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European Federation of Pharmaceutical Industries and Associations

The Expanding World of Bioconjugate Therapeutics: Quality, Control, and Global Regulatory Considerations





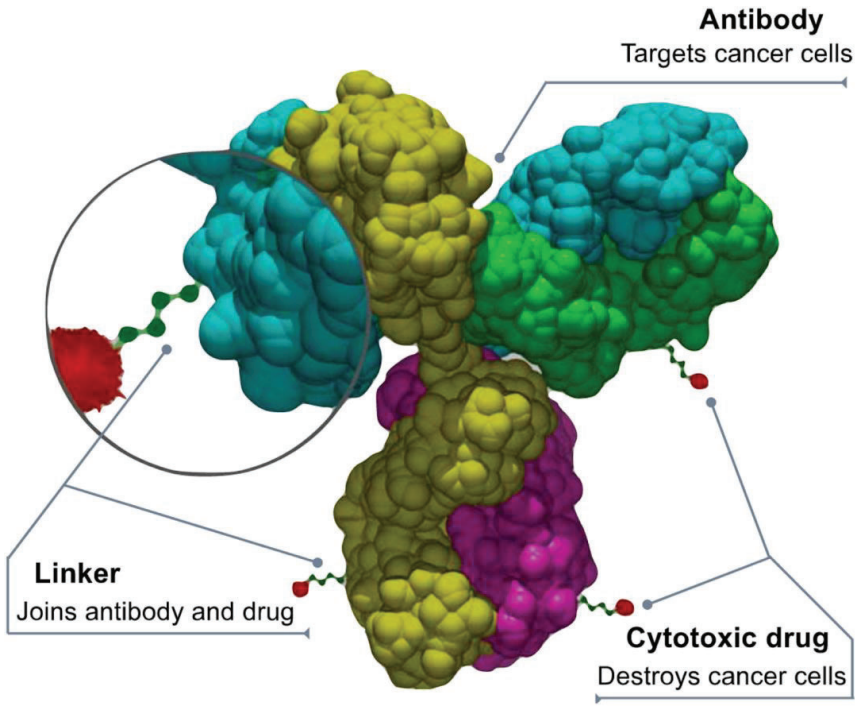

Katie Duncan (GSK)

EFPIA ADC/AxC Workstream

Agenda

1. ADC structure and mechanism of action
2. Evolving global regulatory landscape
3. Manufacturing process
4. Control strategies and key CMC challenges
5. Where the field is going: next generation bioconjugates and collaborative assessments

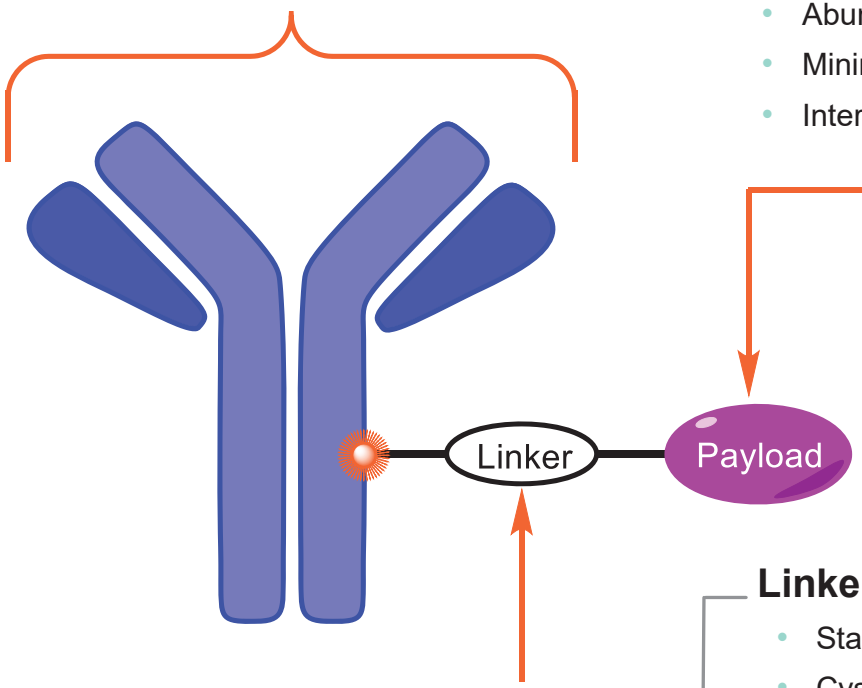
Antibody-Drug Conjugate (ADC) Structure



Combine targeting moiety (antibody) with payload (cytotoxic drug) via a linker, enabling delivery of therapeutics to specific cells or tissues.

File:Antibody-drug conjugate structure.svg - Wikimedia Commons

Typical Antibody-Drug Conjugate (ADC) Structure



Tumor Antigen Recognition Site

- IgG is most frequently used for cancer immunotherapy
- Abundance in tumors
- Minimal expression in normal cells
- Internalization

Payload – Highly Toxic

- Microtubule inhibitors
  - Auristatins (MMAE), Maytansine (DM1/DM4)
- DNA damaging agents
  - Anthracyclines, Calicheamicin, Camptothecin derivatives, Duocarmycins, Indolinobenzodiazepines (IGNs), Pyridinobenzodiazepines (PDDs), Pyrrolobenzodiazepines (PBDs)
- Others (e.g. toxic proteins, RNA inhibitors)

Linker & Conjugation Technologies

- Stable in circulation → prevents premature release of payload
- Cystine or lysine coupled, or engineered
- Cleavable (e.g., acid-labile, protease cleavable, disulfide linkages) or non-cleavable
- Potential to change the number of payloads per antibody (i.e., DAR)

