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THE ADVANTAGES OF CONDUCTING EARLY-PHASE CLINICAL RESEARCH IN CANADA

Timely completion of necessary studies is a critical element of drug development, bringing important treatments to patients, in a safe and cost-efficient way.

A consideration with a measurable impact on early-phase clinical studies is the location where trials are performed; this is especially true for first-in-human (FIH) trials. Conducting early-phase clinical research on novel compounds in Canada can provide significant advantages versus other locations.

IN THIS ISSUE

To initiate a clinical trial in Canada, a Clinical Trial Application (CTA) specific to the given study is submitted to Health Canada (HC) for approval, along with submission of study materials to an Ethics Review Board. The studies conducted under a Canadian CTA can be used to support an IND in the U.S., or a marketing authorization application in the EU, the UK, and any other regulatory regions, such as Asia and Brazil.

According to clinicaltrials.gov, as of October 2024, over 6,700 clinical trials were active (all phases, all stages) in Canada.[1]

Studies in Canada are conducted in accordance with the International Conference on Harmonisation (ICH) guidelines, are of high quality and compliant with regulatory and ethical standards, and are routinely used to support drug applications by global regulatory agencies, including the U.S. FDA and European Medicines Agency (EMA). A well-planned clinical program designed to meet all the regulatory requirements for the jurisdictions where you plan to request market authorization can be conducted cost-efficiently, safely, and in a timely manner in Canada. In fact, the majority of studies conducted at Canadian early-phase CROs are used for ex-Canadian submissions.

Health Canada (HC), the regulatory body responsible for the CTA process, almost always meets or exceeds the performance targets they set for the CTA timelines.

Sponsors, with support from their CRO partner if requested, can engage with Health Canada in a pre-CTA meeting to ask questions, exchange scientific information, and gain clarity on issues that might be related to their particular trial design.

Depending on the specifics of the program, advantages of a Canadian strategy can vary.

CANADIAN CTA TRIALS – TIME AND COST SAVINGS

In Canada, Phase I to III clinical trials require a CTA, and are approved individually. The CTA package is easier to build and less demanding, saving preparation time and cost. HC also has an excellent track record for timely reviews.

Table 1. EXAMPLES OF CANADIAN CTA VS. U.S. IND SUBMISSION REQUIREMENTS

CTA (Health Canada)	IND (U.S. FDA)
Principle • One CTA filed for each trial	**Principle** • One IND filed per product development program
Timelines • 30-day default for formal review for most trials • Information requests – respond within 2 calendar days (short extensions may be granted) **Review Decision:** • NOL (No Objection Letter) • Withdrawal without prejudice • NSN (Not Satisfactory Notice)	**Timelines** • 30-day default review for initial IND filing • Sponsor response to information requests to deficiencies identified by FDA are reviewed for an additional 30 days **Review Decision:** • "Safe to Proceed" letter for initial IND (usually) • Clinical hold (undefined period, depends on response to information requests)
CTA Content • Module 1: Forms, protocol, submission rationale, Investigator's Brochure (IB), informed consent forms (ICF) • Module 2: QOS to meet Phase I CMC Requirements	**IND Content** • CTD Modules 1-5 (forms, protocol, IB, all pharmacology, toxicology and clinical reports must be submitted) • Module 2 QOS to meet Phase I CMC Requirements and Module 3 CMC Summaries • Preclinical reports required • SEND data required
Annual Report • Not required	**Annual Report** • Required

CANADIAN CTA VS. U.S. IND

Canadian CTAs include study-related documents, such as the protocol, Investigator's Brochure, and ICF, as well as chemistry and manufacturing information of the investigational drug.

FIH Trial Initiation in Canada

Initiating FIH trials in Canada requires adequate nonclinical data as described in ICH M3 along with phase-appropriate chemistry, manufacturing, and control (CMC) information. These data are summarized in the Investigator's Brochure and Quality Overall Summary (QOS) Module 2, respectively, to form the basis of the CTA.

There is no requirement for Annual Reports following closure of a clinical trial with Health Canada. In contrast, Annual Reports are required by the FDA for the duration of the development program under an open IND. This reduces administrative tasks and saves resources for studies conducted in Canada.

