www.diahome.org

DIA 2013
49th Annual
Meeting

Regulatory Considerations for Antibody Drug Conjugates

Sarah Pope Miksinski, Ph.D.

Division Director (Acting)

FDA/CDER/OPS/ONDQA/DNDQA 2

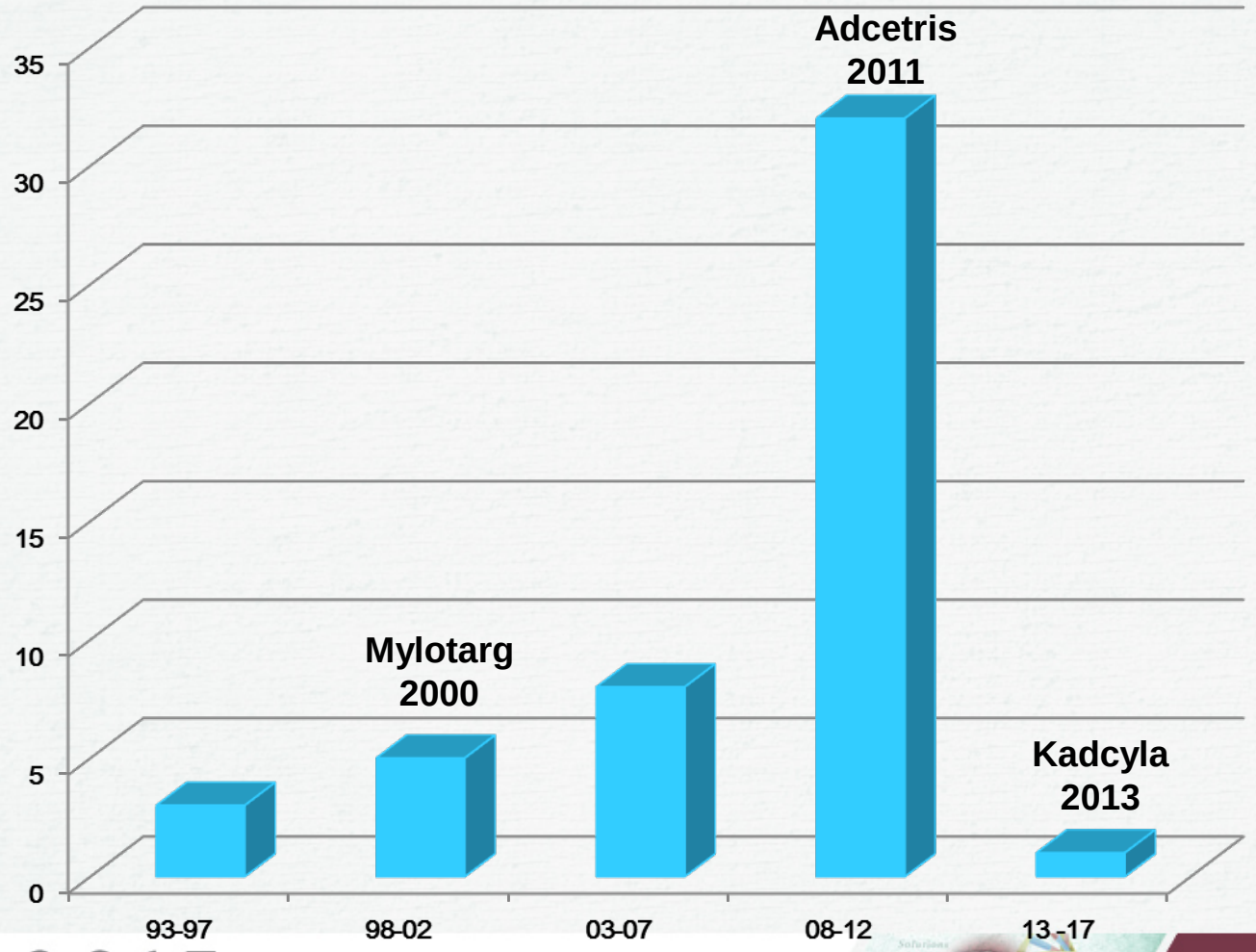
Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Communities (formerly known as SIACs) or affiliates, or any organization with which the presenter is employed or affiliated.
- For work prepared by US government employees representing their agencies, there is no copyright and these work products can be reproduced freely. Drug Information Association, Drug Information Association Inc., DIA and DIA logo are registered trademarks. All other trademarks are the property of their respective owners.

