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Guidance Document Part C, Division 5 of the *Food and Drug Regulations* “Drugs for Clinical Trials Involving Human Subjects”



GUI-0100

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9 For more information, please contact:

10 Health Canada
11 Address Locator 0900C2, Ottawa, ON K1A 0K9
12 Tel.: 613-957-2991
13 Toll free: 1-866-225-0709
14 Fax: 613-941-5366
15 TTY: 1-800-465-7735
16 Email: publications@hc-sc.gc.ca

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Disclaimer

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This document does not constitute part of the *Food and Drugs Act* (the Act) or its regulations and in the event of any inconsistency or conflict between the Act or regulations and this document, the Act or the regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the regulations and the applicable administrative policies.

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89 About this document

90 1. Purpose

91 This guide will help anyone who is involved in the conduct of clinical trials of drugs in humans to
92 understand and comply with Part C, Division 5 of the [Food and Drug Regulations](#) (the
93 Regulations).

94 This guidance document will be a tool that will allow Health Canada to promote and enforce
95 stakeholder compliance with Part C, Division 5, and promote consistency and quality in the
96 conduct of compliance activities.

97 2. Scope

98 These guidelines apply to you if you are a party involved in the conduct of clinical trials of drugs
99 in human subjects in Canada.



Interested parties may include:

- sponsor
- qualified investigator (QI)
- contract research organization (CRO)
- site management organization (SMO)

100 The Regulations clearly establish that the sponsor has the overall responsibility of conducting a
101 clinical trial involving drugs in human subjects. In Canada, a sponsor may transfer responsibility
102 for any or all trial-related duties to other parties. However, sponsors remain accountable in all
103 respects for the trial data's quality and integrity.

104 This guide covers the following clinical trials of drugs conducted in humans in Canada:

- 105 • Phase I to IV
- 106 • commercial or academic
- 107 • ongoing or completed
- 108 • clinical trials involving pharmaceuticals, biologics, gene therapies, blood products,
109 vaccines and radiopharmaceuticals for human use

110 This document does **not** currently apply to:

- 111 • clinical trials involving medical devices
- 112 • clinical trials involving natural health products (NHPs)
- 113 • observational studies, which do not include drug intervention

114 3. Introduction

115 The legislative authority for the *Food and Drug Regulations*, Part C, Division 5 “Drugs for Clinical
116 Trials Involving Human Subjects” is the *Food and Drugs Act* (the Act). The Regulations came into
117 force on September 1, 2001 and set out the federal requirements for the sale and importation of
118 drugs used in human clinical trials in Canada, and include the requirement to comply with good
119 clinical practices (GCP). However, Health Canada does not have jurisdiction over the professional
120 standards regarding practice of medicine, which are enforced by the provincial colleges of
121 physicians.

122 Part C, Division 5 of the Regulations is relatively non-prescriptive in terms of specific
123 requirements, to give flexibility to follow international GCP standards in order to satisfy the
124 requirements of the Regulations.

125 In May 1997, Health Canada adopted the International Conference on Harmonization (ICH)
126 Guidance E6(R1): Good Clinical Practice Consolidated Guideline (ICH E6). GCP is an international
127 ethical and scientific quality standard for designing, conducting, recording and reporting trials
128 that involve the participation of human subjects. Adherence to this guideline provides public
129 assurance that the rights, safety and well-being of trial subjects are protected and that the
130 clinical trial data are credible.

131 Since the finalisation of the ICH GCP Guideline in 1996, the scale, complexity, and cost of clinical
132 trials have increased. Evolutions in technology and risk management processes offer new
133 opportunities to focus on relevant activities resulting in increasing the rigour of clinical trials. ICH
134 E6(R1) was amended in November 2016 to ICH E6(R2) to:

- 135 • encourage sponsors to implement improved oversight and management of clinical
136 trials, while continuing to ensure protection of human subjects participating in trials and
137 clinical trial data integrity
- 138 • update standards regarding electronic records and essential documents intended to
139 increase clinical trial quality and efficiency.

140 The [*Integrated Addendum to ICH E6\(R1\): Guideline for Good Clinical Practice E6\(R2\)*](#) provides a
141 unified standard on GCP. ICH E6(R2) was fully adopted by Health Canada as of **April 1, 2018**.

142 It is important to note that local regulations in ICH regions can exceed the requirements of ICH
143 E6. As such, ICH guidelines should be used in conjunction with the relevant federal regulations,
144 guidelines and any other regional, institutional or local requirements.

145 Health Canada has recognized a need to provide guidance in the interpretation of the
146 Regulations, and specifically in terms of its relationship to ICH E6. This document is intended to
147 fulfill this need, as well as to provide additional guidance where is necessary or when ICH E6
148 does not apply.

149 Compliance with the Regulations and ICH E6(R2) will further promote the protection of subjects
150 as well as ensure the integrity of the data generated by the trial, whether it is for use in
151 academic publications, or to support new or supplementary drug submissions.

152 For detailed guidance on the clinical trial applications (CTA) and amendments, you should refer
153 to [*Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*](#).

154 4. Guidance for implementation

155 Interpretive guidance to Part C, Division 5 of the Regulations is provided in this document. In
156 interpreting the Regulations, ICH E6 should be used in conjunction with the Act, the Regulations,
157 and any relevant policies and guidelines.

158 In this guideline, where guidance to a specific regulation can be found in ICH E6, the section in
159 ICH E6 is noted. If necessary, or where ICH E6 is not applicable, additional guidance is provided
160 or other guidance documents are referenced.

161 At all times, where the Regulations exceeds these guidelines or those in ICH E6, the Regulations
162 take precedence.

163 5. Regulations and Interpretations

164 For each section below, the exact text from Part C, Division 5 of the [*Food and Drug Regulations*](#) is
165 provided first. This is followed by Health Canada's interpretation (what you need to do to be
166 compliant).

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5.1 Interpretation

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C.05.001



The definitions outlined in this section are available in Appendix A.

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5.2 Application

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C.05.002



- (1) Subject to subsection (2), this Division applies to the sale or importation of drugs to be used for the purposes of clinical trials involving human subjects.
- (2) Except for paragraph C.05.003(a), subsections C.05.006(2) and (3), paragraphs C.05.010(a) to (i), section C.05.011, subsections C.05.012(1) and (2), paragraphs C.05.012(3)(a) to (d) and (f) to (h), subsection C.05.012(4) and sections C.05.013, C.05.016 and C.05.017, this Division does not apply to the sale or importation of a drug for the purposes of a clinical trial authorized under subsection C.05.006(2).

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Interpretation

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The Regulations apply to the sale and importation of drugs to be used in clinical trials involving humans that are conducted in Canada. As per section C.05.002, no person can sell or import a drug for the purposes of a clinical trial involving humans **unless authorized** (refer to section 5.6 Authorization). However, Phase IV clinical trials are exempt from this Division, with the exception of the sections of the Regulations set out in subsection C.05.002(2).



Phase IV clinical trials include those trials that involve the use of:

- a new drug that has been issued a notice of compliance (NOC) under subsection C.08.004(1) of the Regulations, if the clinical trial is in respect of a purpose or condition of use for which the NOC was issued; or
- a drug, other than a new drug, that has been assigned a drug

identification number (DIN) under subsection C.01.014.2(1) of the Regulations, if the clinical trial is in respect of a use or purpose for which the DIN was assigned.

Phase IV clinical trials are performed after the drug has been authorized by Health Canada for the market, and within the parameters of the authorized NOC or DIN application.

178 In accordance with subsection C.05.002(2), the sponsor of a Phase IV clinical trial does not have
179 to file an application for importation and/or sale of the study drug. However, the following does
180 apply:

- 181 • the person selling and/or importing the trial drug must be authorized under Part C,
182 Division 5 [C.05.003(a)]
- 183 • a new drug has been issued a NOC [C.05.006(2)(a)] or a drug, other than a new drug,
184 has been assigned a DIN [C.05.006(2)(b)], and the clinical trial is in respect of a purpose
185 or condition of use for which the NOC was issued / DIN was assigned
- 186 • the sponsor cannot sell or import a trial drug during a period of suspension or
187 cancellation of the trial [C.05.006(3)]
- 188 • the trial has to be conducted according to GCP [C.05.010 (a) to (i)]
- 189 • the drug must be labeled according to the Regulations (C.05.011)
- 190 • the sponsor must comply with records requirements referenced in this Division
191 [C.05.012, with the exception of C.05.012(3)(e)]
- 192 • the criteria for submission of information and samples to Health Canada (C.05.013)
- 193 • the criteria for suspension and cancellation of a trial (C.05.016 and C.05.017)

194 Where a clinical trial is conducted on a marketed drug in order to test the safety and/or efficacy
195 of the product under new conditions of use (that is, outside the conditions for which it has
196 received a DIN or NOC), the sponsor must file an application for authorization to conduct the
197 clinical trial in Canada. Health Canada's Therapeutic Products Directorate (TPD) or Biologics and
198 Genetic Therapies Directorate (BGTD) should be consulted for further clarification.

199 For requirements regarding the reporting of adverse drug reactions (ADRs) for Phase IV clinical
200 trial drugs, please see section 5.14 of this document.

201 **Inspection of Phase IV Clinical Trials**

202 In general, Health Canada does not focus its inspection activities on Phase IV trials. However,
203 because Phase IV studies are to be conducted in accordance with GCP, which includes good

204 manufacturing practices (GMP) requirements, they can be subject to inspection at any time
205 using a risk-based approach.

206 **Observational Studies**

207 Observational studies, which do not include drug intervention, are not subject to the [Food and](#)
208 [Drugs Act](#) and its associated regulations. As such, they do not require authorization from Health
209 Canada.



The Clinical Trial Compliance Program of Health Canada does not make inspection observations under this section of the Regulations.

210 Please refer to the [Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications](#) for
211 detailed guidance on the application process. Relevant Health Canada's Directorate (TPD or
212 BGTD) should be consulted for further clarification.

213 **5.3 Prohibition**

214 **C.05.003**



Despite sections C.01.014, C.08.002, C.08.002.02 and C.08.003, no person shall sell or import a drug for the purposes of a clinical trial unless

- (a) the person is authorized under this Division;
- (b) the person complies with this Division and sections C.01.015, C.01.036, C.01.037 to C.01.040, C.01.040.2, C.01.064 to C.01.067, C.01.070, C.01.131, C.01.133 to C.01.136, and C.01.435; and
- (c) if the drug is to be imported, the person has a representative in Canada who is responsible for the sale of the drug.

215 **Interpretation**

216 Drugs that are sold and/or imported for the purpose of a clinical trial do not have to meet the
217 regulatory requirements for a DIN (C.01.014) or a NOC (C.08.002 and C.08.003). However, the
218 use of these drugs in a clinical trial (other than Phase IV) must be authorized through the
219 submission of a clinical trial application (CTA) to Health Canada, including for each amendment.

220 In addition to Part C, Division 5 of the Regulations, as noted in paragraph C.05.003(b), the
221 following requirements apply to any drug sold for a clinical trial whether authorized under
222 C.05.006(1) or C.05.006(2):

- 223 • disintegration times for drugs in tablet form (C.01.015)
- 224 • drugs containing phenacetin in combination with salicylic acid, drugs containing
225 mercury and other ingredients, and drugs described in Schedule C or D to the Act
226 (C.01.036)
- 227 • pediatric doses of salicylic acid, acetaminophen and their derivatives and other
228 ingredients (C.01.037 to C.01.039)
- 229 • drugs containing chloroform or arsenic (C.01.040)
- 230 • use of coloring agents in drug products (C.01.040.2)
- 231 • drugs prepared for use in the eye (C.01.064, C.01.065)
- 232 • drugs prepared for use through injection or IV (C.01.066, C.01.067)
- 233 • instructions for the sale of hypodermic tablets (C.01.070)
- 234 • aminopyrine or dipyron and appropriate warning labels (C.01.131, C.01.133)
- 235 • coated tablets containing potassium salts (C.01.134 to C.01.136), and
- 236 • distribution of promotional material about chloramphenicol and warning statements
237 (C.01.435)



Marketed drugs used in Phase IV clinical trials are subject to the same requirements.

238 **Importation of Clinical Trial Drugs**

239 The sponsor is the regulated party to whom the authorization to sell and/or import a clinical trial
240 drug is issued. A sponsor who is not based in Canada must have a representative in Canada who
241 is responsible for the import and sale of the drug in Canada and must be able to demonstrate
242 compliance to the applicable regulatory requirements. Sponsors must be diligent in their
243 dealings with contracted third parties, including contract research organizations (CROs), to
244 ensure that sponsor's obligations are met.

245 When third parties have been delegated some of a sponsor's responsibilities, written
246 agreements should be in place to clearly set out the division of responsibilities, for example
247 temperature monitoring. It should be noted that the Regulations do not differentiate between a

248 commercial and a non-commercial sponsor (for example Sponsor-Investigator) and as such, the
249 same requirements apply.

250 Drugs may be shipped directly from a foreign provider (manufacturer, distributor, etc.) to a
251 clinical trial site in Canada provided that:

252 1. in accordance with sections C.05.006 or C.05.008 of the Regulations, a No Objection
253 Letter (NOL) has been issued by Health Canada authorizing the importation of the
254 clinical trial material. No clinical trial drugs should be imported prior to the NOL
255 issuance and the NOL should accompany the package at the time of the importation.

256 Furthermore, [Clinical Trial Site Information \(CTSI\) forms](#) for each Canadian site
257 conducting the clinical trial are to be submitted to Health Canada prior to the start of
258 the study. Each party, including individual Canadian clinical trial sites, importing drugs
259 directly should also be identified on Appendix 1 of the Drug Submission Application
260 Form ([HC/SC 3011 form](#)) (submitted with application if known at the time or prior to
261 importation at the site). Appendix 1 may be replicated as many times as necessary to
262 capture all sites;

263 2. systems are in place to monitor the transportation and storage conditions from the
264 foreign source to the various clinical trial sites across Canada;

265 3. there is accountability of the imported drugs used in clinical trials and distributed to
266 various clinical trial sites located in Canada, including the disposition of drugs returned
267 from the clinical trial sites;

268 4. a written agreement is in place between the sponsor and the qualified investigator (QI)
269 describing their specific responsibilities, and this agreement is available at the clinical
270 trial site; and

271 5. there is evidence that the drugs used in clinical trials conducted in Canada meet the
272 GMP requirements. For example, an adequate evidence of GMP compliance would
273 include:

- 274 • certificates of manufacture and certificates of analysis (CoA or batch
275 certificates) for the lots of clinical trial material imported into Canada
- 276 • evidence of approved lot release by a qualified individual.

277 For additional information, refer to the [Guidance Document – Annex 13 to the Current](#)
278 [Edition of the GMP Guidelines: Drugs Used in Clinical Trials \(GUI-0036\)](#).

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Please refer to the [Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications](#) for detailed guidance on importation of clinical trial drugs, including comparator, concomitant and rescue medications using Summary of Additional Drugs Form (SOAD).



Example of observation typically cited under this section of the Regulations includes:

- The drug was sold or imported for use in a clinical trial without getting authorization from Health Canada.

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5.4 General

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C.05.004



Despite these Regulations, a sponsor may submit an application under this Division to sell or import a drug for the purposes of a clinical trial that contains a substance the sale of which is prohibited by these Regulations, if the sponsor establishes, on the basis of scientific information, that the inclusion of the substance in the drug may result in a therapeutic benefit for a human being.

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Interpretation

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If a drug or substance is prohibited under the Regulations (refer to section C.05.003), a sponsor may submit an application to sell and/or import the drug for use in a clinical trial if the sponsor is able to justify that its use may result in a therapeutic benefit to human subjects. Justification should include scientific evidence that the therapeutic benefits outweigh the risks for that particular drug or substance.



The Clinical Trial Compliance Program of Health Canada does not make inspection observations under this section of the Regulations.

