REGULATORY PREPAREDNESS FOR PANDEMIC INFLUENZA VACCINES

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Background

Health Canada is the regulatory authority in Canada that is responsible for maximizing the safety, efficacy, and quality of drugs, including vaccines, for human use marketed in Canada. Vaccine regulation in Canada is subject to the provisions of the *Food and Drugs Act and Regulations*. The Biologics and Genetic Therapies Directorate, within the Health Products and Food Branch of Health Canada, administers the vaccine regulatory programme.

New vaccines are authorized for marketing in Canada following the review of a New Drug Submission (NDS) that must include a complete data set in support of the safety, efficacy and quality of the vaccine. As part of the regulatory approval process, Health Canada performs an on-site evaluation in the form of an inspection of the manufacturing facilities, to assess the production process and the facility because they impact on the safety and efficacy of the product. The manufacturer must also provide samples of at least three and preferably five batches or "lots" of the vaccine for testing in Health Canada laboratories. If, after completion of the review, the on-site evaluation and the testing of samples, the conclusion is that the benefits of the product outweigh its risks and any risks can be managed, then the vaccine is issued a Drug Identification Number (DIN) and a Notice of Compliance (NOC) indicating that it is authorized for sale in Canada. In addition to the NOC and the DIN, any manufacturing sites within Canada or the Canadian importer of a foreign-manufactured vaccine will require an establishment license.

As part of ongoing monitoring of vaccines after authorization for use, Health Canada requires samples of each lot of a vaccine for testing prior to authorizing the manufacturer to release that lot for sale in Canada.

The Regulation of Influenza Vaccines in Canada

Influenza A viruses are classified into subtypes based on their hemagglutinin (H) and neuraminidase (N) antigens. Antibodies to these antigens, particularly to H antigen, can protect an individual against a virus carrying the same antigen. From year to year minor antigen changes ("drift") are common, and it is this antigenic variation from one influenza virus subtype to another that is responsible for continued outbreaks of influenza and that necessitates annual reformulation and administration of the influenza vaccine. The need to reproduce the vaccine each year with the new circulating strains has necessitated a special approach to the regulation of these vaccines.

Changes to the influenza vaccine to reflect the year-to-year strain variation are approved via the filing, by the manufacturer, of revised labelling material (inner labels, outer labels and a revised Product Monograph or Direction Leaflet) together with clinical data for the vaccine with the new strains for review. These clinical data are obtained from a small clinical study to assess the tolerance and efficacy of the vaccine. These are evaluated separately in two groups of health volunteers, one between 18 and 60 years of age and the other over 60 years of age, as per the European guidelines that have been developed by the Committee for Proprietary Medicinal Products. Data to support the quality of production of vaccine with the new strains is also required.

Unlike the abbreviated process used for the approval of the annual influenza vaccine, the regulatory process for approval of a pandemic vaccine will be based ideally on the filing of an NDS. This is because the strain involved will likely be one that has never been a component of any previous influenza vaccine. The unknown factors related to a pandemic vaccine could require changes to the manufacturing process currently used, thus increasing the likelihood that a pandemic vaccine will have many significant differences from an annual influenza vaccine.

Health Canada has made the following public commitments respecting the regulatory approval process for a pandemic influenza vaccine:

- to provide "appropriate degree" of regulatory oversight to ensure safety, efficacy and quality of the vaccine;
- to focus regulatory activity on review of mock vaccine during inter pandemic period
- to refine regulatory plans as appropriate and to partner with international authorities on regulatory preparedness; and
- to develop options to allow for emergency use

The regulatory challenge for a pandemic influenza vaccine will be to have mechanisms in place that can be used to review and authorize a safe and efficacious vaccine for use in Canada, within the shortest time frame possible, and to verify, once that vaccine is in use, that it is effective. However, the timing of the declaration of the pandemic in relationship to the need for vaccine availability will determine how much information is available to Health Canada for review as part of an NDS. This will be a critical factor to determining the regulatory process that will be used in providing access to the vaccine for Canadians.

The Canadian contract manufacturer will proceed with development and production of a mock vaccine and will conduct initial clinical studies with the mock strain. The use of a mock vaccine will allow Health Canada to validate the manufacturer's pandemic production process, and establish minimum standards and requirements for pandemic vaccine safety and efficacy in volunteers. Once the pandemic strain is confirmed, the contract manufacturer will need to manufacture and conduct clinical confirmatory studies of the vaccine produced with the actual pandemic strain. In an ideal scenario, the strain used to prepare the mock vaccine will be identical to the actual pandemic strain, or similar enough to provide some level of cross-protection to the pandemic strain.

