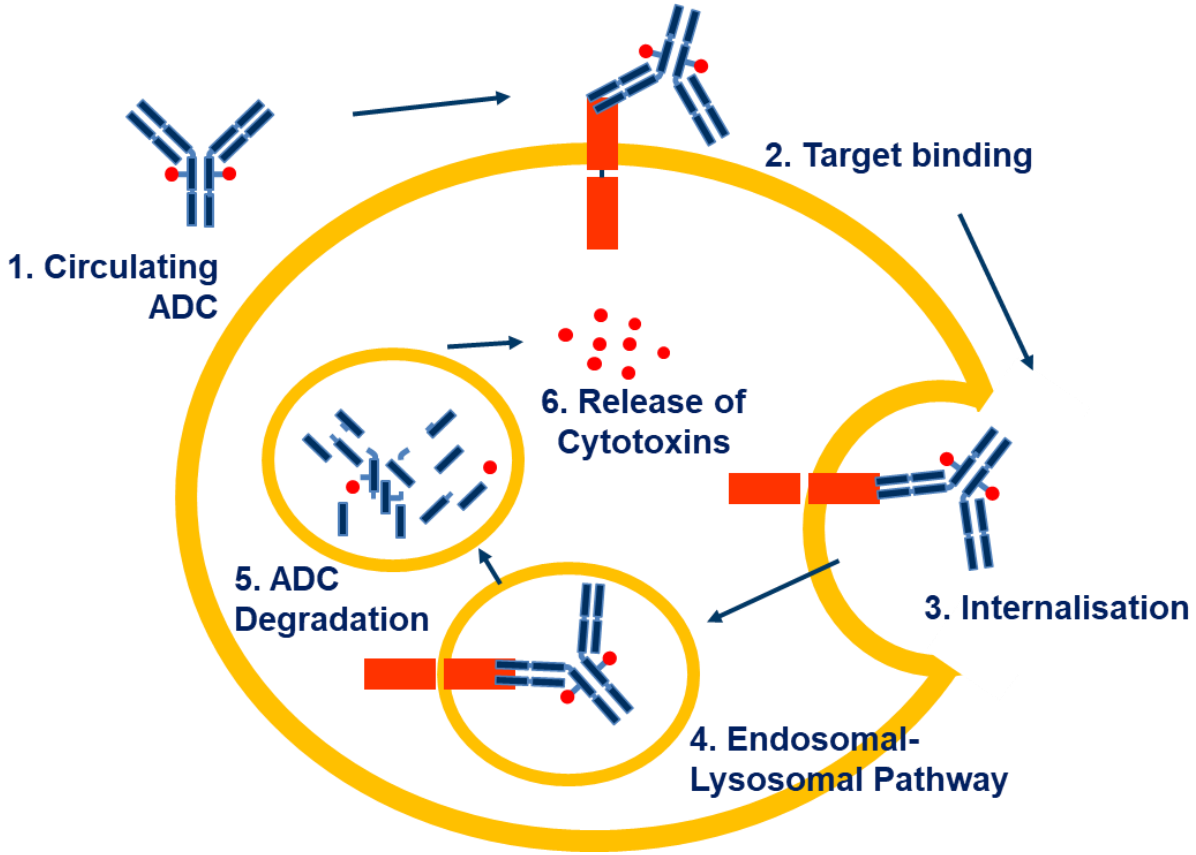
ADC terminology alignment



ADC mechanisms of action

- **Must also consider**
- Bystander effect?
- Fc effector functions?

