Applying Science and Risk Based Principles to Define Specifications

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Contents

- Concepts
  - Principles of benefit risk
  - Clinically relevant, science and risk-based specifications
  - Prior Knowledge
- Revision of ICH Q6 specifications guidance
- What principles to apply specifications?
- Examples: ADCs
- Conclusions

Principles of Benefit Risk

"*The potential risk resulting from the replacement of certain conventional data by **alternative supporting data packages** at time of approval is considered by regulators in the context of the **benefit-risk assessment** during the MAA assessment.*

*This risk-based approach can lead to agreement in providing additional quality data during assessment or post-approval if the **clinical benefits clearly outweigh the risks.** "*

EMA PriMe Quality toolbox

- Development must always deliver a quality product.
- Principles of benefit risk and the consideration of alternative supporting data can be applied universally (not only for unmet medical need).

Patient Centric/Clinically Relevant Specifications

"..a set of tests and acceptance ranges to which product quality attributes should conform ***for the product to be safe and effective*** *when used as labelled.* ***Justifications for acceptance ranges focus on risk-based assessment of the impact to patients****. Patient-Centric Specifications may also be referred to as clinically relevant specifications"*

M.N. Ruesch et al. / *Journal of Pharmaceutical Sciences* 110, **2021**, 771-784

Prior Knowledge

*"**Prior knowledge** includes knowledge from development and manufacturing experience (e.g. experience based on similar compounds, products and processes) as well as reference to scientific and technical publications or application of established scientific principles e.g. within chemistry.*

*The availability of prior knowledge, if demonstrated to be relevant for the product in question, could be a good basis for shifting the time-point for completion of certain quality studies, or supporting an alternative approach to data requirements for certain quality studies (e.g. stability studies, process validation, **justification of specification**)"*

EMA PriMe Quality toolbox

Revision of ICH Q6 Specifications Guidance

From:

1. 6A, B: Two distinct guidelines, separating synthetic and biological products
2. Specification as the focus of control of product quality, safety, efficacy
3. Based on batch experience
4. Specifications typically finalised in development
5. Aligned with standard development and approval pathways

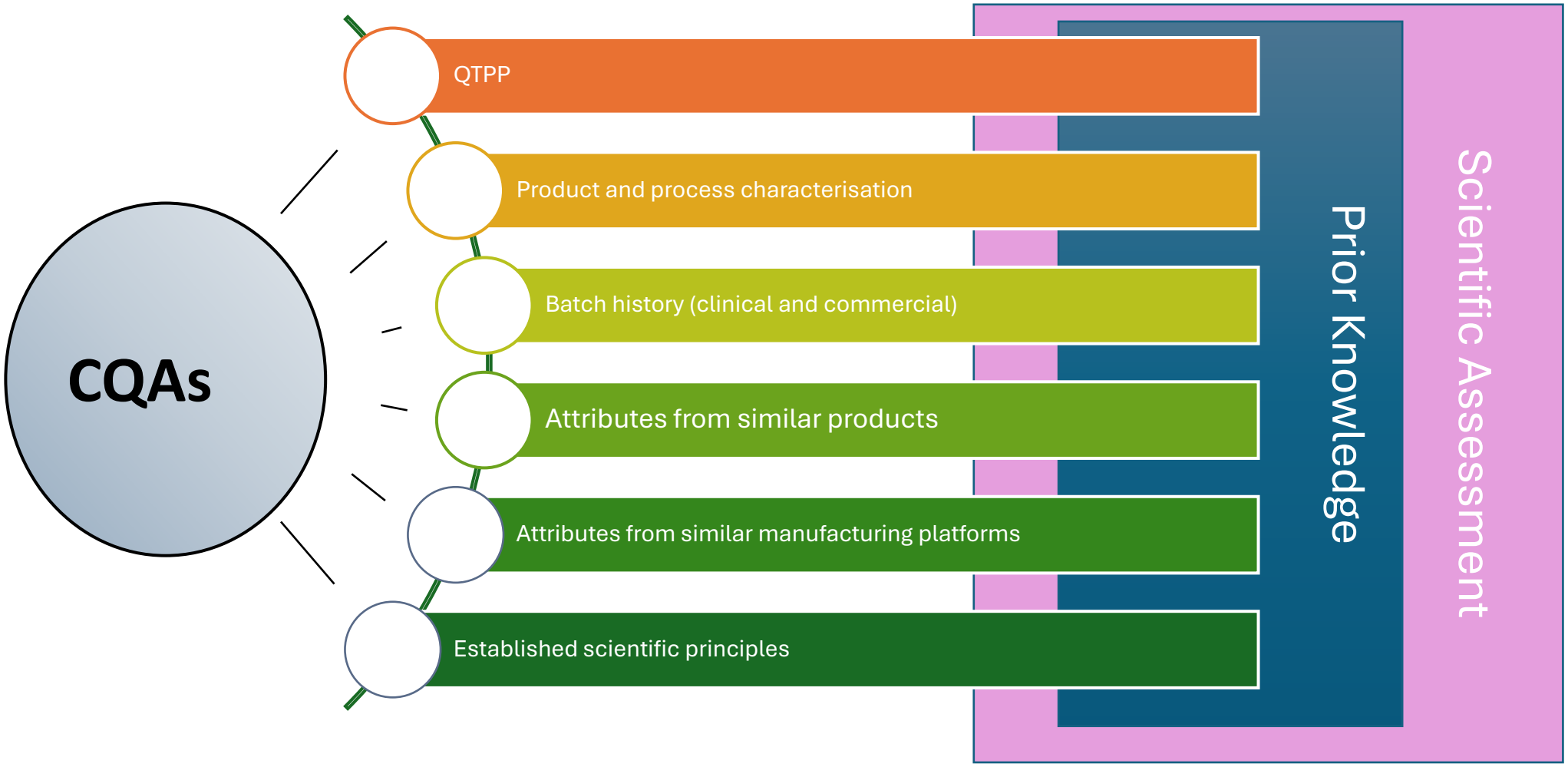
To:

1. Holistic principles for all products with additional considerations for specific product types
2. Specification as part of a holistic control strategy, per ICHQ8-11
3. Science and risk-based; considers clinical relevance, platform and prior knowledge etc
4. Specifications evolve with knowledge over the lifecycle
5. Aligned with rapid development and innovation

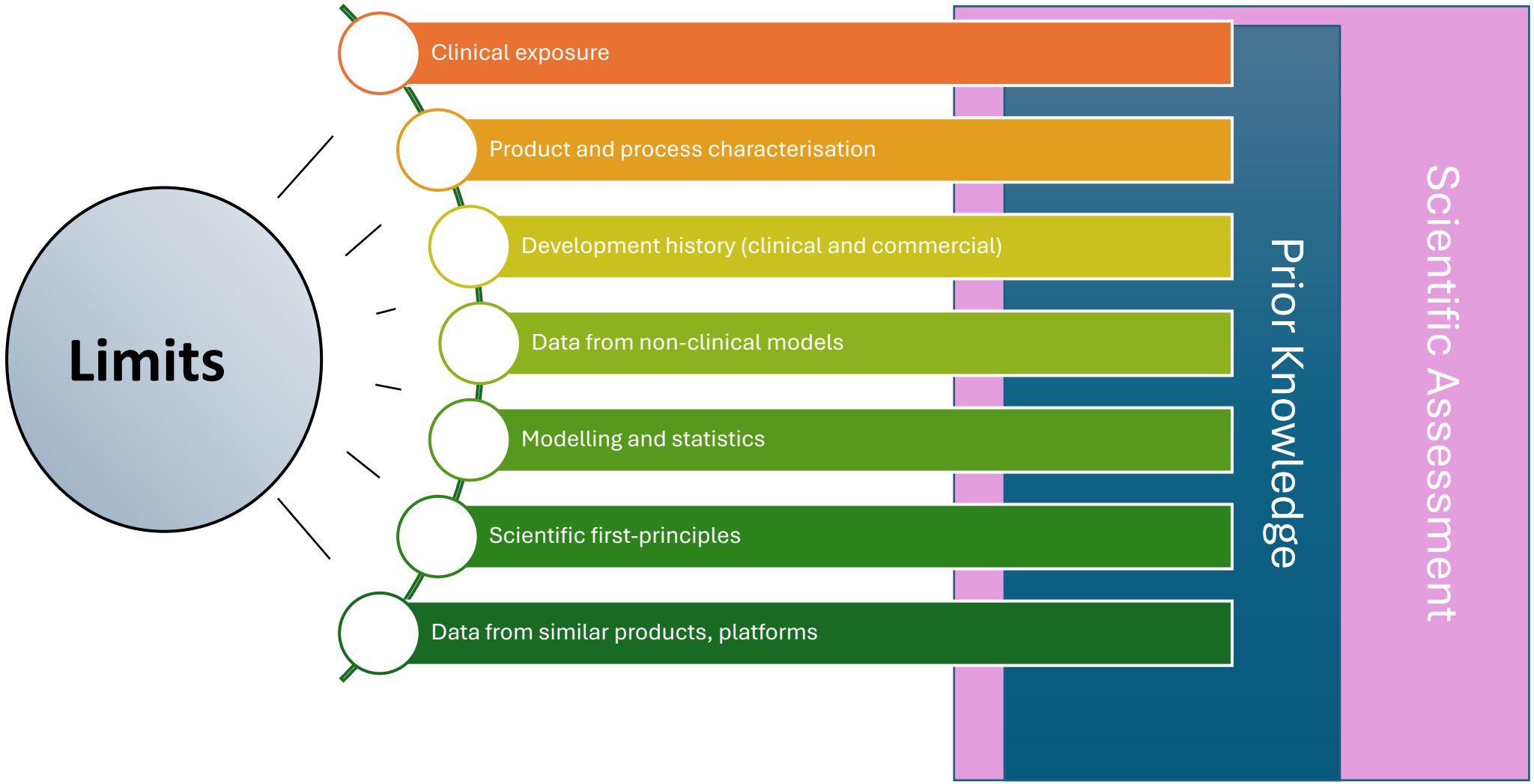
Patient Relevant, Science and Risk-based Specifications