Typical Mechanism of Action

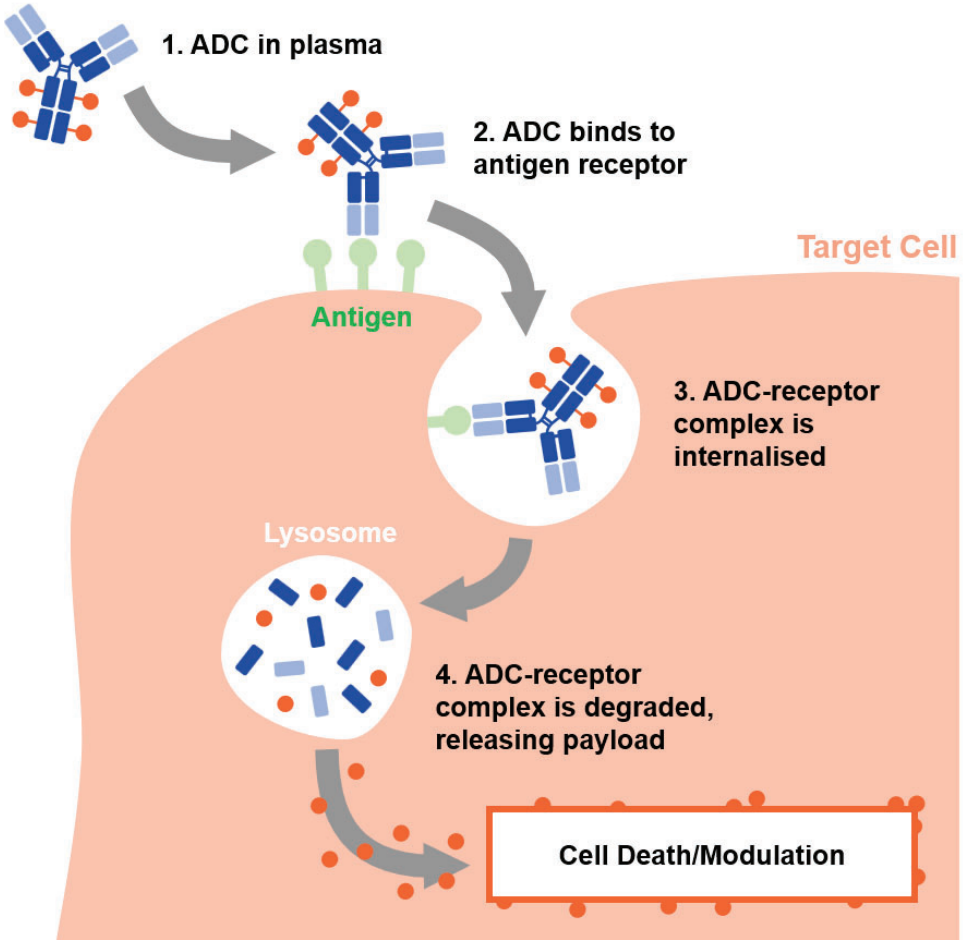
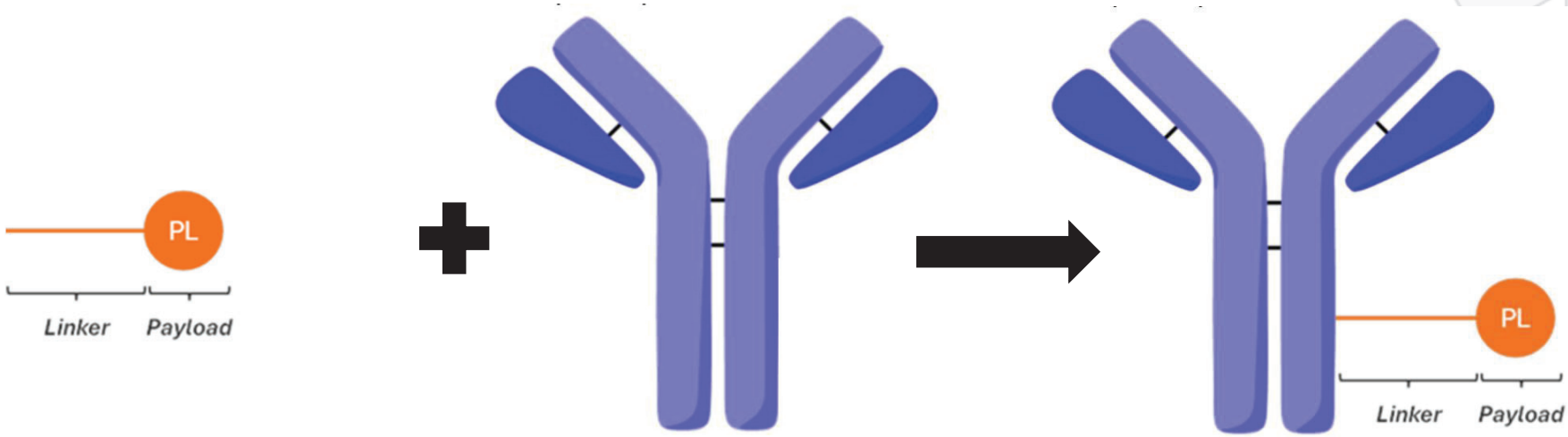


