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Global Regulatory Frameworks for Conjugates: From EFPIA Smart Approaches to Regional Implementation






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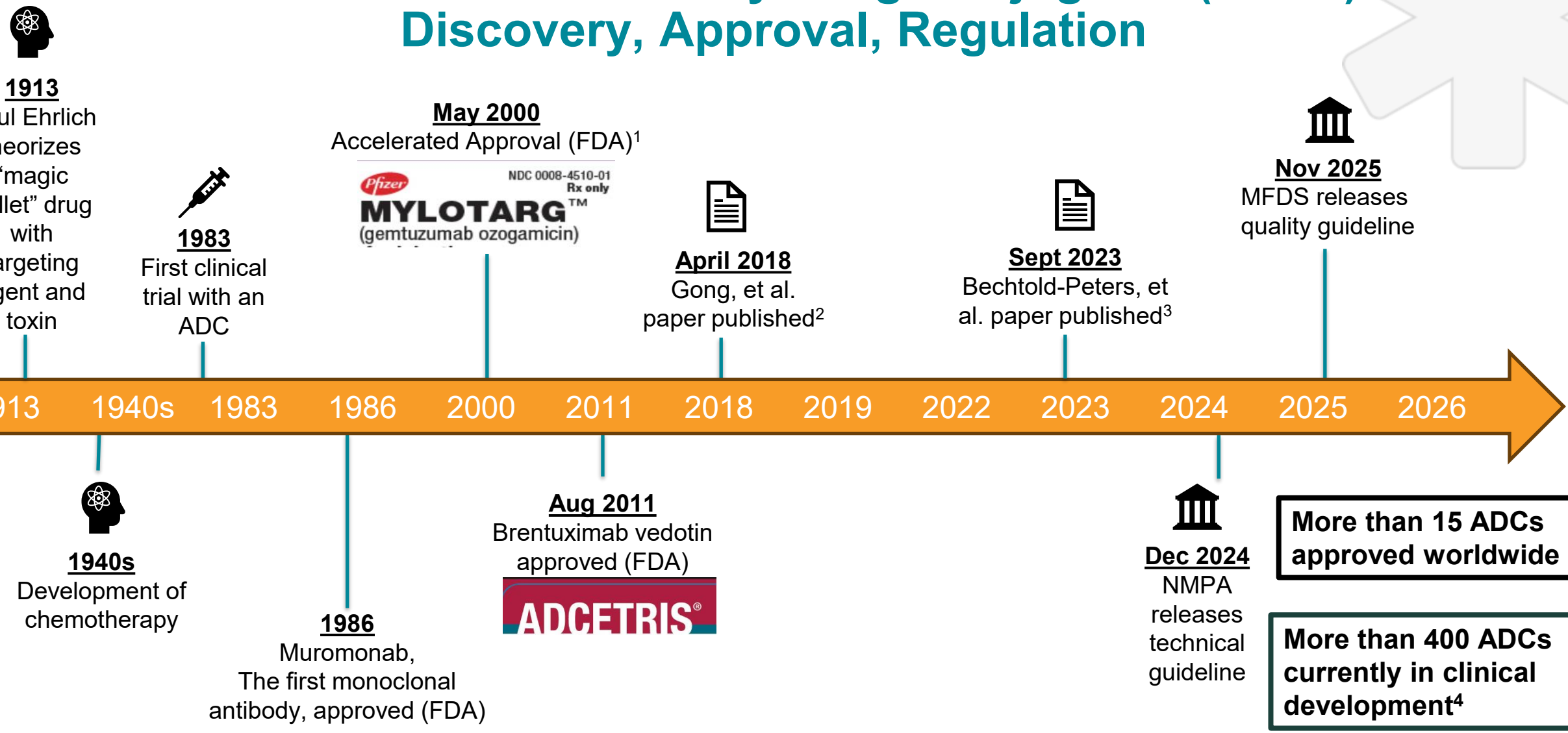
EFPIA ADC/AxC Workstream
CASSS EU Short Course
26 June 2026

Brief Timeline of Antibody-Drug Conjugates (ADCs): Discovery, Approval, Regulation



[1] = withdrawn 2010, reapproved in 2017 (FDA)
[2] = DOI: 10.1208/s12249-017-0943-6
[3] = DOI: 10.1016/j.xphs.2023.09.007
[4] = DOI: 10.1186/s13045-025-01704-3

