Regulatory Review Considerations of Drug-Linker Quality in ADCs

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ONDP/OPQ/CDER/FDA
Outlines

- ADC IND submissions and review
- CMC information in application
  - Drug-linker quality consideration
- Manufacturing changes and comparability considerations
- Conclusions
ADC IND submissions at FDA

# ADC Approvals

<table>
<thead>
<tr>
<th>No</th>
<th>Product</th>
<th>Approval Date</th>
<th>Indication</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mylotarg (gemtuzumab ozogamicin)</td>
<td>2000</td>
<td>CD33-positive acute myeloid leukemia</td>
<td>withdrawn in 2010, and approval in 2017</td>
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<tr>
<td>2</td>
<td>Adcetris (Brentuximab vedotin)</td>
<td>2010</td>
<td>Relapsed Hodgkin Lymphoma and systemic anaplastic large cell lymphoma</td>
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</tr>
<tr>
<td>3</td>
<td>Kadcyla (trastuzumab emtansine)</td>
<td>2013</td>
<td>HER2-positive metastatic breast cancer</td>
<td>---</td>
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<tr>
<td>4</td>
<td>Besponsa (Inotuzumab ozogamicin)</td>
<td>2017</td>
<td>Relapsed or refractory B-cell precursor acute lymphoblastic leukemia</td>
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</tbody>
</table>
**ADC Quality Review Challenges**

- Complexity: Drug and Biologic combination
- Regulated under both biologic (21CFR 610) and drug (21CFR 314) regulations and drugs cGMPs (21 CFR 210 & 211)
- No ICH or FDA guidance specifically for ADCs
- Multiple offices and review disciplines in the FDA
  - Team work and effective communication is imperative
- The FDA has limited experience
  - Four approved BLAs and one NDA (withdrawn)
- Science and technology evolving
OPQ- Organizational Chart

Immediate Office
Director: Michael Kopcha
Deputy Director: Lawrence Yu

Office of Program and Regulatory Operations
Director: Giuseppe Randazzo

Office of Policy for Pharmaceutical Quality
Director: Ashley Boam

Office of Surveillance
Director: Lucinda Buhse

Office of Test Qualification and Research
Acting Director: Sau (Larry) Lee

Office of Biotechnology Products
Director: Steve Kozlowski

Office of New Drug Products
Director: Sarah Pope Miksinski

Office of Lifecycle Drug Products
Director: Susan Rosencrance

Office of Process and Facilities
Director: Robert Iser

- FDA Offices that are directly involved in reviewing ADCs’ marketing approval.
# ADC Review Responsibilities

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>Responsible Office</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug intermediate</td>
<td>Office of New Drug Products</td>
</tr>
<tr>
<td>2</td>
<td>Linker intermediate</td>
<td>Office of New Drug Products</td>
</tr>
<tr>
<td>3</td>
<td>mAb</td>
<td>Office of Biotechnology Products</td>
</tr>
<tr>
<td>4</td>
<td>Drug Substance</td>
<td>• Office of New Drug Products and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Office of Biotechnology Products</td>
</tr>
<tr>
<td>5</td>
<td>Drug Product</td>
<td>• Office of New Drug Products, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Office of Biotechnology Products</td>
</tr>
<tr>
<td>6</td>
<td>Microbiology Facility</td>
<td>Office of Process and Facility</td>
</tr>
</tbody>
</table>
## Terminology

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug intermediate</td>
<td>Warhead or payload prior to conjugation</td>
</tr>
<tr>
<td>2</td>
<td>Linker intermediate</td>
<td>Linker which connecting warhead and mAb</td>
</tr>
<tr>
<td>3</td>
<td>mAb</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>4</td>
<td>ADC Drug substance</td>
<td>Drug-Linker-mAb</td>
</tr>
<tr>
<td>5</td>
<td>Drug Product</td>
<td>Drug-Linker-mAb in final dosage form</td>
</tr>
</tbody>
</table>
ADC Regulatory Pathway

- **Pre-IND, IND (Phase 1, 2, and 3), and BLA**
  - **Initial IND submission**
    - Pre-IND package and/or meetings with the FDA
    - Safety is a major concern supported by nonclinical toxicology data
    - Linkage between the toxicology and clinical batches
  - **Phase 2 and 3**
    - EOP-2 meeting to discuss designation of starting materials, defined manufacturing process, testing attributes, stability studies and other manufacturing issues to support Phase 3 and BLA
    - Pre-BLA meeting to discuss filing requirements and format issues.
    - Other Type C meetings
  - **BLA submission**
    - In Module 3 S, Drug–linker, mAb intermediates and DS as separate sections containing full CMC information (3.2.S1 to 3.2.S7)
    - In Module 3 P, CMC information for drug product (3.2 P1 to 3.2.P8)
Drug Linker Information in IND

