



Regulatory Considerations for Antibody- Drug Conjugates

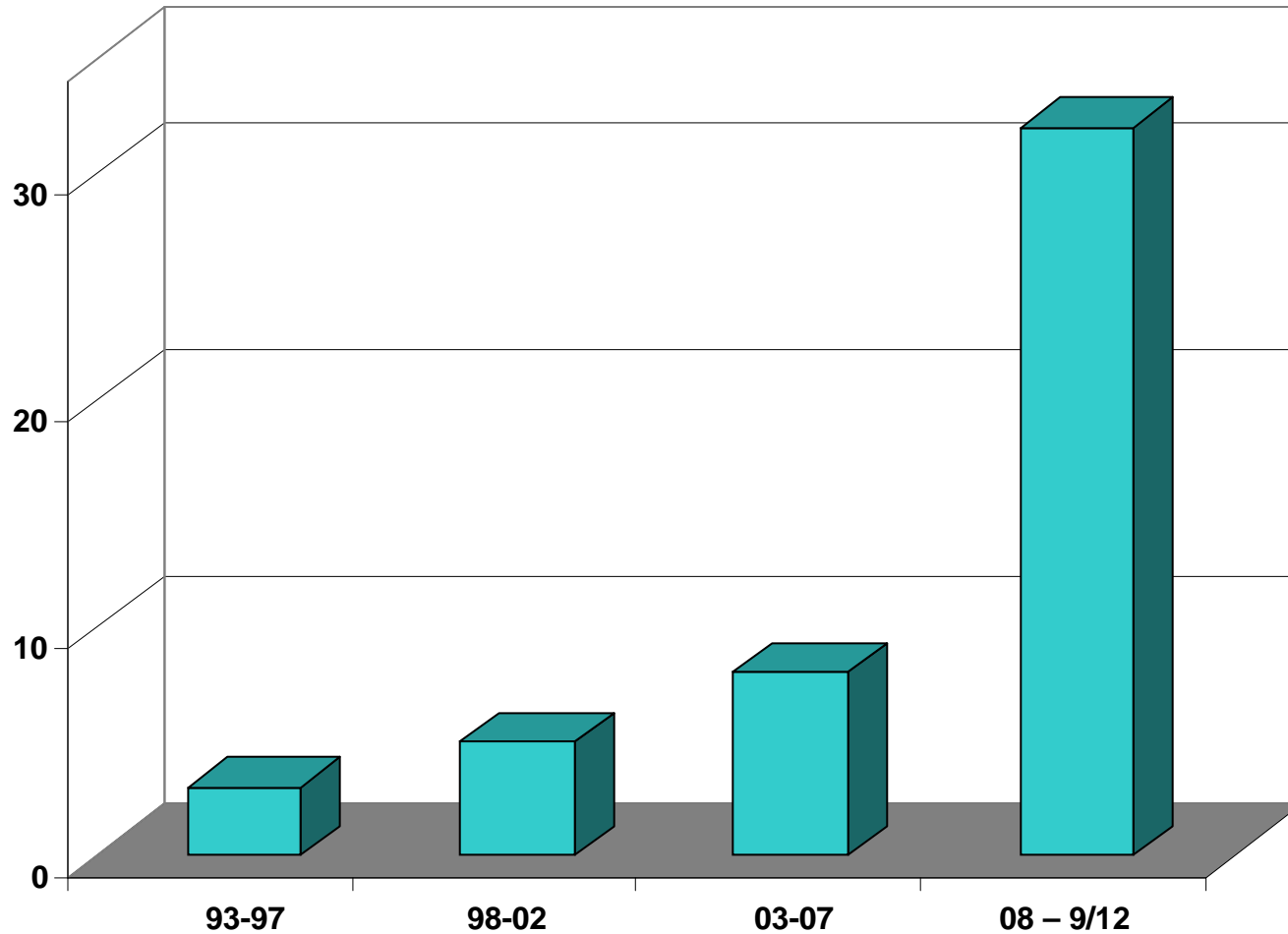