- What to control?
- What are appropriate limits?
- What is the overall control strategy?

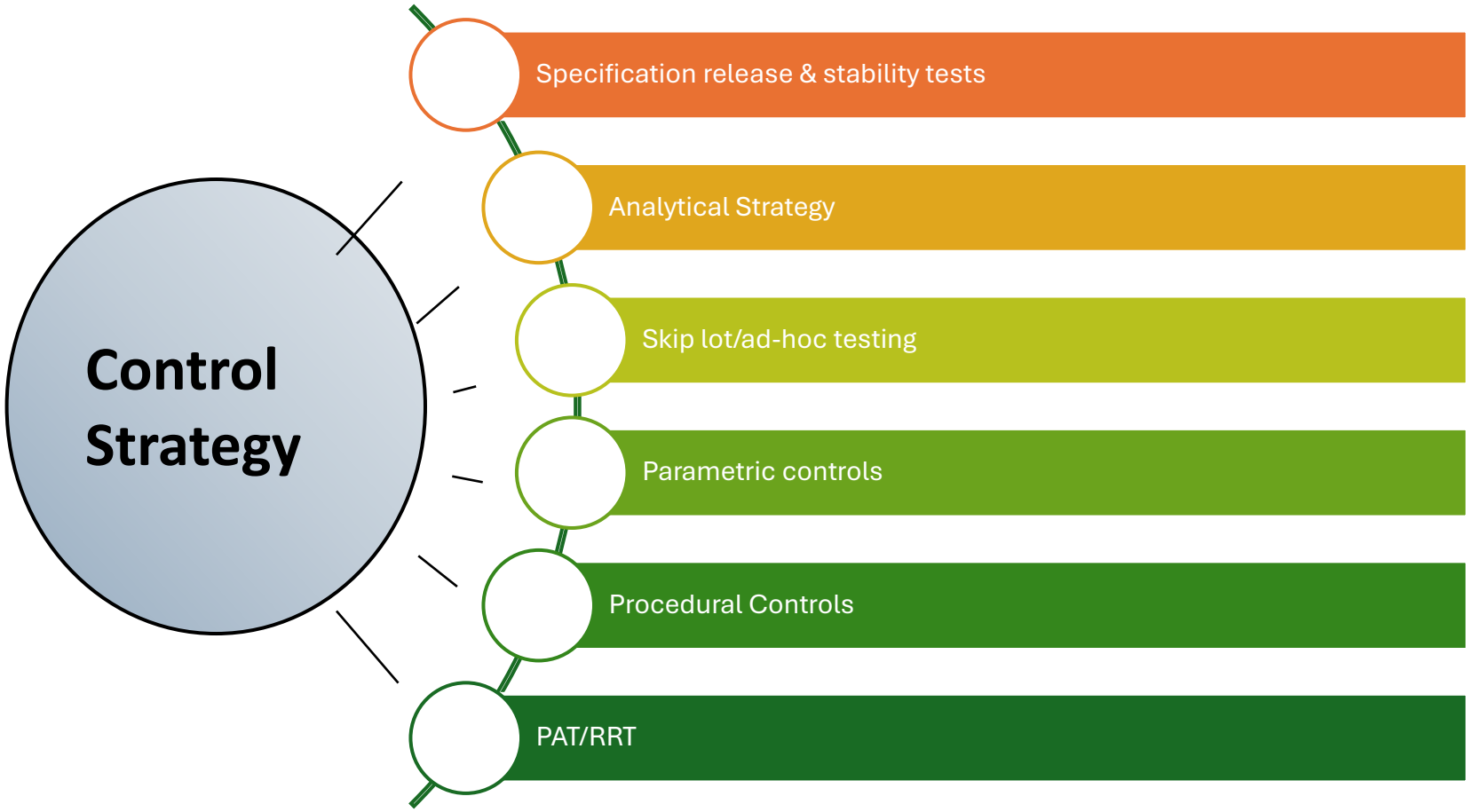
What to control?



