Health Canada Santé Canada

Draft Guidance Document

Public Release of Clinical Information

This guidance document is being distributed for comment purposes only.

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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.

Également disponible en français sous le titre :
Èbauche de la ligne directrice : Diffusion publique des renseignements cliniques

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.

Health Canada invites comments on this draft Guidance document until June 25, 2018. When preparing your comments, please indicate the relevant section(s) and line numbers (in PDF version) to which your comments relate. Comments can be sent by email to: hc.rmod.stakeholders-intervenants.dgro.sc@canada.ca.

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1. Introduction

This draft guidance is being published in advance of the coming into force of the proposed regulations that will govern the Public Release of Clinical Information initiative. Consequently, this draft version is based on the proposed regulations published in Canada Gazette I on December 9, 2017[1]. Revisions, if required, will be published after Canada Gazette II.

Providing public access to clinical information on the safety and efficacy of drugs and on the safety and effectiveness of medical devices can enable independent re-analyses of data, foster new research questions, and benefit Canadians by helping them make informed decisions about their health.

This document is designed to help the public, industry, healthcare professionals and other stakeholders better understand the implementation of Health Canada's Public Release of Clinical Information initiative, including: the procedures to prepare information for release; the categories of information that continue to be subject to the definition of confidential business information (CBI) and that may be eligible for redaction; and how Health Canada will protect personal information.

This document does not apply to the CBI disclosure authority under section 21.1(3)(c) of the Food and Drugs Act, which permits Health Canada to disclose CBI to certain persons for the purpose of protection or promotion of human health or the safety of the public. Information on this authority can be found in Guidance Document – Disclosure of Confidential Business Information under Paragraph 21.1(3)(c) of the Food and Drugs Act (https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/request-disclosure-confidential-business-information/disclosure-confidential-business-information/guidance.html#disclosure).

1.1 About this guidance document

Guidance documents are meant to assist individuals and organizations to comply with Health Canada's policies and its governing statutes and regulations. They also serve to assist Health Canada staff to implement its mandates in a fair, consistent and effective manner.

Guidance documents are administrative instruments. They do not have force of law and as such they allow for flexibility. Alternate approaches to the implementation of the principles, considerations and requirements described in this document may be acceptable provided they comply with relevant laws. Discussion with the relevant program area in advance is encouraged to determine whether an alternative approach meets applicable statutory or regulatory requirements.

1.2 Terminology and definitions

FDA:
Food and Drugs Act

FDR:
Food and Drug Regulations

MDR:
Medical Device Regulations

CBI:
Confidential Business Information, as per the meaning in section 2 of the Food and Drugs Act

[1] Regulatory Proposal for drugs: http://gazette.gc.ca/rp-pr/p1/2017/2017-12-09/html/reg3-eng.html
Regulatory Proposal for medical devices: http://gazette.gc.ca/rp-pr/p1/2017/2017-12-09/html/reg4-eng.html

ICH:
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

CTD:
Common Technical Document submission format of ICH

eCTD:
Electronic Common Technical Document submission format of ICH

IMDRF ToC:
International Medical Device Regulators Forum Table of Contents

Rx-switch:
Submissions to switch an authorized medical ingredient to non-prescription status.

Medical Device:
Has the same meaning as in the Medical Device Regulations:

> For information on the classification of medical devices, please refer to Guidance Document: Guidance for the Risk-based Classification System for In Vitro Diagnostic Devices (IVDDs) and Guidance Document - Guidance on the Risk-based Classification System for Non-In Vitro Diagnostic Devices (non-IVDDs).

Personal Information:
Means information about an identifiable individual that is recorded in any form as defined in section 3 of the Privacy Act.

Clinical Trial:
Means an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug. (Food and Drug Regulations C.05.001)

Clinical Information:
Means information in respect of a clinical trial, as per the meaning in C.08.009.1 (1) of the FDR, or information in respect of clinical studies or investigational testing, as per the meaning in s43.11 of the MDR. For greater clarity, this includes the clinical overviews, clinical summaries, and clinical study reports for drugs, and the summaries and detailed information of all clinical studies and investigational testing that provided evidence of safety and effectiveness for medical devices.

Non-commercial purpose:
Means the information will not be used to support a marketing authorisation application anywhere in the world, or sold or traded to another person.

Manufacturer:
Means the current owner of a drug identification number or person or business holding the medical device licence.

Directly-identifying variable:
Means uniquely-identifying information that is replicable, distinguishable and knowable, and with limited exceptions is not analytically useful.

Indirectly-identifying variable:
Means identifying information that can identify an individual through a combination of indirect identifiers, and is analytically useful.

Anonymization:
Means the process through which personal information (both direct and indirect identifiers) are rendered de-identified: the information is irrevocably stripped of direct identifiers; a code is not kept to allow future re-linkage; and risk of re-identification of individuals from remaining indirect identifiers is equal to or below the threshold of 0.09.

Redaction:
Means a technique of anonymization that suppresses personal information by placing an opaque box over text or image.

Generalization:
Means a technique of anonymization that uses re-categorization within a range for the purpose of enlarging the number of "like" individuals.

Re-synthesis:
Means a technique applied following generalization that converts a general data range to a specific data point within the original generalized range.

Randomization:
Means a technique of anonymization that applies a random small change to variables to reduce the ability of the data to identify a person.

Offsetting:
Means a technique of anonymization that replaces numerical data through the addition or subtraction of a fixed quantity.

Pseudonymization:
Means a technique of anonymization whereby personal information (e.g. subject identification number) is re-coded for the purpose of disassociating the variable from the patient.

Reference population:
Means the group of individuals used to determine the risk of re-identification.

1.3 Policy objective

Health Canada's objective is to make specified de-identified clinical information in drug submissions and medical device applications publicly available for non-commercial purposes while adhering to Canada's Privacy Act, its associated regulations and governance, following the completion of Health Canada's regulatory review process.

2. Scope and application

Health Canada will endeavor to publish de-identified clinical information on a proactive basis, as well as on request for past submissions, as detailed in this guidance. Health Canada receives this clinical information to evaluate the safety and efficacy of drugs (including new drugs and generic drugs) and the safety and effectiveness of medical devices.

For drugs, clinical information is submitted under Division 8 of the FDR in the internationally-harmonized electronic Common Technical Document (eCTD) structure. This includes clinical overviews, summaries within module 2, and clinical study reports within module 5.

For class III and IV medical devices, clinical information is currently received under section 32 (3), and (4) of the MDR. However, Health Canada will soon be adopting an internationally-harmonized structured format for medical device application, known as IMDRF ToC; clinical information will be located within chapter 4 of these applications. Class I and II medical device applications and amendments are out of scope as they do not contain the supporting clinical information that falls within the policy objective.

Chemistry, manufacturing, and other non-clinical information (regardless of location within a drug submission or medical device application) will remain subject to the FDA definition of confidential business information.