Table 2. EXAMPLES OF CANADIAN CTA VS. EMA CTA SUBMISSION REQUIREMENTS

CTA (Health Canada)	CTA (EMA except the UK)	Time and Cost Savings
Principle • One CTA filed for each trial	**Principle** • Single CTA submission to all CMSs (Concerned Member State) with harmonized dossier via EU Clinical Trial Information System (CTIS) portal	• Dealing only with one Health agency (country) • There is no fee to file a CTA in Canada. • Submission via email in Canada is possible, no administrative burden of requesting and maintaining access to CTIS portal.
Timelines • 30-day default for formal review for most trials • Information requests (IR) – respond within 2 calendar days (extension requests is permissible, if granted) **Review Decision:** • NOL (No Objection Letter) • Withdrawal without prejudice • NSN (Not Satisfactory Notice)	**Timelines** • 60 days for CTA (Part I and II) without any issues • 75 days for CTA (Part I and II) with validation issues • 91 days for CTA (Part I and II) with Requests for Information during assessment • 106 days for CTA (Part I and II) with validation issues and Requests for Information during assessment (+ 50 days for ATMPs or biologics for purposes of consulting with experts) • Request for a response extension is not allowed; standard response time is 12 days **Review Decision:** • Acceptable • Acceptable subject to specific conditions • Refusal (Not acceptable)	• Canadian review timelines are significantly shorter, savings of 30 to 76 days.
CTA Content • Module 1: Forms, protocol, submission rationale, Investigator's Brochure (IB), • Informed consent forms (ICF) • Module 2: Quality overall summary (QOS) or IMPD	**CTA Content** • Part I (Scientific/Regulatory review): Protocol, IB, IMPD, GMP documents, label and translation (as required per each member state) • Part II (Ethical review): Trial site information, recruitment arrangements, ICF, suitability of investigator, suitability of facilities, financial arrangements, GDPR documentation	• Language and translation requirements in the EU • Heavier amount of documentation to include (Clinical Labels, CMC information) in the EU
Annual Report • Not required	**Annual Report** • Development Safety Update Report (DSUR)	

CANADIAN CTA VS. EMA CTA SUBMISSION REQUIREMENTS

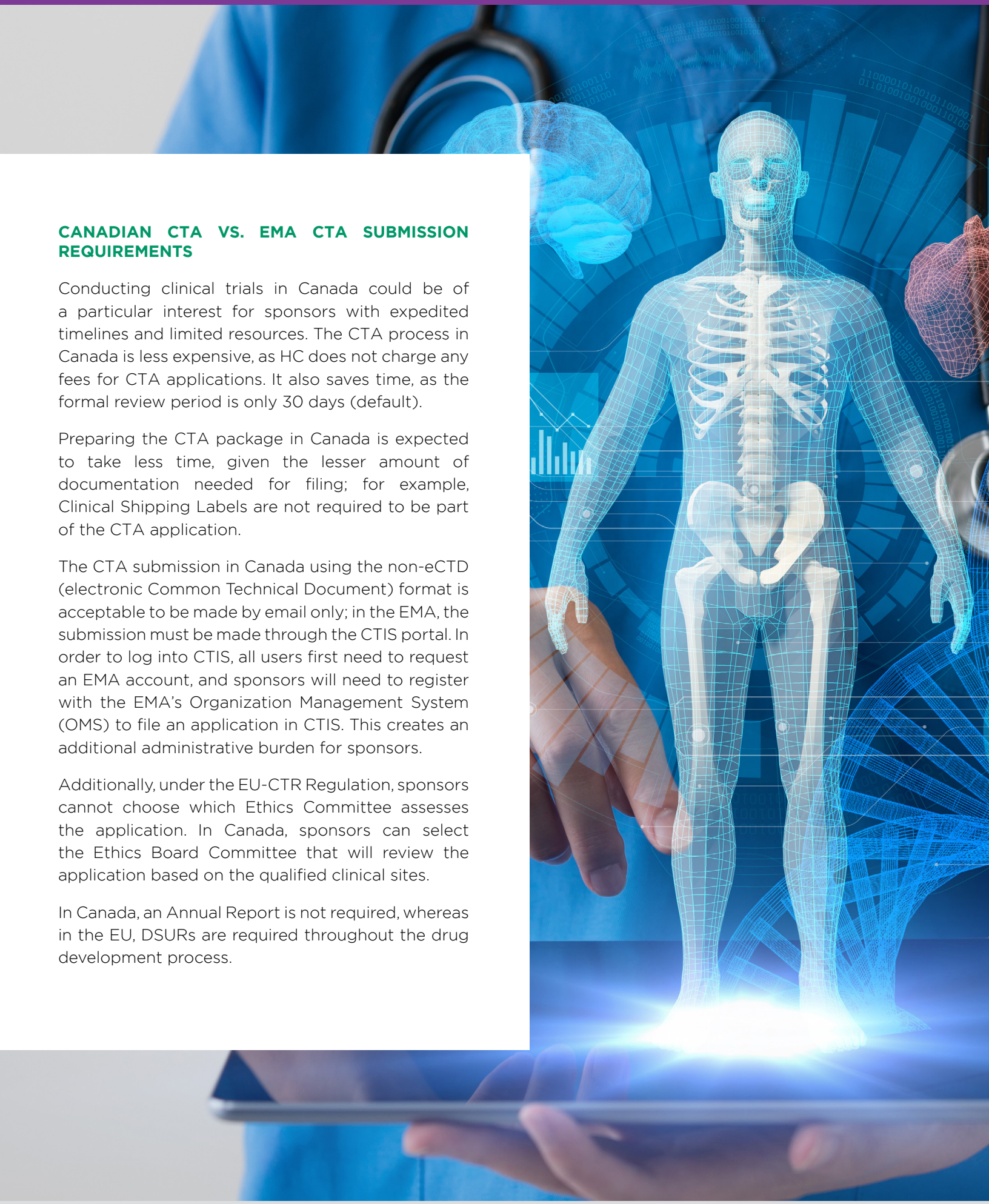
Conducting clinical trials in Canada could be of a particular interest for sponsors with expedited timelines and limited resources. The CTA process in Canada is less expensive, as HC does not charge any fees for CTA applications. It also saves time, as the formal review period is only 30 days (default).