5.5 Application for Authorization

C.05.005



An application by a sponsor for authorization to sell or import a drug for the purposes of a clinical trial under this Division shall be submitted to the Minister, signed and dated by the sponsor's senior medical or scientific officer in Canada and senior executive officer and shall contain the following information and documents:

- (a) a copy of the protocol for the clinical trial;
- (b) a copy of the statement, as it will be set out in each informed consent form, that states the risks and anticipated benefits arising to the health of clinical trial subjects as a result of their participation in the clinical trial;
- (c) a clinical trial attestation, signed and dated by the sponsor's senior medical or scientific officer in Canada and senior executive officer, containing
 - (i) the title of the protocol and the clinical trial number,
 - (ii) the brand name, the chemical name or the code for the drug,
 - (iii) the therapeutic and pharmacological classifications of the drug,
 - (iv) the medicinal ingredients of the drug,
 - (v) the non-medicinal ingredients of the drug,
 - (vi) the dosage form of the drug,
 - (vii) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor,
 - (viii) if the drug is to be imported, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor's representative in Canada who is responsible for the sale of the drug,
 - (ix) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile

- number and electronic mail address of the qualified investigator, if known at the time of submitting the application,
- (x) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the research ethics board that approved the protocol referred to in paragraph (a) and approved an informed consent form containing the statement referred to in paragraph (b), if known at the time of submitting the application, and
 - (xi) a statement
 - (A) that the clinical trial will be conducted in accordance with good clinical practices and these Regulations, and
 - (B) that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading;
- (d) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of any research ethics board that has previously refused to approve the protocol referred to in paragraph (a), its reasons for doing so and the date on which the refusal was given, if known at the time of submitting the application;
- (e) an investigator's brochure that contains the following information, namely,
- (i) the physical, chemical and pharmaceutical properties of the drug,
 - (ii) the pharmacological aspects of the drug, including its metabolites in all animal species tested,
 - (iii) the pharmacokinetics of the drug and the drug metabolism, including the biological transformation of the drug in all animal species tested,
 - (iv) any toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study in respect of the drug,
 - (v) any results of carcinogenicity studies in any animal

- species tested in respect of the drug,
- (vi) any results of clinical pharmacokinetic studies of the drug,
 - (vii) any information regarding drug safety, pharmacodynamics, efficacy and dose responses of the drug that were obtained from previous clinical trials in humans, and
 - (viii) if the drug is a radiopharmaceutical as defined in section C.03.201, information regarding directions for preparing the radiopharmaceutical, the radiation dosimetry in respect of the prepared radiopharmaceutical and a statement of the storage requirements for the prepared radiopharmaceutical;
- (f) if the drug contains a human-sourced excipient, including any used in the placebo,
- (i) information that indicates the human-sourced excipient has been assigned a drug identification number under subsection C.01.014.2(1) or, in the case of a new drug, issued a notice of compliance under subsection C.08.004(1), as the case may be, or
 - (ii) in any other case, sufficient information to support the identity, purity, potency, stability and safety of the human-sourced excipient;
- (g) if the drug has not been assigned a drug identification number under subsection C.01.014.2(1) or, in the case of a new drug, a notice of compliance has not been issued under section C.08.004 or C.08.004.01, the chemistry and manufacturing information in respect of the drug, including its site of manufacture; and
- (h) the proposed date for the commencement of the clinical trial at each clinical trial site, if known at the time of submitting the application.

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Interpretation

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Health Canada's Therapeutic Products Directorate (TPD) and Biologics and Genetic Therapies Directorate (BGTD) are responsible for reviewing the applications for authorization to sell or import drugs for the purposes of conducting clinical trials in Canada.

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Please refer to the [Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications](#) for detailed guidance on the application process. Additional guidance can be found in the relevant sections of ICH E6, including sections 6 and 7. Relevant Health Canada's Directorate (TPD or BGTD) should be consulted for further clarification.

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5.6 Authorization

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C.05.006



- (1) Subject to subsection (3), a sponsor may sell or import a drug, other than a drug described in subsection (2), for the purposes of a clinical trial if
 - (a) the sponsor has submitted to the Minister an application in accordance with section C.05.005;
 - (b) the Minister does not, within 30 days after the date of receipt of the application, send to the sponsor a notice in respect of the drug indicating that the sponsor may not sell or import the drug for any of the following reasons:
 - (i) that the information and documents in respect of the application
 - (A) were not provided in accordance with these Regulations, or
 - (B) are insufficient to enable the Minister to assess the safety and risks of the drug or the clinical trial, or
 - (ii) that based on an assessment of the application, an assessment of any information submitted under section C.05.009 or a review of any other information, the Minister has reasonable grounds to believe that
 - (A) the use of the drug for the purposes of

- the clinical trial endangers the health of a clinical trial subject or other person,
 - (B) the clinical trial is contrary to the best interests of a clinical trial subject, or
 - (C) the objectives of the clinical trial will not be achieved;
 - (c) for each clinical trial site, the sponsor has obtained the approval of the research ethics board in respect of the protocol referred to in paragraph C.05.005(a) and in respect of an informed consent form that contains the statement referred to in paragraph C.05.005(b); and
 - (d) before the sale or importation of the drug at a clinical trial site, the sponsor submits to the Minister the information referred to in subparagraphs C.05.005(c)(ix) and (x) and paragraphs C.05.005(d) and (h), if it was not submitted in respect of that clinical trial site at the time of submitting the application.
- (2) Subject to subsection (3), a sponsor may sell or import a drug for the purposes of a clinical trial in respect of
 - (a) a new drug that has been issued a notice of compliance under subsection C.08.004(1), if the clinical trial is in respect of a purpose or condition of use for which the notice of compliance was issued; or
 - (b) a drug, other than a new drug, that has been assigned a drug identification number under subsection C.01.014.2(1), if the clinical trial is in respect of a use or purpose for which the drug identification number was assigned.
- (3) A sponsor may not sell or import a drug for the purposes of a clinical trial
 - (a) during the period of any suspension made under section C.05.016 or C.05.017; or
 - (b) after a cancellation made under section C.05.016 or C.05.017.

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Interpretation

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In order to sell or import a drug for the purpose of a clinical trial, the sale or importation must be authorized by Health Canada through the submission of a CTA and the subsequent issuance of a

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305 NOL for the trial and all amendments, prior to the initiation of the trial or the implementation of
306 the amendment. Authorization is contingent on the following:

- 307 1. a CTA must be submitted in accordance with section C.05.005 of these Regulations (see
308 also ICH E6, 5.10)
- 309 2. the sponsor should expect, by day 30 of the acceptance of the application into review, a
310 notice (a NOL) in respect of the drug, indicating that the sponsor may sell or import the
311 drug for the purposes of a clinical trial. However, due to the 30-day default period from
312 the date of receipt of a complete application, the sponsor may proceed with the clinical
313 trial after this period without receiving an NOL.



Reasons why sponsor may get a **Not Satisfactory Notice (NSN)** are as follows:

- the information and documents supplied were not provided in accordance with the Regulations
- insufficient information was provided to enable Health Canada to assess the safety and risks of the drug or the clinical trial
- based on the assessment of the application or additional information or samples provided on request (C.05.009), Health Canada has reasons to believe the use of the drug:
 - may endanger the health of clinical trial subjects or other persons
 - the clinical trial is not in the best interest of clinical trial subjects
 - the objectives of the clinical trial will not be achieved

314 3. the sponsor has received, for each clinical trial site, approval from a Research Ethics
315 Board (REB), in respect of the protocol and informed consent referred to in C.05.005(a)
316 and (b)

317 4. before the sale or importation of the drug to a clinical trial site, the sponsor has
318 submitted the following to Health Canada, if it has not already been submitted at the
319 time of application:

- 320 a. name, address, telephone number, fax number, and electronic mail address of
321 the QI for each clinical trial site [C.05.005(c)(ix)]
- 322 b. name, address, telephone number, fax number and electronic mail address of
323 the REB that approved the protocol and informed consent at each clinical trial
324 site [C.05.005(c)(x)]

- 325 c. name, address, telephone number, fax number and electronic mail address of
326 any REB that has previously refused to approve the protocol, including its
327 reason for doing so and the date on which the refusal was given [C.05.005(d)]
- 328 d. the proposed date for the commencement of the clinical trial at each clinical
329 trial site [C.05.005 (h)]

330 A sponsor does not have to submit an application for authorization to sell or import a drug used
331 in a Phase IV clinical trial. Refer to section C.05.002 (Application and its Interpretation), for a list
332 of conditions under which a drug can be used in a Phase IV clinical trial.

333 A sponsor may also not sell or import a drug for the purpose of any clinical trial, including Phase
334 IV clinical trials, if the trial has been suspended or cancelled under either C.05.016 or C.05.017.



Examples of observations typically cited under this section of the Regulations include:

- The drug was sold or imported for use in a clinical trial without receiving authorization from Health Canada.
- The drug was sold or imported for use in a clinical trial before the clinical trial site information was submitted to Health Canada.

335 5.7 Notification

336 C.05.007



If the sale or importation of a drug is authorized under this Division, the sponsor may make one or more of the following changes if the sponsor notifies the Minister in writing within 15 days after the date of the change:

- (a) a change to the chemistry and manufacturing information that does not affect the quality or safety of the drug, other than a change for which an amendment is required by section C.05.008; and
- (b) a change to the protocol that does not alter the risk to the health of a clinical trial subject, other than a change for which an amendment is required by section C.05.008.

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Interpretation

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If a sponsor receives an authorization to sell or import a drug, through the submission of a CTA

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and subsequent receipt of the NOL, the sponsor may make one or more of the following

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changes, but the sponsor shall notify Health Canada in writing **within 15 calendar days after the**

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date of the change:

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- a. a change to the chemistry and manufacturing information that do not affect the quality or safety of the drug

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- b. a change to the protocol that does not alter the risk to the health of a clinical trial subject.

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Examples of notifications may include:

- change of sponsor's address or contact name
- changes made to enable the consent to be read at the appropriate education level
- addition of an observational sub-study to the protocol or other administrative changes

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Further to the above, section 5.13.5 of ICH E6 states that:

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“If significant formulation changes are made in the investigational or comparator product(s)

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during the course of clinical development, the results of any additional studies of the formulated

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product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these

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changes would significantly alter the pharmacokinetic profile of the product should be available

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prior to the use of the new formulation in clinical trials”.

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The impact assessment of this change may require submission of an amendment request to

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Health Canada instead of a notification. If the change meets the requirements of an amendment

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to the protocol as described in section C.05.008 (below), the sponsor must submit a Clinical trial

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application-Amendment (CTA-A).

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Note that Health Canada’s [Guidance Document for Clinical Trial Sponsors: Clinical Trial](#)

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[Applications](#) provides numerous examples of notifications. Relevant Health Canada’s Directorate

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(TPD or BGTD) should be consulted for further clarification.



Examples of observations typically cited under this section of the Regulations include:

- The sponsor did not notify Health Canada within 15 days of making a change to the chemistry and manufacturing information of the drug that does not affect the quality or safety of the drug.
- The sponsor did not notify Health Canada within 15 days of making a change to the protocol that does not alter the risk to the health of a clinical trial participant.

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5.8 Amendment

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C.05.008



- (1) Subject to subsections (4) and (5), when the sale or importation of a drug is authorized under this Division and the sponsor proposes to make an amendment referred to in subsection (2), the sponsor may sell or import the drug for the purposes of the clinical trial in accordance with the amended authorization, if the following conditions are met:
 - (a) the sponsor has submitted to the Minister an application for amendment in accordance with subsection (3);
 - (b) the Minister does not, within 30 days after the date of receipt of the application for amendment, send to the sponsor a notice in respect of the drug indicating that the sponsor may not sell or import the drug in accordance with the amendment for any of the following reasons, namely,
 - (i) that the information and documents in respect of the application for amendment
 - (A) were not provided in accordance with these Regulations, or
 - (B) are insufficient to enable the Minister to assess the safety and risks of the drug or the clinical trial, or
 - (ii) that based on an assessment of the application for amendment, an assessment of any information submitted under section C.05.009 or a review of any other information, the Minister has reasonable

grounds to believe that

- (A) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person,
- (B) the clinical trial is contrary to the best interests of a clinical trial subject, or
- (C) the objectives of the clinical trial will not be achieved;

- (c) before the sale or importation of the drug, the sponsor submits to the Minister
 - (i) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the research ethics board that approved any amended protocol submitted under paragraph (3)(a) or approved any amended statement submitted under paragraph (3)(c), and
 - (ii) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of any research ethics board that has previously refused to approve any amendment to the protocol, its reasons for doing so and the date on which the refusal was given;
- (d) before the sale or importation of the drug, the sponsor maintains records concerning
 - (i) the information referred to in paragraph C.05.005(h), and
 - (ii) the information referred to in subparagraph C.05.005(c)(ix), if any of that information has changed since it was submitted;
- (e) before the sale or importation of the drug in accordance with the amended authorization, the sponsor ceases to sell or import the drug in accordance with the existing authorization; and
- (f) the sponsor conducts the clinical trial in accordance with the amended authorization.

(2) For the purposes of subsection (1), amendments are

- (a) amendments to the protocol that affect the selection,

- monitoring or dismissal of a clinical trial subject;
 - (b) amendments to the protocol that affect the evaluation of the clinical efficacy of the drug;
 - (c) amendments to the protocol that alter the risk to the health of a clinical trial subject;
 - (d) amendments to the protocol that affect the safety evaluation of the drug;
 - (e) amendments to the protocol that extend the duration of the clinical trial; and
 - (f) amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug.
- (3) The application for amendment referred to in subsection (1) shall contain a reference to the application submitted under section C.05.005 and shall contain the following documents and information:
- (a) if the application is in respect of an amendment referred to in any of paragraphs (2)(a) to (e), a copy of the amended protocol that indicates the amendment, a copy of the protocol submitted under paragraph C.05.005(a), and the rationale for the amendment;
 - (b) if the application is in respect of an amendment referred to in paragraph (2)(e), a copy of the amended investigator's brochure or an addendum to the investigator's brochure that indicates the new information, including supporting toxicological studies and clinical trial safety data;
 - (c) if the application is in respect of an amendment referred to in any of paragraphs (2)(a) to (f) and, as a result of that amendment, it is necessary to amend the statement referred to in paragraph C.05.005(b), a copy of the amended statement that indicates the new information; and
 - (d) if the application is in respect of an amendment referred to in paragraph (2)(f), a copy of the amended chemistry and manufacturing information that indicates the amendment, and the rationale for that amendment.
- (4) If the sponsor is required to immediately make one or more of the amendments referred to in subsection (2) because the clinical trial or the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person, the sponsor may immediately make the amendment and shall provide the Minister with the information referred to in subsection (3) within 15 days after the

date of the amendment.

(5) A sponsor may not sell or import a drug for the purposes of a clinical trial

(a) during the period of any suspension made under section C.05.016 or C.05.017; or

(b) after a cancellation made under section C.05.016 or C.05.017.

361 Interpretation

362 Clinical trial application-Amendments (CTA-As) are applications in which a sponsor submits
363 information to support changes to a previously authorized clinical trial. They are required to be
364 submitted when changes are made either to the study drug or the protocol that could affect
365 either the quality or safety of the study drug, or the risk to clinical trial subjects. Amendments
366 must be authorized by Health Canada prior to implementing the changes.

367 If a sponsor needs to make an immediate amendment because the clinical trial or use of the
368 drug endangers the trial subjects or other persons, the sponsor may make the amendment
369 without prior review by Health Canada. However, the sponsor must notify Health Canada of the
370 change, and submit a CTA-A within 15 calendar days after the date of implementation of the
371 amendment. Health Canada will issue a new NOL after the 30-day review period.

372 Prior to implementation of a CTA-A, sponsors are required to complete and submit a [CTSI form](#)
373 for each clinical trial site [C.05.006(1)(d)/C.05.008(1)(c)].

374 In addition, a qualified investigator should obtain documented approval/favourable opinion from
375 the REB prior to implementation (ICH E6, 4.5.2).