Paragraph C.08.009.2 of the FDR describes the circumstances when clinical information within drug submissions ceases to be CBI. These are:

a) the issuance of a notice of compliance,
b) the issuance of a notice of non-compliance-withdrawal, or
c) the issuance of a notice of deficiency-withdrawal.

Similarly, section 43.12 (1) of the MDR describes the circumstances when clinical information within medical device applications that is CBI ceases to be CBI. These are:

a) the issuance of a medical device license,
b) the issuance of a medical device license amendment, or
c) the issuance of a refusal letter.

Paragraph C.08.009.3 of the FDR and section 43.13 of the MDR provide the Minister with the authority to disclose, without notification or consent, clinical information once it has ceased to be CBI under the above circumstances.

This Guidance describes the categories of clinical information Health Canada will disclose proactively, the process for requesting information from past submissions, and the process through which Health Canada will protect personal information and information that continues to be CBI.

2.1 International alignment

Health Canada recognizes the importance of international alignment in clinical data sharing, particularly regarding the release of clinical data that is available in other jurisdictions. Its implementation of the public release of clinical information will seek to align with international best practices, where these conform with Canadian legal requirements and help to advance Canadian policy objectives. Collaboration with the clinical data publication programs of our regulatory partners will help to reduce administrative burden and ensure that personal information is consistently protected.

2.2 Clinical information available to the public

Health Canada will publicly release, following completion of the regulatory process, clinical information regarding the safety and efficacy of drugs in humans and the safety and effectiveness of medical devices.

For drug information provided to Health Canada using the international standard submission format, clinical information is contained in eCTD modules 2.5 (clinical summaries), 2.7 (clinical overviews) and 5.3 (clinical study reports), see appendix A for greater detail. In addition, the released information will include the following appendices to clinical study reports: 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report forms) and 16.1.9 (statistical analysis plan), see appendix B for greater detail.

Medical device information will be made available to the public at the beginning of the third stage of implementation. Health Canada intends to align publication of medical device information with the adoption of the IMDRF-ToC medical device application format. For medical device information provided to Health Canada in the IMDRF-ToC format, clinical information is contained in chapter 4 and includes the summaries, reports, and evidence, see appendix C for greater detail.

2.3 Consideration regarding interim analyses

An interim analysis is any analysis intended to compare treatment arms for efficacy or safety, at any time prior to the formal completion of a trial.

Premature disclosure of clinical data prior to the finalization of a clinical trial risks jeopardizing the reliability of the trial data by affecting patient recruitment, biasing data collection and analysis or weakening confidence in the study conclusions. Disclosure of clinical information will be balanced with the need to retain the scientific integrity of clinical studies. Interim analyses will not be released if disclosure risks affecting the integrity of the study.

The decision to disclose clinical information within interim analyses will be taken case by case based on the following considerations:

Situation involving an interim analysis:	Disclosure
An interim analysis that established clear superiority of the treatment for the condition(s) of use and that is used to stop the trial early	Favoured
An interim analysis of a clinical study that has been either completed or discontinued	Favoured
An *ad hoc* interim analysis of an **ongoing** trial that, if released, may impact the integrity of the study results and possibly weaken confidence in the conclusions drawn	Not favoured

2.4 Individual patient records (individual patient listings and case report forms)

Clinical case report forms (e.g. ICH E3 16.3) are documents designed to record information on each trial subject as required by the clinical study protocol. Individual patient listings (e.g. ICH E3 16.2) include demographic data, individual efficacy response data, and listings of individual laboratory measurements by patient.

Collectively, these records represent a significant volume of a clinical study report. Due to a combination of structured and unstructured personal information, considerable de-identification is required before public release.

Due to this extensive requirement for de-identification, and the effects of these data modifications on overall data utility, individual patient records will not be released proactively as part of this initiative. Health Canada is considering new mechanisms through which individual patient records could be made available on request.

2.5 Implementation schedule for the proactive disclosure of clinical information in drug submissions and medical device applications

Health Canada intends to proactively release clinical information in drug submissions and medical device applications according to the following implementation stages, following the circumstances outlined in paragraph C.08.009.2 of the FDR and Section 43.12 (1) of the MDR.

Table: Implementation steps of proactive public release of clinical information

Stage	Proposed Phase-in	Scope of application types
1	Year 1	NDS-NAS + SNDS-c + Rx-switch
2	Year 2	All NDS + SNDS-c + Rx-switch
3	Year 3	All NDS, all SNDS & Class IV devices
4	Year 4	All NDS, SNDS, ANDS, SANDS + Class III & IV devices

Implementation Step 1

In the first stage of implementation of proactive public release, Health Canada aims to publish the clinical information within drug submissions for:

- new active substances (NDS-NAS), representing submissions for drugs that are not variations of previously approved medicinal ingredients in Canada, i.e. “innovative” drugs;
- supplemental new drug submissions containing confirmatory trials (SNDS-c) following the issuance of a Notice of Compliance with conditions as agreed to in the Letter of Undertaking; and
- submissions to switch an authorized medicinal ingredient to non-prescription status (Rx-switch for full switch and partial switch submissions).

Implementation Step 2

In stage two, Health Canada intends on adding the proactive publication of clinical information within all new drug submissions (both NDS-NAS and those not categorized as new active substances).

Implementation Step 3

In stage three, Health Canada intends on adding the proactive publication of clinical information within all supplemental new drug submissions (SNDS) (e.g. submissions for new indications to a marketed product), and in-scope clinical information within Class IV medical device applications.

It is anticipated that the timing of stage three will align with the adoption of the IMDRF-TOC application structure for medical device applications, to permit the efficient publication of class III and IV clinical information.

Implementation Step 4

In stage four, Health Canada intends on adding the proactive publication of clinical information from abbreviated new drug submissions (ANDS; i.e. generic drug approvals), and from Class III medical device applications.

2.6 On-request publication of clinical information found in past drug submissions and medical device applications

Clinical information from past drug submissions and medical device applications (received by Health Canada prior to 2019) may be requested through Health Canada’s clinical information portal. The information available for public release may be found in the following submission and application types:

- New Drug Submissions (NDS)
- Supplemental New Drug Submissions (SNDS)
- Abbreviated New Drug Submissions (ANDS)
- Supplemental Abbreviated New Drug Submissions (SANDS)
- Extraordinary Use New Drug Submissions (EUNDS)
- Supplemental Extraordinary Use New Drug Submissions (SEUNDS)
- Class III Medical Device Application
- Class III Medical Device Application Amendment
- Class IV Medical Device Application
- Class IV Medical Device Application Amendment

A request for clinical information from past submissions should be submitted using the online request form on Health Canada’s clinical information portal, as described in section 3 (Procedures).

3. Procedures

The publication of clinical information under the Public Release of Clinical Information initiative proceeds through five distinct phases - initiation, submission, review, finalization, and publication.