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	• No dedicated CMC guideline for ADCs
EU	• No dedicated CMC guideline for ADCs
Japan	• 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)

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

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]

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

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journal homepage: www.jpharmsci.org

Perspective

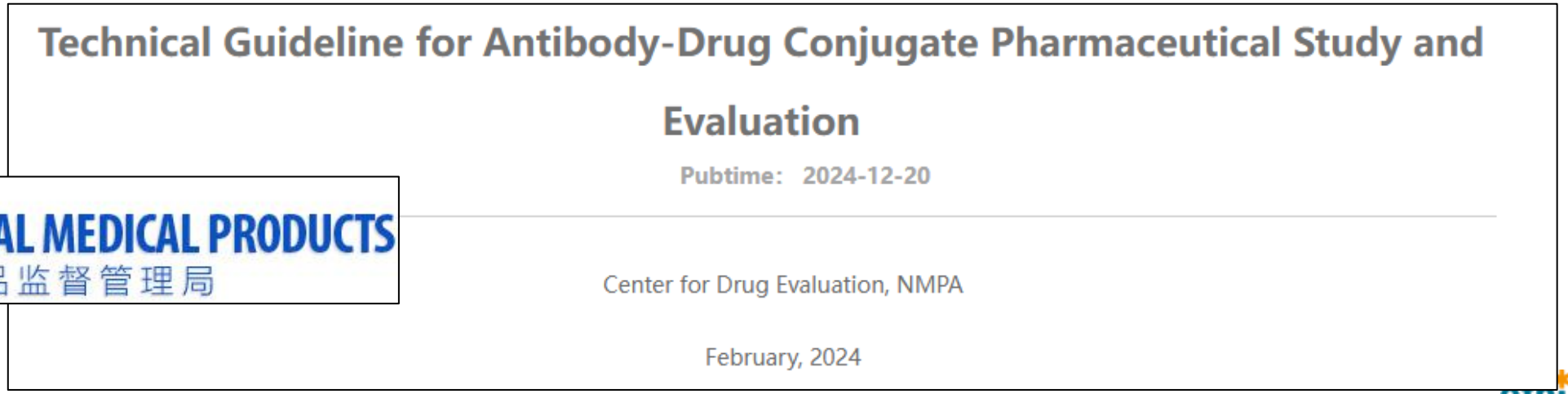
CMC Regulatory Considerations for Antibody-Drug Conjugates

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]

CDE/NMPA: Technical Guideline for Antibody-Drug Conjugate (ADC) Pharmaceutical Study and Evaluation: Overview and Scope

- Provides recommended technical requirements for ADCs to help standardize and guide development
- Includes considerations for clinical trial applications and the marketing authorization
- Focus is on “classic” ADCs with monoclonal antibodies and synthetic cytotoxic drugs linked chemically.
- Principles in the guideline may also apply to other conjugates (e.g., antibody-nuclide conjugates, polypeptide-drug conjugates, and AOCs).
- Dossier content outlined in the draft “Guideline on the Preparation of Quality Overall Summary Dossiers for Marketing Authorization Applications for Antibody-Drug Conjugates” (March 2026)



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MFDS Guideline on Quality Evaluation of ADCs: Overview and Scope

- Provides non-binding public guidance on ADC quality evaluation for regulatory review in South Korea
- Addresses ADC-specific scientific and regulatory challenges for consistent review and clarity
- Covers early development, marketing authorization, and post-approval manufacturing changes
- Focuses on “classic” ADCs with monoclonal antibodies and synthetic cytotoxic drugs linked chemically.
- Excludes emerging conjugate platforms like AOCs, ARCs, and bispecific ADCs

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National Institute of Food and Drug Safety Evaluation

항체-약물 복합체의 품질 평가 가이드라인

Guideline on Quality Evaluation of Antibody-Drug Conjugates

MFDS Guideline on Quality Evaluation of ADCs: References

1) Fu *et al.*, 2022. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduction and Targeted Therapy. 7:93.

