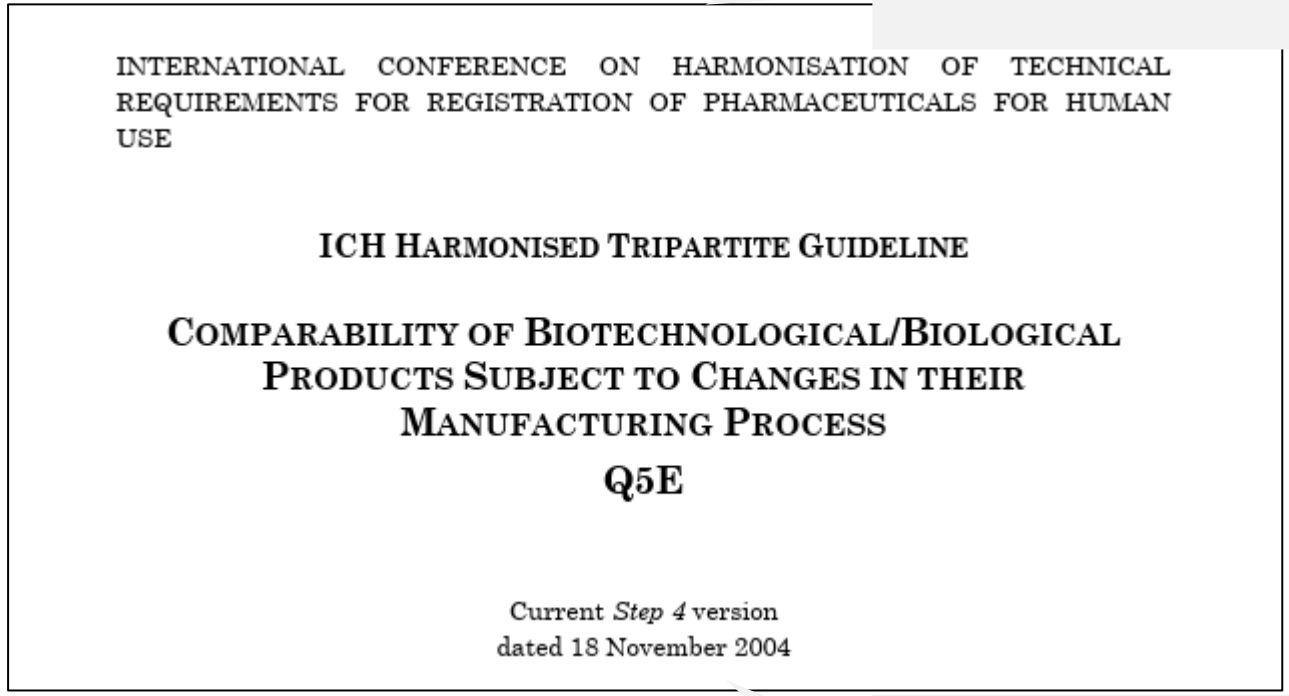
Beyond One-Size-Fits-All:
Experiences with Comparability Strategies for ADCs

Katie Duncan, Ph.D.
Director, CMC Policy and Advocacy
GSK

Comparability Basics: ICH Q5E

The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

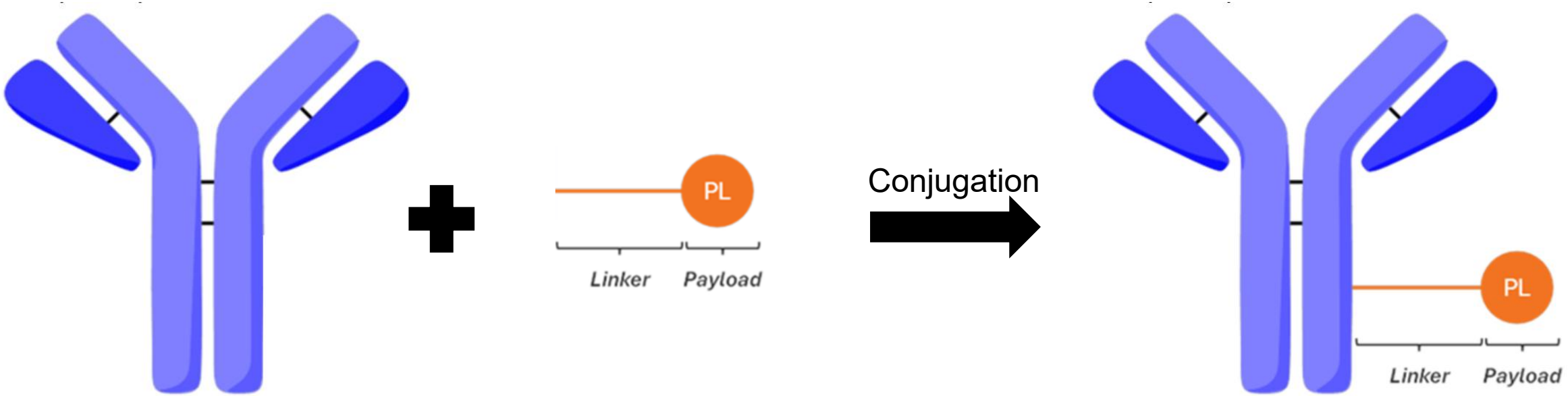
COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

