Health Canada Santé Canada

DRAFT –

GUIDANCE FOR INDUSTRY

SUBMISSION AND INFORMATION REQUIREMENTS FOR EXTRAORDINARY USE NEW DRUGS (EUNDS)

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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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1.0 INTRODUCTION

Health Canada, the federal regulatory authority that evaluates the quality, safety, and efficacy of human drugs available in Canada, recognizes that there are extraordinary circumstances in which manufacturers may be seeking authorization for Extraordinary Use New Drugs (EUNDs). EUND sponsors cannot reasonably provide substantial evidence demonstrating the safety and efficacy of a therapeutic product as there are logistical or ethical challenges in conducting the appropriate human clinical trials.

> ***C.08.002.01(1)*** *A manufacturer of a new drug may file an extraordinary use new drug submission for the new drug if*
>
> *(a) the new drug is intended for*
>
> *(i) emergency use in situations where persons have been exposed to a chemical, biological, radiological or nuclear substance and action is required to treat, mitigate or prevent a life-threatening or other serious disease, disorder or abnormal physical state, or its symptoms, that results, or is likely to result, from that exposure, or*
>
> *(ii) preventative use in persons who are at risk of exposure to a chemical, biological, radiological or nuclear substance that is potentially lethal or permanently disabling; and*
>
> *(b) the requirements set out in paragraphs C.08.002(2)(g) and (h) cannot be met because*
>
> *(i) exposing human volunteers to the substance referred to in paragraph (a) would be potentially lethal or permanently disabling, and*
>
> *(ii) the circumstances in which exposure to the substance occurs are sporadic and infrequent.*

1.1 OBJECTIVE

The objective of this document is to provide guidance to sponsors to enable them to meet the pre-market and post-market information and regulatory requirements under the *Food and Drug Act* and its *Regulations* for the authorization of EUNDs in Canada.

1.2 SCOPE AND APPLICATION

This guidance document is for sponsors seeking to file an extraordinary use new drug submission (EUNDS) or an abbreviated extraordinary use new drug submission (AEUNDS) for drugs considered to be EUNDs.

1.3 POLICY STATEMENTS

1.3.1 The EUND regulatory pathway is only available for those drugs that meet the inclusion criteria in *C.08.002.01(1)*. This regulatory pathway may not be used for a drug which can fulfill the requirements of a New Drug Submission (NDS), in particular *C.08.002 (2)(g)* and *(h*).

1.3.2 Sponsors of EUNDSs are encouraged to consult with Health Canada as early as possible in the drug development process and on an ongoing basis.

1.3.3 Sponsors should provide in an EUNDS, sufficient information and material on the quality, non-clinical and clinical, and post-marketing aspects of an EUND.

1.3.4 While the EUNDS process allows for special considerations such as a reduced clinical information package, it does not allow for a reduction in the requirements for product quality information (i.e. chemistry and manufacturing). Therefore, sponsors are expected to provide a full quality information package as part of the their EUNDS.

1.3.5 For the evaluation of an EUNDS, the non-clinical information package is critical as the regulatory requirements for the clinical information package are reduced. Therefore, sponsors are expected to provide a robust non-clinical information package as part of their EUNDS.

1.3.6 Sponsors are expected to provide an enhanced post-market information package as part of their EUNDS.

1.3.7 Regulatory decisions for the authorization of an EUND/AEUND, will be based on the entire supporting evidence provided by a sponsor in a submission.

1.3.8 Once an EUND has received a Notice of Compliance (NOC) for an EUND/AEUND, the sale of the drug product is restricted to governments (*C.08.002.02*).

1.3.9 A drug product that has received a Notice of Compliance as an EUND can only be a Canadian Reference Product (CRP) in an AEUNDS (*C.08.002.1(4)*).

1.3.10 EUNDSs are not eligible for either priority review status or a notice of compliance with conditions (NOC/c) as “promising” or “substantial” evidence of

(pre-market) clinical effectiveness is required in a submission, and such information is limited for EUNDs.