General Regulatory Considerations

Clinical Trials

In advance of an actual pandemic, it will be desirable to have authorized clinical trial protocols in place to both investigate immunological responses to the pandemic vaccine to support authorization and to study the level of clinical protection during an actual pandemic, as part of post-market conditions.

The contract manufacturer will be required to file a Clinical Trial Application (CTA) to conduct clinical trials with both the mock vaccine and the actual pandemic vaccine, in accordance with Part C, Division 5 of the regulations. The CTA can contain multiple protocols, which could be pre-approved for use in sequence, depending on the outcome of the initial studies, or alternatively CTAs for new protocols could be filed as needed.

Once clinical data are available from any studies with the mock vaccine, they would be submitted to Health Canada for review and decisions on further steps and actions, including the conduct of additional clinical studies. CTAs for clinical trial protocols to be conducted with the actual pandemic strain will need to be developed and filed for review during the Interpandemic Period and be updated as needed based on developing knowledge and changing technologies. This will provide protocols that can be implemented immediately upon declaration of the pandemic.

Clinical trials (Phase 3) for vaccine efficacy can not be performed prior to the implementation of vaccine programs at the time of a pandemic. The estimation of vaccine effectiveness may need to be carried out by studying pre-determined target populations during the pandemic part of post-marketing studies.

New Drug Submission Requirements

To support authorization, by Health Canada, of a pandemic vaccine for wide-scale use in Canada, an NDS, containing information on both the mock and actual pandemic vaccine will be required. It is likely that the bulk of information in the NDS will be on the mock vaccine. Once the pandemic has been declared the NDS would be supplemented with the additional information on the actual pandemic vaccine.

The contract manufacturer will be required to provide extensive data to support the **quality** of the vaccine and its manufacturing process. This data will include information on the production and testing of vaccine seed lots, the manufacturing process and validation, adjuvant and excipient information, reference standards used, product-specific facility information, viral safety information and product stability. The manufacturer will also be required to submit consistency samples to Health Canada laboratories for testing. The extent of **clinical** data necessary to support authorization will depend both on the nature of the process ultimately used to produce the pandemic vaccine, as well as the timing of the identification of the actual pandemic strain relative to the need for an available vaccine in Canada. Clinical data could include immunogenicity data from small animal species, challenge studies in animals, local tolerance studies, clinical (immunogenicity) studies on healthy adults and targeted studies on vulnerable populations, particularly children. Protocols for post-market studies, including any necessary informed consent documents will also be required as part of the NDS.

New Drug Submission Review

Health Canada will perform an expedited review of any NDS for a pandemic vaccine, in accordance with the administrative policy *Management of Biologics Submissions for Public Health Need, January 2004*. This policy was developed to define the criteria and circumstances under which Health Canada would accelerate the review and approval of a biologic product required to treat and/or prevent the consequences of a public health need where there are no other available approved sources or alternative mechanisms of access.

An expedited review requires redirecting and consolidating resources to shorten review time for specific submissions. A review team is formed which sets out a submission review plan, including assembling key information, and scheduling key elements of the review.

Expedited reviews have been used on various occasions by Health Canada to deal with public health issues and have resulted in regulatory approval of vaccines in very short time frames, usually a matter of weeks.

Other Access Mechanisms

In the event that the filing and/or review of an NDS are not possible or cannot be accomplished before the pandemic vaccine is needed are other mechanisms can be used to provide access in the absence or in advance of the issuance of an NOC. These include the Special Access Programme (SAP), the use of interim orders and a clinical trial.

Special Access Programme (SAP)

The SAP enables access to products on a case-by-case basis to products not currently approved for sale in Canada. Access is limited to patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable or unavailable. SAP could be used as a possible short-term solution to vaccinating front-line workers where an emergency situation is localized or when additional time is needed to complete the regulatory review of an NDS.

Interim Orders

An interim order is a regulation that is issued by the Minister in the case of a situation that presents a significant risk, direct or indirect, to human health, public safety, security or the environment. An interim order is intended to address circumstances where there is no time to make a regulation as the law would normally requires. An interim order has the advantage of being able to provide a short-term "tailor-made" solution to a specific situation.

Clinical Trial

In the context of pandemic influenza, a clinical trial would be used to provide access to the vaccine at the same time as accumulating clinical data to support approval and therefore could permit immunization of certain groups while at the same time accumulating of data to support broader use.

Conclusion

Health Canada is committed to working with the contract manufacturer to expedite the regulatory authorization, the release of product lots and the availability of an adequate, safe and effective pandemic influenza vaccine in order to protect Canadians from a pandemic.