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Regulation for the New Biologically Originated Allergenic Products for the Treatment or Diagnosis of Allergic Disorders

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Keywords

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Abstract

The main objective of these analyses is to provide a regulatory framework for biological allergenic products and the management of their lifecycle. And also provide the information required in new drug submissions or clinical trial applications. Unauthorized allergenic products are regulated by Health Canada's Food and Drug Act and Part C of the Food and Drug Regulations as Schedule D (biologic) drugs. The laws and regulations for the development and sale of allergenic products of biological origin must be developed and implemented by Health Canada. There is a lengthy approval procedure for new allergenic products at Health Canada based on a thorough examination of the quality, safety, and efficacy evidence.

1. Introduction

1.1. Purpose

The regulatory framework for allergenic products of biological origin used for the diagnosis or treatment of allergic diseases in Canada is intended to maximize the quality, safety, and efficacy of these products for human use. This review helps to ensure that sponsors have the information required to meet the regulatory requirements for the authorization and life-cycle management of allergenic products in Canada. [1]

1.2. Scopes and application

This can be beneficial to manufacturers of allergenic products made from biologics, which are used for the treatment or diagnosis of allergic diseases in humans. These are also applicable to all unauthorized allergenic products and allergenic product clinical trial applications. That must be applied Health Canada website for schedule D drugs. It also provides a regulatory framework for new allergenic products, including submission requirements and regulatory activities applicable throughout the product's life cycle. The Health Canada Policy on Manufacturing and Compounding of Drug Products in Canada establishes a framework for distinguishing compounding and manufacturing drug product activities in Canada. [1]

1.3. Policy declarations

The following declarations summarize the fundamental concepts and principles of Canada's allergenic product regulatory framework:

Allergenic biological products used in the diagnosis or treatment of allergic diseases are classified as Schedule D (biologics) drugs.

As with all Schedule D (biologic) drugs, regulatory decisions for allergenic products must be based on science and regulatory principles established by the Food and Drugs Act and Part C of the Food and Drug Regulations.

Before sale, every allergenic product authorized for sale in Canada under the Food and Drug Regulations must be assigned a unique Drug Identification Number (DIN) by Part C, section C.01.014 of the Food and Drug Regulations.

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All allergenic products sold in Canada should be standardized. If internationally acceptable standards are not available, the manufacturer should use validated in-house reference standards. Health Canada is committed to working with other national regulatory authorities to achieve as much consistency as possible. [1]

1.4. Context

Allergenic products are used to diagnose as well as treat allergic diseases. Specific immunotherapy with allergen products has traditionally been defined as the repeated administration of allergens to allergic individuals to alleviate the symptoms associated with subsequent exposure to the causative allergen. Typically, the administration takes 3-5 years. Allergenic products vary greatly in nature. The quality of the allergenic products used determines the safety and effectiveness of allergy diagnosis and treatment. New methods and standards have been developed over time to improve the quality, safety, and efficacy of allergenic products. For example, methods for measuring the allergenic activity of some allergenic products are now available. This guidance document incorporates recent advances and is consistent with international initiatives in this field. The regulatory framework that applies to allergenic products throughout their life cycle, from pre-market review to post-market monitoring, is described in this study. [1]

2. Methodology

2.1 Regulatory Concerns

Summary of Law and Regulation

- Unauthorized allergenic products regulated as Schedule D (biologic) drugs under the Food and Drugs Act are subject to the following divisions of Part C of the Food and Drug Regulations:
  Division 1 (general requirements applicable to all drugs),
  Division 1A (Establishment Licensing),
  Division 2 (Good Manufacturing Practices),
  Division 4 (regulatory requirements applicable to Schedule D (biologic) drugs),
  Division 5 (clinical trials),
  Division 8 (requirements for new drugs). [3]
- Quality, pre-clinical and clinical safety, and efficacy information are all considered during the regulatory review of allergenic products for market authorization.
- As part of the regulatory review process, an on-site evaluation of manufacturing facilities and in-house laboratory testing may be performed.
- Once authorized, monitoring continues throughout the product's life cycle.
- The risk-based lot release program developed by Health Canada applies to allergenic products, and systems are in place to monitor and evaluate adverse reactions.
- The Biologics and Genetic Therapies Directorate, in collaboration with the Marketed Health Product Directorate and the HPFB inspectorate, oversees Health Canada regulations.

Meetings before submission

Manufacturers of allergenic products should ask for advice from Health Canada on quality and clinical trial requirements, as well as the preparation of regulatory submissions. Initial and continuous counseling will assist in regulatory requirements. These meetings also help Health Canada in planning and preparing for future submissions.

Submission format [1]

- New drug Submission

✓ According to the Health Canada guidance document Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format, all allergenic product submissions should adhere to the ICH Common Technical Document (CTD) format. Preparation of Drug Submissions in the Electronic Common Technical (eCTD) Document Format is a guidance document that Health Canada strongly recommends.

✓ All drugs that are marketed in Canada are subject to the Food and Drugs Act and Regulations.

✓ The Biologic and Radiopharmaceutical Drugs Directorate (BRDD) reviews and provides market authorization for all drug submissions for biologic drugs for human use. Market authorization by Health Canada is required before a biological drug can be sold in Canada.

- Clinical trial application (CTA)

According to the CTD format, the CTA is divided into three parts (modules):

✓ Module 1 contains administrative and clinical information about the proposed trial;

✓ Module 2 contains Quality (Chemistry and Manufacturing) summaries about the drug product(s) to be used in the proposed trial;

✓ Module 3 contains additional supporting Quality information.