1.4 BACKGROUND

Amendments were made to the *Food and Drug Regulations (FDR)* to include a specific regulatory pathway for Extraordinary Use New Drugs (EUNDs). Typically, clinical trials in human subjects are conducted and the results are provided as part of the clinical information package of an NDS to Health Canada, the federal authority that reviews the safety and efficacy of human drugs. However, it is recognized that under certain extraordinary circumstances, because of logistical or ethical reasons, it is not possible for sponsors to conduct clinical trials in human subjects for its intended use(s) e.g. some drugs that are used as military medical countermeasures. For products with limited clinical information, the standard regulatory pathway for authorization, i.e. New Drug Submission (NDS) or an Abbreviated New Drug Submission (ANDS) cannot be used. The EUND regulatory pathway was developed to address the review of EUNDs.

The amendments to the FDR provide a regulatory pathway for the authorization of new drugs under extraordinary circumstances by recognising the challenges sponsors face when conducting clinical studies for these drugs. These amendments allow sponsors to use results of animal studies in conjunction with results from limited data from human safety and efficacy studies to support their drug submission

The goal of the regulations is to provide Canadians with access to extraordinary use new drugs which have undergone a pre-market review for quality, safety, and efficacy despite limited clinical data packages, and which will be monitored more extensively for clinical safety and effectiveness in the post-market phase.

2.0 GUIDANCE FOR IMPLEMENTATION

2.1 APPLICABLE REGULATIONS

The provisions related to EUNDs are stated in Part C, *Divisions 1*, *1A* (Establishment Licences), *2* (Good Manufacturing Practices), *4* (Biologics), and the applicable sections of *Division 8* (New Drugs) of the *Food and Drug Regulations*.

A sponsor can file an AEUND for a new drug *(C.08.002.1)*, if, in comparison with a Canadian Reference Product (CRP), it meets the criteria below:

a. the new drug is the pharmaceutical equivalent of the CRP;

b. the new drug is bioequivalent to the CRP, based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics;

c. the route of administration of the new drug is the same as that of the CRP; and

d. the condition(s) of use for the new drug will fall within the conditions of use for the CRP (*C.08.002.01(1)*).

For additional information regarding the abbreviated submission process, please consult the Health Canada guidance document titled *Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format.* See also *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs).*

2.1.1 PATENTS, INTELLECTUAL PROPERTY, AND DATA PROTECTION

EUNDs are subject to all applicable patent, intellectual property, and data protection regulations.

Generic drugs may enter the market subsequent to an innovator/reference drug product authorized for sale in Canada, and for which patents have expired or have been successfully addressed under the *Patented Medicines (Notice of Compliance) Regulations*. In instances where the reference drug product has data protection, the generic drug cannot enter the market until after the expiry of the data protection term. Generic drug products are subject to existing laws and regulations outlined in the *Patented Medicines (Notice of Compliance) Regulations* and *C.08.004.1* of the *Food and Drug Regulations*, and related guidance documents entitled, "*Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations*" and "*Guidance Document: Patented Medicines (Notice of Compliance) Regulations*". For an AEUNDS, the generic drug sponsor must clearly identify the product to which it is considered to be making a direct or indirect comparison according to the *Patented Medicines (Notice of Compliance) Regulations* and *C.08.004.1* of the *Food and Drug Regulations*.

2.1. 2 PRE-SUBMISSION MEETINGS

Sponsors wishing to submit an EUNDS to Health Canada are strongly urged to request a pre-submission meeting to discuss all aspects of their submission.

In preparation for this meeting, sponsors are encouraged to submit a rationale in writing stating why their prospective product should be reviewed as an EUND (see section 2.3). Sponsors are encouraged to hold early and ongoing consultation with Health Canada to help ensure that regulatory requirements are met.

Sponsors should also refer to the Health Canada document titled *Management of Drug Submission Guidance* for instructions on how to request pre-submission meetings. Sponsors should forward their pre-submission meeting requests to the appropriate Directorate (Office) located within Health Canada, please refer to Appendix A for relevant contact information.

2.1. 3 SUBMISSION

All submission information should be provided in accordance with the Health Canada guidance document, *Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format*.

The preparation and filing of submissions and/or additional information in an electronic CTD (eCTD) format is encouraged but remains optional. Sponsors who choose to file a submission in the eCTD format should consult Health Canada's *Guidance for Industry: Preparation of Drug Submissions in Electronic Common Technical Document (eCTD) Format.*

Sponsors should refer to the *Management of Drug Submissions Guidance* document for general procedures on how to file submissions.

