Regulatory Considerations for Multispecific Products

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Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

The views expressed in this presentation do not represent official FDA policy but are the opinions of the presenter.

They are based on experience as a member of OPQ assessment staff and should not be used in place of regulations, published FDA guidance, or discussions with the Agency.

OUTLINE

- Approved Bispecific Antibody-Based Drugs at FDA
- Validation of Multispecific Manufacturing Processes
  - Impurity Control
  - Characterization and Method Validation
- Considerations for Specifications
- Wrap-up

TYPES OF MULTISPECIFICS

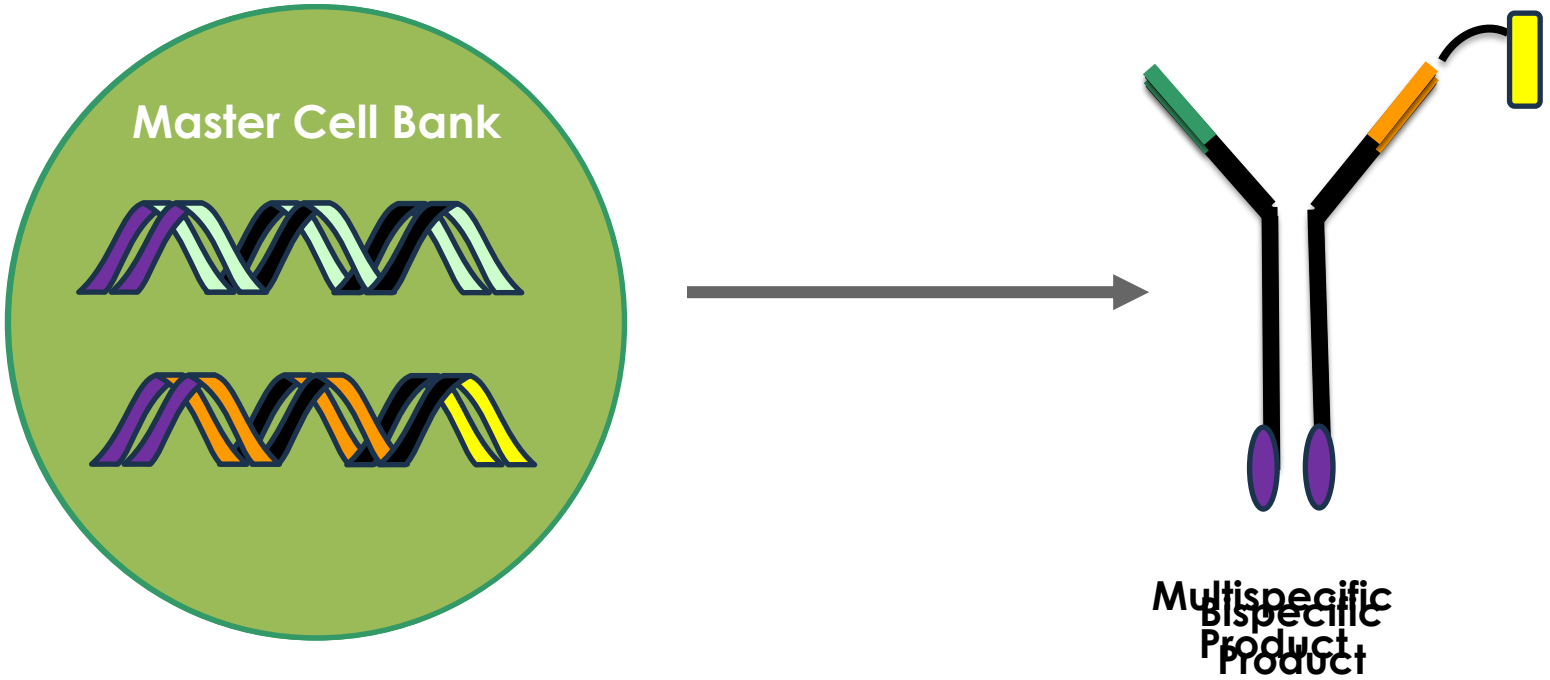
- **Bispecific IgGs**
- **Multispecific antibody fragments (joined with linker(s))**
- **IgGs with tandem binding segments added**
- Multispecific fusion proteins
- Multispecific antibody conjugates