What Limits? (scientifically sound acceptance criteria)



What Overall Control Strategy?
Role of a specification test



efpia
European Federation of Pharmaceutical Industries and Associations

CMC Regulatory Considerations for Antibody-Drug Conjugates
Charles Morgan 16 July 2024
CASSS Summer Strategy Forum North America

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

ELSEVIER

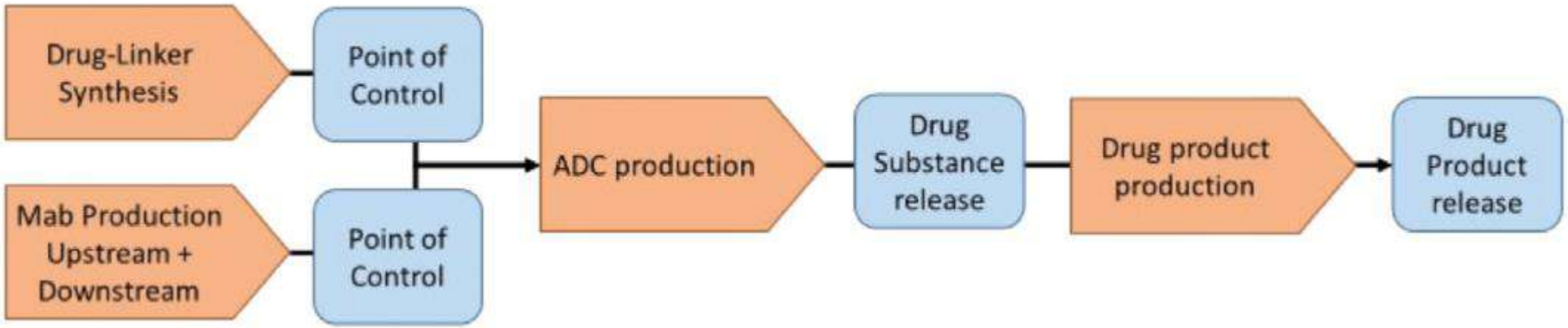
Perspective

CMC Regulatory Considerations for Antibody-Drug Conjugates

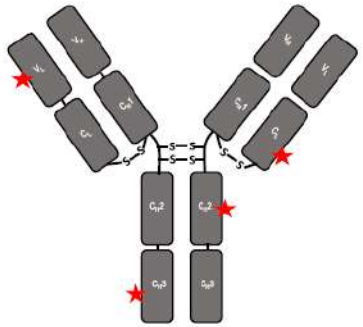
Karoline Bechtold-Peters[a,*], Andrea Ruggiero[c], Nienke Vriezen[e], Nathan Ihle[f], Armin Klein[g], Charles Morgan[h,k,1], Daniel Schweizer[a], Dengfeng Liu[i,o,1], Fred Jacobson[k,1], Jakob Buecheler[a], Mark Panek[l], Naomi Duggan[g], Padma Malyala[m], Philippe Dupraz[c,1], Priyanka Desai[d,1], Shufang Niu[b], Yiqing Feng[n], Xiangyang Wang[j,o,1]