376 ICH E6 section 4.5.4 states that an investigator may deviate from the protocol without prior
377 approval if it is necessary to eliminate an immediate hazard to a trial subject. As soon as
378 possible, however, the deviation or change, and the rationale for the change, should be
379 submitted to:

- 380 • the REB for review and approval/favourable opinion
- 381 • the sponsor for agreement, and
- 382 • the regulatory authority (i.e. Health Canada)

383 Note that Health Canada's [Guidance Document for Clinical Trial Sponsors: Clinical Trial](#)
384 [Applications](#) provides numerous examples of amendments. Relevant Health Canada's
385 Directorate (TPD or BGTD) should be consulted for further clarification.



Examples of observations typically cited under this section of the Regulations include:

- The sponsor did not submit a CTA-A after a change was made to the elements in the design of the study protocol or to the composition/formulation of the study drug that met the criteria for an amendment.
- The sponsor changed the protocol (not for the purpose of mitigating risk) before receiving approval from Health Canada and/or the REB.
- The sponsor did not notify Health Canada within 15 days of making an immediate amendment where the clinical trial or the use of the study drug endangered the health of a clinical trial participant or other person.

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5.9 Additional Information and Samples

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C.05.009



If the information and documents submitted in respect of an application under section C.05.005 or an application for amendment under section C.05.008 are insufficient to enable the Minister to determine whether any of the reasons referred to in paragraph C.05.006(1)(b) or C.05.008(1)(b) exist, the Minister may require the sponsor to submit, within two days after receipt of the request, samples of the drug or additional information relevant to the drug or the clinical trial that are necessary to make the determination.

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Interpretation

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Health Canada may require a sponsor to submit, **within two (2) calendar days after receipt of the request**, samples of the drug or additional information relevant to the drug or the clinical trial that are necessary to make a determination for issuance of the NOL.

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Request for Clarification may be required if the information and documents submitted in an application for authorization, or an application for an amendment, were insufficient in either of the following respects (referred to in C.05.006(1)(b) and C.05.008(1)(b) of the Regulations):

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- the information and documents in respect of the application were either not provided in accordance with these Regulations or were insufficient to enable Health Canada to assess the safety and risks of the drug or the clinical trial, or

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- based on an assessment of the application or any information or drug samples submitted as additional information Health Canada has reasonable grounds to believe that either:

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- the use of the drug for the purpose of the clinical trial endangers the health of a clinical trial subject or other person,

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- the clinical trial is contrary to the best interests of a clinical trial subject; or

404

- the objectives of the clinical trial will not be achieved.



The Clinical Trial Compliance Program of Health Canada does not make inspection observations under this section of the Regulations.

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5.10 Good Clinical Practices

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C.05.010



Every sponsor shall ensure that a clinical trial is conducted in accordance with good clinical practices and, without limiting the generality of the foregoing, shall ensure that

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C.05.010(a)



- (a) the clinical trial is scientifically sound and clearly described in a protocol:

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Interpretation

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Compliance with this paragraph is determined at the time of review by the appropriate Directorate (TPD or BGTD) of Health Canada.

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C.05.010(b)



(b) the clinical trial is conducted, and the drug is used, in accordance with the protocol and this Division;

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Interpretation

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The sponsor must ensure that the clinical trial is conducted in accordance with the requirement of the protocol which has been approved by both Health Canada and REB. The site must have a system in place to identify, document, assess and report all the protocol deviations to the sponsor and REB in accordance with the sponsor's and REB's requirements. It is important to assess the protocol deviations for impact analysis and root cause analysis. The sponsor needs to review the reported protocol deviations and either approve or reject the deviation in accordance with their internal procedures.

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The clinical trial protocol is a study plan. It is designed to ensure that the objectives of the study can be met. In addition, the study protocol standardizes a clinical trial to allow for the external validation and for the generalization of the clinical trial results.

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Clinical trials should be conducted in accordance with the ethical principles.



Examples of observations typically cited under this section of the Regulations include:

- The clinical trial was not conducted according to protocol.
- The clinical trial drug was not used as prescribed in the protocol.

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C.05.010(c)



(c) systems and procedures that assure the quality of every aspect of the clinical trial are implemented;

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Interpretation

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The sponsor, whether commercial or academic, is responsible for the establishment of a quality system consisting of documented procedures (standard operating procedures

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428 (SOPs), protocol procedures, etc.) in order to assure the quality of every aspect of a
429 clinical trial, in accordance with the Regulations and ICH E6. It is the responsibility of the
430 sponsor to implement a system to manage the quality throughout all stages of the trial
431 process and at all sites. Depending on situations and circumstances, various approaches
432 may be taken.

433 Sponsors should focus on trial activities essential to the reliability of the results and
434 ensuring human subject protection. Quality management includes the design of efficient
435 clinical trial protocols and tools and procedures for data collection and processing, as
436 well as the collection of information that is essential to decision making (ICH E6, 5.0).

437
438 The methods used to assure and control the quality of the trial should be proportionate
439 to the risks inherent in the trial and the importance of the information collected. The
440 sponsor should ensure that all aspects of the trial are operationally feasible and should
441 avoid unnecessary complexity, procedures, and data collection. Protocols, case report
442 forms (CRFs), and other operational documents should be clear, concise, and consistent
443 (ICH E6, 5.0).



The quality management system should use a risk-based approach as described in sections 5.0.1 to 5.0.7 of ICH E6. This includes:

- identification of critical processes and data
- risks associated with them (at both the system and clinical level)
- evaluation of the identified risks
- risk control
- risk communication
- risk review*
- risk reporting

444 * As a key component to risk-based quality management systems, Health Canada expects
445 that sponsors will be able to demonstrate that risk control measures are periodically
446 reviewed and remain effective and relevant, taking into account emerging knowledge
447 and experience throughout the trial (ICH E6, 5.0.6).

448 For additional guidance on risk-based quality management in clinical trials, the sponsor
449 may consult other international guidelines (See Appendix B – References).

450

451 **Quality Assurance and Quality Control**

452 The sponsor is responsible for implementing and maintaining quality assurance and
453 quality control systems with written SOPs to ensure that trials are conducted and data
454 are generated, documented (recorded), and reported in compliance with the protocol,
455 GCP, and all applicable regulatory requirements (ICH E6, 5.1.1).

456 As part of a quality system, a sponsor is also responsible for securing an agreement from
457 all involved parties to ensure direct access to all trial related sites, source
458 data/documents, and reports for the purpose of monitoring and auditing by the sponsor
459 themselves, and inspection by regulatory authorities, both domestic and foreign (ICH E6,
460 5.1.2).

461 It is critical that quality control be applied at each and every stage of data handling to
462 ensure that all data are reliable and have been processed correctly (ICH E6, 5.1.3).

463 All agreements made by the sponsor with the investigator/institution and any other
464 parties involved with the clinical trial should be in writing as part of the protocol or in a
465 separate agreement (ICH E6, 5.1.4).

466 **Contract Research Organization (CRO)**

467 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a
468 CRO, but the ultimate responsibility for the quality and integrity of the trial data always
469 resides with the sponsor, as per the Regulations. The CRO should implement quality
470 assurance and quality control (ICH E6, 5.2.1).

471 Any trial-related duty and function that is transferred to and assumed by a CRO should
472 be specified in writing. The sponsor should ensure oversight of any trial-related duties
473 and functions carried out on its behalf, including trial-related duties and functions that
474 are subcontracted to another party by the sponsor's contracted CRO(s) (ICH E6, 5.2.2).

475 Any trial-related duties and functions not specifically transferred to and assumed by a
476 CRO are retained by the sponsor (ICH E6, 5.2.3). All references to a sponsor in this
477 guidance document also apply to a CRO to the extent that a CRO has assumed the trial
478 related duties and functions of a sponsor (ICH E6, 5.2.4).

479 **Standard Operating Procedures (SOP)**

480 An SOP may be trial specific or site specific, and may be provided by the site, the
481 institution or the sponsor. As with any quality system documents, there needs to be a
482 mechanism of approval, revision and communication of new and/or revised documents

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to those parties responsible for the procedures. Health Canada does not require a specific document-type and/or format but there needs to be documentation that adequately covers all critical study-related activities.



Examples of critical procedures which are expected to be documented include, but are not be limited to, the following:

- informed consent process
- recording, management and reporting of adverse events
- storage and handling of clinical trial drugs
- drug accountability
- handling of biological samples
- equipment maintenance and calibration
- training of study personnel
- monitoring (that is, procedure that assures the quality of every aspect of the clinical trial)
- record retention for 25 years

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Monitoring and Auditing

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Monitoring is essential to assure the quality of every aspect of a clinical trial. Its purpose includes verifying the following:

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- that the rights and well-being of human subjects are protected
- that the reported trial data are accurate, complete, and verifiable from source documents
- that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with all applicable regulatory requirements (ICH E6, 5.18.1)

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Section 5.18 of ICH E6 provides detailed guidance with respect to monitoring, including:

- selection and qualification of monitors (ICH E6, 5.18.2)
- extent and nature of monitoring (ICH E6, 5.18.3)
- monitor's responsibilities (ICH E6, 5.18.4)

- monitoring procedures (ICH E6, 5.18.5)
- monitoring reports (ICH E6, 5.18.6)
- monitoring plan (ICH E6, 5.18.7)

495 The sponsor should develop a systematic, prioritized, risk-based approach to monitoring
496 clinical trials. The flexibility in the extent and nature of monitoring described in section
497 5.18.3 of ICH E6 is intended to permit varied approaches that improve the effectiveness
498 and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination
499 of on-site and centralized monitoring, or, where justified, centralized monitoring. The
500 sponsor should document the rationale for the chosen monitoring strategy (for example,
501 in the monitoring plan).

502 In addition to the clear identification and control of risks in the development of an
503 approach, it is also critical to include processes that will be followed to address situations
504 of non-compliance, as well as to identify events which would require either a review or
505 revision of the monitoring plan. Health Canada expects these components to be clearly
506 documented in risk-based monitoring plans.

507 On-site monitoring is performed at the sites at which the clinical trial is being conducted.
508 Centralized monitoring is a remote evaluation of accumulating data, performed in a
509 timely manner, supported by appropriately qualified and trained persons (for example,
510 data managers, biostatisticians).

511 Centralized monitoring processes provide additional monitoring capabilities that can
512 complement and reduce the extent and/or frequency of on-site monitoring and help
513 distinguish between reliable data and potentially unreliable data.

514 For additional information, refer to the U.S. Food and Drug Administration (FDA)
515 [Guidance for Industry – Oversight of Clinical Investigations – A Risk-Based Approach to](#)
516 [Monitoring](#) published in 2013.

517 The sponsor should develop a **monitoring plan** that is tailored to the specific human
518 subject protection and data integrity risks of the trial. The plan should describe the
519 following:

- the monitoring strategy
- the monitoring responsibilities of all the parties involved
- the various monitoring methods to be used
- the rationale for their use

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The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures (ICH E6, 5.18.7).



Institution / Investigator-Initiated Clinical Trials

In the situation where a clinical trial is sponsored by an institution/investigator, and the trial is conducted by a group of physicians at different sites, it is the institution/investigator identified on the CTA as the sponsor, who is required to monitor the trial at all investigative sites.

This institution/investigator assumes the responsibilities of both the sponsor and the qualified investigator. This would include ensuring that all of the sponsor's obligations under Part C, Division 5 of the Regulations are met at each site, and that each site follows GCP in accordance with ICH E6.

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The monitor should submit a **written report** to the sponsor after each trial-site visit or trial-related communication. Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits (ICH E6, 5.18.6).

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In addition to monitoring, a sponsor may perform **audits of trials**. An audit is independent of, and separate from, routine monitoring or quality control functions, and is performed to evaluate a trials conduct and compliance with the protocol, SOPs, ICH E6 and applicable regulatory requirements (ICH E6, 5.19.1).



Additional guidance on the selection and qualification of auditors, as well as auditing procedures, can be found in sections 5.19.2 and 5.19.3 of ICH E6.

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Section 5.20 of ICH E6 states that **noncompliance** with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by a QI/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

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If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should

545 perform a root cause analysis and implement appropriate corrective and preventive
546 actions (ICH E6, 5.20.1).

547 **Equipment and Calibration**

548 Using a risk-based approach, the sponsor should identify critical equipment used in a
549 study and specifications for that equipment. Equipment or measuring devices used to
550 generate critical data should be considered critical equipment, and/or if there is specific
551 level of accuracy that requires a certain equipment type.

552 The risk evaluation should be related to the significance of the data in the trial. Any
553 equipment or measuring device used to generate data that is reported on the case
554 report form (CRF) should be assessed by the sponsor, and requirements for range and
555 accuracy should be determined. This requirement may also apply to temperature devices
556 used to monitor storage conditions of the study drug.

557 The focus should be placed on equipment used solely for the purpose of a clinical trial
558 and unrelated to the delivery of standard-of-care.

559 The control of risks identified for critical equipment (which may include calibration
560 and/or maintenance) should be reviewed, evaluated, and reported in accordance with
561 the quality management system.



Equipment used in the study classified as **medical devices** must be licensed in Canada or have an Investigational Testing Authorization (ITA) for use in that study and must be in compliance with the [Medical Devices Regulations](#).



562 Examples of observations typically cited under this section of the Regulations include:

- The sponsor did not implement systems and procedures to ensure the quality of the clinical trial.
- The sponsor did not implement systems and procedures to ensure adequate monitoring of the clinical trial.
- The sponsor did not implement systems and procedures to ensure that staff was adequately trained on GCP and the appropriate *Food and Drug Regulations*.
- The sponsor did not implement systems and procedures to ensure equipment was maintained and calibrated.



- (d) For each clinical trial site, the approval of a research ethics board is obtained before the clinical trial begins at the site;

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Interpretation

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Health Canada's relevant regulations do include certain requirements related to REBs, but Health Canada does not have jurisdiction over how REBs conduct their operations or establish SOPs. The regulatory obligations to obtain the REB approval fall on the sponsor.

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The REB membership is defined in section C.05.001 of the Regulations (refer to Appendix A) and maybe reviewed during the inspection, as required.

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Nevertheless, Health Canada recommends that REBs overseeing clinical trials in Canada operate according to well established and recognized standards such as the ICH E6, the [*Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans \(TCPS2 2014\)*](#), and provincially established standards.

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Section 3 of ICH E6 describes the responsibilities, composition and operations of REBs. The responsibility of a REB is to protect the rights, safety, and well-being of all human subjects. An REB should pay special attention to trials that may include vulnerable human subjects (elderly, children, mentally ill, prisoners, etc.). This section also lists the documents that should be provided to an REB in order to obtain ethics approval to conduct a clinical trial.

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An REB should review and document a proposed clinical trial within a reasonable time and will document its views in writing, clearly identifying the trial, the documents reviewed and the dates for approval or disapproval (ICH E6, 3.1.2).

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When and if approval is given, an REB should conduct periodic reviews of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at a minimum, at least once per year (that is a trial that is considered to be high risk to a human subject will be reviewed more often to ensure that the highest standards are in place to ensure the human subject's safety) (ICH E6, 3.1.4). An REB should follow its established and documented procedures as per ICH E6 section 3.3.

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Examples of observations typically cited under this section of the Regulations include:

- The sponsor did not receive ethics approval by a REB before the clinical trial began at the clinical trial site.
- The sponsor did not receive ethics approval for amendments to an existing clinical trial before implementing the amendments at the clinical trial site.
- The REB did not have the necessary membership and/or was not sufficiently independent from the sponsor.

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C.05.010(e)



(e) at each clinical trial site, there is no more than one qualified investigator;

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Interpretation

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A clinical trial site is the location where trial-related activities are conducted, such as the administration or dispensing of the drug (directly or by prescription) to the subject and where the subject returns for subsequent assessment.

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The qualified investigator (QI) is the person who is responsible to the sponsor for the conduct of the trial-related activities at a site (see QI definition in Appendix A). Only a licensed physician or dentist (if for dental purposes only) is entitled to provide health care under the laws of the province where that clinical trial site is located can assume the role of a QI. In addition, they must be listed as the QI on the [Qualified Investigator Undertaking \(QIU\) Form](#). There must be **no more than one (1) QI** at each site.