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ISSN: 2309-6152 (Online)
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Drug Identification Numbers (DINs) for allergenic products [1, 5]

- Before a drug product is marketed in Canada, Health Canada assigns it an eight-digit computer-generated number called a Drug Identification Number (DIN). It can be found on the label of prescription and OTC drugs that have been examined and given the all-clear to be sold in Canada. It uniquely identifies every drug product sold in a dosage form.
- A DIN is an eight-digit numerical code initiated by the prefix DIN that is assigned to each drug product that is marketed under or in compliance with the Food and Drugs Act and Food and Drug Regulations.
- The following features of a product are specifically identified by a DIN:

✓ The manufacturer,
✓ Product name,
✓ Active ingredient(s),
✓ Strength(s),
✓ Pharmaceutical form
✓ Routes of administration are all uniquely identified by a DIN.

- According to C.01.014 of the Food and Drug Regulations, each allergenic product must have market authorization in the form of a unique DIN.
- A DIN is an indication that a drug has been evaluated and approved for sale by Health Canada.
- It is also a tracking number that can be used to help with product follow-up, recalls, inspections, and quality monitoring.
- Health Canada issues a Notice of Compliance (NOC) and a Drug Identification Number (DIN) when the benefits exceed risks according to evidence supporting the safety, efficacy, and quality claims for an NDS or SNDS.
- Health Canada has approved the drug for sale in Canada, as shown by the NOC and the DIN.
- Before a manufacturer can sell a drug in the dosage form in Canada, the drug needs to have a DIN.
- A Drug Establishment License is required for all Canadian DIN owners (DEL).

Drug Establishment License [1, 6]

- A company must possess a valid DEL that specifies the following:

✓ The Canadian building where the activity is authorized,
✓ The activity that is authorized to be conducted at the building,
✓ The category of drugs for which the activity is authorized to manufacture, package/label, test, import, distribute, or wholesale a drug in Canada.

- The DEL must approve sterile dosage forms for the drug category in the case of sterile medications.
- **Application Types**

✓ <u>NEW DEL Application</u>

Companies that don't have a DEL are required to submit this kind of application. This includes requests made in applications by companies to reactivate a DEL that has been canceled.

✓ <u>Amendment Application</u>

Companies with a DEL who want to change it must submit this kind of application, which may include the addition, modification, or removal of:

a) A building in Canada where regulated activities are carried out;
b) A building abroad from which a drug is imported;
c) An activity for a specific building.
d) A building in Canada where drugs are kept (Canadian warehouse),
e) An alternative sample retention site (ASR),
f) A category of drugs for a particular activity,
g) The authorization of sterile dosage forms for a particular category of drugs,
h) Terms and conditions.

✓ <u>Annual License Review (ALR) Application</u>

- Companies with an active DEL must submit this kind of application every year before April 1st.
- Health Canada needs to submit this application to conduct the DEL's yearly review.
- Holders of New Licenses
  By April 1st of each year, all DEL holders are required to submit an ALR application. Companies must still submit an ALR application by April 1st even if they receive a DEL in the months leading up to that date (such as March).

✓ <u>NERBY Application</u>

DEL holders are given the choice to sign the "Undertaking B" form as part of their ALR package, committing to submit GMP evidence by the New Evidence Required by (NERBY) the date specified on their DEL, in place of submitting GMP evidence as part of the ALR application for all foreign buildings listed on their license. A NERBY application is a request for a DEL amendment to change the NERBY date and fulfill the commitment the DEL holder made as part of their ALR application. The NERBY amendment

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CODEN: JCLMC4
Journal of Coastal Life Medicine

application must provide valid and up-to-date proof that each foreign fabricator's, packager/ labeler's, and tester's facilities, tools, routines, and practices adhere to the relevant GMP specifications.

✓ Reinstatement Application

- When Health Canada has completely or partially suspended a company's DEL and the company wants to ask for the DEL to be reinstated, they can submit a reinstatement request to Health Canada.
- The request's processing is overseen by an inspection and related performance standard.
- **Important**: A DEL that has been suspended for more than 12 months cannot be reinstated because it has been canceled by FDR section C.01A.018.1, regardless of whether a reinstatement request was made to Health Canada.
- The only DELs that can be reinstated by Health Canada are those that have been suspended. If a DEL is revoked and the company wants to continue operating, it must apply a new DEL by C.01A.005 or if appropriate, a revised DEL by C.01A.006 of the FDR must be submitted.
- Health Canada accepts applications under C.01A.005/C.01A.006 from the holder of suspended DELs who has taken sufficient steps to remedy the situation on which the suspension was based to prevent situations where a DEL would be canceled before a reinstatement decision could be made by Health Canada.
- Health Canada can process the application regardless of whether the DEL is canceled by C.01A.008.1 by submitting a new DEL application or an application to amend an existing DEL as opposed to an application for reinstatement.

✓ Cancellation Application

- A company must send a cover letter or email stating its intention to cancel its DEL if it wishes to do so.
- A contact who is currently listed with Health Canada must make the request.
- Health Canada will send a confirmation once the request has been handled.

LOT RELEASE PROGRAM [1, 7]

Lot release is a mechanism that provides BGTD with a real-time system to continuously monitor product quality, through review and testing, of many of the biological products that it regulates Biological product. Each lot of a Schedule D (biologic) drug must pass the lot release program before being marketed for sale in Canada. This program is also taken in pre & post-market phases of the allergenic product. In the case of allergenic products fax-back form is submitted by manufacturers for the lot release program. There is this program is done in one to four types of evaluation groups & based on risk.

➢ **Evaluation groups**

- Group 1: Pre-Approval Stage

During the review period, Evaluation Group 1 is assigned to all items that are being evaluated as Clinical Trial Applications (CTAs), New Drug Submissions (NDS), and occasionally Supplementary New Drug Submissions (S/NDSs). Group 1 contains two separate subgroups.

✓ Group 1A: Clinical Trial Materials

- Clinical trial materials related to authorizing CTAs to make up this Evaluation Group.
- Before using the clinical trial materials, sponsors must complete and submit a Fax-back form (Appendix IA) and wait for BGTD to sign a response.