Preparing the CTA package in Canada is expected to take less time, given the lesser amount of documentation needed for filing; for example, Clinical Shipping Labels are not required to be part of the CTA application.

The CTA submission in Canada using the non-eCTD (electronic Common Technical Document) format is acceptable to be made by email only; in the EMA, the submission must be made through the CTIS portal. In order to log into CTIS, all users first need to request an EMA account, and sponsors will need to register with the EMA's Organization Management System (OMS) to file an application in CTIS. This creates an additional administrative burden for sponsors.

Additionally, under the EU-CTR Regulation, sponsors cannot choose which Ethics Committee assesses the application. In Canada, sponsors can select the Ethics Board Committee that will review the application based on the qualified clinical sites.

In Canada, an Annual Report is not required, whereas in the EU, DSURs are required throughout the drug development process.



REGULATORY REVIEW PROCESS PREDICTABILITY

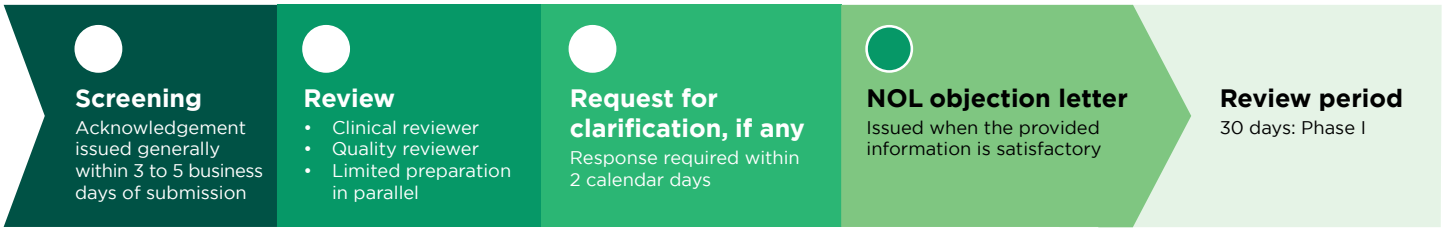
The review process in Canada has proven efficiencies and timeliness that sponsors and CROs can find advantageous. Embracing a collaborative approach with a knowledgeable CRO familiar with HC, EMA, and FDA guidances enables comprehensive study design and submission packages that fulfill the regulatory review and approval requirements in Canada, which can be used to support U.S. and EU marketing authorization application packages.

