Factors Affecting the Implementation of the Three Rs in Canadian Vaccine Quality Control Testing

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Background
• Vaccines must undergo extensive quality control testing for safety and potency before they are released onto the market.
• Testing typically requires large numbers of animals, often involves substantial pain and distress, and may have death as an endpoint (Council of Europe, 2008; Hendriksen, 2002).
• Alternative testing methods exist which have not yet been accepted into Canadian regulation.

Case Study
We are conducting a case study to obtain the perspectives of various stakeholders on obstacles and opportunities to implementing the Three Rs in vaccine quality control testing. Understanding these factors should facilitate the adoption of scientifically sound alternative methods into Canadian vaccine testing.

Participants
• Participants for the study are being selected through purposive sampling and snowball sampling (Palys & Atchison, 2007).
• These preliminary results are based on responses from four participants: two government regulators and two industry scientists.

Methodology
• Perspectives are being collected through in-depth, semi-structured interviews.
• Interviews are based on twelve open-ended questions.
• All interviews are audio recorded and conducted under strict anonymity.
• This study received ethical review and approval from IRB services.

Case Study Test Methods
Interviews focus on understanding factors concerning the implementation of two alternative testing strategies: one currently in use in Canada, and the other under review for implementation.

<table>
<thead>
<tr>
<th>Diphtheria/Tetanus (D/T) Potential Test</th>
<th>Acellular Pertussis Safety Test</th>
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<tbody>
<tr>
<td>Traditional animal method:</td>
<td>Alternative method:</td>
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<td>Lethal challenge in guinea pigs</td>
<td>Serological endpoint</td>
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<td>Histamine sensitization assay</td>
<td>Assay battery: in vitro binding and enzymatic assays, CHO cell assay</td>
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<tr>
<td>Implementation status:</td>
<td>Implemented in Canada in 2008</td>
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<tr>
<td>Currently under consideration</td>
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Preliminary Results
Opportunities
• Variability of Animal Tests
  A motivator for both industry and regulators to replace the histamine sensitivity assay, as varying results have led to false positives.
• Vaccine Complexity
  In vitro assays are well suited to test combination vaccines as they can be tailored to detect specific residues.
• Interest in Reduction
  Both industry and regulators expressed interest in reducing the use of animals in vaccine testing for ethical reasons. Industry also aims to use fewer animals to save resources, manpower and time.
• Harmonization Initiatives
  Industry has spearheaded harmonization efforts with international agencies to implement alternative methods.
• Publication in Pharmacopoeia
  The publication of alternative methods in pharmacopoeia gives Canadian regulators more confidence to accept a new test.

Obstacles
• Level of Assurance Required
  As healthy infants and children are the primary recipients of many vaccines, regulators and industry want a high level of confidence in new test methods, which is gained through extensive studies.
• Correlation Between Methods
  In vitro method validation is difficult due to lack of correlation between in vivo and in vitro results.
• Biological Relevance
  ELISAs for potency testing measure antibody titer, not whether these antibodies neutralize the disease toxin or antigen (N.B. this is not the case with the D/T serological assay, which has been shown to detect neutralizing antibodies).
• Market Requirements
  Manufacturers must comply with a country’s regulations and employ an animal method if requested.

The factors listed here were selected due to their high frequency of response.

Going Forward
The preliminary results suggest that industry and the Canadian government are open to implementing the Three Rs for vaccine quality control testing, but that the methods adopted must be proven to be reliable and biologically relevant. Further harmonization across countries would assist in alternative method implementation. The findings from this preliminary analysis will be expanded through the inclusion of data from an additional 12 participants.

The authors wish to thank all of the people who have participated in this study, as well as Emily Verlinden for her considerable assistance in the preparation of this poster.

For a complete list of references or for more information, please contact Ms. Mara Long at mlong@ccac.ca.