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

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Perspective

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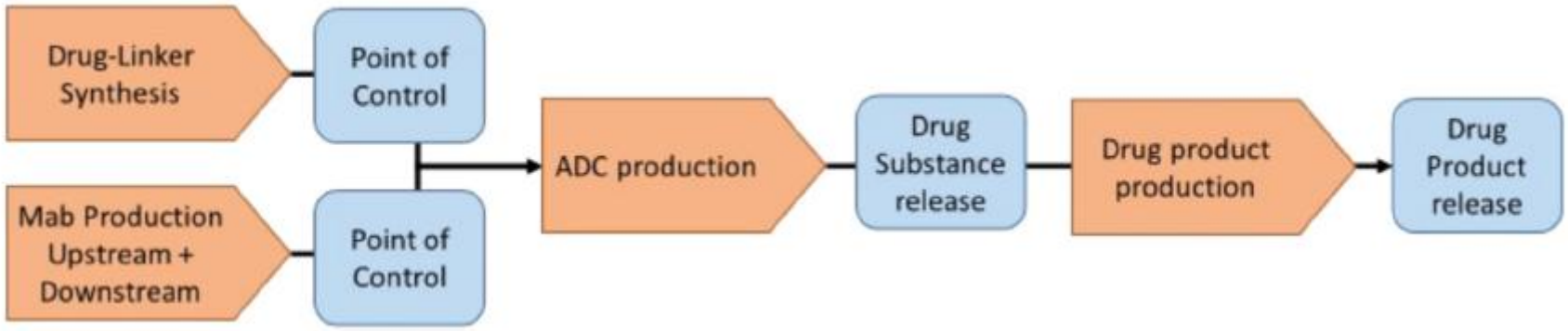
Manufacturing Process

- Both CDE and MFDS acknowledge the complexities of ADC manufacturing, involving multiple manufacturing stages

- Control strategies for the manufacturing process and purification of the antibody intermediate and drug-linker intermediate is stringent and essentially the same as for antibody drug or chemical drug substance, respectively

- The EFPIA paper lays out the flow diagram below for the manufacture of ADCs, demonstrating the multiple control points for performing analytical characterization and establishing specifications.



Manufacturing Process: Starting Materials

- Both MFDS and CDE cite ICH Q11 for considerations around drug linker development and manufacturing

- The CDE guideline explicitly refers to ICH Q11 and Q&A for the selection of starting materials
    - Key area of attention: control of any chiral centers that may impact the biological activity
    - Guideline recommends starting materials should be "comprehensively analyzed and reasonably controlled"

- Starting materials not discussed in the EFPIA paper. Refer to another key industry publication on starting materials:

Critical Quality Attributes

Source	Position

EFPIA 2023 paper	• 6 critical quality attributes essential to ADCs:
	  • Drug-to-Antibody ratio (DAR)
	  • Free Drug and Related Impurities (FDRIs)
	  • Unconjugated Antibody (DAR 0)
	  • Conjugatable small molecule impurities
	  • Antibody variants arising during conjugation
	  • Potency/biological activity
	  • Charged species.

CDE NATIONAL MEDICAL PRODUCTS 国家药品监督管理局	• Same first six as the EFPIA paper plus drug load distribution, conjugation sites, heterogeneity
MFDS MINISTRY OF FOOD AND DRUG SAFETY National Institute of Food and Drug Safety Evaluation	• The first six CQAs in the EFPIA paper

Specifications

Source	Position
MFDS 	• CQAs by manufacturing/development stage detailed (see next slide) • Specifications may be set based on process capability, structure-function relationship studies, historical data, stability data, compendial monograph requirements, clinical suitability • Acceptance criteria should be clearly defined by the approval stage based on development data, batches used in nonclinical and clinical studies and stability data
CDE 	• Specifications for ADC DS and DP generally include description (such as appearance, color), identification, DAR and drug load distribution, purity and impurities, biological activity, assay, general tests, etc • Acceptance criteria should be based on product characteristics, non-clinical exposure and clinical trial exposure, data of batches used for each stage of the study, inter-batch consistency data, and stability data
EFPIA paper	• Quality attributes of the mAb intermediate, DL intermediate, DS, and DP are described (see next slide)