Health Canada aims to upload a final redacted and de-identified clinical information package onto Health Canada's clinical information portal within 60 days from initiation of the process. In the event that a request is received for clinical information that is not currently in an electronic format, additional time may be required for digitization of paper records.

3.1 Health Canada initiation of the publication of clinical information

Positive regulatory decisions

Publication of clinical trial information is initiated upon issuance of the qualifying regulatory decision (i.e. notice of compliance or medical device licence) on the submission / application; initiation triggers an email notification to the manufacturer, though manufacturers may start to prepare clinical information for publication prior to receiving the Health Canada notification.

The notification email identifies the drug submission or medical device application, and lists the documents Health Canada will publicly release (see appendices A, B, and C for a list of these documents). Health Canada requests that within 20 days the manufacturer submit the de-identified documents with proposed redaction(s). A redaction control sheet and anonymization report must also be submitted, as described below.

Negative regulatory decisions

In the event a drug submission is found to not comply with the FDR, Health Canada will initiate publication 31 days after the date of the notice, unless a Letter of Intent for Reconsideration has been received from the manufacturer.

In the event the manufacturer submits a Letter of Intent for Reconsideration, Health Canada will initiate publication upon completion of the reconsideration process, as described in the guidance "Reconsideration of Final Decisions Issued for Human Drug Submissions". This is expected to require 70-140 days, depending on whether the request is referred for internal or external review.

In the event a medical device application is found to not comply with the MDR and the manufacturer submits a Letter of Intent to Appeal, Health Canada will initiate publication upon issuance of a decision of the appeal process, in accordance with the guidance "Management of Applications for Medical Device Licences and Investigational Testing Authorizations".

In the case of a first-level appeal, should the manufacturer not submit the necessary information supporting the appeal, Health Canada will initiate publication 21 days after receipt of a manufacturer's Letter of Intent to Appeal to the Bureau Director. In the case of a second-level appeal, Health Canada will initiate publication upon notification to the manufacturer of the Directorate's decision on the appeal.

How to request clinical information from past submissions

Health Canada intends to publish clinical information from past submissions upon receipt of a request from the public.

Members of the public may request clinical information from past submissions through Health Canada's clinical information portal with an electronic request form identifying the product name and the information requested (e.g. clinical study report, clinical overview, clinical summary).

Where possible, the requester should provide Health Canada with the submission/application number, study name, the name of the manufacturer, and the date of the regulatory decision (e.g. notice of compliance). This additional information is available within Health Canada's Summary Basis of Decision, and Regulatory Decision Summary documents associated with the drug submission or medical device application.

Upon receipt of a request for clinical information, Health Canada will prioritize the request (see below), conduct an internal search for records, and publish the requested information on its clinical information portal.

Prioritization of requests

In the event requests for information exceed Health Canada's administrative capacity, Health Canada will process requests for clinical information in priority sequence. Health Canada's prioritization of requests will consider metrics that identify products and information with high health system impact. These considerations include prioritizing drugs or medical devices that are subject to ongoing queries by health system organizations, products that are abundantly used, and products that have demonstrated to be of high public interest.

3.2 Submission of annotated documents with proposed CBI redaction(s) and anonymization

Health Canada has described limited and specific circumstances, prescribed in regulations, where information found within the clinical component of a drug submission or medical device application may possess ongoing commercial value following the final regulatory decision. The specific categories of information that Health Canada will consider for redaction (with sufficient justification) are described in section 4 of this Guide.

The justification of certain redactions may require the manufacturer to draw on information within their internal corporate plans (e.g. future development of new indications based on secondary outcome data). Consequently, Health Canada requests that the manufacturer submit an annotated version of all clinical information in scope of publication with any and all proposed redactions highlighted. Any text the manufacturer proposes to redact must remain readable, and all proposed redactions should be recorded in the "Proposed redactions control sheet" alongside specific and detailed justification. Please refer to Appendix F for the control sheet template.

The annotated documents must also be de-identified in accordance with the process outlined in section 5 of this Guide. The process of data anonymization should be detailed in a separate Anonymization Report (see Appendix G for the Anonymization Report template).

Once the manufacturer has prepared the above documents, Health Canada requests that the documents be transmitted through the Common Electronic Submissions Gateway (CESG). Documents submitted via the CESG must follow the defined naming convention outlined in Appendix E.

Health Canada may return to the manufacturer on one additional occasion to seek additional justification. The final decision on what clinical information is publicly released rests with Health Canada.

Relying on previously-redacted information

With appropriate certification, the manufacturer may submit to Health Canada final redacted documents that were previously accepted by the EMA. Upon receipt of a Health Canada notification to prepare annotated documents for public release, in the case that this clinical information was previously released by the EMA under policy 0070, the manufacturer can choose this alternative pathway.

Manufacturers must submit final redacted documents using the CESG, as above.

Health Canada requests that manufacturers submit their certification using the template certification form found in Appendix H. Submission of this form attests that the clinical information in scope of Health Canada's Public Release of Clinical Information is identical to the clinical information published under policy 0070.

In circumstances where only a component of the information requested for release by Health Canada was previously redacted for the EMA, manufacturers may resubmit the same information with certification, and only redact the outstanding components for Health Canada.

3.3 Health Canada review of annotated documents

Health Canada will review the manufacturer's justifications for each proposed redaction within the annotated documents. All proposed redactions will be assessed against the exceptions permitted under the regulations (see section 4). Following review, proposed redactions will be accepted or rejected prior to finalization of the clinical information for public release.

Proposed redactions may be rejected for the following reasons:

- When the manufacturer fails to adequately demonstrate how the information was not used to support the conditions of use or purpose for the drug or device, as set out in the submission or application;
- When the manufacturer fails to adequately justify how the proposed information describes a test, method, or assay that is used exclusively by the manufacturer;
- When the proposed redaction pertains to information already in the public domain.

Health Canada will inform the manufacturer of any proposed redactions that the Department rejects. Manufacturers will be given one additional opportunity to further justify a redaction following Health Canada's review.

As outlined in section 5, Health Canada requests the manufacturer to anonymize the clinical information using a risk-based anonymization process. Health Canada's review will reject the transformation of any data that is not accompanied by adequate justification. Health Canada retains final decision on what information is publicly released.

3.4 Finalization of redacted documents

Following Health Canada's review, the manufacturer must submit a final version of the redacted documents, according to Health Canada instruction:

All accepted proposed redactions must be converted into non-readable text; redacted text should not be machine-readable or searchable.

All proposed data transformations for the purposes of anonymization should be finalized; a revised anonymization report which excludes any personal information will be prepared to accompany the final anonymized clinical documents (see Section 5 for more information on the requirements for the anonymization report).

The final redacted documents should be named in accordance with the naming conventions identified in Appendix E, and submitted to Health Canada via the CESG.

