Health Canada Santé Canada

Date: November 13, 2012

NOTICE

Release of Guidance Document: Regulatory Framework for Unauthorized New Allergenic Products of Biological Origin used for the Diagnosis or Treatment of Allergic Diseases

Health Canada is pleased to announce the release of the Guidance Document *Regulatory Framework for Unauthorized New Allergenic Products of Biological Origin used for the Diagnosis or Treatment of Allergic Diseases*. The purpose of the document is to provide guidance to sponsors to facilitate compliance with the regulatory requirements applicable to the authorization and life-cycle management of allergenic products of biological origin in Canada.

The document is available in both French and English on the Health Canada website at the following link:

http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/allergenic_allergenes_2012-eng.php

Questions or Comments regarding the content of the guidance may be directed to**:**

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GUIDANCE DOCUMENT: Regulatory Framework for Unauthorized New Allergenic Products of Biological Origin Used for the Diagnosis or Treatment of Allergic Diseases

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Health Products and Food Branch

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Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	HPFB's Mandate is to take an integrated approach to managing the health-related risks and benefits of health related to health products and food by: • Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

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Également disponible en français sous le titre : Cadre réglementaire applicable aux nouveaux produits allergènes d'origine biologique non autorisés qui sont utilisés pour le diagnostic ou le traitement des affections allergiques

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Policy objectives

The regulatory framework for allergenic products of biological origin used for the diagnosis or treatment of allergic diseases is intended to maximize the quality, safety, and efficacy of these products for human use in Canada. The objective of this guidance document is to help ensure that sponsors have the information necessary to comply with the regulatory requirements for the authorization and life-cycle management of allergenic products in Canada.

1.2. Scope and application

This guidance document applies to sponsors of allergenic products comprised of biological material used for the treatment or diagnosis of allergic or immunological diseases in humans. Throughout the document, these products are referred to as allergenic products.

All unauthorized new products and Clinical Trial Applications (CTAs) for allergenic products should adhere to these guidelines.

Synthetic and recombinant allergenic products are not included in the scope of the document. Sponsors of these products should refer to applicable ICH guidelines and guidance documents applicable to Schedule D (biologic) drugs on the Health Canada website.

The guidance document outlines the regulatory framework for new allergenic products, including the submission requirements and regulatory activities that are applicable across the life-cycle of these products; it should be read in conjunction with Part C of the *Food and Drug Regulations*, Health Canada guidance documents applicable to Schedule D (biologic) drugs, and applicable International Conference on Harmonization (ICH) guidelines. Refer to Appendix A for a list of reference documents. This document does not apply to products set out on Schedule D to the *Food and Drugs Act* when they are prepared in accordance with the practices of homeopathic pharmacy[1], and which are subject to the *Natural Health Products Regulations*.

This document does not apply to products submitted for approval using the DIN application process.

The preparation of prescriptions by health practitioners, diluting laboratories and other establishments is considered compounding and falls under provincial regulations; as such, it will not be addressed in this guidance document. The Health Canada *Policy on Manufacturing and Compounding Drug Products in Canada* (POL-0051) provides a framework to distinguish between compounding and manufacturing activities for drug products in Canada.

In this guidance document, “shall” is used to express a requirement, i.e., a provision that the user is obliged to satisfy in order to comply with the regulatory requirements; “should” is used to

[1] Natural Health Products Directorate. Evidence for homeopathic medicines guidance document. May 2007. http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/ehmg-nprh-eng.php

express a recommendation which is advised but not required; and "may" is used to express an option which is permissible within the limits of the guidance document.

1.3. Policy statements

The following statements outline the fundamental concepts and principles of the regulatory framework for allergenic products in Canada:

1.3.1. Allergenic products of biological origin used for the diagnosis or treatment of allergic diseases are considered Schedule D (biologic) drugs[2]. Regulatory decision-making for allergenic products, as with all Schedule D (biologic) drugs, shall be based on science and regulatory principles existing within the *Food and Drugs Act* and Part C of the *Food and Drug Regulations.*

1.3.2. Every allergenic product authorized for sale in Canada under the *Food and Drug Regulations* shall have a unique Drug Identification Number (DIN) assigned in accordance with Part C, section C.01.014 of the *Food and Drug Regulations* prior to it being sold.

1.3.3. All allergenic products authorized for sale in Canada should be standardized. If internationally acceptable standards are not available, validated in-house reference standards should be used by the manufacturer.

1.3.4. Health Canada is committed to strive for harmonization with other national regulatory authorities wherever possible.

1.4. Background

Allergenic products are used for both the diagnosis and treatment of allergic diseases. Traditionally, specific immunotherapy with allergen products is the repeated administration of allergens to allergic individuals to ameliorate the symptoms associated with subsequent exposure to the causative allergen. Administration is often over a period of 3-5 years. Allergenic products are highly variable in nature. The safety and effectiveness of allergy diagnosis and treatment are dependent on the quality of the allergenic products used. Over time, new methods and standards have been established to enhance the quality, safety, and efficacy of allergenic products. For example, there are now methods available to measure the allergenic activity of some allergenic products. This guidance document incorporates advances made and aligns with international initiatives in this area. The guidance document describes the regulatory framework that applies to allergenic products across their life-cycle, from pre-market review, to post-market monitoring.

[2] Unless prepared in accordance with the practices of homeopathic pharmacy.
Note: program decision regarding classification of non-subcutaneous allergenic products prepared from an alga, a bacterium or a fungus, to be documented when guidance is at final stage.

2. GUIDANCE FOR IMPLEMENTATION

2.1. Regulatory Issues

2.1.1. Legislative and regulatory overview

Unauthorized allergenic products that are 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), and Division 8 (requirements for new drugs).

The regulatory review of allergenic products for market authorization includes consideration of quality, pre-clinical and clinical safety and efficacy information. An on-site evaluation of manufacturing facilities as well as in-house laboratory testing may be conducted as part of the regulatory review process. Once authorized, monitoring continues throughout the life-cycle of the product. All allergenic products are subject to Health Canada's risk-based lot release program and systems are in place to monitor and evaluate adverse reactions.