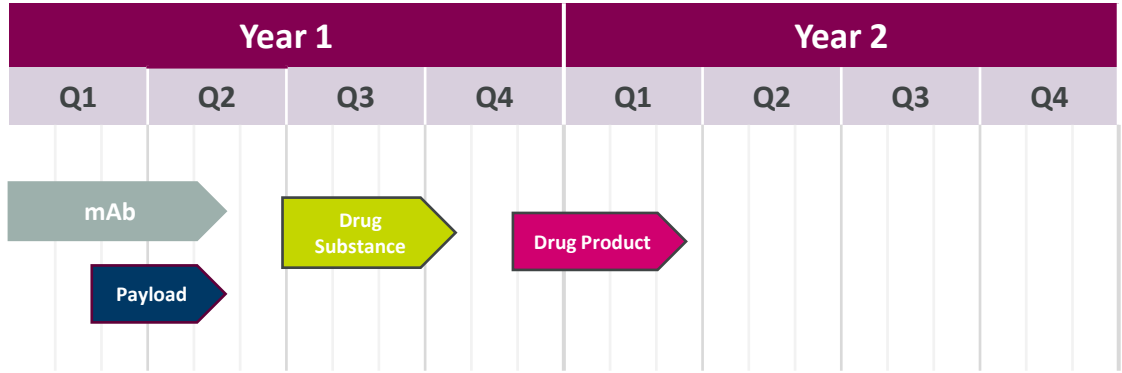
ADCs as “Magic Bullets”:



ADC Challenges

- From a regulatory perspective, it is necessary to assure the quality of **four components**.
  - **1) Antibody intermediate**
  - **2) Drug linker intermediate**
  - **3) Drug substance (ADC)**
  - **4) Drug product**

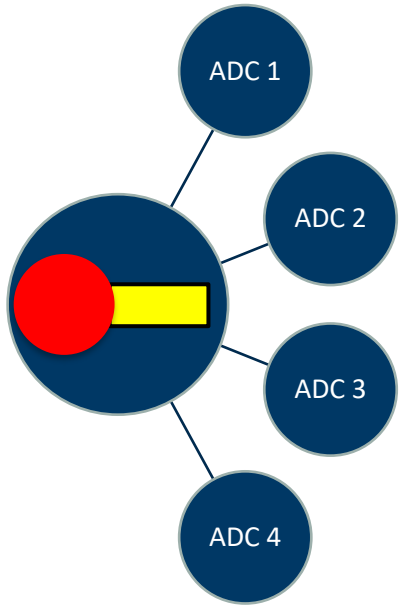
- Long production lead times considering all components



Platform approaches to ADC control strategy

Similarities across ADC portfolios

- Reuse of same payload
- Same conjugation technology



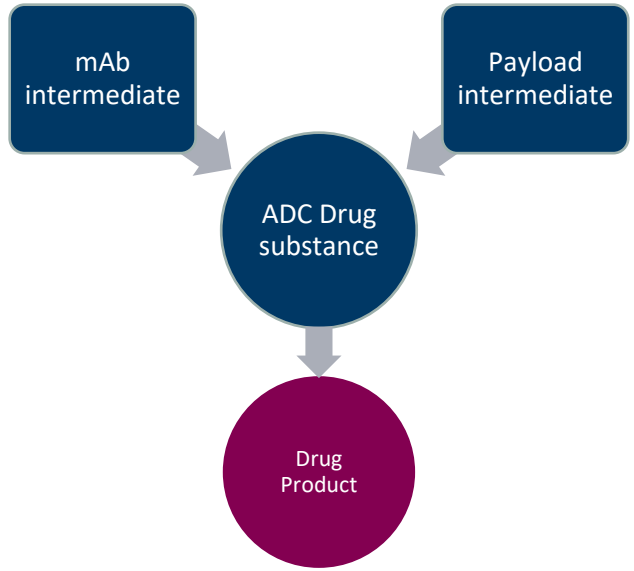
Synergy across portfolio as knowledge increases during development of the first candidate

- Lends itself to adopting a platform approach to control strategy across the portfolio
- Is there a need to repeat certain developmental work?
- How much knowledge gained from one asset be used in another?