Q5E

Current *Step 4* version
dated 18 November 2004

The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

Antibody-Drug Conjugates



Accelerated Development Timelines

Complex Supply Chains

Unclear Comparability Expectations

GSK

Analytical Comparability Demonstration at the Point of Change

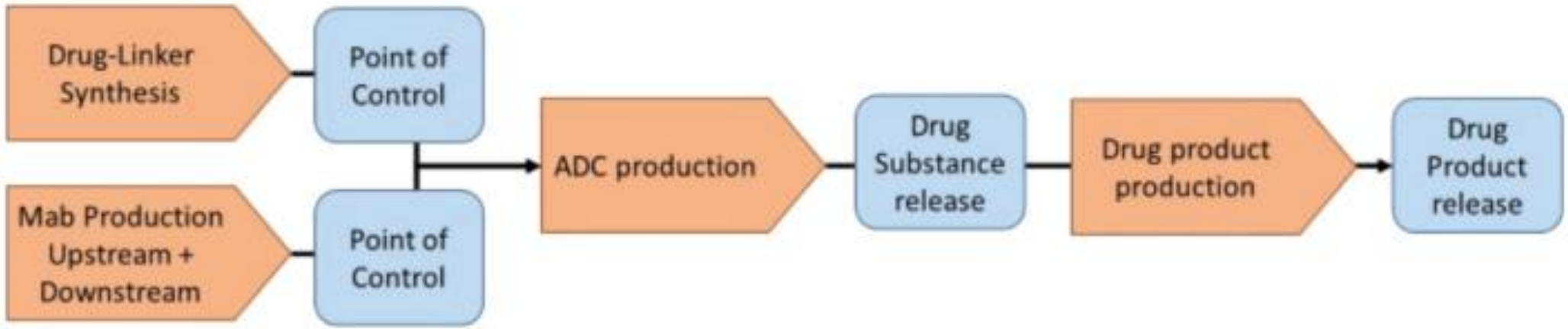


Figure 3. Example of components of an ADC production and control strategy (other sequences of processes possible).

- Comprehensive comparative analytical assessment typically includes:
  - Release testing
  - Characterization testing
  - Stability data
  - Forced degradation

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

Analytical Comparability: Key Attributes

- Purity/Impurity profile: drug-linker related impurities, residual solvents, heavy metals, water content, chiral purity (if applicable)

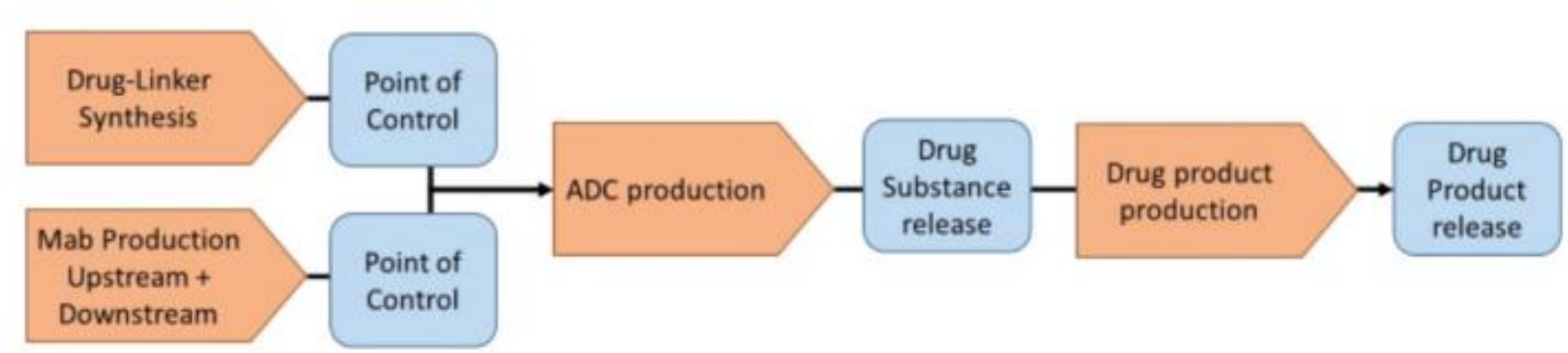


Figure 3. Example of components of an ADC production and control strategy (other sequences of processes possible).