Canada has a well-deserved reputation for an efficient and collaborative review process, which results in timely approval of submissions. HC has a targeted timeline of up to 30 days to complete its formal review of a CTA submission. Certain specific start-up activities that do not involve subject screening, enrollment, or dosing can be conducted in parallel with the review. For example:

- SAP (Statistical Analytical Plan)
- PMP (Project Management Plan)
- Communication Plan
- TMF (Trial Master File) Plan
- RAMP (Risk Assessment and Mitigation Plan)
- IRB submission and approval
- Preparation of the regulatory documents (QIU form, Financial Disclosure Statement, IB acknowledgment by Principal Investigator)
- IP shipping, if locally and for controlled drugs with import permits
- Other activities in the clinic, e.g., protocol training for personnel and sub-investigators involved in the study
  - **NOL must be received before screening and dosing subjects**

This predictable and reliable timeline ensures efficiency and time savings in the conduct of clinical trials.

Figure 1. CTA Process

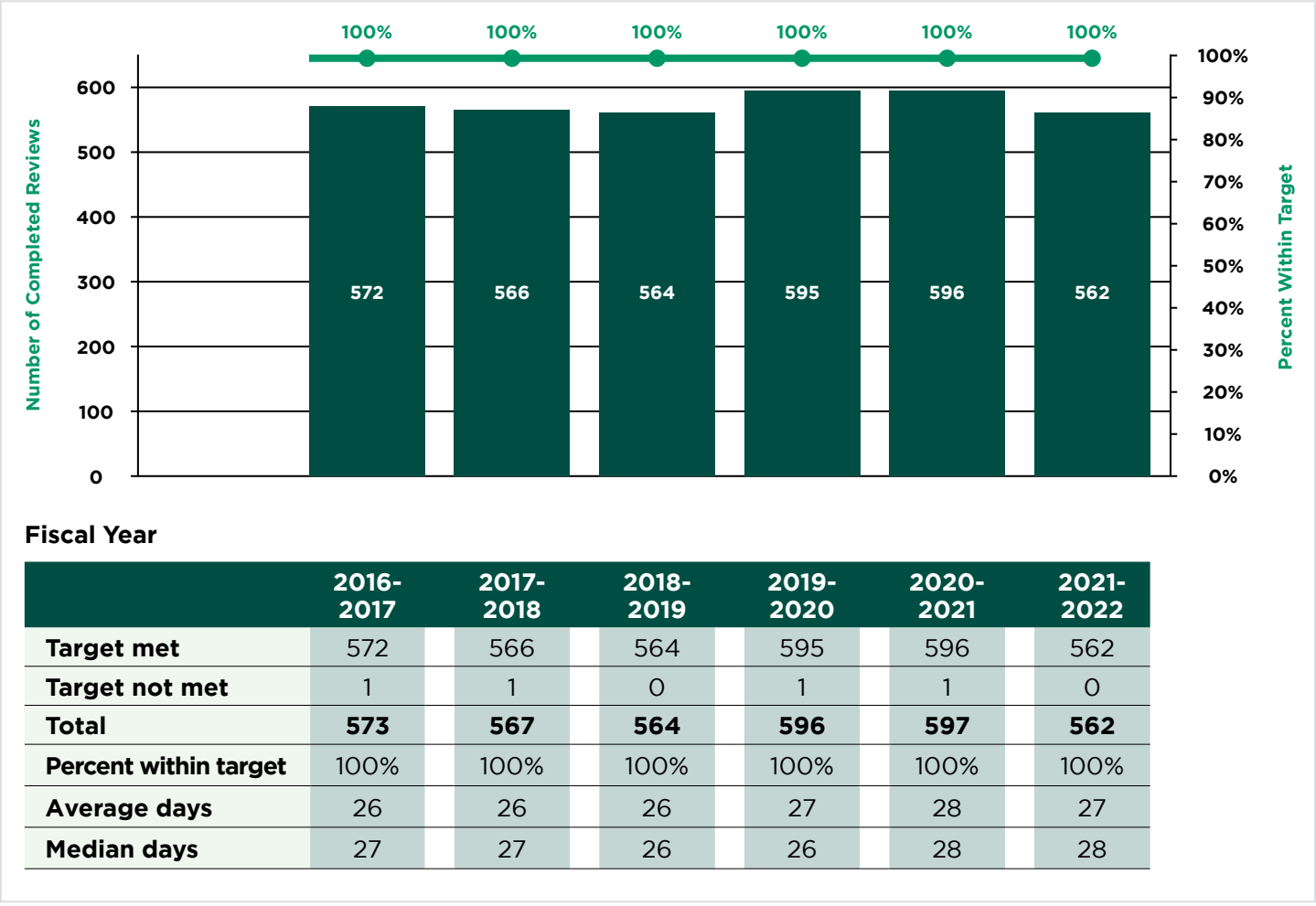


In the Canadian Therapeutic Product Directorate (TPD) Annual Drug Submission Performance Report[2] for the year-end 2022, the TPD reported an average of 524 submissions with a 30-day target reviewed in Canada per year since 2016. Of those submissions, only one received a Not Satisfactory Notice, and an average of 50 (6 to 10% per annum) were cancelled by the company at the time of processing or review (see Table 3 and Figure 2 below).

Table 3
CTA: Number of Decisions by Type (30-day Target)

Document Type	2016-2017	2017-2018	2018-2019	2019-2020	2020-2021	2021-2022
No objection letter	540	519	535	549	563	442