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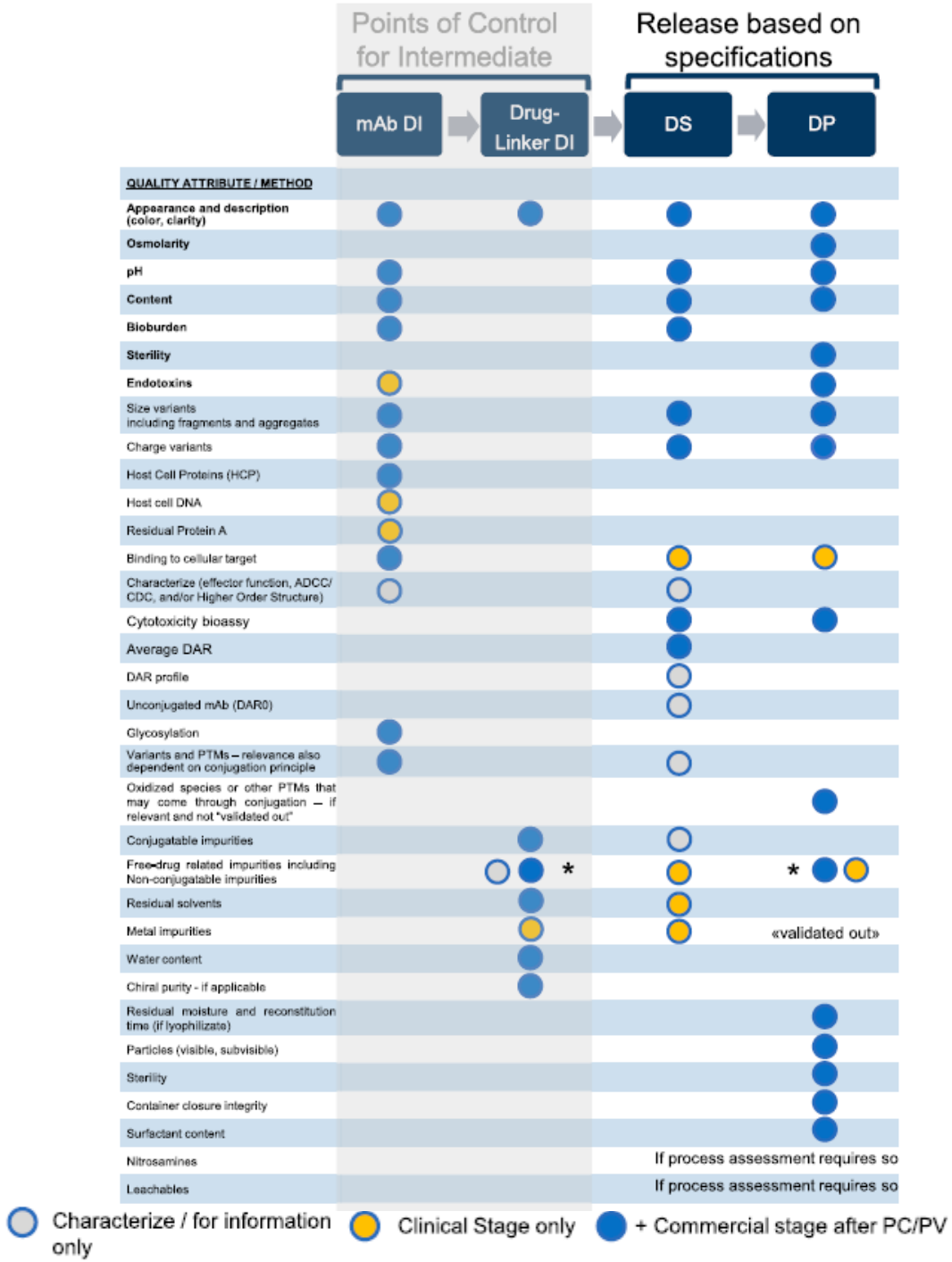
Quality attributes/assay parameters		Manufacturing stage			
		Antibody	Drug-linker	Drug substance	Drug product
Structure (primary, higher-order, PTM)		▲ ◆		▲ ◆	
Glycosylation		▲ ◆		▲ ◆	
Identity		● ■	● ■	● ■	● ■
Content assay		● ■	● ■	● ■	● ■
Purity	Antibody size variants	● ■ ▲ ◆		● ■ ▲ ◆	● ■ ▲ ◆
	Antibody charge variants	● ■ ▲ ◆		● ■ ▲ ◆	● ■ ▲ ◆
Potency	Antibody binding affinity	● ■ ▲ ◆		● ■ ▲ ◆	● ■ ▲ ◆
	Antibody effector function	▲ ◆		▲ ◆	
	Cytotoxicity			■ ◆	■ ◆
Impurities	Residual host cell proteins	● ■ ◆			
	Residual host cell DNAs	● ■ ◆			
	Residual amount of protein A	● ■ ◆			
	Conjugatable small molecule impurities		● ■ ◆	▲ ◆	
	Free drug and related impurities			● ■ ◆	● ■
	Residual solvents		● ■ ◆	● ◆	
	Elemental impurities		● ■ ◆	● ◆	
DAR	Average			● ■ ▲ ◆	
	Profile			● ▲ ◆	
	Unconjugated antibody (DAR 0)			● ▲ ◆	
Appearance		● ■ ◆	● ■ ◆	● ■ ◆	● ■ ◆
pH		● ■ ◆		● ■ ◆	■ ◆
Microbial limit		● ■		● ■	
Endotoxin		●		● ■	● ■
Sterility					● ■
Moisture content			● ■ ◆		● ■ ◆
Surfactant assay					● ■ ◆
Foreign insoluble matter and insoluble particulate matter					● ■ ◆
Uniformity of dosage units or extractable volume					● ■

