



## Notice

Our reference number: 11-120556-783

### **Release of the Draft Guidance Document: Clinical Trial Sponsors - Clinical Trial Applications**

Health Canada is pleased to announce the release of the *Draft Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*. This Guidance serves to assist sponsors in seeking authorization from Health Canada to conduct a clinical trial with a drug (pharmaceutical and/or biologic and radiopharmaceuticals) in human subjects pursuant to Part C, Division 5 of the *Food and Drug Regulations*. This guidance document clarifies application and post-authorization requirements and procedures.

Noteworthy updates include:

- Harmonizing Module 1 with the newly proposed Common Technical Document (CTD) format (please refer to the draft consultation document entitled “*Revised draft guidance document preparation of drug submissions and applications in the common technical document (CTD) format*” posted on the Health Canada website);
- Outlining application requirements with respect to comparative bioavailability studies for pharmaceuticals;
- Providing additional guidance on clinical and quality amendments vs. notifications;
- Adding filing requirements for the importation of clinical trial drugs;
- Elaborating on adverse drug reaction (ADR) reporting criteria and;
- Changing the policy on the 7 day administrative review target.

The document is being released for a 90-day comment period. Health Canada will review the comments received during this comment period and revise the Guidance as necessary. A final version of this document will then be posted.

This consultation is open for comment starting November 7, 2011 until February 4, 2012. Please submit your comments via email, fax or by mail to:

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Therapeutic Products Directorate  
Health Canada  
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# **DRAFT GUIDANCE DOCUMENT FOR CLINICAL TRIAL SPONSORS**

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## **Clinical Trial Applications**

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**This guidance document is being distributed for comment purposes only.**

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Minister of Health



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**Health Products and Food Branch**

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<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by:</p> <ul style="list-style-type: none"><li>• minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,</li><li>• promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.</li></ul> <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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*Également disponible en français sous le titre : Ébauche de la ligne directrice à l'intention des promoteurs d'essais cliniques - demandes d'essais cliniques*

49 **FOREWORD**

50

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

55

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

61

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

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

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## 1 INTRODUCTION

The *Food and Drugs Act* and supporting regulations provide authority to Health Canada to regulate the sale and importation of drugs for use in human clinical trials in Canada. This document provides guidance on the regulatory obligations pursuant to Part C, Division 5 of the *Food and Drug Regulations* (herein referred to as the *Regulations*), Drugs for Clinical Trials Involving Human Subjects.

### 1.1 Policy Objectives

To provide Guidance to sponsors seeking authorization to conduct a clinical trial in Canada that supports the protection of clinical trial subjects and contributes to the high standards of excellence in research and development in Canada. This document clarifies application and post-authorization requirements and outlines procedures for obtaining authorization.

### 1.2 Policy Statements

Clinical trial sponsors must submit a clinical trial application (CTA) to Health Canada for authorization to sell or import a drug for the purpose of a clinical trial.

Clinical trial sponsors must conduct clinical trials according to generally accepted principles of good clinical practice that ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons.

Research Ethics Boards (REBs) have an important role in the oversight of the conduct of clinical trials. Sponsors are required by the *Regulations* to obtain REB approval for each clinical trial site prior to commencing the trial at that site.

The *Regulations* are generally consistent with the principles, definitions and standards found in the International Conference on Harmonisation (ICH) guidance documents on clinical trials. Where inconsistencies exist, the *Regulations* take precedence.

The format for CTAs as outlined in this guidance document is consistent with that used for other types of drug submissions filed to Health Canada, based on the format of the ICH Common Technical Document (CTD). Although the scope of the ICH CTD does not include applications at the clinical research stage of development, the modular format of the CTD is being extended to CTAs to facilitate the preparation of drug submission information throughout the lifecycle of a drug.

### 1.3 Scope and Application

The information provided in this guidance document is for clinical trials involving drugs (pharmaceuticals and/or biologics and radiopharmaceuticals) in human subjects. In the *Regulations* a clinical trial is an investigation in respect of a drug that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

This guidance document applies to:

- Clinical trials for Phases I through III of drug development and comparative bioavailability studies.
- Clinical trials for marketed drugs where the proposed use of the drug is outside the parameters of the Notice of Compliance (NOC) or Drug Identification Number (DIN) application.
- Clinical Trial Amendments (CTA-A) [C.05.008] and Notifications (CTA-N) [C.05.007].

This guidance document does not apply to clinical trials involving medical devices or natural health products.

### 1.4 Background

The regulatory requirements respecting drugs to be used for the purposes of clinical trials were originally developed in the early 1960s. On September 1, 2001, the regulatory amendments to Part C, Division 5 of the *Food and Drug Regulations* (Drugs for Clinical Trials Involving Human Subjects) came into force to strengthen protections for clinical trial subjects in Canada.

Health Canada completed a review of the clinical trials regulatory framework through 2006-2008 that included assessing input received from stakeholders, and considering best practices in other countries, as well as Health Canada's experience with the existing regulatory framework (refer to Appendix 2). Subsequently, Health Canada proceeded with a series of initiatives, one of which included consultations on the type of guidance required by industry to assist in meeting regulatory obligations (Spring/Summer 2008). During the consultations, stakeholders noted the need for better guidance on processes, requirements, and roles and responsibilities in clinical trial activities. Stakeholders called for clear and consistent definitions and guidance on the requirements for various types of clinical trials. Clarification was also requested on information requirements for Health Canada to review CTAs within 30 days and on which applications qualify for the seven-day administrative review target.

205 Additionally, some stakeholders raised concerns regarding the requirements for CTA-As, which  
206 they believed to be burdensome to some groups. Respondents identified the need to clarify the  
207 regulatory requirements, streamline processes and review the amount of information that is  
208 required. In particular, comments indicated that Health Canada should consider limiting full  
209 amendment submissions to filing only substantive changes and to further define “minor” and  
210 “major” changes.

211  
212 In response to these consultations, the *Guidance for Clinical Trial Sponsors - Clinical Trial*  
213 *Applications* has been updated to reflect stakeholder concerns and improve clarify and  
214 communication. The guidance includes new information for sponsors regarding information  
215 needs and processes related to CTAs, CTA-As and notifications.

216

## 217 **2 GUIDANCE FOR IMPLEMENTATION**

218

### 219 **2.1 Abbreviations/Definitions**

220

#### 221 **2.1.1 Abbreviations**

222

223	ADR	Adverse Drug Reaction
224	BGTD	Biologics and Genetic Therapies Directorate
225	CIOMS	Council for International Organizations of Medical Sciences
226	CR	Central Registry
227	CTA	Clinical Trial Application
228	CTA-A	Clinical Trial Application-Amendment
229	CTA-N	Clinical Trial Application-Notification
230	CTSI	Clinical Trial Site Information
231	CTD	Common Technical Document
232	DIN	Drug Identification Number
233	DMF	Drug Master File
234	GCP	Good Clinical Practice
235	HPFBI	Health Products and Food Branch Inspectorate
236	IB	Investigator’s Brochure
237	ICD	Informed Consent Document
238	ICH	International Conference on Harmonisation
239	ITA	Investigational Testing Application
240	NOC	Notice of Compliance
241	NOL	No Objection Letter
242	NSN	Not Satisfactory Notice
243	PSEAT-CTA	Protocol Safety and Efficacy Assessment Template - Clinical Trial
244		Application
245	QIS	Quality Information Summary
246	QIS-PER	Quality Information Summary - Positron-Emitting Radiopharmaceuticals

247	QIS-R	Quality Information Summary - Radiopharmaceuticals
248	QIU	Qualified Investigator Undertaking
249	QOS	Quality Overall Summary
250	QOS-CE	Quality Overall Summary - Chemical Entities (Clinical Trial Applications)
251	REB	Research Ethics Board
252	TPD	Therapeutic Products Directorate

### 2.1.2 Definitions

Most of the definitions listed below were taken from the *Regulations*, and the Health Canada / ICH Guidance Documents *E6: Guideline for Good Clinical Practice: Consolidated Guideline* (ICH E6) and *E8: General Considerations for Clinical Trials*.

**Adverse Drug Reaction:** Any noxious and unintended response to a drug that is caused by the administration of any dose of the drug.

**Adverse Event:** 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.

**Authorized Clinical Trial Application:** For the purposes of this document, an authorized clinical trial application is one that has been filed with Health Canada and has been granted a No Objection Letter (NOL).

**Clinical Trial:** An investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

**Clinical Trial Site:** The location where trial-related activities are actually conducted.

**Date of Commencement of a Clinical Trial:** For the purpose of the Clinical Trial Site Information Form, this is defined as the date when the clinical trial site will be ready to enrol patients in the clinical trial.<sup>1</sup>

**Drug:** For the purpose of this document, 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. Consistent with the *Food and Drugs Act*, a drug is

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<sup>1</sup> Before commencement of a trial, the sponsor must ensure that Health Canada and the Research Ethics Board have raised no objections to the Clinical Trial Application.

286 defined as including any substance used in the diagnosis, treatment, mitigation or  
287 prevention of a disease, disorder or abnormal physical state, and in restoring, correcting  
288 or modifying organic functions.

289  
290 **Good Clinical Practices:** Generally accepted clinical practices that are designed to  
291 ensure the protection of the rights, safety and well-being of clinical trial subjects and  
292 other persons. These are the good clinical practices referred to in section C.05.010 of the  
293 *Regulations*.

294  
295 **Import:** To import a drug into Canada for the purpose of sale in a clinical trial.

296  
297 **Importer:** The sponsor or person designated by the sponsor who is responsible for the  
298 import of the drug into Canada for the purpose of sale in a clinical trial. Individual  
299 investigators at the clinical trial sites in Canada may serve as Canadian Importers.

300  
301 **Informed Consent Document/Form<sup>2</sup>:** Written informed consent, given in accordance  
302 with the applicable laws governing consent is obtained from every person before that  
303 person participates in a clinical trial but only after that person has been informed of:

304  
305 a) The risks and anticipated benefits to his or her health arising from participation in the  
306 clinical trial; and

307  
308 b) All other aspects of the clinical trial that are necessary for that person to make the  
309 decision to participate in the clinical trial.

310  
311 **Institution/Investigator-initiated Clinical Trial:** A clinical trial that is initiated and  
312 conducted by an institution or an individual investigator. For such trials, the institution or  
313 investigator is considered to be the sponsor of the trial and must fill all the regulatory  
314 obligations of the sponsor as outlined in the *Regulations*.

315  
316 **Investigator's Brochure:** In respect of a drug, a document containing the nonclinical  
317 and clinical data on the drug that are described in section C.05.005(e) of the *Regulations*.