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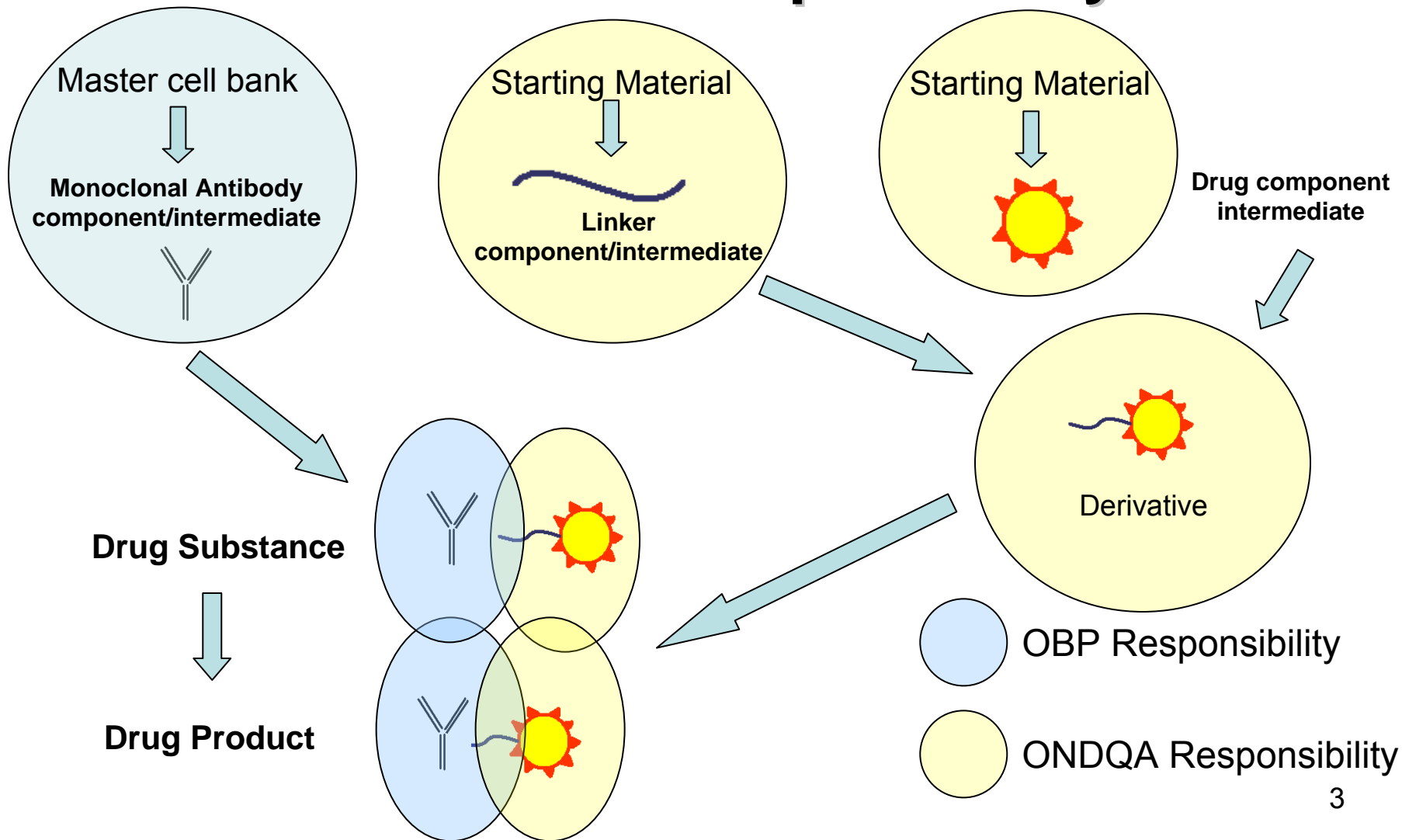
OPS, CDER