2.1.4 USE OF FOREIGN REVIEWS

EUNDSs and AEUNDSs shall contain any available assessment reports regarding the new drug prepared by regulatory authorities, in countries other than Canada (*C.08.002.01(2)(x)*).

For more information on the use of foreign reviews, please refer to the *Draft Guidance Document: The Use of Foreign Reviews by Health Canada.*

2.1.5 REVIEW TIME

There is no change in the projected review times for the EUNDS and the abbreviated version. Hence, the projected review times are 300 days for a EUNDS and 180 days for an AEUNDS.

Information regarding general submission requirements and target performance standards may be found in the Health Canada guidance document *Management of Drug Submission Guidance.*

2.1.6 FEES

There is no change in the fees for the EUNDS and the abbreviated version.

The fees for EUNDS and abbreviated version are consistent with those for NDS and ANDS.

For additional information related to Health Canada's cost recovery policy, refer to the *Guidance Document, Fees for the Review of Drug Submissions and Applications*.

A request and rationale for fee remission can be submitted at time of filing an EUNDS. For additional information regarding drug evaluation fees, contact the following:

Office of Submissions and Intellectual Property (OSIP)
Therapeutic Products Directorate
Health Canada
Phone: (613) 941-7281
Fax: (613) 946-5610
E-mail: cost.recovery@hc-sc.gc.ca

2.2 Clinical Trial Applications

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

Sponsors should include all information identified in *C.05.005* of the *Food and Drug Regulations* in their application for authorization.

2.3 Submission Information and Requirements

> ***C.08.002.01(2)*** *[An EUND] submission shall contain an attestation, signed and dated by the senior executive officer in Canada of the manufacturer filing the submission and by the manufacturer's senior medical or scientific officer, certifying that the requirements specified in C.08.002.01 (1)(a) and (b) are met, and that sufficient supporting information has been provided to enable the Minister to determine that those conditions are met.*

Sponsors must submit a written rationale, preferably not more than 20 pages, on how their product fulfills the requirements outlined in *C.08.002.01(1),* that is, how the product satisfies the intended use conditions in *C.08.002.01(1)(a)(i)* and *(ii)* and how their product cannot satisfy the requirements of *C.08.002 (2) (g)* and *(h))* as stated in *C.08.002.01(1)(b)(i) and (ii).* Generally, such a rationale, in support for a product to undergo the EUND pathway, is provided at pre-submission meetings for Health Canada's consideration.

For EUNDSs, sponsors should provide sufficient information and material on the quality, non-clinical and clinical, and post-marketing aspects of an EUND.

2.3.1 Quality Information and Requirements

For an EUNDS or AEUNDS, sponsors must submit a full chemistry and manufacturing (quality) information package as required for an NDS and ANDS. Sponsors should refer to Appendix B for a comprehensive (but not exhaustive) list of guidance documents that provide further guidance on meeting submission and information requirements.

2.3.1.1 General Considerations: Long-Term Stability

When an EUND may be stockpiled for emergency preparedness or used in extreme environmental conditions, additional considerations should be given to the formulation and stability of the EUND to ensure that it is appropriate for the intended use. For example, formulations suitable for long-term stability with accelerated and or forced degradation stability studies may be required.

2.3.2 Non-Clinical Information and Requirements

All EUNDSs should contain the standard pre-clinical information described in the relevant guidance documents for the product class. Additional non-clinical information may be required to demonstrate the potential for clinical effectiveness under the proposed conditions of use, and to support the safety of the EUND. All studies should be conducted in accordance with *Good Laboratory Practices (GLPs)*, sponsors should refer to *Good Laboratory Practices (GLP) Guidelines*. Please consult Health Canada's *Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice.*

> ***C.08.002.01 (2)(b)(ii)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following**:** information respecting the pathophysiological mechanism for the toxicity of the chemical, biological, radiological or nuclear substance and describing the new drug's ability to treat, mitigate or prevent that mechanism.*

In vitro studies should demonstrate the mechanism of action of the chemical, biological, radiological or nuclear (CBRN) substance and the means whereby the EUND mitigates its effect. For example, where the activity of the CBRN substance involves binding to receptors, the *in vitro* studies should demonstrate the ability of the EUND to interfere with binding of the CBRN substance. If the EUND acts by binding to the CBRN substance, the ability of the EUND to bind to the CBRN substance should be demonstrated. The concentration/response relationship of the EUND should be assessed to determine the most effective concentrations.