Examples: Antibody Drug Conjugates

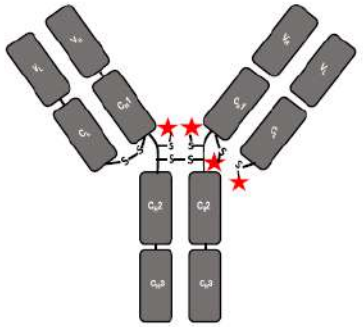
ADC Manufacturing Process



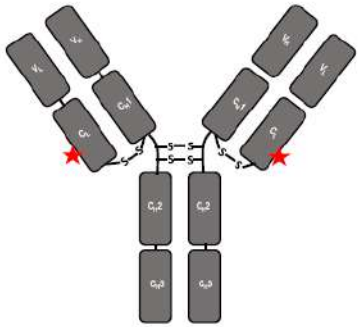
ADC Conjugation technologies



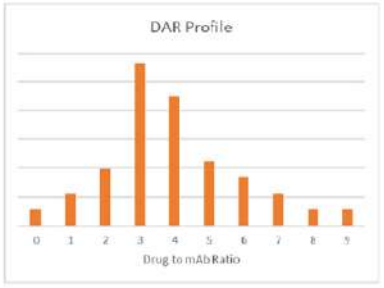
Native Lysine

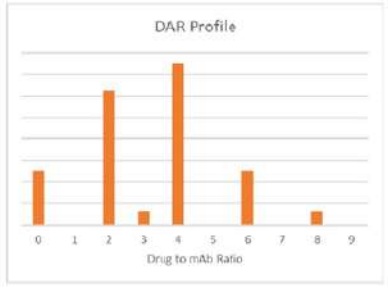


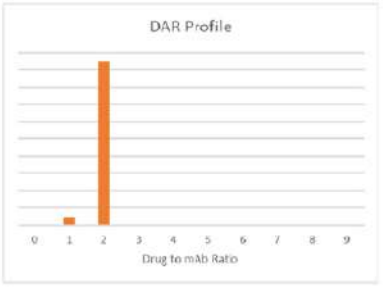
Native Cysteine
(partial reduction
prior to conjugation)



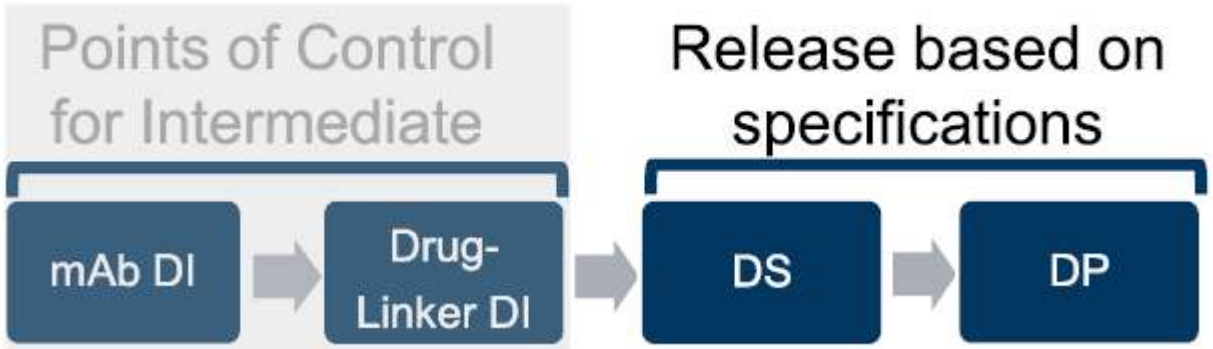
Site specific (cysteine mutation, non-natural amino acids, aldehyde tag, enzyme mediated, and others)







