Phase-Appropriate Analytical Method Validation: A Regulator’s Perspective

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Disclaimer

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

• Background Information
• Clinical Trial Applications
• Method Validation during Development
• General Principles of Method Validation
• Common Method Validation Issues
• Concluding Remarks
Health Canada

Health Products and Food Branch

Biologics and Genetic Therapies Directorate

Therapeutics Products Directorate

+ 11 other branches, offices and bureaus

+ 9 other directorates and offices
Tunney’s Pasture, Ottawa, ON
Biologics & Genetic Therapies Directorate (BGTD)

Health Canada's BGTD is the Canadian federal authority responsible for the regulation of biological drugs and radiopharmaceuticals for human use.
Biologics and Genetic Therapies Directorate

- Centre for Biologics Evaluation (CBE)
- Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB)

Both centres review drug submissions to ensure the quality, safety and efficacy of these products before their sale in Canada.
BGTD Quality Review Divisions

**CBE**
- Viral Vaccines Division
- Bacterial and Combination Vaccines Division
- Blood Products Division
- Blood, Cells, Tissues, Organs Divisions

**CERB**
- Monoclonal Antibodies Division
- Hormones & Enzymes Division
- Cytokines Division
- Radiopharmaceuticals & Gene Therapies Division
Clinical Trial Applications

The Food and Drugs Act and Regulations outlines Health Canada’s authority to regulate clinical trials.

Clinical Trial Applications (CTA) are required for human clinical trials using drugs not authorized for sale in Canada.

- For biologics, the sponsor should submit a completed Quality Overall Summary (QOS-B).
Clinical Trial Applications

Once the application is received by the Office of Regulatory Affairs (ORA), an acknowledgement letter will be issued to indicate that the 30-day default period has commenced.

The sponsor is responsible for resolving issues identified by Health Canada during the review process.

- Sponsors must provide the requested information within 2 days.
Clinical Trial Applications

Canada captures 4% of global clinical trials and is globally recognized for the quality and expertise of its research clinicians.

On average 900 clinical trials are conducted in Canada, yearly.

• >300 CTAs + CTA-As are reviewed by CERB Quality at BG TD, yearly
Terminology

- Qualification
- Validation
- Verification
Method Qualification

An acceptable level of method performance evaluation applied to analytical methods used in early development.

– to assess suitability of purpose
– scientifically sound (accurate, precise, specific)
Method Validation

Documented evidence that an analytical method is suitable for the intended purpose.

- accurate, sensitive, specific, reproducible, robust and transferrable
- for in-house methods

ICH Harmonised Tripartite Guideline

Validation of Analytical Procedures: Text and Methodology
Q2(R1)
Method Verification

A validated method performs according to specifications when executed for the first time using the personnel, equipment, and reagents available.

- compendial methods
- transfer of validated methods
Method Validation Data for CTAs

Fully validated analytical methods are not required for clinical trial applications.

CERB quality does not (directly) review analytical method validation data during the review of clinical trial applications.

– safety is the review priority
Method Validation Expectations

We expect the sponsor to understand the purpose of the analytical method at each phase:

I. ensuring product safety and potency during early development,

II. monitoring manufacturing consistency during late-stage development,

III. to final method validation as per ICH guidelines for market application.
Method Review for a CTA

Does the application contain a suitable method for each quality attribute according to ICH Q6B?

- Appearance and description
- Identity
- Purity / Impurities
- Potency
- Quantity
- Pharmacopoeial specifications

Are there any additional attributes/impurities that may impact product quality that are identified during characterization but not included in the control strategy?
Method Review for a CTA

The methods need to be sufficiently developed to ensure the acceptance criteria are meaningful (at that phase of development).

- Report results
- Comparable to reference standard
  - 50-150% → 60-140% → 70-130%
  - >90% → >95% → >98%
Exceptions

Biosimilars
• Product quality development is expected in advance of the clinical trials
• Characterization of the reference biologic

Process Performance Qualification (PPQ) Approach
• Commercial process is validated prior to the completion of the clinical program
Method Review for a CTA

If, at any point, during the review it is determined that the method is not suitable or the acceptance criteria is not meaningful, an Information Request may be issued.

- The sponsor will be expected to provide data to support that the method is suitable for purpose.
Method Validation during Development

It is the responsibility of the sponsor to ensure that analytical method development mirrors the clinical program in order to have fully validated methods prior to manufacture of the process validation batches.
Method Validation for NDS

- Validated analytical methods are a critical component of the manufacturing process control strategy.

- The overall objective of method validation is to demonstrate that the analytical method is suitable for the intended purpose.
Common Method Validation Issues

- Wide validation acceptance criteria that is not well justified
- Incomplete system suitability criteria
- Inappropriate method controls
- Linearity assessed using serial dilution
- No product/assay control sample in bioassay
- Plate effects not evaluated
- Bioassay does not reflect the mechanism of action
- LOQ is not within the validated linear range
- Specification does not fall within the validated linear range
Common Method Validation Issues

- Validation conditions/equipment are different than the method SOP
- Method is validated for purity but not impurities
- Specificity does not include other products manufactured at the same site
- Stressed samples not used for validation of impurity detection
- Impurities levels detected below the LOQ reported numerically
- Method fails robustness evaluation and parameters not reflected in the method SOP
- Robustness assessment is minimal
Concluding Remarks

Although, at BGTD we do not review method validation in detail for CTAs, we do expect that product development will mirror the clinical development program.

- Full analytical method validation is expected to be completed prior to the manufacture of the process validation batches.
  - ICH Q2, Validation of Analytical Procedures
  - ICH Q6B, Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
Contact

Health Canada invites sponsors to request a pre-CTA consultation meeting, at any time.

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