AAPS (October 18, 2012)

ADC IND Submissions



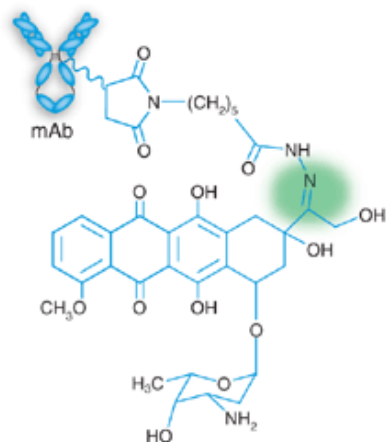
ADC Review Responsibility



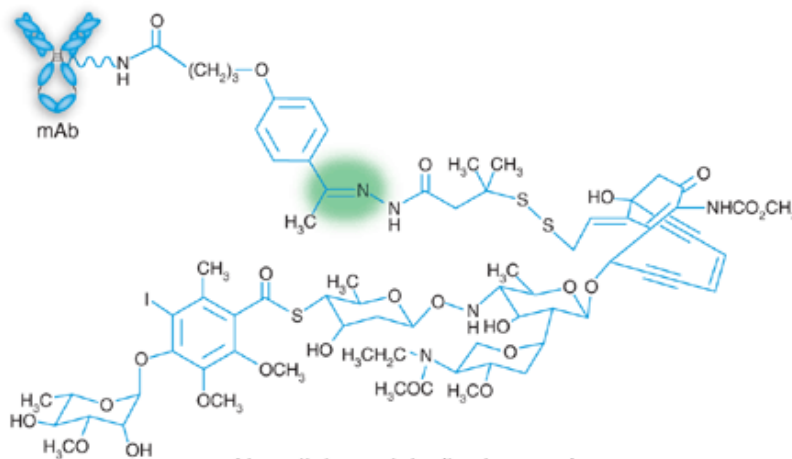
ADC Review: A Collaborative Process

- Quality assessment team includes
 - OBP primary and secondary reviewers
 - ONDQA primary and secondary reviewers
 - BMAB (Office of Compliance) primary and secondary reviewers
 - Sterile manufacturing processes
 - PAI lead inspector
 - Frequent communications during review cycle
 - Informal meetings, discussion
 - Formal interactions (external)
 - Multidisciplinary status meetings
 - GRMP-driven milestones and deliverables (e.g. midcycle)

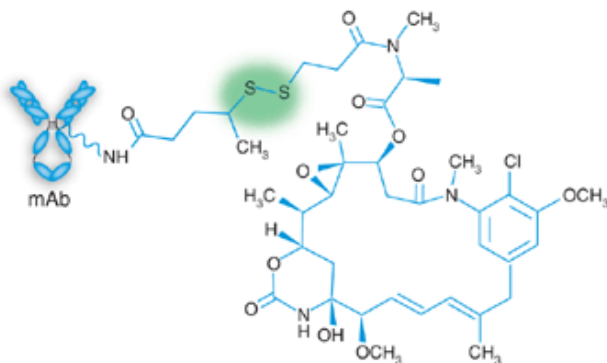
Current ADC Platforms



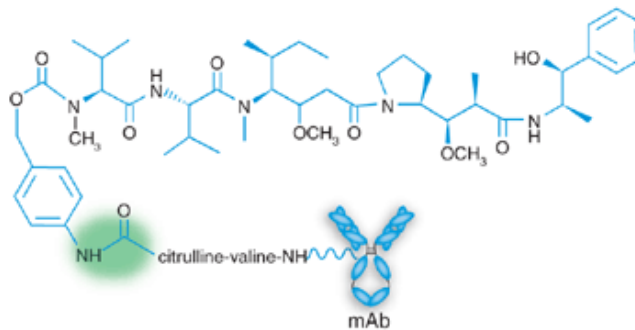
mAb-doxorubicin (hydrazone)



mAb-calicheamicin (hydrazone)



