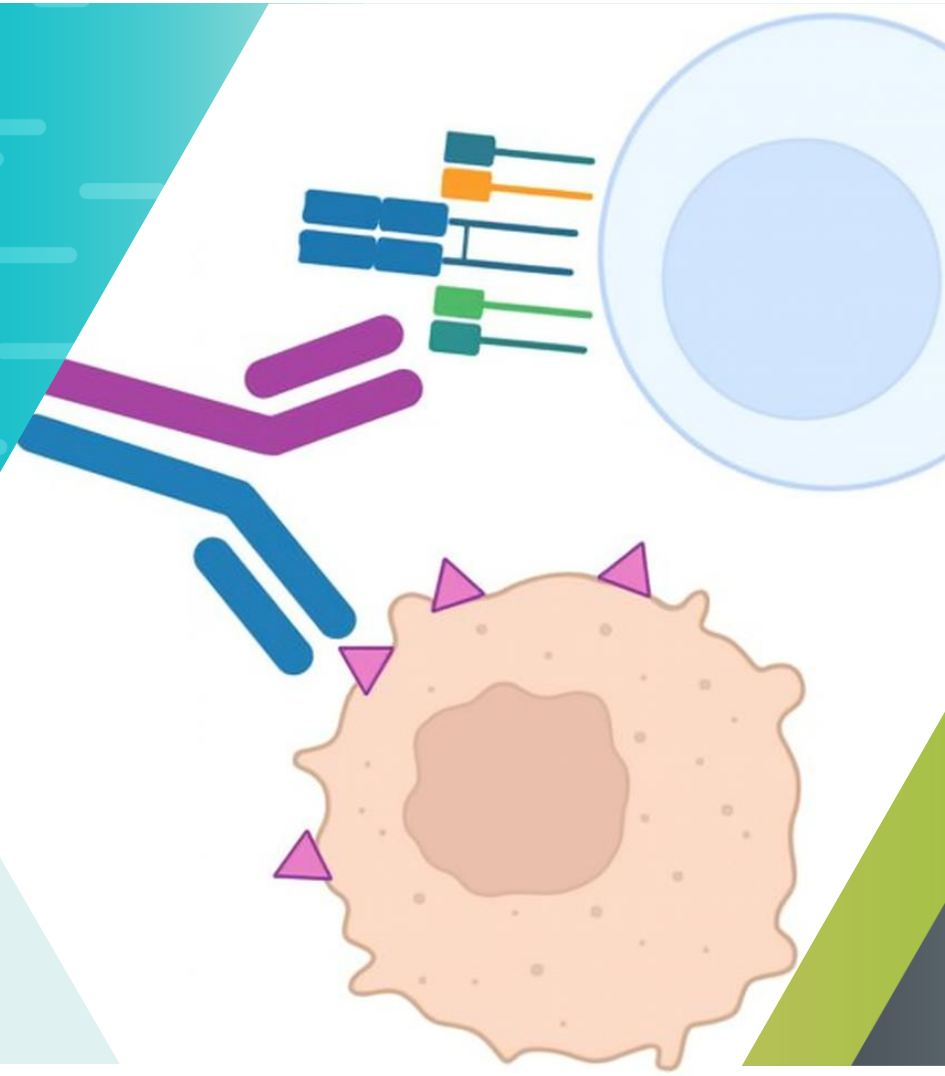
Regulatory Considerations for Early-Stage Development of Multi-specific Therapeutics



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Disclaimer

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Outline

- Review process for clinical trial applications with multi-specifics at Health Canada
- Types of multi-specific molecules
- Regulatory expectations from a biologics review perspective on what should be included in the submission
- Case studies

CMC Review Process for Clinical Trial Applications at BRDD

Office of Regulatory Affairs (ORA)