> ***C.08.002.01(2)(b)(iii)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following: detailed reports of in vitro studies respecting the toxicity and activity of the new drug in relation to the recommended purpose.*

In vitro studies should also investigate the potential for "off-target" effects of the EUND. If the activity of the EUND involves binding to receptors or binding to the CBRN substance, the potential for binding to other receptors or to other naturally occurring chemicals should be assessed.

> ***C.08.002.01(2)(b)(iv)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following: detailed reports of studies, in an animal species that is expected to react with a response that is predictive for humans, establishing the safety of the new drug, and providing substantial evidence of its effect, when used for the purpose and under the conditions of use recommended.*

> ***C.08.002.01(2)(b)(v)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following: information confirming that the end point of animal studies is clearly related to the desired benefit in humans.*

In vitro studies should support the relevance of the proposed animal model to humans. Studies demonstrating the mechanism of action should be conducted using both human and animal *ex-vivo* systems to determine the relevance of the animal model. For example, where the activity of the EUND depends on binding to active sites, the *in vitro* studies should demonstrate the concentration/binding relationship and the potential for cross-reactivity with other binding sites in both human and animal systems. For substances that are metabolized, species differences in metabolic pathways should also be assessed. Interspecies differences in the metabolism of the CBRN substance may determine the relevance of the animal model, for example, if the substance is metabolized by a CYP P450 isozyme which isn't found in humans.

In vivo studies should demonstrate the potential efficacy of the EUND. Studies should demonstrate that the animal model reacts to the CBRN substance in a manner similar to humans, and that the EUND is effective in preventing the unfavourable outcome when the animal model is exposed to the CBRN substance. For CBRN substances where the exposure may vary because of environmental conditions or the nature of the exposure, the studies should be conducted to demonstrate the potential efficacy under various

conditions including those representing the maximum expected exposure to the CBRN substance.

> ***C.08.002.01(2)(b)(vi)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following: information demonstrating that there is a sufficient understanding of the pharmacokinetics and pharmacodynamics of the new drug in animals and in humans to enable inferences to be drawn in respect of humans so as to allow for the selection of an effective dose in humans.*

Pharmacokinetic studies should be used to assess the absorption, distribution, metabolism and excretion (ADME) of the EUND. Where the desired clinical effect is dependent on blood levels or saturation of receptors, pharmacokinetic/pharmacodynamic studies should clearly define the dosage needed to obtain the desired blood levels. Where the activity of the EUND depends on pharmacodynamic action, rather than pharmacokinetics, as in the immune response to a vaccine, the relationship of the pharmacodynamic effect to dose and the duration of the response should be defined.

It is recognized that for some classes of products, such as monoclonal antibodies or oligonucleotides, animals may develop immune reactions to humanized products. Therefore, higher order species, such as primates, may be preferred for testing of these products, but the dose-response relationship should be clearly defined as only a few amino acid substitutions can markedly change the binding efficiency. In other situations, it may be necessary to develop and use animals that respond in a manner analogous to humans to evaluate the effectiveness of the EUND. The animal model developed may also be used for toxicity testing. In such cases, safety information from a second species using the EUND product should also be provided~~,~~ in support of the safety assessment.

2.3.3 CLINICAL INFORMATION AND REQUIREMENTS

Given the nature of the EUNDS, it is not expected that the clinical information package will be similar to that of a regular NDS. But in some instances, it may be possible for sponsors to submit some clinical data to support their application.

> ***C.08.002.01(2)(b)(viii)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following: information, if any, respecting the effectiveness of the new drug in humans for the purpose or under the conditions of use recommended.*

While the EUND cannot be tested under the conditions of use to confirm the effectiveness, the submission should contain sufficient information to demonstrate a high probability of efficacy, and that the EUND does not cause undue harm to recipients. This

is particularly important when the EUND is to be used prophylactically and exposure to a CBRN substance may not occur.

For all appropriate inferences on dosing from *in vitro* tests and animal models *C.08.002.01(2)(b)(vi)*, standard clinical phase I dose escalation studies should be conducted to determine the pharmacokinetics/pharmacodynamics, and to provide preliminary information on safety. Phase II studies should evaluate the consistency of the pharmacokinetic/pharmacodynamic profile in a larger number of subjects, to further refine the appropriate dosing regimen and evaluate safety. Other information (e.g. toxicological studies) pertinent to determining the safe dosage in humans will also be considered.