ADC Critical Quality Attributes (CQA)

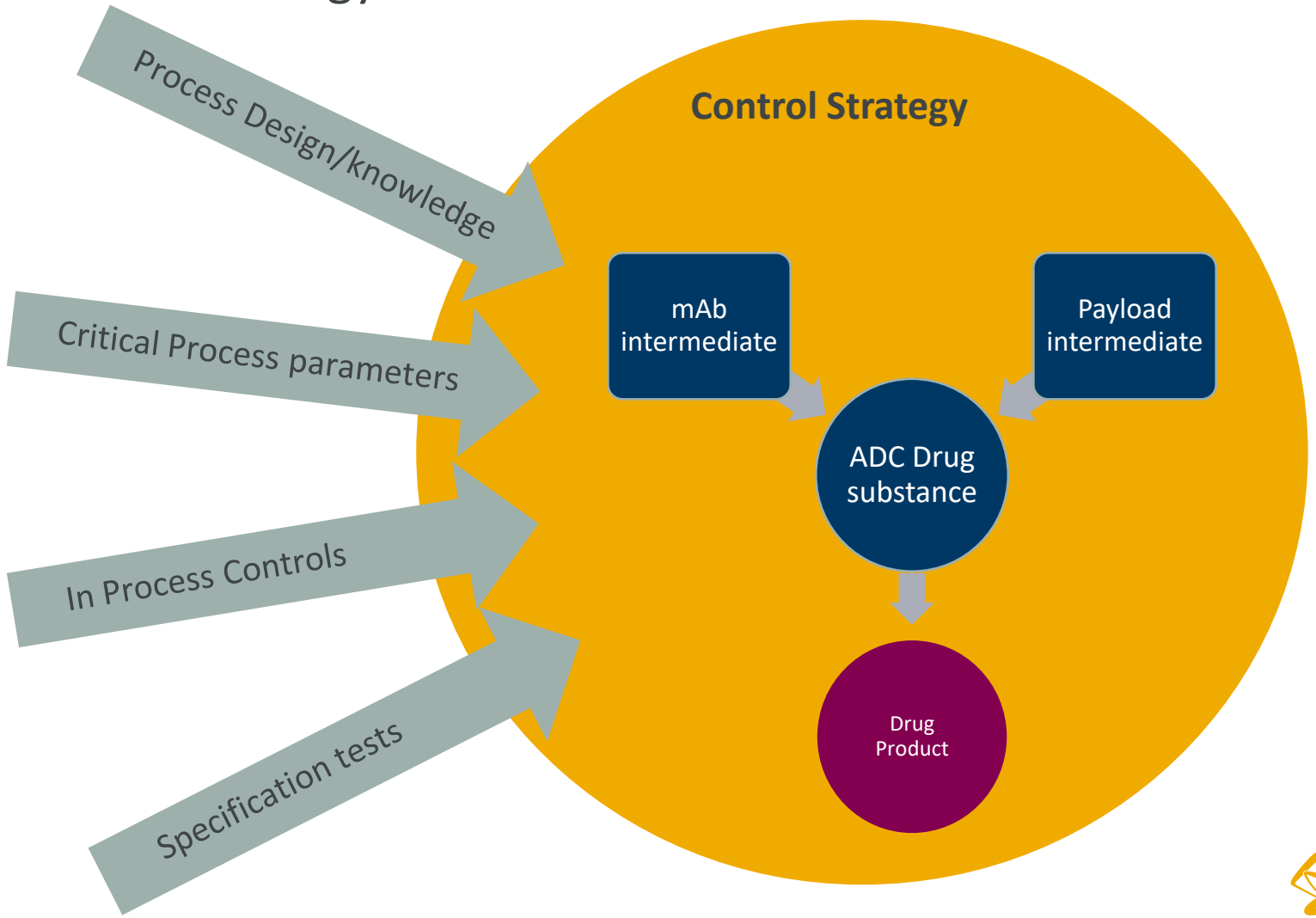
- Appearance
- Identity
- pH
- Osmolality
- Protein concentration
- Endotoxin
- Sterility/Bioburden
- High molecular weight species
- Low molecular weight species and fragments
- Absence of host cell material
- Charge heterogeneity
- **Non-conjugated Mab**
- **Non-Proteinaceous Impurities**
- **Purity of Payload**
- **Drug to Antibody Ratio (DAR)**
- Container Closure Integrity
- Particulate Matter (Visible and Sub-Visible)
- Extractable volume
- Extractable/Leachables
- Water content
- Reconstitution time
- Content Uniformity

ADC specific



How do we establish optimal control strategy?