Image credit: Liz Love, GSK

Evolving Global Regulatory Landscape for ADCs

Region	Guidelines
Global	• ICH Q5A-Q5E: conjugates in scope • ICH Q3A/B and ICH M7: biological conjugates *currently* excluded • Ongoing ICH Q6 revision to include section on ADCs • Other ICH guidelines apply, including ICH Q1, Q8, Q9, Q10, and Q11 and ICH S6(R1) and S9
US, EU, Japan, Mexico, Brazil, Chile, etc.	• No dedicated CMC guideline for ADCs
China	• Technical Guideline for Antibody-Drug Conjugate Pharmaceutical Study and Evaluation (December 2024) • Draft Guideline on the Preparation of Quality Overall Summary Dossiers for Marketing Authorization Applications for Antibody-Drug Conjugates (March 2026) • Guidelines for the Preparation of CMC Dossier for Initial IND Applications for Antibody-Drug Conjugates (ADCs) (April 2026)
South Korea	• Guideline on Quality Evaluation of Antibody-Drug Conjugates (November 2025)

Regulatory Expectations



Drug/Linker Intermediate

- Small molecule guidances typically apply
- Typically, drug-linker expected to follow the same standard as a small molecule drug substance

Monoclonal antibody

- Biologics guidances typically apply
- Typically, antibody expected to follow the same standard as a biological drug substance

ADC Drug Substance and Drug Product

- Typical biologics considerations apply

Select Industry Publications

AAPS PharmSciTech, Vol. 19, No. 3, April 2018 (© 2018)
DOI: 10.1208/s12249-017-0943-6

White Paper

Control Strategy for Small Molecule Impurities in Antibody-Drug Conjugates

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Perspective

CMC Regulatory Considerations for Antibody-Drug Conjugates

Check for updates

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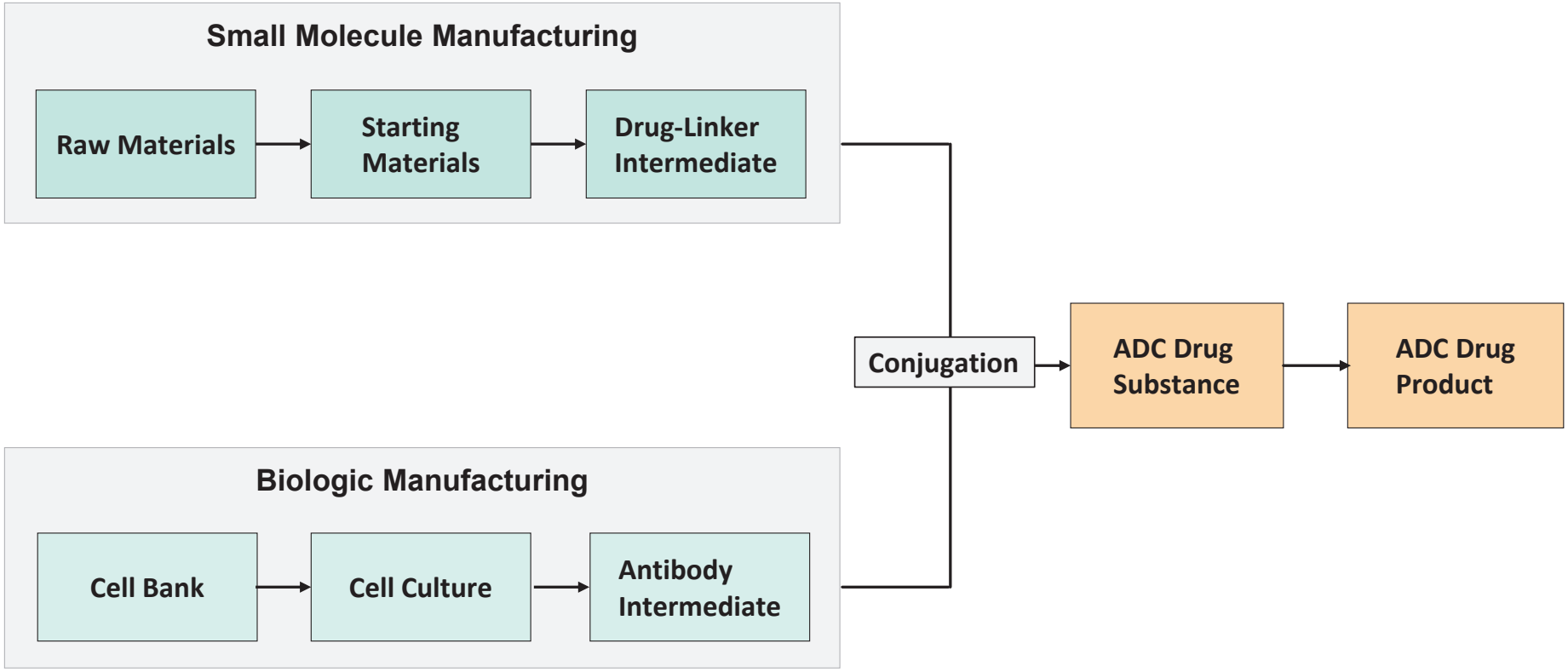
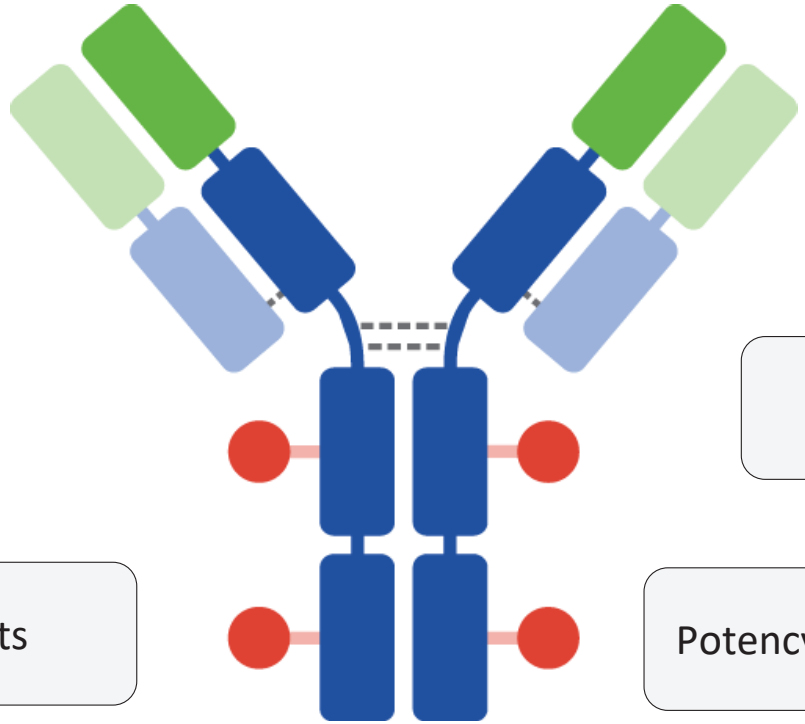
ADC Manufacturing Process