> ***C.08.002.01(2)(b)(vii)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following:* ***information respecting the safety of the new drug in humans, including detailed reports of clinical trials, if any, establishing the safety of the new drug.***

Although the EUND cannot be tested under the conditions of use to confirm the effectiveness, there may exist a body of knowledge, such as case reports or case series, on the use of the EUND in humans under the conditions of use resulting from accidental exposure. Where such information is available, it should be provided to support the evaluation of the effectiveness and safety of the EUND.

For subjects in whom the EUND is to be used prophylactically, the number of subjects should be sufficiently large to demonstrate that the common adverse events of minor severity are rare, particularly when exposures to CBRN substances are rare.

2.4 POST-MARKET REQUIREMENTS

> ***C.08.002.01 (2)(b)(ix)*** *Subject to subsections (3) and (5), an extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following:* ***a plan for monitoring and establishing the safety and effectiveness of the new drug under the conditions of use recommended that includes procedures for gathering and analyzing data.***

The market authorization of EUNDs will be based on limited clinical information. Therefore, sponsors must provide information on the process and procedures for post-market surveillance to establish the efficacy and safety in human subjects under the intended conditions of use.

2.4.1 STUDY PLAN

Sponsors must include "a plan for monitoring and establishing the safety and effectiveness of the new drug under the conditions of use recommended that includes procedures for gathering and analysing data" (*C.08.002.01(2)(b)(ix)*) for both an EUNDS and AEUNDS. This plan is essentially a clinical study or studies, intended to verify the effectiveness of the EUND under the conditions of use (its indications). The plan should be tailored to suit the conditions under which the EUND will be used (its indications). This plan should describe in detail the study design (e.g. registry, cohort, case-control, etc.) and the procedures to gather and analyze information on the effectiveness and safety under the proposed conditions of use. The plan(s) should include a rationale for the study design, a description of population to be studied, including any vulnerable or special populations (e.g. paediatric, elderly etc.), procedures for collecting information, and the proposed statistical analysis. Criteria for determining lack of efficacy should be clearly stated.

This study plan should also include the procedures for collecting and monitoring adverse events, the methods for determining the causal relationship between the EUND and the adverse event, and for assessing the effect of adverse reactions on the benefit-risk profile of the EUND. Where the EUND is being used prophylactically, a separate study may be required for monitoring the safety in subjects who are not exposed to CBRN substances.

The study or studies should be conducted in accordance with Good Clinical Practice to enhance subject safety and ensure data quality.

> ***C.08.006(2)(g)*** *"The Minister may, by notice to a manufacturer, suspend, for a definite or indefinite period, a notice of compliance issued to that manufacturer in respect of a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission, an abbreviated extraordinary use new drug submission or a supplement to any of those submissions if the Minister considers that, in the case of a new drug for extraordinary use, the manufacturer has not adhered to the plan referred to in subparagraph C.08.002.01(2)(b)(ix).*

Failure to adhere to the study plan may result in suspension of the notice of compliance (*C.08.006(2)(g)*) i.e. revocation of market authorization for a definite or indefinite period.

2.4.2 RISK MANAGEMENT PLAN

According to Health Canada's Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E [1], sponsors should also submit a

[1] Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic

Risk Management Plan (RMP). The RMP should describe the known and potential risks of the EUND under the proposed conditions of use, and contain a pharmacovigilance plan (PvP) for monitoring the safety, including any studies submitted under sections *C.08.002.01(2)(b)(ix)*, and proposed risk mitigation strategies, including labelling, to enhance the safe and effective use of the EUND. Sponsors may choose to follow the *European Medicines Agency (EMA) Guideline on Risk Management Systems for Medicinal Products for Human Use*[2] and use the *EMEA Template for European Union (EU) - Risk Management Plans (EU-RMP)* [3] during the development of an RMP for an EUND. In Appendix C, Table 1 depicts an acceptable approach for sponsors to use the EU-RMP template while noting the necessary modifications required for sponsors to meet Canadian requirements. Those sponsors who have developed their RMP(s) in other recognized formats that incorporate all the elements of the EU guidance may submit their RMP(s) as part of their submission.

