Health Canada’s Experience with Bioassays used for Consistency Testing of Biotherapeutic Products

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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
- Quality Review Process for New Drug Submissions
- Lot Release Program for Schedule D Drugs
- Consistency Testing of Biotherapeutic Products
- Case Studies
- Concluding Remarks
Biologics & Genetic Therapies Directorate:

- Health Canada's BGTD is the Canadian federal authority responsible for the regulation of biological drugs (i.e. drugs listed on Schedule D to the Food and Drugs Act) and radiopharmaceuticals for human use.
Schedule D to the Food & Drugs Act
Includes:

• Names of individual products (such as “insulin”).

• Product classes (such as “immunizing agents”).

• References to particular sources (such as “drugs, other than antibiotics, prepared from microorganisms”).

• Methodology (such as “drugs obtained by recombinant DNA procedures”).
Examples of Biological Drugs Regulated by BGTD:

- Viral, bacterial and combination vaccines.
- Cell and gene therapies.
- Blood and blood products.
- Tissues and organs for transplantation.
- Cytokines.
- Hormones.
- Enzymes.
- Monoclonal antibodies.
New Drug Submission (NDS):

- Manufacturer or Sponsor seeking to market a biologic drug in Canada must file a NDS with BGTD.

- Review target of 300 calendar days.

- For NDS with Priority Status review target is shortened from 300 to 180 calendar days.

- BGTD evaluates the safety, efficacy and quality data to assess the potential benefits and risks of the drug.
BGTD Evaluation Centres:

- Centre for Biologics Evaluation (CBE).
- Centre for Evaluation of Radiopharmaceuticals & Biotherapeutics (CERB).
NDS Quality Evaluation:

• For a biological drug, the NDS Quality Review is based on:
  - Dossier review
  - On-Site Evaluation
  - Consistency Testing

• These 3 elements of the Quality Review are leveraged to make rational, science-based risk assessments and develop risk management strategies.
Lot Release Program for Schedule D Drugs:


- The risk-based Lot Release Program covers both pre- and post-market stages.

- Products are assigned to one of four Evaluation Groups, with each group having different levels of regulatory oversight (testing and/or protocol review) based on the degree of risk associated with the product.
GROUP 1: Pre-Approval Stage

• All products under review as a Clinical Trial Application (CTA), or New Drug Submission (NDS), and in some cases a Supplementary New Drug Submission (S/NDS), are assigned to Evaluation Group 1 during the review period.
GROUP 1: Pre-Approval Stage

<table>
<thead>
<tr>
<th>Evaluation Group Description</th>
<th>GROUP 1A</th>
<th>GROUP 1B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Trials</td>
<td>NDS or S/NDS submissions</td>
</tr>
<tr>
<td>Sample Requirements</td>
<td>• <em>Prophylactic Vaccines</em>: Samples submitted for testing by BGTD</td>
<td>Samples from 3 to 5 consecutively manufactured lots are submitted to BGTD for lot-to-lot consistency testing</td>
</tr>
<tr>
<td></td>
<td>• <em>Other Biologics</em>: No samples required</td>
<td></td>
</tr>
<tr>
<td>Document Requirements</td>
<td>• <em>Prophylactic Vaccines</em>: Submission of Protocols of tests and/or CoAs to BGTD for review</td>
<td>Submission of Protocols of tests and/or CoAs to BGTD for review</td>
</tr>
<tr>
<td></td>
<td>• <em>Other Biologics</em>: Sponsors are required to complete and file a Fax-back form, which must include a rationale if testing specifications have not been met</td>
<td></td>
</tr>
</tbody>
</table>
Consistency Testing:

- A subset of the product’s release tests are selected based upon:
  - Probative/investigational value.
  - Available resources.
## GROUP 2 to 4: Post-Approval Stage

<table>
<thead>
<tr>
<th>Evaluation Group Description</th>
<th>GROUP 2</th>
<th>GROUP 3</th>
<th>GROUP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Sample Testing &amp; Protocol Review”</strong></td>
<td>Products requiring the highest level of assessment after issuance of an NOC.</td>
<td>Products requiring a moderate level of assessment after issuance of an NOC.</td>
<td>Products requiring a low level of assessment after issuance of an NOC.</td>
</tr>
<tr>
<td><strong>Sample Requirements</strong></td>
<td>Targeted Testing. Mandatory submission of samples of all lots to BGTD for testing.</td>
<td>No sample testing. At the discretion of BGTD, samples may be requested for Periodic Testing.</td>
<td>No sample testing. At the discretion of BGTD, samples may be requested for Periodic Testing.</td>
</tr>
<tr>
<td><strong>Document Requirements</strong></td>
<td>Submission of Protocols of tests and/or CoAs to BGTD for review.</td>
<td>Submission of Protocols of tests and/or CoAs to BGTD for review.</td>
<td>No protocol review. Drug manufacturer g is required to notify BGTD via Fax-back when a lot is to be sold in Canada.</td>
</tr>
<tr>
<td><strong>Approval Mechanism</strong></td>
<td>A written approval for sale in the form of a Release Letter is required for all lots.</td>
<td>A written approval for sale in the form of a Release Letter is required for all lots.</td>
<td>A Release Letter is not required prior to sale.</td>
</tr>
<tr>
<td><strong>Target Timeline</strong></td>
<td>6 weeks after receipt of all required information and samples. Expedited release may be granted in exceptional cases and upon appropriate justification such as product shortage.</td>
<td>2 weeks after receipt of all required information. If Periodic Testing samples are requested by BGTD, the target timeline is 6 weeks.</td>
<td>If Periodic Testing samples are requested by BGTD, the target timeline is 6 weeks.</td>
</tr>
</tbody>
</table>
Factors Considered During Assignment of Products to Evaluation Groups:

- Product indication.
- Nature of the Product.
- Product history.
- Inspection history.
- Testing history.
- Post-market Experience.
Assignment to Evaluation Group 4:

- Products that are produced from well controlled raw materials through reliable and consistent processes, and that can be readily assessed with respect to identity, purity and potency through reliable test protocols may be assigned to Evaluation Group 4 at the time of approval.
- Products may be re-assignment to a different Evaluation Group.
- Movement through Evaluation Groups may be bi-directional.
BGTD Quality Review
Divisions:

- BGTD
  - CERB
    - Monoclonal Antibodies Division
    - Hormones & Enzymes Division
    - Cytokines Division
    - Radiopharmaceuticals & Gene Therapies Division
    - Viral Vaccines Division
    - Bacterial & Combination Vaccines Division
  - CBE
    - Blood Products Divisions
    - Blood, Cells, Tissues Organs Division
    - Regulatory Research Division
Types of Potency Assays Performed by CERB’s Potency Lab (2005 - 2014):

<table>
<thead>
<tr>
<th>Assay Type</th>
<th>Number of Different Assays Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Proliferation:</td>
<td>10</td>
</tr>
<tr>
<td>Cell Survival:</td>
<td>9</td>
</tr>
<tr>
<td>Reporter Gene:</td>
<td>9</td>
</tr>
<tr>
<td>Binding (other than ELISA):</td>
<td>5</td>
</tr>
<tr>
<td>CDC:</td>
<td>3</td>
</tr>
<tr>
<td>Apoptosis:</td>
<td>2</td>
</tr>
<tr>
<td>ELISA (binding):</td>
<td>2</td>
</tr>
<tr>
<td>Induction (Cell &amp; ELISA):</td>
<td>2</td>
</tr>
<tr>
<td>ADCC:</td>
<td>1</td>
</tr>
<tr>
<td>Cellular Uptake:</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>44</strong></td>
</tr>
</tbody>
</table>
Number of Assays Performed by CERB’s Potency Lab per Year (2005 - 2014):
CERB’s Potency Lab Consistency Lot Testing Process:

1. Documentation Review
2. Feasibility Assessment
3. Sample Request
4. Review of Response to Sample Request
5. In-House Setup of Method & Preliminary Assays
6. Consistency Lot Testing
7. Final Report & Recommendation

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Typical Sample Request for Bioassays:

- Samples from 3 consecutively manufactured Drug Product lots.
- Two frozen vials from assay working cell bank.
- Samples of Reference Standard.
- Samples of Assay Control.
- Critical reagents (e.g. FBS, growth factors, etc.).
- CoAs as well as corresponding bioassay raw data, worksheets, & data analyses for the requested Drug Product lots.
In-House Set-Up of Bioassays:

- For in-house testing, several adaptations are made to the Manufacturer’s SOP in order to accommodate operational limitations as well as differences in equipment & software analysis tools.
- In order to verify the in-house set-up (i.e. evaluate the appropriateness of the adjustments), two additional control samples are included on every assay plate.
- Control samples consist of reference standard preparations at 75% and 125% of the reference standard nominal concentration.
In-House Set-Up of Bioassays (continued):
In-House Set-Up of Bioassays (continued):

![Graph showing estimated relative potency vs. target relative potency with R² = 0.977]
Overview of Case Studies:

<table>
<thead>
<tr>
<th>CASE STUDY #:</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBMISSION TYPE:</td>
<td>NDS</td>
<td>NDS</td>
<td>NDS</td>
<td>Priority NDS</td>
</tr>
<tr>
<td>LOT RELEASE GROUP</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASSIGNMENT</td>
<td>3</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>(POST-APPROVAL)</td>
<td>4</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TYPE OF INFORMATION</td>
<td>CLARIFAX</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SOLICITED DURING REVIEW</td>
<td>NOD</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Clarification Request (CLARIFAX):

- The purpose of a Clarification Request, or CLARIFAX, is to expand on, add precision to or re-analyse existing information or data in the submission.
- The solicited information must be submitted within 15 calendar days from the date of the request.
- The review of the submission will not be interrupted if a complete response is submitted within the given time frame.
Notice of Deficiency (NOD):