Critical Quality Attributes

DAR
(Drug-to-antibody ratio)

Free drug and related impurities (FDRI)



Unconjugated mAb (DAR 0)

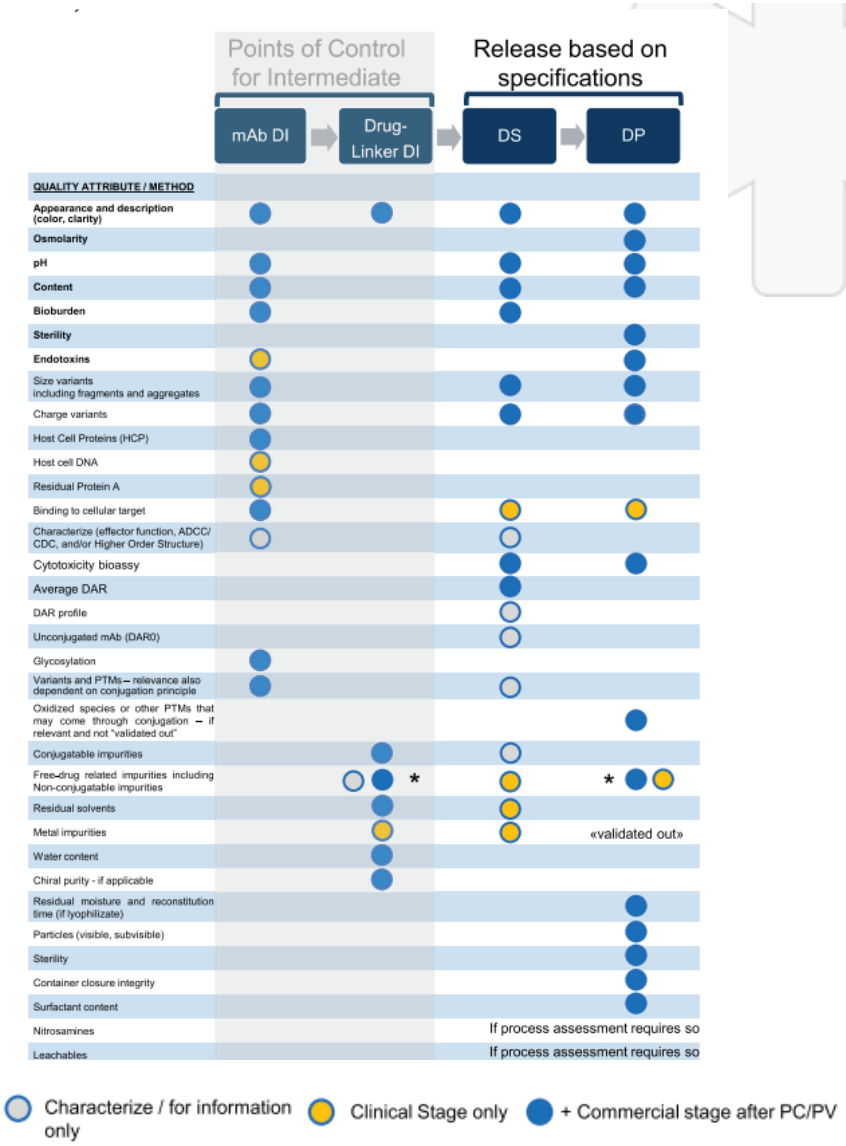
Conjugatable small molecule impurities

Antibody variants

Potency/biological activity

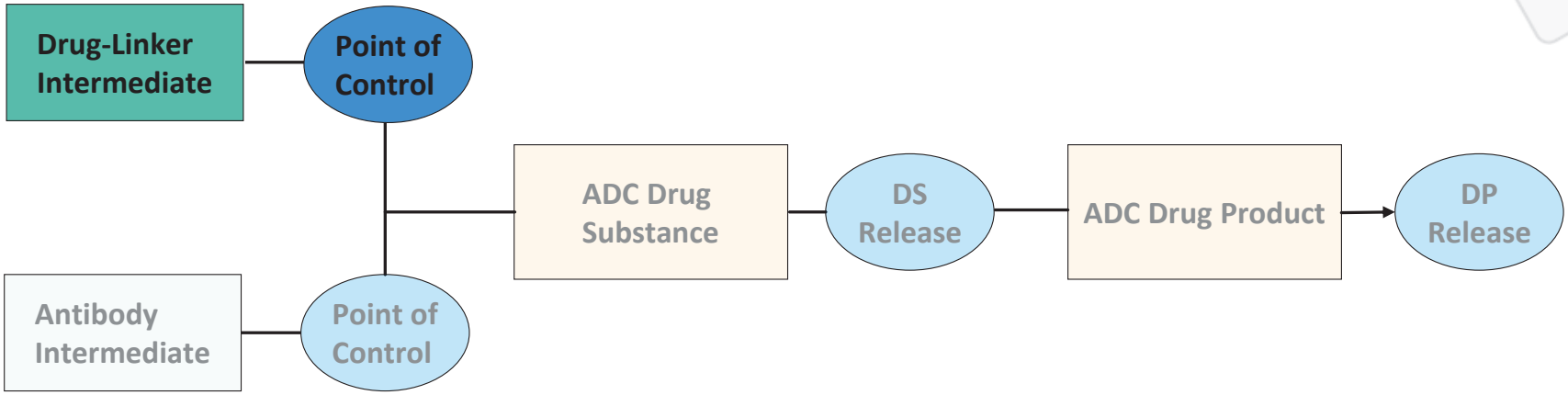
Control Strategies for ADCs

- **Map critical quality attributes across the production process**
  - Multi-step manufacturing process provides multiple nodes for control and characterization
- **Drug-linker and antibody are intermediates, released for forward processing**
  - Control strategies should reflect intended use (i.e., to be conjugated into the ADC drug substance)
- **Apply a risk-based approach demonstrating quality at the relevant point of control**