2.4.3 Serious Adverse Drug Reaction Reporting

The manufacturer must submit reports of any serious adverse drug reaction that occurred in Canada within 15 days of receiving the information (*C.01.017*). When an authorized EUND is sold to a Canadian buyer (*C.08.002.02*) who provided the drug to a Canadian serving outside of Canada, the reaction should be treated as if it occurred in Canada.

2.4.4 Annual Safety Report

> ***C.08.008.1*** *Where a manufacturer has received a notice of compliance issued in respect of an extraordinary use new drug submission, an abbreviated extraordinary use new drug submission or a supplement to either of those submissions, the manufacturer*
>
> *(a) shall adhere to the plan referred to in subparagraph C.08.002.01(2)(b)(ix); and*
>
> *(b) shall, before the first day of October in each year and whenever requested to do so by the Minister for the purposes of assessing the safety and effectiveness of the drug to which the notice of compliance relates, provide a report on the use of the drug, including a critical analysis of any available updated information respecting the drug's safety and effectiveness.*

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_rmp_pgr_e2e-eng.php

[2] *Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic* *http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_rmp_pgr_e2e-eng.php*

[3] *IBID*

On the first of October each year, or as requested by the Minister, the manufacturer shall submit a report on the use of the EUND and a critical analysis of updated information on the safety and effectiveness of the EUND. The report should contain sufficient detail to allow determination of the adherence to the plan referred to in subsection *C.08.002.01(2)(b)(ix)*.

The report should include information on the amount of the EUND sold, and the patient exposure for the indication (i.e. under the conditions of use specified for the EUND product), for the preceding year and cumulatively. The report should contain any new non-clinical and clinical information on the safety and effectiveness of the drug, and an analysis of the impact of this information on the known effectiveness profile of the drug under the proposed conditions of use. Adverse events observed in the time of clinical use should also be listed, and sufficient detail provided for serious adverse events to allow evaluation of the causal relationship with the EUND. The observed safety information should be assessed in relation to the previously known safety profile of the EUND, and the impact of the new safety information on the benefit-risk profile of the EUND must be analysed.

When the drug has received both an EUND NOC and a regular NOC, the manufacturer must prepare and submit a report for the EUND indication (*C.08.008.1 (2)*). The report for the EUND indication should be inclusive of safety information for all the indications of a product. For the indication(s) with a regular NOC, the manufacturer must prepare an annual report as per *C.01.018*. Information related to the safety for the EUND indication should be included in that report. When the drug has received an EUND NOC only, the manufacturer must prepare and submit a report for the EUND indication (*C.08.008.1 (2)*) and the manufacturer does not need to prepare the annual report (*C.01.018*).

2.5 LABELLING

C.04.019 (1)(vi) in the case of a new drug for extraordinary use in respect of which a notice of compliance has been issued under section C.08.004.01, the following statement, displayed in capital letters and in a legible manner:

"HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS EXTRAORDINARY USE NEW DRUG FOR [naming purpose] BASED ON LIMITED CLINICAL TESTING IN HUMANS.

SANTÉ CANADA A AUTORISÉ LA VENTE DE CETTE DROGUE NOUVELLE POUR USAGE EXCEPTIONNEL AUX FINS DE [indication de la fin] EN SE FONDANT SUR DES ESSAIS CLINIQUES RESTREINTS CHEZ L'ÊTRE HUMAIN."

For the EUND indication, Health Canada will expect a unique brand name; distinct labels (*C.01.004(1)(c)(vi)*) i.e. both inner and outer labels will contain prescribed wording

indicating that the NOC has been issued based on limited clinical testing in humans; and a separate product monograph.

2.5.1 PRODUCT MONOGRAPH

Sponsors should consult with Health Canada's *Guidance for Industry: Product Monograph* for guidance on product monograph requirements. For an AEUNDS, sponsors should consult with Health Canada's *Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*.

2.6 CHANGES FOLLOWING AUTHORIZATION / POST NOTICE OF COMPLIANCE (POST-NOC) CHANGES

A sponsor may submit additional post-market information on an EUND or AEUND for changes that are significantly different from those contained in the original submission. There shall be sufficient information to enable the Minister to make the decision on the safety and effectiveness of the drug. Sponsors should also refer to Health Canada's available guidances on post-market changes (see Appendix B).