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

Analytical Comparability: Key Attributes

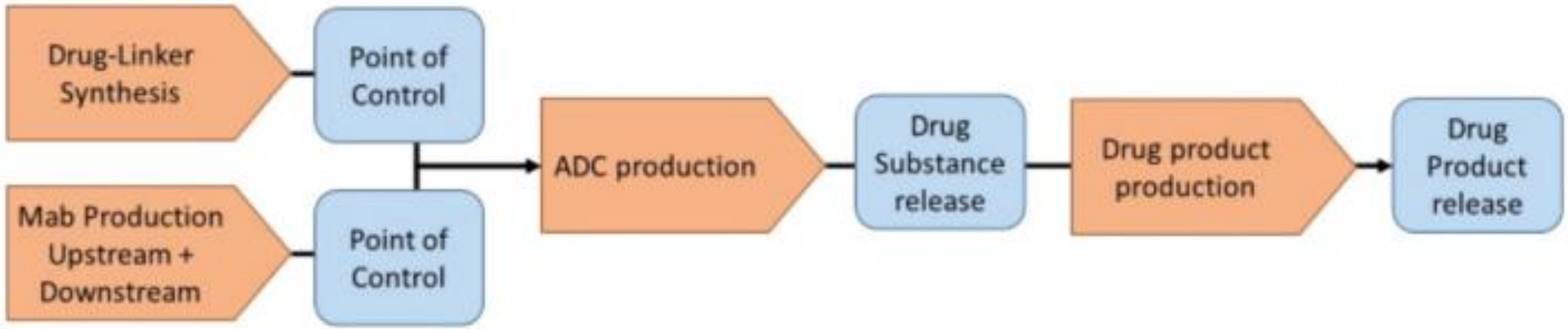


Figure 3. Example of components of an ADC production and control strategy (other sequences of processes possible).

- Appearance
- Purity/Impurity profile: size variants, charge variants, HCP, host cell DNA, residual Protein A
- Biological activity: binding, effector functions (if relevant)
- Primary Structure: amino acid sequence, glycosylation, PTMs

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

Analytical Comparability: Key Attributes

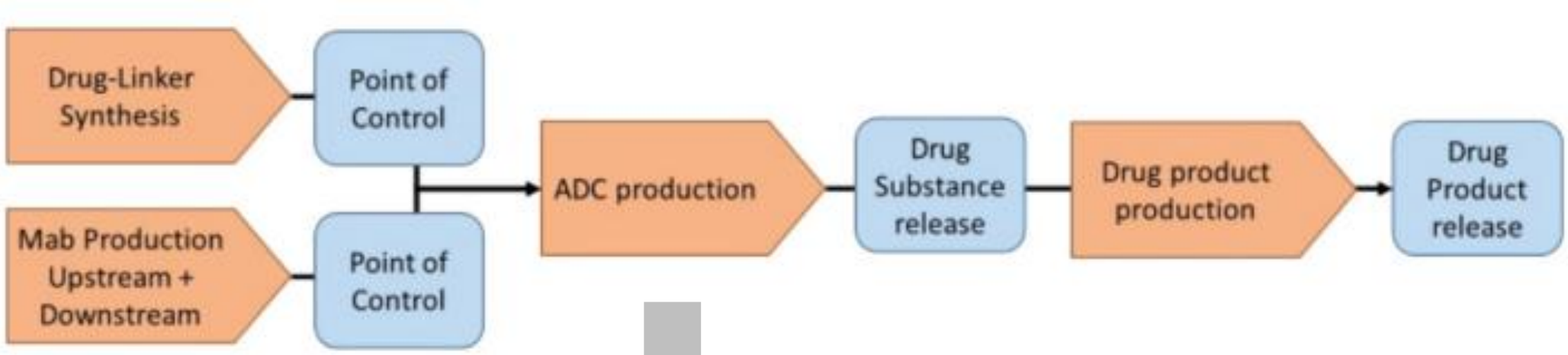


Figure 3. Example of components of an ADC [illegible]ction and control strategy (other sequences of processes possible).

