Antibody-Drug Conjugates:

Regulatory Insights and Lessons Learned

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Outline

1. Industry Positions
2. Control Strategies
    a) Linker-Payload Specification
    b) Antibody Specification
    c) Drug Substance Specification
    d) Drug Product Specification
3. Complex Supply Chains
4. Comparability Considerations
5. Conclusion

CMC Challenges in ADC Drug Development

- Control Strategy
- Accelerated Timelines
- Comparability
- Complex Supply Chains
- Global Regulatory Requirements

Industry Collaborations: IQ ADC WG

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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]

$$\text{Daily Impurity Dose}\left(\frac{\text{mg}}{\text{day}}\right) = \frac{\text{Dose (mg)} \times \frac{\text{Impurity \%}}{100} \times \text{DAR} \times \frac{\text{Impurity MW}}{\text{ADC MW}}}{\text{Dose Frequency (days)}}$$

Industry Collaborations: IQ ADC WG

ORGANIC PROCESS RESEARCH & DEVELOPMENT

OPR&D

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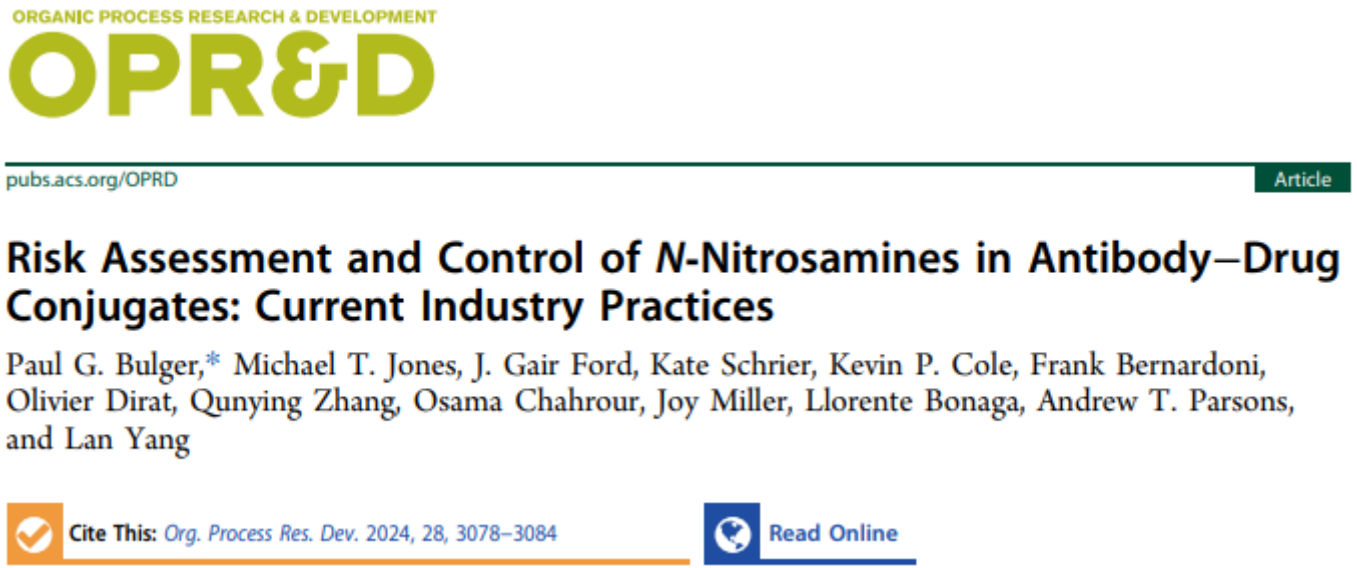
Drug-Linkers in Antibody–Drug Conjugates: Perspective on Current Industry Practices

Paul G. Bulger,* David A. Conlon, Russell D. Cink, Lara Fernandez-Cerezo, Qunying Zhang, Srinath Thirumalairajan, Thomas Raglione, Ruiting Liang, Jinsheng Zhou, and Arun Chalgeri

Cite This: *Org. Process Res. Dev.* 2023, 27, 1248–1257 Read



ORGANIC PROCESS RESEARCH & DEVELOPMENT

OPR&D

pubs.acs.org/OPRD Article

Risk Assessment and Control of *N*-Nitrosamines in Antibody–Drug Conjugates: Current Industry Practices

Paul G. Bulger,* Michael T. Jones, J. Gair Ford, Kate Schrier, Kevin P. Cole, Frank Bernardoni, Olivier Dirat, Qunying Zhang, Osama Chahrour, Joy Miller, Llorente Bonaga, Andrew T. Parsons, and Lan Yang

Cite This: *Org. Process Res. Dev.* 2024, 28, 3078–3084 Read Online

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Industry Collaborations: EFPIA ADC Workstream

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journal homepage: www.jpharmsci.org

Perspective

CMC Regulatory Considerations for Antibody-Drug Conjugates

Check for updates

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]

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Industry Collaborations: EFPIA ADC Workstream

Bechtold-Peters, K. et al, CMC Regulatory Considerations for Antibody-Drug Conjugates. *Journal of Pharmaceutical Sciences.* 112, **2023,** 2965–2980.