2.7 RESTRICTED SALE (DISTRIBUTION)

> ***C.08.002.02*** *Despite sections C.08.002 and C.08.003, no manufacturer or importer shall sell a new drug for extraordinary use in respect of which a notice of compliance has been issued under section C.08.004.01 except to*
>
> 1. *(a) the Government of Canada or the government of a province for the use of a department or agency of that government, on receipt of a written order signed by the minister responsible for the department or by the person in charge of the agency, or by their duly authorized representative; or*
> 2. *(b) a municipal government, or an institution of such a government, on receipt of a written order signed by a senior official of the government or institution or by his or her duly authorized representative.*

The sale of an EUND with an NOC, shall be restricted to authorized entities such as the federal, provincial, territorial, or municipal government(s) or their representatives, or other authorized institutions or agencies (*C.08.002.02*).

APPENDIX A – CONTACT INFORMATION

For all biologics and radiopharmaceuticals - related submission or clinical trial application inquiries:

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

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

For all pharmaceutical products – related submission or clinical trial related inquiries:

Office of Submissions and Intellectual Property (OSIP)
Therapeutic Products Directorate
Health Products and Food Branch
Address Locator: 3106B
Ottawa, Ontario K1A 0K9

E-mail: SIPDMail@hc-sc.gc.ca
Telephone: 613-941-7283
Facsimile: 613-941-0827

Office of Clinical Trials (OCT)
Therapeutic Products Directorate
Health Products and Food Branch
Address Locator: 3106B
Ottawa, Ontario K1A 0K9

E-mail: OCT_BEC_Enquiries@hc-sc.gc.ca
Telephone: 613-954-6493
Facsimile: 613-946-7996

APPENDIX B – A LIST OF RELEVANT GUIDANCE DOCUMENTS

Manufacturers should refer to the most up-to-date versions of the following key Health Canada Guidance documents. This list is provided as a starting point to help manufacturers, and is not exhaustive.

HEALTH CANADA GUIDANCE DOCUMENTS

GENERAL GUIDANCE

- Guidance for Industry: Management of Drug Submissions
- Preparation of Drug Submissions in the Common Technical Document Format
- Preparation of Drug Submissions in the Electronic Common Technical (eCTD) Document Format
- Guidance document: Non-Clinical Laboratory study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice
- Notice: Categorization of Therapeutic Products at the Device/Drug Interface [2012-05-31]
- Drug/Medical Device Combination Products Policy [2005-11-30]
- Guidance for sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) [2010-03]
- Draft Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations
- Guidance Document: Patented Medicines (Notice of Compliance) Regulations

CTA GUIDANCE

- Guidance for Clinical Trial Sponsors: Clinical Trial Applications

DRUG SUBMISSION GUIDANCE

- Guidance for Industry; Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names
- Guidance for Industry: Product Monograph
- Guidance for Industry: Product Monograph, Product Monograph Template - Schedule D.
- Guidance Document - Fees for the Review of Drug Submissions and Applications
- Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E.
- Guidance document: Pre-market Evaluation of Hepatotoxicity in Health Products [2012-04-18]

- Draft Policy: Bioequivalence Requirements: Drugs Exhibiting Non-linear Pharmacokinetics [2003-06-11]
- Guide for the Analysis and Review of QT/QTc Interval Data
- Draft Guidance document for Consultation: Labelling of Pharmaceutical Drugs for Human Use
- Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format.
- Guidance for Industry: Preparation of Drug Submissions in Electronic Common Technical Document (eCTD) Format.
- Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format.

DRUG ESTABLISHMENT LICENSING

- Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)

POST-MARKET GUIDANCE

- Post-Notice of Compliance (NOC) Changes: Framework Document
- Post-Notice of Compliance (NOC) Changes: Quality Document
- Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document.
- Guidance for Industry; Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names
- Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products.
- Guidance Document - Fees for the Review of Drug Submissions and Applications
- Guidance for Industry: Product Monograph
- Guidance for Industry: Product Monograph, Product Monograph Template - Schedule D.