- Quality information to support initial IND
  - Brief description of physicochemical properties
  - Manufacturer and manufacturing process description including raw materials controls
  - Structural characterization
  - Specifications (tests and acceptance criteria) based on limited manufacturing experience and toxicology data
  - Batch analysis data and/or COAs (Tox and clinical batches)
  - Preliminary stability data to support storage conditions
  - Limited data on impurities, but qualification focuses on free drugs and conjugatable impurities
  - Linkage between the toxicology lot and the clinical lot
  - CMC information may be provided by authorized reference to a DMF
Drug-Linker Information in IND
(Cont’d)

- **Quality information in late development stage**
  - Manufacturing process optimized and scale up for the commercial process studied
  - Establish control strategy to remove/reduce impurities
  - Complete characterization of the drug-linker
  - Further characterization of impurity profile, understand the fate of impurities in the manufacturing process and degradation pathway
  - Impurities identified, quantified and qualified for BLA
  - Analytical procedures optimized and validated for BLA
  - Stability indicating method (forced degradation studies)
  - Selection of starting materials and suppliers
  - Stability protocol to support BLA
Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351 (a)(2)(B)) requires drugs, which include IND products, to comply with current good manufacturing practice.

The CGMP requirement for manufacture of the drug linker intermediate should be the same as drug substance.

Certain requirements in 21 CFR 211 may not applicable for Phase 1 clinical trial materials.

Some requirements fulfilled by complying with 21 CFR 312.

Guidance for Industry CGMP for Phase 1 Investigational Drugs (https://www.fda.gov/downloads/drugs/guidances/ucm070273.pdf)
Starting Materials for Drug-Linker Intermediates

- Represent the start of full GMP manufacturing process
- Defined properties and quality
  - Appropriately characterized and quality controlled
  - Structure fragments incorporated into DS
  - Impurity profile established
- Commercially available vs custom manufactured
- Qualification of Starting Materials vendor/source
Starting Materials for Drug-Linker Intermediates

- **Phase 1:**
  - A brief description of drug/linker intermediate manufacturing including synthesis of starting materials

- **End of Phase 2 Meeting (EOP2):**
  - Starting materials designation
    - Justification for the proposed starting materials
    - Impurity control strategy (fate and purge study)
    - Specifications for the starting materials
    - Carry over impurities to the drug substance
    - ICH Q7 and Q11
Starting Materials for Drug-Linker Intermediates

- Fermentation and semi-synthetic compounds
  - Biological sources: cell lines, bacterial strains, plants, etc.

- Peptides and proteins
  - Amino acids and their derivatives

- Chemically synthesized compounds
  - Justification for choosing Starting Materials (SMs)
  - Multiple chemical and purification steps to purge impurities
  - Impurity profile established (carry-over vs. non carry-over) and controlled process to remove/reduce impurities
  - Qualification of SMs vendor/source

- Each compound and manufacturing process are unique
  - EOP 2 meeting in consultation with the FDA
ADC BLA Submission

- ADC BLA Submission should be in CTD format document

- Each intermediates and drug substance should be provided in a standalone section in Module 3.2.S
  - 3.2 S
    - Drug-Linker intermediate: (S1 through S7)
      (Linker intermediate can be a separate section S1 through S7)
    - Antibody intermediate: (S1 through S7)
    - ADC Drug substance: (S1 through S7)
  - 3.2 P
    - Drug product: (P1 through P8)
Drug-Linker Intermediate Information in BLA

- The expectations are the same for the drug/linker intermediates as they are for small molecule drug substance.

- CMC information for drug linker as stand alone information
  - S1 General Information
  - S2 Manufacture
  - S3 Characterization
  - S4 Control of DS (Specification for Drug/linker intermediate)
  - S5 Reference standard
  - S6 Container Closure System
  - S7 Stability
Drug-Linker Manufacturing

- Manufacture
  - Manufacturer
  - Manufacturing process and controls
    - Small synthetic molecule as an example
    - Synthesis flow chart
    - Description of the process
    - In-process controls and intermediates specifications
    - Controls of starting materials, reagents, solvents
    - Manufacturing process development
Drug-Linker Characterization

- **Structural characterization**
  - UV, IR, NMRs, MS, elemental analysis, etc.