318  
319 **Phase I:** Clinical trials designed mainly to determine the pharmacological actions of the  
320 drug and the side effects associated with increasing doses. Pharmacokinetic studies as  
321 well as drug interaction studies are usually considered as Phase I trials regardless of when  
322 they are conducted during drug development. Phase I trials are generally conducted in

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<sup>2</sup> For further guidance regarding the informed consent process, please see International Conference on Harmonisation E6, in particular section 4.8, and the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, in particular chapter 3.

323 healthy volunteers, but may be conducted in patients when administration of the drug to  
324 healthy volunteers is not ethical.

325  
326 **Phase II:** Clinical trials to evaluate the efficacy of the drug in patients with medical  
327 conditions to be treated, diagnosed or prevented and to determine the side effects and  
328 risks associated with the drug. If a new indication for a marketed drug is to be  
329 investigated, then those clinical trials may generally be considered Phase II trials.

330  
331 **Phase III:** Controlled or uncontrolled trials conducted after preliminary evidence  
332 suggesting efficacy of the drug has been demonstrated. These are intended to gather the  
333 additional information about the clinical effectiveness and safety under the proposed  
334 conditions of use.

335  
336 **Phase IV:** All studies performed within the approved indication after the drug has been  
337 approved by the regulator for the market. These studies are often important for  
338 optimizing the drug's use. They may be of any type but must have valid scientific  
339 objectives. Commonly conducted studies include safety studies and studies designed to  
340 support use under the approved indication, for example (e.g.) mortality and morbidity  
341 studies, or epidemiological studies.

342  
343 **Protocol:** A document that describes the objectives, design, methodology, statistical  
344 considerations and organization of a clinical trial.

345  
346 **Qualified Investigator:** The person responsible to the sponsor for the conduct of the  
347 clinical trial at the clinical trial site, who is entitled to provide health care under the laws  
348 of the province where that clinical trial site is located, and who is

349  
350 a) in the case of a clinical trial respecting a drug to be used for dental purposes  
351 only, a physician or dentist and a member in good standing of a professional  
352 medical or dental association; and

353  
354 b) in any other case a physician and a member in good standing of a professional  
355 medical association.

356  
357 **Research Ethics Board:** A body that is not affiliated with the sponsor, and

358  
359 a) the principal mandate of which is to approve the initiation of, and conduct  
360 periodic reviews of, biomedical research involving human subjects in order to  
361 ensure the protection of their rights, safety and well-being; and

362

- 363 b) that has at least five members, that has a majority of members who are  
364 Canadian citizens or permanent residents under the *Immigration Act*, that is  
365 composed of both men and women and that includes at least:  
366
- 367 i) two members whose primary experience and expertise are in scientific  
368 discipline, who have broad experience in the methods and areas of  
369 research to be approved and one of whom is from a medical discipline or,  
370 if the clinical trial is in respect of a drug to be used for dental purposes  
371 only, is from a medical or dental discipline,  
372
  - 373 ii) one member knowledgeable in ethics,  
374
  - 375 iii) one member knowledgeable in Canadian laws relevant to the  
376 biomedical research to be approved,  
377
  - 378 iv) one member whose primary experience and expertise are in a non-  
379 scientific discipline, and  
380
  - 381 v) one member who is from the community or is a representative of an  
382 organization interested in the areas of research to be approved and who is  
383 not affiliated with the sponsor or the site where the clinical trial is to be  
384 conducted.  
385

386 **Senior Medical or Scientific Officer:** A scientific or medical officer residing in Canada,  
387 representing the sponsor, who is responsible for providing an attestation with respect to  
388 the Clinical Trial Application/Amendment at the time of filing, as outlined in Appendix 3  
389 of the Drug Submission Application Form (HC/SC 3011).  
390

391 **Serious Adverse Drug Reaction:** An adverse drug reaction that requires in-patient  
392 hospitalization or prolongation of existing hospitalization, that causes congenital  
393 malformation, that results in persistent or significant disability or incapacity, that is life  
394 threatening or that results in death.  
395

396 **Serious Unexpected Adverse Drug Reaction:** A serious adverse drug reaction that is  
397 not identified in nature, severity or frequency in the risk information set out in the  
398 investigator's brochure or on the label of the drug.  
399

400 **Sponsor:** An individual, corporate body, institution or organization that conducts a  
401 clinical trial. The sponsor must comply with its obligations as set out in the *Regulations*  
402 (C.05.010-C.05.015) in adhering to good clinical practices for the proper use of the drugs,  
403 drug labelling requirements, record keeping, submission of information, reporting of  
404 ADRs, and trial discontinuation reporting requirements.

405 **2.2 Pre-Clinical Trial Application (CTA) Consultation Meeting**  
406

407 Health Canada invites sponsors to request a pre-CTA consultation meeting. Such consultations  
408 may be particularly useful for new active substances or applications that will include complex  
409 issues that may be new to Health Canada.

410  
411 The pre-CTA consultation meeting provides an opportunity for the sponsor to present relevant  
412 data, discuss concerns and issues regarding drug development. It also gives Health Canada an  
413 opportunity to provide guidance on the acceptability of the proposed trial(s). Sponsors may  
414 invite the qualified investigator(s) who will be involved in the proposed trial(s) in Canada to  
415 attend the meeting.

416  
417 **2.2.1 Request for a Pre-Clinical Trial Application (CTA) Consultation Meeting**  
418

419 Requests for a pre-CTA consultation meeting should be submitted in writing by the  
420 sponsor to the appropriate Directorate (refer to Appendix 1).

421  
422 Requests should be submitted in the form of a cover letter proposing four dates and times  
423 suitable for a pre-CTA consultation meeting. The cover letter should be accompanied by  
424 the following information:

- 425
- 426 • A brief synopsis of the proposed study;
  - 427 • A list of questions to be addressed by the Directorate during the meeting; and
  - 428 • Sufficient information for Health Canada to assess the utility of the meeting and  
429 identify the appropriate staff necessary to discuss the proposed issues. This will  
430 assist in ensuring efficient use of Health Canada resources.

431  
432 The Directorate will acknowledge the request for consultation. If the Directorate agrees  
433 with the request, the acknowledgement letter will indicate the number of copies of the  
434 pre-CTA information package to be provided and confirm the pre-CTA consultation  
435 meeting date.

436  
437 **2.2.2 Pre-Clinical Trial Application (CTA) Information Package**  
438

439 The Information Package should contain:

- 440
- 441 a) proposed agenda, any prepared slides, and a complete list of attendees  
442 *[it is recognized that the slides may change prior to the meeting]*  
443
  - 444 b) a brief summary of all data including:  
445
    - 446 i) a tabular listing of completed nonclinical and clinical studies,

- 447 ii) an outline of the observed toxicological manifestations and a discussion  
448 of their impact on the use of the drug in humans,  
449
- 450 iii) an outline of the observed adverse events and a discussion of potential  
451 safety problems;  
452
- 453 c) a proposed global clinical plan for the current stage of drug development  
454 including regulatory status in other countries;  
455 *[It is recognized that this plan is subject to change as new information becomes*  
456 *available.]*  
457
- 458 d) details of the proposed clinical trials to be conducted in Canada, within the  
459 scope of the intended CTA, including:  
460
- 461 i) a statement of trial design,  
462
- 463 ii) parameters, values, ranges or limits for indication(s) and clinical use(s),  
464 patient study population(s) and routes of administration,  
465
- 466 iii) parameters, values, ranges or limits for dosage form(s), dosage  
467 regimen(s) and formulation(s),  
468
- 469 iv) proposed procedures and/or criteria for patient monitoring, clinical  
470 efficacy and safety assessments, alternative treatments, premature patient  
471 discontinuation and other considerations, as appropriate;  
472
- 473 e) a summary of significant Quality (Chemistry and Manufacturing) aspects of the  
474 drug;  
475
- 476 i) a listing of all production site(s) - **only for biologics and**  
477 **radiopharmaceuticals,**  
478
- 479 ii) a summary of the method of manufacture for both drug substance and  
480 dosage form,  
481
- 482 iii) relevant flow charts,  
483
- 484 iv) a listing of quality control procedures and specifications, and  
485
- 486 v) a summary of product characteristics.  
487

488 Should the pre-CTA package be found deficient, the sponsor may be requested to  
489 reschedule or postpone the meeting to allow the sponsor to assemble a more thorough  
490 package. Please note that the Directorate reserves the right to modify or truncate the  
491 proposed agenda as it sees fit to better achieve the stated goals of the meeting.  
492

### 493 **2.2.3 Pre-Clinical Trial Application (CTA) Consultation Meeting Record**

494  
495 The sponsor should prepare and send to the appropriate Directorate a written record of  
496 the discussions and conclusions of the consultation meeting within 14 days of the  
497 consultation date. All records of this consultation will be added to the Central Registry  
498 (CR) file for the drug.  
499

500 Meeting minutes approved by all parties in attendance at the meeting should be included  
501 in the subsequent CTA.  
502

## 503 **2.3 Clinical Trial Applications (CTAs)**

504  
505 The sponsor must file a CTA **prior** to the initiation of the trial [C.05.005]. CTAs are required for  
506 human drug clinical trials in Phases I through III of drug development and comparative  
507 bioavailability studies; this includes trials involving marketed drugs, where the proposed use of  
508 the drug is outside the parameters of the NOC or DIN, e.g., one or more of the following is  
509 different:  
510

- 511 a) Indication(s) and clinical use;
- 512
- 513 b) Target patient populations(s);
- 514
- 515 c) Route(s) of administration; or
- 516
- 517 d) Dosage regimen(s).
- 518

519 **Sponsors are *not* required to file a CTA for clinical trials involving marketed drugs where**  
520 **the investigation is to be conducted within the parameters of the approved NOC or DIN**  
521 **[C.05.006(2)]; these trials are referred to as Phase IV clinical trials.**  
522

523 Sponsors must conduct all clinical trials, including Phase IV trials, in accordance with the  
524 principles of GCPs [C.05.010] and obtain REB approval.

525 **2.3.1 Filing a Clinical Trial Application (CTA)**

526  
527 CTAs should be sent directly to the appropriate review Directorate (refer to Appendix 1).

528  
529 The outer label should be clearly identified with “**Clinical Trial Application**”.

530  
531 **2.3.1.1 Joint Reviews**

532  
533 CTAs or CTA-As that involve the use of:

- 534 i) pharmaceuticals **and** biologics or radiopharmaceuticals;  
535 ii) a medical device and drug combination that is classified as a drug; or  
536 iii) a natural health product and a drug, must be submitted to the appropriate lead  
537 Directorate / Bureau **in duplicate**.