3.5 Publication of final redacted documents

Final redacted documents will be made publicly available for non-commercial purposes through Health Canada's clinical information portal. All pages within the final redacted documents will bear a non-machine-readable watermark to reinforce the terms of use that indicate they were disclosed by Health Canada for non-commercial purposes. Health Canada aims to publish clinical information 60 days following the initiation of publication.

4. Requirements for the Redaction of Confidential Business Information

Two categories of clinical information will remain subject to the FDA definition of CBI. With justification by the manufacturer, Health Canada may protect the following from public release:

- Clinical information that was not used by the manufacturer in the submission, application or supplement to support the proposed conditions of use for the new drug or the purpose for which the new drug is recommended; or
- Clinical information that describes tests, methods or assays used exclusively by the manufacturer.

1) As per C.08.009.2(2)(a) of the FDR, clinical information submitted by the manufacturer but that did not support the proposed conditions of use for the drug, or the purpose for which the drug is recommended, does not cease to be confidential business information following Health Canada's regulatory decision.

Similarly, as per s43.12(2)(a) of the MDR, clinical information submitted by the manufacturer but that did not support the features of the device that permit it to be used for the medical conditions, purposes and uses for which it is manufactured, sold, or represented, does not cease to be confidential business information following Health Canada's regulatory decision.

As an example, a manufacturer may be using secondary or exploratory outcome measure data described in the submitted CSR to support future trials to gain approval for a new indication of use. Release of this information could provide a competitor with insight about the drug's future uses.

Clinical study reports, overviews, and summaries may contain data and discussion about secondary or exploratory end points that do not support the conditions of use or purpose of the product for which the submission or application seeks market authorization. In the rare instance where this information may form a component of an on-going development programme for new claims, given adequate justification Health Canada will protect this information from public release.

2) As per C.08.009.2(2)(b) of the FDR and s43.12(2)(b) of the MDR, clinical information in respect of tests, methods or assays that are used exclusively by the manufacturer do not cease to be CBI following Health Canada's regulatory decision.

As an example, a manufacturer may develop novel modifications to a bioassay that is then used to collect clinical data. In certain instances, such modifications may rely on considerable effort and investment by the manufacturer and may be used for other ongoing studies or other routine use. Such modifications may be considered to be exclusively used by the manufacturer.

Clinical study reports, overviews, and summaries may include details, specifications, and validation information on assays and/or test methods developed exclusively by the submission sponsor or another third party and used exclusively by the submission sponsor. In the event that these methodological details have not been published in the public domain, and with adequate justification, Health Canada will protect this information from public release.

5. Anonymization of Personal Information

5.1 Principles of protecting personal information

The federal Privacy Act defines "personal information" as information about an identifiable individual that is recorded in any form; specific and non-exhaustive examples are then listed. Clinical information contains information that falls under this definition of personal information.

The federal court has adopted the "serious possibility" test to determine when information is about an identifiable individual (Gordon v. Canada (Health), 2008 FC 258). Clinical information must be therefore be adequately de-identified prior to public disclosure to avoid the serious possibility of identifying individual clinical trial patients; this requires the application of an objective, systematic, and documented process of anonymization.

In order to maximize the release of analytically-valuable information and to retain the most utility of the published clinical information, the anonymization of clinical information should be guided by the following principles:

1 - All transformation of data should be conducted for the sole purpose of preventing the disclosure of personal information;

2 - All data transformations should be accompanied by robust justification, and be applied to limited variables that risk re-identification, not to broad sections of clinical information;

3 - Data transformation should favour methods that retain analytical value, e.g. generalization, randomization and offsetting, as opposed to redaction.

5.2 Anonymization process:

Many anonymization frameworks currently exist and are publicly available. Health Canada encourages a 3 step process adapted from the 2016 Information and Privacy Commissioner of Ontario de-identification guidance (https://www.ipc.on.ca/wp-content/uploads/2016/08/Deidentification-Guidelines-for-Structured-Data.pdf). The process of anonymization should broadly follow the following three stages:

Step 1: Classify the variables

Step 2: Measure the data risk

Step 3: De-identify the data

By adopting an anonymization process that follows these broad steps, the risk of disclosing personal information can be reliably reduced in an objective and documented manner. An anonymization approach which includes risk measurement and accurate reference population selection provides further benefits by maximizing data utility while inherently adjusting for variable sensitivities of certain study populations.

Step 1: Classify the variables

Directly-identifying and indirectly-identifying variables must be classified prior to processing the clinical information for anonymization.

Directly-identifying variables are commonly described as information that meets the test of being:

A - Replicable, in the sense that the variable is unlikely to frequently vary over time;

B - Distinguishable, in the sense that individual patients may have distinct recognizable values; and

C - Knowable, in the sense that someone knows the variable associated with a certain individual.

Directly-identifying variables can be either uniquely identifying (e.g. a patient's social insurance number), or not uniquely identifying (e.g. date of birth). Generally, variables classified as directly-identifying are not considered analytically useful (e.g. patient initials), with limited exceptions (e.g. subject identification numbers). The disclosure of directly-identifying variables poses a serious risk of re-identifying an individual.

Indirectly-identifying variables are other identifying variables that fall within the definition of 'personal information' within Canada's *Privacy Act*. In order for an indirectly-identifying variable to require anonymization, its disclosure must pose a serious risk of re-identifying an individual, when combined with other available information (e.g. demographic data). Indirectly-identifying variables are analytically useful, and therefore their anonymization must be carefully justified, in line with the guiding anonymization principle number 2.

Step 2: Measure the data risk

Once the variables have been classified, the data risk needs to be measured. This risk measurement provides justification for any data transformation that may follow. Variables which do not present a serious risk of re-identifying an individual are not considered personal information and should not be transformed.

The overall risk of re-identification associated with the disclosure of clinical data is the product of the risk inherent to the data and the risk associated with the context of the release. For the public release of clinical information (to the general public), the calculation of risk of re-identification needs to reflect this environment; in a public release environment, the context risk is unreducible, so the overall risk of re-identification is equivalent to the risk inherent to the data (as opposed to the release of information to a small and select group of individuals, which would constitute a lower context risk, and therefore a lower risk of re-identification).

Measurement of data risk for directly-identifying variables

Directly-identifying variables possess a serious risk of identifying a trial participant, and should be assumed to carry a 100% risk of re-identification (risk=1.0); invariably these variables require anonymization in order to sufficiently reduce the risk of trial participant re-identification.

Measurement of data risk for indirectly-identifying variables

The risk of re-identification for indirectly-identifying variables associated with a patient needs to be calculated on a patient level. One straightforward method of calculating the risk of re-identification for indirectly-identifying variables is to measure the cell size.

Cell size is defined as the number of patients with the same indirectly-identifying variable values. Adopting a risk threshold of risk=0.09 equates to a target cell size of 11 patients. Once indirectly-identifying variables in need of anonymization are identified, the data for the corresponding patients should be de-identified in order to achieve a cell size of 11.