The regulations are administered by Health Canada's Biologics and Genetic Therapies Directorate (BGTD), in partnership with the Marketed Health Products Directorate (MHPD) and the HPFB Inspectorate

2.1.2. Pre-submission meetings

Manufacturers/sponsors of allergenic products should consult with Health Canada in order to seek advice on quality and clinical trial requirements and the preparation of regulatory submissions. Early and ongoing consultation will help ensure that regulatory requirements are met. These meetings also help Health Canada to plan and prepare for upcoming submissions.

Refer to the Health Canada *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* and the *Management of Drug Submissions Guidance* for instructions on how to request pre-submission meetings.

2.1.3. Submission format

All allergenic product submissions should follow the ICH Common Technical Document (CTD) format, in accordance with the Health Canada guidance document *Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format.* Health Canada strongly recommends the filing of electronic submissions in the eCTD format, in accordance with the guidance document, *Preparation of Drug Submissions in the Electronic Common Technical (eCTD) Document Format.*

Clinical Trial Applications (CTA) should be formatted in accordance with the guidance documents referenced above as well as the *Guidance for Clinical Trial Sponsors: Clinical Trial Applications.*

Refer to the *Guidance for Clinical Trial Sponsors* and *Management of Drug Submissions* guidance documents for procedures on how to file applications and submissions.

2.1.4 Drug Identification Numbers (DINs) for allergenic products

Each allergenic product shall have market authorization in the form of a unique DIN, in accordance with C.01.014 of the *Food and Drug Regulations*. A DIN is an indication that a drug has been evaluated and authorized for sale by Health Canada, and it is a tracking number that serves as a tool to help in the follow-up of products on the market, recall of products, inspections, and quality monitoring.

More information about DINs is available in the following Health Canada document: *Guidance for Industry: Management of Drug Submissions* and the *Drug Identification Number (DIN) Enforcement Policy* (POL-0040).

2.1.5 Establishment Licensing and Good Manufacturing Practices

Allergenic products are subject to the requirements of Division 1A (Establishment Licences) and Division 2 (Good Manufacturing Practices) of Part C of the *Food and Drug Regulations*.

Part C, Division 1A of the *Food and Drug Regulations* defines the activities for which compliance with Good Manufacturing Practices (GMP) is to be demonstrated prior to the issuance of a drug establishment licence. The licensable activities include fabrication, packaging, labelling, testing, wholesale, distribution and importation of allergenic products. For further information on the establishment licensing process, refer to the establishment licensing section of the Health Canada website and the most recent version of the *Guidance Document on Drug Establishment Licences* (GUI-0002). These establishments will be subject to inspection by the Inspectorate.

The Health Canada *Good Manufacturing Practices (GMP) Guidelines* (GUI-0001) provide guidance to the regulated industry on how to comply with requirements of Part C, Division 2 of the *Food and Drug Regulations.* Establishments carrying out a licensable activity involving allergenic products should refer to the *GMP Guidelines, GMP Questions and Answers document,* and *Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)* (GUI-0027), which is intended to address special considerations and issues pertinent to the manufacture and control of biological drugs including allergenic products.

2.2. Clinical trial applications (CTAs)

Clinical trials conducted in Canada involving allergenic products are subject to Part C, Division 5 of the *Food and Drug Regulations*, which outlines the requirements applicable to the sale and importation of drugs for use in human clinical trials in Canada. CTAs should be submitted in accordance with Health Canada's *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* and the Health Canada *Clinical Trials Manual*.

Before submitting a CTA, sponsors are encouraged to seek input from Health Canada on scientific, quality, clinical, and other regulatory issues at an appropriate stage of product development. Refer to section 2.1.2 for guidance on requesting pre-submission meetings.

Clinical trial materials are subject to BGTD's risk-based lot release program, as described in the Health Canada guidance document *Lot Release Program for Schedule D (Biologic) Drugs.* Generally, sponsors of allergenic products are required to complete and file a Fax-back form (Appendix IA of the Lot Release guidance document) and await a signed response from BGTD prior to use of the clinical trial material.

For allergenic products used in clinical trials in Canada, adverse drug reactions (ADRs) that are *both* serious and unexpected are subject to expedited reporting to Health Canada. During a clinical trial, the sponsor is required to inform Health Canada/BGTD of any serious, unexpected ADR that has occurred inside or outside Canada. An ADR report must be filed in the cases:

- where the ADR is neither fatal nor life-threatening, within 15 days after becoming aware of the information
- where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information within 8 days after having informed Health Canada of the ADR, submit as complete as possible, a report which includes an assessment of the importance, relatedness and implication of any findings.

Each ADR which is subject to expedited reporting should be reported individually in accordance with the Health Canada guidance document *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (ICH E2A). Ongoing safety information respecting a drug should be conveyed to Investigator(s) and their Research Ethics Board(s). For further information refer to the Health Canada guidance documents*: Guideline for Good Clinical Practice* (ICH E6) and *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (ICH E2A).

When filing a clinical trial ADR report to Health Canada/BGTD, a completed ADR Expedited Reporting Summary Form should be attached to the front of the completed ADR report. The suggested ADR report format is the Council for International Organizations of Medical Sciences *Suspect Adverse Reaction Report* form.

Section 2.4.3 provides guidance on post-market adverse reaction reporting.

2.3. Information and submission requirements

Part C, Division 8 of the *Food and Drug Regulations* sets out the requirements for the sale of new drugs in Canada, and prohibits the sale of a new drug unless the manufacturer has filed a submission that is satisfactory to the Minister. Section C.08.002 of the *Food and Drug Regulations* outlines the requirements for an NDS.

This section provides guidance on the information that should be provided in submissions filed to Health Canada. A New Drug Submission (NDS) shall be filed for any allergenic extract that

meets the definition of a new drug as set out in C.08.001 of the *Food and Drug Regulations*[3]. The onus is on the sponsor to provide the necessary evidence to support all aspects of a submission. Sponsors are encouraged to consult with Health Canada when preparing their submission. In addition to this document, sponsors should refer to relevant ICH guidelines and other Health Canada guidance documents that are applicable to Schedule D drugs. Information regarding general submission requirements and target performance standards may be found in the Health Canada guidance document: *Management of Drug Submissions*.