● Parameters for quality control at the clinical stage (clinical batch), ■ Parameters for quality control at the approval stage (commercial production-scale batch), ▲ Parameters for characterization, ◆ Parameters for manufacturing process change



Drug-to-Antibody Ratio (DAR)

Source	Position
MFDS MINISTRY OF FOOD AND DRUG SAFETY National Institute of Food and Drug Safety Evaluation	• Demonstrate consistent DAR through adequate characterization • Manufacturing parameters like drug-linker concentration must be tightly controlled to ensure reproducible DAR.

CDE
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	• CDE details the methods used to evaluate DAR:
	  • Hydrophobic interaction high performance liquid chromatography (HIC-HPLC)
	  • reverse-phase high performance liquid chromatography (RP-HPLC)
	  • MS

EFPIA 2023 paper	• A key quality attribute for drug substance comparability studies

Free Drug and Related Impurities (FDRIs)

Source	Position
MFDS 	• Requires risk assessment, toxicity evaluation, and monitoring via stability and stress studies to control FDRIs • FDRIs should proactively managed, not retrospectively justified
CDE 	• Recommends understanding the fate and purge of small molecule-related impurities and establishing a reasonable control strategy
EFPIA 2023 paper	• Describes considerations for the control of FDRIs, including patient risk and thorough process and product understanding • Suggests that the test for FDRIs may be removed from routine control if low levels are consistently observed during development and process validation

Conjugatable impurities

Source	Position
MFDS 	• Recommends structured assessments to evaluate the safety and efficacy impact of conjugatable small-molecule impurities. • MFDS uses the following calculation to estimate impurity levels from drug-linker to final ADC (assuming 100% conjugation): $y(\%) = x(\%) \times DAR \times \text{Molecular weight of drug-linker} / \text{Molecular weight of ADC}$ • For example, for a drug linker with a molecular weight of 4 kDa and an ADC of 160 kDa and a DAR of 2, if a conjugatable impurity in the drug linker is 3%, the level in the resulting ADC will be ≤ 0.15%
CDE 	• Guidance recommends formulating “strict control criteria” for conjugatable impurities because they can be difficult to quantify and remove after the completion of the conjugation reaction. • The draft QOS guideline recommends providing a strategy for further investigation and control” when control levels of impurities are above ICH Q3A
EFPIA 2023 paper	• Takes a risk-based approach to the control of conjugatable impurities and the mass-dilution of the drug-linker intermediate relative to the final ADC product • Assure patient safety by controlling conjugated impurities to a level that assures exposure will never exceed ICH Q3A level in DS or DP $DS\ Impurity\% = Intermediate\ Impurity\% \times DAR \times \frac{Intermediate\ MW}{DS\ MW}$

Unconjugated mAb (DAR 0)