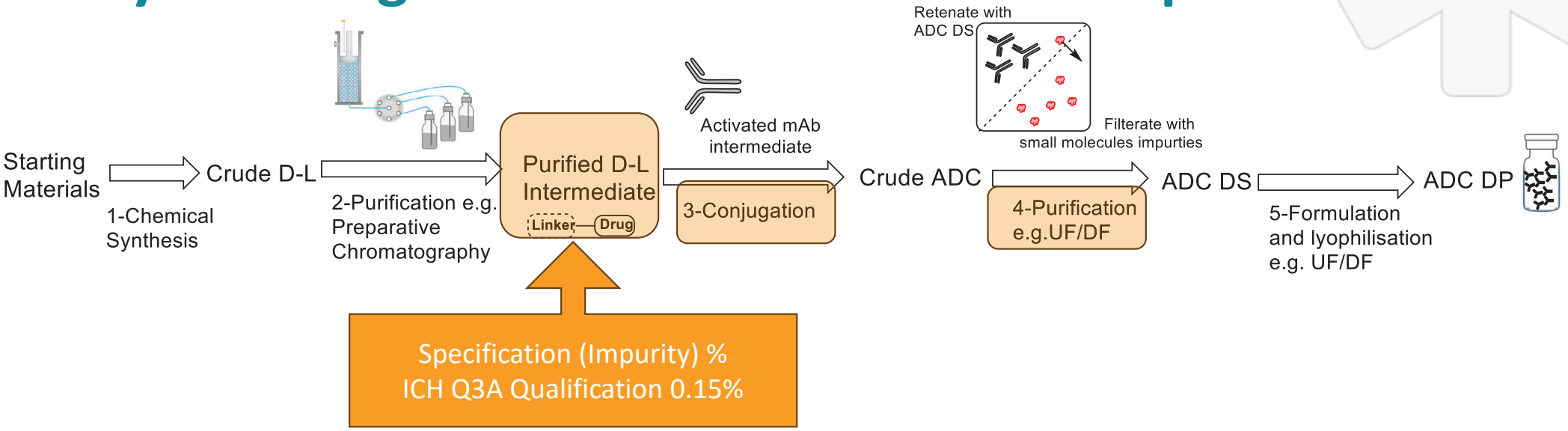
1: HTTPS://DOI.ORG/10.1016/J.XPHS.2023.09.007

Drug-Linker Intermediate: Key Considerations



- Key specification tests: appearance/description, identification, assay, purity, chiral purity (if applicable), residual solvents, elemental impurities, water content
- ICH Q11 principles apply to starting material designation
- Impurity considerations:
  - **Non-conjugatable impurities** cannot conjugate to the mAb: Typically purged by downstream manufacturing processes (e.g., UF/DF)
  - **Conjugable impurities** can react with mAb sites and can impact ADC potency
- Key is to understand the impurity purge and the impact to quality of the ADC drug substance

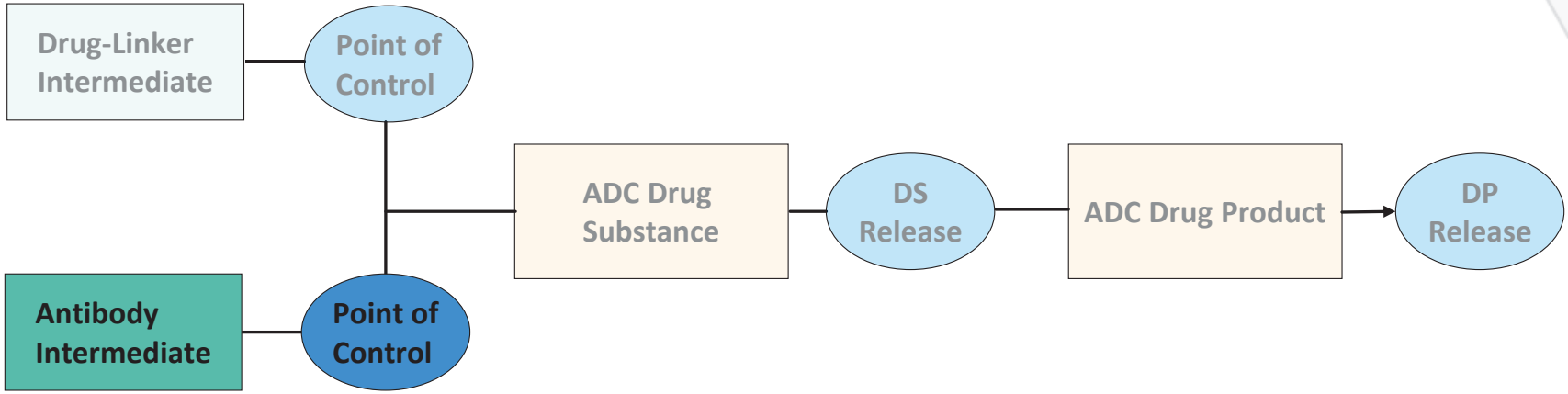
Key Challenge: Control of D-L Related Impurities