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Delegation Logs

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All tasks remain the responsibility of the QI unless delegation is documented in a log.

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A delegation log has to be legible, properly completed and clearly identifies the names and signatures of key personnel, their key duties, and the start and end dates of those duties. Using this as a reference, Inspectors will then ensure that all personnel delegated trial tasks are appropriately qualified for the tasks they have been delegated.

606 The delegation log should be completed before commencement of the study and
607 updated as necessary. The QI should sign and date the log prior to a task being
608 delegated. Site personnel should not initiate a task until the QI has documented the
609 delegation.

610 Within the log, a QI may designate other physicians or in some instances other
611 appropriate professionals (for example, PhDs, nurses, optometrists, radiologists, etc.) to
612 perform critical trial-related procedures and/or to make important trial-related decisions.
613 However, the QI is always accountable for the actions and decisions taken.
614 Documentation should be available to demonstrate that the QI has discussed their
615 involvement in the trial, as well as any potential issues, prior to their involvement in the
616 study.

617 A QI may also identify a 'sub-investigator' (who meets the criteria of a QI) who can, for
618 short absences only, assume the qualified investigator's full responsibilities. It must be
619 well documented who is acting as the QI at any point in time.

620 When tasks are delegated to a person in charge of other staff (for example, a nurse
621 manager, laboratory manager, etc.) further sub delegation to individual staff does not
622 need to be documented in the log, provided that evidence of qualification of those
623 individuals is available.

624 Procedures which are standard practice of care (for example, routine X-ray), or as part of
625 care provided on an *ad hoc* basis (for example, emergency room procedures) and are not
626 specific study procedures do not require specific training and delegation from the QI.



Delegated duties, to be captured in a delegation log, are dependent on the trial, and may include, but not limited to:

- obtaining informed consent
- review of subject eligibility (inclusion/exclusion criteria)
- collection, assessment and reporting of (serious) adverse events (AEs)
- investigational drug administration
- investigational drug accountability
- biological samples (collecting, processing and shipment)
- randomization
- any function requiring specific training (for example, psychiatric scales/questionnaires)

- medical history
- physical examination
- maintenance of essential records – data source capture
- CRF data entry
- data query resolution and response (including signature)
- CRF sign off
- laboratory results review
- correspondence with REB
- the “other task” section should be used to declare and assign functions specific to the protocol

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Clinical Trial Site Information Forms

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Locations where ancillary medical procedures (such as imaging, blood collections) are conducted do not require [CTSI forms](#).

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Where the actual dosing occurs may also affect the CTSIs to be submitted. For example, if the sub-investigators are only doing follow-up visits and the QI is still able to oversee these activities, proper delegation and description of activities at both locations should be sufficient hence, no CTSI form should be filed. Other deciding factors with the CTSI forms may be: patient population at the two sites (same or different), where enrolment is done and other Sub-Investigator versus QI responsibilities.

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Please refer to the [Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications](#) for detailed guidance. For further clarifications, contact the appropriate Health Canada’s Directorate (TPD or BGTD).

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Examples of observations typically cited under this section of the Regulations include:

- More than one QI at the clinical trial site was responsible for the clinical trial.
- The QI was not a physician or dentist entitled to provide health care under the laws of the province where the clinical trial site was located.



(f) at each clinical trial site, medical care and medical decisions, in respect of the clinical trial, are under the supervision of the qualified investigator;

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Interpretation

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The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose (ICH E6, 5.3). The medical care given to subjects, and medical decisions made on behalf of subjects, should always be the responsibility of a qualified physician, or, when appropriate, a qualified dentist (ICH E6, 2.7 and 4.3.1).

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The sponsor delegates the responsibility of medical care and medical decisions and day-to-day running of the clinical trial site to the QI.

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It is recommended that the QI inform a subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed (ICH E6, 4.3.3).

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During and following a subject's participation in a trial, the QI should ensure that adequate medical care is provided to a subject for any adverse events (AEs), including clinically significant laboratory values, related to the trial. The QI should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware (ICH E6, 4.3.2).

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Adequate medical oversight of a clinical trial

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Per the Regulations, every sponsor shall ensure that a clinical trial is conducted in accordance with GCP and shall ensure that at each clinical trial site, medical care and medical decisions, in respect of the clinical trial, are under the supervision of the QI. In practice, this means that activities which fall under the purview of medical care must be conducted by qualified, licensed physician or dentist, within their scope of practice/expertise. This could be either the QI, or adequately qualified individual to whom the QI has delegated the activities.

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Such activities include, but are not limited to:

- physical examinations
- review and interpretation of diagnostic and laboratory results
- review and assessment of AEs and serious adverse drug reactions (SADRs)
- review of eligibility criteria outlined in the study protocol

666 All delegated activities must be documented on the delegation log (ICH E6, 4.1.5).

667 The QI is responsible for supervising any individual or party to whom the investigator
668 delegates trial-related duties and functions conducted at the trial site (ICH E6, 4.2.5).
669 Evidence of this timely oversight may be assessed through the review of signatures and
670 file notes on source data and CRFs, including electronic signatures where applicable, and
671 through interviews with study staff and the QI. Alternative verification methods
672 consistent with ICH principles may also be acceptable.



Example of observation typically cited under this section of the Regulations includes:

- Medical care and/or medical decisions for the clinical trial were not under the supervision of the QI at the clinical trial site.

673 C.05.010(g)



(g) each individual involved in the conduct of the clinical trial is qualified by education, training and experience to perform his or her respective tasks;

674 Interpretation

675 The sponsor must ensure that all individuals involved with the clinical trial (for example,
676 biostatisticians, clinical pharmacologists, physicians, clinical trial coordinators, etc.) are
677 qualified by education, training and experience to perform their respective task(s) (ICH
678 E6, 2.8).

679 The qualification should be appropriate to the tasks to be performed by the individual.

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The sponsor must also ensure that individuals remain qualified throughout all stages of the trial process, from trial design, to conduct of a trial at sites, through to the analysis of data and the preparation of final clinical trial reports (ICH E6, 5.4.1).



Documentation to support the qualification of individuals must be available for inspection. Documentation could include:

- professional licences
- curriculum vitae (CVs)
- copies of degrees, certificates and/or diplomas
- records of participation to training

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The QI should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s) (IP), and their trial-related duties and functions (ICH E6, 4.2.4).

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If the QI/institution retains the services of any individual or party to perform trial-related duties and functions, the QI/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated (ICH E6, 4.2.6).

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Training for clinical research

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Training should be relevant to the study related duties performed by personnel, and include, at a minimum the relevant sections of trial protocol for which the person is responsible, as well as relevant supporting guidance, including, but not limited to ICH E6. An awareness and understanding of the regulatory requirements (Part C, Division 5) pertaining to the conduct of clinical trials is also recommended.



Training may take place by various formats, such as:

- sponsor-provided training (e.g. during study start-up meetings)
- site-initiated training (e.g. during staff meetings or seminars)
- events or materials provided by industry or clinical research associations, as well as educational institutions

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The frequency of training should be commensurate with the activity at the site, and be of sufficient regularity to ensure that new clinical research personnel are promptly trained

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and existing personnel maintain familiarity with the requirements. The frequency should be decided by the sponsor based on the specifics of the site and protocol.

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Documentation of training should include the content of the training such as the learning objectives, who attended and when the training occurred. This may include slide decks from presentations, course manuals, training certificates, meeting minutes and attendance logs, or updated staff CVs with supporting documentation.



Example of observation typically cited under this section of the Regulations includes:

- Not all individuals conducting the clinical trial had the education, training and experience to perform their respective tasks.

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C.05.010(h)



- (h) written informed consent, given in accordance with the applicable laws governing consent, is obtained from every person before that person participates in the clinical trial but only after that person has been informed of
- (i) the risks and anticipated benefits to his or her health arising from participation in the clinical trial, and
 - (ii) all other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial;

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Interpretation

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Informed consent is defined as a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate (ICH E6, 1.28). Potential participants in a clinical trial have the right to know the foreseeable risks or inconveniences and expected benefits that are part of the study they are thinking about joining [ICH E6, 4.8.10 (g) and (h)].

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The risks and inconveniences should not outweigh the anticipated benefits when participating in a trial (ICH E6, 2.2). It is the risks and anticipated benefits associated with a study that tends to have the greatest impact on the decision of an individual to participate or not in a trial. The rights, safety and well-being of the trial subjects are the

717 most important considerations and should prevail over interests of science and society
718 (ICH E6, 2.3).

719 Informed consent is documented by means of a written, signed and dated informed
720 consent form (ICF) (ICH E6, 1.28). The ICF must be made available for subject in either
721 official language or other as appropriate. Freely given informed consent should be
722 obtained from every subject prior to clinical trial participation (ICH E6, 2.9). A clinical trial
723 subject cannot be involved in any aspect of a clinical trial until he/she has gone through
724 the ICF process with a trial staff member (doctor, study nurse, clinical trial coordinator,
725 etc.) and signed the document indicating that he/she has read, understood, and has
726 agreed to participate in the trial. Neither the investigator, nor the trial staff, should, in
727 any way, coerce or influence a subject to participate or to continue to participate in a
728 trial (ICH E6, 4.8.3). The qualified physician should be available to answer any medical
729 questions that the subject may have regarding his/her participation in the study.

730 The original, and all amended ICFs and any other written information to be provided to
731 subjects, must be approved by an REB prior to being presented to trial participants (ICH
732 E6, 4.8.1). The QI must have a documented SOP in place for obtaining informed consent.
733 The site personnel to whom the consenting process is delegated to must be trained on
734 the process and comply with said SOP. A trial's participant must be re-consented on any
735 REB approved amended ICFs at their earliest visit to the clinical trial site, unless there are
736 specific recommendations from the sponsor and/or REB.

737 In obtaining and documenting informed consent, the investigator should comply with the
738 applicable regulatory requirement(s), and adhere to GCP and the ethical principles that
739 have their origin in the Declaration of Helsinki (ICH E6, 4.8.1)



Health Canada expects that sponsors can demonstrate that the subject has read and understood the entire informed consent document(s). This could be through initialing each page of the ICF, or a statement included at the end stating that the subject has read and understood the number of pages.

The ICF should be paginated to ensure that the complete document is presented to the subject.

740 ICFs submitted by sponsors to Health Canada are reviewed as part of their application for
741 authorization to conduct a clinical trial.



During a clinical trial inspection, the ICF is reviewed to ensure that:

- the correct version, approved by the REB, has been signed and dated by the subjects prior to any study-related procedures
- the statements of risk submitted to Health Canada are included
- additional and specific requests from Health Canada and/or the REB and/or the institution/hospital, have been included
- any new information concerning the safety of the patients/subjects has been included
- the subjects have been informed of this information in either official languages, or other as appropriate

742 Additional guidance on the informed consent document and the process of obtaining the
743 informed consent can be found through ICH E6 (section 4.8), and the current version of
744 the [*Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans \(TCPS2*](#)
745 [*2014*](#)), in particular chapter 3.

746 **Amended ICFs**

747 Section 4.8.2 of ICH E6 states that clinical trial subjects should be made aware of
748 important new information added to the ICF as soon as it becomes available, as it may
749 affect a subject's willingness to participate. It also states that the new information should
750 be explained to the subject or the subject's legally acceptable representative in a timely
751 manner, especially if the new information can have an immediate impact on the subject's
752 health. Any revised written ICF and written information should receive the REB's
753 approval/favorable opinion in advance of use.

754 A subject should sign an amended ICF no later than their next scheduled visit. It is
755 recommended that a site have a system in place to ensure control over the re-consenting
756 process, including documenting and tracking all versions of the ICF, approvals by Health
757 Canada and the REB and clinical trial subject re-consent. This is especially valuable when
758 there are a large number of amendments and/or subjects enrolled in a study.

759 **Subjects not capable of informed consent**

760 In studies where assent is used in lieu of subject consent (for example, minors,
761 incapacitated or otherwise disabled subjects), written procedures for this process should
762 be followed. The process can be incorporated into an existing SOP for obtaining informed
763 consent or be a stand-alone procedure.

764 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be
765 enrolled in the trial with the consent of the subject's legally acceptable representative
766 (for example, minors, or patients with severe dementia), the subject should be informed
767 about the trial to the extent compatible with the subject's understanding and, if capable,
768 the subject should sign and personally date the written informed consent (ICH E6,
769 4.8.12).

770 As per section 4.8.15 of ICH E6, in emergency situations, when prior consent of the
771 subject is not possible, the consent of the subject's legally acceptable representative (as
772 defined by provincial requirements), if present, should be requested. When prior consent
773 of the subject is not possible, and the subject's legally acceptable representative is not
774 available, enrolment of the subject should require measures described in the protocol
775 and/or elsewhere, with documented approval/favorable opinion by the REB, to protect
776 the rights, safety and well-being of the subject, and to ensure compliance with applicable
777 regulatory requirements.

778 The subject or the subject's legally acceptable representative should be informed about
779 the trial as soon as possible and consent to continue and other consent as appropriate
780 (see ICH E6, 4.8.10) should be requested.

781 **Fasting before signing the ICF**

782 The acceptability of such practice would have to be a decision based on a case-by-case
783 basis as every effort must be made to obtain informed consent when the clinical trial
784 subject is in an appropriate state of mind to make an informed decision with respect to
785 his or her participation in the study. It is important that subjects are fresh and alert when
786 signing the ICF.

787 The practice of having a subject fast before the screening visit is sometimes used for the
788 benefit of the subject (for example, subjects coming out of town, elderly or disabled
789 subjects who have difficulty reaching the site, etc.). Some options to resolve this issue
790 could be to send the ICF by mail or to document (for example, a note to file) the reason
791 why this method was used. When it is a site's common practice, the site's SOP for
792 obtaining informed consent, must incorporate the process. In addition, documentation
793 must be available to justify this practice, and should include the reason for the decision
794 as well as a risk assessment to ensure any risks to the subject are mitigated.

795 **Electronic ICFs**

796 The use of electronic ICFs is generally considered acceptable if all applicable regulatory
797 and ICH requirements are met.



These requirements include, but are not limited to the following:

- the system must be properly validated (ICH E6, 5.5.3), with documented procedures and appropriate training
- all required elements (C.05.010(h); ICH E6, 4.8.10) must be present in the ICF
- the information must be kept for 25 years

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The process for obtaining informed consent using an electronic form should also be well detailed in an SOP, including how the form will be explained and discussed with the clinical trial subject (for example, will the subject have the option to sign a paper copy or bring a copy home, etc.).

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There are also requirements applicable to electronic signatures if that is the method the subject will use to sign the ICF. Electronic signatures are considered acceptable, again only if the electronic system is fully validated. The proper controls should be in place to assure that the signature belongs to the user who applied it. Limited access or passwords should be used accordingly. The clinical trial subject must understand that any electronic signature is as legally binding as a handwritten signature on paper.

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For more information on computerized system validation, refer to section 5.12 (Records) of this document.



Example of observation typically cited under this section of the Regulations includes:

- The sponsor did not get written informed consent for every person before they participated in the clinical trial or the amended clinical trial.

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C.05.010(i)



- (i) the requirements respecting information and records set out in section C.05.012 are met; and

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Interpretation

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The collection and maintenance of clinical trial records, including the retention of records, is a critical component of any clinical trial. The sponsor is responsible to ensure that trial information is recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification (ICH E6, 2.10).

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Further guidance respecting information and records can be found in this document under section 5.12 Records (C.05.012).

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C.05.010(j)



(j) the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 except sections C.02.019, C.02.025 and C.02.026¹.