ADC Control Strategy



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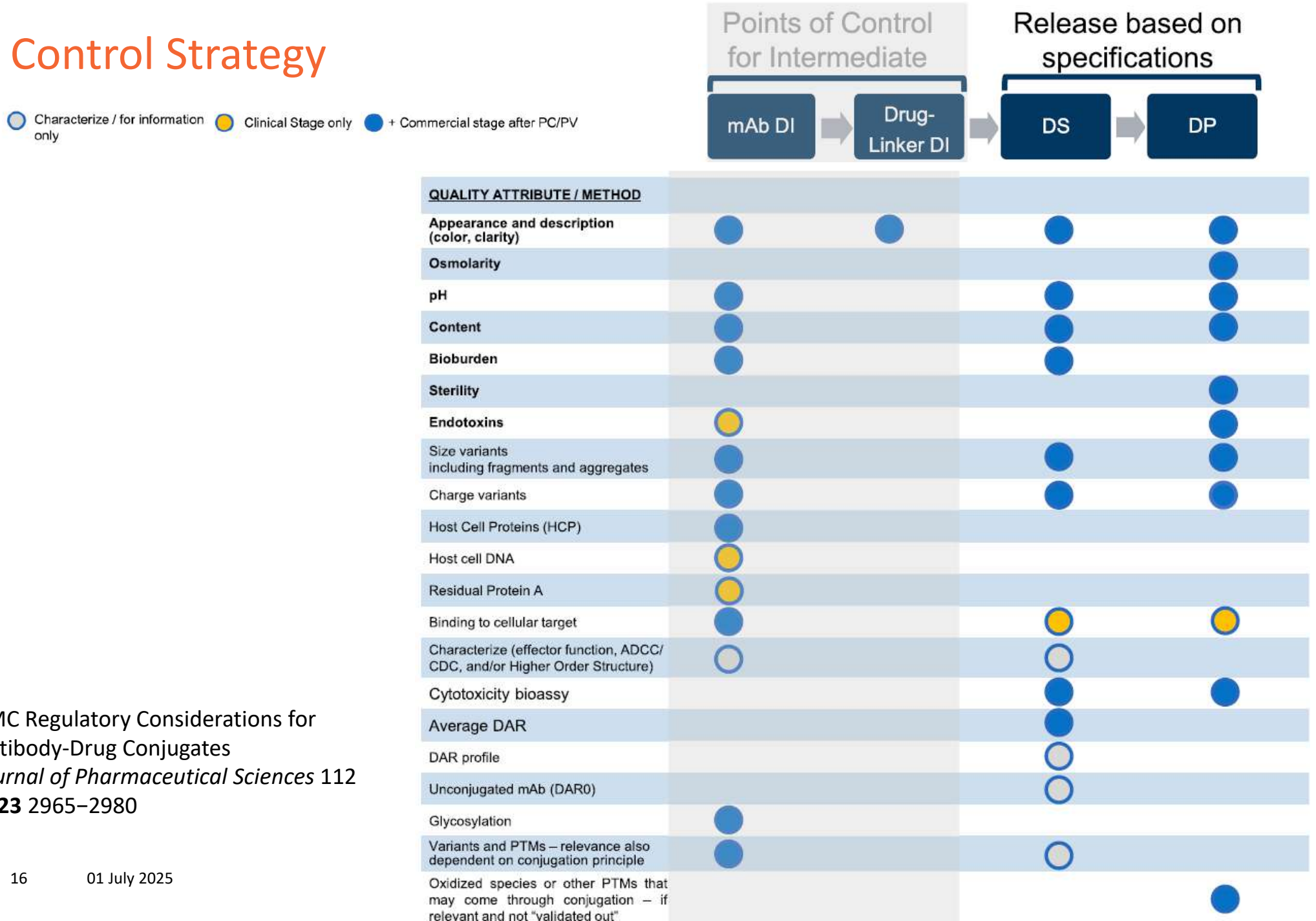
Control Strategy



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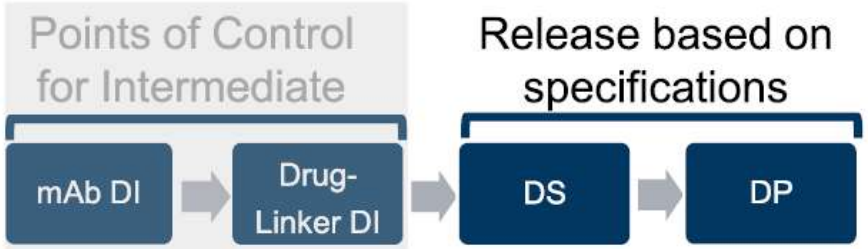
Control Strategy

Characterize / for information only | Clinical Stage only | + Commercial stage after PC/PV



QUALITY ATTRIBUTE / METHOD	mAb DI	Drug-Linker DI	DS	DP
Conjugatable impurities	●		○	
Free-drug related impurities including Non-conjugatable impurities	○ ● *		◐	* ● ◐
Residual solvents	●		◐	
Metal impurities	◐		◐	«validated out»
Water content	●			
Chiral purity - if applicable	●			
Residual moisture and reconstitution time (if lyophilizate)				●
Particles (visible, subvisible)				●
Sterility				●
Container closure integrity				●
Surfactant content				●
Nitrosamines			If process assessment requires so	
Leachables			If process assessment requires so	

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Journal of Pharmaceutical Sciences 112 **2023** 2965−2980

Small Molecule Impurities from ADC Drug Linker Intermediate

1. Non-conjugatable Impurities

What to Control?