- ICH Q8R1 principals
  - Holistic view required across components for optimal control strategy

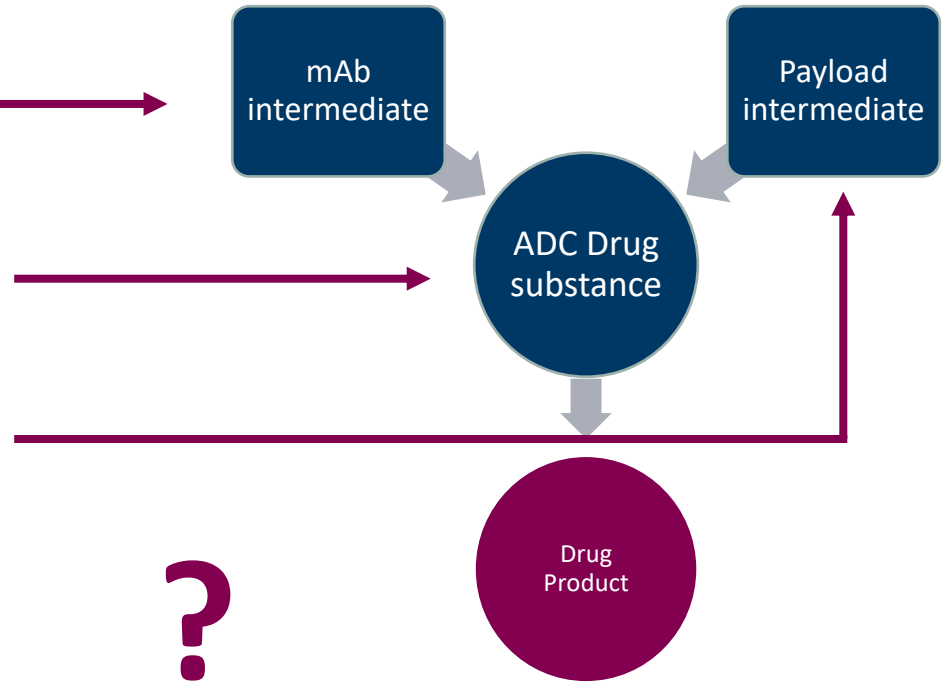


Appropriate control points

- Controls need to be in place at the most appropriate step in the process
- Does it make sense to repeat testing in subsequent component?