2.3.1. Quality information

Sponsors should refer to the Health Canada guidance document: *Preparation of Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products* for general guidance on the format and submission of quality information. This section provides specific guidance on the quality information that should be provided in a submission for market authorization of an allergenic extract. As part of the quality assessment, an on-site evaluation of the manufacturing facility may be performed and consistency testing may be conducted at the pre-market stage in accordance with BGTD's lot release program. Refer to the Health Canada guidance document: *Lot Release Program for Schedule D (Biologic) Drugs*.

2.3.1.1. Standardization

Allergenic products are complex products manufactured from biological starting materials which make them prone to variability and difficult to characterize. This limits a practitioner's ability to use products from different manufacturers and complicates the transition from one batch to another from the same manufacturer. Standardization of allergenic products should promote consistency of the product quality. Reference standard materials should be established and characterized for all types of allergen products.

International reference standards:
Preference for international reference standards such as those developed by Center for Biologics Evaluation and Research (CBER), United States Pharmacopeia (USP), or European Pharmacopeia (EP), with defined allergen content and activity, exist for a limited number of allergenic products.

Unauthorized new allergenic products would typically be standardized to existing international reference standards for authorization in Canada.

[3] C.08.001. For the purposes of the Act and this Division, "new drug" means
(a) a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug;
(b) a drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or
(c) a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug.

In-house reference standards:
In cases where an international reference standard does not exist, the allergenic extract should be standardized to an in-house reference standard (IHRS), as is the case for other biologic drugs. An IHRS should promote batch-to-batch consistency within production runs. The IHRS should be manufactured according to the manufacturing batch record as described in the submission. Any differences introduced must be justified. The IHRS is designed to serve as an internal reference to control the qualitative and quantitative composition of commercial batches over time.

In cases where an international reference standard does exist, an in-house reference standard which is traceable and representative of the acceptable international reference standard can be prepared and used.

The specific allergenic activity (potency) of the IHRS should be established; additionally it should be characterized using available relevant physicochemical methods. The presence of all relevant allergens in the IHRS should be demonstrated and the internationally accepted allergen nomenclature should be used, as appropriate. The storage conditions and shelf-life of the IHRS should be established and documented. The allergenic properties of the IHRS should be determined using pooled patient serum. The potency of the IHRS should be determined by immunoassay. The IHRS should be biologically standardized on the basis of skin reactivity test or a suitable *in vitro* method if appropriately justified.

Qualification of a new IHRS should be performed by testing in parallel with the existing IHRS using a predefined set of tests which should include the routine release tests as well as additional characterization tests to demonstrate that there is no shift in the potency and quality.

Serum pools:
A serum pool containing the sera of 10-15 individuals should be established for batch control and for the qualification of individual IHRS. The sensitization patterns, frequency of Immunoglobulin E (IgE)-recognition of different allergens, content of allergen-specific IgE antibodies, previous specific immunotherapy treatment, and the clinical relevance of desensitization should be considered when preparing the pool. In addition, sera containing antibodies directed against reagents used in the immunoassay such as bovine serum albumin or gelatin should be avoided.

Serum pools should be qualified based upon predefined acceptance criteria, which should include the reactivity profile of the pool.

2.3.1.2. Drug substance

The manufacturing process for many allergenic products defies the conventional division of the manufacturing process into drug substance and drug product as a continuous manufacturing process. For the purposes of this guidance, a continuous manufacturing process where there is no clear drug substance release or shelf-life, the manufacturing process from receipt of raw materials to the formulated bulk should be considered the drug substance and filtration through to the final filled container the drug product. A justification for the lack of drug substance

release testing and evidence that there is no hold time associated with the formulated bulk should be included.

Manufacture
All steps in the manufacturing process, from receipt of the raw source material to the storage of the bulk drug substance should be described in detail, including modifications such as absorption and process scale. A flow chart indicating all processing steps, in-process controls, intermediates and hold-times should be included.

Process Validation
Process validation provides evidence that the process consistently results in a drug substance that meets predetermined quality attributes when operated within established parameters. Prospective validation with 3-5 consecutive successful production batches should be performed. Alternates should be discussed with Health Canada with appropriate scientific justification. Concurrent or retrospective validation may be undertaken in special circumstances with appropriate justification.

Manufacturing processes should be periodically evaluated to verify that they are operating in a valid manner. In the absence of revalidation due to process changes, this may take the form of periodic quality review.

Control of source materials
While the following is not an exhaustive list of all possible source materials, the principles expressed in the subsequent paragraphs should be applied, where possible, to other source materials**.**

The quality of source raw materials is critical to the manufacture of consistent, high quality allergenic products. The name and address of the supplier(s) as well as the scientific and common name and type of the allergenic source material should be provided. The quality attributes of the source material required to manufacture an allergenic extract of the desired quality should be identified during development. Details of how these attributes are controlled including cultivation, collection, pre-treatment, shipping and storage should be provided for each source material.

Any processing steps (e.g. defatting) performed by the supplier should be validated, monitored and justified. Control methods with acceptance criteria for the source material should include identity and purity testing. The shipping and storage conditions should be justified based upon stability data. Uniformity of the source material from different origins should be demonstrated.

Additional requirements for control of the following source materials:

Pollens:
Collection areas should be described with respect to location, field characteristics, treatments, visual control, collection method and sampling procedures. Pollens should be tested for identity and purity from foreign pollen, mould spores, and extraneous plant material from the same and foreign species. The purity of pollen should be 99% with respect to other pollens, as determined by microscopic examination, with no individual foreign pollen species accounting for more than

0.5%. Contamination by non-pollen plant material should be minimized and the limit justified. Mould contamination should be minimized and not more than 1% should be permitted.

The content of relevant pesticides, heavy metals and solvents should be monitored and justified, in order to demonstrate that their levels are kept to a minimum in the allergenic source material. This may be accomplished by setting justifiable standards and providing evidence that the supplier meets the standards through supplier audits and periodic testing.