538  
539 Authorization for the sale and importation of all investigational products to be used  
540 within a CTA or CTA-A must be obtained prior to the initiation of the clinical trial or  
541 implementation of the protocol amendment.

542  
543 The lead Directorate / Bureau will be responsible for communicating the regulatory  
544 decision to the sponsor.

545  
546 For CTAs that involve the use of an unlicensed class 2, 3, or 4 medical device, a separate  
547 ITA and CTA must be filed and authorized before the trial can commence.

548  
549 **2.3.2 Clinical Trial Application (CTA) Format**

550  
551 The CTA is composed of three parts (modules):

- 552  
553 • Module 1 - contains administrative and clinical information about the proposed  
554 trial;  
555  
556 • Module 2 - contains Quality (Chemistry and Manufacturing) summaries about the  
557 drug product(s) to be used in the proposed trial; and  
558  
559 • Module 3 - contains additional supporting Quality information.

560  
561 The CTA should be submitted in hard copy and in electronic copies in a file format  
562 accepted by Health Canada. In accordance with electronic specifications, all documents  
563 should be submitted in electronic format and must be identical to the hard copies  
564 provided in the CTA.

565

566 Refer to Appendix 2 for guidance documents that may be useful in the preparation of the  
567 application.  
568

569 **For Biologics and Radiopharmaceuticals:** if the CTA contains both Clinical and  
570 Quality (Chemistry and Manufacturing) information, Module 1 (Administrative / Clinical  
571 Information) should be submitted in **duplicate**.  
572

Module	Type of submission	Contents of submission package
1		<b>Administrative and Product Information for Canada</b>
1.0		<b>Correspondence</b>
1.0.1	<b>CTA/CTA-A</b>	Cover letter For CTA-As, a cover letter indicating the original CTA(s) and previous CTA-As with file number and control number(s).
1.0.5	<b>CTA/CTA-A</b>	Meetings Including e.g., a copy of the record of the discussions and conclusions of the pre-CTA consultation meeting or other relevant correspondence with Health Canada, if applicable.
1.1	<b>CTA/CTA-A</b>	Table of Contents A listing of the contents of Module 1 (Administrative / Clinical Information), Module 2 (Common Technical Document Summaries) and Module 3 (Quality), if applicable.
1.2		<b>Administrative Information</b>
1.2.1	<b>CTA/CTA-A</b>	Application Forms A completed and signed Drug Submission Application Form (HC/SC 3011) including Appendix 3, signed by the Senior Medical or Scientific Officer in Canada and the Senior Executive Officer. (Appendices 1 and 2 of the HC/SC 3011 Form should be completed and submitted if applicable). Please refer to Appendix 2 of this document for the relevant URL address.  For Institution/Investigator-initiated clinical trials, Appendix 3 of the Drug Submission Application Form (HC/SC 3011) may be signed by the appropriate Department head in lieu of the Senior Executive Officer and the Qualified Investigator in lieu of the Senior Medical or Scientific Officer.

1.2.3	<b>CTA/CTA-A</b>	<p>Certification and Attestation Forms</p> <p>Including a Letter of Attestation for electronic documents in accordance with the electronic specification requirements for CTAs and CTA-As (refer to Appendix 2 for link).</p>
1.2.5.1		Clinical Trial Site Information
	<b>CTA</b>	<p>The Clinical Trial Site Information (CTSI) Form should be provided for each proposed clinical trial site, if known at the time of the application as per C.05.005(c). The CTSI Form must be submitted prior to commencement of a clinical trial. Please refer to section 2.7.3 for additional information.</p> <p>If any changes are made to the CTSI Form (for example, change of qualified investigator) a revised CTSI Form should be submitted.</p>
	<b>CTA-A (Clinical)</b>	<p>An updated CTSI form should be provided for each site participating in the clinical trial to report that the amendment has been implemented. Health Canada recognizes that not all information required in the CTSI form may be available at the time of filing a CTA-A. In this case, sponsors are requested to state a commitment to filing the completed form prior to implementation of the amendment at a site as per C.05.008(c). Please see section 2.7.3 for additional information.</p>

1.2.6	CTA/CTA-A	<p>Authorization for Sharing Information</p> <p>Letters authorizing Health Canada to access related files (for example, a previously authorized CTA, Drug Master Files, Manufacturing Site Reference Files), if applicable. For example, a letter of access may be required to satisfy requirements for a CTA if a sponsor is utilizing a drug in a clinical trial that has not received a NOC and/or a DIN and the manufacturer of the drug does not wish to disclose confidential information about the drug to the clinical trial sponsor.</p> <p><b>Reference to a Drug Master File (DMF):</b></p> <ul style="list-style-type: none"> <li>- A letter written by the holder of the DMF permitting Health Canada to reference information in the DMF in support of the sponsor’s CTA should be submitted.</li> <li>- The CTA sponsor should ensure that the supporting DMF (including submission of the letter of access and payment of related fees) has been submitted to and accepted by Health Canada prior to filing a CTA.</li> </ul> <p><b>Reference to an application previously submitted to and authorized by Health Canada:</b></p> <ul style="list-style-type: none"> <li>- A letter written by the sponsor of the referenced application authorizing Health Canada to access the information in support of the sponsor's CTA should be submitted.</li> <li>- The referenced information should meet the regulatory requirements for CTAs.</li> <li>- The letter of access should include the file number and control number(s) of the referenced submission(s).</li> </ul> <p><b>For Pharmaceuticals:</b> Where chemistry and manufacturing information is referenced, sponsors are still required to complete the appropriate Quality Overall Summary (QOS) template (Module 2, [2.3]) including the introduction and any sections not covered by the letter of access.</p>
1.2.7	CTA/CTA-A (Clinical)	<p>International Information</p> <p>Information regarding refusals by regulatory authorities outside Canada, if applicable.</p>

1.2.9	<b>CTA/CTA-A</b>	<p><b>Other Administrative Information</b></p> <p>This section is for any administrative information that does not have a designated location in the CTD format. This section should NOT contain any scientific information.</p>
1.3		<b>Product Information</b>
1.3.4		Investigator’s Brochure for Clinical Trial Applications (CTA)/CTA-A
	<b>CTA</b>	<p>A copy of the current Investigator's Brochure (IB), supplemented as appropriate with up-to-date safety, non-clinical and clinical data.</p> <p>The IB containing all information regarding the product to date should be prepared in accordance with the ICH E6, and should be reviewed at least annually and revised as necessary. If the IB has been updated relative to a version contained within a previously authorized CTA or CTA-A, a tabulated summary of the changes should be provided, including a rationale for each change that includes any omissions or deletions from previous versions. Sectional reports should not be submitted unless requested. Please refer to section 2.8.4 for additional information.</p> <p>For products marketed in Canada, a reference to the Canadian Product Monograph (PM) may be submitted if an updated IB is not available.</p>
	<b>CTA-A (Clinical)</b>	If the CTA-A proposes to extend the duration of the trial, an updated IB with supporting toxicological studies and clinical safety data to support the extension should be provided. The amendment to the IB may be included as an addendum.
	<b>CTA-A (Quality)</b>	<b>For Biologics and Radiopharmaceuticals only:</b> a revised IB or an Addendum to the IB describing any new Quality (Chemistry and Manufacturing) information, including supporting data as required, if applicable.
1.4		<b>Health Canada Summaries</b>
1.4.1	<b>CTA</b>	<p>Protocol Safety and Efficacy Assessment Template - Clinical Trial Application (PSEAT-CTA)</p> <p>A Protocol Synopsis in the format of the Protocol Safety and Efficacy Assessment Template - Clinical Trial Application (PSEAT-CTA).</p>

1.7		<b>CTA Specific Requirements</b>
1.7.1		Protocol
	<b>CTA</b>	A copy of the final proposed protocol(s), including version number.
	<b>CTA-A (Clinical)</b>	A copy of the <b>amended or working protocol</b> with a clear description of the changes that are being proposed (that is, original wording vs. revised wording), a rationale for <i>each</i> proposed change, and a copy of the most recently authorized protocol, including version number.  The changes may be listed in a separate document or an annotated version of the protocol. Cross-referencing is not acceptable.
1.7.2		Informed Consent Forms
	<b>CTA</b>	A copy of the Informed Consent Forms/Document(s) (ICDs) to be used in conjunction with the clinical trial, including a statement regarding the risks and anticipated benefits to the clinical trial subjects as a result of their participation in the clinical trial.  ICDs to be used in conjunction with the clinical trial should be prepared in accordance with applicable laws governing consent. The ICH E6 and the Tri-Council Policy Statement (TCPS) provides standards for the ICD.
	<b>CTA-A (Clinical)</b>	The revised ICDs must be submitted if the changes to the study protocol(s) or other supporting documentation (nonclinical study results, adverse events, revisions to the IB) affect the information in the ICD. The ICD with changes clearly indicated (annotated) should be provided.
1.7.3	<b>CTA/CTA-A (Clinical)</b>	Research Ethics Board (REB) Refusals The name, address and telephone number and, if applicable, the fax number and electronic mail address of any REB that has previously refused to approve the clinical trial protocol or amendment, its reasons for doing so and the date on which the refusal was given, if known at the time of submitting the application as per C.05.005(d) and C.05.008(c). Please refer to section 2.7.1 for additional information.