- Appearance
- 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

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

Analytical Comparability: Key Attributes

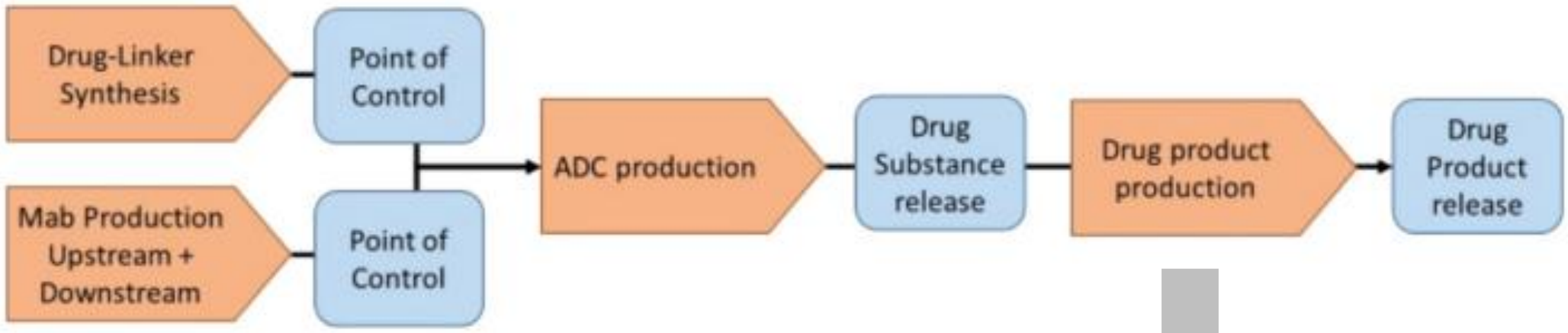


Figure 3. Example of components of an ADC production and control strategy (other sequence[illegible]rocesses possible).

- Appearance
- 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

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

Phase Appropriate Comparability

- Comparability approaches depend on the:
  - Phase of development
  - Extent of the change and the impact on critical quality attributes (product quality, safety and efficacy)
  - Availability of pre- and post-change material
  - Analytical method development

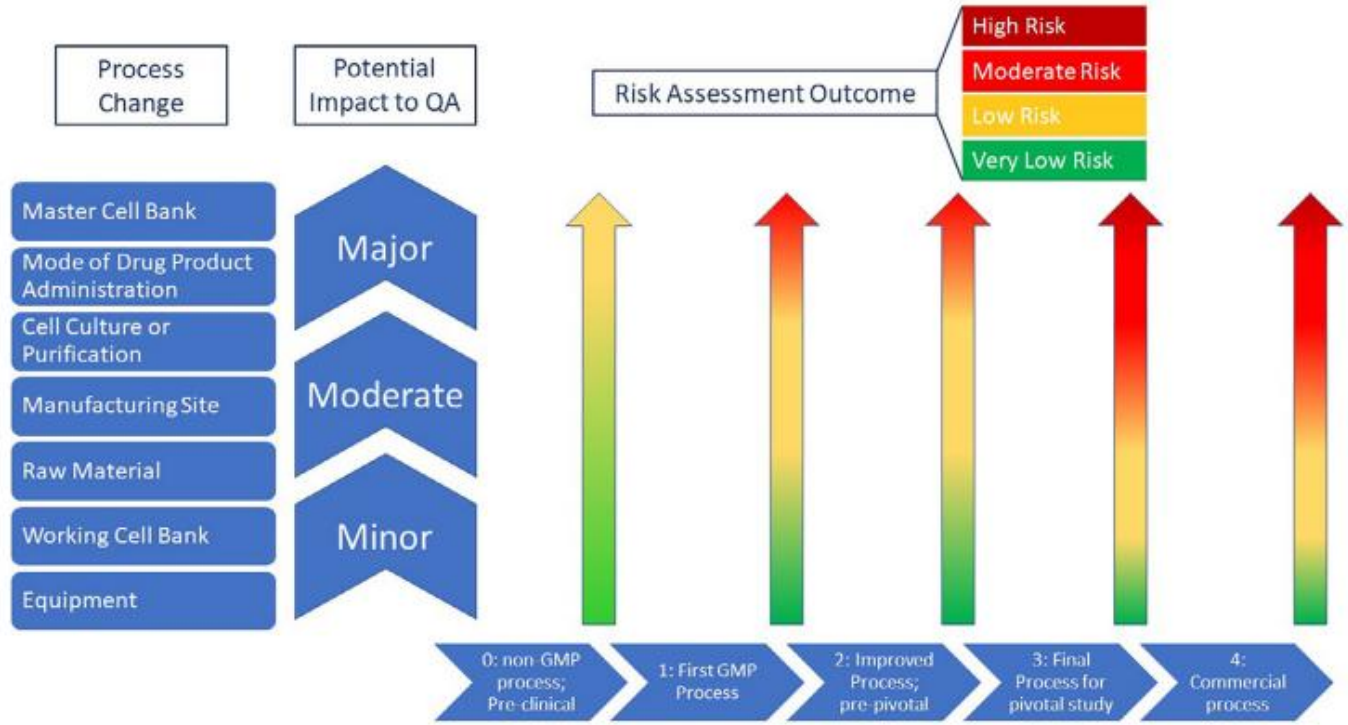
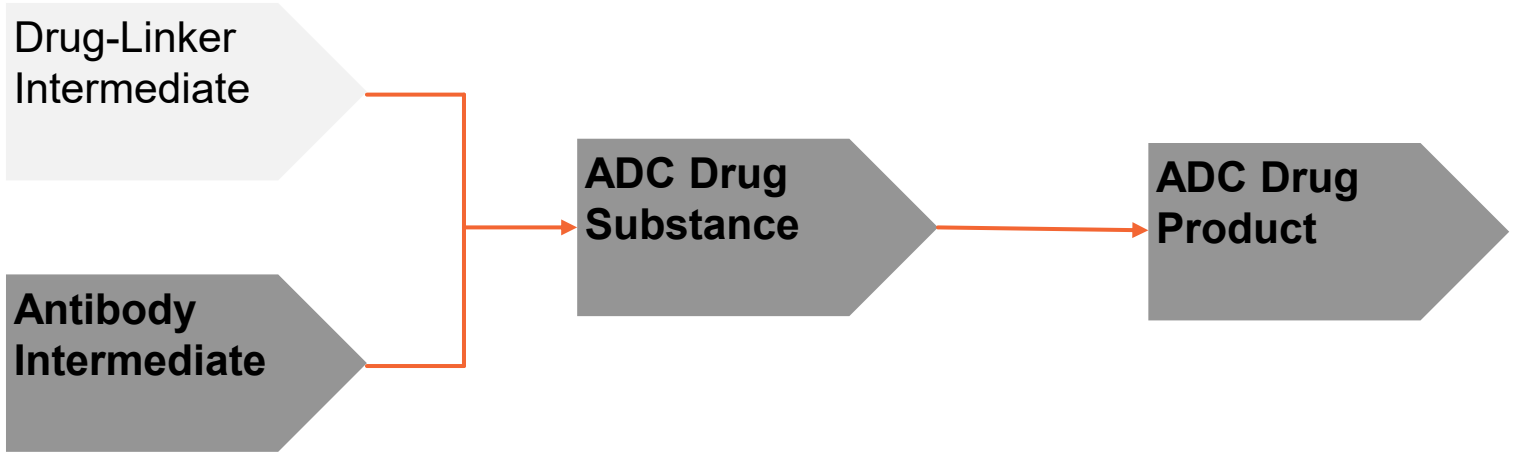


