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Guidance Document

Regulatory Requirements for

Intravenous Immunoglobulin

Products in Canada

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

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Lignes directrices à l'intention des promoteurs -Exigences réglementaires canadiennes applicables aux produits d'immunoglobuline intraveineuse

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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.

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1. Introduction

1.1 Purpose/Overview

The purpose of this document is to provide guidance to sponsors of IVIG products on the regulatory requirements, particularly minimum clinical data requirements for submissions involving approved and non-approved IVIG products.

1.2 Scope and application

This guidance applies to IVIG products which are:

- Non-approved in Canada.
- Approved but seeking to add indication(s) for use in Canada.

1.3 Policy Statement

Intravenous Immunoglobulin (IVIG) is a fractionated blood product manufactured from pooled human plasma. IVIG preparations contain intact IgG molecules (immune antibodies) with a distribution of IgG subclasses similar to that of normal serum. IVIG preparations are used as replacement therapy in patients with inherited or acquired immune globulin deficiencies (Kazatchkine et al., 2000). All IVIG products currently marketed in Canada, have been approved for the treatment of primary immune deficiencies (PID) and idiopathic thrombocytopenic purpura (ITP). Some IVIG products have also been approved for secondary immune deficiency (SID) indications, including allogeneic bone marrow transplantation, B-cell chronic lymphocytic leukemia, and pediatric HIV infection. IVIG preparations are not considered identical, and no consideration can be given to approve a specific IVIG product, based on the proven safety and efficacy in established indications for other marketed IVIG products.

1.4 Background

At the October 2000 Consensus conference on the optimal use of IVIG organized by the Canadian Blood Services, held in Toronto some of the issues discussed included the need to ensure that the utilization of IVIG was appropriate and that utilization of IVIG should be based upon evidence of its efficacy and safety. A recommendation from the consensus conference to Health Canada was for it to assure that licensing and labelling kept pace with published evidence on efficacy and safety.

The main challenge associated with IVIG submissions is the paucity of data from well-designed clinical trials to support claims of safety and efficacy in specific indications. Sponsors must provide adequate data to demonstrate the safety, efficacy, and quality of their IVIG product as required by the Food and Drugs Act and Regulations. However, considering the known similarities and, in many cases, the level of marketing experience for some products previously

approved in other jurisdictions, a relatively limited proof of safety and efficacy based on well designed and properly conducted clinical trials can be accepted by Health Canada. This document highlights the regulatory and minimum information requirements for the approval of IVIG submissions in Canada.

2. Submission Information Requirements

2.1 Non-approved IVIG Products Seeking Approval

2.1.1 General

A New Drug Submission (NDS) must be filed as required by Part C, Division 8 of the Food and Drug Regulations. Data submitted should conform with current guidance.

2.1.2 Chemistry and Manufacturing (Quality) Information

Full and complete chemistry and manufacturing (quality) data must be provided as required by Part C, Division 8 of the Food and Drug Regulations.

2.1.3 Clinical Safety and Efficacy Information

a) For Indications other than PID/SID and ITP

Full and complete data from clinical trials designed to support safety and efficacy of the specific product in respect of the claimed indication must be submitted. The data must satisfy all the requirements of current relevant Canadian regulations and policy documents (See also section 3.2.2).

b) For PID/SID and ITP

Limited clinical data can be accepted (i.e. a minimum of one trial each with the specific product for PID and for ITP) as evidence of safety and efficacy. Secondary Immune Deficiency indications can be accepted based on evidence in PID. Pharmacokinetic data is required, particularly in PID (See also section 3.2.3).

2.2 Approved IVIG Product Seeking to Add a Non-Approved Indication

2.2.1 General

A Supplemental New Drug Submission (S/NDS) must be filed as required by Part C, Division 8 of the Food and Drug Regulations.

2.2.2 Chemistry and Manufacturing (Quality) Information

- a) Where there are no changes to chemistry and manufacturing information, cross-referencing to the original submission can be made.
- b) Where changes have been made to manufacturing, submit a S/NDS or Notifiable Change as per the relevant Canadian regulations and policy documents. For further information refer to:

Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document

https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-final-eng.pdf

2.2.3 Clinical Safety and Efficacy Information

Full and complete data from clinical trials designed to support safety and efficacy of the specific product in respect of the claimed indication must be submitted. The data must satisfy all the requirements of current relevant Canadian regulations and policy documents (Also refer to Section 3 of this document).

3. Safety and Efficacy Information Requirements

3.1 Pre-Clinical Information

3.1.1 Non-approved IVIG Products seeking approval

- a) Pharmacology data: primary therapeutic activity, secondary therapeutic activity, metabolism, other studies considered pertinent to the efficacy or safety of the new drug.
- b) Whereas basic pre-clinical safety and pharmacology data relevant to the claimed indication (e.g. applicable animal models of the disease) must be submitted, exceptions can be made on a case by case basis, when the sponsor can present convincing evidence of lack of relevance.

3.1.2 Non -Approved IVIG Products Seeking Approval for ITP and PID/SID

Pre-clinical information is not needed but if available, general animal and other pre-clinical safety data should be submitted.

3.1.3 Approved IVIG Product Seeking to Add an Indication(s) for Use

Pre-clinical safety data specific to the new claimed indication may be required. Exceptions can be made on a case by case basis, when the sponsor can present convincing evidence of lack of relevance.

