Health Canada’s human vaccine lot release program: impact on the 3Rs

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Abstract

Health Canada (HC) is Canada’s national regulatory body that oversees the review, authorization, and lot (batch) release of human vaccines. All biologic drugs, including vaccines, are subject to the Biologics and Genetic Therapies Directorate’s Lot Release Program (LRP) before approval and sale. The LRP classifies biologics into one of four risk managed Evaluation Groups based on pre- and post-market evaluation. The extent of lot release testing conducted at HC varies for each group. All vaccines submitted for a Clinical Trial Application or as New Drug Submissions are placed in Group 1a or 1b, respectively. Generally, only Group 1b (manufacturing consistency lots) undergoes targeted testing in addition to a review of manufacturer’s test protocols. Targeted testing focuses primarily on potency and can include animal studies, although in vitro assays are favoured when available. In vitro safety assays may also be conducted. Once approved, vaccines are first classified as Group 2 products for which a protocol review and targeted testing are continued. Although HC reserves the right to test all vaccine batches, the percentage of batches tested and types of assays used depends on risk evaluation. Vaccines that are well characterized and have a strong history of consistent manufacture can be placed in Group 3, in which lot release is based on a protocol review with only periodic testing. Vaccines are not placed in Group 4, which is a rapid approval without protocol review for specific biologics. Since its inception in 1995, this testing strategy has led to a significant reduction in animal use at HC.

All animal testing conducted at HC for the LRP is reviewed annually by an Institutional Ethics Review Board and subject to the guidelines established by the Canadian Council on Animal Care, which includes the application of 3R principles. HC remains open to the incorporation of alternative testing strategies for vaccine lot release by (1) reviewing and adopting new assays as they become available and are validated, and (2) contributing to the development of new assays for potency and safety through an active vaccine research program.

Keywords: human vaccines; Health Canada; lot release; alternative methods
1. Introduction

Monitoring biological therapeutics to verify their compliance with established safety and potency profiles are the key priorities of the Lot Release Program (LRP) in the Biologics and Genetic Therapies Directorate (BGTD) of Health Canada (HC). All pharmaceuticals listed in Schedule D (Biologics) of Canada's Food and Drugs Regulations are subject to the LRP, including human vaccines. Although veterinary drugs are also regulated by HC, veterinary vaccines are controlled by the Canadian Food Inspection Agency. This paper outlines the current LRP at HC, in particular as it pertains to the release of human vaccines, and how this program has influenced a positive change on animal testing.

2. Implementation of the lot release program

HC has conducted lot release testing since 1959. The LRP has continually evolved in order to adapt to advances in biotechnology, the introduction of new products, and changes in testing strategies. A major rationalization of the LRP began in the mid-1990s to review and update the program, with the latest version being adopted in 2005 [1]. This new program acknowledges the importance of ensuring manufacturing consistency in the maintenance of potency and safety of biologics. As biologics are derived from complex manufacturing processes, monitoring the consistency of each manufacturing step helps to ensure that the lot-to-lot variability remains within the acceptable specifications established during clinical trials. Under this strategy, the manufacturer is required to test and report on every lot using assays described within the product license; however, the current LRP does not require that all of the assays be repeated at a HC testing laboratory. In particular, the number of potency and other assays that require the use of animals has been reduced, and the focus of testing at HC is more on monitoring the final product consistency through the use of in vitro assays, where available.

The strength of any biologics monitoring program lies in its ability to monitor the consistency of each production run from seed lot through to the final product. This approach provides a strong assurance that each batch produced is the same as that established during the original clinical trials. Consistency monitoring at HC includes not only in-house testing of the final product, but also the collection and monitoring of data supplied by the manufacturer. This information is provided for each batch before release to the Canadian market, and the manufacturer also submits a Yearly Biologics Product Report (YBPR) for all lots produced, including any information on batches which failed in production. These data are compiled for continual trend analyses. Long-term trend monitoring can detect small changes in reference standards, reagents, and/or the manufacturing environment that could eventually lead to variations from the product’s established potency and safety profiles.

3. Four evaluation groups in the lot release program

Under the current LRP, all human biologics are assigned to one of four evaluation groups, each with a different level of regulatory oversight. The evaluation group to which a product is assigned depends on its approval status for market (pre- or post-market), indication, risk assessment, nature of the product, production and inspection histories, and history of safe use. For those biologics associated with a higher risk, such as vaccines, every lot may be tested, whereas manufacturers of low-risk biologics only need to notify BGTD of each lot produced and supply a certification of testing. Biologics are not necessarily bound to a particular group but can be reassigned upon evaluation. This graduated lot release approach allows HC to focus its attention on products that may require greater surveillance, particularly vaccines. The groups are described below and summarized in Table 1:

- **Group 1**: Biologics submitted for pre-market approval or major changes. When biologics are submitted for clinical trials (Group 1a), all of the manufacturer’s protocols are reviewed but the products are generally not tested; however, samples may be requested for analysis. For New Drug Submissions and major changes to existing drugs (Group 1b), all of the manufacturer’s protocols are reviewed and samples may be tested in HC laboratories. When testing by HC is undertaken, three to five consecutive lots are requested to verify consistency of manufacture. These lots may be released for sale pending the issuance of a Notification of Compliance (NOC).
- **Group 2**: Biologics that require a high level of monitoring. Most approved human vaccines fall within this group. All of the manufacturer’s protocols are reviewed, and samples from every lot are submitted to HC for
testing. Samples are subject to targeted testing in which a subset of available LRP assays are performed. Upon approval, a release letter is issued to the manufacturer, allowing sale of that lot.