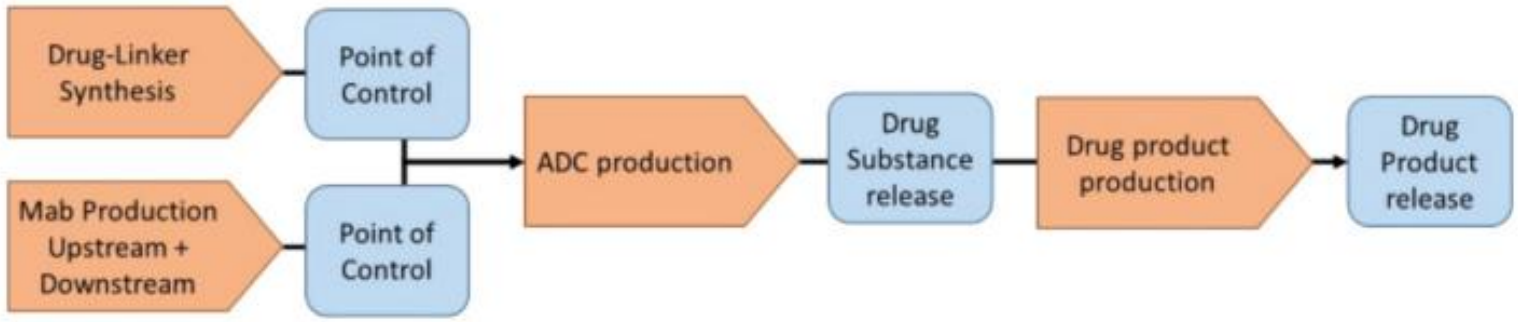
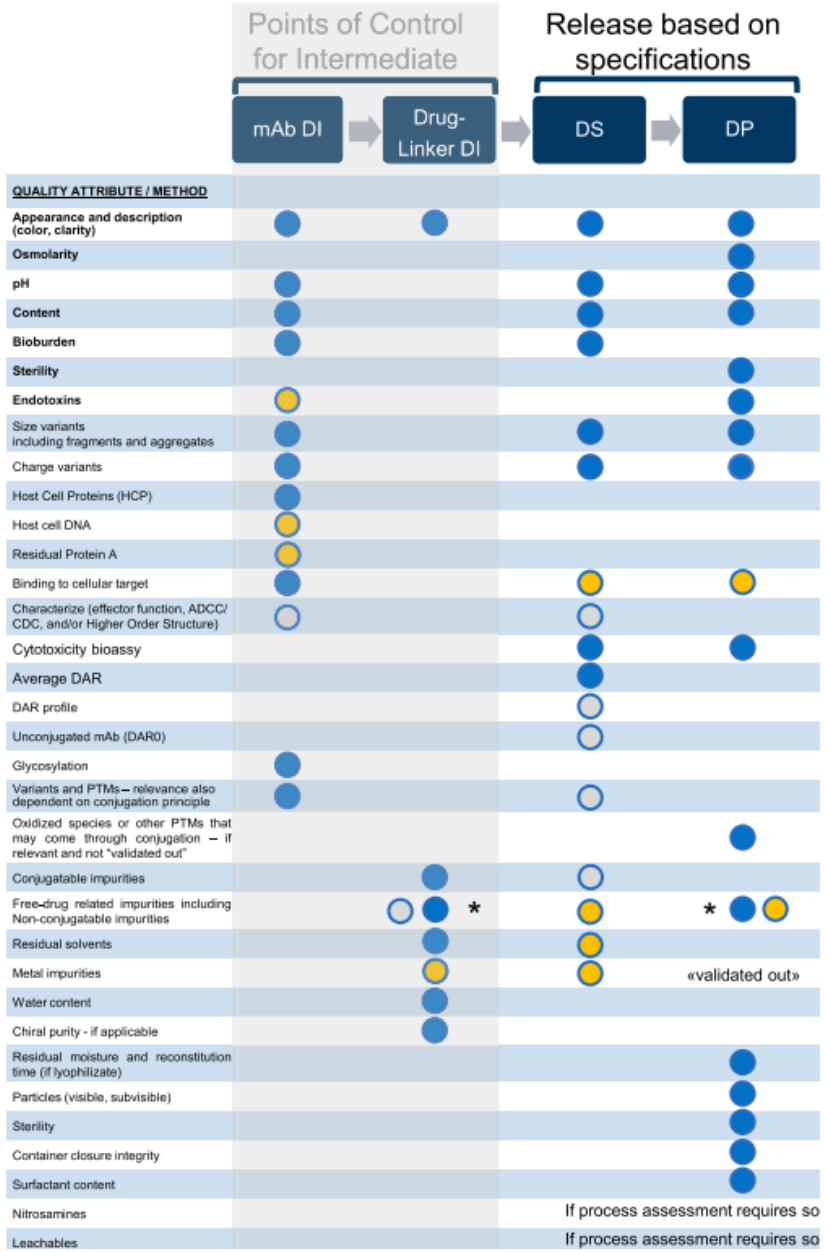


Figure 3. Example of components of an ADC production and control strategy (other sequences of processes possible).