Example control points

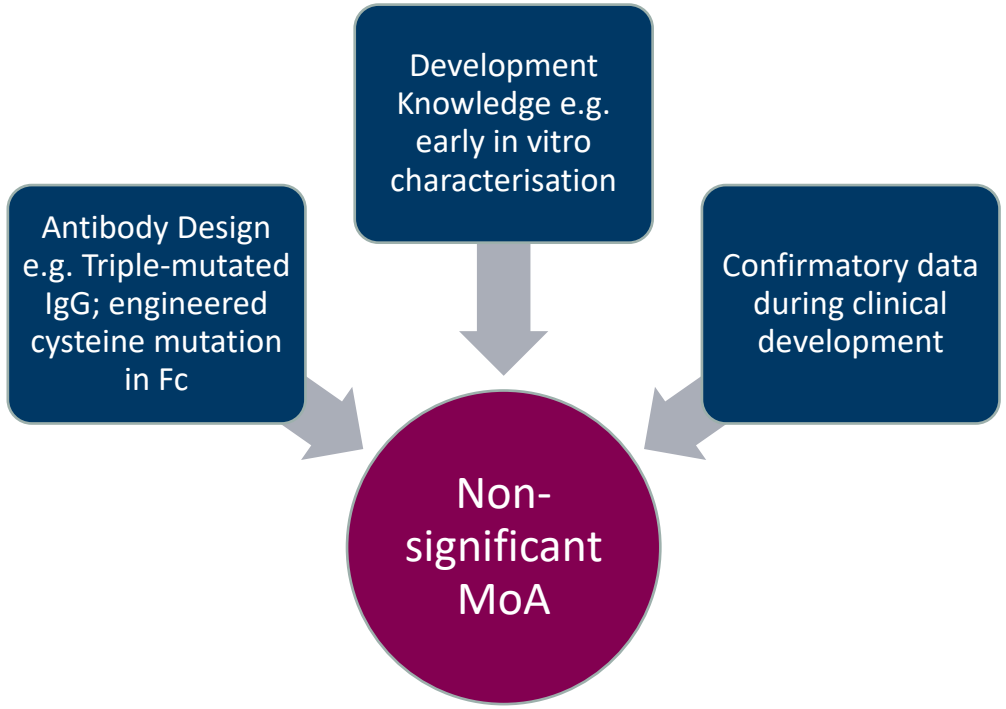
- HCP/DNA
- Unconjugated payload
- Conjugatable impurities
- **Non conjugatable impurities**
- **ADCC/Glycosylation**



Process design & development knowledge v's Spec test

Knowledge gained during development should inform the commercial control strategy

- **Example: Fc Effector function activity**

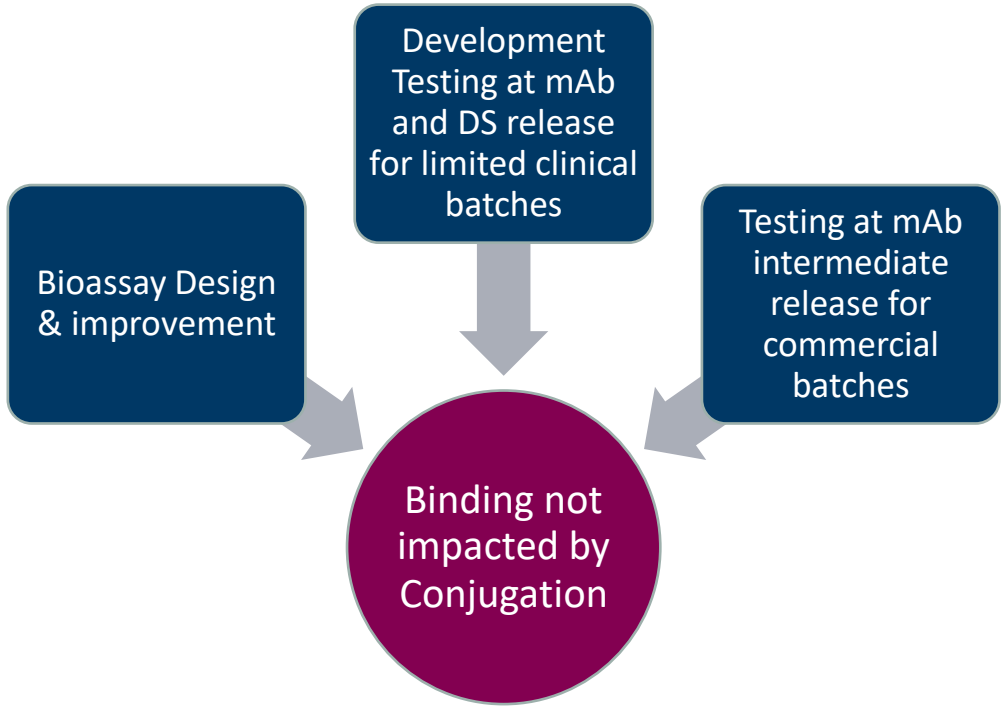


Is it necessary to include release specification tests for Fc effector activity or glycans in this situation?