- Some agencies expect the drug-linker impurities to be controlled according to ICH Q3A principles/thresholds
- ICHQ3A approach does not acknowledge that unlike small molecule APIs, D-L are **intermediates**, making up 5-6% of the mass of the ADC
- Downstream purification allows for significant purge of small molecule impurities, residual solvents, and reagents

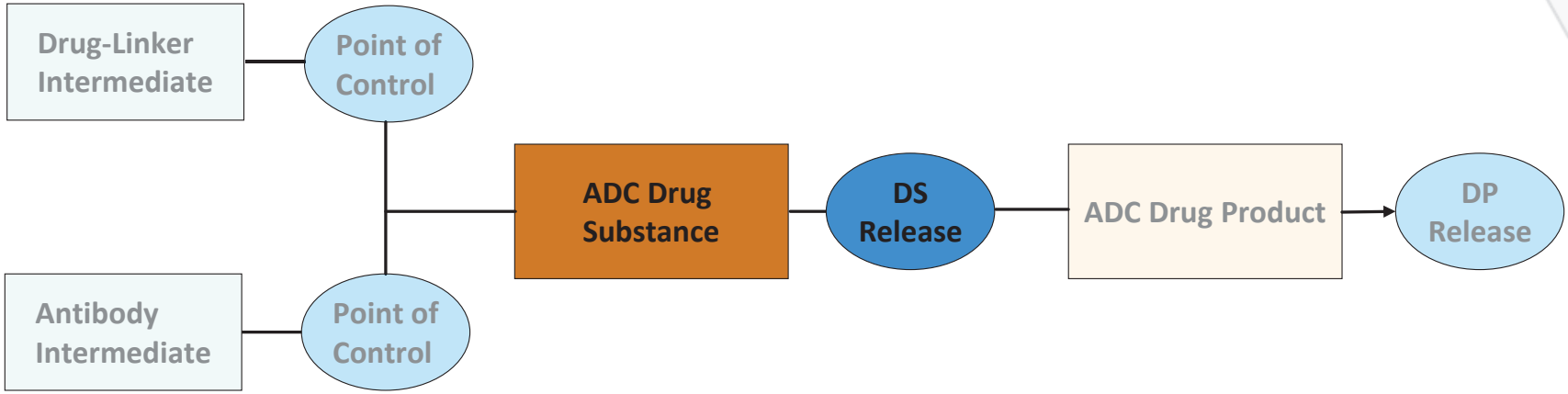
Impurity qualification requirements for drug-linkers related impurities used to generate antibody-drug conjugates

Antibody Intermediates: Key Considerations



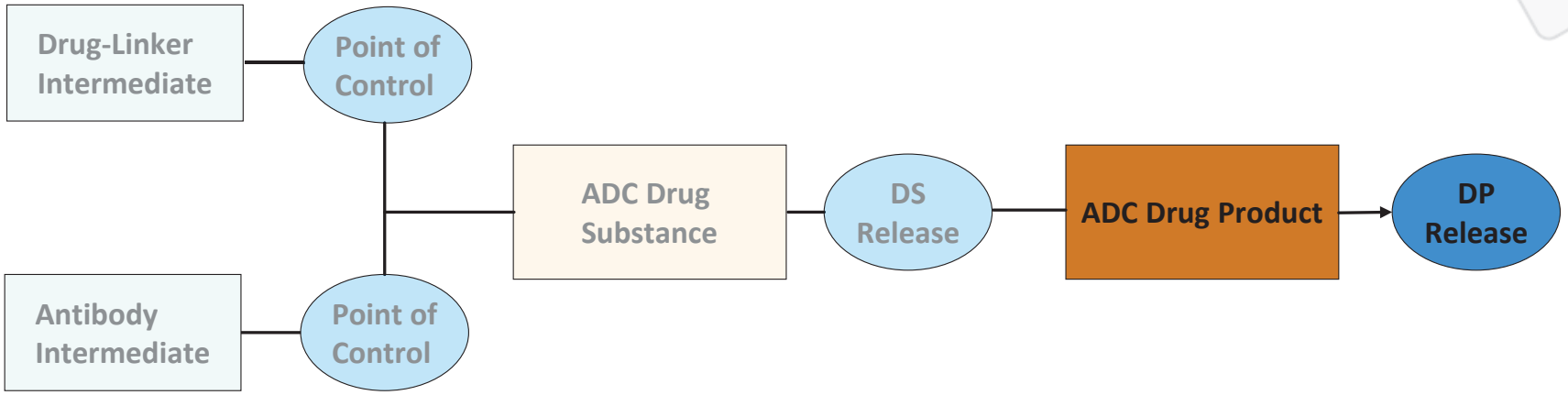
- mAb is a drug substance intermediate
- Key attributes associated with intended use: specificity in binding to target and absence of harmful impurities and contaminants
  - Primary Structure: amino acid sequence, glycosylation, post-translational modifications (PTMs)
  - Purity/Impurity profile: size variants, charge variants, host cell proteins, host cell DNA, adventitious viral agents, residual Protein A
  - Biological activity: binding, effector functions (if relevant)