- If deficiencies and/or significant omissions that preclude continuing the review are identified during the review of a submission, a NOD will be issued.
- For NDSs & SNDSs, Sponsors are given 90 calendar days (or such time as agreed upon) to submit all of the solicited information.
- When the response to a NOD is found acceptable for review, a new review period (with an associated performance target) is assigned.
Case Study # 1:

Test Results (mean ± 95 %CI)

<table>
<thead>
<tr>
<th>LOTS</th>
<th>LOT A</th>
<th>LOT B</th>
<th>LOT C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98.4%</td>
<td>95.8%</td>
<td>104.8%</td>
</tr>
<tr>
<td>75% RS</td>
<td>95.5%</td>
<td>98.0%</td>
<td>104.5%</td>
</tr>
<tr>
<td>125% RS</td>
<td>3.0%</td>
<td>-2.2%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

BGTD Mean Relative Potency ($\alpha$):

Sponsor’s Mean Relative Potency ($\beta$):
Case Study # 1 - Outcome:

- Product in question was assigned to Lot Release Evaluation Group 4 (Notification & Periodic Testing).
Case Study # 2:

Test Results (mean ± 95 %CI)

RELATIVE POTENCY (%)
Case Study # 2:

- Manufacturer was asked via CLARIFAX to comment the unexpected Assay Control results obtained by BGTD.

- Manufacturer confirmed that the Certificate of Analysis (CoA) for the Assay Control contained insufficient direction to correctly perform the dilution and was confusing when compared with the method SOP.
Case Study # 2 - Outcome:

• In response to the CLARIFAX, Manufacturer committed to revise CoA for the Assay Control & to review all supporting documentation.

• Response to CLARIFAX was satisfactory.

• Product in question was assigned to Lot Release Evaluation Group 4 (Notification & Periodic Testing).
## Case Study #3:

### LOT A

<table>
<thead>
<tr>
<th>PLATE</th>
<th>Sponsor %RP</th>
<th>BGTD %RP</th>
<th>%Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>119.7</td>
<td>120.7</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>102.4</td>
<td>102.4</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>111.1</td>
<td>137.3</td>
<td>23.6</td>
</tr>
</tbody>
</table>

RP% (n=3) | 111.1 | 120.1 | 8.15 |

### LOT B

<table>
<thead>
<tr>
<th>PLATE</th>
<th>Sponsor %RP</th>
<th>BGTD %RP</th>
<th>%Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141.8</td>
<td>158.1</td>
<td>11.5</td>
</tr>
<tr>
<td>2</td>
<td>98.6</td>
<td>101.9</td>
<td>3.4</td>
</tr>
<tr>
<td>3</td>
<td>109.1</td>
<td>132.6</td>
<td>21.5</td>
</tr>
</tbody>
</table>

RP% (n=3) | 116.5 | 130.9 | 12.32 |
Bioassay Best Practices:

1. Fit separate curves for test and reference sample.

2. Test the curve-shape parameters for similarity.

3. If similar, fit constrained model in order to estimate relative potency.
Constrained Model:

- Relative potency is best determined by fitting the constrained model.

- The reason for this is that relative potency can only be strictly defined between two perfectly parallel functions.
Constrained Model (continued):

• If the two dose-response curves are perfectly parallel, then every point on the curve is equidistant from its counterpart on the other curve and the ratio of IC50 (or EC50) is an accurate representation of relative potency.

• However, if the two curves are not perfectly parallel, then it is not possible to predict a priori which point on the curve represents an accurate measure of relative potency.
Unconstrained Model:
Unconstrained Model (continued):
Case Study # 3 – Outcome:

• Manufacturer was requested to revise bioassay SOP in order to incorporate the use of the constrained curve fit model.

• Product in question was assigned to Lot Release Evaluation Group 3 (Protocol Review and Periodic Testing).
Case Study # 4:

- Use of incorrect equation for calculating relative potency.
- Use of unconstrained model.
- Lack of adequate potency assay system suitability/acceptance criteria to ensure that the method is performing consistently from assay to assay and in agreement with validated parameters.
Case Study # 4 (continued):

• Due to these deficiencies, the results generated by this method were highly variable, inconsistent and unreliable which seriously hindered the evaluation and precluded any reasonable assessment of the data contained in the New Drug Submission.

• Consistency Testing was stopped.

• Notice of Deficiency was issued.
Case Study # 4 Outcome:

- Response to NOD was satisfactory.
- Product in question was assigned to Lot Release Evaluation Group 4 (Notification & Periodic Testing).
Concluding Remarks:

• The selection & design of a bioassay are crucial steps in method development & within a biological drug’s lifecycle.
• Oversights often result in bioassays that are difficult to perform and that generate questionable data.
• Complex issues are difficult to address within review timelines.
• Discuss bioassay plans & issues with regulatory agencies as early as possible.
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