Process design & development knowledge v's Spec test

Knowledge gained during development should inform the commercial control strategy

- **Example: Bioassay strategy**

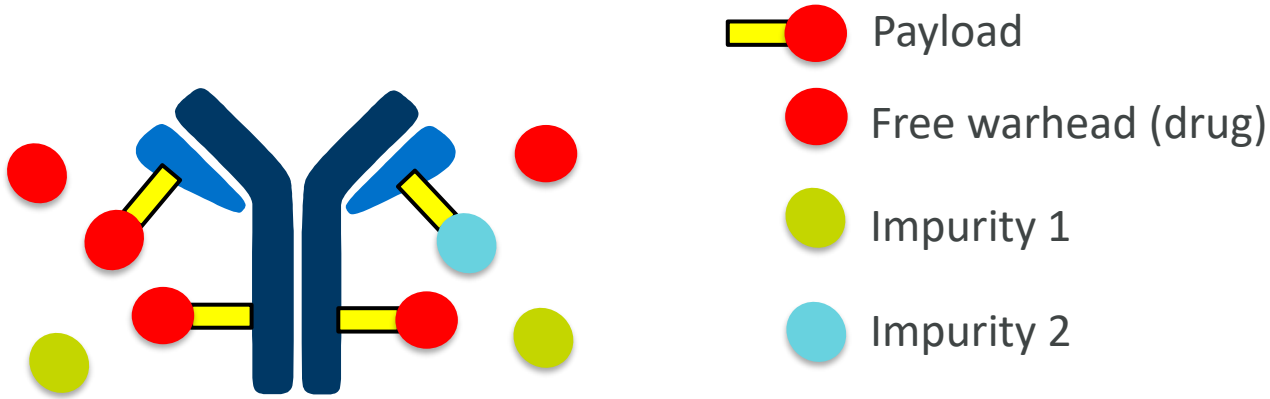


Is it necessary to repeat bioassay in both mAb intermediate and drug substance release specification tests?

Payload impurity control

Common approach possible across multiple ADCs

- Impurity risk
  - Do the known drug linker impurities conjugate or not?
  - Decision tree for assessment of impurities in linker-drug intermediates (IQ 2018 paper)[1]