Source	Position
MFDS 	• Levels of unconjugated antibody should be controlled • Low and consistent DAR 0 levels may be excluded from routine testing if justified
CDE 	• Select appropriate analytical methods to monitor the percentage of unconjugated naked antibody based on properties of the conjugated payload (such as charge, hydrophobicity)
EFPIA 2023 Paper	• May not need to have a test for unconjugated mAb in the ADC DS or DP if there are low or reproducible levels during product/process characterization

mAb Size and Charge Variants

Source	Position
MFDS 	• Guideline highlights size variants like aggregates and charge variants impact stability, target binding affinity and efficacy.
CDE 	• Recommends using appropriate methods to separate and/or identify product-related impurities, evaluate their safety risks, and design an appropriate control strategy • For studying molecular size variants, the guideline recommends using size exclusion chromatography (SEC-HPLC), capillary electrophoresis sodium dodecyl sulfate (CE-SDS), size exclusion multi-angle light scattering (SEC-MALS), AUC, dynamic light scattering (DLS), particle measurements, and LC-MS • For charge variants, the guideline recommends methods such as capillary zone electrophoresis (CZE), ion exchange chromatography (IEX-HPLC), capillary isoelectrofocused electrophoresis (CIEF), or whole-column imaging capillary isoelectrophoresis (iCEF) • Recommends understanding the types and levels of aggregates and to product-related impurities
EFPIA paper	• Recommends evaluating size variants (fragments, higher order structures/aggregates) for the mAb intermediate, DS, and DP

Potency

Source	Position
MFDS MINISTRY OF FOOD AND DRUG SAFETY National Institute of Food and Drug Safety Evaluation	• Potency assessment should include antibody binding activity and cell-based cytotoxicity assays reflecting ADC mechanism of action. • Fc-mediated functions like ADCC and CDC are evaluated only when clinically relevant, avoiding unnecessary tests
CDE NATIONAL MEDICAL PRODUCTS 国家药品监督管理局	• Biological activity assays should reflect the mechanism of action of the ADC • For cell-based bioassays, appropriate cell lines expressing the target antigens should be selected • Recommends ELISA, surface plasmon resonance or biolayer interferometry to evaluate the binding activity • Recommends carrying out biological activity assessment if Fc-mediated effector function (ADCC, CDC, ADCP, etc.) may affect the efficacy of the drug or show nonspecific toxicity associated with the effector binding function
EFPIA paper	• Argues that a binding assay should be acceptable in early development when a cell-based functional assay may not be available • For late-stage development, a cell-based potency assay should be in the specification • Recommends evaluating effector functions only if they are part of the MOA

Comparability: Attributes

Source	Position
MFDS MINISTRY OF FOOD AND DRUG SAFETY National Institute of Food and Drug Safety Evaluation	• MFDS expects a risk-based method to manage manufacturing changes while maintaining product integrity • Comparability is applied at antibody, drug-linker, drug substance, or drug product levels based on change impact. • Comparability studies should be proportional to risk, avoiding unnecessary tests but ensuring safety and efficacy. • Key Attributes to Assess: DAR, impurity profiles, potency, and stability are critical in comparability assessments.
CDE NATIONAL MEDICAL PRODUCTS 国家药品监督管理局	• Conduct comparability studies according to the principles in ICH Q5E • May be necessary to perform comparative studies or production-scale process qualification on the ADC DS or DP following changes to the drug linker or antibody intermediates
EFPIA paper	• Details risk-based framework and decision trees for evaluating process changes

Comparability: Phase Considerations

Source	Position
MFDS	• Comparability studies in early development can be conducted with a single batch
CDE	• Comparability studies can be based on data from limited batches, but pay attention to attributes related to safety and efficacy (DAR, impurity profile, biological activity) • Comparability studies should be more extensive in later stages of development
EFPIA paper	• Comparability studies should be phase appropriate: early phase studies should focus on safety (impurities) and potency (DAR profile), for late stage, CQAs related to safety, efficacy, quality, and stability should be included.

