Expectations on potency assays for antibody-based novel modalities – a regulatory perspective

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A quality product of any kind consistently meets the expectations of the user.

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Disclaimer

Please refer to any cited guidance, as this talk only refers to them at a high level. Specific regulatory issues need to be addressed with the relevant assessment team.

Outline

- ❑ Regulations of potency for biologics
- ❑ Connecting mechanisms of action (MOAs) and potency assays
- ❑ Expectations on potency assays at different development stages

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Potency Definition and Regulations

- PHS Act section 351 (42 USC 262):

  "…approve a biologics license application…on the basis of a demonstration that:
  (I) the biological product that is the subject of the application is safe, pure, and **potent**; and
  (II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and **potent**;"

- 21 CFR 600.3(s):

  "The word potency is interpreted to mean **the specific ability or capacity of the product**, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, **to effect a given result**."

- 21 CFR 610.10:

  "Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been **specifically** designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by definition in § 600.3(s) of this chapter."

Additional Guidance

- ICH Q6B: Specifications for Biotechnology Products:
  - Potency: The measure of the biological activity using a suitably quantitative **biological assay** (also called **potency assay** or **bioassay**), based on the attribute of the product which is linked to the relevant biological properties.
  - Drug substance specifications: appearance and description, identity, purity and impurities, **potency**, quantity.
  - Drug product specifications: appearance and description, identity, purity and impurities, **potency**, quantity, general tests, additional testing for unique dosage forms.
  - "Often, for complex molecules, the physicochemical information may be extensive but unable to confirm the higher-order structure which, however, can be inferred from the **biological activity**."

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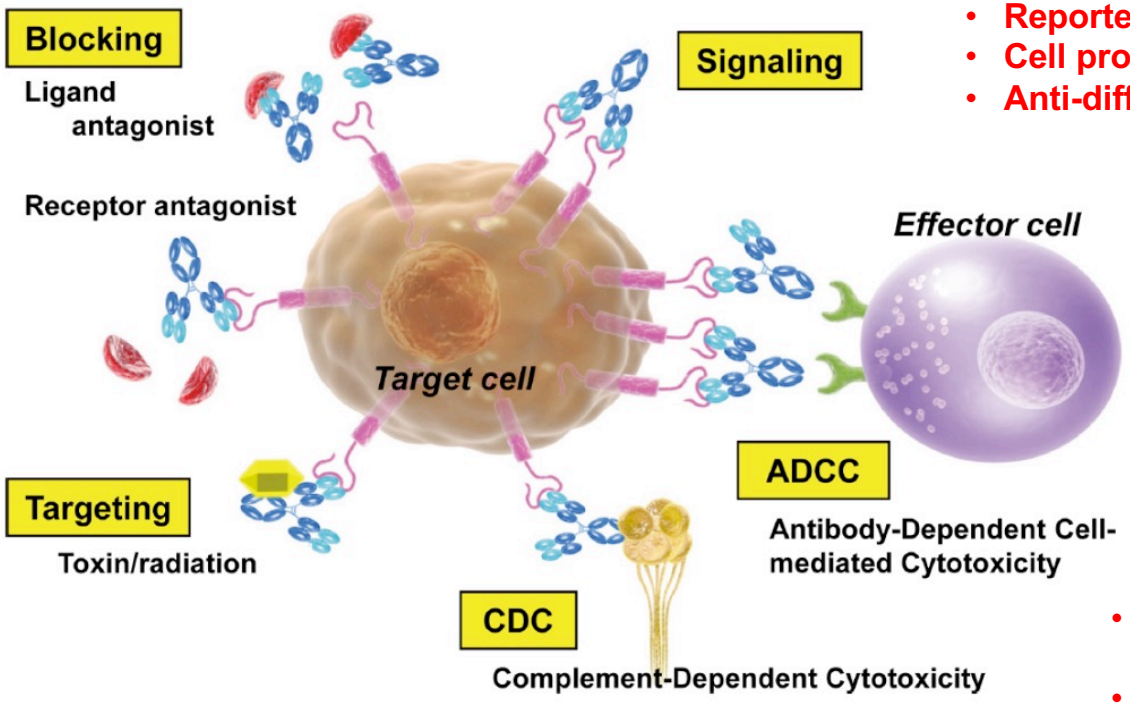
Common MOAs and Potency Assays for Therapeutic Antibodies

