Regulatory perspectives on comparability evaluation of Antibody-Drug Conjugates (ADCs)

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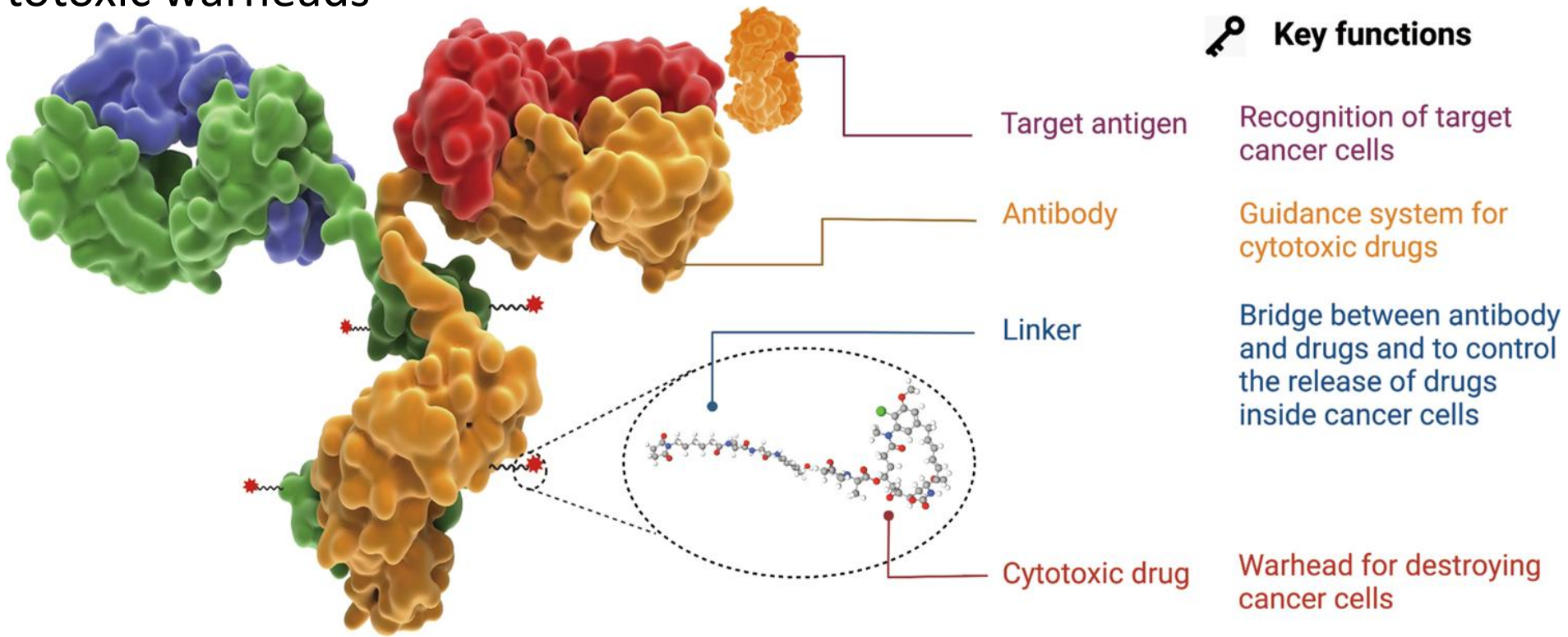
Antibody-Drug Conjugates

- **"Seek & Destroy"** concept
- "Homing missile" combining the precision of antibody with the potency of cytotoxic warheads