Moulds:
The strain, cultivation method and type of material harvested should be specified along with characteristics used for identification such as morphology or genetic properties. The cultivation method should be described in detail (including the composition of growth medium) and key in-process parameters (temperature, pH etc.) justified. The absence of mycotoxins should be demonstrated. Sufficient controls should be in place to prevent the contamination of the source material by other mould strains.

Mites:
The species, cultivation method and type of material harvested (mites, mite faeces, whole mite culture or mixes) should be specified along with characteristics used for identification such as morphology or genetic properties. The cultivation method should be described in detail (including the composition of growth medium) and key in-process parameters justified.

Animal allergens:
Only animals certified by a qualified source material collector as healthy and not recently treated with anti-parasitic or other drugs should be used. Parameters used for the identification of the allergenic source material should be described. The composition of the source material (hair, pelt, epithelium, etc.) should be indicated. Source material collected from killed animals should be collected and stored under conditions that have been demonstrated to maintain the quality of the source material.

The methods used for the collection, shipment and storage of source material should be described and should be designed to avoid contamination with mites, moulds etc.

Hair and dander must be collected without injuring the skin of the animal.

Hymenoptera venoms:
The parameters used for the identification and characterization should be specified and the collection method described. Contamination with pesticides should be avoided.

Food Allergens:
Only foodstuffs fit for human consumption should be used. Details regarding the portion of the foodstuff used, pre-treatment and shelf-life should be justified.

Control of raw materials
The specifications, supplier information and justification for its use should be provided for each raw material.

Control of allergenic products
Characterization and quality control of allergen products should be performed at the drug substance level. Where this is not possible for technical reasons, testing at an intermediate stage may be acceptable, if justified. In this case, the testing should be performed immediately prior to the point where it becomes technically impossible and quality specifications should be defined, which will be included in the release specification for the drug substance. The following aspects of the drug substance should be tested against appropriate specifications at release: appearance and description, identity, purity and impurities, bioburden, potency (typically measured by allergenic activity allergen determination using the appropriate assays.

The allergens relevant to the efficacy of the product must be defined and justified. The content of relevant allergens and any antigen that may pose a safety risk should be measured by validated assays. The allergen profile should correspond to the IHRS and whenever possible to international reference standards.

Potency testing by a validated specific analytical method will be performed for each drug substance.

The corresponding specifications should be justified and based on process capability, critical quality attributes and method variability.

In-process controls
The progress and performance of the manufacturing process should be monitored and controlled through the application of in-process testing and controls. The in-process step should be evaluated with respect to the potential impact on the quality characteristics of intermediates or drug substance. These controls and the associated acceptance criteria should be based on developmental and historical data.

Modified allergen preparations
Validated analytical methods such as antibody-based assays should be used to identify the relevant allergen in the modified form. Complementary validated analytical methods should be used in the characterization of the modification and to monitor the consistency of the modification process.

Validation of analytical methods:
Analytical methods should be validated according to the ICH Q2 (R1) guideline, *Validation of analytical procedures: text and methodology*.

Reference standards or materials
Refer to section 2.3.1.1.

Container closure system
The container closure system(s) should be described in detail. Suitability with respect to integrity testing, extractables and leachables should be demonstrated.

Applicability of the container closure system used in the stability studies to the drug substance container closure system should be discussed.

Stability
The standardization of allergenic products provides meaningful information upon which to base stability studies. Stability studies should be carried out on the drug substance according to the ICH Q5C guideline *Stability testing of biotechnological/ biological products*, to the extent possible.

2.3.1.3. Drug Product

Description and composition of the drug product
A detailed description of the drug product should be given. A table listing all active and inactive ingredients, their amount and their function should be provided. Excipients of biological origin should be identified, justified and supported by a risk assessment.

Mixtures
The number of allergen products in a mixture should be kept to a minimum and both the number and the relative proportion should be justified.

Allergens with proteolytic activities should not be used in mixtures in order to avoid unintended degradation; therefore, hymenoptera venoms should not be mixed with any other allergens, and venoms from different genera should not be mixed.

Perennial and seasonal allergens should not be mixed.

Manufacture
The manufacturing process should be described in detail, including process scale. A flow chart indicating all process steps, appropriately justified hold times and in-process controls should be included.

Process validation
Process validation provides evidence that the process consistently results in a drug product that meets predetermined quality attributes when operated within established parameters. Prospective validation with at least 3 consecutive successful production batches should be performed. Concurrent or retrospective validation may be undertaken in special circumstances with appropriate justification.

Manufacturing processes should be periodically evaluated to verify that they are operating in a valid manner. In the absence of revalidation due to process changes, this may take the form of periodic quality review.

Media fills:
Aseptic processing should be validated using media fills. Three media fill runs should be performed for each container closure size and type. Periodic requalification may utilize an appropriately justified matrixing approach. Refer to the *Good Manufacturing Practices (GMP) Guidelines* (GUI-0001) for more information.

Control of the drug product
Specifications should be set to adequately monitor the quality of the product. When it is not possible to perform the control tests on the finished product due to a modification that interferes with the assay, it may be acceptable to define the specification for the intermediate at the step immediately prior to the modification step. The results of these control tests on the intermediate should be included as release specifications for the finished product. The release specifications should be set for each strength (dilution) and differences between strengths should be justified.

Potency testing of allergenic products:
1. Non-modified products

A competitive IgE-binding assay should be used to determine the total allergenic activity for the standardization and batch control of finished products and the label should indicate the content in potency units. Where an international standard exists, it should be applied and the content of individual antigens in weight per volume should be included in the specifications in addition to potency. In cases where risks to patient safety have been identified with respect to the presence of specific minor allergens, these should be measured as well.

2. Allergen mixtures

Potency testing for each individual allergen in the mixture should be performed. It may be acceptable to measure the total potency of the finished product by a competitive IgE-binding assay in cases where the constituent allergens cross-react.

3. Absorbed products

The efficacy and stability of the adsorption process should be determined by measuring the amount of total soluble protein and the presence of IgE-binding components in the supernatant (unbound fraction) at release and throughout the shelf-life. Other tests may be used if appropriately justified. The concentration of free IgE-binding components should be limited and followed throughout the shelf-life in the stability studies.