1.7.4	CTA/CTA-A	<p>Information on Prior-related Applications</p> <p>A list of ongoing clinical trials in Canada for which authorization has been granted by Health Canada, if applicable.</p>
2		<p><b>Common Technical Document Summaries</b></p> <p>This module contains Quality (Chemistry and Manufacturing) Information only. <b>This section does not apply if the drug product to be used in the clinical trial has received a NOC and/or DIN and has not been modified.</b></p> <p>If the Quality information was previously submitted to, and authorized by, Health Canada and <b>has not changed</b>, re-submission of the applicable Quality Summary may not be required. However, sponsors should refer to the control number of the prior application.</p>
	CTA-A (Quality)	<p>The Common Technical Document Summaries Module should include:</p> <p>An applicable updated Quality Overall Summary (QOS) or Quality Information Summary (QIS). The rationale for each proposed change should be submitted. Revised information should be clearly identified. The changes may be listed in a separate document or a marked up annotated version of the QOS/QIS-R/QIS-PER, as applicable. Cross-referencing is not acceptable.</p>
2.1	CTA/CTA-A (Quality)	<p>Common Technical Document Table of Contents</p> <p>A listing of the contents of Modules 2 and 3, if applicable.</p>
2.2		

2.3	CTA	<p>Quality Overall Summary (QOS)</p> <p>a) <b>For Pharmaceuticals:</b> a QOS is required (refer to Appendix 2 for links).</p> <p>b) <b>For Biologics and Radiopharmaceuticals:</b></p> <p>There are four QOS guidance documents to be used as direction for the completion of the quality section for biologic drug submissions and two QIS (Quality Information Summary) templates for radiopharmaceutical drug submission applications (refer to Appendix 2 for links). The applicant should submit a completed QOS/QIS with, as a minimum, those subsections or parts which have a check mark (✓) beside the guidance or heading, including the facility information. Note that these guidances were not written specifically for CTAs and may not necessarily apply to the same extent. It is understandable that depending upon the stage of drug development, a limited amount of information may be available for a CTA; in which case, the sponsor should provide whatever data are available at that time. Sponsors should also refer to the applicable Health Canada quality guidance documents and updated notices for additional information.</p> <p>c) <b>For Placebo-controlled studies:</b> a qualitative list of the ingredients in the placebo should be submitted.</p>
3		Quality (if submitted)
3.1	CTA/CTA-A (Quality)	<p>Table of Contents of Module 3</p> <p>A listing of the contents of Module 3.</p>
3.2	CTA/CTA-A (Quality)	<p>Body of Data</p> <p>Where there is additional supporting quality information to that provided in the QOS-CE (Module 2), this information should be provided separately in the appropriate Module 3 section and cross-referenced in the applicable QOS/QIS. Sponsors should refer to the applicable Health Canada quality guidance documents for additional information.</p> <p><b>For Biologics and Radiopharmaceuticals:</b> For a product early in development, submission of Module 3 is not always necessary if sufficient information is provided in the QOS/QIS-R/QIS-PER, as appropriate.</p>

3.3	<b>CTA/CTA-A (Quality)</b>	Literature References Literature references related to quality information should be provided here if applicable.
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### 2.3.3 Comparative Bioavailability Trial Application Requirements

This section outlines the application requirements for sponsors wishing to conduct comparative bioavailability studies for pharmaceuticals only where:

- The studies are performed on healthy adult volunteers;
- The reference drug product is marketed in Canada, United States, European Union, Australia, Switzerland or Japan; and
- The maximum single or total daily dose of the study drug does not exceed that specified in the labelling of the reference drug product; or the simultaneous administration of a radioactive labelled and unlabelled drug product.

**This section does not apply to biologics, radiopharmaceuticals and cellular therapies, which includes Phase I trials using somatic cell therapies, xenografts, gene therapies, prophylactic vaccines or reproductive and genetic technologies.**

Additionally, this section does not apply to comparative bioavailability studies involving different formulations of investigational drugs or comparing different routes of administration (please refer to section 2.3.2 for filing requirements).

CTAs for comparative bioavailability studies should be filed directly to the Therapeutic Products Directorate, addressed to the attention of the Director. The outer label of the shipping carton should be clearly identified with “**Clinical Trial Application for Bioavailability Studies**”. In general, the CTA filing requirements (Section 2.3.2) also apply to the comparative bioavailability studies that meet the criteria provided above, with some exceptions as follows:

- The cover letter to the application should include a rationale for the study and be provided in hard copy and in electronic format;
- A hard and electronic copy of the current labelling or PM/Prescribing Information for the reference product in lieu of the IB; and
- A completed Quality Overall Summary - Chemical Entities (Clinical Trial Application - Bioavailability Studies) (QOS-CE (CTA-BA)) template, as well as any additional quality information as outlined in the template.

CTA-A and CTA-Notification (CTA-N) filing requirements (refer to sections 2.4 and 2.6, respectively) also apply to comparative bioavailability studies.

610 **2.4 CTA Amendments (CTA-As)**

611  
612 CTA-As are applications in which a sponsor proposes information to support changes to a  
613 **previously authorized** application [C.05.008]. CTA-As are required for changes to clinical trial  
614 drug supplies that affect the quality or safety of the drug, changes to an authorized protocol that  
615 alter the risk to clinical trial subjects, or both.

616  
617 **CTA-As must be authorized by Health Canada prior to implementation of the changes**  
618 **[C.05.008]. However, if the sponsor is required to immediately make one or more of the**  
619 **amendments referred to in subsection (2) of C.05.008 because the clinical trial or the use of**  
620 **the drug for the purposes of the clinical trial endangers the health of clinical trial subjects**  
621 **or other persons, the sponsor may immediately make the amendment without prior review**  
622 **by Health Canada. Sponsors must notify Health Canada of this change, provide the**  
623 **relevant rationale in support of the immediate implementation and file a CTA-A that**  
624 **clearly identifies the change and the rationale for immediate implementation of the change**  
625 **within 15 days after the date of implementation of the amendment [C.05.008(4)].**

626  
627 Amendments submitted when the CTA is under review will not be accepted. Where a sponsor  
628 wishes to make changes to the CTA under review, the sponsor should withdraw the active CTA  
629 and submit the amendment as a new CTA. Changes requested by Health Canada during the  
630 review process may be filed later as amendments or notifications, as appropriate.

631  
632 **2.4.1 Clinical Trial Application-Amendments (CTA-A): Clinical**

633  
634 Sponsors are required to file CTA-As for changes to the protocol made after the original  
635 CTA that will impact on the safety of the subjects or will affect the analysis and the  
636 interpretation of the safety and efficacy of the drug(s) under investigation. As per section  
637 C.05.008(2), a CTA-A must be filed when the proposed amendments to the protocol:

- 638  
639 a) Affect the selection, monitoring, or dismissal of a clinical trial subject;  
640 b) Affect the evaluation of the clinical efficacy of the drug;  
641 c) Alter the risk to the health of a clinical trial subject;  
642 d) Affect the safety evaluation of the drug; and  
643 e) Extend the duration of the clinical trial.

644  
645 Examples of protocol changes that require a CTA-A are provided below to aid in  
646 determining whether a CTA-A should be filed. These examples are not all inclusive,  
647 when in doubt of whether a CTA-A is warranted, sponsors should contact the  
648 corresponding Directorate.

649

CLINICAL AMENDMENTS
<b>Examples include, but are not limited to:</b>
1. Criteria, tests or procedures required to select or dismiss a clinical trial subject. These include changes to eligibility criteria, tests or procedures for selecting the study population, as well as tests, procedures, or criteria for dismissing clinical trial subjects prematurely or at the end of the trial;
2. Criteria, tests or procedures required for the monitoring of clinical trial subjects, including monitoring of safety, or evaluation of safety and efficacy. This includes protocol changes as a result of serious unexpected ADRs;
3. Study design, study population, duration of use, objectives, or hypotheses, including adding or discontinuing a study arm that was not included as a provision in the original CTA protocol;
4. Changes in the primary efficacy endpoint(s), important secondary efficacy endpoints (e.g., those that could be used in support of a marketing application), safety endpoints, sample size estimation, or addition of interim analyses that will affect the analysis and interpretation of the study results;
5. Dose level, dosage schedule, or treatment duration;
6. The follow-up period, in particular if the follow-up period is being shortened;
7. Adding or removing a concomitant medication, which may impact on the analysis of efficacy or increase the risk to clinical trial subjects;
8. Criteria for expedited reporting of serious, unexpected adverse drug reactions;
9. Blood volume, procedure, repeat testing, or confirmatory testing in PK studies that were not specified in the original CTA protocol; and/or
10. Aspects of the conduct of the study that may increase the risk to the health of clinical trial subjects.

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Protocol changes should be reflected in a revised ICD, as applicable. Additionally, new information related to the safety of the drug may affect a subject's decision to participate in the trial, and hence should be added to the risks section of the ICD. An updated copy of the ICD should be included in the CTA-A, as applicable, with changes clearly indicated (annotated).

Protocol changes that extend the duration of the clinical trial pertain to extensions in the treatment period of individual study subjects. All protocol changes that involve an extension in treatment duration or treatment period require filing of a CTA-A; such CTA-As must be accompanied by an IB or equivalent information to support the extension in treatment duration. Changes in the projected duration of the entire trial are normally not considered to require a CTA-A.

664 **2.4.2 Clinical Trial Application-Amendments (CTA-A): Quality (Chemistry and**  
665 **Manufacturing)**  
666

- 667 **a) For Biologics and Radiopharmaceuticals:** A list of all proposed quality changes  
668 from the authorized application should be provided in the cover letter.  
669

670 It should be noted that for Biologics and Radiopharmaceuticals, differences in  
671 manufacturing strategies can lead to the production of a novel drug product requiring  
672 both non clinical and clinical data to support its use and are considered **beyond the**  
673 **scope** of an authorized CTA. In such cases, a new CTA is required. Examples of  
674 differences in manufacturing strategies include, but are not limited to:  
675

- 676 1. Change in the source of drug substance (e.g., from a fermentation process to  
677 transgenic milk);
- 678 2. Change in the host cells used to express the same coding sequence;
- 679 3. Use of an alternate expression cassette;
- 680 4. Change in the strain of virus used in manufacturing a vaccine;
- 681 5. Change in the strain of oncolytic virus used in cancer treatment;
- 682 6. Change in the animal source of an immune globulin (e.g., from rabbit to sheep);
- 683 7. Change in the source of a radionuclide (e.g., from nuclear reactor to cyclotron or  
684 linear accelerator) for labelling kits;
- 685 8. Change in the source of the parent radionuclide (e.g., from nuclear reactor to  
686 cyclotron or linear accelerator) used in a generator;
- 687 9. Change in the design, structure and operation of a radionuclidic generator.  
688

689 For additional guidance regarding the classification of a quality change, sponsors are  
690 encouraged to consult with BGTD.  
691

692 Sponsors must file a CTA-A or CTA-N to a previously authorized application when  
693 changes that may affect the quality or safety of the clinical trial drug supplies are  
694 proposed. Changes to the Quality summary subsections of Module 2.3 and Module 3 (if  
695 applicable) including, but not limited to those listed below, warrant the filing of a CTA-A  
696 or a CTA-N.  
697

698 For a product commercially available and used in clinical trials for which a quality  
699 change has been made and approved according to the post-NOC Changes guidance  
700 document, supporting data are not required in support of the same change affecting the  
701 clinical product. The change can be notified to the BGTD with cross-reference to the  
702 approved submission filed for the commercial product. In the situation where a change  
703 made to the commercial product has not yet been approved and is affecting the clinical  
704 material, a CTA-A or a CTA-N must be submitted according to the tables below.  
705

<b>DRUG SUBSTANCE (Biologics and Radiopharmaceuticals)</b>	
1. Replacement or addition of a manufacturing site and/or manufacturer involving:	
a. production of the starting material, intermediate, or drug substance	Amendment
b. testing (e.g., release, stability)	Notification
2. Change in the manufacturing process for the drug substance or intermediate, involving:	
a. the fermentation process (e.g., scale-up, new bioreactor technology, use of new raw materials of biological origin); or change in the route of synthesis of the radiopharmaceutical drug substance or critical component*	Amendment
b. the purification process (e.g., addition/removal/replacement of a purification step)	Amendment
3. Change in the specifications for the drug substance involving:	
a. deletion or replacement of a test, relaxation of an acceptance criterion or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
4. Change in the primary container closure system(s) for the storage and shipment of the drug substance	
5. Change in the shelf life for the drug substance, involving:	
a. Extension	
i. if the approved shelf life is less than or equal to 18 months	Amendment
ii. if the approved shelf life is more than 18 months	Notification
b. Reduction (due to stability concerns)	

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\*For the manufacture of some radiopharmaceuticals, “critical components” (e.g., F-18 radionuclide used to manufacture F-18-FDG and F-18-NaF) are considered analogous to drug substance (consult BGTD).