✓ Group 1B: Consistency Testing

- The consistency samples related to an NDS or S/NDS are the target audience for this evaluation group.
- To confirm the consistency of the production process, BGTD often tests samples from 3 to 5 successively created lots. Consistency lots may be made available for sale in Canada upon request following the issuance of a NOC; BGTD must provide a formal release letter.

- Group 2 to 4: Post-Approval Stage
- Group 2: Sample Testing and Protocol Review

✓ This Evaluation Group is given the products that require the highest level of examination following the receipt of a NOC. Products in this category go through targeted testing (Appendix II).

✓ Before each lot is sold, BGTD is required to provide a formal Release Letter approving the sale of the property in Canada. After receiving all necessary data and samples, a projected release date for goods in this Group is six weeks.

✓ Some products, including those requiring lengthy bioassays, may have a longer period. If necessary and in rare circumstances, a release may be given sooner (such as a product shortage in Canada).

- Group 3: Protocol Review and Periodic Testing

✓ This Evaluation Group is given products that, following the issue of a NOC, need a moderate

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CODEN: JCLMC4
Journal of Coastal Life Medicine

level of inspection.

- ✓ Before each lot is sold, BGTD is required to provide a formal Release Letter approving the sale of the product in Canada. Although the manufacturer does not frequently submit samples for targeted testing for items in this group, the BGTD assesses testing methods.
- ✓ Instead, samples may be sought for periodic testing at the BGTD's discretion (Appendix III). Two weeks from the moment that the necessary information is obtained is the desired period for the products in this Group to be on sale.

- Group 4: Notification and Periodic Testing

- ✓ Products in this Evaluation Group do not go through protocol review or sample testing by BGTD.
- ✓ The manufacturer of a Schedule D (biologic) product must notify BGTD by Fax-back (Appendix I) when a lot is to be marketed in Canada if the drug has been assigned to Evaluation Group 4.
- ✓ Before to selling, a Release Letter is not necessary.
- ✓ Products in Evaluation Group 4 may also be subjected to Periodic Testing, at the BGTD's discretion (Appendix III)

2.2 Clinical trial applications (CTAs) [2]

Part C, Division 5 of the Food and Drug Regulations, which describes the criteria applicable to the sale and importation of medicine for use in human clinical studies in Canada, governs clinical trials utilizing allergenic goods conducted in Canada.

At a suitable point of product development, sponsors are encouraged to consult Health Canada for advice on scientific, quality, clinical, and other regulatory problems before submitting a Clinical trial application.

Manufacturers must submit clinical trial materials to BGTD's risk-based lot release program before they begin a clinical trial by submitting a Fax-back form (Appendix IA of the Lot Release guidance paper) and waiting for a signed response from BGTD before using the clinical trial materials.

Adverse drug reactions (ADRs) for allergenic products used in clinical trials in Canada that are both severe and unexpected are subject to expedited reporting to Health Canada.

Any significant, unexpected ADR that occurs within or outside of Canada must be reported to Health Canada/BGTD by the sponsor during a clinical trial.

When an ADR is fatal or life-threatening, it must be reported as soon as possible and, in any case, within seven days of becoming aware of the information. When an ADR is not fatal or life-threatening, it must be reported within fifteen days. When it is fatal or life-threatening, it must be reported within eight days.

ADR Expedited Reporting Summary Form should be completed and attached to the front of the clinical trial ADR report when submitting it to Health Canada/BGTD. The Suspect Adverse Reaction Report form from the Council for International Organizations of Medical Sciences is the advised format for ADR reports.

2.3 Information and submission requirements [1]

2.3.1. Quality information:

The quality information that should be included in a proposal for market authorization of an allergenic extract is specifically advised in this section. An on-site examination of the manufacturing facility may be carried out as part of the quality assessment, and consistency testing may be carried out at the pre-market stage by BGTD's lot release policy.

2.3.1.1. Standardization

Biologics, which are unstable and difficult to detect, are used to make allergenic products. This makes it harder for physicians to alter from one batch of a certain manufacturer to another & restricts their potential to use a product from manufacturers. The uniformity of product quality should be encouraged by the standardization of allergenic items. All kinds of allergy products should have reference standard materials that are established and described.

Unapproved new allergenic products are often harmonized with current global reference standards before being approved in Canada.

To ensure its quality throughout your process and to support regulatory filings, standards are essential.

Biologics requirements:

- ○ Ensure that biological therapies are consistent and high quality are available to patients worldwide.
- ○ Maintain the integrity of the global biologics supply chain.
- ○ Give analytical testing a constant baseline throughout the product lifetime.
- ○ Support new drug regulatory applications.
- ○ Set a consistent standard for quality for biologics that are developing and becoming

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CODEN: JCLMC4
Journal of Coastal Life Medicine

more complex.

- **International reference standards:**

✓ Standards are key to ensuring quality throughout your process and supporting regulatory filings. Biologics standards: Help ensure the quality and consistency of biological treatments reaching patients globally. Protect the integrity of the global medical supply chain for biologics.

✓ Unapproved new allergenic products are often standardized to current international reference standards before being approved in Canada.

✓ For a limited few allergenic products, there is a preference for international reference standards with known allergen content and activity, such as those developed by the Center for Biologics Evaluation and Research (CBER), the United States Pharmacopeia (USP), or the European Pharmacopeia (EP).

- **In-house reference standards:**

✓ The allergenic extract should be standardized to an In house reference standard (IHRS), as is the case for other biologic products, in situations where there is no international reference standard. Batch-to-batch uniformity within production runs should be encouraged by an IHRS. The manufacturing batch record for the IHRS should be followed exactly, as stated in the submission. Any new differences must be explained. The objective of the IHRS is to act as an internal reference for monitoring the qualitative and quantitative composition of commercial batches over time.