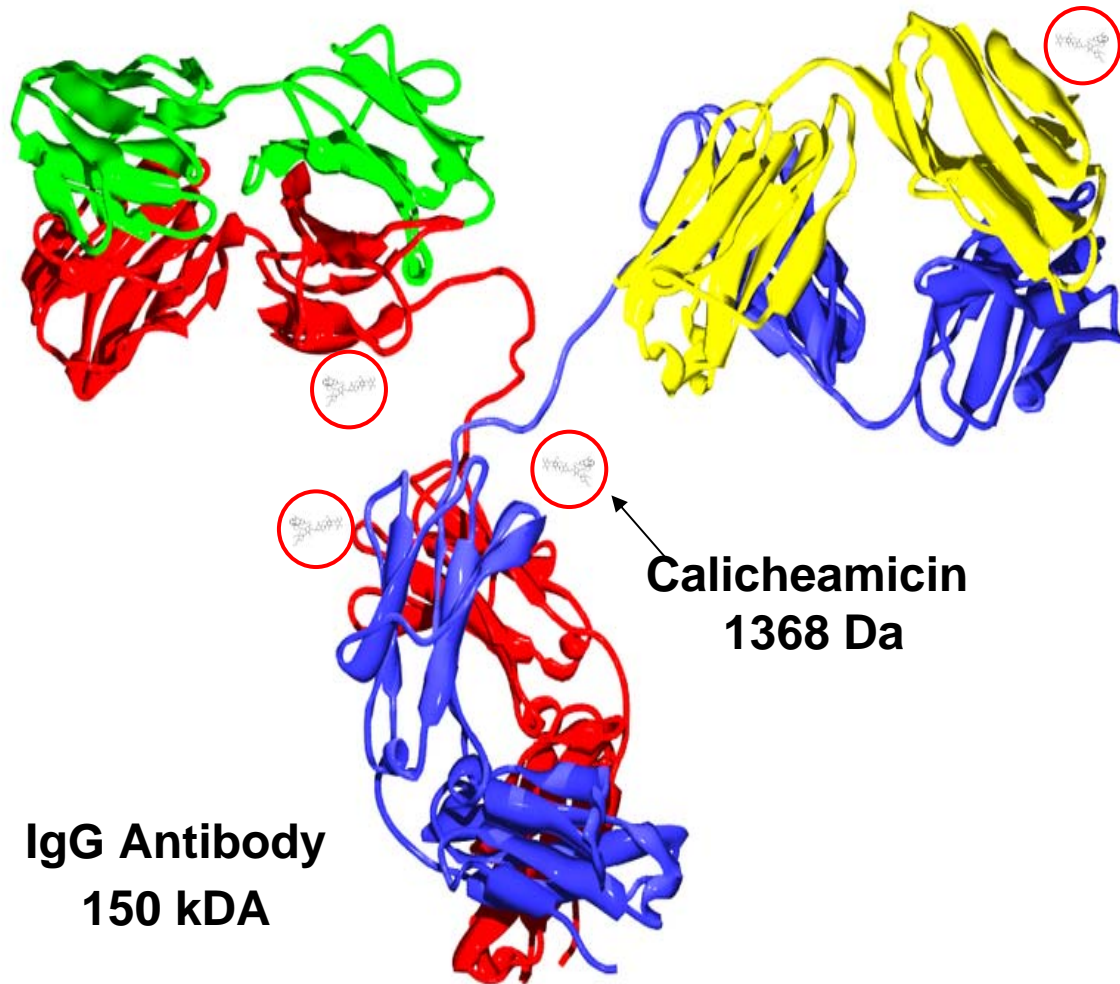
mAb-DM1 (disulfide)



mAb-auristatin (peptide)

Katje Riis

What ADCs Really Look Like!



Product Quality: Perspectives

- **OBP Perspective**
 - Characterization (mAb, DS, DP)
 - Comparability (mAb, DS, DP)
 - Impurities
 - Testing and specifications
- **ONDQA Perspective**
 - Starting materials and intermediates
 - Characterization [drug/linker, drug substance (DS), drug product (DP)]
 - Testing and specifications
- **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 Effector Function and Biological Activity

- Most ADCs utilize IgG1 or IgG4 mAbs
- If mAb is engineered to reduce effector function or reduce IgG4 half antibody formation, characterization should demonstrate this.
- mAb should be characterized for effector function and other biological activity. The target, tumor location and rate of internalization may play a role.
- If the mAb has effector function or biological activity, this activity may contribute to the overall MOA of the ADC

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 of DP
 - Removal of impurities should be assessed during mAb manufacture unless subsequent steps are needed to provide further reduction.
 - Risk assessments may be acceptable initially for some process related impurities.