Reference population

The selection of the estimated population size determines the group size and the amount of anonymization (i.e. data transformation) that is required to be applied. The reference population can be informed from patients in the single trial in question (smallest population), all patients in similar trials by a specific study sponsor, all patients in similar trials (i.e. by disease or therapeutic intervention category), or all patients in a geographic area (largest population).

A sampling fraction from the reference population can be used to achieve an estimate of the population size. In keeping with the first and second guiding principle, risk of re-identification should be informed not only by the number of individuals in a single study, but rather by the number that reflects real-world risk.

Risk threshold

Health Canada encourages adopting a 9% re-identification risk threshold (risk=0.09). This aligns with the risk threshold cited in the EMA Policy 0070 External Guidance and is in agreement with other public data disclosure risk thresholds. While a qualitative approach to risk measurement can be taken, a quantitative approach has the advantage of being based on empirical measurement and consequently is more precise, less subjective, and typically retains more data utility.

Step 3: De-identify the data

Data utility

The process of anonymization, including the method of de-identification applied, can have a detrimental effect on the utility of the data. Data that is preserved retains the greatest utility. Consequently, it is advisable to not transform (de-identify) variables that do not contribute to the risk of re-identification, and to adopt methods that have the lowest impact on data utility.

De-identification of directly-identifying variables

Directly-identifying variables may be anonymized through the process of redaction, pseudonymization, or randomization. While directly-identifying variables that do not possess analytical utility may be redacted, other directly identifying variables which possess analytical utility, such as subject IDs, may be pseudonymized (re-coded) in order to preserve the capacity to link clinical trial participant data throughout the study records.

Directly identifying variables that may be redacted include:

names	fax numbers
initials	email addresses
signatures	health plan beneficiary numbers
job titles/positions	batch/serial numbers
addresses	telephone numbers

De-identification of indirectly-identifying variables

Health Canada encourages the generalization of indirectly identifying variables. These variables may include: city, state/province, zip/postal code, demographic data (race, gender, etc.), medical history, serious adverse events, dates, height, weight, and BMI. Note that the country should remain unmodified.

In certain circumstances, following generalization, the variable should be resynthesized to avoid the appearance of anonymization. The subsequent resynthesis is expected to achieve further risk reduction due to inability to identify leaked identifiers.

Documenting the anonymization process and governance

The process of anonymization should be thoroughly documented to provide the necessary audit trail. Health Canada requests that the manufacturer submit a completed Anonymization Report (template provided in Appendix G) with the submission of all anonymized clinical information.

Appendix A: Structure and content of ICH CTD/eCTD M2.5, M2.7 and M5

Section	CBI	Proactive release
2.5 Clinical Overview	Not CBI	Yes
2.5.1 Product Development Rationale	Not CBI	Yes
2.5.2 Overview of Biopharmaceutics	Not CBI	Yes
2.5.3 Overview of Clinical Pharmacology	Not CBI	Yes
2.5.4 Overview of Efficacy	Not CBI	Yes
2.5.5 Overview of Safety	Not CBI	Yes
2.5.6 Benefits of Risks Conclusions	Not CBI	Yes
2.5.7 Literature References	Not CBI	Yes
2.7.1 Summary of biopharmaceutics and associated analytical methods	Not CBI	Yes
2.7.1.1 Background and Overview	Not CBI	Yes
2.7.1.2 Summary of Results of Individual Studies	Not CBI	Yes
2.7.1.3 Comparison and Analyses of Results Across Studies	Not CBI	Yes
2.7.1.4 Appendix	Not CBI	Yes
2.7.2 Summary of clinical pharmacology studies	Not CBI	Yes
2.7.2.1 Background and Overview	Not CBI	Yes
2.7.2.2 Summary of Results of Individual Studies	Not CBI	Yes
2.7.2.3 Comparison and Analysis of Results Across Studies	Not CBI	Yes
2.7.2.4 Special Studies	Not CBI	Yes
2.7.2.5 Appendix	Not CBI	Yes
2.7.3 Summary of clinical efficacy	Not CBI	Yes
2.7.3.1 Background and Overview of Clinical Efficacy	Not CBI	Yes
2.7.3.2 Summary of Results of Individual Studies	Not CBI	Yes
2.7.3.3 Comparison and Analyses of Results Across Studies	Not CBI	Yes
2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations	Not CBI	Yes
2.7.3.5 Persistence of Efficacy and/or Tolerability Effects	Not CBI	Yes
2.7.3.6 Appendix	Not CBI	Yes
2.7.4 Summary of clinical safety	Not CBI	Yes
2.7.4.1 Exposure to the Drug	Not CBI	Yes
2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies	Not CBI	Yes
2.7.4.1.2 Overall Extent of Exposure	Not CBI	Yes

2.7.4.1.3 Demographic and Other Characteristics of Study Population	Not CBI	Yes
2.7.4.2 Adverse Events	Not CBI	Yes
2.7.4.2.1 Analysis of Adverse Events	Not CBI	Yes
2.7.4.2.2 Narratives	Not CBI	Yes
2.7.4.3 Clinical Laboratory Evaluations	Not CBI	Yes
2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety	Not CBI	Yes
2.7.4.5 Safety in Special Groups and Situations	Not CBI	Yes
2.7.4.5.1 Intrinsic Factors	Not CBI	Yes
2.7.4.5.2 Extrinsic Factors	Not CBI	Yes
2.7.4.5.3 Drug Interactions	Not CBI	Yes
2.7.4.5.4 Use in Pregnancy and Lactation	Not CBI	Yes
2.7.4.5.5 Overdose	Not CBI	Yes
2.7.4.5.6 Drug Abuse	Not CBI	Yes
2.7.4.5.7 Withdrawal and Rebound	Not CBI	Yes
2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability	Not CBI	Yes
2.7.4.6 Post-marketing Data	Not CBI	Yes
2.7.4.7 Appendix	Not CBI	Yes
2.7.5 Literature References	Not CBI	No
2.7.6 Synopses of Individual Studies	Not CBI	No
5.1 Table of Contents of Module	Not CBI	No
5.2 Tabular Listing of All Clinical Studies	Not CBI	No
5.3.1.1 Bioavailability (BA) Study Reports	Not CBI	Yes
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports	Not CBI	Yes
5.3.1.3 In vitro- In vivo Correlation Study Reports	Not CBI	No
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	Not CBI	No
5.3.2.1 Plasma Protein Binding Study Reports	Not CBI	Yes
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies	Not CBI	Yes
5.3.2.3 Reports of Studies Using Other Human Biomaterials	Not CBI	Yes
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	Not CBI	Yes
5.3.3.2 Patient PK and Initial Tolerability Study Reports	Not CBI	Yes
5.3.3.3 Intrinsic Factor PK Study Reports	Not CBI	Yes
5.3.3.4 Extrinsic Factor PK Study Reports	Not CBI	Yes
5.3.3.5 Population PK Study Reports	Not CBI	Yes

