Health Canada Santé Canada

Canada

Bioconjugates: Navigating the Regulatory Landscape

Félix Jules, Ph.D. - Senior Biologist/Evaluator, Biotherapeutics Quality Division 2,
Biologic and Radiopharmaceutical Drugs Directorate, Health Canada

Presented at: CMC Strategy Forum North America: 2024, July 17 2024

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Disclaimers

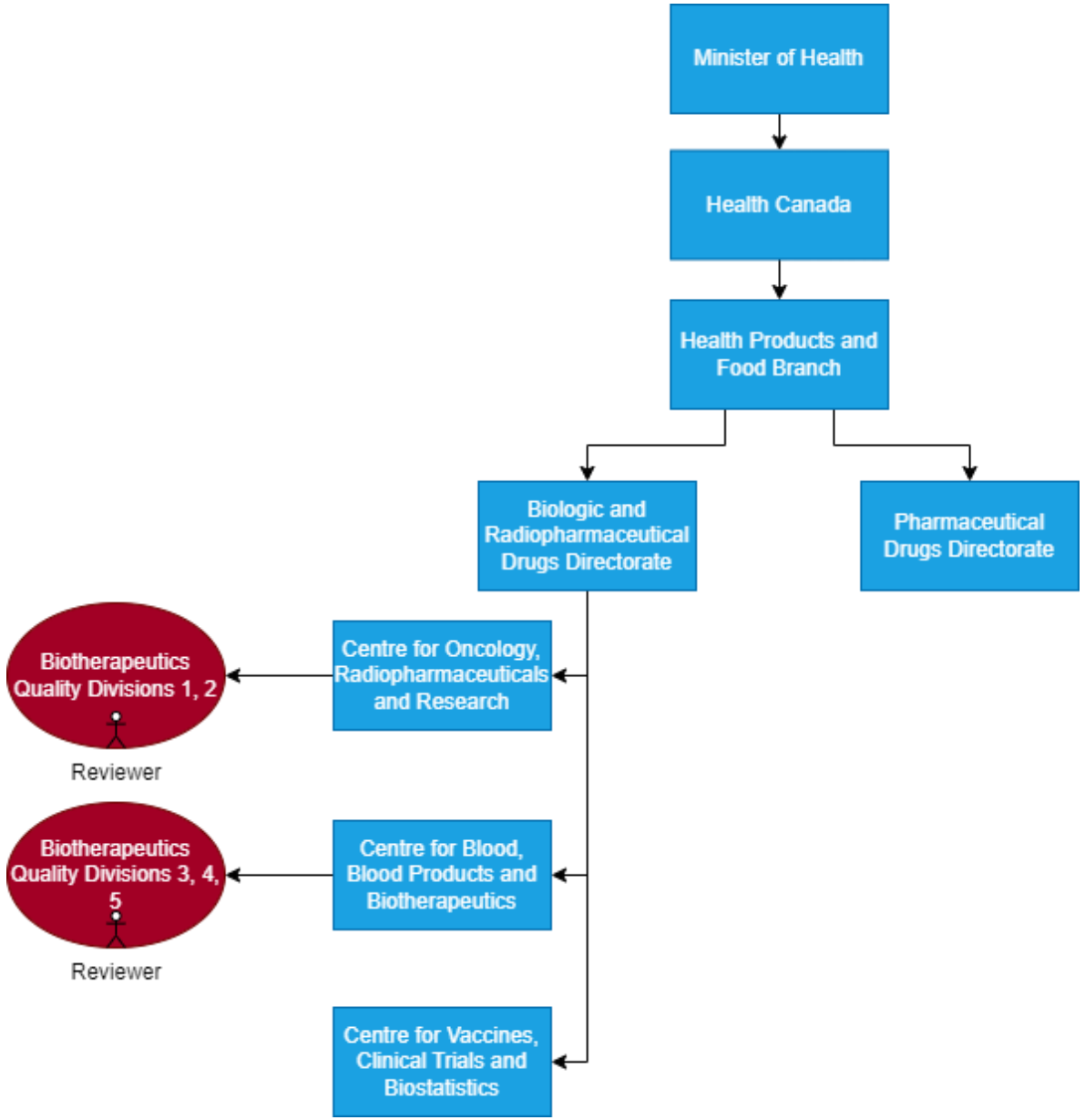
- The views expressed in this presentation are those of the presenter and do not convey official Health Canada policy