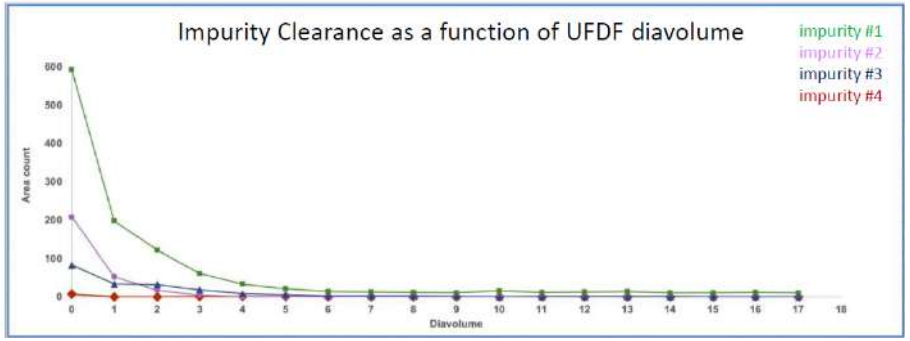
- Impurities from synthesis and input materials

What are appropriate limits?

- Inherently purged by UF/DF processing steps
- Control Limits in intermediates can be significantly higher than impurities control in chemical drug intermediates

What is the overall control strategy?

- DLI is not a drug substance
- Test for known impurities at significant levels at DLI
- Test for unidentified impurities at DLI
- No need for general unqualified impurities test in ADC drug substance



Assay by HPLC (% w/w, as-is)	Not less than 90.0
Purity by HPLC (% area)	Not less than 96.0
Related Impurities Content by HPLC (% area)	
N-hydroxy benzotriazole (HOBt)	Not more than 1.0
Impurity A	Not more than 0.70
Impurity B	Not more than 1.0
Impurity C	Not more than 1.0
Impurity D	Not more than 0.90
Single largest unspecified impurity[1]	Not more than 0.50
Total related impurities	Not more than 4.0
Related Impurity E Content by HPLC (% area)[1,2]	Not more than 1.2
TFA Content by IC (% w/w)	Not more than 2.0
Water Content by Karl Fischer (% w/w)	Not more than 5.0

Small Molecule Impurities from Drug Linker Intermediate

2. Conjugatable Impurities

What to Control?

- Impurities which can conjugate to the mAb

What are appropriate limits?

- Consider to be of equivalent or less toxicity than the drug payload
- Could be cleaved from ADC DS in-vivo
- Consider ICHQ3 principles
  - Acceptable levels can be qualified in non-clinical studies and based on exposure

What is the overall control strategy?

- Test for CQA conjugatable impurities at DLI
- No need for control in ADC drug substance

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White Paper

Control Strategy for Small Molecule Impurities in Antibody-Drug Conjugates

Hai H. Gong,[1] Nathan Ihle,[2] Michael T. Jones,[3,6] Kathleen Kelly,[4] Laila Kott,[5] Thomas Raglione,[4] Scott Whitlock,[2] Qunying Zhang,[1] and Jie Zheng[1]

From CTD S.4.5Justification of Specification DLI

"an individual impurity present at 0.50% in [DLI] would be present at 40.8 µg in the drug product. As patients receive a dose once every 21 days, the average daily exposure is significantly lower than the levels present per dose. Based on this, an impurity present at 0.50% would have an average daily exposure of 1.9 µg/day"

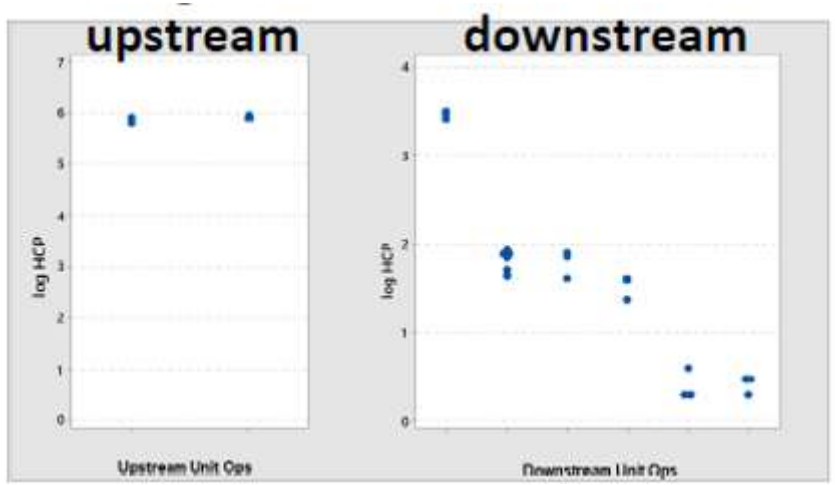
Host Cell Protein Control

What to Control?