FDA APPROVED BISPECIFICS

Blincyto (Blinatumomab)	Amgen	α-CD3, α-CD19	2014
Hemlimbra (Emicizumab)	Genentech/Roche	α-FIXa, α-FX	2017
Rybrevant (Amivantamab)	Janssen Biotech	α-EGFR, α-MET	2021
Kimmtrak (Tebentafusp-tebn)	Immunocore	α-CD3, α-gp100/MHC	2022
Vabysmo(Faricimab-svoa)	Genentech/Roche	α-VEGF-A, α-Ang-2	2022
Tecvayli (Teclistamab-cqyv)	Janssen Biotech	α-CD3, α-BCMA	2022
Lunsumio (Mosunetuzumab-axgb)	Genentech	α-CD3, α-CD20	2022
Epkinly (Epcoritamab-bysp)	Genmab/ Abbvie	α-CD3, α-CD20	2023
Columvi (Glofitamab-gxbm)	Genentech	α-CD3, α-CD20	2023
Talvey (Talquetamab-tgvs)	Janssen Biotech	α-CD3, α-GPRC5D	2023
Elrexfio (Elranatamab-bcmm)	Pfizer	α-CD3, α-BCMA	2023
Imdellra (Tarlatamab-dlle)	Amgen	α-CD3, α-DLL3	2024
Ziihera (Zanidatamab-hrii)	Zymeworks/Jazz	Distinct HER2 epitopes	2024
Bizengri (Zenocutuzumab-zbco)	Merus	α-HER2, α-HER3	2024
Lynozyfic (Linvoseltamab-gcpt)	Regeneron	α-CD3, α-BCMA	2025