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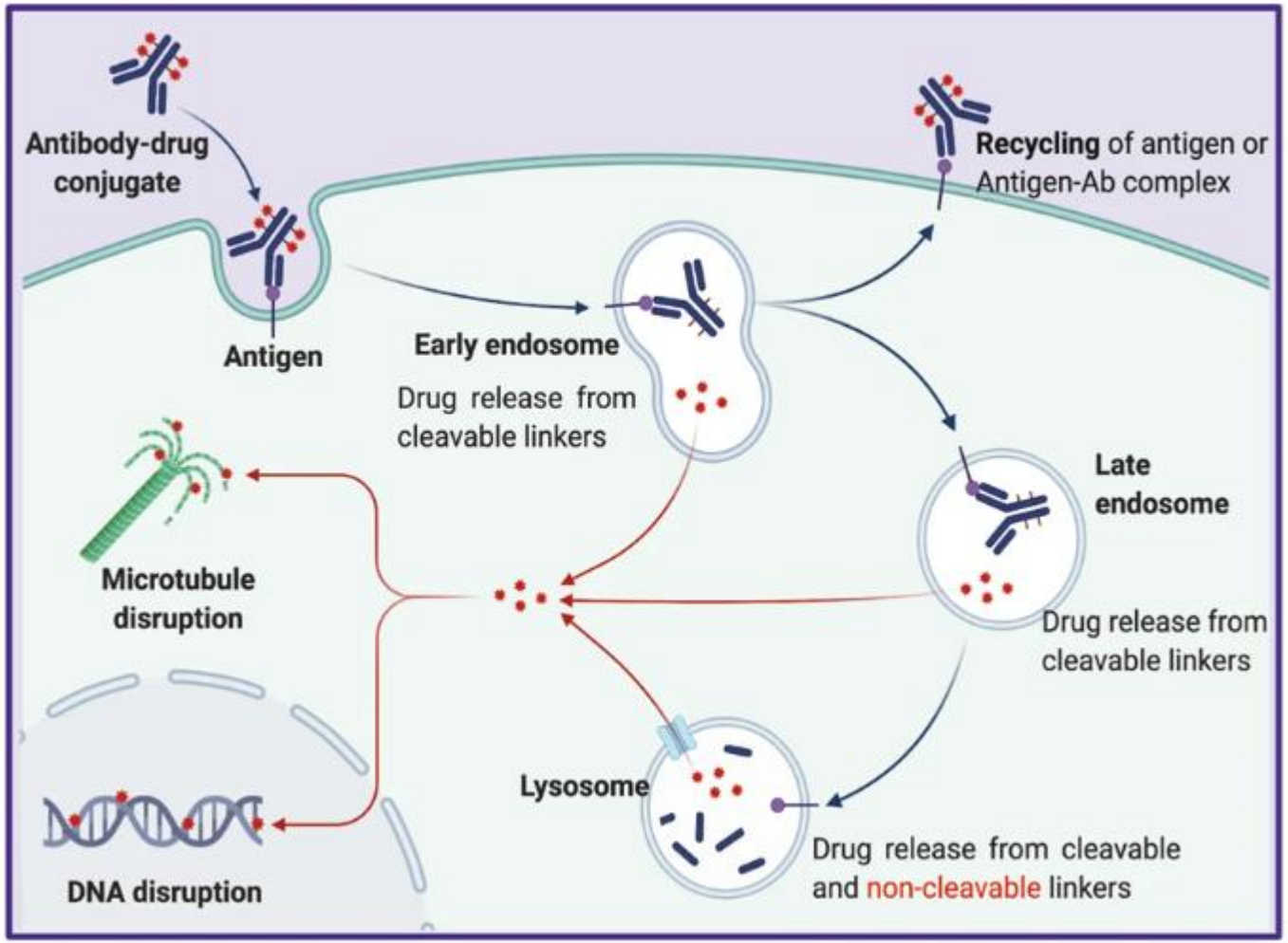
Core Mechanism of Action

- Targeting & Internalization
- Cleavage & Release
- Cytotoxic activity
- Apoptosis
- "Bystander" effect

mAb contributing effects:
ADCC, CDC, ADCP, interference with a target function



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Analytical comparability

- Manufacturing process changes are an inherent part of CMC development
- Demonstration of comparability is essential both throughout clinical development and post-approval
- ICH Q5E principles shall apply but specific guideline for ADCs is absent

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

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Challenges in comparability demonstration

- Comparability demonstration is recognized as one of key challenges in ADC development
- Efforts to develop refined comparability strategy to streamline development without impact on quality, safety or efficacy
- Requires relying on risk-based approach and leveraging the product specific and platform knowledge

Dual nature of the molecule
Combining requirements for biological and small molecule

Complexity
Molecular heterogeneity arising from biological molecule and conjugation sites/payload species distribution

Limited data
Limited batch availability during decoupled manufacturing strategies

Industry position: Risk-based approach

- *If comparability can be demonstrated **at the point of change** 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*

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Perspective

CMC Regulatory Considerations for Antibody-Drug Conjugates

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Industry position: Process stage specific comparability evaluation

- QAs recommended for comparability studies at different stages (mAb, drug-linker, DS, DP)
- Evaluation of process changes at the specific **"point of control"** where the change occurs