- The information in this presentation relates to the regulation of bioconjugates from a biologic drug perspective

- While the topics discussed in this presentation may be applied to bioconjugates at large, the perspectives pertain mainly to antibody-drug conjugates and pegylated proteins, which are the drugs most commonly submitted to our divisions

Presentation objectives

- Explain the bioconjugate review process at Health Canada
- Explain the regulatory expectations from a biologics review perspective on what should be included in the submission
- Provide examples from bioconjugate submissions (from clinical trials to post-approval changes)


Minister of Health
Health Canada
Health Products and Food Branch
Biologic and Radiopharmaceutical Drugs Directorate
Pharmaceutical Drugs Directorate
Centre for Oncology, Radiopharmaceuticals and Research
Biotherapeutics Quality Divisions 1, 2
Reviewer
Centre for Blood, Blood Products and Biotherapeutics
Biotherapeutics Quality Divisions 3, 4, 5
Reviewer
Centre for Vaccines, Clinical Trials and Biostatistics

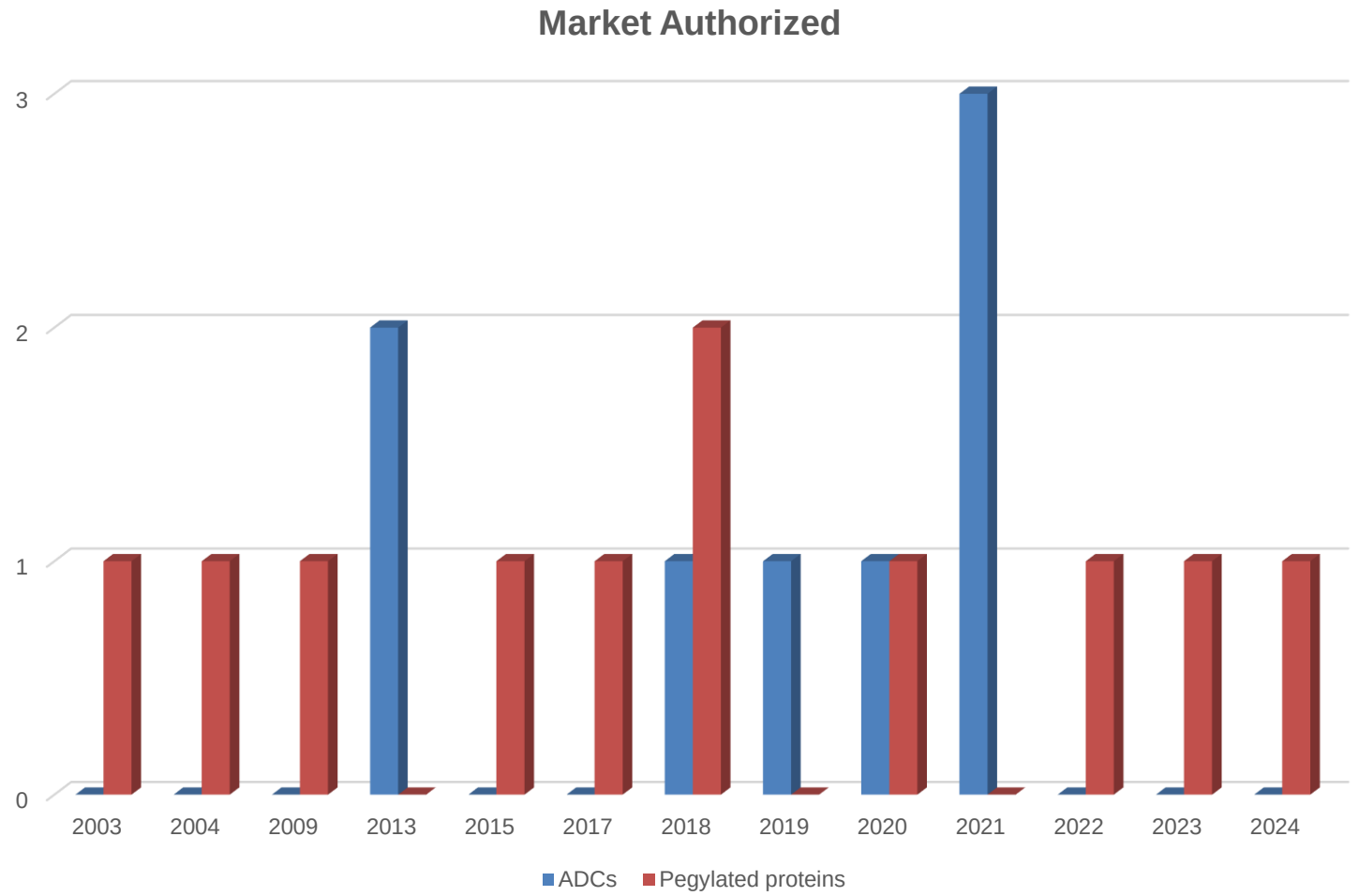
Currently authorized bioconjugates

ADCs 8:

- Adcetris
- Besponsa
- Enhertu
- Kadcyla
- Mylotarg
- Padcev
- Polivy
- Trodelvy

Pegylated proteins 11:

- Asparlas
- Cimzia
- Fulphila
- Lapelga
- Neulasta
- Niopeg
- Nivepria
- Oncaspar
- Palynziq
- Pegasys
- Plegridy



CMC review process

- Biologic and Radiopharmaceutical Drugs Directorate (BRDD) reviews
  - Biologic intermediate (e.g. antibody for an ADC)
  - Conjugated Drug substance (biologic + small molecule conjugated)
  - Drug product
  - On-site Evaluation

- Pharmaceutical Drug Directorate (PDD) reviews
  - Small molecule intermediate (linker, payload, PEG)

- Regulatory Operations and Enforcement Branch
  - Establishment licensing
  - GMP compliance (inspections)

CMC review process

- BRDD and PDD quality reviews are performed jointly
  - Pre-submission meetings