- Binding assay



- Receptor phosphorylation
- Reporter gene assay
- Cell proliferation
- Anti-differentiation

- Cytotoxicity assay

- Surrogate FcγIIIa or C1q binding
- Cell-based ADCC or CDC assays

Suzuki M, Kato C and Kato A, J Toxicol Pathol 2015; 28: 133–139

General Considerations for Potency Assays

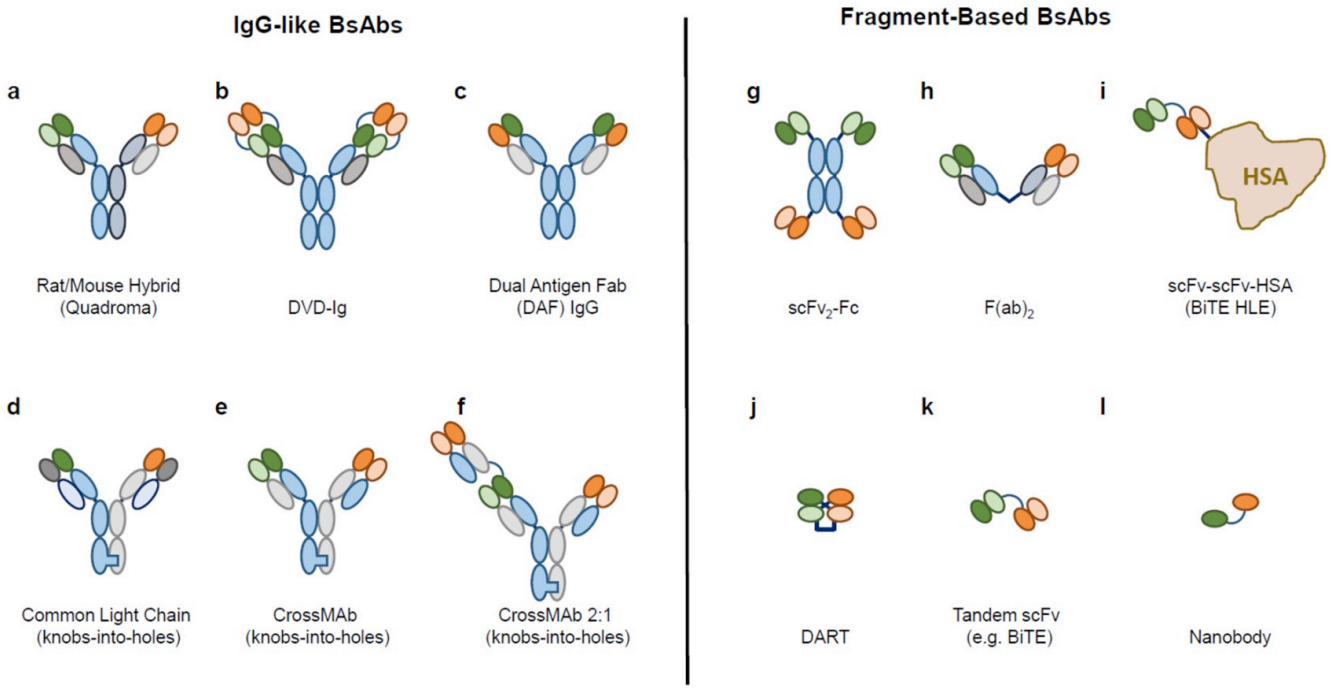
Potency assays should:

- Reflect the proposed MOA(s)
- Quantitatively measure biological activity(ies) that is/are relevant to clinical efficacy
- Be suitable for quality control environment
- Be stability-indicating
- Account for all biologically active constituents of the product

  e.g., bispecific antibodies (BsAb), antibody-drug conjugates (ADC), other antibody-fusion proteins (cytokines, enzyme, etc.)