GMP GUIDANCE

- Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001)

GLP GUIDANCE

- Good Laboratory Practices (GLP) Guidelines - 1998 Edition, Version 2 (DIR-9801)

QUALITY-SPECIFIC GUIDANCE

- Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Blood Products
- Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotechnological/Biological (Biotech) Products
- Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products
- Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD Format: Vaccines
- International Conference on Harmonisation (ICH); Q7 Guideline – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- Health Canada; Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)**.**

INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH) GUIDANCE DOCUMENTS

REFERENCES FOR QUALITY REQUIREMENTS

- ICH; Q5D Guideline - Derivation and Characterization of Cell Substrates Used for the Production of Biotechnological/Biological Products.
- Health Canada; Good Manufacturing Practices (GMP) Guidelines (GUI-0001).
- ICH; Q5B Guideline - Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products.
- ICH; Q3C(R5) Guideline - Impurities: Guideline for Residual Solvents.
- Health Canada; Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs.
- ICH; Q6B Guideline - Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.
- ICH; Q5A(R1) Guideline - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.
- European Medicines Agency (EMA); Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 3 – July 2011).

REFERENCES FOR NON-CLINICAL AND CLINICAL REQUIREMENTS

- ICH; S5 (R2) Guideline - Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility.
- ICH; S6 Guideline - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

- ICH; S8 Guideline - Immunotoxicity Studies for Human Pharmaceuticals.
- ICH; M3 Guideline - Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.
- World Health Organization (WHO); WHO guidelines on nonclinical evaluation of vaccines.
- ICH Guidelines in the Safety ("S") series on the Health Canada website
- ICH Guidelines in the Efficacy ("E") series on the Health Canada website

APPENDIX C – A CANADIAN APPROACH TO RISK MANAGEMENT PLANS (RMPS)

Table 1. The European Medicines Agency *Guideline on Risk Management Systems for Medicinal Products for Human Use – EMA Template for European Union Risk Management Plans (EU-RMPs)* [4] - An acceptable approach to meeting Canadian requirements for RMPs

EMEA Guideline Section	Canadian Approach
Entire Guideline	Replace Summary of Product Characteristics (SmPC) with the Canadian Product Monograph (CPM).
Section 3: Legal Basis	Specific to the European Context: Not applicable in Canada
Section 4.1: Description of the risk management system	Refers to legislation requiring a description of the Risk Management System: Not applicable in Canada.
Sections 4.3.1 to 4.4	Requirements for EU-RMP in Europe; Processes regarding Central authorization: Not applicable in Canada.
Section 4.5.2.2 Populations not studied in the pre-authorization phase: Post-marketing experience	A discussion of post-marketing experience in the Canadian context should be presented.
Section 4.5.2.5: Epidemiology	The epidemiology of the medical condition in the Canadian population should be discussed.
Section 4.5.2.7 Additional EU requirements	All of these components should be included in the Canadian submission.
Section 4.6.1. Routine Pharmacovigilance	In the Canadian context this would involve: monitoring of Canadian adverse events from the Market Authorization Holder's database; reconciliation of such reaction with Health Canada's Canada Vigilance Database and routine pharmacovigilance of foreign reports.
Section 4.10 Marketing authorization	Refers to recommendations provided by the Committee for Medicinal Products for Human Use (CHMP): Not applicable in Canada.
Section 4.13 Submission of updated EU-RMP documents	Timelines for submission of updated RMP documents in Canada will be decided on a case-by-case basis until Health Canada and stakeholders gain experience in this area.

[4] Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_rmp_pgr_e2e-eng.php

APPENDIX D - ACRONYMS

ADME	Absorption, Distribution, Metabolism, and Excretion
ANDS	Abbreviated New Drug Submission
AEUND	Abbreviated Extraordinary Use New Drug
AEUNDS	Abbreviated Extraordinary Use New Drug Submission
BGTD	Biologics and Genetic Therapies Directorate
CBRN	Chemical, Biological, Radiological and Nuclear [substances]
CRP	Canadian Reference Product
CTD	Common Technical Document
CTP	Clinical Trial Protocol
DIN	Drug Identification Number
eCTD	Electronic Common Technical Document
EUND	Extraordinary Use New Drug
EUNDS	Extraordinary Use New Drug Submission
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
LA/SA	Look-Alike Sound-Alike
NDS	New Drug Submission
NOC	Notice of Compliance
PvP	Pharmacovigilence Plan
RMP	Risk Management Plan