✓ It is important to determine the specific allergenic activity (potency) of the IHRS and to describe it using the appropriate physicochemical techniques. It is necessary to show that the IHRS contains all relevant allergens and, when applicable, to utilize the globally recognized allergen nomenclature. Pooled patient serum should be used to assess the IHRS allergenic potential. The IHRS potency should be assessed using an immunoassay. Based on a skin reactivity test or, if justifiable, a suitable in vitro procedure, the IHRS should be physiologically standardized.

✓ A predefined set of tests, including standard release tests and additional characterization tests to show that there has been no change in the potency and quality, should be used to qualify a new IHRS in parallel with testing the existing IHRS.

- **Serum pool:**

✓ To regulate batches and qualify individual IHRS, a serum pool with the sera of 10 to 15 people should be created. When setting up the pool, it is important to take into account the patterns of sensitization, the frequency of Immunoglobulin E (IgE)-recognition of various allergens, the quantity of allergen-specific IgE antibodies, any prior specific immunotherapy treatments, and the clinical significance of desensitization. Additionally, sera that include antibodies against immunoassay reagents like gelatin or bovine serum albumin should not be used.

✓ Serum pools should be qualified using established acceptance criteria, which should take the pool's reactivity profile into account.

2.3.1.2. Drug substance

The drug product should be regarded as a continuous manufacturing process for this advice since there is no visible drug substance release or shelf-life. The absence of drug substance release tests should be explained, and there should be evidence that the produced bulk does not have a hold time.

2.3.1.2.1. Manufacture

Every step of the production process, from the receiving of the raw material through the storage of the bulk drug substance, should be documented in depth. This includes adjustments like process scale and absorption. A flowchart with all the processing steps, in-process checks, transitions, and hold periods should be included.

2.3.1.2.2. Process Validation

✓ Process validation shows that, when carried out within specific limits, the process consistently produces a drug substance that meets specified quality standards.

✓ Three to five consecutive successful manufacturing batches should be used for prospective validation.

✓ In unique situations with adequate evidence, concurrent or retrospective validation may be conducted.

✓ It's important to regularly assess manufacturing processes to make sure they're still functioning properly. This might look like a recurring quality evaluation if revalidation is not necessary because of process changes.

2.3.1.2.3. Control of source material

✓ The consistency and quality of the raw materials used as a basis are essential for the production of high-quality allergic products.

ISSN: 2309-5288 (Print)
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CODEN: JCLMC4
Journal of Coastal Life Medicine

- ✓ During development, it is important to identify the source material's quality characteristics that are necessary to produce an extract that is allergic and of the desired quality.
- ✓ Each source material should be accompanied by information on how these characteristics are controlled, including cultivation, collection, pre-treatment, shipping, and storage.
- ✓ Any processing processes carried out by the supplier (such as defatting) should be validated, maintained, and justified.
- ✓ Based on stability data, the transportation and storage conditions should be justified.

Additional specifications for the control of the following sources:

Pollens: Collection sites should be characterized in terms of their geographic location, field characteristics, treatments, visual controls, collection methodology, and sample techniques. It is important to distinguish native pollen, mould spores, and extraneous plant matter from native and alien species when testing pollens for identity and purity. According to microscopic analysis, the purity of pollen should be 99% of other pollen, with no one foreign pollen species making up more than 0.5% of the total. It is important to reduce contamination from the non-pollen plant material and to ensure the limit. Mold contamination should be kept to a minimum and shouldn't be allowed to exceed 1%.

Moulds: The strain, culture method, and type of material taken should all be mentioned, as well as any morphological or genetic traits that can be used to identify the material. The cultivation process should be thoroughly explained, including the growth medium's composition, and important in-process variables (temperature, pH, etc.), should be supported. It should be shown that mycotoxins don't exist. To prevent additional mould strains from contaminating the source material, adequate precautions should be in place.

Mites: The species, cultivation method, and kind of harvested material (mites, mite faeces, whole mite culture, or mixes) should all be stated, as well as any morphological or genetic traits that can be used to identify the species. Key in-process factors should be justified and the growing method should be defined in full, including the make-up of the growth media.

Animal allergens: Only animals that have been confirmed as healthy and untreated with anti-parasitic or other medications by a qualified source material collector should be utilized. It is important to describe the criteria utilized to find the allergic source material. It should be stated what the composition of the raw materials is (hair, pelt, epithelium, etc.). Animal source material should be collected and preserved under conditions that have been shown to preserve the source material's quality.

It is important to explain the procedures used to harvest, transport, and store the source material. These procedures should be developed to prevent mites, mould, and other types of contamination. It's important to remove hair and dander without harming the animal's skin.

Hymenoptera venoms: The factors utilized for identification and classification should be stated, as well as the technique of collection. Pesticide contamination should be avoided.

Food Allergens: Only foods suitable for human consumption should be utilized for addressing food allergies. Justifications should be provided for any information on the portion of the food used, any pre-treatment, and the shelf life.

2.3.1.2.4. management of allergic products

At the level of the pharmacological substance, allergen products should be characterized and subjected to quality control. Testing at an intermediate stage may be appropriate, if warranted, in cases where this is not possible due to technical constraints. In this situation, testing should be carried out as soon as it is technically feasible to do so, and quality requirements should be established, which will be part of the release specification for the drug substance. At the time of release, the drug substance's appearance, description, identification, purity, bioburden, and potency should all be tested by the relevant standards. Validated tests should be used to determine the concentration of any relevant allergens and any antigens that could be harmful. When possible, the allergen profile should meet international reference standards and the IHRS. For each drug substance, potency testing using a particular analytical method that has been validated will be done. The associated specifications must be supported and should be based on technique variability, critical quality features, and process capacity.