710

<b>DRUG PRODUCT (Biologics and Radiopharmaceuticals)</b>	
1. Replacement or addition of a drug product manufacturing site / manufacturer, involving:	
a. production of a drug product (including primary packaging)	Amendment
b. secondary packaging	Notification
c. testing (e.g., release, stability)	Notification
2. Change in the drug product manufacturing process (e.g., scale-up, changes to the formulation process); change from manual synthesis of positron-emitting radiopharmaceutical to use of Automatic Synthesis Unit (ASU) or change in type of ASU	
3. Deletion of a drug product manufacturer / manufacturing site, secondary packaging site or testing site	
4. Change in the specifications for the drug product, involving:	
a. deletion or replacement of a test, relaxation of an acceptance criterion or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for new impurity) or tightening of an acceptance criterion	Notification
5. Change in the shelf life for the drug product, involving:	
a. Extension	
i. if the approved shelf life is less than or equal to 18 months	Amendment
ii. if the approved shelf life is more than 18 months	Notification
b. Reduction (due to stability concerns)	Amendment
6. Change in the storage conditions for the drug product	
7. Changes in drug substance and/or final product dosage form (e.g., liquid to lyophilized formulation);	
8. Changes in drug substance and/or final product strength	
9. Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution; change in radiolytic protective agent or antioxidant	

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**b) For Pharmaceuticals:**

<b>DRUG SUBSTANCE (Pharmaceuticals)</b>	
1. Replacement or addition of a manufacturing site and/or manufacturer involving:	
a. production of the starting material, intermediate, or drug substance	Amendment
b. testing (e.g., release, stability)	Notification
2. Change in the manufacturing process for the drug substance or intermediate	
Amendment	
3. Change in the batch size for the drug substance (no impact on quality)	
Notification	
4. Change in the specification for the drug substance involving test and acceptance criteria:	
a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification
5. Change in the re-test period (or shelf life) for the drug substance, involving:	
a. Extension	Notification
b. Reduction	Amendment
<b>DRUG PRODUCT (Pharmaceuticals)</b>	
6. Addition of a dosage form or strength	
Amendment	
7. Change in the composition of a dosage form	
Amendment	
8. Qualitative or quantitative addition, deletion or replacement of a colour or flavour with no negative impact on stability	
Notification	
9. Change in diluent, involving replacement or addition of a diluent for a lyophilized powder or concentrated solution	
Amendment	
10. Replacement or addition of a drug product manufacturer / manufacturing site involving:	
a. Production of an immediate release drug product (tablet, capsule, liquids, semi-solids) within the same Company	Notification
b. Production of an immediate release drug product (tablet, capsule, liquids, semi-solids) to a new Company	Amendment
c. Production of a modified release product	Amendment

d. Production of a sterile drug product	Amendment
e. Primary packaging (non-sterile products)	Notification
f. Testing (e.g., release, stability)	Notification
11. Change in the drug product manufacturing process	Amendment
12. Change in the specification for the drug product tests and acceptance criteria, involving:	
a. Deletion or replacement of a test, relaxation of an acceptance criterion, or addition of a test for a new impurity	Amendment
b. addition of a test (other than a test for a new impurity) or tightening of an acceptance criterion	Notification
13. Change in the shelf life for the drug product, involving:	
a. Extension	Notification
b. Reduction (due to stability concerns)	Amendment
14. Change in the storage conditions for the drug product	Amendment

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**2.4.3 Filing a Clinical Trial Application-Amendments (CTA-A)**

CTA-As should be filed directly to the appropriate Directorate (Appendix 1). The outer label should be clearly labelled with “**Clinical Trial Application - Amendment**”.

For joint reviews, refer to Section 2.3.1.1.

**2.4.4 Clinical Trial Application-Amendments (CTA-A) Format**

Similar to CTAs, CTA-As should be organized and numbered as per the CTD format.

CTA-As should be submitted in hard copy and in electronic copy in a format accepted by Health Canada.

**2.4.4.1 Clinical Amendments**

Please refer to Section 2.3.2 CTA Format for guidance in completing filing requirements for Clinical CTA-As; subsection 1.4.1 is not applicable.

733 2.4.4.2 Quality (Chemistry and Manufacturing)

734  
735 Please refer to Section 2.3.2 CTA Format for guidance in completing filing requirements;  
736 subsections 1.2.5.1, 1.2.7, 1.4.1, 1.7.2-1.7.4 are not applicable.

737  
738 **2.5 Clinical Trial Application (CTA) and Clinical Trial Application-Amendments**  
739 **(CTA-A) Review Process**

740  
741 Health Canada reviews the documents submitted in CTAs and CTA-As to assess the quality of  
742 the products and determine that the use of the drug for the purposes of the clinical trial does not  
743 endanger the health of clinical trial subjects or other persons, the clinical trial is not contrary to  
744 the best interests of a clinical trial subject, and the objectives of the clinical trial may be achieved  
745 [C.005.006(1)(b)(ii)]. All CTAs including those for comparative bioavailability studies are  
746 subject to the 30 day default period from the date of receipt of the completed application as per  
747 C.05.005 or C.05.008. However, comparative bioavailability studies that meet the criteria  
748 provided in Section 2.3.3 are targeted to be reviewed within **7 days**; sponsors are reminded that  
749 this expedited review process is an administrative target. An acknowledgement letter will be  
750 issued to indicate the start of the review period and to indicate that the Minister is in receipt of a  
751 complete application.

752  
753 **2.5.1 Screening Process**

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755 All CTAs and CTA-As will be screened for completeness and if deficiencies are  
756 identified at screening, these will be addressed by a Request for Clarification or a  
757 Screening Rejection Letter.

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759 2.5.1.1 Requests for Clarification during screening

760  
761 Requests for Clarification that are issued during screening should be responded to within  
762 2 calendar days. If the application is considered complete, an acknowledgement letter  
763 will be issued to indicate the commencement of the 30-day default period.

764  
765 2.5.1.2 Screening Rejection Letter

766  
767 A Screening Rejection Letter may be issued when information required under C.05.005  
768 or C05.008 has not been included in the CTA or CTA-A or responses to Requests for  
769 Clarification have not been received in a timely manner. Sponsors will be issued a letter  
770 itemizing each deficiency. If the sponsor wishes to resubmit the information and material  
771 at a future time, it will be processed as a new CTA or CTA-A, and will be assigned a new  
772 control number as per the *Management of Drug Submissions Guidance*.<sup>3</sup>

---

<sup>3</sup> *Management of Drug Submissions Guidance 2011/04/01* is located on the Health Canada website.

773 **2.5.2 Review process**

774  
775 The sponsor is responsible for resolving issues identified by Health Canada during the  
776 review process. Sponsors must provide the requested information within 2 calendar days  
777 [C.05.009].

778  
779 Should the sponsor be unable to provide the requested information within the specified  
780 time frame, the submission may be withdrawn and resubmitted without prejudice.

781  
782 A Not Satisfactory Notice (NSN) may be issued if significant deficiencies are identified  
783 during the review of the CTA or CTA-A, or if a timely response to information requested  
784 has not been provided. If the sponsor wishes to resubmit the information and material at  
785 a future time, it will be processed as a new CTA or CTA-A, and will be assigned a new  
786 control number as per the *Management of Drug Submissions Guidance*.<sup>5</sup>

787  
788 If the CTA or CTA-A is deemed acceptable, a No Objection Letter (NOL) will be issued  
789 within the review period.

790  
791 **2.6 Notifications**

792  
793 Notifications must be provided for changes to CTAs that do not meet the criteria for CTA-As.  
794 The changes may be implemented immediately, but Health Canada must be informed in writing,  
795 within 15 calendar days of the day of the change [C.05.007]. Information regarding the change  
796 should be submitted in the form of a cover letter and any supporting documentation. This  
797 information will be reviewed and added to the file.

798  
799 Notifications include the following:

800  
801 a) Changes to the protocol that do not affect the safety of the trial participants and which would  
802 not be considered an amendment under section 2.4. Examples include, but are not limited to the  
803 following:

804 <b>NOTIFICATIONS</b>
1. Minor changes to the inclusion and exclusion criteria, such as laboratory chemistry cut-off values that reflect clinical practice and improve the safety of clinical trial subjects;
2. Increasing the screening period or other administrative changes to accommodate logistical constraints in study conduct that do not affect the safety of the trial participants;
3. Changes to administrative information such as new contact names and numbers and addresses of individuals, organizations, or other entities, involved in the conduct of the trial;
4. Updating the ICD with new safety information that does not require a protocol amendment.

805

806 b) Changes to Quality (Chemistry and Manufacturing) information that does not affect the  
807 quality or safety of the drug (refer to section 2.4.2 CTA-As: Quality (Chemistry and  
808 Manufacturing)).

809

## 810 **2.7 Additional Requirements Prior to Commencing a Clinical Trial**

811

812 Prior to initiating a clinical trial or implementing an amendment to a clinical trial at a site, the  
813 sponsor must ensure that the REB Attestation and Qualified Investigator Undertaking forms have  
814 been completed, and that the Clinical Trial Site Information form has been filed with Health  
815 Canada. For all biologics, the BGTD requires that the lot release information be provided by the  
816 CTA sponsor/manufacturer before its use in the trial (see section 2.7.4).