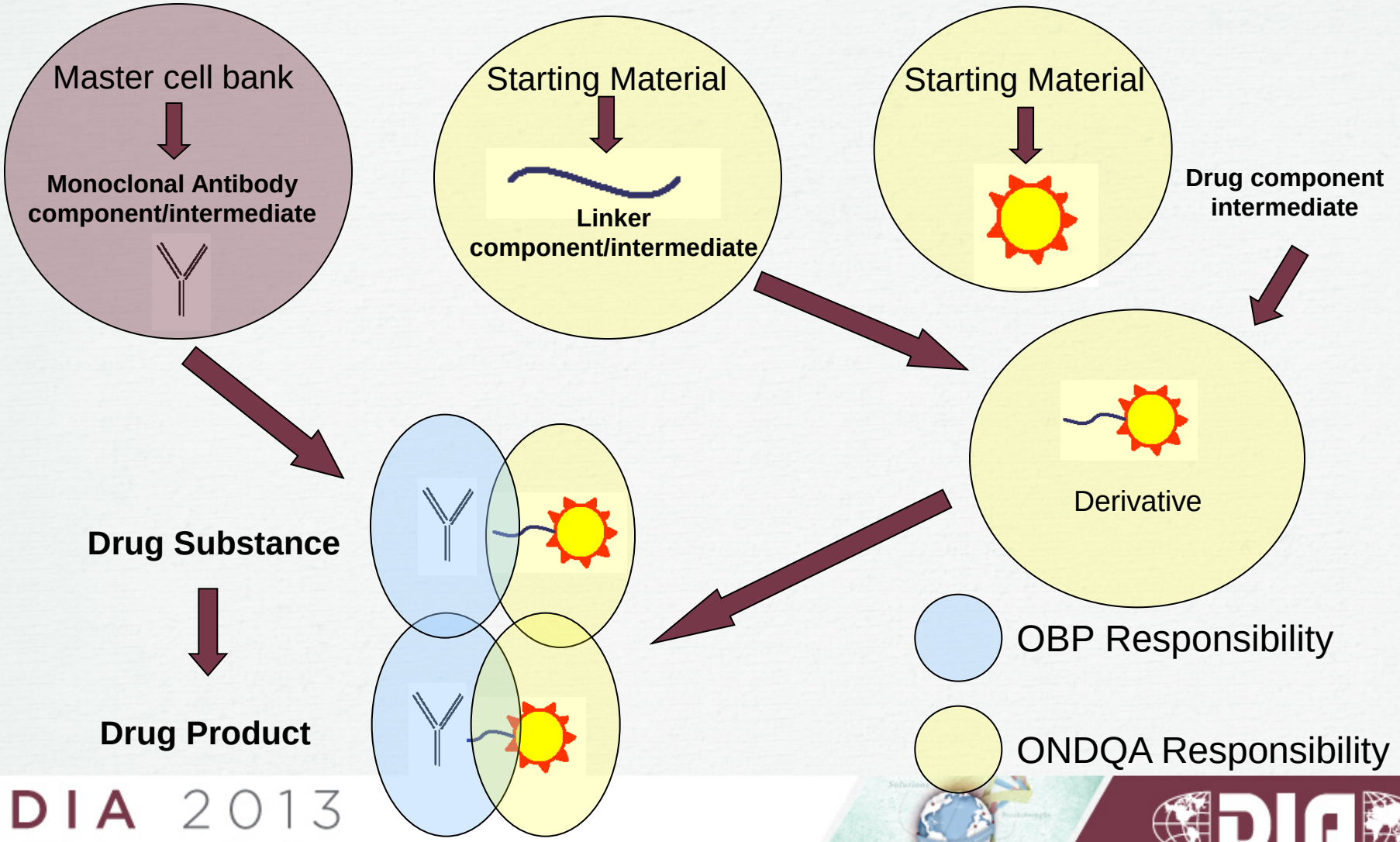
Outline

- Current submissions
- The collaborative review process for ADCs
  - Office of Biotechnology Products (OBP)
  - Office of New Drug Quality Assessment (ONDQA)
- Conclusions