2.3.1.2.5. In-process control

Application of in-process testing and controls should be used to monitor and regulate the development and performance of the manufacturing process. The potential impact on the quality attributes of intermediates or drug substances should be considered while evaluating the in-process stage. Developmental and historical data should serve as the foundation for these

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CODEN: JCLMC4
Journal of Coastal Life Medicine

controls and the accompanying acceptance criteria.

2.3.1.2.6. Modified preparations for allergens

To identify the pertinent allergen in the changed form, verified analytical techniques such as antibody-based assays should be applied. To characterize the modification and check on the uniformity of the modification process, complementary approved analytical approaches should be applied.

2.3.1.2.7. Container-closure system

It should be specified in detail how the container closure system(s) works. Demonstrating suitability for extractable, leachable, and integrity tests is necessary. It is important to talk about how the container closure system from the stability studies can be applied to the container closure system for medicinal substances.

2.3.1.2.8. Stability

Stability studies might be based on useful information that is provided by the standardization of allergenic products. According to the ICH Q5C recommendation, stability studies should be performed on the drug substance. As much as feasible, stability testing of biological and biotechnological products.

2.3.1.3. Drug Product

2.3.1.3.1. Description and composition of the drug product

It is important to provide a thorough description of the drug product. There should be a chart with a list of all the constituents, both active and inert, along with their quantity and purpose. A risk analysis should be used to identify, justify, and support excipients of biological origin.

2.3.1.3.2. Mixture

A mixture should have a minimal amount of allergen-containing items, and both the quantity and the relative percent should be justified. Hymenoptera venoms should not be mixed with any other allergens, and venoms from various genera should not be mixed, as these allergens have proteolytic capabilities and should not be utilized in combinations to prevent unexpected degradation. Allergens that are seasonal and perennial shouldn't be combined.

2.3.1.3.3. Manufacture

The production process should be documented, taking process scale into account. All process phases, justifiable hold times, and in-process controls should be shown on a flow chart.

2.3.1.3.4. Process validation

Process validation shows that, when carried out within predetermined limitations, a drug product consistently possesses the desired quality characteristics. It is recommended to carry out prospective validation with at least three successful manufacturing batches in a row. In unique situations with adequate rationale, concurrent or retrospective validation may be conducted. To ensure that they are operating legally, manufacturing processes should be frequently assessed. This could take the form of routine quality reviews if revalidation is not necessary because of process changes.

2.3.1.3.5. Media fills

For each size and style of container closure, three media fill runs should be made. Periodic requalification may make use of a matrix strategy that is properly justified.

2.3.1.3.6. Control of the drug product

To effectively monitor the product's quality, specifications should be specified. It may be permissible to establish the specification for the intermediate at the stage immediately preceding the modification phase when it is not possible to execute the control tests on the end product due to a modification that interferes with the assay. Release standards for the finished product should take into account the outcomes of these control tests on the intermediate. Each strength should have its release requirements, and any variations in strengths should be explained.

2.3.1.3.7. Potency testing for allergens

✓ Non-modified allergens:

To quantify the total allergenic activity for batch control and standardization of final products, a competitive IgE-binding assay should be employed, and the label should specify the content in potency units. Where an international standard is available, it should be used, and the requirements should include potency in addition to the weight per volume of each particular antigen. Risks to patient safety that have been linked to the presence of particular, small allergens need to be monitored as well.

ISSN: 2309-5288 (Print)
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✓ Allergen combinations

It is recommended to conduct a potency test on each allergen contained in the mixture. If the individual allergens in the finished product react with one another, it might be appropriate to test the finished product's overall potency using a competitive IgE-binding assay.

✓ Absorbable products

Measuring the total soluble protein content and the presence of IgE-binding substances in the supernatant upon release and during the period of the shelf life will help determine the effectiveness and stability of the adsorption process. If properly justified, other tests may be applied. In the stability experiments, keeping the concentration of free IgE-binding components within reasonable limits is important.

✓ Physicochemical standardization

It is recognized that in some extremely rare circumstances, it is impractical to establish the sera pool required for biological standardization. If properly justified, a physicochemical standardization may be acceptable in this situation. A variety of in vitro techniques should be used to regulate these products, including the assessment of an antigen profile, protein profile, and total protein concentration, with the results being compared to a certified IHRS. Biological uniformity is expected to be the norm, it should be underlined. In the absence of biological standardizations, clinical efficacy evidence may be needed to justify physicochemical standardization.

2.3.1.3.8. Container closure system

A thorough description of the container closure system(s) is required. Discussions about suitability should include extractable, leachable, and integrity tests.

2.3.1.3.9. Tests for preservatives

An efficient preservative should be used when filling multi-use containers with allergenic goods. To support the labeled use, the preservative's antibacterial efficacy should be shown. The USP or EP should be consulted by manufacturers and sponsors for the pertinent monographs.

2.3.1.3.10. Stability

According to ICH Q5C, stability studies should be performed on the therapeutic product as real-time stability testing using stability-indicating assays. For parenteral products, the stability program should include sterility testing. The stability program for multi-use containers should include preservation testing.

2.3.1.4. Stages that apply to drug substances and drug products

2.3.1.4.1. Reprocessing:

When a batch or lot of a drug is in progress, a final biological bulk intermediate or a bulk drug from a single batch or lot is subjected to a previous step in the validated manufacturing process because it didn't meet predetermined specifications, this is referred to as reprocessing. Reprocessing processes are evaluated and pre-approved by the quality control department or as part of the marketing authorization and are expected to be sometimes essential. The submission should specify the steps where reprocessing is allowed as well as the maximum number of reprocessing occurrences that can be carried out in a batch. There should be a procedure for the concurrent validation of the reprocessing stage. Any batch included in the reprocessing validation procedure needs to be added to the stability program.