817

818 The information required on the Qualified Investigator Undertaking, REB Attestation, HC/SC  
819 3011, and Clinical Trial Site Information Form, is necessary because of differences in signing  
820 authority and attestation.

821

### 822 **2.7.1 Research Ethics Board Review**

823

824 Prior to initiating a clinical trial or implementing an amendment to a clinical trial at a site,  
825 the proposed trial protocol and ICD must be reviewed and approved by a REB as defined  
826 in the *Regulations*.

827

828 The sponsor must:

829

830 a) Submit the name of the REB that approved the trial or trial amendment prior to  
831 the commencement of the trial or trial amendment at that site (see Clinical Trial  
832 Site Information Form);

833

834 b) Retain as records a REB Attestation, signed by the REB Chair that approved the  
835 protocol or protocol amendment at each site in a manner consistent with GCPs.  
836 REBs may wish to use the REB Attestation form provided on Health Canada's  
837 website or develop similar documentation that meets the requirements of the  
838 *Regulations* (see additional information below); and

839

840 c) Submit information pertaining to the refusal of the protocol for any reason by a  
841 REB.

842

843 A REB may use its own letter of attestation in lieu of the form provided by Health  
844 Canada. If a REB uses its own letter, it must attest to the following 3 points:

845

- 846 • The membership of the REB complies with the membership requirements for REBs  
847 defined in the *Regulations*;

- 848
- The REB carries out its functions in a manner consistent with GCPs; and
  - The REB has reviewed and approved the clinical trial protocol and ICD for the trial
- 849 which is to be conducted by the qualified investigator named on the attestation for the
- 850 specified clinical trial site. The approval and the views of the REB have been
- 851 documented in writing.
- 852
- 853

854 The REB letter does not need to include all the elements contained in PART 1, PART 2

855 and PART 3 of the Health Canada REB Attestation Form.

856

857 If the REB is approving the clinical trial for multiple sites, the sites may be identified by

858 duplicating Part 3 of the REB Attestation as many times as necessary to capture all site

859 addresses approved by the same REB. Only the final page of the REB Attestation would

860 contain the REB representative signature. The additional pages listing multiple clinical

861 trial sites are attached to Parts 1 and 2, and the complete document should be paginated

862 (e.g., 1 of 5, 2 of 5, etc.).

863

864 The REB Attestation should not be submitted unless requested by Health Canada but

865 must be available at each clinical trial site as per C.05.012.

866

#### 867 2.7.1.1 Refusals

868

869 Following regulatory authorization of a CTA or CTA-A, information regarding refusals

870 by other regulatory authorities or REBs should be submitted as a notification. This

871 information will be added to the file, but will not be subject to an acknowledgement

872 letter, nor will a No Objection Letter (NOL) be issued.

873

#### 874 2.7.2 Qualified Investigators

875

876 There must be no more than one (1) qualified investigator at each site. These restrictions

877 do not apply to co-investigators.

878

879 Qualified Investigators must complete the Qualified Investigator Undertaking (QIU) or

880 develop similar documentation that meets the requirements of the *Regulations*.

881

882 When the Qualified Investigator is conducting the trial at multiple sites, these sites may

883 be identified by duplicating Part 3 of the QIU form as many times as necessary to capture

884 all site addresses under the responsibility of the same QI. Only the final page of the QIU

885 would contain the QI's signature. The additional pages listing multiple clinical trial sites

886 are attached to Parts 1 and 2, and the complete document should be paginated (e.g., 1 of

887 5, 2 of 5, etc.).

888

889 If there is a change in the Qualified Investigator at a site, a new Clinical Trial Site  
890 Information Form must be submitted to Health Canada, and a new QIU form must be  
891 kept at the site.

892  
893 Please note that the QIU form should not be submitted unless requested by Health  
894 Canada but must be kept at each clinical trial site as per C.05.012.

### 895 **2.7.3 Filing of Trial Commencement Information**

896  
897  
898 Prior to commencement of the clinical trial or implementation of a CTA-A, sponsors are  
899 required to complete and submit a **Clinical Trial Site Information (CTSI) form** for  
900 each clinical trial site.

901  
902 A clinical trial site is the location where trial-related activities are conducted, such as the  
903 location where the drug is administered or dispensed (directly or by prescription) to the  
904 subject and where the subject returns for subsequent assessment. Locations where  
905 ancillary medical procedures such as X-rays, magnetic resonance images (MRIs), or  
906 blood collections are conducted do not require CTSI forms.

907  
908 When the Qualified Investigator will be conducting the clinical trial at multiple sites  
909 overseen by the same REB, all sites may be identified by duplicating Part 3 of the CTSI  
910 form as many times as necessary. The additional pages listing multiple clinical trial sites  
911 should be attached to Parts 1 and 2, and the complete document should be paginated (e.g.,  
912 1 of 5, 2 of 5, etc.).

913  
914 Health Canada recognizes that all information requested in the CTSI form (e.g. dates for  
915 Boxes 35 and 47) may not be available at the time of submission. In that case, sponsors  
916 should provide a commitment to submit the CTSI form prior to the commencement of the  
917 trial at a site. The forms may be faxed or mailed to the addresses in Appendix 1.

918  
919 ***For Pharmaceuticals, the forms may be sent electronically in Microsoft Word,***  
920 ***WordPerfect or unlocked PDF format to:*** clinical.trials.site@hc-sc.gc.ca.

921  
922 If any changes are made to the CTSI form, a revised form should be submitted.

### 923 **2.7.4 Lot Release Information (for Biologics)**

924  
925  
926 All investigational biologic drug product lots to be used in a clinical trial are subject to  
927 the Lot Release requirements drugs as outlined in *Guidance for Sponsors: Lot Release*  
928 *Program for Schedule D (Biologic) Drugs.*

929

930 With the exception of prophylactic vaccines, the BGTD will require that the CTA  
931 sponsor/manufacture provide the Directorate, before its use in the trial, with the  
932 following information via the “Fax-back” process on the final product and bulk product  
933 of their material:

- 934
- 935 a. Lot numbers of materials being used during the trial and any Batch
  - 936 Identification Numbers that are assigned to lots received from elsewhere [that is
  - 937 (i.e.) all numbers associated with a particular lot]; and
  - 938 b. The lot number(s) and manufacturing source of any associated human-derived
  - 939 excipient (e.g. human albumin).
- 940

941 The sponsor/manufacture is required to sign a certification stating that all testing, on the  
942 drug substance as well as any human-derived excipients, is complete and within  
943 specification. A completed "Fax-Back" form, including the required certification, should  
944 be sent to the BGTD. This will be faxed back to the sponsor/manufacture within 48  
945 hours, providing the CTA has received prior BGTD authorization. If the CTA has not  
946 been cleared by the BGTD, the Fax-Back will be held until such time as authorization for  
947 the CTA has been given. Upon receipt of the faxed-back form, the sponsor/manufacture  
948 may implement the use of the particular lot(s).

949

950 If the sponsor/manufacture wishes to use a lot that has failed one or more specifications,  
951 they must provide the testing protocol, an explanation, and the rationale for its use along  
952 with the completed Fax-Back form. The lot must not be used until such time as it has  
953 been released by the BGTD.

954

955 For investigational prophylactic vaccines lot release for use in an authorized CTA, the  
956 BGTD will require the submission of testing protocols and/or Certificates of Analysis  
957 before its use in the trial. The BGTD issues a formal release letter for use of a  
958 prophylactic vaccine lot in a clinical trial. The lot must not be used until such time as it  
959 has been released by the BGTD.

960

### 961 **2.7.5 Importation of Clinical Trial Drugs**

962

963 For sponsors of Canadian clinical trials who wish to import a drug into Canada for the  
964 purpose of a clinical trial, a No Objection Letter should be provided at the time of  
965 importation to facilitate shipment and to demonstrate compliance with section C.05.006  
966 or section C.05.008 of the *Food and Drug Regulations*. We ask that a copy of this  
967 authorization be provided at the port of entry.

968

969 Any delegation of importation duties to third parties should be clearly articulated through  
970 written agreement. Systems must be in place for the monitoring, storage conditions,  
971 transportation and disposition of the drug to be imported. Regardless of the agreements

972 in place for the importation of the product, the sponsor ultimately bears responsibility for  
973 the correct manufacture, handling and storage of the product to be used in the clinical  
974 trial.

975  
976 Sponsors who are located outside of Canada must have an authorized Canadian agent (the  
977 sponsor, in terms of regulatory responsibility in Canada) responsible for the importation  
978 of all clinical trial drugs. This information must be included in Appendix 1 of the HC/SC  
979 3011 form and should be provided at the time of application. If the drugs will be shipped  
980 to individual clinical trial sites, Appendix 1 may be replicated as many times as necessary  
981 to capture all sites.

982  
983 In the event that additional drugs which are not specifically the subject of the CTA (e.g.  
984 comparator, concomitant and rescue medications) are being imported for the purpose of  
985 the clinical trial, we ask that a list of these drugs be specified in Section 1.2.9 of the  
986 Clinical Trial Application. For each associated drug listed in this section, the following  
987 information should be provided by the clinical trial sponsor at the time of application:

- 988
- 989 • Name of the country where the investigational drug is marketed;
  - 990 • Name of the company as stated on the market label;
  - 991 • Name of the drug as stated on the label;
  - 992 • Common name of the active ingredient;
  - 993 • Dosage form;
  - 994 • Strength;
  - 995 • Attestation that the drug has undergone review from, and is market authorized in, an  
996 ICH or equivalent region (e.g. Australia, Japan, Europe, United States), and that it  
997 will be used in the proposed clinical trial under the indication and conditions of use  
998 for which the authorization was granted
- 999

1000 If this information is not known at the time of application, or changes between the time of  
1001 application and the actual import of the clinical trial drugs, sponsors may submit that  
1002 information to the appropriate review directorate when it becomes available as a CTA-  
1003 Notification.

1004  
1005 This information is collected to facilitate the assessment of a clinical trial shipments'  
1006 admissibility into Canada.

1007  
1008 To that end, a copy of Appendix 1 of the HC/SC 3011 form as well as the Summary of  
1009 Additional Drugs should be included with the shipment.

1010 **2.8 Post-Authorization Requirements**

1011  
1012 **2.8.1 Premature Discontinuation of a Trial**

1013  
1014 In the event of the premature discontinuation of a trial in its entirety or at a clinical trial  
1015 site for which a CTA or CTA-A has been filed in Canada, the responsible Directorate  
1016 must be notified as soon as possible, but no later than 15 calendar days after the date of  
1017 discontinuance.