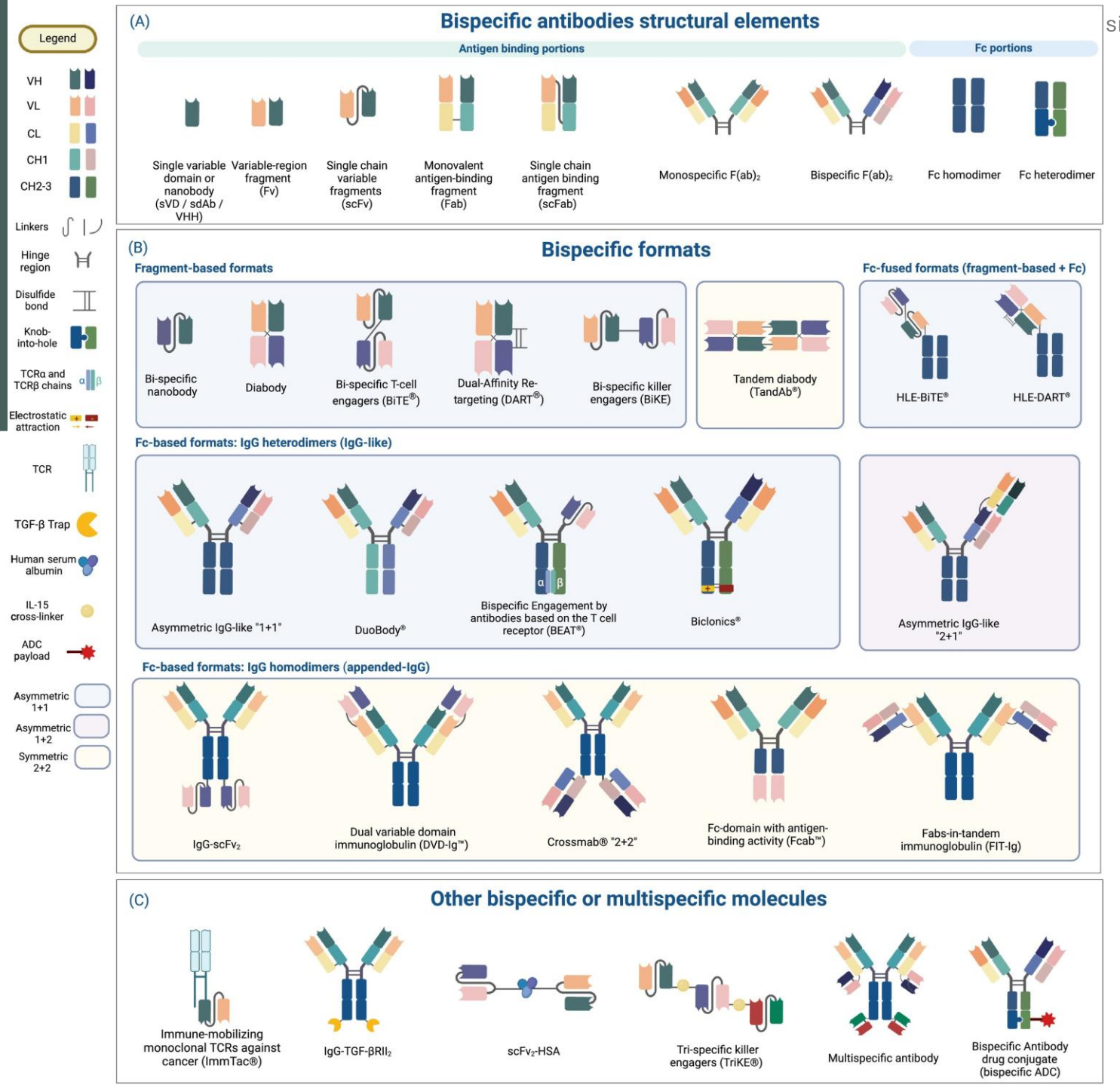
- Regulatory screening and processing (Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications - Canada.ca)
- Screening information requests for any deficiency

Biotherapeutics Quality Divisions (BQDs)

- Critical assessment of CMC information
  - QOS/IMPD in Module 2
- Quality information requests
- Final decision by BRDD issued within 30 calendar days

Bi-, tri-, and multi-specific molecules

Herrera et. al.,
Trends in Cancer, 2024



Regulatory Review of Multi-specific Molecules

FDA guidance document

- Bispecific Antibody Development Programs - Guidance for Industry.pdf

Health Canada uses risk-based approach

- Emphasis on patient safety for early-stage trials
- Harmonize requirements with other regulatory agencies

Review of Early-stage Regular IgGs vs Multi-specifics

- **Cell line development** (construct, host cell)
- **Manufacturing Process** (intermediates, affinity chromatography)
- Raw materials
- **Process-related impurities** (reagents)
- **Product-related impurities** (homodimers, mis-paired species)
- **Characterization** (correct assembly, potency)
- Comparability
- **Specifications** (aggregates, fragments)
- Batch analysis
- Reference standard
- **Stability/in-use stability**

Manufacturing Process

Cell culture

- Intermediates – culture of two mono-specifics
- Single culture with technologies for correct assembly
  - E.g. Knob-in-hole, charge pairing

Purification

- Multi-specific with Fc region
  - Protein A affinity chromatography
- Multi-specific without Fc region
  - Alternative purification strategy
    - E.g. Ion exchange, hydrophobic interaction, Histidine tag-metal affinity

Process-related impurities

Similar to regular IgG	• E.g. host cell DNA, host cell protein, antifoam, insulin, bioburden, endotoxin
Additional impurities	• Specific reagents used during cell culture or purification
Virus clearance	• Not needed if the host is bacterial cells (e.g. BiTEs)

Product-related impurities

- Aggregates and fragments
- Homodimers
- Mis-paired species
- Charged species

Characterization

Mostly similar to regular IgG

- Primary, secondary, and higher order structures
- Glycosylation pattern (if applicable)
- Other PTMs as appropriate
  - E.g. oxidized, deamidated
- Size and charge variants

Correct assembly

Homodimers and other mis-paired species

Characterization (cont.)