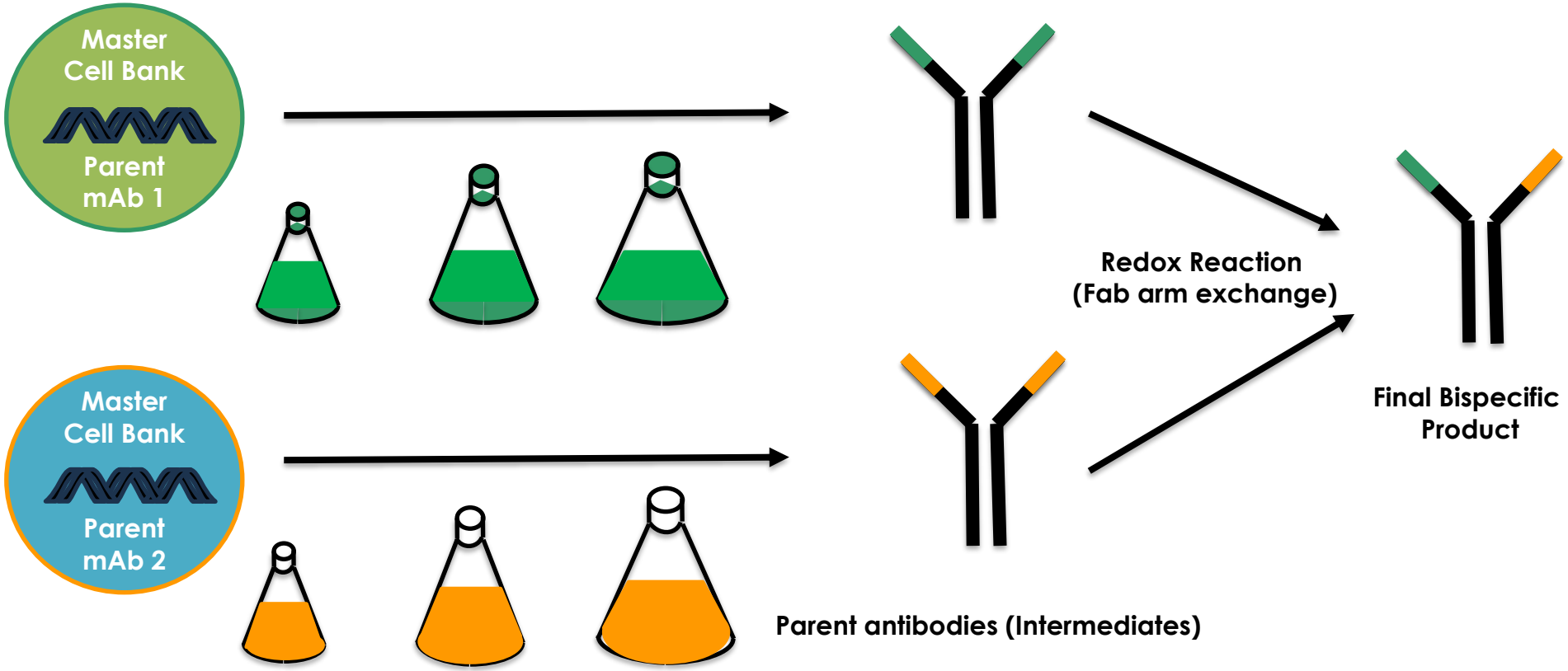
Bispecific antibody expression

- Can have multiple constructs in one cell line
- Often, engineering of heavy chains favors bispecific pairing



Process Validation

- However, many products utilize multiple cell lines and parallel upstream processes



PROCESS VALIDATION

Multiple upstream processes means:

- Multiple cell banks need to be qualified
- **Multiple seed trains: more raw materials, more time**
- Adequate control needs to be demonstrated for
  - Intermediates (e.g., parent antibodies)
  - Arm exchange (redox) reaction

PROCESS VALIDATION

Regardless of design of upstream, validation of downstream:

- Removal of unpaired and mispaired products- as well as aggregates and fragments- by downstream steps
- Methods should be adequate to demonstrate control both process- and product-related impurities specific to such a process
- Process criticalities based on CQAs; **methods pivotal in control strategy**

CRITICAL QUALITY ATTRIBUTES

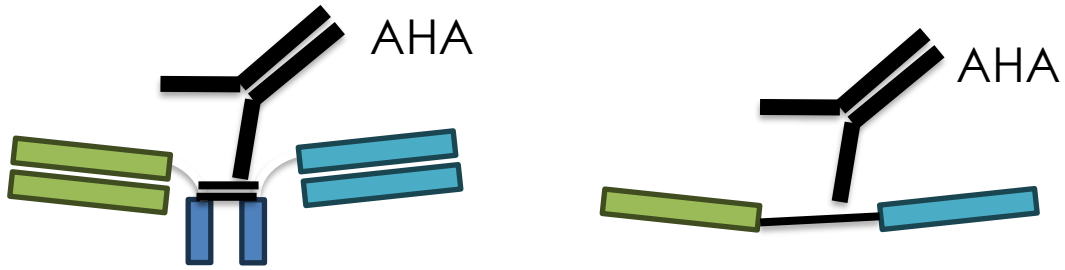
Some critical quality attributes to consider for multispecifics:

- **Homodimers** should be characterized to inform criticality (of attribute and of process steps/parameters that affect them)
- Product **aggregates** can be hyperpotent: Synergistic T-cell activation is a potential safety issue
- Products comprised of fragments joined by **gly-ser linkers: O-linked glycans** can be CQAs

Both process and product control may require more precision- and **more assays**- than with a typical mAb

"AHA!": Another Attribute

- IgG-based sequences used in novel constructs can result in increased accessibility of sequences



  - Find reactivity w/ pre-existing **"AHA"=** anti-hinge antibodies
  - Higher levels found in autoimmune populations, cancer patients, e.g.
- Does not necessarily preclude approval, but risk assessment, ADA/NAb assay validation and performance, and discussion with interdisciplinary FDA team are important

Zhou et al, 2022; JITC

CD3 homodimers: Characterization

- Despite accelerated development, solid risk assessment required. Supportive data might include:
  - Nonclinical studies (e.g., cytokine release profile of homodimer)
  - Levels present in clinical batches (and use of these batches)

Additional methods may be required for adequate control of all product-related impurities, given their potential for increased clinical impact for many therapeutics in this class

Haber, L., Olson, K., Kelly, M.P. *et al.* Generation of T-cell-redirecting bispecific antibodies with differentiated profiles of cytokine release and biodistribution by CD3 affinity tuning. *Sci Rep* **11**, 14397 (2021). https://doi.org/10.1038/s41598-021-93842-0