BsAb Products

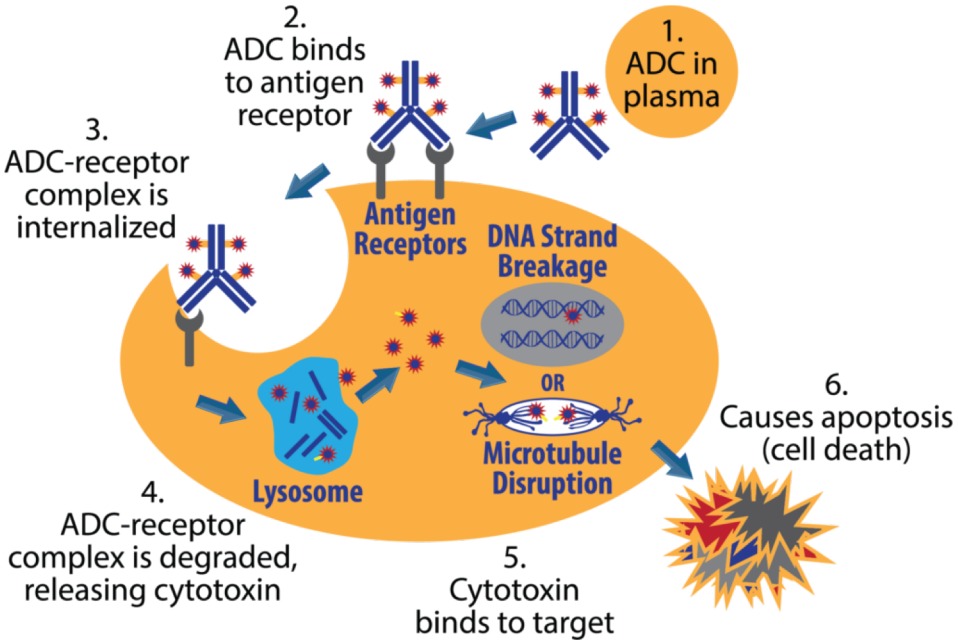
- Fab-mediated antigen binding (two or more antigens)
- Fc-mediated effector function
- Other constituents (e.g., anti-HSA single domain antibody)



Register AC, Tarighat SS and Lee HY, Int J Mol Sci. 2021 May 19;22(10):5350

ADC Products

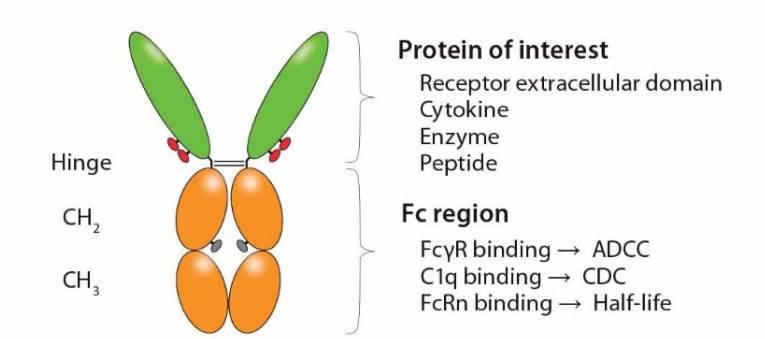
- Antigen binding assay: Demonstrates a critical step in the ADC MOA.
- Cell-based cytotoxicity assay: Demonstrates the ADC MOA, including target binding, internalization, drug release, and cell killing.
- Bystander effect: If the bystander effect is a proposed MOA for an ADC, bystander effect activity should be characterized.
- Effector function.