4. Physicochemical standardization

It is acknowledged that in certain rare cases, it is not feasible to create the sera pool necessary to perform biological standardization. In this case, a physicochemical standardization may be acceptable, if appropriately justified. The control of these products should include a range of in vitro methods such as determination of an antigen profile, protein profile and total protein content and these results should be compared to a qualified IHRS. It should be noted that biological standardization is expected to be the norm. Clinical efficacy data may be required to support physicochemical standardization in the absence of biological standardization.

Reference standards or materials
Refer to section 2.3.1.1.

Container closure system
The container closure system(s) should be described in detail. Suitability with respect to integrity testing, extractables and leachables should be discussed.

Preservative testing

Allergenic products filled into multi-use containers should contain an effective preservative. The antimicrobial effectiveness of the preservative should be demonstrated to support the labelled use. Manufacturers/sponsors should refer to the USP or EP for the relevant monographs.

Stability
Stability studies should be carried out on the drug product as real-time stability testing using stability indicating assays according to ICH Q5C. Sterility testing should be included in the stability program for parenteral products. Preservative testing should be included in the stability program for multi-use containers.

2.3.1.4. Steps applicable to drug substance and drug product

Reprocessing
Reprocessing is when all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a single batch/lot is subjected to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary and are validated and pre-approved by the quality control department or as part of the marketing authorization. Steps where reprocessing is permitted and a limit to the number of reprocessing events permitted per batch should be clearly defined in the submission. A protocol for the concurrent validation of the reprocessing step should be provided. Any batch that is part of the reprocessing validation exercise should be placed into the stability program.

Reworking
Reworking is when an in-process drug, a bulk process intermediate (final biological bulk intermediate), or drug product of a single batch/lot is subjected to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization. It must be demonstrated that the reworked batch is comparable to batches manufactured by the established process. It may be necessary to use additional analytical tools to assess comparability where routine quality control testing is inadequate to characterize the reworked batch. A reworked batch should not be sold on the Canadian market without notification and explicit authorization by letter from the BGTD.

Cleaning validation
Cleaning validation should be performed on product contact equipment used in the manufacture of the drug substance or drug product according to the Health Canada *Cleaning Validation Guidelines* (GUI-0028).

Comparability and Characterization
The complex nature of allergenic products and the limited tools available to evaluate and characterize them make it more difficult to evaluate the impact of changes to the manufacturing process or key raw materials on the drug product. A strategy incorporating information from characterization studies and the entire process including process validation, in-process controls and stability data should be undertaken to ensure comparability.

ICH guidelines and the Health Canada *Post-Notice of Compliance Changes - Quality* document should be consulted in designing the comparability studies**.**

2.3.2. Clinical information

The guidance provided in this section has been prepared taking into consideration deficiencies observed by Health Canada during the premarket review of NDSs for allergenic products. The guidance should be read in conjunction with Part C of the *Food and Drug Regulations* and applicable ICH efficacy guidelines.

If sponsors intend to seek authorization on the basis of international guidelines, it is recommended that they discuss their relevance to the Canadian context with Health Canada beforehand.

There are no specific requirements for non-clinical and clinical pharmacology studies of allergenic products. The need and the type of these studies would be determined on an individual basis for each allergenic extract product. Therefore, sponsors are encouraged to seek for input from Health Canada during the development of the products.

2.3.2.1 Clinical trial considerations

This section outlines considerations common to phase 1 and phase 2 clinical trials (referred to as "early clinical trials") and phase 3 clinical trials (referred to as "confirmatory trials"). These considerations might be revised with evolution of knowledge.

Early Clinical trials
Early phase clinical trials evaluate safety, optimize the dose and schedule, and identify evidence of biological activity of candidate allergenic extract products.

Tolerated dose: Allergenic products for specific immunotherapy should be investigated in allergic patients. Different doses of the products should be tested (depending on the nature of the product) in order to provide data on safety and tolerability.

Dose-response: After determining a tolerated dose range, dose-response studies should be performed to establish their relationship with the clinical efficacy. Provocation tests (e.g., conjunctival, nasal or bronchial provocation or allergen exposure in allergen challenge chambers) and/or clinical endpoints may be used as endpoints. Laboratory parameters such as allergen specific antibodies, T cell reactivity or cytokines may provide supportive information for therapeutic dose.

Cross-reactivity
Geographical and climatic differences of allergens such as grass may influence the distribution, number, and diversity of the sensitization sources in the environment of the individual patients. In addition, individual allergens are not homogeneous and exist in multiple isoforms. Therefore,

evidence of cross-reactivity of allergen products sourced from overseas with Canadian species of allergens should be provided[4,5].

Confirmatory clinical trials

Based on the data gathered in early phase clinical trials, confirmatory trials are aimed to evaluate the clinical benefit of the product by conducting specific immunotherapy studies. The design of these clinical trials should be based on the safety and efficacy data from early phase clinical trials to define eligible patient populations, primary and secondary trial endpoints, assumptions of treatment effect and sample size as well as other parameters. These clinical trials should be conducted with the preparation to be-marketed and targeting specifically the indication, the dosing, the route of administration and the duration of the treatment sought.

These studies should be performed using (wherever possible) a randomised placebo controlled double-blind design. The use of placebo is recommended because of the variability in individual clinical responses, unpredictability and variability of allergen exposure, and the subjective nature of symptom assessments. Blinding to study medication should be carefully described in the study protocol (e.g., how the study drug is masked). Measures to maintain the blinding should also be described. If a double blinding is not possible, a rationale for this should be provided, along with a discussion of the means for reducing or eliminating observational bias. Randomization could be performed in blocks and depending on the statistical model, stratifying them by severity of the disease and other relevant factors. Stratification should occur prior to the randomization.

For the conduct of active controlled trials (with or without placebo), the choice and the suitability of the comparator should be justified. Sponsors are encouraged to seek input from Health Canada, prior to conducting such trials.

For market authorization of a new allergenic product, it is expected that data obtained from well-controlled phase 3 clinical trials for each indication (e.g., seasonal allergic rhinitis, perennial allergic rhinitis) sought by the sponsor would be the norm. The appropriate endpoints to be selected vary with the condition targeted and the claims to be made.