Figure 2. Comparability risks at different stages of clinical development.

Blümel, M. et al, Patient-centric Comparability Assessment of Biopharmaceuticals. *Journal of Pharmaceutical Sciences.* **2024,** 113, 1415-1425.

Case Studies

Case Study #1: Introducing Two New Supply Chains during Phase 3



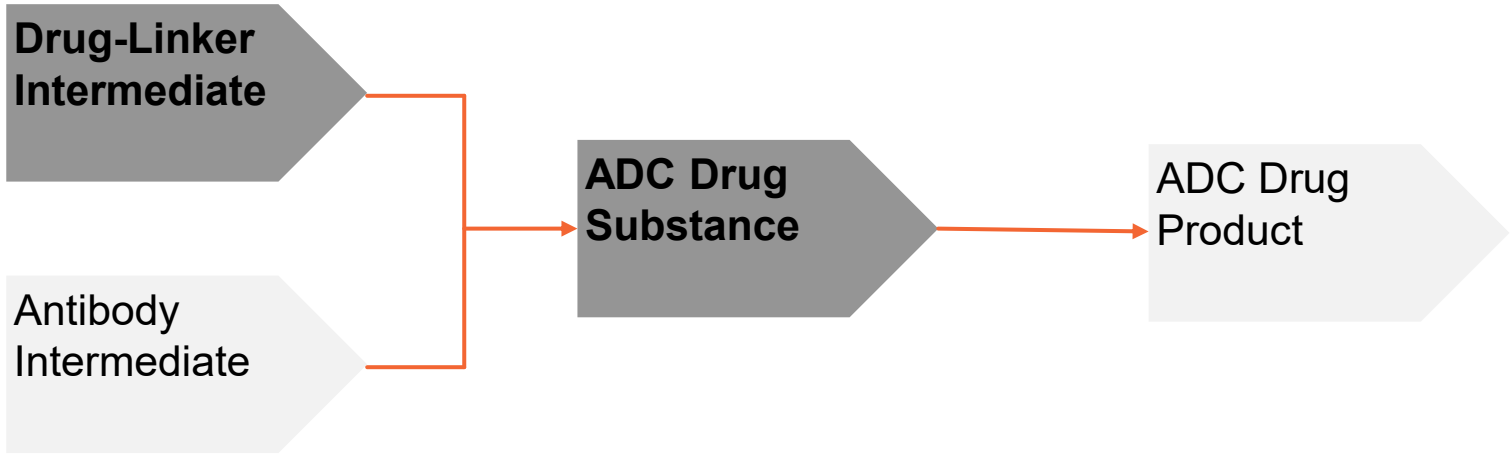
Node	Supply Chain 2	Supply Chain 3
Drug-linker Intermediate	No changes	No changes
Antibody	Manufacturing site, scale up and facility fit	Change in MCB, Manufacturing site, facility fit
Drug Substance	Manufacturing site, facility fit, scale up,	Manufacturing site, minor process changes, scale up
Drug Product	Scale up	Manufacturing site, facility fit and scale up