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Interpretation

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Good Manufacturing Practices (GMP) is part of a quality system covering the manufacture and testing of active pharmaceutical ingredients, diagnostics, foods, pharmaceutical, radiopharmaceutical, biological, veterinary products, and medical devices. These practices ensure that these products are manufactured to the highest standards, assuring their safety for use in humans and animals. GMP also applies to the manufacture of drugs to be used in clinical trials. To see the complete guidelines refer to the [Good Manufacturing Practices \(GMP\) Guidelines \(GUI-0001\)](#) available on the Health Canada website.

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Additional information regarding the requirements pertaining to GMP for clinical trial drugs is available in [Guidance Document – Annex 13 to the Current Edition of the GMP Guidelines: Drugs Used in Clinical Trials \(GUI-0036\)](#), as well as sections 2.12, 5.14 and 8.2.16 of ICH E6.

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The certificate of analysis (CoA) of clinical trial drug would be considered an adequate evidence of GMP compliance. The alternate approaches to assure GMP compliance would be up to the sponsor to determine and could be considered. Proper justification and rationale should be used. The GMP compliance of the investigational drug(s) maybe

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(1) Sections C.02.019, C.02.025 and C.02.026 refer to drug testing and sample retention.

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assessed during a clinical trial inspection. The documentation regarding GMP compliance should be kept by the sponsor.



It should be noted that marketed drugs which are not indicated on the NOL (and thus, are not considered investigational drugs) must:

- have received a NOC and/or a DIN, or
- be a marketed Canadian equivalent sourced from an acceptable foreign jurisdiction (i.e. Australia, Switzerland, Japan, European Union, United States), and
- be used within the marketing authorization

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For additional information, refer to the [*Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*](#).

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Traceability of the investigational drug(s)

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All drugs included on the NOL are considered investigational and thus, must be in compliance with Part C, Division 5 of the Regulations. The sponsor of a clinical trial is responsible for ensuring that a clinical trial drug is manufactured, stored and handled in accordance with GMP even in cases where commercial supply of drug is used and dispensed through community pharmacies (that is, the commercial drug is not supplied by the sponsor).

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The sponsor should establish and maintain a system to ensure that a drug can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the QI/clinical trial site where the product is used, administration of the drug to clinical trial subjects, to the reconciliation and disposal or destruction of the drug. The system should include collection of sufficient detail to allow linking of each clinical trial drug to the individual subject who received it. Where multiple parties are involved in the distribution chain (for example, pharmacy, CRO, central warehouse) the sponsor should ensure that the role of each party is clearly outlined in writing.

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As per section C.05.012 of the Regulations, records of the clinical trial drug's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused clinical trial drugs, should be available in order to demonstrate traceability.



These records should include, but are not limited to:

- dates
- quantities
- batch/serial numbers
- expiration dates
- unique code numbers assigned to the investigational product(s) and trial subjects

859 Essential to this process is adequate labelling in accordance with section C.05.011 of the
860 Regulations (see section 5.11 of this document).

861 **Storage and transportation conditions**

862 Using a risk-based approach, the sponsor should identify critical conditions for storage
863 and transportation taking into consideration the labelling and existing stability data.
864 Scientific/technical justification should exist to demonstrate that product quality is not
865 affected.



Factors to be taken into consideration by the sponsor when determining the approach for storage and transportation may include, but not limited to:

- nature of the drug products (e.g. temperature sensitive vs stable tablets)
- modes / distance of transport, and any seasonal variations to be experienced
- special handling precautions (e.g. relative humidity, light, use of dry ice, etc.)
- level of control of storage conditions (e.g. environmentally controlled areas, such as an hospital vs. office clinic)
- transportation container, packaging configuration

866 Inadequate transportation and storage conditions may affect a sponsor's ability to trace
867 a clinical trial drug as well as have an impact on the quality and safety of the clinical trial
868 drug. For example, inadequate shipping and receiving records may result in "missing"
869 drugs. In addition, the improper maintenance of transportation and storage
870 temperatures may result in a loss of efficacy of the drug or affect the safety of the drug.

871 The sponsor must be able to demonstrate that the product was handled and stored
872 according to the temperature range on the label. If there is potential for the drug to be
873 exposed to temperatures outside this range, manufacturers must be able to provide
874 stability data, which proves the drug is not compromised in such conditions. If
875 manufacturers cannot provide this stability data, then they must provide adequate
876 rationale for why such testing was not done or arrangements must be made by the
877 sponsor to ensure the drug is not exposed to temperature extremes (for example, use of
878 validated shipping containers).

879 This applies also to marketed drugs used in clinical trials as investigational products and
880 applies to all conditions required including ambient temperatures. If the drug product is
881 stored in a controlled environment at the hospital according to the information on the
882 label, a risk-based approach will be used.

883 Complete guidelines for the transportation and storage of clinical trial drugs can be
884 found in the [Guidelines for Temperature Control of Drug Products during Storage and](#)
885 [Transportation \(GUI-0069\)](#) and the [ICH guideline Q1A\(R2\) on Stability Testing of New](#)
886 [Drug Substances and Products](#).



It should be noted that these guidelines apply not only to drugs that require refrigerated or frozen transportation and storage temperatures, but also those that must be transported and stored at ambient temperature.

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Examples of observations typically cited under this section of the Regulations include:

- The drug was not manufactured in keeping with GMP.
- The drug was not handled and stored in keeping with GMP.

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5.11 Labelling

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C.05.011



Despite any other provision of these Regulations respecting labelling, the sponsor shall ensure that the drug bears a label that sets out the following information in both official languages:

- (a) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator;

- (b) the name, number or identifying mark of the drug;
- (c) the expiration date of the drug;
- (d) the recommended storage conditions for the drug;
- (e) the lot number of the drug;
- (f) the name and address of the sponsor;
- (g) the protocol code or identification; and
- (h) if the drug is a radiopharmaceutical as defined in section C.03.201², the information required by subparagraph C.03.202 (1)(b)(vi)³.

890 Interpretation

891 As defined in section 2 of the *Food and Drugs Act*, a label includes any legend, word or mark
 892 attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or
 893 package.

894 The sponsor is responsible for ensuring that the labelling of a clinical trial drug meets the
 895 requirements of section C.05.011 of Division 5 of the Regulations. The required information,
 896 outlined in this section, must be attached to, included with, or accompany each container of the
 897 drug product, and be available in both English and French.

898 While it would be preferable to Health Canada that all the required information be attached to
 899 the primary container, the definition of a label states that the required information may
 900 accompany the drug (primary container, secondary container, package inserts, etc.).

901 Therefore, as long as a label provides all of the required information in both official languages, it
 902 would be considered to have met the requirements of section C.05.011 of the Regulations.
 903 However, traceability to the manufacturing lot must be maintained on the label immediately
 904 attached to the investigational product (i.e. primary container) such that its identity can be
 905 determined, and, if necessary, which unit was dispensed to each subject.

(2) **C.03.201** In these Regulations, “radiopharmaceutical” means a drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons

(3) **C.03.202 (1)** Every package containing a radiopharmaceutical, other than a radionuclide generator, shall carry,
 (b) on the outer label
 (vi) the radiation warning symbol required by the Atomic Energy Control *Regulation* and the statement “Caution — Radioactive Material”



Information not appearing on the label as required by section C.05.011 should be justified and authorized by Health Canada (TPD or BGTD).

906 Adequate labelling of a drug used in a clinical trial is essential to ensure traceability of the drug,
907 through the use of identifying information and lot numbers, to ensure that it is dispensed to the
908 correct clinical trial subject, and to ensure it is stored at the proper temperature and has not
909 expired. The labelling must comply with regulatory requirement(s) and be coded and labelled in
910 a manner that protects the blinding, if applicable (ICH E6, 5.13.1).

911 For additional information on labelling, please refer to section 8.7 of [*Guidance Document –*](#)
912 [*Annex 13 to the Current Edition of the GMP Guidelines: Drugs Used in Clinical Trials \(GUI-0036\)*](#).

913 **Clinical Trial Drug Lot Numbers**

914 The purpose of having a lot number on a drug label is to ensure traceability back to the
915 manufacturer's records, in the event a problem with the drug is identified or a recall is
916 necessary. However, for blinded clinical trials the sponsor must ensure that labeling information
917 does not compromise the blinding. Labeling of a clinical trial drug with a manufacturer's lot
918 number may compromise a blinded clinical trial.

919 Identifiers other than a "lot" or "(L)" number (for example, a batch number, a kit number or a
920 bar code) may be considered compliant with section C.05.011, provided traceability is
921 maintained. Where a bar code is included as the identifier on the label, the code on the drug
922 label should readily link to information, such as the lot number and expiration date, through a
923 validated computerized system. During an inspection, Health Canada may verify that there is a
924 system of traceability in place to ensure patient safety and that the computerized system, if
925 applicable, is fully validated (refer to section 5.12 Records).

926 **Clinical Trial Drug Expiry Dates**



As per section C.01.001 of the Regulations, an expiration date is defined as:

- (a) in the case of a drug in dosage form, the earlier of the following dates, expressed at minimum as a year and month:
 - (i) the date up to and including which the drug maintains its labelled potency, purity and physical characteristics, and
 - (ii) the date after which the manufacturer recommends that the drug not be used; and

- (b) in the case of an active ingredient, whichever of the following dates is applicable, expressed at minimum as a year and month:
- (i) the retest date, or
 - (ii) the date after which the manufacturer recommends that the active ingredient not be used.

927 During an inspection, Health Canada may verify that the clinical trial drug has a valid expiration
928 date. The valid expiration date assures that the drug meets the standards for potency, purity and
929 physical characteristics.

930 If stability studies to support expiry dating for a clinical trial drug are still ongoing at the time of
931 labelling, the following may be considered acceptable in lieu of an expiration date:

- 932 • a re-test date on the label if the sponsor has data to support the extended shelf-life of
933 the drug, and
- 934 • a manufacturing date is listed on the label, as long as the clinical trial site where the
935 drug is dispensed has a document from the sponsor documenting the shelf-life of the
936 drug. The sponsor must have data to support the shelf-life of the drug. As an example,
937 this principle would apply to radiopharmaceuticals.

938 The process should be documented; procedures and quality control systems should be in place
939 and in accordance with the approved CTA. The operation should be performed in accordance
940 with GMP principles and specific SOPs. Furthermore, this additional labelling info should be
941 properly documented in both the trial documentation and in the packaging records.

942 In the cases where a drug product requires reconstitution or further preparation prior to being
943 administered to a subject, the sponsor is responsible for demonstrating that the drug used at
944 the clinical trial site meets all of the requirements of section C.05.011. The reconstitution or
945 preparation of a clinical trial drug must be done in accordance with the clinical trial protocol and
946 must be documented. The label for any new packaging of the drug must bear an expiration date
947 and information on the reconstitution or preparation of the drug, and the required storage
948 conditions should be included in accompanying documentation.

949 In all cases, regardless of the approach taken, the sponsor must be able to demonstrate, through
950 adequate data, that a clinical trial drug maintains its characteristics of potency, quality and safety
951 during its period of use.

952 Refer to section 8.7 of [*Guidance Document – Annex 13 to the Current Edition of the GMP*](#)
953 [*Guidelines: Drugs Used in Clinical Trials \(GUI-0036\)*](#) for additional guidance.

954

Labels of Marketed Drugs Used as Comparators

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It is acceptable for a marketed drug used in a clinical trial, to be labelled in accordance with its marketing authorization, including all relevant sections of the *Food and Drugs Act* and its associated regulations, provided that the labelling on the marketed drug is appropriate for the trial. However, for blinded clinical trials, the sponsor should ensure that the labeling does not compromise the blinding.

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Example of observation typically cited under this section of the Regulations includes:

- The label of the drug did not contain the required information.

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5.12 Records

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C.05.012



- (1) The sponsor shall record, handle and store all information in respect of a clinical trial in a way that allows its complete and accurate reporting as well as its interpretation and verification.
- (2) The sponsor shall maintain complete and accurate records to establish that the clinical trial is conducted in accordance with good clinical practices and these Regulations.
- (3) The sponsor shall maintain complete and accurate records in respect of the use of a drug in a clinical trial, including:
 - (a) a copy of all versions of the investigator's brochure for the drug;
 - (b) records respecting each change made to the investigator's brochure, including the rationale for each change and documentation that supports each change;
 - (c) records respecting all adverse events in respect of the drug that have occurred inside or outside Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;
 - (d) records respecting the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the sale of the drug may endanger the health of the clinical trial subjects or other persons;

- (e) records respecting the shipment, receipt, disposition, return and destruction of the drug;
 - (f) for each clinical trial site, an undertaking from the qualified investigator that is signed and dated by the qualified investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that
 - (i) the qualified investigator will conduct the clinical trial in accordance with good clinical practices, and
 - (ii) the qualified investigator will immediately, on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial subjects or other persons;
 - (g) for each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the research ethics board for that clinical trial site; and
 - (h) for each clinical trial site, an attestation, signed and dated by the research ethics board for that clinical trial site, stating that it has reviewed and approved the protocol and informed consent form and that the board carries out its functions in a manner consistent with good clinical practices.
- (4) The sponsor shall maintain all records referred to in this Division for a period of 25 years.

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Interpretation

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As per C.05.012(4), the sponsor shall maintain all records referred to in this Division for a period of 25 years. The Regulations take precedence over any other timelines stated in ICH E6.

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Of note, Part C, Division 5 record retention requirements also apply to clinical trials using drugs that will never be marketed regardless of the trial data's statistical significance.

Therefore, clinical trial records created and/or used during the conduct of a statistically negative trial must be retained according to the regulatory requirements as outlined in this document and in the Regulations.

965 Please note there may be additional record retention requirements under provincial jurisdiction,
966 contractual agreements with sponsors, REBs or others, which should also be complied with.

967 All clinical trial information should be recorded, handled and stored in a way that allows its
968 accurate reporting, interpretation and verification. This ICH GCP principle applies to all records
969 referenced in the guideline, irrespective of the type of media used (ICH E6, 2.10).

970 All clinical trial records shall be made available for inspection (ICH E6, 4.9.7) by Inspectors of
971 Health Canada, in accordance with section 23 of the Act. While a unique identifier is assigned by
972 the QI to each trial subject, to protect the identity of the subject when the investigator reports
973 AEs and/or other trial related data (ICH E6, 1.58), clinical trial subjects grant Health Canada
974 Inspectors a direct access to their original medical records by signing the ICF, which should
975 include a statement to this effect as per section 4.8.10 (n) of ICH E6.

976 **Roles and Responsibilities (Sponsors, QIs and REBs)**

977 Many parties usually share the responsibilities of record retention through delegation by the
978 sponsor. It is however the ultimate responsibility of the sponsor to ensure that all parties
979 involved in the conduct of the trial are in compliance with record retention requirements.

980 **Sponsor**

981 Part C, Division 5 of the Regulations clearly establishes that the sponsor who submits the CTA is
982 the party to whom an authorization to sell or import a drug for use in a clinical trial is issued.
983 Therefore, the sponsor of a clinical trial is responsible for maintaining all records for the required
984 record retention period.

985 The sponsor is required to maintain complete and accurate records to demonstrate that the
986 clinical trial is conducted in accordance with the Regulations and GCP (ICH E6, 5.5.6-7).

- 987 • As the sponsor bears responsibility for study records, it is recommended that the
988 sponsor clarify at the outset of the trial what documents are defined as source and how
989 they are to be maintained.
- 990 • Sponsors may delegate record retention to third parties (such as QIs, CROs,
991 laboratories, and others). As the responsible party for the conduct of a clinical trial, the
992 sponsor should relay their expectations to third parties and expect due diligence from
993 all involved in the management of clinical trial records. As such, written agreements
994 with these third parties should be secured by sponsors, prior to the commencement of
995 the trial to ensure full compliance with the regulatory requirements with respect to
996 records.

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- Written procedures and training of personnel in their implementation should be documented to demonstrate that the maintenance and retention of records conducted correctly and consistently. The procedures may be trial- or site-specific and be provided by the sponsor or the third party that was delegated the responsibility.
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- In situations where a sponsor undergoes a change of ownership, the record retention responsibility remains with the sponsor who initially submitted the CTA, unless a written agreement is otherwise secured with the new owner. Furthermore, before the clinical trial begins, the sponsor should have a documented procedure for record retention continuity that outlines the measures to be taken in the event that the sponsor ceases to exist.
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- The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data (ICH E6, 8.1).