Current mAb Conjugation Sites

- Cysteine (polar)
 - 4 interchain disulfide bonds in IgG1/IgG4
 - 8 conjugation sites
- Lysines (basic)
 - 25/22 lysines in IgG1/IgG4 constant region
 - 8 lysines in κ constant region
 - Additional lysines in VH or VL regions
 - Number depends on germline sequence and somatic mutations

Antibody- Drug Conjugate: Characterization and Comparability

- Primary, secondary and higher order structure
- Size and charge variants
- Glycosylation
- Other PTMs as appropriate
- Antigen binding
- Other biological activity

- Assessment of impact of conjugation chemistry on:
 - important biological functions of Ab (binding, effector function, other)
 - size and charge (?) variants

Antibody- Drug Conjugate: Identity

- Generally more focus on mAb rather than drug-linker
- Binding, charge based, peptide map, sequence based.
- The need for multiple assays depends on the properties/characteristics of the mAb/conjugate and if other conjugates are manufactured at the same facility.
- Charge based assays may not be possible/meaningful after conjugation to lysine residues.

Antibody - Drug Conjugate: Purity

- Largely the same methods as before conjugation.
- SDS-PAGE/CGE, SEC-HPLC, charge based.
- Charge based assays may not be possible/meaningful after conjugation to lysine residues.
- Need to control for aggregates and fragments.
- Need to understand what is stability indicating.
- If mAb well characterized and process well controlled, may be able to eliminate some release tests but this should be a pre-BLA discussion
 - Pre- and post marketing process changes may require accumulative data.

Antibody - Drug Conjugate: Potency

- MOA = cytotoxicity, but binding to antigen is a necessary component
- Need antigen binding for unconjugated mAb
- Need to demonstrate conjugation does not affect antigen binding
- If conjugation process is well controlled, may be able to eliminate antigen binding assay provided cytotoxicity assay is robust.
 - Need sufficient data, including stability data of ADC, linkage of potency across lots and discussion with Agency.
 - This will be a BLA review issue, but can discuss at pre-BLA meeting
- Effector function as MOA

Testing and Specifications

- Phase 1 INDs: specification for cytotoxicity assay should not be broader than dose escalation scheme
 - Or ensure that the single clinical lot to be used in the dose ranging study is sufficient to complete the study.
- If an ADC is believed to have multiple MOAs, include additional potency assay(s).
 - mAb intermediate release and/or DS or DP release.

Antibody - Drug Conjugate: Comparability

- Extent of study depends on life cycle stage.
- If changes were made to mAb, cytotoxic drug, or linker intermediates, should perform comparability on ADC drug substance.
 - Comparability study should be performed on mAb intermediate.
- Appropriate methods should be used to assess comparability between the toxicology, clinical, and/or commercial batches.
- Small drug perspective – main concern is with drug loading (distribution).
- mAb perspective, if certain tests are dropped for mAb, ADC DS or DP for release, will data be collected for future comparability studies?



Considerations from the ONDQA perspective

Starting Materials for Drug/Linker Intermediates

- Fermentation and semi-synthetic compounds
 - Microbial strains
- Peptides
 - Amino acids and their derivatives
- Chemically synthesized compounds
 - Appropriately characterized and stable molecules
 - Impurity profile established (carry-over vs. non carry-over)
 - Multiple chemical and purification steps preferred
 - Controlled process to remove/reduce impurities
- Discussion of designation for SMs at the EOP-2 meeting

Characterization of Drug/Linker (as intermediates)

- The expectations are the same for the drug/linker intermediates as they are for a final drug substance.
- Structural characterization
 - UV, IR, NMR, MS, elemental analysis, etc.
- Impurity profile
 - Drug/linker related impurities
 - Process impurities
 - Structural determination for the impurities present at the levels higher than 0.1%