5.3.4.1 Healthy Subject PD and PK/PD Study Reports	Not CBI	Yes
5.3.4.2 Patient PD and PK/PD Study Reports	Not CBI	Yes
5.3.5.1 Study Reports of Controlled Clinical Pertinent to the Claimed Indication	Not CBI	Yes
5.3.5.2 Study Reports of Uncontrolled Clinical Studies	Not CBI	Yes
5.3.5.3 Reports of Analysis of Data from More than One Study	Not CBI	Yes
5.3.5.4 Other Study Reports	Not CBI	Yes
5.3.6 Reports of post-marketing experience	Not CBI	No
5.3.7 Case report forms and individual patient listings, when submitted	Not CBI	No
5.4 Literature References	Not CBI	No

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Appendix B: Structure and Content of ICH CTD/eCTD Module 5.3 Clinical Study Reports

Section	Description	CBI	Public Proactive Release
1	Title page	Not CBI	Yes
2	Synopsis	Not CBI	Yes
3	Table of contents for the individual clinical study report	Not CBI	Yes
4	List of abbreviations and definition of terms	Not CBI	Yes
5	Ethics	Not CBI	Yes
5.1	Independent ethics committee (iec) or institutional review board (irb)	Not CBI	Yes
5.2	Ethical conduct of the study	Not CBI	Yes
5.3	Patient information and consent	Not CBI	Yes
6	Investigators and study administrative structure	Not CBI	Yes
7	Introduction	Not CBI	Yes
8	Study objectives	Not CBI	Yes
9	Investigational plan	Not CBI	Yes
9.1	Overall study design and plan – description	Not CBI	Yes
9.2	Discussion of study design, including the choice of control groups	Not CBI	Yes
9.3	Selection of study population		
9.3.1	Inclusion Criteria	Not CBI	Yes
9.3.2	Exclusion Criteria	Not CBI	Yes
9.3.3	Removal of Patients from Therapy or Assessment	Not CBI	Yes
9.4	Treatments		
9.4.1	Treatments Administered	Not CBI	Yes
9.4.2	Identity of Investigational Product(s)	Not CBI	Yes
9.4.3	Method of Assigning Patients to Treatment Groups	Not CBI	Yes
9.4.4	Selection of Doses in the Study	Not CBI	Yes
9.4.5	Selection and Timing of Dose for each Patient	Not CBI	Yes
9.4.6	Blinding	Not CBI	Yes
9.4.7	Prior and Concomitant Therapy	Not CBI	Yes
9.4.8	Treatment Compliance	Not CBI	Yes

9.5	Efficacy and safety variables		
9.5.1	Efficacy and Safety Measurements Assessed and Flow Chart	Not CBI	Yes
9.5.2	Appropriateness of Measurements	Not CBI	Yes
9.5.3	Primary Efficacy Variable(s)	Not CBI	Yes
9.5.4	Drug Concentration Measurements	Not CBI	Yes
9.6	Data quality assurance	Not CBI	Yes
9.7	Statistical methods planned in the protocol and determination of sample size		
9.7.1	Statistical and Analytical Plans	Not CBI	Yes
9.7.2	Determination of Sample Size	Not CBI	Yes
9.8	Changes in the conduct of the study or planned analyses	Not CBI	Yes
10	Study patients		
10.1	10.1 disposition of patients	Not CBI	Yes
10.2	Protocol deviations	Not CBI	Yes
11	Efficacy evaluation		
11.1	Data sets analysed	Not CBI	Yes
11.2	Demographic and other baseline characteristics	Not CBI	Yes
11.3	Measurements of treatment compliance	Not CBI	Yes
11.4	Efficacy results and tabulations of individual patient data	Not CBI	Yes
11.4.1	Analysis of Efficacy	Not CBI	Yes
11.4.2	Statistical/Analytical Issues	Not CBI	Yes
11.4.2.1	Adjustments for Covariates Selection	Not CBI	Yes
11.4.2.2	Handling of Dropouts or Missing Data	Not CBI	Yes
11.4.2.3	Interim Analyses and Data Monitoring	Not CBI	Yes
11.4.2.4	Multicentre Studies	Not CBI	Yes
11.4.2.5	Multiple Comparison/Multiplicity	Not CBI	Yes
11.4.2.6	Use of an "Efficacy Subset" of Patients	Not CBI	Yes
11.4.2.7	Active-Control Studies Intended to Show	Not CBI	Yes
11.4.2.8	Examination of Subgroups	Not CBI	Yes
11.4.3	Tabulation of Individual Response Data	Not CBI	Yes
11.4.4	Drug Dose, Drug Concentration, and Relationships to Response	Not CBI	Yes
11.4.5	Drug-Drug and Drug-Disease Interactions	Not CBI	Yes
11.4.6	By-Patient Displays	Not CBI	Yes
11.4.7	Efficacy Conclusions	Not CBI	Yes

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12	Safety evaluation		
12.1	Extent of exposure	Not CBI	Yes
12.2	Adverse events (aes)	Not CBI	Yes
12.2.1	Brief Summary of Adverse Events	Not CBI	Yes
12.2.2	Display of Adverse Events	Not CBI	Yes
12.2.3	Analysis of Adverse Events	Not CBI	Yes
12.2.4	Listing of Adverse Events by Patient	Not CBI	Yes
12.3	Deaths, other serious adverse events, and other significant adverse events	Not CBI	Yes
12.3.1	Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events	Not CBI	Yes
12.3.1.1	Deaths	Not CBI	Yes
12.3.1.2	Other Serious Adverse Events	Not CBI	Yes
12.3.1.3	Other Significant Adverse Events	Not CBI	Yes
12.3.2	Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse	Not CBI	Yes
12.3.3	Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events	Not CBI	Yes
12.4	Clinical laboratory evaluation	Not CBI	Yes
12.4.1	Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each Abnormal Laboratory Value (14.3.4)	Not CBI	Yes
12.4.2	Evaluation of Each Laboratory Parameter	Not CBI	Yes
12.4.2.1	Laboratory Values Over Time	Not CBI	Yes
12.4.2.2	Individual Patient Changes	Not CBI	Yes
12.4.2.3	Individual Clinically Significant Abnormalities	Not CBI	Yes
12.5	Vital signs, physical findings and other observations related to safety	Not CBI	Yes
12.6	Safety conclusions	Not CBI	Yes
13	Discussion and overall conclusions	Not CBI	Yes
14	Tables, figures and graphs referred to but not included in the text		
14.1	Demographic data	Not CBI	Yes
14.2	Efficacy data summary figures and tables	Not CBI	Yes
14.3	Safety data summary figures and tables	Not CBI	Yes
14.3.1	Displays of Adverse Events	Not CBI	Yes
14.3.2	Listings of Deaths, Other Serious and Significant Adverse Events	Not CBI	Yes
14.3.3	Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	Not CBI	Yes