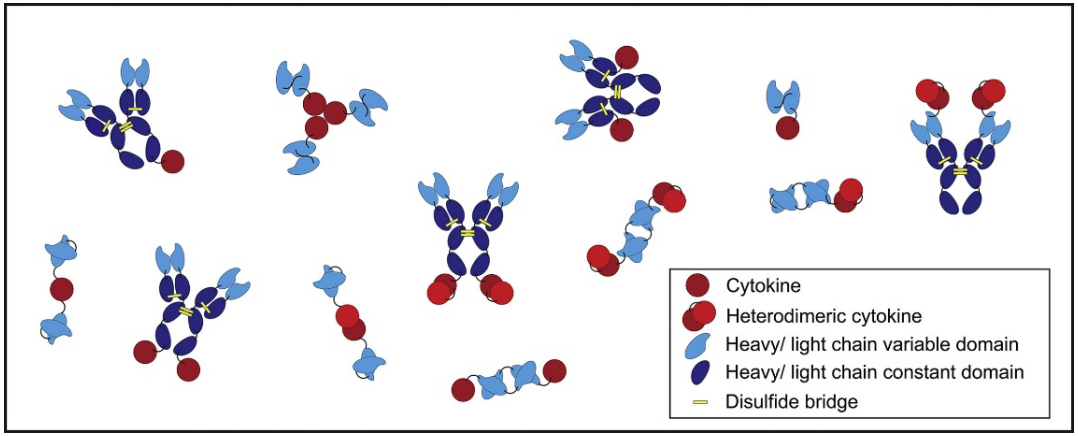
https://njbio.com/antibody-drug-conjugates/

Other Antibody-Fusion Proteins

- Fusion protein portion
  - Receptor extracellular domain
  - Cytokine
  - Enzyme
  - Peptide
- Antibody portion
  - Fab
  - Fc



https://bioprocessintl.com/manufacturing/monoclonal-antibodies/immunoglobulin-fc-fusion-proteins-part-1-design-manufacture/



Hutmacher C and Neri D, Adv Drug Deliv Rev. 2019 Feb 15;141:67-91.

Common Issues in IND Submissions

- Potency assay(s) only reflect part of the MOAs.
  - No potency assays for effector functions, where effector functions are part of the MOAs.
  - No cytotoxicity assay for ADC products.
- For BsAb products, is binding to both antigens at the same time required for efficacy?
  - When required, e.g., a BsAb that is designed to bridge two target cells, potency assay(s) that reflect simultaneous engagement of both targets are preferred.
  - When not required, e.g., a BsAb that targets two soluble cytokines, two independent potency assays can be developed to measure the engagement of each target individually.

Example Comments for INDs

For a bispecific antibody with effector function as part of MOA:

It appears that besides the Fab region mediated binding and inhibition of xxxxxx activity, the **Fc region mediated effector function** is also part of the proposed mechanisms of action (MOA) and therefore **should be monitored as part of the quality control strategy**….a potency assay measuring the effector function should be included in xxxxxx release and stability specifications.

A comment may be communicated regarding additional control of effector function by a release specification for drug substance to assess the glycan profile:

…This release test generally provides control over levels of **individual and total afucosylated glycans(including high mannose) and galactosylation**, which are generally accepted/known to impact binding to FcγRIIIa and C1q, respectively.

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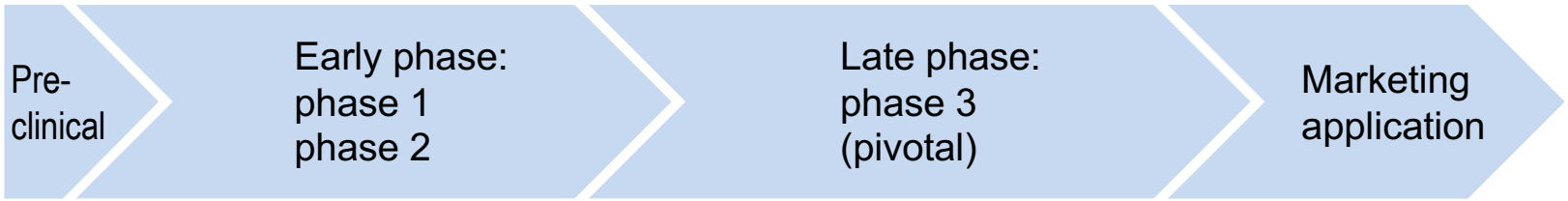
Phase-appropriate Potency Assay Development