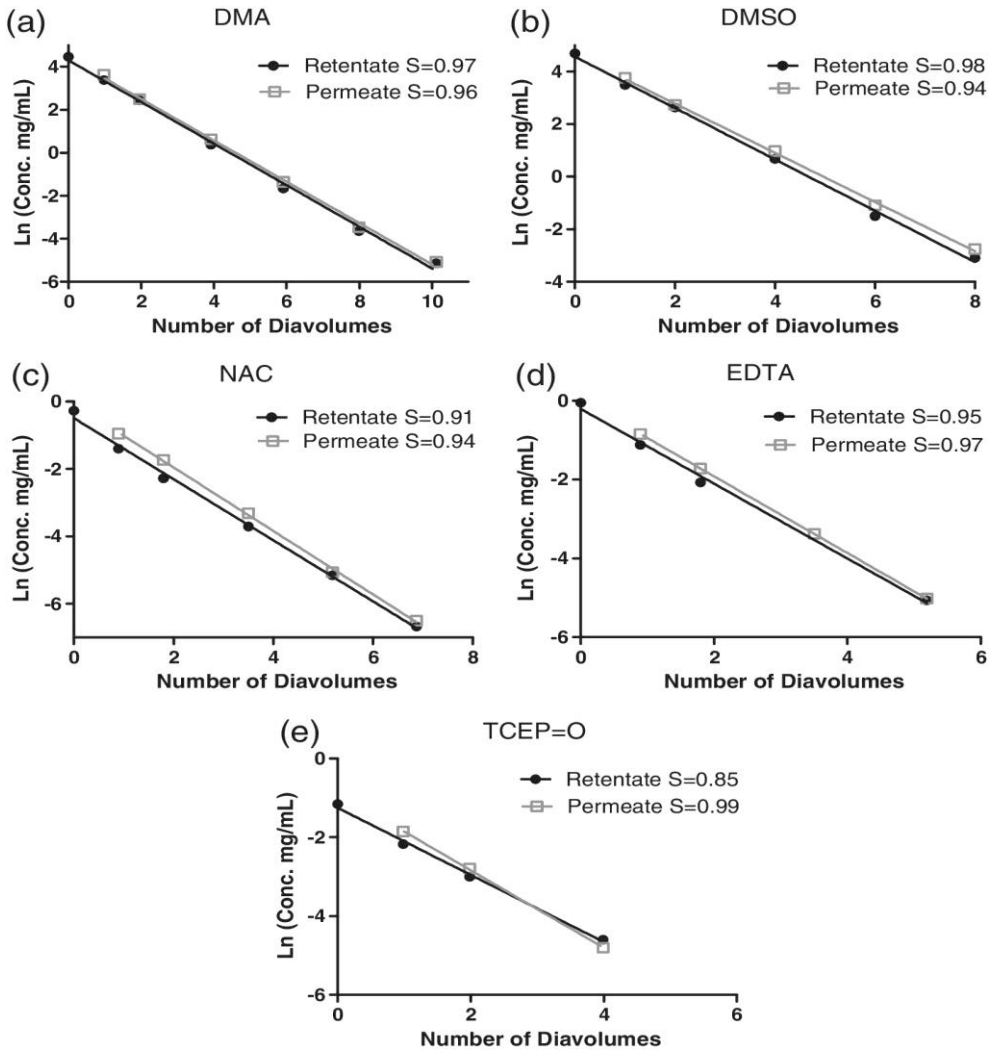
  - What is the likelihood of carryover?
    - Use of in silico modelling & purge factor calculations
    - ADCs referred to in EMA PRIME Toolbox guidance[2]

1. Gong et al. AAPS PharmSciTech 19, 971-977 (2018) DOI: 10.1208/s12249-017-0943-6
2. https://www.ema.europa.eu/en/documents/scientific-guideline/toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime-certain_en.pdf

Process knowledge

Do we need to routinely control non conjugatable & small molecule process impurities?

Clearance of solvents and small molecule impurities in antibody drug conjugates via ultrafiltration and diafiltration operation[1]



Ethylenediaminetetraacetic acid (EDTA),
Dimethyl sulfoxide (DMSO)
N,N-dimethylacetamide (DMA),
N-acetyl-L-cysteine (NAC),
Tris (2-carboxyethyl)phosphine (TCEP)

1. Gates *et* al. *Biotechnol Prog*, Vol:36, 1, 2923. (2020) DOI: (10.1002/btpr.2923)

Adapted control strategy for ADCs

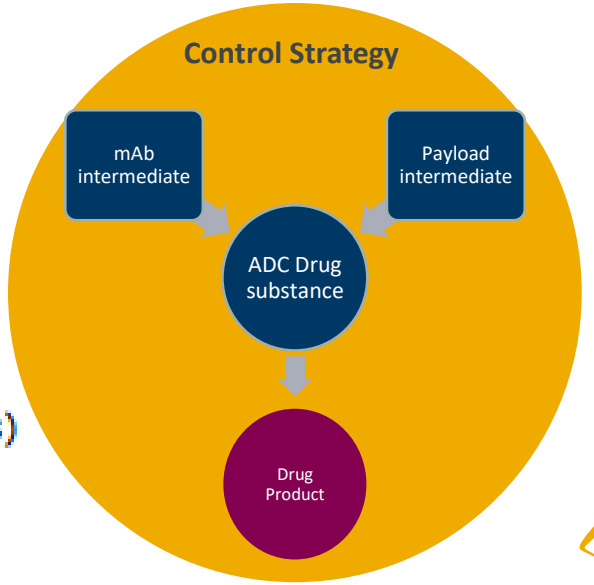
Majority of ADC's in development are for conditions of high unmet medical need

- Frequently subject to clinical acceleration
- For ADCs considering long processing times, increased likelihood for CMC to be on critical path

Potential for an Adapted Control Strategy[1] as outlined in EMA PRIME guidance impact ADCs?

