Navigating the Regulatory Landscape for Bioconjugates & Multispecifics

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Presented at: CMC Strategy Forum North America: July 14, 2025

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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 and multispecifics from a biologic drug perspective

The topics discussed in this presentation may be applied to bioconjugates and multispecifics, however; the perspectives pertain mainly to antibody-drug conjugates (ADC) and bispecific antibodies as these are the most common types submitted to Health Canada

Presentation Objectives

Explain the bioconjugate and multispecifics 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 and bispecific submissions

Bioconjugates & Multispecifics

Authorized bioconjugates

- Pegylated proteins (11)
- Antibody drug conjugates (9)

Authorized bispecifics

- Bispecific mAbs (5)

Novel bioconjugates & multispecifics (CTA)

- Antibody siRNA conjugate
- Antibody radiochemical conjugate
- Multispecific ADC

Health Canada

Biologic and Radiopharmaceutical Drugs Directorate (BRDD) reviews

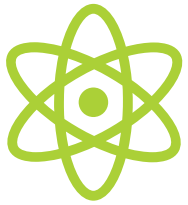
Biologic intermediate (e.g. antibody for an ADC)

Conjugated Drug substance (biologic intermediate + small molecule)

Drug product

Consistency lot testing

On-site Evaluation



Pharmaceutical Drugs Directorate (PDD) reviews

Small molecule intermediate (linker, payload, siRNA moiety, PEG)

Regulatory Operations and Enforcement Branch (ROEB)

Establishment licensing

GMP compliance (inspections)

CMC Review Process

BRDD and PDD quality reviews are performed jointly

- Information requests are generally issued independently
- Informal meetings and discussions
- Multidisciplinary status meetings may be held
- Final decision is issued by BRDD with recommendation by PDD

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 Drug Master File (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

Biologic Intermediate

Biologic Intermediate: Characterization

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

Biologic Intermediate: Biological activity

For mAbs	For all bioconjugates	For novel multispecifics
• Target binding activity • Effector functions • Engineered mutations	• Biolgical activity before conjugation should be measured and the impact of conjugation should be assessed	• Multiple assays may be needed for each function

Biologic Intermediate: Impurities

Product-related impurities

- Charge and size variants (characterized, impact on biological function, impact on conjugation, potential impact on safety)

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

Bioconjugate Drug Substance & Drug Product: Characterization

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

- Assessment of the impact on conjugation chemistry:
  - Important biological functions (binding, effector function, other)
  - Size and charge variants

Bioconjugate Drug Substance & Drug Product: Identity

Need to distinguish between other products using the same biologic moiety

May need to have multiple identity assays

Bioconjugate Drug Substance and Drug Product: 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

Bioconjugate Drug Substance and Drug Product: Process-related Impurities

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

Bioconjugate Drug Substance and Drug Product: Potency

- Assay reflective of mechanism of action (MOA)
  - If effector function is part of MOA, should be controlled at DS and DP release
- Need to demonstrate conjugation does not affect biological activity
- If the conjugation process is well controlled, the potency assay of the biological intermediate may be eliminated, however; this should be discussed in a pre-submission meeting with Health Canada.

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 release tests are dropped for biological intermediate, conjugated DS or DP, 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

- Antibody radiochemical conjugate

Gaps in submission:

- Identification of radiochemical supplier and source
- Impurity clearance of quenching agents and buffer ingredients
- Appropriate shelf-life should be established

Case Study 2: Clinical Trial

- Multispecific ADC

- Considerations for control strategy development
  - For two different targeted antigens (e.g. inflammatory and cancer cell) the control strategy should include the potential from mis-match on safety
  - For two targeted antigens on the same cell type the potential impact on potency from mis-match should be addressed (characterization)

Conclusions

Bioconjugate Review Process

Different directorates review the CMC information for bioconjugates

Module 3 should be organized to separate the small molecule information from the biologic intermediate, conjugated DS, and DP information

Novel bioconjugates and multispecifics

Control strategy considerations during development should ensure that the potency assays reflect the MOA

Pre-submission Meetings

For all types of submissions (e.g. pre-CTA, pre-NDS, pre-SNDS)

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thank you
gracias
danke
merci
obrigado
謝謝
teşekkür ederim
go raibh maith agat
dziękuję
bedankt
sukriya
kop khun krap
mochchakkeram
terima kasih
arigatō
dakujem
ngiyabonga
спасибо
Баярлалаа
рахмат
мерси
хвала
dank je
grazie
takk
tapadh leat
hvala
maururu
sagolun
감사합니다
ありがとう
ευχαριστώ
شكراً جزيلاً
taafetai lava
kiitos
dankie
blagodaram
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vinaka
misaotra
matondo
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manana
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murakoze
mamnun
djiere dieuf
chnorakaloutioun
gracies
sulpáy
taiku
tanemirt
rahmet
diolch
dhanyavadagalu
shukriya
trugarez
xiexie
najis tuke
mèsi
dekuji
sobodi
enkosi
bayarlalaa
gracie
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kam sah hamnida
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