Case Study #1: Proposed Testing Strategy and Regulatory Feedback

	Batches		Testing Proposed			
	Supply Chain 1 x Supply Chain 2 x Supply Chain 3					
	In the IND/CTA	In the BLA/MAA	Extended Characterization	Batch Release	Stability	Forced Degradation
Antibody	3 x 3 x 3	3 x 3 x 3	✓	✓	✓	✓
Drug Substance	3 x 3 x 3	3 x 3 x 3	✓	✓	✓	✓
Drug Product	3 x 3 x 1	3 x 3 x 3	✓	✓	✓	✓

- Regulatory feedback: strategy appears reasonable

Case Study #2: Introducing New Drug Linker Manufacturing Site and Drug Substance Scale Up in Phase 3



Node	Change
Drug-linker Intermediate	Manufacturing site, scale up and facility fit
Antibody	No change
Drug Substance	Scale up
Drug Product	No change

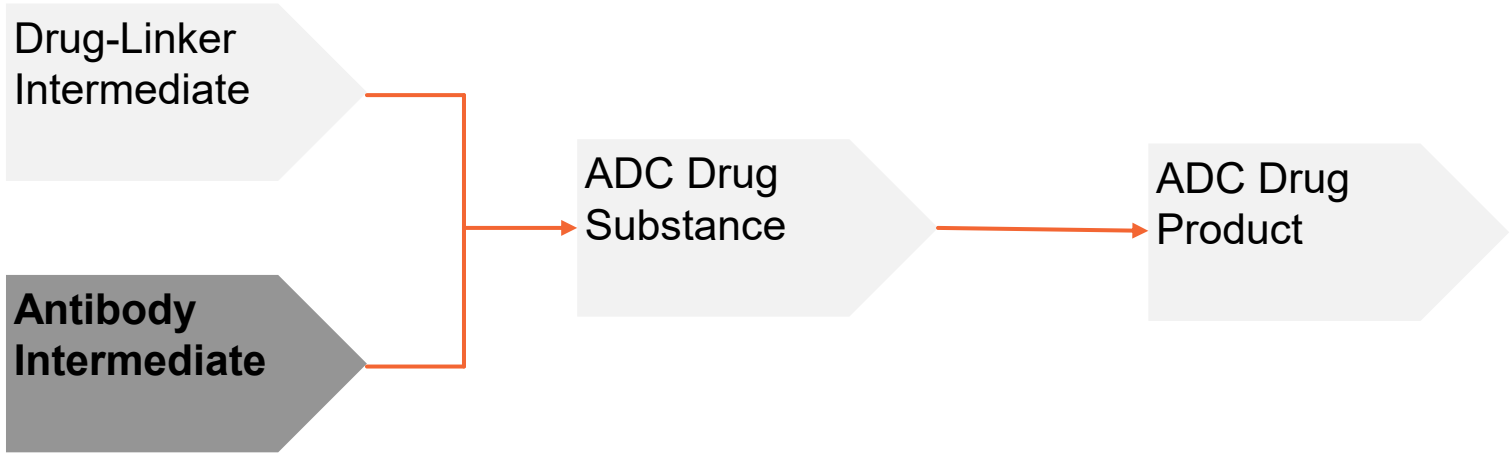
Case Study #2: Proposed Testing Strategy and Regulatory Feedback

	Batches Pre-change x Post-change		**Testing Proposed**			
	In the IND/CTA	In the BLA/MAA	Extended Characterization	Batch Release	Stability	Forced Degradation
Drug Linker	1 x 1	3 x 3	✗	✓	✓ **(3 months)**	✗
Drug Substance	1 x 1	1 x 1	✓	✓	✓ **(3 months)**	✓