Characterization of Antibody-Drug Conjugate

- Structural characterization
 - Molar absorption coefficient
 - Drug load distribution
 - Individual drug load variants
 - Drug/Antibody ratio
- Impurity profile
 - Free drugs (drug related substances and quenching agents)
 - Residual solvents and other process related impurities
- Risk based approach to control impurities
 - Conjugatable vs. non-conjugatable impurities

Drug/Linker Testing and Specifications (as intermediates)

- Appearance
- Identity
 - IR, UV, NMR, MS, etc.
 - Optical rotation if applicable
 - Melting point if applicable
- Assay (HPLC)

Drug/Linker Testing and Specifications (as intermediates)

- Purity
 - HPLC (drug-related impurities/degradants)
 - Residual solvents
 - Heavy metals and/or residue on ignition
 - Water content
 - Chiral HPLC if applicable
- Stability testing
 - Physical and chemical stability
 - Photo-stability
 - Freeze thaw studies

Drug/Linker Testing and Specifications of Antibody-Drug Conjugate

- Identity
 - UV absorption
- Assay
 - Total drug content (UV)
- Purity
 - Free drug related substances (including quenching agent)
 - Residual solvents
 - Heavy metals
- Stability testing
 - Free drug

Drug/Linker Testing and Specifications of Antibody-Drug Conjugate

- Phase 1 INDs:
 - Free drug related impurities in clinical lot should be qualified relative to data from toxicology studies.
 - Comparable drug/antibody ratios should be maintained between the toxicology lot and the clinical lot.
- Phase 3 clinical trials: Characterization of the impurity profile of drug/linker intermediates, including structure determination of individual impurities at levels $>0.1\%$, is recommended prior to pivotal clinical trials.



Collaborative Considerations

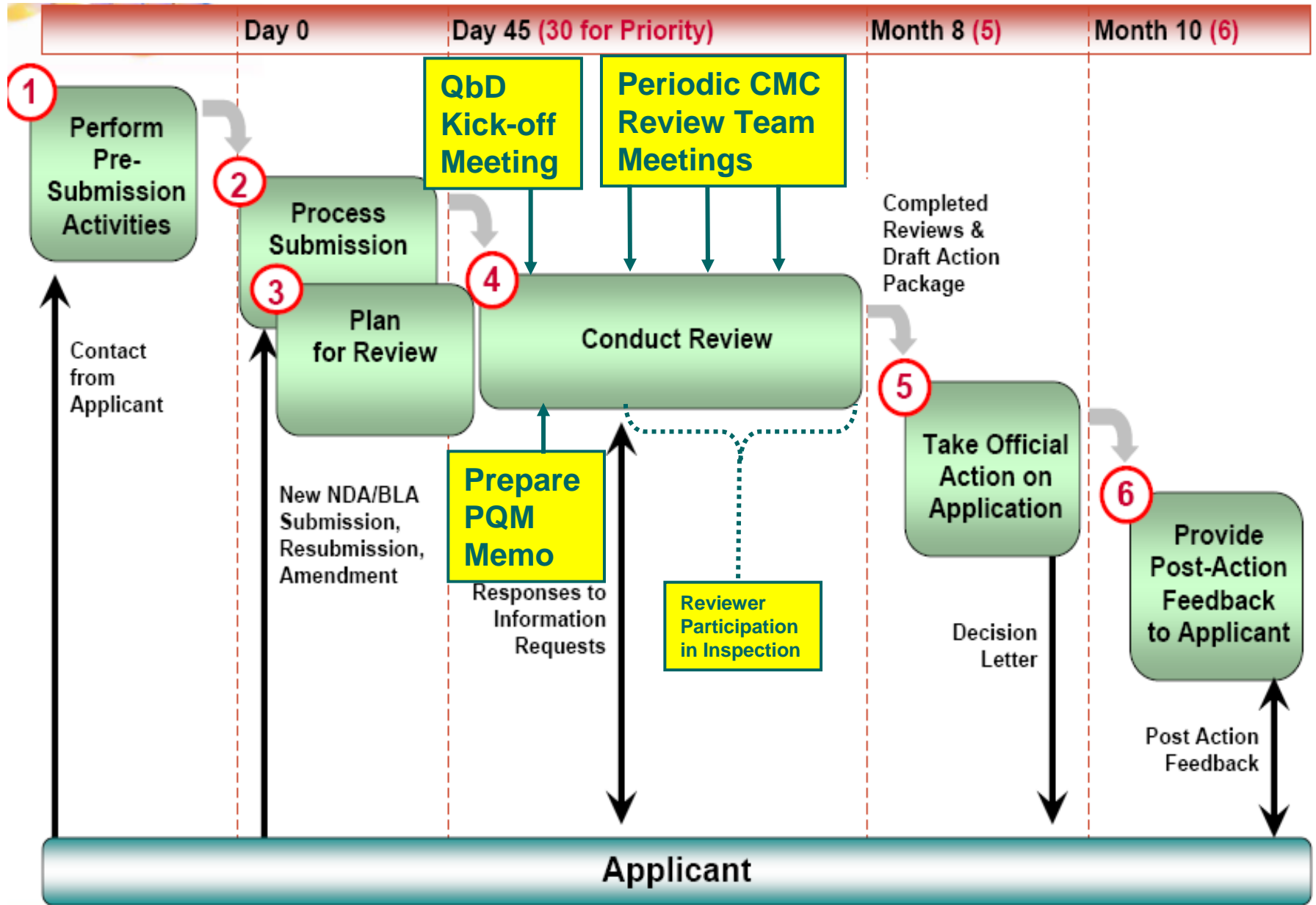
Antibody - Drug Conjugate: Purity and Potency