CD3 homodimers: Clearance/Control

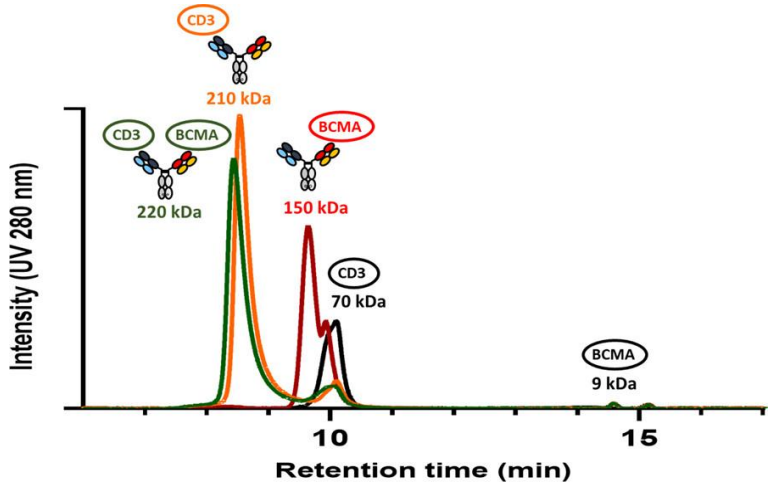
If assays have either poor or undefined sensitivity for homodimers,

- Cannot assert that no homodimers are present just because levels are ≤ LOQ
  - **Levels required for bioactivity can be very low**
- Does not justify their absence from the control strategy
  - Cannot demonstrate robust clearance/ process control
  - Higher criticality due to uncertainty
  - Engineering reduces but often doesn't fully prevent these and other high-risk impurities

Kuhn, C., & Weiner, H. L. (2016). Therapeutic Anti-CD3 Monoclonal Antibodies: From Bench to Bedside. *Immunotherapy*, *8*(8), 889–906. https://doi.org/10.2217/imt-2016-0049

Method performance

- Assay characterization
  - assays must distinguish all product-related impurities
    - Each homodimer
    - Each unpaired chain
    - This may not be the assay for aggregates/smaller fragments



- Assay validation
  - Demonstrate sensitive, reproducible, and accurate measurement of each product-related impurity

Huang et al, 2020; Anal. Chem.

Process-Related Impurity Removal

- Processes that require reduction/oxidation reactions or other reaction conditions to ensure proper pairing
- Validation of **process-related impurity clearance** is often straightforward, as small molecules are easily cleared by downstream
  - Must be demonstrated by sensitive, adequately qualified assays

SPECIFICATIONS & Analytical control strategy

- Rigorous control of product-related impurities required vs. typical mAb due to potential for higher risk
  - May require more orthogonal assays due to analytical limitations
  - Narrower acceptance criteria
    - Patient-centric approach for release and stability AC
- Method qualification and precision are paramount due to importance of impurities

Potency Control Strategy

- When simultaneous binding is not obligate
  - Can have separate binding or cell-based assays for separate activities
- When simultaneous binding is required
  - Bioassay(s) should model recruitment of effector function or other unique targeting/ proximity induction
- Surrogate cellular potency assay requires qualification against assay that reflects primary mechanism of action
  - Both may be required in characterization
- **Comparability, pre- and post-approval:**
  - Monitor individual affinities separately: Can be impacted due to cooperative binding from other modules in cell-based assays

Parting thoughts/ Related topics

- Most approved drugs in this class thus far have been granted priority status due to their clinical indications. If so, consider:
  - *Expedited Programs for Serious Conditions/Drugs and Biologics* Guidance for Industry (2014)
  - CDER OPQ MAPP 5015.13:

    "Quality Assessment for Products in Expedited Programs"

- Compatibility/in-use stability studies to ensure consistent quality upon preparation and administration
  - Describe companion diluent manufacture and control in BLA
  - Compatibility and in-use stability studies to support labeling

Current Industry Best Practice on in-use Stability and Compatibility Studies for Biological Products
Blümel, M.; Liu, J.; de Jong, I.; Weiser, S.; Fast, J.; Litowski, J.; Shuman, M.; Mehta, S.B.; Amery, L.; Tan, D.C.T. et al. *J. Pharm. Sci.* **2023**, *112*, 2332–2346, https://doi.org/10.1016/j.xphs.2023.05.002.