- Regulatory feedback: strategy appears reasonable

GSK

Case Study #3: Introducing a New Working Cell Bank for Commercial Supply



Node	Change
Drug-linker Intermediate	No changes
Antibody	Introduction of a new WCB
Drug Substance	No changes
Drug Product	No changes

Case Study #3: Proposed Comparability Testing Strategy

	Batches	**Testing Proposed**			
	Pre-change x Post-change	Extended Characterization	Batch Release	Stability	Forced Degradation
Antibody Intermediate	3 x 3	✘	✓	✘	✘
Drug Substance	No testing	✘	✘	✘	✘

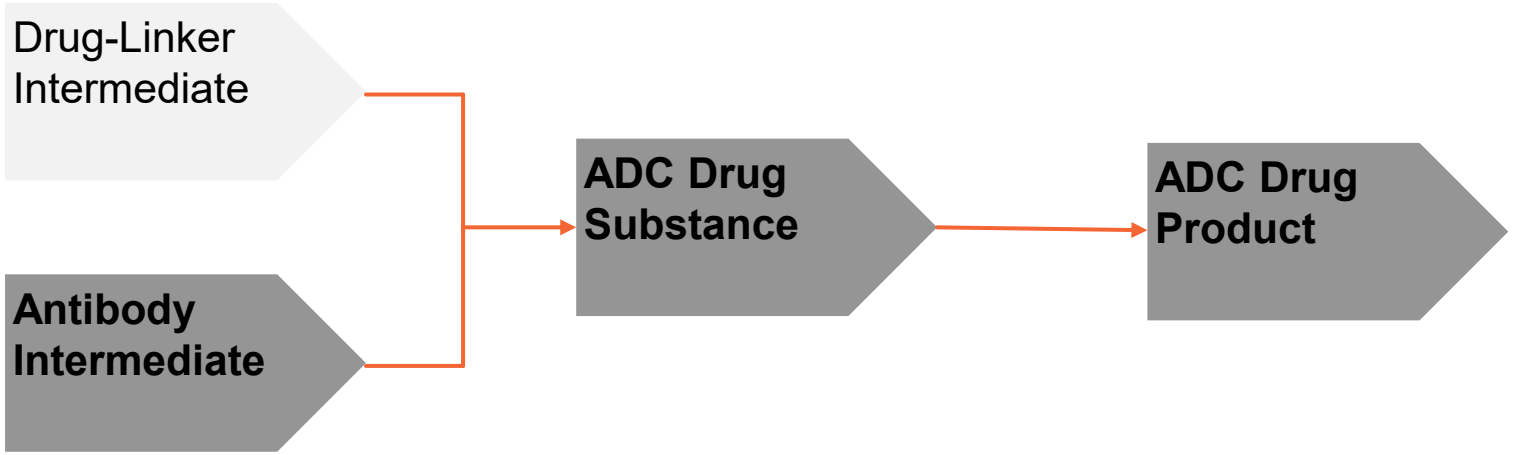
GSK

Case Study #3: Regulatory Feedback and Updated GSK Strategy

- Health Authory 1: Comparability assessment for the antibody should include comparison of the extended characterization and stability/degradation profile. Include at least one drug substance batch to the study
- Health Authority 2: Approach appears reasonable
- Revised analytical comparability strategy:

	Batches	**Testing Proposed**			
	Pre-change x Post-change	Extended Characterization	Batch Release	Stability	Forced Degradation
Antibody	3 x 3	✘ → ✓	✓	✘ → ✓	✘
Drug Substance	No testing → 1 x 1	✘	✘ → ✓	✘ → ✓	✘

Case Study #4: Introducing a New Supply Chain in Phase 3



Node	Change
Drug-linker Intermediate	No changes
Antibody	Manufacturing site, facility fit and process optimization (minor)
Drug Substance	Manufacturing site, scale up
Drug Product	Manufacturing site, facility fit and process optimization (minor), scale up