1010 Qualified investigator

1011 A QI is responsible for the proper conduct of the clinical trial at his/her site. It should be noted
1012 that an independent QI, initiating a clinical trial under his/her own sponsorship, is responsible for
1013 all aspects of that trial, both as a QI and as a sponsor.

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- The QI should ensure that essential records created and/or used under his/her supervision, including all source documents, are retained in accordance with the requirements of the Regulations and in accordance with the written agreement secured with the sponsor prior to the commencement of the clinical trial (ICH E6 4.9.4).



Sites that **neither screen nor enrol any subjects** in a given clinical trial and that have not been delegated the responsibility of record retention by the sponsor do not need to retain clinical trial records in accordance with Part C, Division 5.

However, clinical trial sites with **screen failures but no subjects enrolled** in a given clinical trial should retain all records, including ones pertaining to screen failures for the entire record retention period as per Part C, Division 5. All source documents should also be retained for the entire record retention period even if a subject has withdrawn from the clinical trial.

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- Appropriate measures should be taken to prevent accidental or premature destruction of the records (ICH E6, 4.9.4).

1020 • Written agreements describing the procedures for records retention in accordance with
1021 the Regulations should be in place between all parties concerned.

1022 For example, QIs conducting clinical trials within a hospital or a medical clinic should
1023 secure a written agreement, if applicable, with the institution to ensure that hospital
1024 records and/or medical charts of clinical trial subjects are retained according to the
1025 federal Regulations as these prevail over provincial laws and regulations.

1026 Agreements should also outline the conditions of record retention, such as the location
1027 of records, as well as the procedure to be followed to ensure record retention in the
1028 event that a company ceases to exist or QI ceases her/his affiliation with their
1029 institution, for various reasons such as closure of practice or retirement, new position
1030 elsewhere, or death, within the 25-year period.

1031 • The QI may delegate record-related tasks to other parties such as the institution's
1032 pharmacy, a local laboratory or a radiological clinic, with the sponsor's agreement:

1033 ○ Prior to the commencement of the clinical trial, the delegated tasks should be
1034 documented, signed and dated by the QI and the party to whom the functions
1035 are delegated. The delegation may be amended if necessary during the course
1036 of the clinical trial.

1037 ○ The extent of the delegation, including the retention of the records created by
1038 the other party, should be clearly stated.

1039 ○ Tasks that are not delegated remain under the direct responsibility of the QI or
1040 the sponsor, depending on the written agreement secured between these two
1041 (2) parties. However, QIs always remain responsible to oversee the delegated
1042 tasks because they are responsible for the trial at their site.

1043 • The QI/institution should maintain adequate and accurate source documents and trial
1044 records that include all pertinent observations on each of the site's trial subjects.
1045 Source data should be attributable, legible, contemporaneous, original, accurate, and
1046 complete. Changes to source data should be traceable, should not obscure the original
1047 entry, and should be explained if necessary (e.g. via an audit trail) (ICH E6, 4.9.0).

1048 • Section 4.9.1 of ICH E6 states that the investigator should ensure the accuracy,
1049 completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs
1050 and in all required reports. Furthermore, section 4.9.2 of ICH E6 states that data
1051 reported on the CRF, that are derived from source documents, should be consistent
1052 with the source documents or the discrepancies should be explained.

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- If any changes or corrections are made to a CRF, either written or electronic, the changes should be dated, initialed, and explained (if required) and the original entry should be legible (ICH E6, 4.9.3).
 - All changes made to a CRF, including electronic CRFs, should be traceable/auditable. Sponsors are expected to provide guidance, such as a written procedure, to investigators on how these corrections should be made and documented (ICH E6, 4.9.3).
 - The written procedure should assure that changes or corrections in CRFs made by the sponsor’s designated representative are documented, explained, and endorsed by the investigators. It is the investigator’s responsibility to retain records of the changes and corrections (ICH E6, 4.9.3).

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Types of records

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Different types of records are created and are to be retained before, during and after the conduct of a clinical trial, in accordance with section C.05.012 of the Regulations and section 8 “Essential Documents for the Conduct of a Clinical Trial” of ICH E6.

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Essential documents

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Any documentation created and/or used during the conduct of clinical trials that allow the evaluation of the conduct of a study as well as the quality of the data produced during the study (ICH E6, 1.23).



These include, but are not limited to:

- investigator’s brochure (including records respecting each change)
- serious adverse event (SAE) and serious adverse drug reaction (SADR) reports that have occurred inside or outside Canada
- chemistry and manufacturing information
- records respecting the enrolment of clinical trial subjects
- records respecting the shipment, receipt, disposition, return and destruction of the drug
- signed and dated QIU forms
- protocols and protocol amendments
- REB approved ICF(s)
- signed and dated REB attestations
- standard operating procedures (SOPs)

- site personnel training records
- source documents

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Source documents

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A type of essential documents that consist of original documents, data, and records (ICH E6, 1.52).

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These include, but are not limited to:

- signed and dated ICFs
- hospital records
- clinical site and physician office medical charts
- laboratory records
- medical instrument records
- X-rays
- subject diaries
- appointment/scheduling records
- AEs and ADRs records
- pharmacy dispensing records
- drug accountability records

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Essential and/or source documents may be in paper, magnetic or electronic form (ICH E6, section 8). It is acceptable for essential and/or source records to be transferred to secondary media (see “Transfer of records to secondary medium” section below).

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Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial (ICH E6, 8.1).

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A method is expected to be in place to identify those data elements requiring source documentation, and sites can then declare the type of source documents (e.g. chart-based, electronic record, a combination).

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Only specific and unique documents that belong solely to the sponsor, the REB, the QI or other entities, must be kept at the conclusion or termination of a trial. Retention of copies of original documents is not a requirement.

For example:

- **Sponsors** are to keep: AEs records as per C.05.012(3)(c), REB attestation form, QIU form
- **QIs** are to keep: records that identify clinical trial subjects, medical records of subjects
- **REBs** are to keep: membership, qualifications of members, minutes of the meetings

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The QI/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial (ICH E6, 8.1).

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In order to allow traceability of all source data, any source documents should be signed and dated by the person collecting, recording, reviewing and/or assessing the information or data.



Signing and dating a source document as evidence that it was reviewed is a common practice often supported by the site internal policies.

This practice is also recommended by Health Canada, although alternative verification methods, consistent with the principles of ICH E6, may also be acceptable.

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In situations where original source documents cannot be retained for the 25-year record retention period due to their deterioration in uncontrolled environment conditions (such as thermal paper used for electrocardiograms), certified copies can be acceptable (see “Transfer of records to secondary medium” section below).



A **certified copy** is a copy (irrespective of the media used) of the original record that has been verified (e.g. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure as the original (ICH E6, 1.63).

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Refer to section 8 of ICH E6 for a more detailed list of essential and source documents.

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Electronic source records

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Electronic source records may be generated during clinical trials. They consist of any piece of information that is created, modified, retrieved, and/or transmitted during the conduct of a clinical trial.

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These may include, but are not limited to:

- electronic case report forms (eCRFs) including electronic signatures
- electronic subject diaries
- other instruments provided to the QI or subjects to record trial data

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- Electronic source records should be maintained and retained in accordance with section C.05.012 of the Regulations.

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- The validation of an electronic system is performed to confirm that the system's specifications meet the goals and requirements for the clinical trial in a consistent manner. These include, but are not limited to, completeness, credibility and accuracy of recorded information as well as reliability of the system. Therefore, any electronic system used to capture, process, manage and/or archive clinical trial information should be adequately validated and evidence of validation should be kept for the required record retention period and should be readily available for inspection by Health Canada's Inspectors.

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- The approach for validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results (ICH E6, 1.65 and 5.5.3).

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- As part of the validation process for electronic systems, documentation of the system design specifications and a validation plan based on those should be developed.

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- The validation plan should include:
 - objectives and scope
 - nature of and time at which validation activities should be performed
 - delegated personnel for the conduct of the validation
 - security measures
 - main features of the system, including the mode of interaction with other systems and procedures

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- Detailed documented procedures for validation activities should be developed and followed at all times to ensure consistency in the performance of the tasks. The SOPs should cover system setup, installation, and use. The SOPs should describe:
 - system validation and functionality testing
 - data collection and handling
 - system maintenance
 - system security measures
 - change control
 - data backup, recovery, contingency planning, and decommissioning.
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1129 The responsibilities of the sponsor, QI, and other parties with respect to the use of these
1130 computerized systems should be clear, and the users should be provided with training in
1131 their use (ICH E6, 5.5.3).

- The validation results should provide a clear indication that the system can be used as created. As such, a validation report, including detailed test results and an assessment of the results demonstrating that the system has met the specifications, should be produced for each validation test and allow traceability to the delegated person who conducted the activity.
 - Any modifications or additions made to the electronic system, such as software upgrades or migration of data, can impact its intended functions by altering the quality of validated applications and the system itself. This may affect the integrity of the electronic information and the reliability of the system. Therefore, adequate documented assessment and approval of changes to hardware or software during the course of the clinical trial are required. The impact of such a change should be evaluated and documented, and partial validation of some components of the electronic system may be required.
 - The electronic system should allow for the retrieval of the records the generation of complete and accurate paper copies of the electronic source data as well as provide audit trails for the entire 25-year record retention period.
 - Records created, maintained and processed by outsourced systems (i.e. cloud computing) are subject to the same requirements as the data/records generated by company owned systems.
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Health Canada expects that sponsors take into consideration the following factors as part of the risk assessment of a computerised system and its associated validation, but not limited to:

- type of research (e.g. commercial vs. non-commercial)
- purpose of the clinical trial (e.g. research for publication vs. drug submission for marketing authorization)
- status of the drug (e.g. market authorized product vs. IP)
- safety profile / history of use of the drug

In addition, the sponsor should periodically review the risk control measures identified in their assessment to ascertain whether the implemented systems remain effective and relevant, taking into account experience and emerging knowledge (ICH E6, 5.0.6).

1151 For additional information on computerized system validation and electronic records, refer to:

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- 1153
- [Annex 11 to Pharmaceutical Inspection Co-Operation Scheme \(PIC/S\) Guide to Good Manufacturing Practice for Medicinal Products: Computerised Systems](#)
 - 1154 • [PIC/S Guidance: Good Practices for Computerised Systems in Regulated “GXP”](#)
1155 [Environments](#)
 - 1156 • the [U.S. Code of Federal Regulations Title 21 Part 11 – Electronic Records; Electronic](#)
1157 [Signatures](#)
 - 1158 • the standard [Electronic Records as Documentary Evidence, CAN/CGSB-72.34-2017](#)
1159 developed by the Canadian General Standard Board (CGSB).

1160 Pharmacy records

1161 Pharmacy records should be retained as either as part of the subject-specific source document
1162 or the medical or hospital chart.



These records include, but are not limited to:

- clinical trial drug prescriptions
- calculations for clinical trial drug dispensing
- drug accountability records
- clinical trial drug storage temperature logs

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Laboratory records

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The retention of laboratory records allows review and confirmation of the diagnoses and

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results/reports as well as appropriate further testing, if needed, for the protection and well-

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being of participating clinical trial subjects.



These records include, but are not limited to:

- normal values and/or ranges for test(s) included in the protocol
- laboratory certification and/or accreditation
- established quality control and/or external quality assessment
- laboratory results/reports
- X-ray films, digital images, microfilms and compact disks

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Medical instrument records

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In the course of a clinical trial, measuring and laboratory equipment, scientific instruments and

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other pieces of equipment are generally used. Using a risk-based approach, the sponsor should

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identify critical equipment used in a study and specifications for that equipment (refer to section

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C.05.010(c) Equipment and calibration).

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- All service, maintenance, cleaning and calibration records, as well as the product manual for critical piece of equipment used in the clinical trial, should be retained for the 25-year record retention period. This would include for example certificates, calibration data, and records of faults, breakdowns and misuse of the equipment.

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- The manual calibration of certain pieces of equipment or instruments, such as body weight scales, does not generate a certificate or a print-out of the calibration data to demonstrate that the calibration was indeed performed and successful. In those circumstances, the QI should retain the calibration procedure and a log stating the following information:

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- dates of calibration

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- device details (type, supplier, and purchase date)

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- person responsible for the instrument

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- person who performed calibrations

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Approved specifications for calibration should also be documented and a record of the

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actual calibration results kept.

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- Certain pieces of equipment or instruments may require frequent automated calibration and consequently generate considerable amounts of print-outs. In these instances, a log should be kept with all of the information listed under the bullet point above; except it should include the name of the person who assessed the calibration data and certified that calibration was successful, instead of the person who calibrated the instrument.
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- The manufacturer's warranty cannot replace calibration/maintenance records as equipment calibration assures that equipment works within specifications.
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Drug accountability records



Drug accountability records should include the following information on the drug, but not limited to:

- date of arrival on site
- quantity received
- identification (batch/lot number)
- expiration date
- quantity dispensed, on what date and to whom
- quantity returned by subjects, on what date
- quantity and date of destruction or return to sponsor

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In order to ensure that subjects received the specified dose identified in the protocol, investigators should maintain documented evidence.

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Reconciliation of all investigational products received from the sponsor is also required (ICH E6, 4.6.3).

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Drug accountability records are required for:

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- drugs that are the subject of the clinical trial, and do not have market authorization
 - drugs that are the subject of the clinical trial, have market authorization, but are used off-label
 - comparator drug, if it does not have market authorization
 - comparator drug, if it has market authorization, but its labelling was changed (for blinding purposes, for example)
 - comparator drug, if it has market authorization, but is used off-label

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- drugs listed on section 8 (Brand or Proprietary Name) of [HC/SC form 3011](#) (Drug Submission Application for Human, Veterinary or Disinfectant Drugs and Clinical Trial Applications/Attestation)

1211 Drug accountability records are **not** required for:

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- drugs that are the subject of a Phase IV clinical trial
 - comparator drug, if it has market authorization, is used on-label, and hasn't been altered in any manner
 - rescue or concomitant medications that may be used off-label but are not subject of the clinical trial (for example, they are used as supportive medications for known clinical applications)

1218 For example, marketed drugs which are commercially available, for which a CTA has been filed,

1219 should be managed as commercial drugs and good practice guidelines for pharmacies followed.

1220 Trial-specific drug accountability logs are required **only** for drugs specifically labelled as clinical

1221 trial supply.

1222 Financial Records



Records pertaining to financial details of the clinical trial include, but are not limited to:

- any subject compensation records
- financial agreements between parties (ICH E6, 4.9.6, 5.9 and 8.2.4)
- insurance statements (ICH E6, 8.2.5)

1223 Financial details related to clinical trial records are at the sponsor's discretion and outside of

1224 Health Canada scope.

1225 Refer to section 8 of ICH E6 for more information on this type of record.

1226 Research Ethics Boards (REBs) records

1227 Records relevant to a clinical trial that pertain to the roles and responsibilities of the REB should

1228 be retained for 25 years in accordance with Part C, Division 5 of the Regulations.



These records include, but are not limited to:

- REB membership including roles and responsibilities (e.g. chair, ethics, community representative)

- CVs indicating qualifications of REB members
- REB decisions (such as approvals, denials, required modifications, orders to stop clinical trials, etc.)
- communications with sponsors and QIs

1229 Other essential documents that are not unique to the REB (such as records of ADRs and
1230 reviewed documents) should be retained for a period of at least three (3) years after completion
1231 of the trial as per ICH E6.

1232 **Transfer of records to secondary medium**

1233 The transfer of essential records from their original medium to a secondary one may be
1234 acceptable if the conditions described in this section are fulfilled.