- Drug:Antibody ratio
- Drug loading distribution
 - homogeneity of the ADC population
- Free Drug
- Free Antibody

Antibody - Drug Conjugate: Setting Specifications

- 1 lot of **drug/linker** + 1 lot of **mAb** = ≥ 1 lot of ADC drug substance
- Use as many combinations of distinct drug/linker/mAb lots as possible during clinical development
- Plan different combinations for conformance lots
- A good topic for a pre BLA discussion

GRMPs - Timelines



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

Highly Potent Substances in Multi-Product Facilities

- Understand your responsibility as sponsor; understand the responsibility of the CMO.
- Contract Manufacturers
 - Limited number of facilities capable of handling highly potent biological drug substances
 - If not already licensed as multi-product facility, expect it will become a multi-product facility during life of your product
- For multi-product facilities handling highly potent substances, a risk assessment is expected to identify cross-contamination risks. Segregations and controls mitigating the identified risks should be implemented.
 - Responsibility of CMO!
 - Good communication with customer (You!)
- ISPE Baseline Guide Volume 7: Risk-Based Manufacture of Pharmaceutical Products: A Guide to Managing Risks Associated with Cross-Contamination 2010

Module 3 Organization

- ICH M4 Guidance (Q&A R1)
 - When more than one drug substance is used in a drug product, information should be presented separately as one complete Drug Substance section followed by other complete Drug Substance sections. (Section 2.1 Separate or Repeated Sections)
- What we've seen in INDs
 - Integrate drug/linker and mAb intermediates information within DS module S.2.6, S.4 and other relevant sections
 - Within Module 3S, 3 separate folders, 1 each for drug substance, drug/linker intermediates, mAb intermediate
- What FDA reviewers prefer
 - 3 separate folders

Future Trends

- Site specific conjugation
 - non-natural amino acids
 - aldehyde tagging
- New drug platforms
 - duocarmycin
 - pyrrolobenzodiazepines
 - topoisomerase inhibitors
 - kinase inhibitors
- New/improved linker technologies
- Optimizing payloads
- Extracellular release at tumor environment
- 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.
- Current ADCs are highly potent substances. Appropriate measures are needed regarding potential cross-contamination in multi-product facilities.
- Good communication between Sponsor and Quality review team (OBP/ONQDA/BMAB) helps overall review process.

Acknowledgements

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