ADC IND Submissions



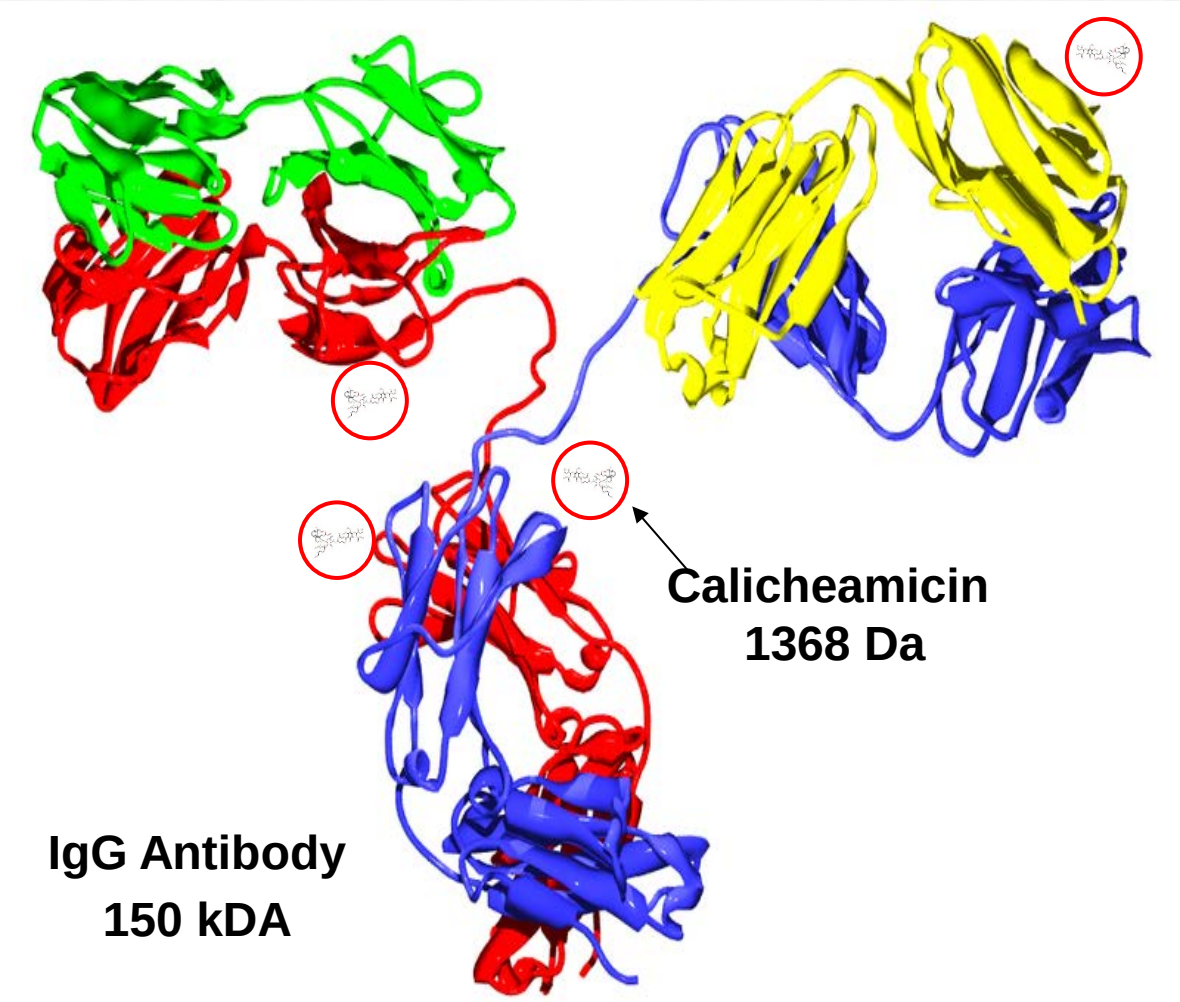
ADC Review Responsibility



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!



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
- Glycoslation
- 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

Acknowledgements

- ONDQA
  - Xiao-Hong Chen
  - Debasis Ghosh
- OBP
  - Marjorie Shapiro
- BMAB/Office of Compliance
  - Bo Chi
  - Patricia Hughes

Thank You!