2.3.1.4.2. Reworking:

When a drug that is still in the manufacturing process, a final biological bulk intermediate or a drug product from a single batch or lot is put through a different manufacturing process because it didn't satisfy preset standards, this is known as reworking. Reworking happens unexpectedly and is not covered by the marketing authorization. The modified batch must be shown to be equivalent to batches produced using the established technique. In cases where regular quality control testing is insufficient to adequately define the reworked batch, it may be required to apply additional analytical instruments to evaluate comparability. Without prior notice and written consent from the BGTD, a revised batch should not be marketed or sold in Canada.

2.3.1.4.3. Characterization and Comparison:

Evaluating the effects of modifications to the manufacturing process or important raw materials on the therapeutic product is more challenging because of the complexity of allergic products and the limited instruments available to analyze and define them. To ensure comparability, a plan should be developed that takes into account data from characterization studies as well as the complete process, including process validation, in-process controls, and stability data. The Health

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CODEN: JCLMC4
Journal of Coastal Life Medicine

Canada and ICH guidelines designing the comparability studies should take into account the Post-Notice of Compliance Changes - Quality document.

2.3.2. Clinical information:

For non-clinical and clinical pharmacology research of allergenic products, there are no particular specifications. For each allergenic extract product, the type and necessity of these investigations would be decided on an individual basis. Therefore, sponsors are urged to consult Health Canada for advice while the products are being developed.

2.3.2.1. Considerations for clinical trials

This section describes factors that apply to phase 1, phase 2, and phase 3 clinical studies (sometimes known as "early clinical trials" and "confirmatory trials," respectively).

- **Early clinical trials**
  - **Tolerable dose:** Patients who suffer from allergies should research the use of allergenic items for particular immunotherapy. Depending on the nature of the product, several doses of the items should be evaluated to gather information on their safety and tolerability.
  - **Dose-response:** To prove their relevance with clinical efficacy, dose-response studies should be carried out once a tolerated dose range has been established. Outcomes may include provocation tests as well as clinical endpoints. Laboratory measurements of T cell reactivity, allergen-specific antibodies, or cytokines may offer supporting data for the therapeutic dose.
  - **Cross-reactivity:** The location, quantity, and variety of the sources of sensitization in each patient's environment may be impacted by geographic and climatic variances in allergens like grass. Individual allergens are also not homogeneous and come in a variety of isoforms. Therefore, proof of the cross-reactivity between foreign-sourced allergen products and Canadian species of allergen should be offered.
  - **Confirmatory clinical trials:** Confirmatory trials are designed to assess the clinical benefit of the product by carrying out particular immunotherapy studies based on the information acquired in early-phase clinical trials. To determine the eligible patient populations, primary and secondary study objectives, assumptions of treatment impact, and sample size, these clinical trials should be designed based on the safety and efficacy results from early-phase clinical studies. These clinical studies must be carried out with attention toward commercialization and with a focus on the desired treatment's indication, dosage, method of administration, and duration. Wherever practical, a randomized placebo-controlled double-blind design should be used for this research. Because of the diversity in each person's clinical responses, the unpredictable and variable exposure to allergens, and the subjective nature of symptom evaluations, the use of a placebo is advised. The study protocol should include a thorough description of blinding to study medication (e.g., how the study drug is masked). It is also important to detail the steps taken to keep the blinding. A justification for the lack of double blinding should be given, along with information on how to minimize or eliminate observational risk. Block randomization may be used, stratifying the participants based on the severity of the disease as well as other pertinent criteria, as determined by the statistical model. Before the randomization, there should be stratification. The selection and suitability of the comparator for actively controlled trials (with or without a placebo) should be supported. Before undertaking such trials, sponsors are urged to consult with Health Canada. For a new allergenic treatment to be approved for sale, results from carefully monitored phase 3 clinical studies are typically required for each indication (such as seasonal allergic rhinitis or persistent allergic rhinitis) requested by the sponsor. Depending on the disease being studied and the claims being made, several endpoints should be used.
  - **Therapy goals and potential claims for symptoms or exposure time:**

Due to immune system alterations, the main goal of specialized immunotherapy is sustained efficacy. The duration of allergy contact varies greatly based on the allergen. Therefore, depending on the allergy condition treated and the sought-after efficacy claims, the trial's length would vary.

- **Evaluation of effectiveness:**

A. Primary efficacy endpoints in clinical trials

Both physician and patient self-rated symptom scores have been utilized in clinical trials. Patient-rated scores are preferable as the primary outcome, nevertheless, as patients experience the clinical manifestations. If the primary endpoint is a combined symptoms-medications score, the

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CODEN: JCLMC4
Journal of Coastal Life Medicine

mechanism to combine the two values must be pre-specified and supported. The study protocol must include the time points at which the endpoints will be evaluated. The use of concurrent drugs, a combined score, or both may be used to assess the symptoms using a well-defined, validated scoring system as the major clinical outcomes of immunotherapy.

B. Secondary efficacy endpoints in clinical trials

Other possible secondary endpoints include changes in allergen-specific immunoglobulins and cytokines, symptom-free days, physician and patient-rated clinical global improvement, health-related Quality of Life (HRQoL) (validated Survey questions), individual symptom scores, total symptom score, total medication score, symptom load on a visual analog scale (VAS), and individual symptom scores.

C. **Supportive evidence for efficacy**

Particularly in years with low allergen exposure, provocation tests carried out concurrently as part of clinical trials can be used to support the efficacy and demonstrate that the clinical efficacy is maintained. Additionally, if the allergen concentration required to cause the same symptoms grows during the course of the research, this growth is suggestive of the treatment's effectiveness. Such provocation tests haven't been proven to be reliable substitutes for effectiveness tests, nevertheless. Provocation tests can be thought of as a supporting technique for the efficacy assessment in environmental exposure units (EEUs). However, it is necessary to authenticate the unit's results by comparing them to clinical symptoms caused by outside exposure. Seasonal allergy priming should be a part of EEU studies. In any instance, it is advised that the Sponsor seek advice from Health Canada to obtain regulatory and scientific feedback before starting studies employing the allergen chambers. Patients with a history of allergy to the allergens in question should be used to determine the safety and effectiveness of any trials including a combination of those allergens.