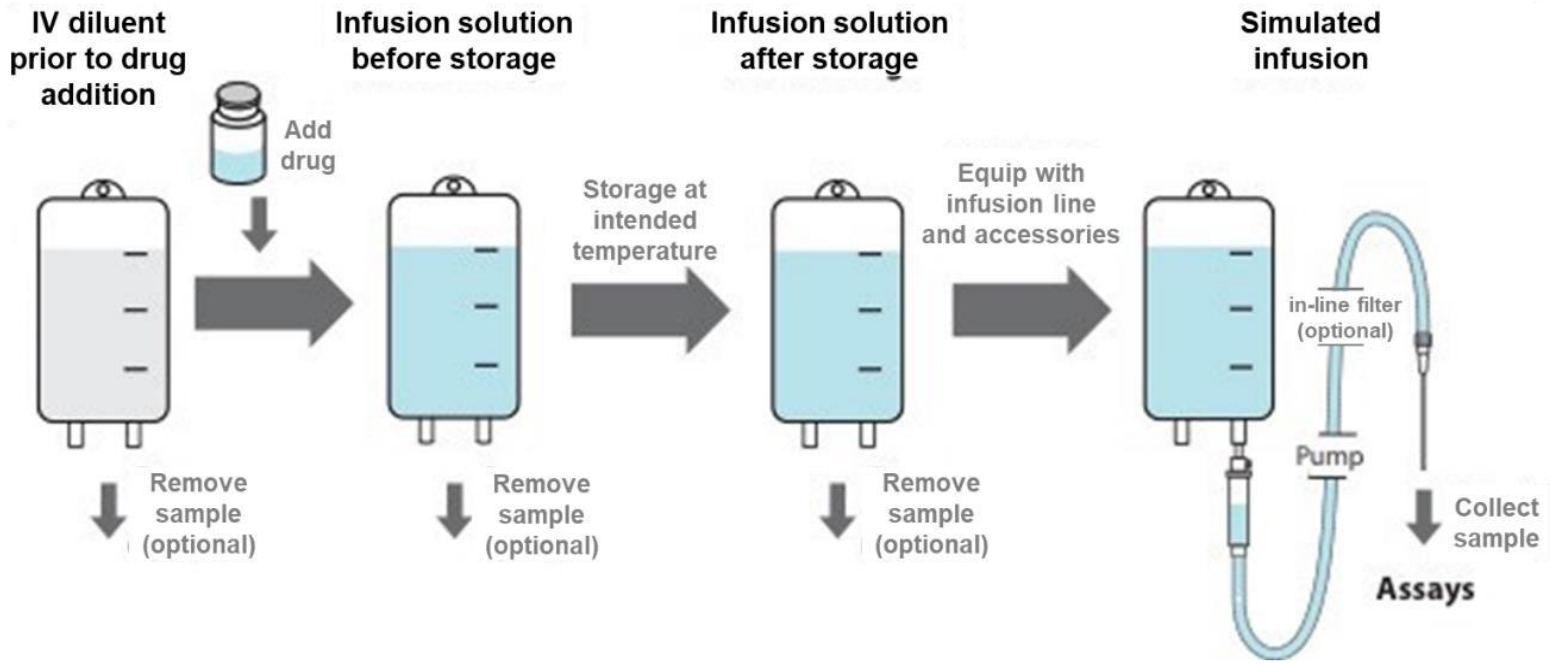


Figure 1: Elements of an in-use study for an IV administration

2024 CASS CMC Strategy Forum is summarized in ***Securing Patient Well-Being Best Practices for In-Use Stability and Compatibility Studies.*** Liu, Jing, Bluemel, Markus, Swisher, Jennifer, Jules, Felix, de Jong, Isabella, Litowski, Jennifer, Moses, Michael, Weiser, Sarah, Ibrahim, Basma, Clark, Nicholas and Hu, Qingyan (2025) BioProcess international., 23 (4). pp. 19-26.

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