Regulatory Considerations for Antibody Drug Conjugates

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Outline

• Current submissions
• The collaborative review process for ADCs
  – Office of Biotechnology Products (OBP)
  – Office of New Drug Quality Assessment (ONDQA)
• Conclusions
ADC IND Submissions

- Mylotarg (2000)
- Adcetris (2011)
- Kadcyla (2013)

Bar chart showing IND submissions over years with peak in 2011.
ADC Review Responsibility

Master cell bank

Monoclonal Antibody component/intermediate

Drug component intermediate

Drug Substance

Monoclonal Antibody component/intermediate

Linker component/intermediate

Starting Material

Derivative

OBP Responsibility

ONDQA Responsibility

Drug Product

Starting Material

Starting Material

Drug component intermediate

Drug Product

Starting Material
ADC Review: A Collaborative Process

• Quality assessment team includes
  – OBP primary and secondary reviewers
  – ONDQA primary and secondary reviewers
  – BMAB (Office of Compliance) primary and secondary reviewers
  – Frequent communications during review cycle
  – Informal meetings, discussion
  – Formal interactions (external)
  – Multidisciplinary status meetings
  – GRMP-driven milestones and deliverables
What ADCs Really Look Like!

IgG Antibody
150 kDA

Calicheamicin
1368 Da
Product Quality: Perspectives

• OBP Perspective
  – Characterization (mAb, DS, DP)
  – Comparability (mAb, DS, DP)
  – Impurities
  – Testing and specifications
Product Quality: Perspectives

• ONDQA Perspective
  – Starting materials and intermediates for Drug-linker (DL)
  – Characterization, Testing and Specifications of Drug-linker (DL), Drug Substance (ADC-DS), and Drug Product (ADC-DP)
  – Stability Studies (DL, ADC-DS, ADC-DP)

• Collaborative Perspective
Considerations from the OBP Perspective
Characterization and Comparability of mAb Intermediate

The expectations are the same for the mAb intermediate as they are for a final drug substance.

- Primary Structure
- Secondary/Tertiary Structure
- Fragments/aggregates
- Charge
- Glycosylation
- Other post translational modifications
- Antigen binding
- Biological activity as appropriate
mAb Impurities

• Product related impurities
  – Charge and size variants
  – Identify, may need to characterize biological function
  – Understand impact on ADC

• mAb process related impurities
  – Clearance of Virus and DNA
  – Calculate based on maximum human dose
  – Assess removal during mAb manufacture unless subsequent steps are needed to further reduce.
  – Risk assessments may be acceptable initially for some process related impurities
Antibody-Drug Conjugate: Characterization and Comparability

- Primary, secondary and higher order structure
- Size and charge variants
- Glycosylation
- Antigen binding
- Other biological activity
- Assess impact of conjugation chemistry on:
  - important biological functions of Ab (binding, effector function, other)
  - size and charge (?) variants
Antibody - Drug Conjugate: Comparability

- Extent of study depends on life cycle stage
- If changes were made to mAb, cytotoxic drug, or linker intermediates, consider comparability of ADC drug substance
  - Comparability of mAb intermediate
- Appropriate methods to assess comparability between the toxicology, clinical, and/or commercial batches
- Small drug perspective – main concern is with drug loading (distribution).
- mAb perspective – data for future comparability
Considerations from the ONDQA Perspective
Drug-Linker: Starting Materials

• Fermentation/natural, semisynthetic compounds
  – Microbial strains/biological origin etc.

• Peptides - amino acids and their derivatives

• Chemically synthesized compounds
  – Appropriately characterized and stable molecules
  – Impurity profile (carry-over vs. non carry-over)
  – Multiple chemical and purification steps preferred
  – Controlled process to remove/reduce impurities

• Discussion of SMs at the EOP2 meeting
Drug-Linker: Testing and Specifications

- Appearance
- Identity
  - IR, UV, NMR, MS, etc.
  - Optical rotation, if applicable
  - Melting Range/Point, if applicable
- Assay (HPLC)
- Purity
  - HPLC (drug-related impurities/degradants)
  - Residual solvents
  - Heavy metals
  - Residue on ignition
  - Water content
  - Chiral HPLC, if applicable
- Stability testing
  - Physical and chemical stability under long-term and accelerated conditions
  - Photo-stability
Antibody-Drug Conjugate: Characterization

- Structural characterization
  - Molar absorption coefficient
  - Drug/Antibody ratio

- Impurity profile
  - Free drugs (drug related substances and quenching agents)
  - Residual solvents and other process related impurities

- Consider risk-based approach for impurities
  - Risk assessment, risk mitigation strategy
Antibody-Drug Conjugate: Testing and Specifications

- Identity
- Assay
- Purity
  - Free drug related substances (including quenching agent)/non-proteinaceous
  - Residual Solvent
  - Microbiological (endotoxin, sterility)

- Stability testing
  - Long-term
  - Accelerated
  - Freeze-thaw
Collaborative Considerations
Antibody–Drug Conjugate: Purity and Potency

- Drug:antibody ratio
- Drug loading distribution
  - homogeneity of the ADC population
- Free drug
- Free antibody
Application of QbD Principles to ADCs

- Quality attributes of ADC
- Criticality of attributes
- Linkage of Drug Product attributes to drug/linker or mAb intermediates and manufacturing process.
- Encourage discussion with Agency
Future Trends

• Site specific conjugation
  – non-natural amino acids
  – aldehyde tagging

• New drug platforms
  – duocarmycin
  – pyrrolobenzodiazepines
  – topoisomerase, kinase inhibitors

• New linker technologies

• Optimizing payloads

• Non-oncology indications

• FDASIA/PDUFA V initiatives
Conclusions

• Antibody-drug conjugates are **both** drug and biologic molecules!

• Regardless of the regulatory pathway, characterization, comparability, release and stability assays need to be appropriate for the molecule.

• Good communication between Applicant and Quality review team (OBP/ONQDA/BMAB) facilitates overall review process
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