1235 **Transfer**

1236 The transfer process should be validated and documented in appropriate procedures, and
1237 should ensure that:

- 1238 • measures are in place to verify that the transfer is accurate and done by appropriately
1239 trained individuals (e.g. attestation or certification of copies by a person not involved in
1240 the transfer)
- 1241 • corrections to the original data can be clearly captured in the secondary medium
- 1242 • process follows existing standards when possible (i.e. Canadian General Standard
1243 Board)
- 1244 • the secondary medium allows the successful retrieval and use of the records for the
1245 entire 25-year record retention period

1246 Where records are copied off-site, a contract signed by the sponsor/qualified
1247 investigator/institution and the service provider must detail specific requirements such as those
1248 for transport to that site, copy quality, storage conditions, and, where relevant, destruction of
1249 original documents.

1250 **Electronic or Other System**

1251 The format and system where documents are retained should also be validated for its intended
1252 use.



Features should include the following:

- design to ensure the tracing of any alterations and updates, if permitted, such as source, date and content (i.e. audit trail)
- back-ups at regular intervals
- security measures in place and documented to protect against data corruption, whether through accidental deletion, equipment failures, material deterioration, or a variety of other hardware and software problems
- controlled access to appropriate individuals (through use of passwords for example)
- plan in place for future accessibility (in light of changes over time in technology, personnel, or third-party contractors)
- location of records that permits immediate access to records for inspection

1253 **Destruction of original records**

1254 The destruction of original paper records following their transfer to a secondary medium may be
1255 acceptable with the principles described in this section in place.

1256 In addition, the process to describe the destruction of the original paper records should be
1257 documented in appropriate procedures. Considerations should be given to additional
1258 requirements that may apply to the destruction of personal/confidential information.

1259 **Other considerations**

1260 Other requirements may apply to the transfer, storage and destruction of records, including:

- 1261 • provincial (for example, medical records)
- 1262 • institutional
- 1263 • legal requirements (for example, transfer to an electronic format may not be acceptable
1264 when it contains a watermark or official seal)

1265 It is considered acceptable, for example, to scan documents in an electronic format and store
1266 them on specific software or networks as well as on other devices such as compact discs (CDs)
1267 and flash drives (e.g. USB keys). That being said, all requirements stated in this guidance should
1268 be met when using any of these storage methods. While only one copy of each document in

1269 archive must be retained, whether in hardcopy or electronic format, records from their original
1270 medium (e.g. hardcopies) should be kept for as long as they are needed.

1271 The above conditions apply to transfers of essential records from an original to a secondary
1272 medium performed by all parties involved in the conduct of a clinical trial.

1273 For more information with regards to the transfer of essential records to a secondary medium,
1274 refer to the CGSB standard [Electronic Records as Documentary Evidence, CAN/CGSB-72.34-2017](#).

1275 **Record retention period**

1276 The retention period for all records created and/or used during the conduct of a clinical trial is
1277 **25 years** in accordance with subsection C.05.012(4) of the Regulations. This period of time will
1278 allow for subject follow-up throughout the subsequent stages of drug development, assessment,
1279 marketing, as well as provide the ability to assess the impact on the next generation.

1280 Although the retention period of records starts on the date the record is created, sponsors may
1281 choose to "start the clock" for retention of all study records upon completion or termination of
1282 the trial to simplify the process.

1283 **Location of records**

1284 Often, third parties (such as the QI, the REB, the CRO) retain originals of specific and unique
1285 records created by them. Nevertheless, due to their nature, specific records may be retained by
1286 more than one party. It should be noted that it is not a requirement for a party to retain multiple
1287 and identical copies of an original document. Third parties should consult the sponsor prior to
1288 destroying any record.

1289 A detailed list of essential/source records which specifies the party(ies) who should retain them,
1290 and where they should be located throughout the period of a trial, is described in section 8 of
1291 ICH E6.

1292 All records should be kept in a secure location prior to, throughout and after the conduct of the
1293 clinical trial. To maintain the integrity of all records, their location should assure protection from
1294 possible damage (for example, water or fire damage) and from a possible breach in
1295 confidentiality for the entire record retention period. As such, access to the records should be
1296 restricted to authorized personnel that are adequately trained in the handling and management
1297 of clinical trial records according to an established documented procedure.

1298 The sponsor and QI/institution should maintain a record of the location(s) of their respective
1299 essential documents including source documents. The storage system used during the trial and

1300 for archiving (irrespective of the type of media used) should provide for document identification,
1301 version history, search, and retrieval (ICH E6, 8.1).

1302 It should be noted that specific timelines for the provision of clinical trial information to Health
1303 Canada are outlined in section C.05.013 of the Regulations (see section 5.13 of this document).
1304 These timelines should be taken into consideration when determining the location of the clinical
1305 trial records for the retention period.

1306 If the records are stored in the cloud, there should be an agreement between the regulated
1307 party and the cloud provider that sets out the parties' respective responsibilities. Direct and
1308 immediate access to the records needs to be available for inspectors and provision of passwords
1309 or encryption keys to inspectors at the time of inspection.



Examples of observations typically cited under this section of the Regulations include:

C.05.012(1)

- The clinical trial records had errors and/or missing information that did not allow for complete and accurate reporting, interpretation, and verification.
- The sponsor did not record, handle and store all information for a clinical trial to ensure the data transcribed from the original documents to case reports was accurate and complete.
- The sponsor did not ensure the electronic data system met the requirements for completeness, accuracy, and reliability.

C.05.012(2)

- The sponsor did not keep complete and accurate records to show the clinical trial was conducted in keeping with GCP and the Regulations.

C.05.012(3)

- The sponsor did not keep complete and accurate records for the use of the drug in a clinical trial, as required by the Regulations.
- The sponsor did not keep all versions of the Investigator's Brochure, including the rationale for any changes.
- The sponsor did not keep records of all adverse events.
- The sponsor did not keep records for the shipment, receipt, use, return and/or destruction of the drug.

- The sponsor did not keep records of the commitment signed and dated by the qualified investigator, before the clinical trial began at the site.
- The sponsor did not keep copies of the protocol, informed consent and/or any amendments approved by the REB at the clinical trial site.

C.05.012(4)

- The sponsor did not have provisions in place to keep all clinical trial records for a period of 25 years.

5.13. Submission of Information and Samples

C.05.013



- (1) The Minister shall require a sponsor to submit, within two days after receipt of the request, information concerning the drug or the clinical trial, or samples of the drug, if the Minister has reasonable grounds to believe that
 - (a) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person;
 - (b) the clinical trial is contrary to the best interests of a clinical trial subject;
 - (c) the objectives of the clinical trial will not be achieved;
 - (d) a qualified investigator is not respecting the undertaking referred to in paragraph C.05.012(3)(f); or
 - (e) information submitted in respect of the drug or the clinical trial is false or misleading.
- (2) The Minister may require the sponsor to submit, within seven days after receipt of the request, any information or records kept under section C.05.012, or samples of the drug, in order to assess the safety of the drug or the health of clinical trial subjects or other persons.

1312 Interpretation

1313 Health Canada may at any time request that a sponsor submit either information or samples of a
1314 study drug, **within 2 calendar days of that request**, should Health Canada have reasonable
1315 grounds to believe that:

- 1316 a. the use of the drug endangers the health and safety of a subject or other person
- 1317 b. the trial is not in the best interests of a clinical trial subject
- 1318 c. the objectives of the trial will not be achieved
- 1319 d. the QI is not respecting the undertaking (QIU form) described in C.05.012(3)(f), or
- 1320 e. information submitted in respect of the drug or the clinical trial is thought to be false or
1321 misleading

1322 Furthermore, Health Canada may request that a sponsor submit information or records
1323 described in C.05.012, or samples of the drug, **within 7 calendar days of the request**, in order to
1324 assess the safety of the drug or the health of any of the clinical trial subjects or other persons.

1325 Retention Samples

1326 Although the Regulations do not specifically state that samples of clinical trial drugs must be
1327 kept, in order to be able to fulfill a Health Canada's request for a sample, as specified in this
1328 section, it is implicit that retention samples be kept from the start of a clinical trial through the
1329 end of the drug submission review process.

1330 Retention of Biological Study Samples

1331 The Regulations do not specify how long biological study samples must be kept. However, it
1332 would be best if the sponsor maintains serum samples, for example, until the clinical trial report
1333 has been prepared in order to enable confirmation of results, and specifically in the event of
1334 inconsistent results. In addition, the sponsor should also consider retaining such samples for a
1335 longer period of time, especially if the intent is to use the data from the trial in support of an
1336 application seeking marketing authorization for the drug.



Example of observation typically cited under this section of the Regulations includes:

- The sponsor did not submit requested information concerning the drug or the clinical trial, and/or requested samples of the drug, within the required time frame.

5.14 Serious Unexpected Adverse Drug Reaction Reporting

C.05.014



- (1) During the course of a clinical trial, the sponsor shall inform the Minister of any serious unexpected adverse drug reaction in respect of the drug that has occurred inside or outside Canada as follows:
 - (a) if it is neither fatal nor life threatening, within 15 days after becoming aware of the information; and
 - (b) if it is fatal or life threatening, within seven days after becoming aware of the information.
- (2) The sponsor shall, within eight days after having informed the Minister under paragraph (1)(b), submit to the Minister a complete report in respect of that information that includes an assessment of the importance and implication of any findings made.
- (3) Sections C.01.016 and C.01.017 do not apply to drugs used for the purposes of a clinical trial.

Interpretation

The collection, assessment and reporting of adverse events (AEs, as defined in Appendix A) is a critical component of the conduct of any clinical trial. It is a sponsor's responsibility to keep records of all AEs in respect of the drug used in a clinical trial, whether those events occur inside or outside of Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the AE [C.05.012(3)(c)]. The assessment of the AEs should be done by the QI or the delegated sub-investigator(s) for seriousness, expectedness and causality determination.

Section 4.11.1 of ICH E6 states that all serious adverse events (SAEs, as defined in Appendix A) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should comply with the applicable regulatory requirement(s) related to the reporting of serious unexpected adverse drug reactions (SUADR, as defined in Appendix A) to the regulatory authority(ies) and the REB.

1356 In accordance with section C.05.014 of the Regulations, it is the responsibility of a sponsor to
1357 inform Health Canada, in an expedited manner, of all **SUADRs** in respect of a drug during the
1358 course of the clinical trial, whether or not the event occurred inside or outside of Canada:

- 1359 a. this information must be submitted **within 15 calendar days** after becoming aware of
1360 the event if it is neither fatal nor life threatening
- 1361 b. if the event is **fatal or life threatening**, Health Canada must be advised of the event
1362 **within 7 calendar days** after the sponsor first became aware of it.

1363 In cases where the event is **fatal or life threatening**, the sponsor must submit a **complete report**
1364 to Health Canada **within 8 calendar days** after the first notification to Health Canada of the event.
1365 Follow-up reports of fatal or life threatening reactions must include an assessment of the
1366 importance of the event and the implication of any findings, including relevant previous
1367 experience with the same or similar drugs.

1368 In addition, in keeping with ICH GCP, the sponsor should expedite reporting of all SUADRs to all
1369 concerned investigator(s)/institution(s), the REB(s) where required (ICH E6, 5.17.1).

1370 Such expedited reports should comply with the applicable regulatory requirement(s) and with
1371 the ICH guideline for [Clinical Safety Data Management: Definitions and Standards for Expedited](#)
1372 [Reporting \(ICH E2A\)](#) (ICH E6, 5.17.2).

1373 The sponsor should also submit to the regulatory authority(ies) all safety updates and periodic
1374 reports, as required by applicable regulatory requirement(s) (ICH E6, 5.17.3).



Note that **sections C.01.016 and C.01.017** of the Regulations (listed below), which also refer to prohibition and serious ADR reporting, do **not** apply to drugs used for the purpose of a clinical trial, **except clinical trial drugs used in Phase IV trials**.

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C.01.016

No manufacturer shall sell a drug unless the manufacturer complies with the conditions set out in sections C.01.017 to C.01.019.

C.01.017

The manufacturer shall submit to the Minister a report of all information relating to the following serious adverse drug reactions within 15 days after receiving or becoming aware of the information, whichever occurs first:

- (a) any serious adverse drug reaction that has occurred in Canada with respect to the drug; and
- (b) any serious unexpected adverse drug reaction that has occurred outside Canada with respect to the drug.

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Please refer to the [Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications](#) for detailed guidance on how to report.



Examples of observations typically cited under this section of the Regulations include:

- The sponsor did not inform Health Canada within 15 days of becoming aware of serious unexpected adverse drug reactions in or outside Canada that were not fatal or life threatening.
- The sponsor did not inform Health Canada within 7 days of becoming aware of serious unexpected adverse drug reactions in or outside Canada that were fatal or life threatening.
- The sponsor did not submit a complete report with an assessment of its findings within 8 days of informing Health Canada of a fatal or life threatening serious unexpected adverse drug reaction.

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5.15 Discontinuance of a Clinical Trial

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C.05.015



- (1) If a clinical trial is discontinued by the sponsor in its entirety or at a clinical trial site, the sponsor shall
 - (a) inform the Minister no later than 15 days after the date of the discontinuance;
 - (b) provide the Minister with the reason for the discontinuance and its impact on the proposed or ongoing clinical trials in respect of the drug conducted in Canada by the sponsor;
 - (c) as soon as possible, inform all qualified investigators of the discontinuance and of the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons; and

(d) in respect of each discontinued clinical trial site, stop the sale or importation of the drug as of the date of the discontinuance and take all reasonable measures to ensure the recovery of all unused quantities of the drug that have been sold.

(2) If the sponsor has discontinued the clinical trial in its entirety or at a clinical trial site, the sponsor may resume selling or importing the drug for the purposes of a clinical trial in its entirety or at a clinical trial site if, in respect of each clinical trial site where the sale or importation is to be resumed, the sponsor submits to the Minister the information referred to in subparagraphs C.05.005(c)(ix) and (x) and paragraphs C.05.005(d) and (h).

1380 Interpretation

1381 Please refer to section 2.8.1 of the [Guidance Document for Clinical Trial Sponsors: Clinical Trial](#)
1382 [Applications](#) for further requirements.

1383 Reporting to Health Canada of a temporary suspension by the sponsor of subject enrolment at a
1384 clinical trial site is required through notification.

1385 If a sponsor discontinues the clinical development of an investigational product (that is, for any
1386 or all indications, routes of administration, or dosage forms), the sponsor must maintain all
1387 sponsor-specific essential documents in conformance with the applicable regulatory
1388 requirement(s) (ICH E6, 5.5.8).

1389 If the sponsor discontinues the clinical development of an investigational product, the sponsor
1390 must notify Health Canada, all the trial investigators/institutions and other regulatory authorities
1391 which may be involved (ICH E6, 5.5.9).



Example of observation typically cited under this section of the Regulations includes:

- The sponsor did not inform Health Canada within 15 days of a clinical trial being discontinued.

5.16 Suspension and Cancellation

C.05.016



- (1) Subject to subsection (2), the Minister shall suspend the authorization to sell or import a drug for the purposes of a clinical trial, in its entirety or at a clinical trial site, if the Minister has reasonable grounds to believe that
 - (a) the sponsor has contravened these Regulations or any provisions of the Act relating to the drug;
 - (b) any information submitted in respect of the drug or clinical trial is false or misleading;
 - (c) the sponsor has failed to comply with good clinical practices; or
 - (d) the sponsor has failed to provide
 - (i) information or samples of the drug as required under section C.05.009 or C.05.013, or
 - (ii) information or a report under section C.05.014.
- (2) Subject to section C.05.017, the Minister shall not suspend an authorization referred to in subsection (1) unless
 - (a) the Minister has sent to the sponsor a written notice of the intention to suspend the authorization that indicates whether the authorization is to be suspended in its entirety or at a clinical trial site and the reason for the intended suspension;
 - (b) the sponsor has not, within 30 days after receipt of the notice referred to in paragraph (a), provided the Minister with information or documents that demonstrate that the authorization should not be suspended on the grounds that
 - (i) the situation giving rise to the intended suspension did not exist, or
 - (ii) the situation giving rise to the intended suspension has been corrected; and
 - (c) the Minister has provided the sponsor with the opportunity to be heard in paragraph (b).
- (3) The Minister shall suspend the authorization by sending to the

sponsor a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in its entirety or at a clinical trial site and the reason for the suspension.