14.3.4	Abnormal Laboratory Value Listing (Each Patient)	Not CBI	Yes
15	Reference list	Not CBI	Yes
16	Appendices		
16.1	Study information		
16.1.1	Protocol and protocol amendments	Not CBI	Yes
16.1.2	Sample case report form (unique pages only)	Not CBI	Yes
16.1.3	List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms	Not CBI	No
16.1.4	List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	Not CBI	No
16.1.5	Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	Not CBI	No
16.1.6	Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used 28 Structure and Content of Clinical Study Reports	Not CBI	No
16.1.7	Randomisation scheme and codes (patient identification and treatment assigned)	Not CBI	No
16.1.8	Audit certificates (if available) (see Annex IVa and IVb of the guideline)	Not CBI	No
16.1.9	Documentation of statistical methods	Not CBI	Yes
16.1.10	Documentation of inter-laboratory standardisation methods and quality assurance procedures if used	Not CBI	No
16.1.11	Publications based on the study	Not CBI	No
16.1.12	Important publications referenced in the report	Not CBI	No
16.2	Patient data listings		
16.2.1	Discontinued patients	Not CBI	No
16.2.2	Protocol deviations	Not CBI	No
16.2.3	Patients excluded from the efficacy analysis	Not CBI	No
16.2.4	Demographic data	Not CBI	No
16.2.5	Compliance and/or drug concentration data (if available)	Not CBI	No
16.2.6	Individual efficacy response data	Not CBI	No
16.2.7	Adverse event listings (each patient)	Not CBI	No
16.2.8	Listing of individual laboratory measurements by patient, when required by regulatory authorities No	Not CBI	No

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16.3	Case report forms		
16.3.1	CRFs for deaths, other serious adverse events and withdrawals for AE	Not CBI	No
16.3.2	Other CRFs submitted	Not CBI	No
16.4	Individual patient data listings (us archival listings)	Not CBI	No

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Appendix C: Structure and content of Section 4 of IMDRF ToC medical device application

Section	Description	CBI	Public Proactive Release
4.1 - Chapter Table of Contents		Not CBI	No
4.2 - Overall Clinical Evidence Summary	A brief summary of the available clinical evidence being presented in support of the submission	Not CBI	Yes
4.2.1 Clinical Evaluation Report	An objective critical evaluation of all of the clinical data submitted in relation to the device.	Not CBI	Yes
4.2.2 Device Specific Clinical Trials			
4.2.2.1	Trial description, protocol number, date of initiation	Not CBI	Yes
4.2.2.1.1	Clinical Trial Synopsis	Not CBI	Yes
4.2.2.1.2	Clinical trial report	Not CBI	Yes
4.2.2.1.3	Clinical trial data	Not CBI	Yes
4.2.3	Clinical literature review and other reasonable known information	Not CBI	Yes
4.3 - IRB Approved Informed Consent Forms	US regional information not submitted to Health Canada	NA	NA
4.4 - Investigators Sites – IRB Contact Information	US regional information not submitted to Health Canada	NA	NA
4.5 - Other Clinical Evidence		Not CBI	Yes
4.5.1.1	Summaries of specific studies	Not CBI	Yes
4.5.1.2	Full test report for specific studies	Not CBI	Yes

Appendix D: Process flow chart

PRCI Process step(s):	1 – Commence PRCI process:	2 – Product sponsor provides data package for PRCI:	3 – Health Canada internal review	4 – Sponsor review of PRCI package (if required):	5 – Publication of records in scope of PRCI:
Positive regulatory decision: FDR: C.08.004, C.08.004.01 MDR: 36(1)(a) or (b)	Process starts on day of decision	i. Sponsor notified, PRCI data package requested; ii. *If required, Health Canada provides digitised records; iii. Sponsor prepares proposed redactions & anonymizations, as per guidance; iv. Sponsor provides Health Canada with PRCI data package.	i. Health Canada receives redaction & anonymization package from sponsor; ii. Health Canada conducts quality assurance for data completeness; ii. Health Canada vets proposed redactions & anonymization report; v. (If required, Health Canada returns package to sponsor for corrections (triggering step-4 otherwise Health Canada proceeds to step-5).	i. Sponsor makes corrections to PRCI data package; i. Sponsor provides corrected database package to Health Canada; i. Health Canada will consider revised and valid redaction justifications.	i. Health Canada publishes data in accordance with applicable regulations; ii. Requestor(s) and sponsors of data notified, if applicable.
Negative regulatory decision: FDR: C.08.004(3) C.08.004.01(3) MDR: 38	Process delayed for 30 days for sponsor reconsideration(s) or appeal. Trigger of reconsideration or appeal process would delay process an additional 70-120 days.				
Negative Decision	**Day 0 + 30**	**Day 31-50**	**Day 51-65**	**Day 66-80**	**Up to 90 days total**
Time forecasts:	**(pos) = 0 days (neg) = +30 days**	**+20 days**	**+15 days**	**+15 days (if required)**	**+10 days**

Appendix E: Document naming convention for submissions through the CESG

Anonymized clinical information with proposed redactions and accompanying redaction justification tables and anonymization reports should be submitted via the CESG.

The file format in which documents must be submitted is PDF format.

The file naming convention for all documents with proposed redactions should follow the original file naming convention used in the original submission with the addition of "-PR" as a suffix. It is assumed that the original file naming convention was chosen in accordance with Health Canada's Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document Format (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/ectd/preparation-drug-submissions-electronic-common-technical-document.html).

"-PR" = proposed redaction

E.g. clinical-overview-PR.pdf, summary-clin-safety-PR.pdf, study-XXXXXX-PR.pdf

Once redactions are finalized, Health Canada will apply the "-RED" suffix, to the final anonymized documents prior to publication.

"-RED" = final redaction

E.g. clinical-overview-RED.pdf, summary-clin-safety-RED.pdf, study-XXXXXX-RED.pdf

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Appendix F: Proposed redaction control sheet

Document Name	Page Number(s)	Text proposed for redaction	Qualifying exception for regulations	Not clinical information	Detailed justification of proposed redaction	Health Canada's response to proposed redaction	Health Canada's rationale
			E.g. exceptions: C.08.009.2 (2)(a) or C.08.009.2 (2)(b)	E.g. chemistry, manufacturing information		Rejected / Partially Accepted / Accepted	

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Appendix G: Anonymisation report template

*Note: two versions of the anonymization report will be generated. The first submitted version must include detailed information on the anonymization methodology. Each data transformation must be identified and a rationale provided. Upon acceptance of the anonymization approach, Health Canada will remove any information that presents a risk of disclosing personal information within the anonymization report.

Product name:

Active substance:

Submission control number:

Applicant/ Market Authorization Holder:

1. Anonymization methodology

- Describe the approach taken, the risk threshold used and the rationale for the chosen approach.

2. Identification of data variables (direct and indirect identifiers) and measurement of re-identification risk

- Classify the variables considered personal information into directly-identifying and indirectly-identifying categories.

