Antibody Drug Conjugates - Introduction to a new EBE initiative

EBE Satellite Session
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Presented by Fred Jacobson (Genentech) on behalf of the ADC task force
How it got started...

May 2015
• EBE Biomanufacturing WG decided to collect current challenges faced by companies developing ADCs

December 2015
• Experts nominated by companies

September 2015
• Presentation of collected input to EBE WG
• Decision to form a task force to address issues

January 2016
• Kick off meeting
EBE task force on ADCs

- Formed in January 2016
  - Led by U Busse (Novartis) & members of the EBE Biomanufacturing WG

- Participation by Abbvie, AstraZeneca, Bayer, Genentech/Roche, Janssen J&J, MedImmune, Merck, MSD, Novartis, Pfizer, Vortex
  - Diverse team in terms of experience, function (regulatory, quality, technical development) and geographical coverage

- Objective: address current challenges related to ADCs
  - Formulate problem statements on ADC-related challenges currently faced by industry
  - Agree on how these challenges could be addressed
  - Engage with regulators to discuss proposed solutions in view of developing best practices
  - Share outcomes of the team’s effort with the broader stakeholder community
    - White papers, conferences, etc.
Sneak preview of the team’s ongoing work

ADC CHALLENGES
Overview of challenges

- Diversity of ADCs (attachment sites, drug distribution, mAb properties, etc)
- Early versus late stage requirements
- General biological and chemical guidelines – applicability
  - How where to apply QBD principles
- Classification of ADCs and components
- Regulatory dossier content/format
- Filing strategies
- Divergent expectations from different Health Authorities
- Analytics: control system, specifications, stability, impurities...
- Comparability requirements
- Terminology
Guidelines & Classification

• Immunoconjugates (i.e. ADCs) discussed briefly in the 1997 “Points to consider in the manufacture and testing of monoclonal antibody products for human use”; No updated regulatory guidance since then; Technology has changed significantly
  - Global alignment on expectations

• General biological and chemical guidelines - applicability
  - Which chemical / biological guidelines apply to ADCs and their constituents (small molecule drug/linker, conjugate, antibody)?
  - Which guidelines/requirements apply to the manufacturing sites?
    ▪ e.g. with regards to raw materials used in the small molecule manufacture or in DS conjugation, cleaning strategies, specific requirements for potent compounds etc.?)?
  - Control of particulate matter & solvents for the small molecule part of ADCs

• Classification of ADCs
  - Is the conjugate considered Drug Substance, pharmaceutical form (small molecule drug = API, mAb = intermediate, excipient or delivery vehicle), combination product?
  - Impact on definition of dose/strength (based on linked drug or on ADC)?
Regulatory submission

- Regulatory dossier content/format
  - Sections to be filled and level of description in the dossier for the API/DS part
  - Currently, mAb, small molecule drug, and ADC are all treated separately in IND and filed/reviewed as if each were final DS; we would likely want to advocate for having payload and mAb treated as process intermediate and filed accordingly
  - Alignment of ADC submissions with CTD

- Filing strategies
  - Drug-linkers/mAbs can be mixed and matched - what can we do to simplify/speed up regulatory filings when we do this (e.g. use of previously approved mAb in new drug)
Analytics & Control strategy

- Specifications and strategies for **stochastic vs site specific conjugation** and regulatory impact of improving DAR control and decreasing heterogeneity
  - Impact of “unconjugated antibody” on ADC properties
- Is impact of conjugation on mAb properties important
  - The conjugate, not the antibody, is the product
- **Stability:** Strategies for **degradation of payload** attached to ADC with time and approaches for controlling in specifications
- Redundant testing: Analytics and specifications that are NOT required on ADC (conjugate) since tested on mAb (e.g., HCP)
- Charge analytics for ADCs; requirements and utility
- Impurities: Stage-specific strategies for dealing with free drug-related impurities at release and over time (what to quantify; how to control, etc)
- How do QBD principles fit into ADC development?
Comparability

- Comparability requirements regarding manufacturing changes for the ADC building blocks (drug, mAb, linker), ADC drug substance, and ADC drug product

- Type of Classification of changes when touching only the small molecule part of the DS

- Considerations for Tox - GMP comparability at early stages (Guidelines on acceptable changes and approaches, given low knowledge of structure/function and high impact)

- How to relate toxicology of bound drug and ADC obtained from pre-clinical tox studies to specifications for ADC in clinical phase (not likely to be a CMC question only)
Terminology

- Many different terms used to designate the bound small molecule
  - **Toxin**
  - **Payload**
  - **Warhead**
  - **Drug** (as the “D” in ADC) is preferred.
  - Is this considered as an “API”? 

- **mAb**
  - **Antibody intermediate**
  - **Unconjugated mAb**

- **ADC**
  - **DAR** (drug to antibody ratio) seems to have become standard
  - Use of the term **Drug Substance** to refer to the conjugate, in line with recent ICH guidance documents. DS is applicable to both biologics and small molecules.
THANK YOU!