(4) If the Minister has suspended an authorization under subsection (1), the Minister shall

(a) reinstate the authorization in its entirety or at a clinical trial site, as the case may be, if within 30 days after the effective date of the suspension the sponsor provides the Minister with information or documents that demonstrate that the situation giving rise to the suspension has been corrected; or

(b) cancel the authorization in its entirety or at a clinical trial site, as the case may be, if within 30 days after the effective date of the suspension the sponsor has not provided the Minister with the information or documents referred to in paragraph (a).

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Interpretation

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Health Canada shall suspend the authorization to sell or import a drug for the purposes of a clinical trial, in its entirety or at a clinical trial site, if Health Canada reasonably believes that any of the circumstances outlined in C.05.016 (1)(a) through (d) apply. Before suspending under C.05.016, Health Canada will send the sponsor a written notice of the intention to suspend the authorization that indicates whether the authorization is to be suspended in its entirety or at a clinical trial site, and the reason for the intended suspension.

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The sponsor then has **30 calendar days after receipt of this notice** to provide Health Canada with information or documents that demonstrate that the authorization should not be suspended on the grounds that:

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- the situation giving rise to the intended suspension did not exist, or

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- the situation giving rise to the intended suspension has been corrected, and will be given an opportunity to be heard as required under the Regulations.

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If a suspension is deemed necessary, Health Canada shall suspend the authorization by sending to the sponsor a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in its entirety or at a clinical trial site, and the reason for the suspension.

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Health Canada shall reinstate the authorization if, within **30 calendar days after the effective date of the suspension**, the sponsor provides Health Canada with information or documents that

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1413 demonstrate that the situation giving rise to the suspension did not exist or it has been
1414 corrected. Failure to provide any or adequate information within 30 calendar days after the
1415 effective date of suspension will result in cancellation of the authorization, either in its entirety
1416 or at a clinical trial site, as the case may be.

1417 Health Canada shall also suspend an open trial as a result of an inspection with a “non-
1418 compliant” (NC) rating. Depending on the risk involved, Health Canada would give the sponsor
1419 an opportunity to be heard by first issuing a “Notice of Intent to Suspend”. The Notification of
1420 Intent to Suspend will be issued along with the Final Inspection Exit Notice. The sponsor will be
1421 given **30 calendar days to respond** to the observations noted in the final inspection report, as
1422 well as to provide an impact analysis on the safety of the subjects in the study and the integrity
1423 of the collected data at that site. Health Canada will review the received response and make a
1424 decision as to whether or not suspension is necessary.



The Clinical Trial Compliance Program of Health Canada does not make inspection observations under this section of the Regulations.

1425 5.17 Suspension and Cancellation

1426 C.05.017



- (1) The Minister shall suspend an authorization to sell or import a drug for the purposes of a clinical trial, in its entirety or at a clinical trial site, before giving the sponsor an opportunity to be heard if the Minister has reasonable grounds to believe that it is necessary to do so to prevent injury to the health of a clinical trial subject or other person.
- (2) The Minister shall suspend the authorization by sending to the sponsor a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in its entirety or at a clinical trial site and the reason for the suspension.
- (3) If the Minister has suspended an authorization, the Minister shall
 - (a) reinstate the authorization in its entirety or at a clinical trial site, as the case may be, if within 60 days after the effective date of the suspension the sponsor provides the Minister with information or documents that demonstrate that the

situation giving rise to the suspension did not exist or that it has been corrected; or

- (b) cancel the authorization in its entirety or at a clinical trial site, as the case may be, if within 60 days after the effective date of the suspension the sponsor has not provided the Minister with the information or documents referred to in paragraph (a).

1427 Interpretation

1428 Health Canada shall suspend an authorization to sell or import a drug for the purposes of a
1429 clinical trial in its entirety or at a clinical trial site, **before giving the sponsor an opportunity to be**
1430 **heard** if Health Canada reasonably believes that it is necessary to do so to prevent injury to the
1431 health of a clinical trial subject or other people involved with the clinical trial.

1432 Health Canada shall suspend the authorization by sending to the sponsor a written notice of
1433 suspension of the authorization that indicates the effective date of the suspension, whether the
1434 authorization is suspended in its entirety or at an individual clinical trial site, and the reason for
1435 the suspension.

1436 If Health Canada has suspended an authorization, Health Canada shall reinstate the
1437 authorization in its entirety or at a clinical trial site, if **within 60 calendar days after the effective**
1438 **date of the suspension** the sponsor provides Health Canada with information or documents that
1439 demonstrate the situation giving rise to the suspension did not exist or that it has been
1440 corrected; or cancel the authorization in its entirety or at a clinical trial site, if within 60 calendar
1441 days after the effective date of the suspension the sponsor has not provided Health Canada with
1442 the required information.

1443 Investigator / Institution's Responsibilities

1444 Section 4.12 of ICH E6 sets out the responsibilities of an investigator/institution in the event of
1445 premature termination or suspension of a clinical trial.

1446 If a trial is prematurely terminated or suspended for any reason, the investigator/institution
1447 should:

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- promptly inform all trial subjects
 - ensure appropriate care and follow up of subjects
 - where required by regulatory requirement(s), inform the regulatory authority(ies)
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If an **investigator** terminates or suspends a trial without prior agreement of the sponsor:

- the investigator should inform the institution where applicable
- the investigator/institution should promptly inform the sponsor and the REB, and provide them with a detailed written explanation of the termination or suspension (ICH E6, 4.12.1)

If a **sponsor** terminates or suspends a trial (see ICH E6, 5.21):

- the sponsor should promptly inform the institution where applicable
- the investigator/institution should promptly inform the REB and provide them with a detailed written explanation of the termination or suspension (ICH E6, 4.12.2)

If the **REB** terminates or suspends its approval/favourable opinion of a trial (see ICH E6 3.1.2 and 3.3.9):

- the investigator must inform the institution where applicable
- the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension (ICH E6, 4.12.3).

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Sponsor's Responsibilities

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In addition to those requirements set out in the Regulations with respect to the discontinuance, suspension or cancellation of authorisation to sell or import a drug for the purpose of a clinical trial, section 5.21 of ICH E6 states that in the event of such an occurrence, the sponsor should:

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- promptly inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension, and provide the reason(s) for the termination or suspension
- promptly inform the REB and provide the reason(s) for the termination or suspension

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This can be done by either the sponsor or the investigator/institution, as specified by the applicable regulatory requirement(s).



The Clinical Trial Compliance Program of Health Canada does not make inspection observations under this section of the Regulations.

1460 Appendices

1461 Appendix A – Glossary

1462 Acronyms

1463 ADR: Adverse Drug Reaction

1464 AE: Adverse Event

1465 BGTD: Biologics and Genetic Therapies Directorate

1466 CGSB: Canadian General Standards Board

1467 CoA: Certificate of Analysis

1468 CRF: Case Report Form

1469 CRO: Contract Research Organization

1470 CTA: Clinical Trial Application

1471 CTA-A: Clinical Trial Application Amendment

1472 CTSI: Clinical Trial Site Information

1473 CV: Curriculum Vitae

1474 DIN: Drug Identification Number

1475 eCRF: Electronic Case Report Form

1476 GCP: Good Clinical Practices

1477 GMP: Good Manufacturing Practices

1478 GUI: Guide

1479 HC-SC: Health Canada-Santé Canada

1480 ICF: Informed Consent Form

1481	ICH:	International Conference on Harmonization
1482	ICH E6:	International Conference on Harmonization Guidance E6: Good Clinical Practice
1483		Consolidated Guideline
1484	IEC:	Independent Ethics Committee
1485	IP:	Investigational Product
1486	IRB:	Institutional Review Board
1487	ITA:	Investigational Testing Authorization
1488	NC:	Non-Compliant
1489	NHP:	Natural Health Product
1490	NOC:	Notice of Compliance
1491	NOL:	No Objection Letter
1492	NSN:	Not Satisfactory Notice
1493	PIC/S:	Pharmaceutical Inspection Co-Operation Scheme
1494	QI:	Qualified Investigator
1495	QIU:	Qualified Investigator Undertaking
1496	REB:	Research Ethics Board
1497	SAE:	Serious Adverse Event
1498	SADR:	Serious Adverse Drug Reaction
1499	SMO:	Site Management Office
1500	SOAD:	Summary of Additional Drugs Form
1501	SOP:	Standard Operating Procedure
1502	SUADR:	Serious Unexpected Adverse Drug Reaction
1503	TCPS:	Tri-Council Policy Statement
1504	TPD:	Therapeutic Products Directorate

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Terms



These definitions explain how terms are used in this document. If there is a conflict with a definition in the [Food and Drugs Act](#) or associated regulations, the definition in the Act or regulations prevails. Definitions quoted from other documents are identified in brackets at the end of the definition.

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Adverse drug reaction (ADR) – means any noxious and unintended response to a drug that is caused by the administration of any dose of the drug.



This definition is consistent with, but further expanded on, in section 1.1. of ICH E6, which reads:

“In the pre-approval clinical experience, with a new medicinal product or its new usages particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase *responses to a medicinal product* means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, that is, the relationship cannot be ruled out.”

If the study includes marketed medicinal products, that is, Phase IV: “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.”

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Adverse event (AE) – means any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and includes an adverse drug reaction.



Further expanded on in section 1.2 of ICH E6, the definition of “adverse event” reads:

“Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.”

1511 **Clinical trial** – means an investigation in respect of a drug for use in humans that involves human
1512 subjects and that is intended to discover or verify the clinical, pharmacological or
1513 pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study
1514 the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or
1515 efficacy of the drug.



This definition is consistent with section 1.12 of ICH E6.

1516 **Drug** – means a drug for human use that is to be tested in a clinical trial.



ICH E6 does not define the word “drug”.

In the context of clinical trials, a drug would include a drug for human use that is to be tested in a clinical trial and includes pharmaceuticals, biologics, gene therapies, blood products, vaccines and radiopharmaceuticals ([Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications](#)).

Consistent with Section 2 of the [Food and Drugs Act](#), a drug is defined as any substance or mixture of substances used in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, and in restoring, correcting or modifying organic functions.

1517 **Good clinical practices (GCP)** – means generally accepted clinical practices that are designed to
1518 ensure the protection of the rights, safety and well-being of clinical trial subjects and other
1519 persons, and the good clinical practices referred to in section C.05.010.



Consistent with, but further expanded on in section 1.24 of ICH E6, which defines GCP as:

“A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible, accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.”

1520 **Import** – means to import a drug into Canada for the purpose of sale in a clinical trial.



ICH E6 does not make reference to importation of clinical trial drugs.

1521 **Importer** – The sponsor or person designated by the sponsor who is responsible for the import of
1522 the drug into Canada for the purpose of sale in a clinical trial. Individual investigators at the
1523 clinical trial sites in Canada may serve as Canadian Importers ([Guidance Document for Clinical](#)
1524 [Trial Sponsors: Clinical Trial Applications](#)).

1525 **Investigator’s brochure** – means, in respect of a drug, a document containing the preclinical and
1526 clinical data on the drug that are described in paragraph C.05.005(e).



- This is consistent with the definition of “investigator’s brochure” in ICH E6, 1.36.
- Paragraph C.05.005(e) of the Regulations describes the content that must be included in an investigator’s brochure that is submitted to Health Canada.
- Section 7 of ICH E6 provides additional guidance on the content of an investigator’s brochure.

1527 **Protocol** – means a document that describes the objectives, design, methodology, statistical
1528 considerations and organization of a clinical trial.



- The use of the term “protocol” is consistent with ICH E6, 1.44.
- In accordance with paragraph C.05.005(a) of the Regulations, the application by a sponsor to sell or import a drug for the purpose of conducting a clinical trial in Canada must submit a protocol as part of their application.
- Section 6 of ICH E6 describes the information found in a protocol.

1529 **Qualified investigator (QI)** – means the person responsible to the sponsor for the conduct of the
1530 clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the
1531 province where that clinical trial site is located, and who is

- (a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and
- (b) in any other case, a physician and a member in good standing of a professional medical association.



ICH E6 uses the word “Investigator” to describe the individual responsible for the conduct of a clinical trial at a site.

The use of the term “Principal Investigator” is commonly used to refer to an investigator that is leading a team of individuals conducting a trial at a site, and though would have the same meaning as qualified investigator (QI), however “Principal Investigator” is not a legally defined term used in Canada.

Note that paragraph C.05.010(e) of the Regulations states that there be no more than one QI at each clinical trial site. However, there may be Sub-Investigators/Co-Investigators in the study under the supervision of a QI.

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Research ethics board (REB) – means a body that is not affiliated with the sponsor, and

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(a) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being; and

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(b) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents under the *Immigration and Refugee Protection Act*, that is composed of both men and women and that includes at least

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(i) two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline,

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(ii) one member knowledgeable in ethics,

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(iii) one member knowledgeable in Canadian laws relevant to the biomedical research to be approved,

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(iv) one member whose primary experience and expertise are in a non-scientific discipline, and

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(v) one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted.



ICH E6 uses the terms “**institutional review board**” (IRB) and “**independent ethics committee**” (IEC) interchangeably, the definition of which is consistent with that of an REB. In ICH E6, an IRB or an IEC is defined as:

“An independent body (a review board or committee, institutional, regional, national or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things,

reviewing and approving/providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.”

Note: REBs in Canada are held to more stringent composition requirements than are described in this section for ICH E6.

1557 **Sell** – includes offer for sale, expose for sale, have in possession for sale and distribute, whether
1558 or not the distribution is made for consideration.



The definition is broad in scope, and includes dispensing of drugs to subjects by physicians.

1559 **Site or trial site** – The location(s) where trial-related activities are actually conducted (ICH E6,
1560 1.59).



Health Canada’s interpretation is one site equals one trial by one QI at one location (address).

1561 **Serious adverse drug reaction (SADR)** – means an adverse drug reaction that requires in-patient
1562 hospitalization or prolongation of existing hospitalization, that causes congenital malformation,
1563 that results in persistent or significant disability or incapacity, that is life threatening or that
1564 results in death.

1565 **Serious unexpected adverse drug reaction (SUADR)** – means a serious adverse drug reaction
1566 (SADR) that is not identified in nature, severity or frequency in the risk information set out in the
1567 investigator’s brochure or on the label of the drug.



The definitions for SADR and SUADR are consistent with those found in sections 1.50 and 1.60 of ICH E6.

These definitions are expanded on in [*ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting \(ICH E2A\)*](#).

1568 **Sponsor** – means an individual, corporate body, institution or organization that conducts a
1569 clinical trial.



ICH E6 elaborates on this definition in section 1.53 to include individuals, companies, institutions or organizations that take responsibility for the initiation, management and/or financing of a clinical trial.

The sponsor is ultimately responsible for all regulatory requirements regarding the conduct of the trial in Canada. Where a third party, such as a contract research organization (CRO) or a site management office (SMO), has been delegated by written contract to carry out some or all of the sponsor's responsibilities, they must also demonstrate adherence to the applicable regulatory requirements.

If a physician is identified on the clinical trial application (CTA) as the sponsor, he/she must assume the responsibilities of both the sponsor and the QI. This would include ensuring that all of the sponsor's obligations under section C.05.010 of Part C, Division 5 are met at all sites at which the trial is being conducted, as well as all other applicable sections of Part C, Division 5.

Note: Part C, Division 5 of the Regulations does not differentiate between a commercial and a non-commercial sponsor.

1570 **Standard operating procedure (SOP)** – Detailed, written instructions to achieve uniformity of the
1571 performance of a specific function (ICH E6, 1.55).

1572 **Icons** found within this document include:

Important	Information	Tip

1573

1574 Appendix B – References



Web addresses were accurate at the time of publication of this document.

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