Aims of treatment and potential claims for indications/duration of exposure

The main aim of specific immunotherapy is persistent efficacy due to the changes in the immune system. The time of exposure to allergens is highly variable and depends on the allergen. Thus the duration of the trials will vary depending on the allergic condition targeted and the efficacy claims that are being sought (e.g. reduction of allergic symptoms, biological response modifier).

Assessment of efficacy

A. Primary efficacy endpoints in clinical trials

In clinical trials, both physician-rated scores and patient self-rated symptom scores have been used. However, since patients suffer the clinical manifestations, patient-rated scores are preferred as primary endpoint. If a combined symptoms-medications score is used as a primary endpoint, the method to combine both scores has to be pre-specified and justified. The time points of

[4] Cox, L., Li, J., Nelson, H., Lockey, R. Allergen immunotherapy: a practice parameter second update. J. Allergy Clin. Immunol. 2007;120(suppl):S25-85.

[5] Cox, L., Nelson, H., Lockey, R. Allergen immunotherapy: a practice parameter third update. J. Allergy Clin. Immunol. 2011;127(1 Suppl):S1-55.

assessment of the endpoints have to be pre-specified in the protocol of the studies. The primary clinical endpoints of immunotherapy may include an assessment of the symptoms via a well-defined validated scoring system and the use of concomitant medications or a combined score or both[6].

B. Secondary endpoints in clinical trials
Possible secondary endpoints are: total symptom score, total medication score, individual symptom scores, health related Quality of Life (HRQoL) (validated Questionnaires), symptom load on a visual analogue scale (VAS), changes in allergen-specific immunoglobulins and cytokines, symptom free days, and physician and patient rated clinical global improvement.

C. Supportive evidence for efficacy
Provocation tests performed in parallel as part of clinical studies can be considered to support the efficacy especially in years with low allergen exposure to show that the clinical efficacy is maintained in provocation tests. Moreover, if the allergen concentration needed to provoke the same symptoms increases over time of the study, this increase is supportive for the efficacy of the treatment. However, such provocation tests are not validated as surrogate markers for efficacy.

The use of provocation tests in environmental exposure units (EEU) can be considered as a supportive tool for the evaluation of efficacy. However, the results obtained in the units have to be validated in comparison with clinical symptoms by natural exposure. Studies in EEU should include a priming phase for seasonal allergies. In any case, it is recommended that the Sponsor consult with Health Canada to get scientific and regulatory input prior to conducting studies using the allergen chambers.

For trials evaluating a mixture of allergens, the safety and efficacy should be established in patients with documented allergy to those allergens (i.e. clinical history, in vitro tests).

Patient population
Subjects enrolled in immunotherapy clinical trials should have a well-documented medical history of their allergic condition. Documentation of sensitivity by current positive skin testing or by adequate in-vitro tests for specific allergen of subjects should be ascertained before study entry. The eligibility (inclusion and exclusion) criteria should be clearly defined in the study protocol. These criteria should be particularly defined in relation to age, gender, disease severity, co-morbid conditions, previous immunotherapy and excluded concomitant medications.

Statistical considerations
The specific design selected for a particular study is important and should be explicitly stated. Sponsors should consult all relevant ICH guidelines that would be appropriate for the selected trial design (e.g. E6, E8, E9, E10 etc.). Both the study design and the statistical methods to be used for data analysis should be clearly specified in the clinical trial protocol. The protocol should also be clear on the hypotheses to be tested, the primary and secondary endpoints, and a statistical justification of the sample size proposed for the study. The proposed sample size

[6] Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy: a statement of a World Allergy Organization (WAO) taskforce. Allergy 2007; 62:317–324.

should be large enough for the primary objective of the trial to be met, and simultaneously allow the safety profile of the product to be adequately assessed. The basis of estimates of any quantities used in the sample size calculation should be clearly explained, and can be based on results from earlier trials with the product or published literature. In particular, information gathered from pilot/feasibility studies with the product should be used to better understand the expected distribution of the data, and will allow reliable estimates of any quantities used in the sample size calculation necessary to adequately power the study to be obtained.

Statistical methods appropriate for the type of endpoint being analyzed should be specified. The different types of endpoints include continuous, longitudinal, or time to event. The intention-to-treat patient population should be the primary analysis of efficacy, and should be supported by the results based on a per protocol population. The results of the study should be presented not only in terms of statistical significance by the use of p-values, but also by providing estimates of the treatment effect and the corresponding 95% confidence intervals so that the relevance of the observed treatment effect can be determined.

Depending on the distribution of the data either parametric or nonparametric methods should be applied in the analysis. In case of longitudinal measurements (e.g. daily) of scores (symptom and/or use of concomitant medications), repeated measures analysis is preferred. Such methods are also available for non-normally distributed data (WAO guidance, Canonica et al 2007).

The selection of the time frame for assessing efficacy should always be given careful consideration, and should consider the potential for missing values. Missing data can be a major problem in clinical trials for allergenic products, and mechanisms should be put in place to minimise the occurrence of missing data during the trial. Methods for handling missing data should be justified and clearly stated in the trial protocol, and should include sensitivity analysis to be conducted to assess the robustness of the study results to the selected method for handling missing data.

Any potential biases should be adequately addressed during the planning of the trial, and results from well conducted phase 2 study (ies) should be used to understand any potential biases that will need to be addressed in the phase 3 study. It is also important to account for at the design stage any factors that could confound the assessment of efficacy. Important covariates should be accounted for in the statistical analysis, and any sub-group analyses of interest should be pre-specified in the study protocol.

Assessment of safety

Safety data should be collected in accordance to protocols of clinical trials. Data should be appropriately tabulated and with adverse events classified according to their seriousness and their likely causal relationship (see ICH E2A). Preferably, all adverse events should be coded using MedRA terminology.