1018  
1019 This notification should include:

- 1020  
1021 a) Detailed reason(s) for this action;
- 1022  
1023 b) Description of the impact on the proposed or ongoing trials conducted in Canada;
- 1024  
1025 c) Confirmation that all qualified investigators have been notified of the discontinuation  
1026 and the reasons for the discontinuance and have been advised in writing of any  
1027 potential risks to the health of clinical trial subjects or other persons;
- 1028  
1029 d) Confirmation that the sale or importation of the drug to all sites involved has been  
1030 stopped; and
- 1031  
1032 e) Confirmation that reasonable measures to ensure the return of all unused quantities of  
1033 the drug will be taken.

1034  
1035 **Note: Notification of a premature discontinuation of a clinical trial outside Canada,**  
1036 **for which there are ongoing trials with the drug in Canada, should also be**  
1037 **submitted to the appropriate Directorate.**

1038  
1039 The sponsor may resume the trial in its entirety or at a site that was previously  
1040 discontinued if the sponsor submits the following information:

- 1041  
1042 a) The name, address and telephone number, and if applicable, the fax number and  
1043 electronic mail address of the qualified investigator for each site and of the REB that  
1044 approved the re-initiation of the trial at each site;
- 1045  
1046 b) The name, address and telephone number and, if applicable, the fax number and  
1047 electronic mail address of any REB that has previously refused to approve the re-  
1048 initiation of the trial, if applicable; and
- 1049  
1050 c) The proposed date of re-initiation of the clinical trial at each clinical trial site.
- 1051

1052 **The above information may be submitted as a CTA-Notification if there are no**  
1053 **changes to the study protocol or to the Chemistry and Manufacturing, and the trial**  
1054 **may resume accordingly. When there has been a change to the study protocol or to**  
1055 **the Chemistry and Manufacturing, the information should be submitted with a**  
1056 **CTA-A (see Section 2.4). The sponsors may only resume the trial when a No**  
1057 **Objection Letter (NOL) has been issued from the appropriate Directorate within 30**  
1058 **days of the submission of a CTA-A.**

## 1060 **2.8.2 Safety Reporting Post- No Objection Letter (NOL)**

### 1062 2.8.2.1 Adverse Drug Reactions (ADRs)

1064 During a clinical trial the sponsor is required to inform Health Canada, in an expedited  
1065 manner, of any serious unexpected adverse drug reaction, in respect of the drug that has  
1066 occurred inside or outside Canada:

- 1067
- 1068 a) Where it is neither fatal nor life-threatening, within 15 days after becoming aware of  
1069 the information;
  - 1070
  - 1071 b) Where it is fatal or life-threatening, within 7 days after becoming aware of the  
1072 information. Within 8 days after having initially informed Health Canada of the fatal  
1073 or life-threatening ADR, submit as complete a report as possible. Follow-up reports  
1074 of fatal or life-threatening reactions **must** include an assessment of the importance  
1075 and implication of the findings, including relevant previous experience with the same  
1076 or similar drugs.

### 1078 2.8.2.2 Adverse Drug Reactions (ADRs) Reporting criteria

1080 Each ADR which is subject to expedited reporting should be reported individually in  
1081 accordance with the data element(s) specified in the Health Canada/ICH Guidance  
1082 Document E2A: “*Clinical Safety Data Management: Definitions and Standards for*  
1083 *Expedited Reporting*”. Expedited reports are required for events that meet all of these  
1084 three criteria: serious, unexpected and a suspected causal relationship.

#### 1086 1) Serious:

1087 *Any untoward medical occurrence that at any dose:*

- 1088
- 1089 • *results in death,*
  - 1090 • *is life-threatening,*
  - 1091 • *requires inpatient hospitalisation or prolongation of existing hospitalisation,*

- 1092
- results in persistent or significant disability/incapacity, or
  - is a congenital anomaly/birth defect.
- 1093
- 1094

1095 2) Expectedness:

1096 An "unexpected" adverse reaction is one in which the nature or severity is not consistent  
1097 with information in the relevant source document(s), such as the IB or Product  
1098 Monograph. Until source documents are amended, expedited reporting is required for  
1099 additional occurrences of the reaction.

1100  
1101 Reports which add significant information on specificity or severity of a known, already  
1102 documented serious ADR constitute unexpected events. For example, an event more  
1103 specific or more severe than described in the IB would be considered "unexpected" and  
1104 should be reported (i.e., hepatitis with a first report of fulminant hepatitis).

1105  
1106 3) Causality:

1107 Causality assessment is required for clinical investigation cases:

1108  
1109 - All cases judged by **either** the reporting health care professional or the sponsor as  
1110 having a reasonable suspected causal relationship to the medicinal product qualify as  
1111 ADRs and should be reported.

1112  
1113 - Concomitantly, adverse reactions that are considered to be unrelated to the study drug  
1114 by both the investigator and the sponsor should not be reported. However, in situations  
1115 when causality assessment and determination of expectedness is not straightforward, the  
1116 report should be submitted in the expedited manner and the relevant issues **should be**  
1117 addressed in a cover letter.

1118  
1119 2.8.2.3 How to Report

1120  
1121 When submitting an ADR report to Health Canada, a complete ADR Expedited  
1122 Reporting Summary Form (Form 01-03) and the CIOMS Form should be attached and as  
1123 applicable be mailed or faxed to:

1124  
1125 **Biologics and Genetic Therapies Directorate**

1126 Biologics and Radiopharmaceuticals      **Fax: 613-957-0364**

1127  
1128 **Therapeutic Products Directorate**

1129 Pharmaceuticals      **Fax: 613-941-2121**

1130 2.8.2.4 Submission of Safety Information

1131

1132 Health Canada may request a sponsor, at any time during an ongoing clinical trial, to  
1133 submit information or records kept under C.05.012 in order to assess the safety of the  
1134 drug. The safety report could include a line listing of **all serious** events and/or other  
1135 expected ADRs.

1136

1137 2.8.2.5 Study Endpoints

1138

1139 When a fatal or other serious outcome is the **primary efficacy endpoint** in a clinical  
1140 investigation, it may be appropriate to reach agreement with Health Canada in advance  
1141 concerning serious events that would be treated as disease-related and not subject to  
1142 routine expedited reporting.

1143

1144 2.8.2.6 Additional Safety Information

1145

1146 There are situations in addition to the above that may necessitate rapid communication to  
1147 Health Canada, and appropriate scientific and medical judgment should be applied to  
1148 each situation. For example, information that might influence the risk-benefit assessment  
1149 of a drug, or that would be sufficient to consider changes in drug administration, or in the  
1150 overall conduct of a clinical trial, represent such situations; including:

1151

1152 a) For an “expected” serious ADR, an increase in the rate of occurrence which is judged  
1153 clinically important;

1154

1155 b) A significant hazard to the patient population, such as lack of efficacy with a drug  
1156 used in treating a life-threatening disease; and

1157

1158 c) A major safety finding from a newly completed animal study.

1159

1160 This information should be submitted where applicable to either:

1161

1162 **Biologics and Genetic Therapies Directorate**

1163 Biologics and Radiopharmaceuticals

**Fax: 613-957-0364**

1164

1165 **Office of Clinical Trials, Therapeutic Products Directorate**

1166 Pharmaceuticals

**Fax: 613-954-4474**

1167

1168 Sponsors should refer to ICH Guidance Documents *E6: Guideline for Good Clinical*  
1169 *Practice* and *E2A: Clinical Safety Data Management* for safety reporting  
1170 requirements to Qualified Investigator(s) and their Research Ethics Board(s).

1171

### 1172 **2.8.3 Other Communications**

1173  
1174 The sponsor is requested to notify the relevant Directorate(s) when a clinical trial is  
1175 completed.

### 1176 **2.8.4 Updated Investigator’s Brochure**

1177  
1178  
1179 In accordance with ICH GCP, the IB, including all safety information and global status,  
1180 should be reviewed at least annually and revised as necessary. More frequent revision  
1181 may be appropriate depending on the stage of development and the generation of relevant  
1182 new information. If the sponsor is planning to submit a CTA, or planning or required to  
1183 submit a CTA-A or CTA-N, the updated IB should be submitted with the application.  
1184 Otherwise, the updated IB should be submitted separately as a CTA-N, and include a  
1185 statement confirming that the protocol and/or ICF of all ongoing trials do not require  
1186 changes as a result of the updated IB. In all cases, the updated IB should be accompanied  
1187 by a list of changes that clearly describes the sections that have changed, including a  
1188 rationale for each change.

### 1189 **2.8.5 Records related to Clinical Trial Applications (CTAs) and Clinical Trial** 1190 **Application-Amendments (CTA-As)**

1191  
1192 As required in Part C, Division 5 of the *Food and Drug Regulations* [C.05.012]:

- 1193  
1194  
1195 a) The sponsor shall record, handle and store all information in respect of a clinical trial  
1196 in a way that allows its complete and accurate reporting as well as its interpretation  
1197 and verification.  
1198  
1199 b) The sponsor shall maintain complete and accurate records to establish that the clinical  
1200 trial is conducted in accordance with GCPs and the *Regulations*.  
1201  
1202 c) The sponsor shall maintain complete and accurate records in respect of the use of a  
1203 drug in a clinical trial, including:  
1204 i) a copy of all versions of the IB for the drug;  
1205  
1206 ii) records respecting each change made to the IB, including the rationale for  
1207 each change and documentation that supports each change;  
1208  
1209 iii) records respecting all adverse events in respect of the drug that have  
1210 occurred inside or outside Canada, including information that specifies the  
1211 indication for use and the dosage form of the drug at the time of the  
1212 adverse event;  
1213

- 1214 iv) records respecting the enrolment of clinical trial subjects, including  
1215 information sufficient to enable all clinical trial subjects to be identified  
1216 and contacted in the event that the sale of the drug may endanger the  
1217 health of the clinical trial subjects or other persons;  
1218  
1219 v) records respecting the shipment, receipt, disposition, return and  
1220 destruction of the drug;  
1221  
1222 vi) for each clinical trial site, an undertaking from the qualified investigator  
1223 that is signed and dated by the qualified investigator prior to the  
1224 commencement of his or her responsibilities in respect of the clinical trial,  
1225 that states that:  
1226 • the qualified investigator will conduct the clinical trial in accordance  
1227 with GCPs, and  
1228 • the qualified investigator will immediately, on discontinuance of the  
1229 clinical trial by the sponsor, in its entirety or at a clinical trial site,  
1230 inform both the clinical trial subjects and the REB of the  
1231 discontinuance, provide them with the reasons for the discontinuance  
1232 and advise them in writing of any potential risks to the health of  
1233 clinical trial subjects or other persons;  
1234 vii) for each clinical trial site, a copy of the protocol, ICD and any amendment  
1235 to the protocol or ICD that have been approved by the REB for that  
1236 clinical trial site; and  
1237 viii) for each clinical trial site, an attestation, signed and dated by the REB for  
1238 that clinical trial site, stating that it has reviewed and approved the  
1239 protocol and ICD and that the board carries out its functions in a manner  
1240 consistent with GCPs.  
1241  
1242 d) The sponsor shall maintain all records referred to in the applicable *Regulations* for  
1243 a period of 25 years.  
1244