- **Group 3**: Biologics that require a moderate level of monitoring. All manufacturing protocols are reviewed and samples are required only upon request (periodic testing). Samples are subject to targeted testing, in which a subset of available LRP assays are performed. Upon approval, a release letter is issued to the manufacturer, allowing sale of that lot.

- **Group 4**: Non-vaccine biologics. Manufacturing protocols are not reviewed. In general, sample testing is not conducted for this group, although periodic testing may occasionally be required by BGTD. Notification is required by the manufacturer when each batch of the biologic is to be sold in Canada.

**Table 1. Regulatory oversight of different biologics evaluation groups in the lot release program at Health Canada**

<table>
<thead>
<tr>
<th>Group</th>
<th>Approval Status</th>
<th>Protocol Review</th>
<th>Targeted Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>Clinical trial application (CTA)</td>
<td>Yes</td>
<td>No (Periodic)</td>
</tr>
<tr>
<td>1b</td>
<td>Supplement to/New Drug Submission (s/NDS)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Post-approval</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Post-approval</td>
<td>Yes</td>
<td>Periodic</td>
</tr>
<tr>
<td>4</td>
<td>Post-approval</td>
<td>No</td>
<td>No (Periodic)</td>
</tr>
</tbody>
</table>

**4. Reduction, refinement, and replacement in animal use after implementation of the lot release program**

The LRP program at HC is not obligated to perform the same *in vivo* or *in vitro* protocols established in the product’s authorization. This has the advantage of allowing for the use of independent assays, rather than simply repeating the same assays conducted by the manufacturer. This also allows some flexibility in adopting alternative strategies in the HC testing regime, so long as the alternative assay provides a rational scientific basis for the assessment of vaccine potency and/or safety. Manufacturers are less flexible in their abilities to integrate new or modified assay protocols for vaccines already on the market because the assays used must conform to those established within their product’s authorization. Generally, any changes to a manufacturer’s assay procedures require the manufacturer to submit a Notifiable Change to HC.

Since the rationalization of the LRP began in 1995, there has been a significant reduction in animal use for vaccine testing, as well as the introduction of improved *in vivo* test models using endpoints that are considered more humane and/or that produce higher-quality results. Much of the impact of the LRP rationalization on reduction of animal use was summarized in a review by Dr. Gerald Calver in 2002 [2]. That review clearly illustrated the favorable effect of the rationalized LRP on animal testing after only a four-year period of program implementation, a trend that has continued during the past decade. For example, in 2000 the potency testing at HC for all pertussis vaccines required 3840 mice, which was a third of the animals needed for the same testing in 1996. By 2009, this had been further reduced to 540 animals by the adoption of a single dose immunological assay that requires fewer animals per vaccine batch. This reduction in animal numbers occurred despite an increase in the annual number of pertussis vaccine lots released in Canada.

A significant reduction in animal requirements has also been achieved by no longer duplicating at HC the *in vivo* safety tests that are conducted by manufacturers. Although HC has the option to resume such safety testing if deemed necessary, the LRP currently only conducts *in vitro* assays used as indicators of product safety. In addition, HC is phasing out the use of, and manufacturer requirement to perform, the General Safety Test on vaccines approved for human use. Instead, the general safety of these vaccines is considered unchanged when the product is manufactured under Good Manufacturing Process (GMP) conditions and meets all specifications established within its authorization.
Potency assays that still require in vivo testing are also undergoing refinement at HC. One example of this is the adoption of a serological conversion assay for monitoring diphtheria and tetanus vaccine potencies, as opposed to the lethal challenge assay. This modified assay allows for monitoring of potencies of both vaccine components within each animal, thereby reducing the number of animals required. This assay also provides for a more humane endpoint as it does not require animals to be challenged with live pathogens thereby avoiding the morbidity associated with these infections. Similar serological conversion assays for monitoring potency have also been adopted for other bacterial and viral vaccine products.

5. International harmonization

More recently, effective collaborations have been established between HC and regulatory testing agencies in other countries. This has allowed acceptance by HC of assay results generated at these external regulatory agencies for vaccine sublots that a manufacturer intends to also market in Canada. This is particularly the case for vaccines that require in vivo potency tests or when only a few lots may be distributed annually, such as for the tick-borne encephalitis vaccine.

Unlike many other regulatory agencies, HC has not established its own guidance documents requiring the implementation of 3R practices. Instead, all animal testing is subject to the 3R guidelines established by the Canada Council on Animal Care (CCAC) [3], the organization that oversees the licensing of Canadian animal testing facilities, the establishment of animal care committees, and the development of animal research guidelines. As with all other studies requiring the use of animals in Canada, the LRP must submit their protocols and requests for animals to an Institutional Ethics Review Board that verifies compliance with the CCAC 3R guidelines.

Despite the success of the rationalized LRP in controlling biologics safety and potency, as well as reducing animal use, it is not possible for HC to force the utilization of alternative testing strategies on manufacturers. This is particularly so for vaccines and their associated testing protocols that have already been approved, validated, and supported by clinical data. However, HC does conduct research in the development and improvement of in vitro assays to monitor vaccines, often in collaborative relationships with external scientists or other regulatory agencies, and also participates in international studies to validate alternative assays. Involvement in this type of research not only promotes the future reduction of animal use, both for HC and the manufacturer, but also helps HC to characterize an assay’s limitations and understand its biological relevance prior to its introduction into the LRP.

References