3.2 Clinical Information

3.2.1 General

Strict adherence to Good Clinical Practices (GCPs) must be observed during the conduct and documentation of all clinical trials as required by current regulations and policies. For details refer to the International Conference on Harmonization (ICH) guidance:

Guidance Document: Good Clinical Practice: Integrated Addendum to E6(R1)ICH Topic E6(R2)

https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/ich/efficac/e6r2-step4-eng.pdf

In addition, adherence to local and international ethics guidelines is required.

3.2.2 Approved and Non-Approved IVIG Products Seeking Approval for Indications Other than PID/SID and ITP

Full and complete data from clinical trials designed to support safety and efficacy of the specific product in respect of the claimed indication must be submitted. The data must satisfy all the requirements of current relevant Canadian regulations and policy documents.

3.2.3 Non -Approved IVIG Products Seeking Approval for ITP and PID/SID

3.2.3.1

The following minimum criteria are recommendations for the design and execution of trials where the indication is for replacement therapy such as Primary Antibody Deficiency (PAD), Primary Immunodeficiency syndromes (PID), and Secondary Immune deficiencies (SID):

A trial should include a minimum of 20 evaluable patients treated with study drug, i.e. not including patients treated with the control drug, if any, for a minimum six-month period. A sufficient number should be enrolled to account for possible drop-outs and loss to follow-up of some patients during the study period. The patient population within a trial should be homogeneous: all patients should be either previously treated patients or previously untreated patients.

- a) Diagnosis criteria (IgG levels and recurrence of infections) should be clearly defined in the study protocol, according to current up-to-date clinical guidelines, and strictly adhered to, for all patients to be enrolled in the trial.
- b) Comparison can be made to an approved existing IVIG during a six-month period in two randomized groups or, alternatively, intra-patient comparisons can be made:
 - i) for previously treated patients, a six-month treatment period with the study drug can be compared to a similar six-month period when the patient is receiving an approved IVIG product;
 - ii) for previously untreated patients, a six-month treatment period with the study drug can be compared to the previous six-month preceding study drug administration.
- c) Comparisons should include IgG levels, frequency of infections, use of antibiotics, periods of hospitalization due to severe infection and missed days of school or work. All parameters should be well documented during the two six-month periods to be compared;
- d) Clinically significant effects should be demonstrated to show a clear study drug effect on laboratory and clinical parameters to the approved IVIG product;
- e) Safety can be compared in a similar manner and related to known IVIG adverse reactions
- f) Criteria defining infections (mild, moderate or severe) to be recorded and compared should be clearly stated and adhered to during the study. This also applies when patients' diaries are used to record infectious events.
- g) Criteria and rules to be followed during the trial for prophylactic and therapeutic use of antibiotics (oral and IV) should be clearly defined.

3.2.3.2

The following minimum criteria are recommendations for the design and execution of trials of IVIG in Idiopathic Thrombocytopenic Purpura (ITP):

- a) A trial should include a minimum of 20 evaluable patients with a diagnosis of chronic ITP, to be treated with the study drug. Patients should be treated and followed for a minimum six-month period. A sufficient number of patients should be enrolled to account for possible drop-outs and loss to follow-up of some patients during the study period.
- b) The trial should preferably be designed with a control group, comparing study drug to treatment with an approved IVIG.
- c) Criteria for the diagnosis of chronic ITP, according to current up-to-date clinical guidelines should be clearly defined in the study protocol and adhered to, for all patients to be enrolled in the trial. Patients should have a baseline platelet count equal or below $20 \times 10^9/L$ at the time of study entry.

- d) Allowed and restricted concomitant treatments (e.g. corticosteroids) must be clearly stated.
- e) Efficacy criteria should be clearly defined and evaluated, including expected minimum increase in platelet count, time to reach an acceptable platelet count, duration of effect and objective measurement of effect on bleeding whether spontaneous or during surgical procedures.

3.2.3.3 Additional Requirements

- a) Adverse events, vital signs and routine safety parameters should be recorded and analysed with comparison between different groups included in the trial. Patients should be monitored for treatment effect on renal function and for abnormal thrombo-embolic events, as well as for any unexpected viral or other transmissible infection.
- b) Complete up-to-date information from post-marketing experience should be provided.

Contact Information

For additional information and questions concerning regulatory requirements and/or the possible need for a pre-submission meeting should be directed to:

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
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Appendices

Appendix A – Glossary

a) Acronyms

GCP – Good Clinical Practices

HIV – Human Immunodeficiency Virus

ICH – International Conference on Harmonization

IgG – Immunoglobulin G

ITP – Idiopathic thrombocytopenic purpura

IVIG – Intravenous Immunoglobulin

NDS – New Drug Submission

NOC – Notice of Compliance

PAD - Primary Antibody Deficiency

PID – Primary Immune Deficiency

SID – Secondary Immune Deficiency

S/NDS – Supplemental New Drug Submission

b) Terms

Approved IVIG - an IVIG product which has been approved by Health Canada (received a Notice of Compliance) and is currently marketed in Canada.

Non-approved IVIG - an IVIG product which has not been approved by Health Canada, this product may be available in other markets.

Appendix B – References

Kazatchkine MD, Bellon B, Kaveri SV. Mechanisms of action of intravenous immunoglobulin. *Multiple Sclerosis* 2000 (6)S2, S24-S26.

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Pi, David; Petraszko, Tanya. IVIG Utilization Management Handbook, First Edition. Chapter 1. Pp.1-3. British Columbia Provincial Blood Coordinating Office, British Columbia, Canada, 2002.