Industry Collaborations: EFPIA ADC Workstream



Characterize / for information only

Clinical Stage only

+ Commercial stage after PC/PV

Bechtold-Peters, K. et al, CMC Regulatory Considerations for Antibody-Drug Conjugates. *Journal of Pharmaceutical Sciences*. 112, **2023**, 2965–2980.

Control Strategies

Linker-Payload Specification

Control of Small Molecule Impurities

- Non-conjugatable impurities
  - Inherently purged by UF/DF processing steps
- Test for those impurities present at significant levels in the Linker-Payload
- Limits may be higher than controls in chemical drug intermediates
- Non-conjugatable impurities (i.e., residual solvents) not tested in the drug substance
- Approach has typically been accepted during the clinical trial phase and in marketing applications

Linker-Payload Specification

Control of Small Molecule Impurities

- Conjugatable impurities are those that can conjugate to the mAb
- Specification for the linker payload typically includes
  - Specified impurities
  - Single largest unspecified impurity
  - Total related impurities
- Generally assume all unspecified impurities are conjugatable
- Typically rely on the “Gong Calculations”
- Generally do not control these impurities at the DS stage
- Approach has typically been accepted during the clinical trial phase but inconsistently in marketing applications
- HAQs include requests for additional characterization data for the impurities or tightening of acceptance criteria

Gong, H.H., et al, Control Strategy for Small Molecule Impurities in Antibody-Drug Conjugates. *AAPS PharmSciTech*, Vol. 19, No. 3, April **2018** (# 2018) DOI: 10.1208/s12249-017-0943-6

Antibody Specification

Control of Residual Host Cell Protein

- Host Cell Protein typically quantified using an ELISA assay
- Acceptance criterion typically based on prior knowledge for other mAb drugs
- Levels will be reduced by further downstream processing steps
- Typically, do not control HCP at the DS level as well
- Health Authorities have generally accepted this approach

Drug Substance Specification

Free mAb (DAR0)

- Test at the drug substance level
- Acceptance criteria based on:
  - Understand the relative binding potency between the free mAb and the ADC
  - Platform understanding of the downstream purging capabilities
  - Can be confirmed by batch data
- No need for control in the finished product

Drug Product Specification

Residual Free Drug Linker

- Strategy: Collect data on this attribute during development to support potentially excluding this test in the marketing application
- Feedback: Health Authorities reluctant to accept Company A's justification for removing this test. Company A's position:
  - RFDL levels are adequately controlled in the DS specification
  - No changes in RFDL levels are observed during DS and DP storage
  - Drug-antibody ratio, drug-load distribution, and potency are adequately monitored and controlled by multiple analytical methods

Drug Product

Gross Content and Deliverable Volume

- Do not typically include a gross content test and deliverable volume test in the drug product specification
  - Existing in-process controls are sufficient to ensure gross and net content meet the label claim
    - IPCs include bulk drug product concentration, fill volume, filling accuracy
  - Vial content controlled by tests for protein concentration and uniformity of dosage units in the DP release specification
  - Dosing based on patient weight, requiring multiple vials for adult patients
- Companies report receiving feedback to include this test from one health authority

Complex Supply Chains

Complex Supply Chains

- Companies report multiple manufacturing and testing sites for the linker-payload, mAb, Drug Substance and Drug Product
- Sites spread out worldwide, subject to external global political pressures
- Companies report challenges with managing in-licenced products and partner-managed contract manufacturers
- Complex supply chains require robust comparability strategies

Comparability Considerations

Comparability Considerations

- Typically take a risk-based approach to performing comparability assessments
- Comprehensive comparative analytical assessment typically includes:
  - Release testing
  - Characterization testing
  - Stability data
  - Forced degradation
- Depending on the type of change, Health Authorities have asked for additional extended characterization data or forced degradation data to support comparability claims
- Limited success in leveraging stability data across different container closure configurations

Reflections and Conclusions

- Gaps between industry perspectives (i.e., the EFPIA paper[1] and the IQ paper[2]) and regulators' positions
- Complex supply chains for ADCs highlight need for robust comparability packages
- Diversity in regulatory expectations resulting in divergent dossiers globally
- Recommend early engagement with regulators to align on control strategy and risk-based approaches prior to BLA submission
  - Useful for discussing regulatory starting materials, PPQ strategies, and comparability assessment plans

1. Bechtold-Peters, K. et al, CMC Regulatory Considerations for Antibody-Drug Conjugates. *Journal of Pharmaceutical Sciences.* 112, **2023,** 2965–2980.
2. Gong, H.H., et al, Control Strategy for Small Molecule Impurities in Antibody-Drug Conjugates. *AAPS PharmSciTech*, Vol. 19, No. 3, April **2018** (# 2018) DOI: 10.1208/s12249-017-0943-6

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