  - Informal meetings and discussions
  - Multidisciplinary status meetings may be held
  - Information requests are generally issued independently
  - Final decision is issued by BRDD

Quality submission expectations

- Complete CMC information
  - Biologic intermediate
  - Small molecule intermediate
  - Drug substance
  - Drug product
  - Diluent (if applicable)
  - Placebo (clinical trials)

Module 3 organization

- Reviewer preference
  - For each intermediate, information should be presented separately as one complete Drug Substance section (i.e. multiple 3.2.S Drug Substance sections)
  - Separate A.1 Facilities and Equipment sections (i.e. one for the small molecule intermediate(s) and one for the biologic intermediate, drug substance, and drug product)
  - If the same small molecule intermediate is used for multiple products, a DMF can be useful and should be considered
  - Letter of Access for the DMF should be provided, references within the dossier should be made to the Canadian DMF (not the same as FDA!)

BIOLOGIC INTERMEDIATE

Characterization of biologic intermediate

- Expected to be fully characterized
  - Structure (primary, secondary/tertiary)
  - Size variants
  - Charge variants
  - Post-translational modifications
  - Binding/Biological activity (if applicable)

Biological activity

- For mAbs:
  - effector functions
  - Engineered mutations

- For other molecules
  - Biological activity before conjugation should be measured and impact of conjugation assessed

Impurities

- Product-related impurities
  - Charge and size variants (characterized, impact on biological function understood, impact on conjugation)

- Process-related impurities
  - Same as for all other unconjugated biologics (viral clearance, residual DNA, bioburden, endotoxin)
  - Efficient removal should be demonstrated at the intermediate biologic manufacturing stage
  - Safety assessments for residual levels of process-related impurities should be included