- State and justify the reasons for describing information as personal information.

- State and justify the reference population used.

- Discuss the measured data risk associated with individual trial subjects found to be at risk of re-identification and how the data was transformed to reduce the risk.

- State the measured risk following the process of anonymization.

3. Data utility considerations

- State the efforts made to maximize the utility of the anonymized information.

Appendix H: Certification letter with table of previously redacted information

Certification Form

Drug Product Name:
Company:

I certify that the following information and data listed and provided in this submission is complete, accurate and correctly represents the redacted and anonymized information and material provided to the European Medicines Agency under policy 070 and the Canadian submission to which it refers.

Health Canada submission control number:

EMA procedure:

Module 2:
Section 2.5 (pages xxx to xxx)
Section 2.7 (pages xxx to xxx)

Module 5
Clinical Study Name 1 (pages xxx to xxx)
Clinical Study Name 2 (pages xxx to xxx)

I certify that the following information has not been redacted and anonymized, and is unique to the Canadian submission:

Module 2:
Section 2.5 (pages xxx to xxx)
Section 2.7 (pages xxx to xxx)

Module 5
Clinical Study Name 1 (pages xxx to xxx)
Clinical Study Name 2 (pages xxx to xxx)

OR Not applicable

Signature of the responsible officer of the company certifying the accuracy of this document.

Signature	Date
Name	Position Title
Company	

It is prohibits a person against knowingly making false or misleading statements or providing false or misleading information to the Minister in connection with any matter under the Act concerning a therapeutic product. (Food and Drugs Acts, 21.6)

Appendix I: Terms and conditions of use

These Terms of Use govern the access and use of Clinical Information released by Health Canada for non-commercial purposes. By clicking the box "I agree" and accepting these Terms of Use and upon being granted access to the Clinical Information, you, and, if applicable, the organization on behalf of which you are accessing the Clinical Information, agree to be bound by these Terms of Use.

IT IS IMPORTANT TO READ THESE TERMS OF USE CAREFULLY.

1. Definitions

"Manufacturer" means the current owner of a Drug Identification Number, or person or business holding a medical device licence.

"Clinical Information" means clinical trial information as per the meaning in C.08.009.1 (1) of the FDR, or information on a clinical study or investigational testing as per the meaning in s43.11 of the MDR, which includes clinical overviews, clinical summaries, clinical study reports, clinical study report appendices 16.1.1, 16.1.2, and 16.1.9, for drugs and the detailed information of all clinical studies and investigational testing that provided evidence of biological safety for medical devices.

"You" means you personally and, as applicable, if you are accessing and using the information on behalf of your employer, that employer, and its affiliates.

2. Representations and Warranties

You represent and warrant:

a. the accuracy of the information you submitted to create your User Account in order to obtain Clinical Information.

b. that if you are accessing Clinical Information on behalf of your employer, that you have the full legal authority to bind your employer.

c. that your access to Clinical Information is solely for non-commercial purposes.

3. Use of Clinical Information

3.1 For greater certainty, you are permitted to download, save and print Clinical Information, subject to your compliance with these Terms of Use.

3.2 You agree to only use, reproduce or communicate reasonable parts of Clinical Information (a) for non-commercial purposes, and not to (b) use the information to support a marketing authorisation application anywhere in the world, (c) sell or trade the information to another person, or (c) otherwise make any unfair commercial use of Clinical Information.

3.3 You acknowledge that Clinical Information may be protected by copyright or other intellectual property rights of the Manufacturer. You are not granted any intellectual property or other commercial rights in relation to Clinical Information other than as expressly set out in these Terms of Use.

3.4 When reproducing Clinical Information, you agree to not misrepresent the source of the Clinical Information and to acknowledge that the source of the information is the Manufacturer and not use the information in a way that suggests that the Manufacturer endorses your use of the Clinical Information for any other purpose other than non-commercial purposes.

3.5 You agree not to seek to re-identify the trial subjects or other individuals from Clinical Information and to report to Health Canada if Clinical Information includes any inadvertent disclosure of personal information.

3.6 You agree not to provide any copy of Clinical Information to any other entity or person without an undertaking to the benefit of Health Canada that the other entity or person will use the information solely for non-commercial purposes and otherwise in accordance with these Terms of Use.

3.7 You agree that you will not share your username, password or other account details with a third party or otherwise provide a third party with access to your User account.

3.8 You agree to notify Health Canada of any possible unauthorized uses of your User Account.

3.9 You agree to provide Health Canada with all the information that Health Canada may request from time to time to confirm your identity, role or activities, in accordance with the conditions, including deadlines, set out in any such request.

3.9 If you provide false information in your request for a User Account or breach any of these Terms of Use, your right to further access to Clinical Information and use of Clinical Information will be revoked.

4. Amendments

4.1 Health Canada reserves the right to modify these Terms of Use at any time without advanced notice. Such modification(s) shall be effective immediately upon notice of the change or on such other date as it may be specified in the notice.

4.2 Your acceptance of the modified Terms of Use will indicate your agreement to the modifications which will extend to your use, after the date of acceptance, of Clinical Information previously accessed, downloaded, saved or printed by you.

5. Limitation of liability and Indemnification

5.1 Health Canada accepts no liability for your compliance with these Terms of Use or otherwise arising in any manner whatsoever from your acts, omission or conduct in the use of Clinical Information.

5.2 You agree to indemnify and hold harmless Health Canada, Her Majesty the Queen in Right of Canada, Her Assigns and Successors, officers, employees, or agents, from and against all claims, actions, injury, losses, expenses, damages, and costs, including reasonable attorney's fees, resulting from any violation of these Terms of Use or other arising in any manner whatsoever from your acts, omission or conduct in the use of Clinical Information.

6. Disclaimer

Without prejudice to any of the obligations of the Manufacturer under the laws of Canada, Clinical Information is provided on an "AS IS" and "AS AVAILABLE" basis. By accessing and using Clinical Information, you agree that said access and use is entirely at your own risk. Health Canada and the Manufacturer exclude all representations, warranties, obligations and liabilities in relation to Clinical Information as made accessible to you to the maximum extent permitted by law. Neither Health Canada nor the Manufacturer are liable for any errors or omissions in Clinical Information as made accessible to you and shall not be liable for any loss, injury or damage of any kind caused by its use.

7. Severability

If any provision of these Terms of Use is declared by an arbitrator or a court of competent jurisdiction to be invalid, illegal or unenforceable, such provision shall be severed from these Terms of Use and all other terms shall remain in full force and effect.

8. Governing Laws and Jurisdiction

All matters relating to your access to, or use of, the Clinical Information shall be governed by the laws of the Province of Ontario, exclusive of their conflicts-of-laws principles, and the laws of Canada. The courts of the Province of Ontario shall have non-exclusive jurisdiction to settle any dispute or claim arising out of or in connection with these Terms of Use or their subject matter or formation (including non-contractual disputes or claims).