Stability

Source	Position
MFDS	• Expectations not detailed
CDE	• References ICH Q1 • Forced degradation studies and study of the risk of protein instability, • Highlights risk of protein instability and the need to pay attention to aggregation and particle formation
EFPIA paper	• Stability discussed only in the context of comparability studies

Dossier Considerations

- Both MFDS and CDE recommend separate drug substance sections for the drug-linker and the antibody
- Proposed CTD structure are aligned to EFPIA proposal (below)

Option B

3.2.S - DL DI
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 - mAb DI
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 - DS
S.1 – DS
S.2 – DS
S.3 – DS
S.4 – DS
S.5 – DS
S.6 – DS
S.7 – DS

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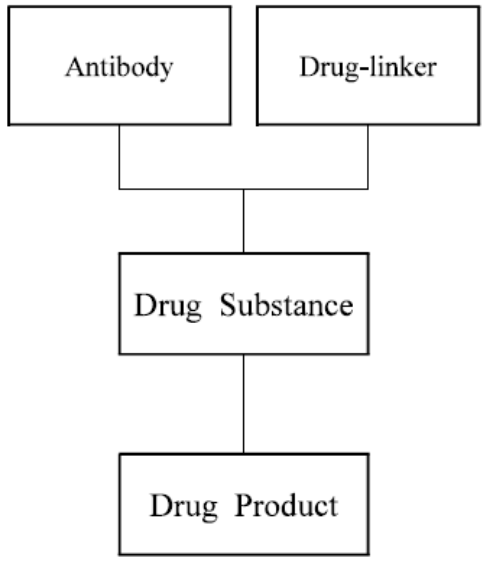
[Appendix 2] Composition of the CTD for Quality Dossiers



3.2.S. Antibody
3.2.S.1. General Information
3.2.S.2. Manufacture
3.2.S.3. Characterization
3.2.S.4. Control of Drug Substance
3.2.S.5. Reference Standards or Materials
3.2.S.6. Container Closure System
3.2.S.7. Stability

3.2.S. Drug-Linker
3.2.S.1. General Information
3.2.S.2. Manufacture
3.2.S.3. Characterization
3.2.S.4. Control of Drug Substance
3.2.S.5. Reference Standards or Materials
3.2.S.6. Container Closure System
3.2.S.7. Stability

3.2.S. Drug Substance
3.2.S.1. General Information
3.2.S.2. Manufacture
3.2.S.3. Characterization
3.2.S.4. Control of Drug Substance
3.2.S.5. Reference Standards or Materials
3.2.S.6. Container Closure System
3.2.S.7. Stability

3.2.P. Drug Product
3.2.P.1. Description and Composition
3.2.P.2. Pharmaceutical Development
3.2.P.3. Manufacture
3.2.P.4. Control of Excipients
3.2.P.5. Control of Drug Product
3.2.P.6. Reference Standards or Materials
3.2.P.7. Container Closure System
3.2.P.8. Stability

* A flexible format can be applied through consultation with the Ministry of Food and Drug Safety

Clinical Development Considerations

- Both guidelines discuss the evolution of manufacturing processes, specifications and control strategies over the course of development
- Both guidelines detail increasing expectations as process understanding and development phase increase

Clinical Development Considerations: Early-Stage

MFDS	CDE
• Recommends establishing tests for identity, content, purity, and potency • Specifications can be less rigorous for early phase studies	• Recommends control of adventitious agents, viral safety, microbial safety, sterility • Specifications based on platform experiences, product knowledge and multi-batch testing • Expectation of reasonable control of impurities, with the non-clinical studies serving as an important reference • Preliminary stability studies • Comparability studies can be conducted on limited batches

Clinical Development Considerations: Late-Stage

MFDS	CDE
• For pivotal studies: Use fully validated analytical methods and justified specifications • Clearly define upper limits for product and process-related impurities	• For the marketing application: Critical process procedures and critical process parameters determined, control of CQAs

Conclusions

- Both CDE and MFDS provide clear guidelines for ADC-specific CMC and quality evaluation emphasizing patient safety and consistency
- Both CDE and MFDS outline expectations for quality control during development, in the marketing application and for managing post-approval changes
- Understanding and aligning with the guideline can reduce regulatory risk and support efficient global ADC development

Reflections

- **Harmonization**
  - Will other regions issue ADC-specific guidelines?
  - What will the revised ICH Q6 include for ADCs?
  - Do we need an ICH guideline specific to ADCs?

- **Scope:** Guidelines were written with “classic” ADCs with oncology indications in mind
  - What happens when the field broadens to other clinical indications with different types of payloads?
  - What (if anything) needs to change to enable these newer modalities?

THANK YOU