- Initial potency assay based on proposed MOA
- Binding assay is generally acceptable
- Broad acceptance criteria

- Knowledge build-up on MOA
- Cell-based functional bioassay should be developed
- Bridging of potency assays at different stages

- Validated cell-based functional bioassay
- Defined acceptance criteria

Example Comment for INDs

For IND submissions with only binding assays for release and stability:

While the current potency assay (i.e., antigen binding ELISA) is acceptable for initiating the proposed phase 1 clinical study, **cell-based bioactivity potency assay(s)** that reflects the mechanism(s) of action of xxxxxx should be developed and incorporated into drug substance and drug product lot release and stability testing **prior to entry into a major efficacy trial**. **Sufficient retain samples** should be appropriately stored for use **in the bridging studies** to support the development of a new potency assay and ensure lot-to-lot consistency with regard to potency.

Example Comment for INDs

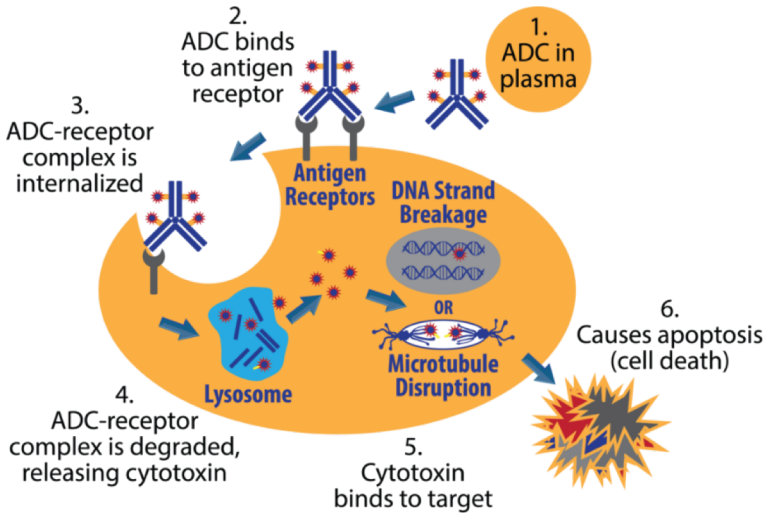
For a bispecific antibody with effector function as part of MOA:

Surrogate assays (e.g., binding to FcγRIIIa or C1q) may be sufficient to initiate the IND, but we encourage you to introduce **a functional assay** as soon as possible and, where necessary, bank samples in order to ensure lot-to-lot consistency with regard to potency and support a future specification or control strategy (i.e., an in-process test with reject limit).

Although a cell-based bioassay is recommended to assess and control potency, **it may be possible to justify the continued use of a surrogate assay** during development for activities such as lot release, provided **the surrogate assay is demonstrated to be suitably sensitive to product variants and modifications expected to affect potency**, e.g., through a direct comparison to the assay(s) developed to reflect the in vivo mechanism of action. We recommend that you collect adequate data from the cell-based assay(s) during development to inform the control strategy during development and in the license application."

ADC Products

- **Both antigen binding and cell-based cytotoxicity assays** are generally expected to be included in the drug substance/drug product release and stability specifications **in the original IND submission**.
- If a cell-based cytotoxicity assay is not available as a potency assay initially, it should be at least included in ADC characterization. In addition, potency should be controlled by additional attributes/methods, e.g., by a well-controlled drug-to-antibody ratio (DAR).
- The lack of antigen binding assay for drug substance and drug product may possibly be justified with supporting data.



https://njbio.com/antibody-drug-conjugates/

Take-Home Messages

- Ideally, potency assays should account for all biologically active constituents of the product

- Development of potency assays should be phase-appropriate

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