Cancelled by company during review	33	50	32	52	42	22
Cancelled by company at processing	4	10	9	13	10	22
Not satisfactory notice	0	0	1	0	0	0

Figure 2
CTA: Reviews Completed for Phases With a 30-Day Target
(excluding Phase I BE with a 7-day administrative target)



Fiscal Year

	2016-2017	2017-2018	2018-2019	2019-2020	2020-2021	2021-2022
Target met	572	566	564	595	596	562
Target not met	1	1	0	1	1	0
Total	**573**	**567**	**564**	**596**	**597**	**562**
Percent within target	100%	100%	100%	100%	100%	100%
Average days	26	26	26	27	28	27
Median days	27	27	26	26	28	28

BUSINESS EFFICIENCY COST SAVINGS

There are many additional advantages and cost efficiencies for sponsors who maintain a location, and conduct business in Canada. According to the Department of Finance, Government of Canada, Canada has the lowest tax rate on new business investment in the G7.[3]

When sponsors conduct clinical research in Canada, they may also benefit from tax credits.

For companies that have a business presence in Canada, attractive tax credits can contribute to the cost effectiveness of the development program. Read more about the Scientific Research and Experimental Development (SRED) Tax Incentive Program and Provincial and Territorial Research and Development (R&D) Tax Credits on the Government of Canada website (**here** and **here**).[4,5]

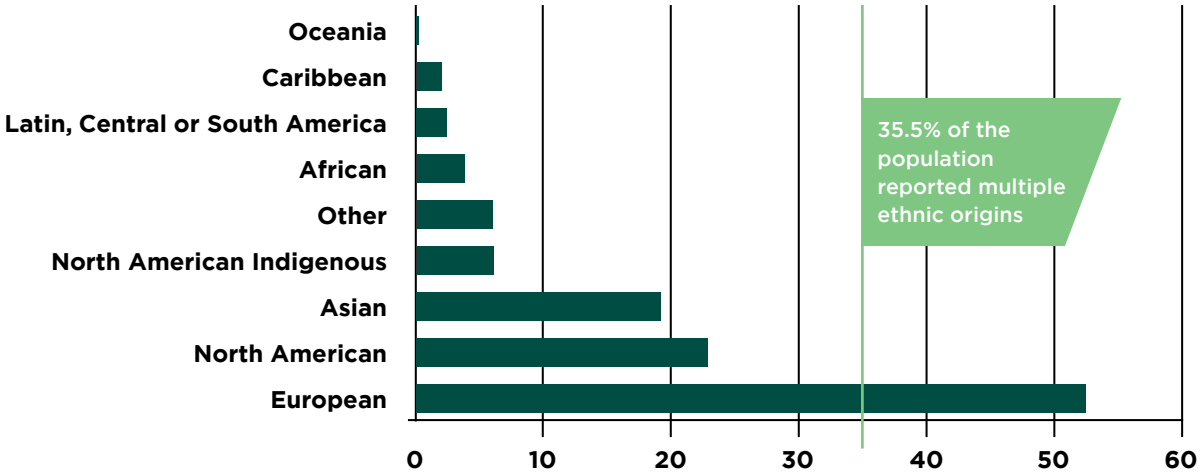
Provincial tax credits are also available. The rates vary from province to province, with a range of benefits offered depending on the location of the research projects. For sponsors without a long-term business presence in Canada, tax credits may be realized through collaborative arrangements with scientific partners, for example when engaging scientific guidance and support at the outset of the trial conduct.