The nature, severity, and frequency of adverse events should be compared between the study product and the comparator and be based on safety data from a sufficient number of patients treated for an acceptable period of time. Efforts should be made to ensure that comparative clinical studies have a sufficient number of patients treated for an acceptable period of time in order to allow the detection of significant differences in safety between the study drug and the

comparator. It is important that a product have an adequate safety profile before moving forward to phase 3 clinical trials. Allergenic product specific adverse events such as local and systemic allergic reactions should be reported separately and analysed as appropriate.

Sponsors are encouraged to discuss safety issues with Health Canada at the planning stage of phase 3 trials.

Pediatric indication
The pediatric age ranges selected in clinical trials should be justified by the sponsor based on the presence of the disease and the need for treatment in the different age groups. Sponsors are encouraged to discuss the pediatric program with Health Canada on a case-by-case basis.

For allergenic products not previously studied in adults, the clinical program would be the same as the one required for adults. For those already studied or approved in adults, the appropriate pediatric dose should be investigated and determined, and adequate short and long term safety information for each of the proposed age groups should be provided. The duration and number of pediatric patients exposed to the study drug would be determined on an individual basis for each product taking into account the anticipated side effects and potential safety concerns.

Change in formulation/dosage form
Sponsors are encouraged to seek input from Health Canada regarding changes in formulation or dosage form during drug development or after approval (Refer to section 2.4.2 on post-market changes).

2.3.3. Adjuvants

The value of the use of an adjuvant and the quality, safety, immunologic effects and efficacy of the adjuvant should be demonstrated. Sponsors may refer to the World Health Organization *Guidelines on nonclinical evaluation of vaccines* and the European Medicines Agency *Guideline on adjuvants in vaccines for human use* for additional information on the use and regulatory evaluation of adjuvants. If it is a novel adjuvant in Canada, sponsors should consult with Health Canada regulatory staff in advance of filing the submission to determine data requirements.

2.3.4. Product labelling

Sponsors shall comply with all of the applicable labelling requirements in the *Food and Drugs Act* and *Food and Drug Regulations.* In addition, the labelling requirements specific to Schedule D drugs are outlined in Part C, Division 4 of the *Food and Drug Regulations.*

The product monograph for a new allergenic extract should be developed in a manner consistent with the principles, practices, and processes outlined in the Health Canada guidance document, *Guidance for Industry: Product Monograph.* Questions regarding the Product Monograph may be forwarded to Health Canada. Contact information is provided in section 4.

2.3.5. Risk management plans

Risk management plans may be requested by Health Canada during the pre or post-market stage if they are considered relevant to decisions regarding the benefit to risk profile of the allergenic product. For more information, sponsors should refer to ICH guideline, Pharmacovigilance Planning (ICH E2E) and the Health Canada notice entitled *Notice Regarding Implementation of Risk Management Planning including the adoption of ICH Guidance Pharmacovigilance Planning - ICH Topic E2E.*

2.4. Post-market activities

2.4.1. Lot release and Yearly Biologic Product Reports

Allergenic products are subject to BGTD's risk-based lot release program, as described in the Health Canada guidance document *Lot Release Program for Schedule D (Biologic) Drugs*. At the time of authorization, products are assigned to one of three evaluation groups, with each group having different levels of regulatory oversight based on the degree of risk associated with the product.

Sponsors are required to submit a Yearly Biologic Product Report (YBPR) on an annual basis to BGTD. For ease of preparation and of review, scientifically justified groupings may be submitted as one YBPR. Proposed groupings should be included in the submission for review and approval by Health Canada. Questions regarding groupings may be forwarded to Health Canada. Contact information is provided in section 4.

The date of first submission of the YBPR may be negotiated with BGTD. Sponsors should inform BGTD when the first YBPR will be submitted, after which subsequent reports should be submitted every 12 months. Alternatively, the YBPR may be submitted as an addendum to the Annual Drug Notification Report no later than October of each year. Refer to the guidance document *Lot Release Program for Schedule D (Biologic) Drugs* for additional information on the submission of YBPRs.

2.4.2. Post-market changes

Following the issuance of a notice of compliance (NOC), manufacturers may make changes to the product manufacturing process or the indication for use. Any proposed changes that may have an impact on the quality, safety, efficacy or effective use of the product are reviewed by Health Canada using a risk-based approach. To enable Health Canada to manage risks that may be associated with a change to an authorized drug, the change should be reported according to one of the four following categories: Level I (Supplements), Level II (Notifiable Changes) Level III (Annual Notifications) and Level IV (Record of Changes).

Sponsors should refer to the series of Post-Notice of Compliance Changes guidance documents (Framework Document, Quality Document, and Safety and Efficacy Document) for recommendations on the type of submission and data requirements necessary to support a

particular change. In the absence of a guidance document specific to quality changes to drugs which were authorized under the DIN (biologics) licensing scheme, the quality post-Notice of Compliance Changes guidance document should be applied to these products.

For assistance in classifying a proposed change, sponsors are advised to contact Health Canada. Contact information is provided in section 4.

2.4.3. Post-market surveillance and post-market adverse reaction reporting

Every market authorization holder (MAH) shall report certain ADRs known to them, including serious ADRs that occur in Canada as well as serious unexpected ADRs that occur outside of Canada. ADRs should be reported to the Marketed Health Products Directorate (MHPD) via the Canada Vigilance Program. The Health Canada guidance document entitled *Reporting Adverse Reactions to Marketed Health Products* provides MAHs with assistance on how to comply with the *Food and Drugs Act* and its associated *Regulations* with respect to reporting ADRs and includes relevant definitions and the timelines for reporting suspected reactions. The success of Health Canada's ADR reporting system depends on the quality, completeness, and accuracy of the information submitted. Reporting of ADRs and the monitoring thereof is one means of identifying previously unrecognized, rare or serious ADRs. Refer to section 4 for contact information for the Canada Vigilance Program and Appendix A for a copy of the Canada Vigilance reporting form.

Refer to section 2.2 for guidance on ADR reporting for clinical trials.