Biological activity/Potency

- May require multiple assays
- Binding assays may be acceptable for early-stage, but an assay representative of MOA required prior to pivotal clinical trials
  - Capture simultaneous binding
  - Fc functions, if applicable
  - Sensitive to structural changes

Types of assay

- Enzyme linked immunosorbent assay (ELISA)
- Surface plasmon resonance (SPR)
- Reporter gene assay
- Cytotoxicity assay
- Apoptosis assay

Specifications

General tests

- E.g. color, clarity, quantity, osmolality, process-related impurities, microbial safety

Product-related impurity specifications

- Aggregates and fragments
  - Medium molecular weight (MMW) species
- Homodimers and other mis-paired species
- “Report results” may be acceptable at early-stage with justification
  - E.g. Charged species

Potency

Stability

Similar to regular IgG

- Long-term, accelerated, and stressed storage conditions
- Container closure representative of the actual container closure
- Stability data support the proposed shelf life
  - Comparability demonstrated if using supportive batches

Prone to aggregation and/or degradation

- Assays to monitor aggregates, fragments, homodimers, and/or other mis-paired species

In-use stability/compatibility

- Recovery

Submission Examples

Case study 1: Asymmetric heterodimeric bispecific antibody

- Amino acid modifications to Fc region to promote heterodimer formation
- Gaps identified related to bispecific nature:
  - Homodimer impurities were not monitored
    - Indirectly monitored through SE-UPLC (HMW ≤ 5.0%)
    - Removal through CEX during manufacturing
    - Will be monitored as development progresses
    - HC assessment
      - Low levels (HMW 0.3-0.8%)
      - No safety risk from homodimers
        - Design of the bispecific antibody did not allow for formation of a sole T-cell binding molecule
        - Contribute to the mechanism of action

Case study 2: Asymmetric heterodimeric bispecific fusion protein

- Several amino acid substitutions to Fc region including for knob-into-hole
- Gaps identified:
  - Homodimer impurities were not monitored
    - No masses corresponding to homodimers during characterization
    - Hole-into-hole homodimers detected in fermentation supernatant but were removed during purification
    - Knob-into-knob homodimers were not detected
    - SE-UHPLC and non-reduced CE-SDS will be assessed for resolution of mis-paired species as the development progresses
    - Comprehensive risk assessment (biological effects) for each of the homodimers

Case study 2: Asymmetric heterodimeric bispecific fusion protein (cont.)

- Gaps identified:
  - LMW species were controlled as ≤ 15% by non-reduced CE-SDS with no justification
    - Given that this is a fusion protein, potentially include disrupted fragments
    - Characterization of each LMW variant is unavailable at the early-stage (Phase 1 / 2)
    - Strong justification for safety (no potential biological activity)
    - Increase up to ~7% observed during stability of an investigational batch (batch results < 3%)
    - The limit will be re-evaluated as the development progresses

Case study 3: Homodimeric bispecific antibody (IgG1-scFv fusion protein)

- Gaps identified:
  - Surface Plasmon resonance (SPR) based potency assay
    - Measures simultaneous binding, however, not representative of MOA (apoptosis)
    - Advised to develop a functional potency assay prior to pivotal clinical trials

Case Study 4: Homodimeric Bispecific antibody (IgG1-scFv fusion protein)

- Gaps identified:
  - Acceptance criteria for HMW species are 7% at release and 10% on stability
    - Proposed based on the limited data (2 development and 1 clinical batches)
    - Data range 2.6 - 3.2%
    - Drug product stored frozen at -20°C
    - Limits will be re-evaluated once more batch data available

Summary

- Multi-specifics pose unique challenges due to their unpredictable nature
- Monitoring of product-related impurities at early-stage
- Early focus on potency aligned with MOA
- Comprehensive clinical trial application package

Pre-submission meetings

- For all types of submissions (e.g. pre-CTA, pre-NDS, pre-SNDS)
- CMC and clinical teams can be met separately
- Can request written feedback only
- Follow-up meetings can be organized
- brdd.ora@hc-sc.gc.ca


Thank
You
Merci
Gracias
TapadhLeat
Köszönöm
Murakoze
aDank
Grazzi
Grazie
Buznyg
WaadMahadsantahay
Takk
BarakAllahuFiik
Mèsi
Chokrane
Kiitos
ThintKo
Blagodaram
Rahmat
Xièxie
Dziakuju
Mauruuru
Matondo
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TänanVäga
Aciu
Dankie
Motashakkeram
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