Case Study #4: Proposed Comparability Strategy

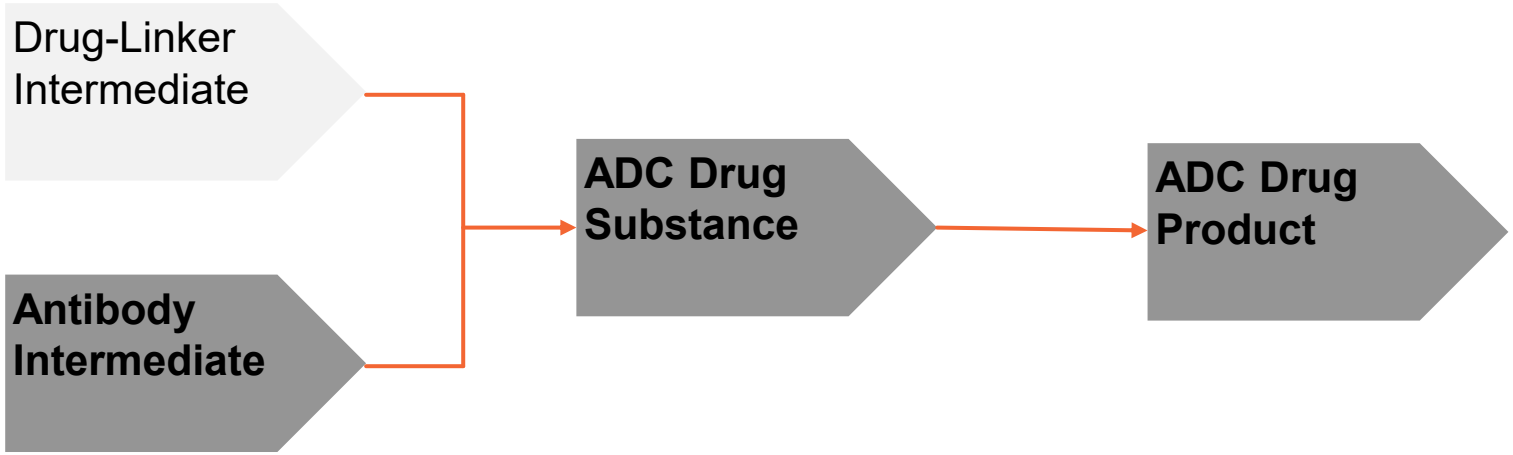
	Batches	**Testing Proposed**			
	Pre-change versus Post-change	Batch Release	Extended Characterization	Stability	Forced Degradation
Antibody	1x1	✓	✓	✓ **(3 months)**	✓
Drug Substance	1x1	✓	✓	✓ **(3 months)**	✓
Drug Product	1x1	✓	✗	✓ **(1 month)**	✗

Case Study #4: Regulatory Feedback and Updated GSK Strategy

- Health Authory 1: 1 pre and post-change batch is not sufficient; include all batches of pre-change and post-change material into the comparability exercise
- Health Authority 2: Proposal appears reasonable at the current phase of development
- Revised analytical comparability strategy:

	Batches	**Testing Strategy**			
	Pre-change x Post-change	Batch Release	Extended Characterization	Stability	Forced Degradation
Antibody	1x1 → 2x2	✓	✓	✓ **(3 months)**	✓
Drug Substance	1x1 → 2x2	✓	✓	✓ **(3 months)**	✓
Drug Product	1x1 → 2x2	✓	✗	✓ **(1 month)**	✗

Case Study #5: Introducing a New Supply Chain Post Approval



Node	Change
Drug-linker Intermediate	No changes
Antibody	Manufacturing site, facility fit and process optimization (minor)
Drug Substance	Manufacturing site, facility fit and scale up
Drug Product	Manufacturing site, facility fit and process optimization (minor)

Case Study #5: Proposed Comparability Strategy

	Batches	**Testing Proposed**			
	Pre-change x Post-change	Batch Release	Extended Characterization	Stability	Forced Degradation
Antibody	3 x 3	✓	✓	✓ **(3 months)**	✓
Drug Substance	3 x 3	✓	✓	✓ **(3 months)**	✓
Drug Product	2 x 2	✓	✓	✓ **(3 months)**	✓

Case Study #5: Regulatory Feedback and Updated GSK Strategy

- Health Authority 1: A minimum of 6 months of stability data should be provided and data from three drug product batches should be provided
- Health Authority 2: Requested 6 months of stability data

	Batches	**Testing Proposed**			
	Pre-change x Post-change	Batch Release	Extended Characterization	Stability	Forced Degradation
Antibody	3 x 3	✓	✓	✓ **(3 months)** → 6 months	✓
Drug Substance	3 x 3	✓	✓	✓ **(3 months)** → 6 months	✓
Drug Product	2 x 2 → 3 x 3	✓	✓	✓ **(3 months)** → 6 months	✓

Conclusions

- Health authorities recommend implementing major changes to manufacturing processes before the start of the pivotal clinical studies.
- A risk assessment on the proposed change and its potential impact on product quality is recommended
- Recommend early discussions with regulators
- Variable HA feedback on proposed comparability is common
- Potential for reduction of comparability data sets possible: may not need to provide a comparison of 3 pre-change and 3 post-change batches at all stages of development

gsk.com