CLINICAL TRIAL PARTICIPANTS

Canada has an ethnically diverse population; therefore, a clinical trial can easily include representation from many targeted patient populations.

According to the 2021 Canadian census, over 450 "ethnic or cultural origins" were self-reported by Canadians; see graph below. Statistics Canada reports that 35.5% of the population reported multiple ethnic origins; thus, the overall total is greater than 100%.[6]

Figure 3
Percentage of Multiple Ethnic Origin Responses by Region of Ethnic or Cultural Origin, Canada 2021



Study participants in Canada are supported by a publicly funded and delivered healthcare system referred to as Medicare, which is administered universally and free at the point of use. This initiative is supported by the Government of Canada and managed by each province individually. The intent is to assure a "continuum of care" across the country. This healthcare management philosophy has allowed pharmaceutical and biotechnology communities to leverage the high quality of participant health for pivotal early-phase clinical trials. The continuum of care means patient health is properly managed, and makes recruiting for trials more efficient.

In addition, the Canadian population is highly concentrated in the urban areas where research clinics are located. This facilitates recruitment efforts and increases the chances of having a full panel in place, on time, to start key trials. Affordable, comprehensive public transit that provides easy access to the clinical pharmacology units facilitates patient/healthy participant screening and return visits.

CANADIAN CTA FREQUENTLY ASKED QUESTIONS

Are Phase I studies conducted in Canada accepted by the U.S. FDA in support of NDA, 505(b)(2), or ANDA regulatory pathways, or are any additional bridging studies in the U.S. required?

Most trials conducted at Canadian sites are in support of NDA and ANDA submissions, and Canadian CROs are routinely and successfully audited by the U.S. FDA. The FDA regulations permit the use of foreign clinical trials to support an IND and/or Market Application (Title 21 CFR Part 314.106. The studies comply with Title 21 CFR Part 312.120 and GCP regulations).

Can Canadian Phase I studies support marketing authorization by the EMA?

Yes, Phase I studies in Canada are permitted in support of EMA marketing authorizations.

What type of documentation is needed to initiate a clinical study in Canada?

To initiate a clinical study in Canada, a CTA is required. While the data requirements for a first-in-human (FIH) study in Canada, the U.S., and the EU are the same (per ICH M3[R2]), the documentation for a CTA in Canada is less onerous. The focus is primarily on the protocol and the Investigator's Brochure (IB), without the need for nonclinical and clinical summaries (Module II) that are required in the U.S. In contrast, a full IND submission in the U.S. requires Modules 1 to 5.

In terms of screening/enrollment and dosing, is Canada a faster route for first-dose administration?

In Canada, certain documents, such as nonclinical reports, are not required in the CTA. This allows submissions to be completed more quickly, leading to faster progression through screening, enrollment, and first-dose administration.

What are the typical review timelines once we submit the CTA?

All CTAs are reviewed and approved within a 30-day default period upon receipt of the acknowledgement letter, typically received within three to five business days following CTA submission.

Will Altasciences take care of the CTA submission or do we need other Canadian representation for submission?

Altasciences can handle the entire CTA process on your behalf, including pre-CTA meetings; you do not need another Canadian representative to complete these tasks for you. This is a routine process for us; we successfully submit more than 120 CTA filings each year (approximately one third of all the CTAs filed with Health Canada in a given year).

After completion of our Phase I study, do we need to submit the clinical study report to Canadian regulatory authorities?

No. Health Canada does not review CSRs that are not intended to be submitted in Canada. However, the CSRs should be made available if requested by Health Canada.

Do we need to update the product development status to Canadian regulatory authorities on a regular basis (protocol amendments, annual reports, etc.)?