ADC Drug Substance: Key Considerations



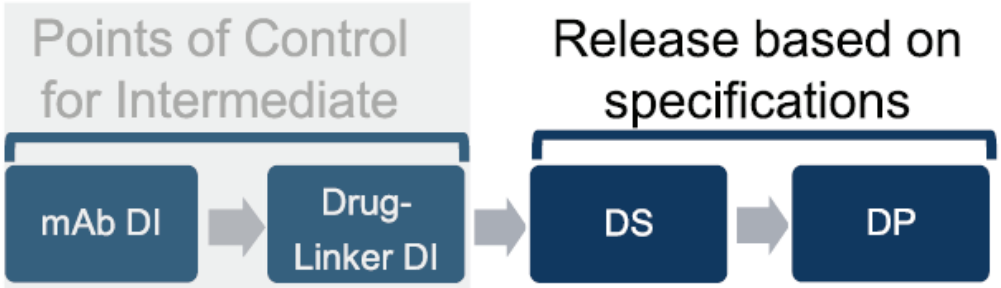
- Need a consistent profile of drug linked to the antibody in the ADC drug substance
- Key quality attributes
  - Drug Antibody Ratio (DAR) and DAR distribution
  - Purity/Impurity profile (mAb related): size variants, charge variants, unconjugated mAb
  - Impurities (drug related): free drug and related substances, residual solvents, elemental impurities
  - Potency: binding, cytotoxicity, effector functions (if relevant), conjugated peptide map

ADC Drug Product: Key Considerations



- Residual moisture and reconstitution time (for lyophilizate)
- Purity/Impurity profile (mAb related): size variants, charge variants
- Impurities (drug related): free drug and related substances
- Potency: binding, cytotoxicity, effector functions (if relevant)
- Particles
- Sterility
- pH

ADC Control Strategy: Example



Attribute to Control?

- Unconjugated Antibody (Drug-Antibody Ratio 0 or 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
- No need for control in finished ADC drug product

Comparability Considerations

- **Analytical assessment of comparability typically includes release testing, characterization testing, stability data and forced degradation studies**

- **The EFPIA ADC team proposes a knowledge-driven, risk-based approach[1] regarding comparability assessment**
  - If comparability can be demonstrated at the point of change (i.e., to the drug-linker or to the mAb) and a risk assessment excludes impact on the ADC DS and DP, no further downstream data need to be provided
  - If comparability can be demonstrated by analytical comparability studies alone, no further actions are needed

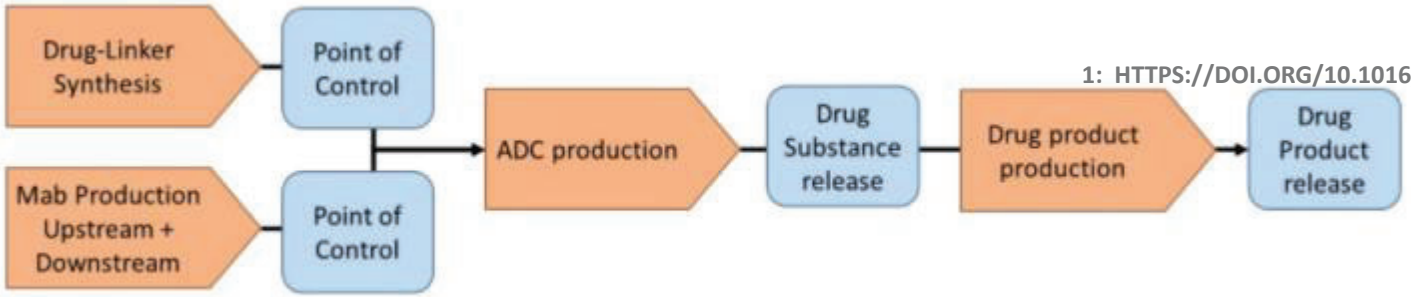


Figure 3. Example of components of an ADC production and control strategy (other sequences of processes possible).

1: HTTPS://DOI.ORG/10.1016/J.XPHS.2023.09.007

Future Directions for ADCs and Bioconjugates

Complex payloads

Peptides, oligonucleotides, and immune-modulating agents

Innovative linkers

Hydrophilic moieties (PEG, saccharides) and multivalent linkers

Dual-payload ADCs

Two distinct payloads on a single antibody scaffold

Alternatives to mAbs

Bispecific conjugates, peptide-drug conjugates, Fc-conjugates

Beyond oncology

Infectious disease, immunology, and neurology

Is further ICH guidance needed for new ADC/AxC technologies?

- ICHM4Q and Q6 revisions will all address ADCs
- Ongoing international debate: is there a need for further ADC/AxC ICH guidance?
- ICH Q8-12 principles are generally fit for purpose & enable development of innovative modalities via general principles of CQA identification, quality risk management

Other Approaches? Collaborative Assessments

ICMRA Exec committee

Making collaborative assessments more sustainable
in the medium to long term

Transitioning to operationalisation in 2026
Governance model to be decided

Collaborative Assessments: Future Scope

Post-approval changes impacting supply

- collaborative assessments
- hybrid inspections

supporting increased **manufacturing capacity** for important medicines

Innovative manufacturing technologies

- **new technologies** e.g. continuous manufacturing
- process **models**
- artificial intelligence **(AI)**
- advanced process control, etc.

Types of submissions that could be considered

- Pre-submission scientific advice?
- Post-approval supplements/variations?
- Initial marketing authorisation applications?
- Pre-approval hybrid inspections?

Key Takeaways

- ADCs are no longer an emerging modality, with 21+ globally approved products
- ADC/AxC development is accelerating and diversifying, including rapid uptake of more complex linker and payload chemistries and expansion to indications beyond oncology.
- ADC/AxCs have complex manufacturing processes and supply chains, leading to challenges in establishing control strategies and demonstrating comparability
- No ICH-level CMC guidance exists for ADCs

Global harmonization — and active engagement from regions like Latin America in shaping it — will be essential as the field keeps expanding.