- **Impurity profile**
  - Drug/linker related impurities
  - Process impurities
  - Inorganic impurities and metal/elemental impurities
  - Residual solvents
  - Structural characterization and qualification of impurities
  - Degradation pathways and impurity fate in the manufacturing
Drug-Linker Impurity Qualification and Characterization

• Drug related impurities include free drug and drug-linker substances, etc.
• ICH Q3A guidance applied at the intermediates
• Qualification based on non-clinical toxicology studies and/or justified based on available safety data
• Impurity identification expected at Phase 3
• Emphasis on conjugatable impurities
Drug-Linker Specifications

- Appearance
- Identity
  - Specific method (ICH Q6A) or two non-specific orthogonal methods
- Assay
  - Reference standard
- Purity
  - Drug related substances
  - Individual (specified and unspecified) and total impurities
  - Chiral purity if applicable
- Residual solvents
- Inorganic impurities and metal/elemental impurities
Drug-Linker Stability

- Drug-linker intermediate stored prior to the conjugation reaction
- Stability studies using the real time storage conditions to support the hold time.
- Stability studies
  - Physical and chemical stability
  - Forced degradation study (under stress conditions)
  - Photo-stability
  - Freeze thaw studies if applicable
ADC Drug Substance Information in BLA

• ADC drug substance in Module 3
  – S1 General Information
  – S2 Manufacture
    • Conjugation and purification
  – S3 Characterization
    • DAR, drug distribution, individual drug load variants, free drugs, potency assay, etc.
  – S4 Control of Drug Substance
  – S5 Reference standard
  – S6 Container Closure System
  – S7 Stability
Conjugation and Purification

• Process description
  – Process and in process controls and intermediate specification
  – Process parameters (pH, temperature, time, concentrations of input materials, etc.)

• Process characterization
  – Critical steps, critical process parameters (CPPs) and Critical Quality Attributes (CQAs)
  – Study how process parameters affecting CQAs
  – Quality by Design (QbR) approach

• Process consistency
  – Drug to Antibody Ratio (DAR) and drug load distribution
  – Remove impurities
  – Impact on antibody (binding, cytotoxicity, aggregation, etc.)
Characterization of Antibody-Drug Conjugate

Tests unique to ADCs:

• Structural characterization
  – Molar absorption coefficient
  – Drug load distribution
  – Individual drug load variants (drug load on heavy and light chains)
  – Drug/Antibody ratio (DAR)
  – Conjugations sites

• Impurity profile
  – Free drugs (related substances and quenching agents)
  – Catalysts, residual solvents, heavy metals and other process related impurities

• Risk based approach to control product quality

• Not included above are the common characterization tests for the antibody.
ADC DS Specifications

• Identity
  – ELISA, Isoelectric Focusing, HIC, etc.

• Physical characteristics
  – Appearance, pH, color and clarity of solution, osmolality, etc.

• Assay
  – Total protein content (UV)

• Potency
  – Bioassay, Binding Assay (ELISA)

• Drug loading
  – DAR
  – Drug load distribution
ADC DS Specifications (continued)

• Purity (product)
  – Antibody (Size Exclusion Chromatography, Ultrafiltration, reduced and non-reduced SDS, RP-HPLC)
  – Drug related impurities (free drug and related substances, quenching agent, individual and total impurities)

• Purity (process)
  – Residual solvents
  – Heavy metals

• Microbiology
  – Bioburden
  – Endotoxins
ADC DS Stability

Stability tests should include the tests that maybe trending:

- **Physical properties**
  - Appearance, pH, clarity of solution, etc.
- **Assay**
  - Total protein content (UV)
- **Potency**
  - Bioassay, Binding Assay (ELISA)
- **Purity (product)**
  - DAR and Drug load distribution
  - Antibody (IEF, SEC, reduced and non-reduced SDS, RP-HPLC)
  - Free drug
- **Particulates**
- **Microbiology**
  - Bioburden
  - Endotoxins
In-Use ADC Drug Product Stability

- Demonstrate compatibility between the ADC solution and the infusion solution and the infusion set
- Demonstrate stability of the diluted drug solution during administration
- Using the drug concentrations in the range that is intended for patient administration
- Using the intended diluents and infusion sets
- Test attributes: Stability indicating tests
- Plasma stability recommended

In-Use ADC Drug Product Stability

FDA
CMC Changes during Drug Development and Comparability Issues

- Manufacturing changes
  - Site change
  - Manufacturer change
  - Process change and equipment change
  - Scale change
  - Raw materials and reagents change
  - Supply change

- Demonstrate Comparability
  - Change at early vs late stages
  - Comparative batch analysis data and characterization data
  - Major concerns are the changes in antibody manufacturing
  - Changes related to drug-linker manufacturing should focus on impurity profile (conjugatable impurities)

- Seek the Agency feedback: Type B and C Meetings and IND amendments
Conclusions

• ADCs review challenges
• CMC information for Drug Linker in IND submission
• cGMP manufacturing of drug-linker and starting material designation
• CMC information for Drug Linker and ADC in BLA submission
• Manufacturing changes and comparability of ADCs
• Communication between the sponsor and the Agency is imperative
Key Guidance Documents

- ICH Q6B; Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (http://www.fda.gov/cder/guidance/Q6Bfnl.PDF)
- ICH Q1A, Q3A, Q3B, Q3C, and Q3D, etc.
Acknowledgement

- Anamitro Banerjee
- Thomas F. Oliver
- Ramesh Sood
- Andre Raw
- Kimberly Rains