During the conduct of the trial and until study completion, Altasciences will update Health Canada of any changes brought to the proposed protocol via a CTA-A (A for Amendments) or a CTA-N (N for Notifications), depending of the nature of the change. Upon study completion, we will inform Health Canada of the end of the trial. Annual Reports (e.g., DSUR) are not required by Health Canada.

CANADIAN CTA FREQUENTLY ASKED QUESTIONS (CONT'D)

Does the Drug Product Labeling have to meet the language requirements of Canada?

Health Canada requires similar labeling requirements as are mandated internationally where the clinical trials are conducted. Canadian Food and Drug Regulations (C.05.011) require that both official languages (English and French) be listed. Altasciences' pharmacy ensures this regulation is met.

Is it true that Health Canada's CTA is complex, slow, and inefficient compared to the submission processes in the U.S. or the European Union?

No. In fact, it's the opposite. When the process is properly understood, the CTA in Canada is relatively simple, as is the review process. The submission structure is also simple, and is limited to the clinical trial listed in the CTA for approval.

WHY ALTASCIENCES?

Altasciences offers horizontal integration of its services. In addition to designing, conducting, and reporting on clinical trials, the CRO/CDMO also has a reputable presence in the preclinical, bioanalytical, data management, and biostatistics space that brings additional efficiencies and savings. Altasciences' Integrated offerings in manufacturing are also a benefit, as your program is developed, analyzed, and approached holistically from the start. Altasciences has decades of experience and expertise, with the right teams in place, to deliver quality results. With attention to preplanning, many sponsors can benefit from placing their early-phase clinical trials in Canada.

Altasciences has a clinical pharmacology unit (CPU) in Montréal, Québec, Canada, and the expertise to ensure efficient, compliant trial conduct. In 2022, the last year for which we have complete data, Altasciences submitted 45 innovator CTAs (30-day default review) which represents almost 30% of the total HC CTA submission volume for 2021-2022. We also submitted 46 BA/BE CTAs, which corresponds to 25% of the total HC BA/BE CTA submission volume for 2021-2022.

Altasciences' Montréal CPU Highlights

- 25-year history and over 2,850 clinical trials conducted
- 265-bed unit
- Central location across from public transport
- 15-minute drive to Altasciences' bioanalytical laboratory for small/large molecule analysis, PD biomarkers, and flow cytometry
- Active participant database > 50K, including special populations/patients for proof-of-concept arms
- Dedicated research pharmacy compliant to USP 797 and local regulations
- Neurological/CNS specialization
    - CSF collection
    - On-site driving simulators
    - Human abuse potential evaluation
    - Cognition expertise
    - Strong pain models experience
- Biological sample processing expertise, PBMCs, and flow cytometry
- 14 Principal Investigators; 4 with GI, ophthalmology, and general practitioner background
- 200 clinical trial experts
- Access to specialty physicians for protocol-specific needs
- And more!

REFERENCES

1 Clinical Trials active in Canada, accessed October 2024 at https://clinicaltrials.gov/ct2/results?cntry=CA&Search=Apply&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=.

2 Therapeutic Product Directory (TPD) Annual Drug Submission Performance Report 2022, July 2022. https://publications.gc.ca/collections/collection_2022/sc-hc/H166-6-2022-eng.pdf. Accessed April 12, 2023.

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4 Health Canada Website, Scientific Research and Experimental Development (SR&ED) tax incentives. https://www.canada.ca/en/revenue-agency/services/scientific-research-experimental-development-tax-incentive-program.html Accessed September 2024.

5 Health Canada Website, Summary of provincial and territorial research and development (R&D) tax credits. https://www.canada.ca/en/revenue-agency/services/scientific-research-experimental-development-tax-incentive-program/provincial-territorial-research-development-tax-credits.html. Accessed September 2024.

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ALTASCIENCES' RESOURCES

Webinars

Leading Your CTAs with Confidence

Comparison of U.S. FDA and Health Canada CTA Submission to Support First-in-Human Phase I

A Hop Across the Pond - The Many Advantages of Conducting Early Phase Clinical Trials in Canada

Demystifying the CTA Process in Canada

Demystifying the Conduct of Clinical Trials in Canada

Blog

Five Reasons to Place Early Phase Clinical Research in Canada

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

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