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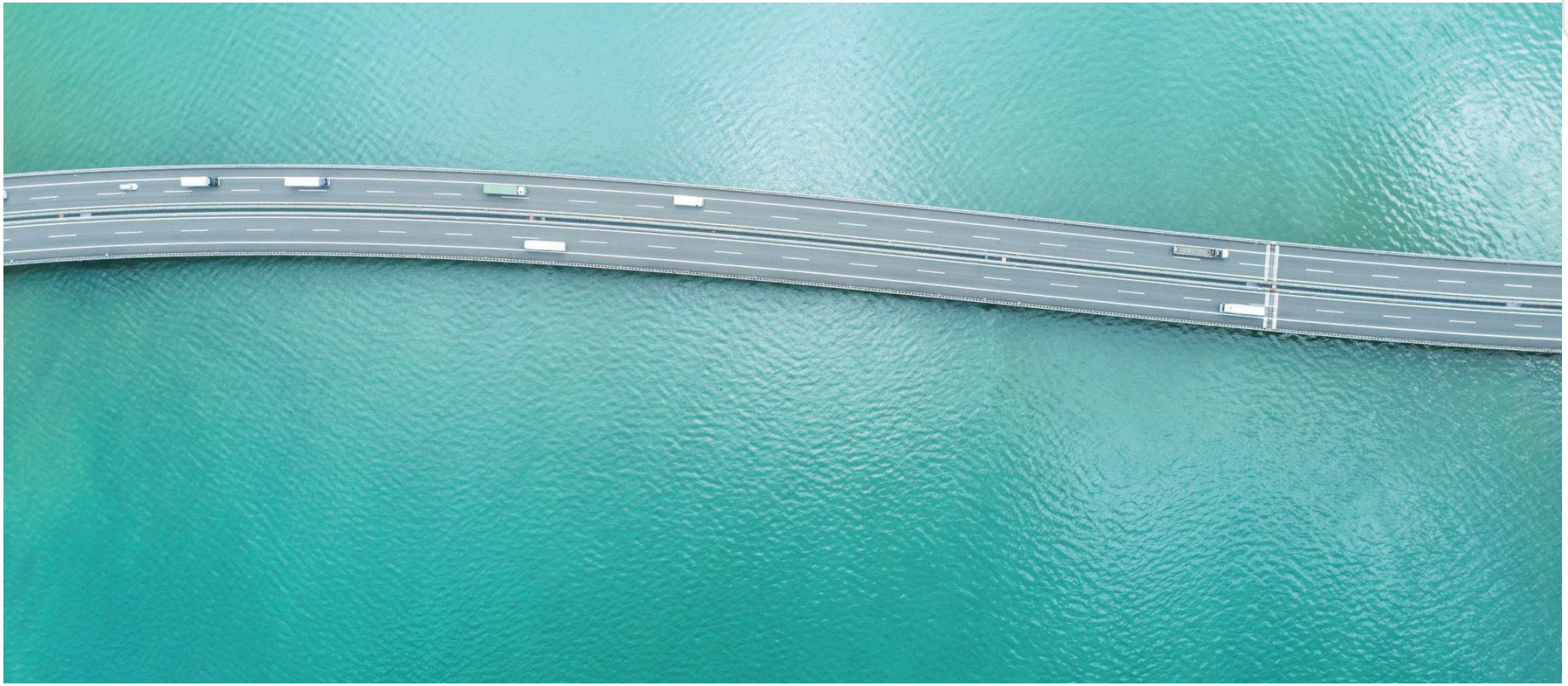
THANK YOU



Back Ups

ADCs: Then and Now

	1980s–1990s **Early ADCs**	Late 1990s–2010 **1st Generation**	2010–2020 **2nd Generation**	2018–Present **3rd Generation**	Emerging **Next Generation**
mAb	Murine/chimeric antibodies • *Immunogenicity issues* • *Modest specificity* • *Low internalization*	Humanized mAb (CD33/CD22) • *Improved specificity* • *Better internalization*	Optimized humanized/ fully human mAb (CD30, HER2, CD70b) • *Strong affinity* • *Improved PK, targeting & internalization*	Fully humanized mAbs (HER2, TROP2, HER3) • *Optimized internalization* • *Heterogeneous-expression targets*	• Bispecific mAbs • Engineered residues for site-specific conjugation
Linker	Random lysine conjugation with unstable linkers • *Premature release* • *Heterogeneous (DAR 0-8+)*	Acid-labile hydrazone & disulfide linkers • *Partial plasma instability* • *Premature/inconsistent release*	Stable linkers: Protease-cleavable (Val-Cit) & non-cleavable (SMCC) • *Random heterogeneous conjugation* • *DAR ~3–4*	Highly stable cleavable linkers with site specific conjugation • *Higher DAR (~8)/ homogeneity* • *low-expression tumors*	• Improved site-specific conjugation • Multivalent: higher DAR/ multi-payload • Smart linkers
Payload	Conventional chemo drugs (doxorubicin, methotrexate, vinblastine) • *Low potency*	Calicheamicin • *Picomolar potency (1,000–10,000× vs. chemo)*	Auristatins & Maytansinoids • *Highly potent anti-tubulin payloads*	DNA damaging payloads (Topo1 inhibitors, PBD) • *Membrane-permeable, effective against slowly dividing tumors/solid tumors*	New classes: duocarmycins, immune-stimulating payloads (STING/TLR agonists), PROTACs/ molecular glues, multi-payload
Representative Products	vindesine-αCEA conjugate	Mylotarg, Besponsa	Kadcyla, Elahere, Adcetris, Padcev	Enhertu, Trodelvy, Datroway	