BIOCONJUGATE DRUG SUBSTANCE AND DRUG PRODUCT

Characterization

- 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 (binding, effector function, other)
  - size and charge variants

Identity

- Need to distinguish between other products using the same biologic moiety
- May need to have multiple identity assays

Purity

- Largely the same methods as before conjugation
- Some methods may not be applicable to the bioconjugate
- Need to control for aggregates and fragments
- Need to control for unconjugated biologic intermediate and small molecule intermediate.
- Know which attributes are stability indicating.
- Some release tests of the biological intermediate may not be needed for the bioconjugate but this should justified

Impurities

- Residual conjugation reagents
- Carry-overs from the small molecule intermediate process
- Nitrosamines

Potency

- Assay reflective of mechanism of action
- Need to demonstrate conjugation does not affect biological activity
- If conjugation process is well controlled, may be able to eliminate potency assay of the biological intermediate but should be discussed in a pre-submission meeting with Health Canada.
- For ADCs, if effector functions are part of the mechanism of action, needs to be controlled at DS and DP release

OTHER CONSIDERATIONS

Comparability

- Comparability study expectations depend on the development stage (clinical trial vs market application)
- Comparability of the conjugated drug substance should be demonstrated when changes are made to the biologic intermediate or the small molecule intermediate
- Appropriate methods should be used to assess comparability between the toxicology, clinical, and/or commercial batches
- If certain tests are dropped for biological intermediate, conjugated DS or DP for release, data should be collected for future comparability studies

Facilities

- Segregations and controls mitigating cross-contamination risks should be well described.
- Cleaning validation reports should be provided.
- Good communication should be in place between Sponsor and CMO to provide answers to information requests
  - A facility DMF may be used to provide information directly to Health Canada
  - If there is no DMF, the information should be provided in the dossier

SUBMISSION EXAMPLES

Case study 1: Clinical trial

- ADC with MMAE

Gaps in submission:

- No safety assessments for free unconjugated cytotoxic payload and unconjugated mAb
  - Potential risk assessment supported by toxicology studies in two relevant species and clinical information available for patients treated with mAb and other approved MMAE-targeted therapies
  - Free-drug related impurities are controlled at DS release to low levels.
  - Approved doses for other MMAE-based ADCs result in higher exposure to MMAE.

Case Study 2: Clinical Trial

- Antibody-drug-siRNA conjugate

Gaps in submission:

- No safety assessment for free siRNA, free linker, free drug
  - No published data to support: requires demonstration of clearance capability and safety assessment of residual levels

Case Study 3: Biosimilar to pegylated protein

Gaps in submission:

- No CMC information provided for the PEG
- DMF referenced in the submission were not Canadian DMF
- Potentially issued Notice of Deficiency; however:
  - Canadian DMF did exist for the PEG used to manufacture the biosimilar
  - CMC information or letter of Access requested
  - Sufficient time for the PEG information to be reviewed

Case Study 4: Post-approval change

- ADC: Supplemental New Drug Submission for a new linker manufacturing site
  - Sponsor communicated with Health Canada prior to submitting the change
  - Current guidance has gaps for this type of product
    - If the quality change is to the **pharmaceutical drug only**, sponsors can refer to the requirements under Appendix 1 (Pharmaceuticals) of the Post-NOC quality guidance;
    - If the quality change is to the **mAb only**, sponsors can refer to the requirements under Appendix 3 (Biologics) of the Post-NOC quality guidance;
    - If the quality change is to the **linker only**, sponsors should consult with BRDD regarding the appropriate classification and requirements.

Conclusions

- Different directorates review the CMC portion of bioconjugates
  - BRDD is the lead directorate
- Module 3 should be organized to separate the small molecule information from the biologic intermediate, conjugated DS, and DP information
- Biologic intermediate review expectations similar to regular biologic DS

Pre-submission meetings

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

Thank you/Merci!