- Host cell proteins from upstream process

What are appropriate limits?

- Can be established based on prior knowledge
  - What are typical limits in mAb drugs?
  - How does the downstream coupling and purification purge?



What is the overall control strategy?

- Test at mAb intermediate
- Further downstream controls will reduce levels

Unconjugated Drug Antibody Ratio 0 (DAR0)

What to Control?

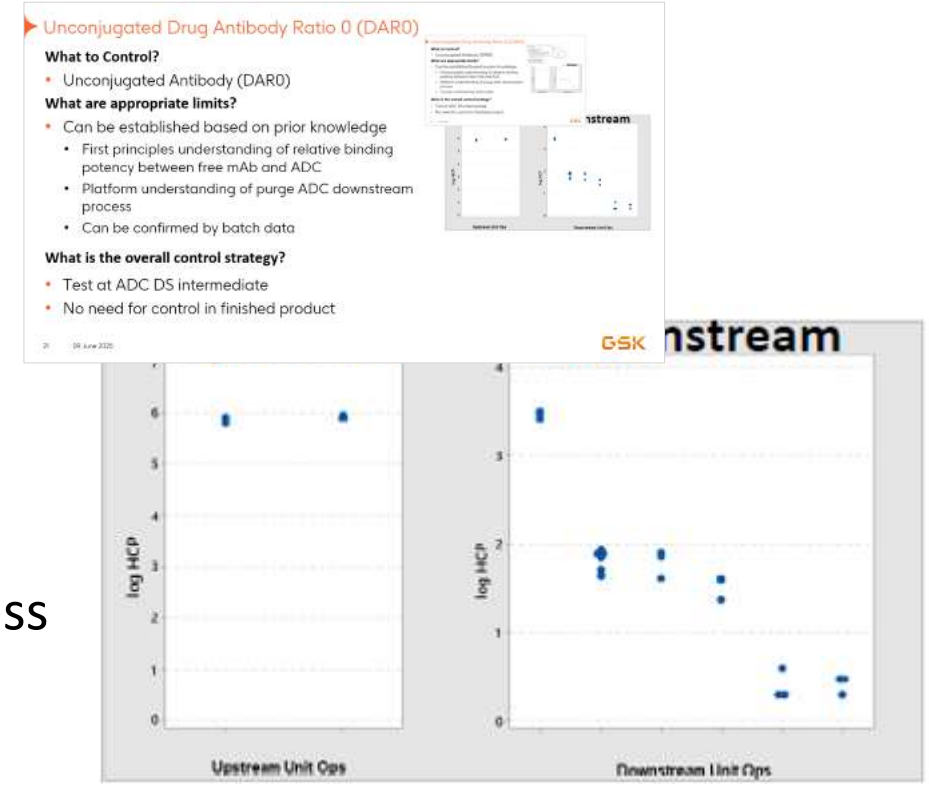
- Unconjugated Antibody (DAR0)

What are appropriate limits?

- Can be established based on prior knowledge
  - First principles understanding of relative binding potency between free mAb and ADC
  - Platform understanding of purge ADC downstream process
  - Can be confirmed by batch data

What is the overall control strategy?

- Test at ADC DS intermediate
- No need for control in finished product



Lifecycle Management of Specifications

ICHQ6 Concept paper:

"Include considerations on lifecycle management of specifications, in line with concepts agreed in ICH Q12."

From:

4. Specifications typically finalised in development

To:

4. Specifications evolve with knowledge over the lifecycle

- Illustrative scenarios:
  - Updates to CQAs
  - Updates to acceptance criteria, considering increased product and process understanding
  - Removal/addition of tests
  - Significant control strategy changes (eg inclusion of PAT, process models linked to RTR)

Summary: Principles for Specifications

1. **What:** Focusing specification on CQAs

2. **Limits:** Identification of scientifically sound acceptance criteria. (limits not based on limited batch data)

3. **Control Strategy**: Integration of the specification within the overall control strategy

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- Matt Popkin
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