1245 Records must be made available to the relevant Directorate within 2 days if there is a  
1246 concern regarding the use of the drug for the purposes of a clinical trial and a risk to  
1247 health of the subjects involved in that trial. In any other case, records must be provided  
1248 within 7 days of a request [C.05.013].  
1249

### 1250 3 INDEX OF APPENDICES

1251 **APPENDIX 1: RELEVANT ADDRESSES**

1252

1253 **Pharmaceutical Drugs**

1254

1255 ***CTAs and CTAAAs***

1256 Office of Clinical Trials

1257 Therapeutic Products Directorate

1258 5th Floor, Holland Cross, Tower B

1259 Address Locator 3105A

1260 1600 Scott Street

1261 Ottawa, Ontario

1262 Canada

1263 K1A 0K9

1264

1265

1266 ***Clinical Trial Site Information Forms***

1267

1268 Fax #: 613-946-7996

1269

1270

1271 ***The forms may also be sent electronically in WordPerfect or unlocked PDF format to:***

1272 clinical.trials.site@hc-sc.gc.ca

1273

**Biologic and Radiopharmaceutical Drugs**

Regulatory Affairs Division

Biologics and Genetic Therapies Directorate

Health Protection Building, 1st Floor

Address Locator 0701A

200 Tunney's Pasture Driveway

Ottawa, Ontario

Canada

K1A 0K9

Fax #: 613-941-1708

1274 **APPENDIX 2: USEFUL INTERNET WEBSITES**

- 1275
- 1276 Bioavailability and Bioequivalence ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/index-eng.php)
- 1277 [demande/guide-ld/bio/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/index-eng.php))
- 1278
- 1279 Biologics and Genetic Therapies Directorate ([http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-eng.php)
- 1280 [eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-eng.php))
- 1281
- 1282 Clinical Trials for Natural Health Products ([http://www.hc-sc.gc.ca/dhp-](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/clini_trials-essais_nhp-psn-eng.php)
- 1283 [mps/prodnatur/legislation/docs/clini\\_trials-essais\\_nhp-psn-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/clini_trials-essais_nhp-psn-eng.php))
- 1284
- 1285 Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework
- 1286 ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ct_regrev_ce_exareg-eng.php)
- 1287 [exam/ct\\_regrev\\_ce\\_exareg-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ct_regrev_ce_exareg-eng.php))
- 1288
- 1289 Good Clinical Practices ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/index-](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/index-eng.php)
- 1290 [eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/index-eng.php))
- 1291
- 1292 Health Canada (<http://www.hc-sc.gc.ca/index-eng.php>)
- 1293
- 1294 Health Products and Food Branch ([http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-](http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/index-eng.php)
- 1295 [dgpsa/index-eng.php](http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/index-eng.php))
- 1296
- 1297 International Conference on Harmonisation (<http://www.ich.org/>)
- 1298
- 1299 Medical Devices Guidance Documents ([http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-](http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php#guidance_devices)
- 1300 [demande/guide-ld/index-eng.php#guidance\\_devices](http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php#guidance_devices))
- 1301
- 1302 Review of the 2001 Clinical Trials Regulatory Framework: Part C, Division 5 of the Food and
- 1303 Drug Regulations (Drugs for Clinical Trials Involving Human Subjects) ([http://www.hc-](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ctrf_dd_eccr_dt_2007-03-26-eng.php)
- 1304 [sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ctrf\\_dd\\_eccr\\_dt\\_2007-03-26-](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ctrf_dd_eccr_dt_2007-03-26-eng.php)
- 1305 [eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/consultation/clini-rev-exam/ctrf_dd_eccr_dt_2007-03-26-eng.php))
- 1306
- 1307 Therapeutic Products Directorate (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index-eng.php>)
- 1308
- 1309 Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2<sup>nd</sup> edition)
- 1310 (<http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/>)

1311 **The following documents may be useful in the preparation of the application:**

- 1312
- 1313 Notice - Release of Draft Electronic Specifications for Clinical Trial Applications and  
1314 Amendments filed in accordance with Guidance for Clinical Trial Sponsors: Clinical Trial  
1315 Applications ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/notice\\_cta\\_avis\\_dec-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/notice_cta_avis_dec-eng.php))
- 1316
- 1317
- 1318 Notice: Revised Quality Guidances on the Implementation of the Common Technical Document  
1319 for Biological Products ([http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd\\_bgtd-dpbgt\\_notice-avis-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_bgtd-dpbgt_notice-avis-eng.php))
- 1320
- 1321
- 1322 ADR Expedited Reporting Summary for ADRs Occurring During Clinical Trials  
1323 ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctadr\\_dceim-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctadr_dceim-eng.php))
- 1324
- 1325 CIOMS Form I ([http://www.cioms.ch/form/frame\\_form.htm](http://www.cioms.ch/form/frame_form.htm))
- 1326
- 1327 Clinical Trial Site Information Form ([http://www.cioms.ch/form/frame\\_form.htm](http://www.cioms.ch/form/frame_form.htm))
- 1328
- 1329 Health Canada 3011: Drug Submission Application Form for Human, Veterinary, Disinfectant  
1330 Drugs and Clinical Trial Application/Attestation ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/hc3011\\_sc3011-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/hc3011_sc3011-eng.php))
- 1331
- 1332
- 1333 Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial  
1334 Applications (CTAs) for Pharmaceuticals ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/qual\\_cta\\_dec-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/qual_cta_dec-eng.php))
- 1335
- 1336
- 1337 Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications  
1338 and Submissions: Adherence to Good Laboratory Practice ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/glp\\_bpl-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/glp_bpl-eng.php))
- 1339
- 1340
- 1341 Guidance for Records Related to Clinical Trials (GUIDE-0068) ([http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui\\_68-eng.php](http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_68-eng.php))
- 1342
- 1343
- 1344 Revised Draft Guidance Document: Preparation of Drug Submissions and Applications in the  
1345 Common Technical Document (CTD) Format ([http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/ctd\\_prep\\_draft\\_rev\\_ebauche\\_nds\\_2011-eng.php](http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/ctd_prep_draft_rev_ebauche_nds_2011-eng.php))
- 1346
- 1347
- 1348 For Biologics - Guidance Documents:
- 1349 Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD  
1350 Format: Biotechnological/ Biological (Biotech) Products, Date: 2004-05-25 ([http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd\\_biotech-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/prod/tech-doc-biologic/ctd_biotech-eng.php))
- 1351
- 1352

- 1353 Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD  
1354 Format: Blood Products, Date: 2004-05-25 (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic->  
1355 [demande/guides/qualit/prod/tech-doc-biologic/ctd\\_blood-sang\\_prods-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/guides/qualit/prod/tech-doc-biologic/ctd_blood-sang_prods-eng.php))  
1356  
1357 Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD  
1358 Format: Conventional Biotherapeutic Products, Date: 2004-05-25 (<http://www.hc-sc.gc.ca/dhp->  
1359 [mps/brgtherap/applic-demandede/guides/qualit/prod/tech-doc-biologic/ctd\\_convbio-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/guides/qualit/prod/tech-doc-biologic/ctd_convbio-eng.php))  
1360  
1361 Guidance for Industry, Preparation of the Quality Information for Drug Submissions in the CTD  
1362 Format: Vaccines, Date: 2004-05-25 (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic->  
1363 [demande/guides/qualit/prod/tech-doc-biologic/ctd\\_vacc-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/guides/qualit/prod/tech-doc-biologic/ctd_vacc-eng.php))  
1364  
1365 Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs, Date: 2005-06-  
1366 01 ([http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/guides/lot/gui\\_sponsors-](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/guides/lot/gui_sponsors-)  
1367 [dir\\_promoteurs\\_lot\\_program-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/guides/lot/gui_sponsors-dir_promoteurs_lot_program-eng.php))  
1368  
1369 For Radiopharmaceuticals/Generators - Guidance Document:  
1370  
1371 The Draft Guidance for Industry, Preparation of the Quality Information for  
1372 Radiopharmaceuticals (Schedule C Drugs) using the Quality Information Summary-  
1373 Radiopharmaceuticals (QIS-R) and Certified Product Information Document-  
1374 Radiopharmaceuticals (CPID-R) Templates (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic->  
1375 [demande/guides/radiopharm/qisr-sdqr\\_guide-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/guides/radiopharm/qisr-sdqr_guide-eng.php))  
1376  
1377 For Radiopharmaceuticals - Templates:  
1378  
1379 Blank QIS-R template (<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/templates->  
1380 [modeles/radiopharm/blnkqisr-eng.php](http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demandede/templates-modeles/radiopharm/blnkqisr-eng.php))  
1381  
1382 Blank QIS-PER template [not yet posted externally as of January 2011]



### Summary of Additional Drugs to be Imported for a Clinical Trial

Please note that this form is only to be completed for products not explicitly authorized under the No Objection Letter. The completed form will be sent to the sponsor at the time of issuance of a No Objection Letter.

Clinical Trial Protocol Number (must be assigned)	Clinical Trial Protocol Title
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Name of the country where the product is marketed	
Name of the company as stated on the marketed label	
Name of the drug product as stated on the marketed label	
Common name of the active ingredient	
Dosage form	
Strength	
Attestation that the product has undergone review from an International Conference on Harmonisation (ICH) or equivalent jurisdiction (Japan, United States, Europe, Australia)	

**This table may be replicated as many times as necessary to cover all additional medicinal products to be imported.**

**I, the undersigned, certify that the information and material included in this appendix is accurate and complete.**

Name of Authorized Signing Official	Signature	Date		
		YYYY	MM	DD
Title	Telephone:	Fax:		
Name of Company to which the Authorized Signing Official Belongs				

#### FOR HEALTH CANADA USE ONLY

Date Received			Drug Submission Tracking System (DSTS) Control Number		
YYYY	M	DD			
Name of Signing Official		Telephone:	Signature		
Title: Fax		:	Date Sent:		
			YYYY	M	DD