Caution Required for ADCs

- Additional specification tests
- Additional in-process controls
- Additional process parameters
- A higher number of critical process parameters
- Narrower ranges for critical process parameters (CPPs)

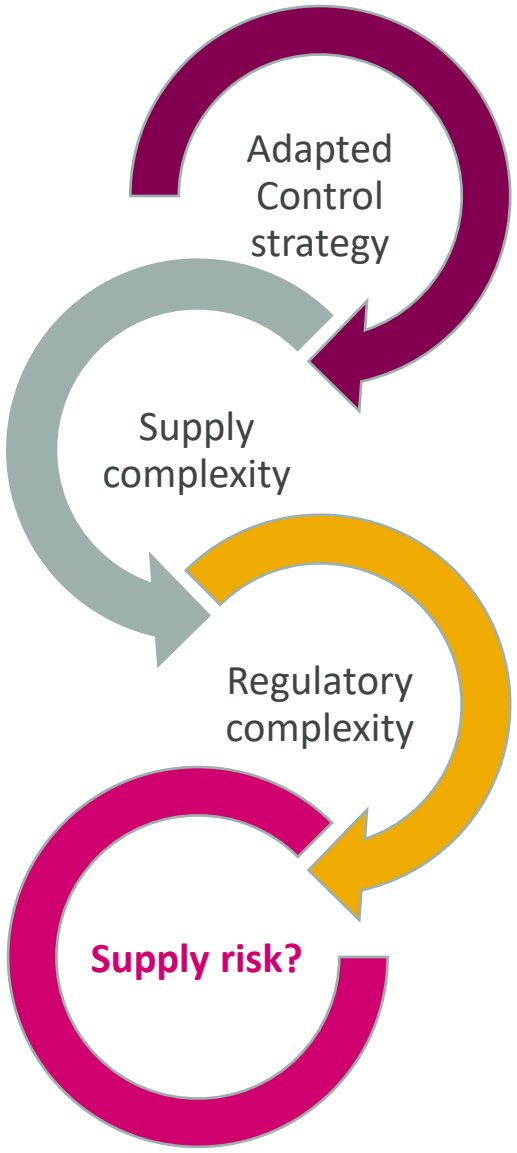


1. https://www.ema.europa.eu/en/documents/scientific-guideline/toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime-certain_en.pdf

Adapted control strategy for ADCs

Is this an appropriate approach for medicines of high unmet need with inherent supply chain complexity?

Potential significant impact for ADCs



- Additional testing (IPC, Release)
- Tighter CPPs

- Global supply chain
- Additional testing potentially leading to increase in production lead times
- Narrower ranges of CPPs risks more batch deviations, increasing lead time

- Global changes can take years to implement, widening a limit or removing a specification test is intensely difficult
- EMA increasingly important as a global reference authority for international markets, however reliance procedures still relatively new, often only MAAs in scope, not variations

- **Ultimately an Adapted Control strategy can persist much longer into the product lifecycle as product needs to be manufactured to the tightest spec/parameters**

Conclusion

- ADCs are complex products, with complicated supply chains
- Establishing a control strategy to ensure the highest quality medicinal product for patients is essential
- Optimising the control strategy to avoid duplication of testing is desired to reduce supply chain complexity and increase sustainability

Acknowledgements

- Michaela Wendeler
- Patrick Hussmann
- Chunlei Wang
- Shakir Muradymov
- Hayley Jackman
- Dawn Spiller
- Mark Pellet

Questions?