2.4.4. Summary reports

In accordance with Part C.01.018 of the *Food and Drug Regulations*, the MAH shall prepare an annual summary report of all information relating to ADRs and serious ADRs to the drug that it received or became aware of during the previous 12 months. The MAH shall inform MHPD if they conclude from the annual summary report that there is a significant change in the risk-benefit profile of a product. As per Part C.01.019 of the *Food and Drug Regulations*, MAH's may also be requested to submit a specific issue-related summary report for the purposes of assessing the safety and effectiveness of a particular drug. Guidance on the preparation and submission of summary reports can be found in the guidance document entitled *Reporting Adverse Reactions to Marketed Health Products*.

If Health Canada requests the annual summary report, it is preferred that it be submitted in the Periodic Safety Update Report (PSUR) format in accordance with the standards defined in the ICH E2C (R1) guideline. For ease of preparation and of review, scientifically justified product groupings may be incorporated and submitted as one PSUR. Potential groupings with scientific justification should be proposed to MHPD for approval. Where a previously approved grouping exists, for example homologous groupings or those otherwise agreed upon for the submission of the YBPR, those groupings should be conserved. Questions regarding groupings may be forwarded to Health Canada. Contact information is provided in section 4.

2.4.5. Risk communication

Risk communication is an important element of any risk management program, which involves identifying, assessing, understanding, acting on, and communicating risk issues to support better decision making. Within the public health field, risk communication may be defined as the development and dissemination of information concerning potential or existing health risks to enable patients and their healthcare professionals to make better-informed decisions about their health.

The Health Canada guidance document *Description of Current Risk Communication Documents for Marketed Health Products for Human Use* provides information on the considerations for issuing risk communication documents regarding health products available on the Canadian market and that fall under the regulatory oversight of the Health Products and Food Branch.

The Health Canada guidance document *Issuance of Health Professional Communications and Public Communication by Market Authorization Holders* provides guidance in developing and disseminating health professional communications and their accompanying public communications to address health and safety concerns associated with health products.

3. EFFECTIVE DATE

This guidance document is effective as of November 13, 2012.

4. CONTACT INFORMATION

Questions concerning allergenic product clinical trial applications, drug submissions, biologics lot release program, post-market changes or the YBPR should be directed to -

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
200 Tunney's Pasture Driveway
Address Locator 0701B
Tunney's Pasture
Ottawa, Ontario K1A 0K9

Telephone: 613-957-1722
Fax: 613-946-9520
E-mail: BGTD_ORA@hc-sc.gc.ca
Teletypewriter: 1-800-267-1245 (Health Canada)

Questions concerning adverse drug reaction reporting should be directed to –

Canada Vigilance Program
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
200 Tunney's Pasture Driveway
Postal Locator: 0701E
Ottawa, Ontario
K1A 0K9

Telephone: 613-957-0337
Fax: 613-957-0335
E-mail: CanadaVigilance@hc-sc.gc.ca

Questions concerning post-market summary reports should be directed to –

Marketed Biologic, Biotechnology and Natural Health Products Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
200 Tunney's Pasture Driveway
Address Locator 0701B
Tunney's Pasture
Ottawa, Ontario K1A 0K9

Telephone: 613-954-6522
Fax: 613-952-7738
Email: MHPD_DPSC@hc-sc.gc.ca

Appendix A: Reference list of relevant guidance documents

Sponsors should refer to the most up-to date versions of the following guidance documents:

Health Canada guidance documents

Policy on Manufacturing and Compounding Drug Products in Canada (POL-0051)

Guidance for Clinical Trial Sponsors: Clinical Trial Applications

Clinical Trials Manual

Guidance for Industry: Management of Drug Submissions

Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format

Preparation of Drug Submissions in the Electronic Common Technical (eCTD) Document Format

Drug Identification Number (DIN) Enforcement Policy (POL-0040)

Guidance on Drug Establishment Licences (GUI-0002)

Good Manufacturing Practices (GMP) Guidelines (GUI-0001)

Good Manufacturing Practices (GMP) Questions and Answers

Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

Lot Release Program for Schedule D (Biologic) Drugs

Preparation of Quality Information for Drug Submissions in the CTD format: Conventional Biotherapeutic Products

Cleaning Validation Guidelines (GUI-0028)

Guidance for Industry: Product Monograph

Notice Regarding Implementation of Risk Management Planning including the adoption of ICH Guidance Pharmacovigilance Planning - ICH Topic E2E

Post-Notice of Compliance Changes – Framework Document

Post-Notice of Compliance Changes – Quality Document

Post-Notice of Compliance Changes – Safety and Efficacy Document

Guidance Document for Industry: Reporting Adverse Reactions to Marketed Health Products

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

Adverse drug reaction reporting forms

Adverse Drug Reactions (ADRs) for Clinical Trials - Expedited Reporting Summary Form

CIOMS Suspect Adverse Reaction Report Form

Adverse Reaction Reporting Form for Industry

ICH and other Guidelines

Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A)

Guideline for Good Clinical Practice (ICH E6)

Validation of Analytical Procedures: Text and Methodology (ICH Q2(R1))

Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (ICH Q5C)

Pharmacovigilance Planning (ICH E2E)

Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (ICH E2C(R1)).

World Health Organization. Guidelines on nonclinical evaluation of vaccines. WHO Expert Committee on Biological Standardization Fifty-fourth report. Geneva, 2003 (WHO Technical Report Series, No. 927).

European Medicines Agency. Guideline on adjuvants in vaccines for human use. 2005 (EMEA/CHMP/VEG/134716/2004).

European Medicines Agency. Guideline on allergen products: production and quality issues. 2008 (EMEA/CHMP/BWP/304831/2007).

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Appendix B: Abbreviations and acronyms

ADR	Adverse Drug Reaction
BGTD	Biologics and Genetic Therapies Directorate
CTA	Clinical Trial Application
CTD	Common Technical Document
DIN	Drug Identification Number
eCTD	Electronic Common Technical Document
GMP	Good Manufacturing Practices
HPFI	Health Products and Food Inspectorate
ICH	International Conference on Harmonization
IgE	Immunoglobulin E
IHRS	In-house Reference Standard
ITT	Intention-To-Treat
MAH	Market Authorization Holder
MHPD	Marketed Health Products Directorate
NDS	New Drug Submission
PSUR	Periodic Safety Update Report
YBPR	Yearly Biologic Product Report