- **Population of patients**

Clinical trial participants for immunotherapy should have a comprehensive medical history of their allergic illnesses. Before study admission, it is important to confirm that subjects' sensitivity is documented by current positive skin tests or by adequate in-vitro tests for a particular allergen. The study protocol should provide a clear definition of the eligibility (inclusion and exclusion) requirements. Age, gender, illness severity, co-morbid diseases, prior immunotherapy, and excluded concomitant drugs should all be taken into consideration when defining these parameters.

- **Statistics-related factors**

The precise design chosen for a certain study is significant and needs to be made clear. Sponsors should review any pertinent ICH guidelines that are appropriate for the trial design they have chosen (e.g. E6, E8, E9, E10, etc.). The clinical trial protocol should make it very clear what research design will be used as well as what statistical techniques will be applied to the data analysis. The primary and secondary goals of the study, as well as a statistical basis for the suggested sample size, should all be clearly stated in the protocol. The suggested sample size should be sufficient to achieve the trial's main goal while also enabling a thorough evaluation of the product's safety profile. The findings of earlier trials with the product or previously published research can serve as the foundation for estimates of any numbers utilized in the sample size calculation as long as they are explicitly stated. To better comprehend the expected distribution of the data, information gathered from pilot/feasibility studies with the product, in particular, should be used. This information will also make it possible to obtain accurate estimates of any quantities used in the sample size calculation required to sufficiently power the study. It is important to specify the statistical techniques that are most suited for the endpoint being examined. Endpoints might be continuous, longitudinal, or time-to-event, among others. The results based on per protocol population should support the results based on the intention-to-treat patient population, which should be the main study of efficacy. To assess the importance of the observed treatment impact, the study's findings should be provided not only in terms of statistical significance using p-values but also with estimates of the treatment effect and the related 95% confidence intervals. Either parametric or nonparametric approaches should be used in the study, depending on how the data are distributed. Repeated measures analysis is preferred when scores (symptom and/or use of concurrent drugs) are measured across time, such as daily. Always choose a period carefully and take into account the possibility of missing values when choosing the period for evaluating efficacy. In clinical trials for allergenic goods, missing data can be a significant issue, hence methods should be put in place to reduce the likelihood of missing data occurring during the trial. The trial protocol should contain methods for treating missing data that are justified and clearly explained. These methods should also include sensitivity analyses that will be used to

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CODEN: JCLMC4
Journal of Coastal Life Medicine

determine how robust the study results are to the way of handling missing data that has been chosen. The results of well-conducted phase 2 studies should be used to determine any potential biases that will need to be addressed in the phase 3 research. Any potential biases should be thoroughly addressed throughout the trial planning. It is also crucial to take into consideration during the design stage any elements that can skew the evaluation of efficacy. The statistical analysis should take important confounders into account, and the study protocol should specify any relevant sub-group analyses.

- **Evaluation of safety**

Data on safety should be gathered by clinical study procedure. Adverse events should be properly recorded and categorized according to their seriousness and their most likely cause. All adverse events need to ideally be coded using MedDRA language.

Comparing the study drug and the comparator's kind, severity, and frequency of adverse events should be done based on safety information from a sufficient number of patients treated for a sufficient amount of time. To allow for the identification of meaningful differences in safety between the study drug and the comparator, efforts should be made to guarantee that comparative clinical studies have a sufficient number of patients treated for an adequate amount of time. A product must have a sufficient safety profile before entering phase 3 of the clinical trial process. Adverse events unique to allergenic products, like local and systemic allergic reactions, should be reported separately and appropriately analyzed. At the phase 3 trial preparation stage, sponsors are encouraged to speak with Health Canada about safety-related concerns.

- **Pediatric caution**

The sponsor shall justify the pediatric age ranges chosen for clinical trials based on the prevalence of the disease and the need for therapy in the various age groups. Sponsors are invited to speak with Health Canada about the pediatric program on an individual basis.

The clinical program would be the same as that necessary for adults for allergenic products that have not been previously examined in adults. The appropriate pediatric dose for those currently researched or approved in adults should be identified, and sufficient short- and long-term safety information should be included for each of the suggested age categories. Each product's duration and several pediatric patients exposed to the study medicine would be decided individually, taking into account any potential safety issues as well as anticipated side effects.

- **Changes in the formulation or dosage form**

Sponsors are urged to consult with Health Canada about any changes to the formulation or dosage form when developing a medication or after approval.

2.3.3. Adjuvants

It is important to show the benefits of adjuvant use as well as the adjuvant's effectiveness, quality, safety, and immunologic effects. For more information on the use and regulatory examination of adjuvants, sponsors can consult the World Health Organization Guidelines on Nonclinical Evaluation of Vaccines and the European Medicines Agency Guideline on Adjuvants in Vaccines for Human Use. Sponsors should speak with Health Canada regulatory officials before submitting the proposal to determine the necessary data if the adjuvant is a unique one in Canada.

2.3.4. Labeling of products

The Food and Drugs Act and Food and Drug Regulations' relevant labeling requirements must all be followed by sponsors. In addition, Part C, Division 4 of the Food and Drug Regulations contains a description of the labeling requirements particular to Schedule D medications. A novel allergenic extract's product monograph should be created by the guidelines provided in Health Canada's advice paper, Guidance for Industry: Product Monograph. You can contact Health Canada with inquiries about the Product Monograph.