Manufacturing stage	Quality attributes
Drug-linker intermediate	▪ General test such as Appearance ▪ Purity / Impurity profile ➢ Drug-linker related purity & impurities (as appropriated by e.g. UV, IR, NMR, MS, elemental analysis,…) ➢ Residual solvent ➢ Heavy metals ➢ Water content ➢ Chiral purity if applicable
mAb intermediate	▪ General test such as Appearance ▪ Purity/Impurity ➢ Size variants (fragments and High Order Structures / aggregates) ➢ Charge variants ➢ HCP ➢ Host cell DNA ➢ Residual Protein A ▪ Biological activities ➢ Binding ➢ Effector functions – if significant for MOA (i.e. killing effect relevant compared to killing effect due to drug conjugation) ▪ Primary Structure ➢ Amino acid sequence ➢ Glycosylation profile ➢ PTMs – relevance also dependent on conjugation principle

Drug-Linker intermediate & mAb intermediate
If comparability can be demonstrated for relevant QAs before and after a change, no comparability study is required for the derived ADC DS or DP

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Regulatory perspectives

- **Key concept of ICH Q5E:** Determination of product comparability can be based solely on quality considerations provided that the available data allow to conclude no impact on clinical performance
- **Risk-based approach:** Focus on Critical Quality Attributes (CQAs) and leveraging product and process understanding to avoid redundant studies is recognized as valid approach if supported by relevant scientific evidence
- **Point of control:** Evaluation of process changes at specific stage where the change occurs is feasible if supported by relevant risk assessment
- **Comparability studies at DS/DP:** Need for additional comparability evaluation is heavily influenced by the comparability conclusions on the intermediate level and corresponding risk assessment

Specific considerations on scientific evidence

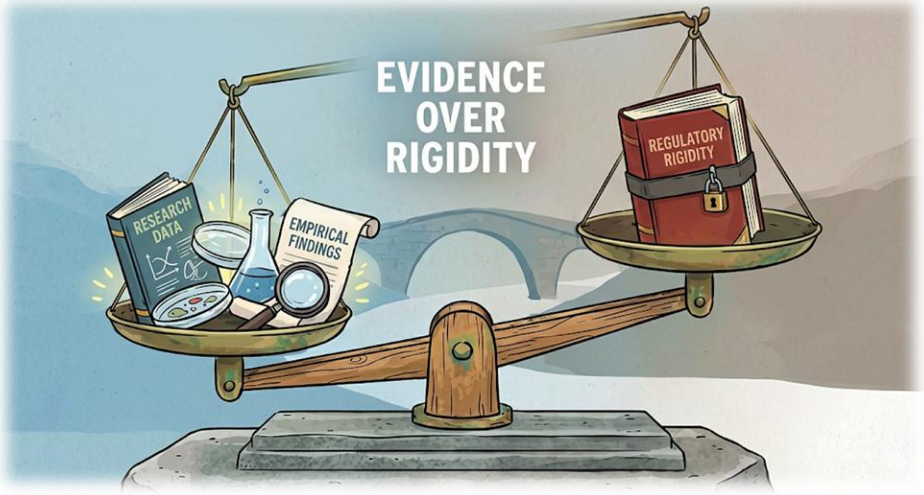
- **CQA identification:** Understanding of intermediate QAs with potential impact on the final DS/DP quality
- **Product and process understanding:** Attention to demonstration product-specific knowledge
- **Platform knowledge:** Leveraging prior knowledge if appropriately justified
- **Comparability conclusions:** no changes in ADC specific CQAs with potential impact on PK, efficacy, safety/immunogenicity
- **Case-by-case assessment:** Published decision trees to determine downstream comparability needs can be applied provided that decisions are supported by product-specific scientific justification
- **Complex nature of mAb intermediate:** Inherent heterogeneity of biological molecule increases the difficulty of proving comparability

Comparability considerations regarding biological molecule

- **Focus on structural characterisation:** Sufficiently sensitive analytical techniques addressing potential differences (including QAs critical for conjugation)
- **Evaluation of biological activity:** Fab binding affinity is relevant to MoA, evaluation of Fc-mediated activity may be relevant if contributes to the clinical performance
- **Critical impact of conjugation:** Changes in conjugation sites and payload distribution may potentially impact mAb structure and biological activity
- **Detailed knowledge of the molecule:** Characterisation of payloads attachment is essential – change in steric hindrance and hydrophobicity leading to potential structural conformational changes impacting stability of the molecule

Conlusions

- Drafting a definitive regulatory guideline for ADC comparability is challenging due to the molecular complexity and inherent heterogeneity of these multi-component therapeutics
- Even in the absence of formal guidance, **risk-based approach** is recognized as a valid scientific concept when backed by robust evidence and process understanding



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