2.3.5. Plans for risk management

Health Canada may ask for risk management strategies during the pre- or post-market phases if they are thought to be important in making decisions about the benefit-to-risk profile of the allergenic product. Sponsors can consult the Health Canada notification titled Notice Regarding Implementation of Risk Management Planning including the adoption of ICH Guidance Pharmacovigilance Planning - ICH Topic E2E for further information and the ICH guideline, Pharmacovigilance Planning (ICH E2E).

2.4 Post-market activities

2.4.1 Lot release and Yearly Biologic Product Reports

According to the Health Canada guideline paper Lot Release Policy for Schedule D (Biologic) Drugs, allergenic products are subject to BGTD's risk-based lot release program. Products are

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Journal of Coastal Life Medicine

assigned to one of three evaluation groups at the time of authorization, with each group having varying degrees of regulatory scrutiny based on the level of risk associated with the product. Annual Yearly Biologic Product Reports (YBPRs) must be submitted by sponsors to BGTD. Scientifically defensible groupings may be presented as one YBPR for simplicity of preparation and evaluation. The submission to Health Canada for assessment and approval should include proposed groups. Inquiries about groups can be sent to Health Canada. Section 4 has contact information.
The YBPR's initial submission date may be arranged with the BGTD. Following the initial submission of the YBPR, sponsors are required to submit the following reports every 12 months. Alternatively, no later than October of each year, the YBPR may be submitted as an addition to the Annual Drug Notification Report. (See section 2.1)

2.4.2 Post-market changes

Manufacturers may alter the method used to manufacture the product or its intended use after receiving a notice of compliance (NOC). Health Canada evaluates any proposed modifications using a risk-based methodology if they could affect the product's quality, safety, efficacy, or effective usage. A modification to an approved medicine should be notified by one of the four categories below: Level I (Supplements), Level II (Notifiable Changes), Level III (Annual Notifications), and Level IV (Record of Changes). This will allow Health Canada to manage any risks that may be connected to the change. For advice on the kind of submission and data needs required to support a specific modification, sponsors should consult the Post-Notice of Compliance Changes guidance materials (Framework Document, Quality Document, and Safety and Efficacy Document). The quality post-Notice of Compliance Improvements guideline document should be used for medications that were approved under the DIN (biologics) licensing scheme in the absence of a guidance document specifically for quality changes to such goods. Sponsors are urged to get in touch with Health Canada for help classifying a planned modification. Section 4 provides contact information.

2.4.3 Post-market surveillance and reporting of adverse reactions

Every market authorization holder (MAH) is required to disclose certain known ADRs, including serious unexpected ADRs that happen outside of Canada as well as serious ADRs that occur in Canada. ADRs must be reported via the Canada Vigilance Program to the Marketed Health Products Directorate (MHPD). The Health Canada guidance document Reporting Adverse Reactions to Marketed Health Products, which includes pertinent definitions and the deadlines for reporting suspected reactions, offers MAHs guidance on how to comply with the Food and Drugs Act and its associated Regulations about reporting ADRs. The quality, completeness, and accuracy of the data provided determine how well Health Canada's ADR reporting system performs. One way to find rare, serious, or previously undetected ADRs is by reporting them and monitoring them.

2.4.4 Summary reports

By Part C.01.018 of the Food and Medicine Regulations, the MAH is required to submit an annual summary report detailing all information regarding ADRs and serious ADRs to the drug that it has been made aware of or received over the course of the previous 12 months. If the MAH determines from the annual summary report that the risk-benefit profile of a product has significantly changed, the MAH shall notify the MHPD. By Part C.01.019 of the Food and Medicine Regulations, MAHs may also be asked to produce a summary report focused on a particular issue to evaluate the efficacy and safety of a certain drug.

The Periodic Safety Update Report (PSUR) format, as specified in the ICH E2C (R1) guideline, is preferred when the yearly summary report is requested by Health Canada. Scientifically supported product groupings can be combined and submitted as one PSUR for simplicity in preparation and review. MHPD should be asked to approve any potential groupings that have a scientific basis. When a grouping has already been authorized, such as homologous groupings or those chosen in another manner for the submission of the YBPR, that grouping should be preserved. You can contact Health Canada with any grouping-related queries.

2.4.5 Risk reporting

Any risk management program that involves identifying, assessing, interpreting, responding to, and communicating risk issues to enable better decision-making must include risk communication as a key component. Risk communication is the process of creating and disseminating knowledge about possible or current health risks to help patients and the healthcare professionals who care for them make better decisions about their health. The advice from Health Canada Information on the

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Journal of Coastal Life Medicine

factors to be taken into account when releasing risk communication documents for health products sold on the Canadian market and subject to the regulatory control of the Health Products and Food Branch is provided in the Description of Current Risk Communication Documents for Marketed Health Products for Human Use. Issuance of Health Professional Communications and Public Communication by Market Authorization Holders, a guidance document from Health Canada, offers instructions on how to create and distribute health professional communications and the accompanying public communications to address health and safety issues related to healthcare products.

3. Conclusion

This study examines developing and marketing new biologically derived allergic products in Canada. This information was compiled from various Canadian government documents. The outcome demonstrates that the development of allergenic products in Canada is subject to the strictest rules and regulations, and the various licenses as well as documentary evidence (such as drug establishment licenses, notices of compliance, fax-back forms, etc.) necessary to get marketing authorization for allergenic products in Canada. ADRs and serious ADRs to the drug that the manufacturers have been made aware of or received over the course of the previous 12 months must be included in an annual summary report or periodic safety update report.

Reference

1) https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/regulatory-framework-unauthorized-allergenic-products-biological-diagnosis-treatment-allergic-diseases.html
2) https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html
3) https://laws-lois.justice.gc.ca/eng/Regulations/c.r.c.,_c._870/index.html
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7) https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/release/guidance-sponsors-program-schedule-biologic-drugs.html