The Altascientist
SCIENTIFIC JOURNAL

ISSUE NO. 31

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 concurrent submission of study materials to an Ethics Review Board. The studies conducted as part of a Canadian CTA can be used to support an IND in the U.S., or a marketing authorization request in the EU, the UK, and many other regulatory regions, such as Asia and Brazil.

According to clinicaltrials.gov, as of April 2023, over 6,100 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, has strategic alliances and formal information-sharing agreements with many of the worldwide ICH Members, including the FDA, the EMA, as well as agencies in Australia, Japan, Switzerland, Iceland, and Norway. Their collaborative and firm but flexible approach gives sponsors a clear, non-adversarial platform to work from, and HC always meets or exceeds the performance targets they set for the CTA timelines.

Sponsors or their CRO partner are able to easily organize a pre-CTA meeting, where they can bring representatives from their CRO partner and their own company to meet with a team of HC subject matter experts to ask questions, exchange, and gain clarity around the trials to be conducted.

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

CANADIAN CTA TRIALS – TIME AND COST SAVINGS

In Canada, unlike some other jurisdictions, all clinical trials involving novel drugs require a CTA, and are approved individually. The CTA data requirements are specific to each trial, which narrows the scope of preclinical and CMC data required for submission to ensure the safety of subjects in first-in-human trials. This approach provides sponsors conducting trials in Canada with additional flexibility in their selection and timing for individual studies.

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

CTA (Health Canada)	IND (U.S. FDA)	Time and Cost Savings
Principle • One CTA filed for each trial	**Principle** • One IND filed per product development program	The CTA package is easier to build and less demanding, saving preparation time and cost. There is no Health Canada fee to file a CTA.
Timelines • 30-day default for formal review for most trials • 7 days for administrative review for eligible comparative BA/BE studies • Information requests – respond within 2 calendar days (extension requests is permissible, if granted) **Review Decision:** • NOL (No Objection Letter) • Withdrawal without prejudice • NSN (Non-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)	HC has an excellent track record for timely responses, faster review times. Sponsors can withdraw and resubmit CTA request without penalty or prejudice as additional information becomes available. Non-satisfactory notice prevents the sponsor from resubmitting a CTA for the same drug. Clinical hold of an IND stops the entire program for an undefined period of time.
CTA Content • Module 1: Forms, protocol, submission rationale, Investigator's Brochure (IB), informed consent forms (ICF) • Module 2: Quality overall summary (QOS; NCE use templates) or IMPD • SEND data not required	**IND Content** • Parts 1 to 10 or CTD Modules 1-5 (forms, protocol, IB, all pharmacology, toxicology and clinical reports must be submitted) • Full CMC required • Final audited preclinical reports required	In Canada, detailed CMC information is not required for Phase I trials compared to IND, allowing for faster program advancement.
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. The requested data is less stringent than that required for an IND, and Canadian CROs have support services on hand to compile and submit the CTA on behalf of sponsors. The CTA process in Canada is less expensive as HC does not charge for CTA applications, and involves significant time saving as the formal review period is only 30 days (default).

FIH Trial Initiation in Canada

Starting FIH trials via Canadian CTA requires adequate preclinical, toxicological, and CMC information supplied in accordance with Part C, Division 5 of the Food and Drug Regulations and ICH E6 Good Clinical Practices (GCP). The outcome-conclusive data from the preclinical research, along with additional supporting data from scientific literature, will be utilized for protocol development and writing the Investigator's Brochure.

After trials are closed with HC, there is no demand for annual updating and file maintenance as opposed to the FDA for U.S. IND packages. This reduces the administrative cost and burden for initial conduct of clinical trials, which may be particularly of interest to sponsors who have limited funding opportunities and/or resources.

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 MSCs (Member State Concerned) 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, no administrative burden of requesting and maintaining access to CTIS portal.
Timelines • 30-day default for formal review for most trials • 7 days for administrative review for eligible comparative BA/BE studies • Information requests (IR) – respond within 2 calendar days (extension requests is permissible, if granted) **Review Decision:** • NOL (No Objection Letter) • Withdrawal without prejudice • NSN (Non-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 purpose 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. An extension for IR response can be requested from HC allowing sponsors additional time to prepare and provide the information for the IR response. In Canada, sponsors can withdraw and resubmit CTA request without penalty or prejudice as additional information becomes available.
CTA Content • Module 1: Forms, protocol, submission rationale, Investigator's Brochure (IB), • Informed consent forms (ICF) • Module 2: Quality overall summary (QOS; NCE use templates) or IMPD • SEND data not required	**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, and amount of documentation to include (Clinical Labels, CMC information…) is heavier in the EU.
Annual Report • Not required	**Annual Report** • Development Safety Update Report (DSUR)	Flexible regulatory requirement (no filing is required)

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 provides time savings, as the formal review period is only 30 days (default).

The start of a trial with a first-dose administration could be faster in Canada given the approval (NOL) to be received within a 30-day timeclock. Also, the preparation of the CTA package in Canada will take less time, given the lesser amount of labor and 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, submission must be made through the new 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) in order to file an application in CTIS. This creates additional administrative, personal, and financial burden to sponsors.

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

A Canadian CTA can be withdrawn without prejudice during the formal review, meaning that the sponsor has the opportunity to withdraw their application if HC has any major concerns about the proposed study, and the sponsor is not able to address questions by the requested deadline. This reduces the cost exposure for sponsors, as they have the opportunity to resubmit the application at a later date, once they have compiled all necessary information. A non-satisfactory notice may be issued if significant deficiencies are identified during the review of the CTA, or if a timely response to information requested has not been provided.

Individual Canadian CTA trials are not required to be updated annually, unlike the DSUR in the EU. Once trial conduct is completed, the files are closed and the data can be used to support a regulatory filing without further administrative effort.

REGULATORY REVIEW PROCESS PREDICTABILITY

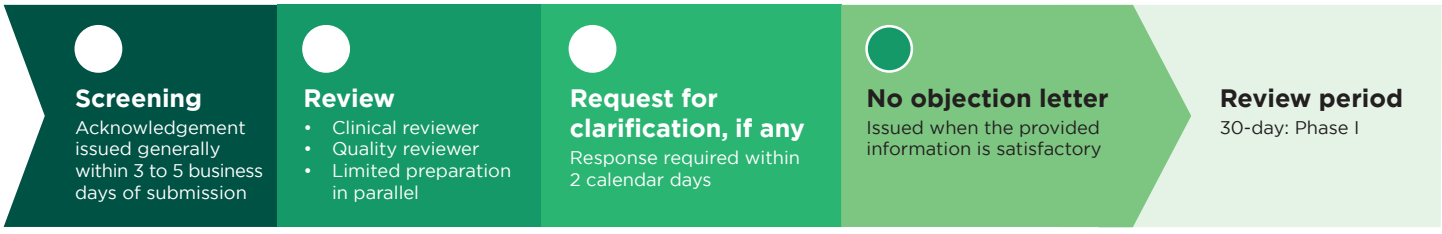
The review process in Canada has proven efficiencies and timeliness that sponsors and CROs can find advantageous. Embracing a collaborative approach with a knowledgeable CRO familiar with HC, EMA, and FDA guidances enables comprehensive study design and submission packages that fulfill the requirements for regulatory review and approval 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 their formal review of a CTA submission, and an administrative 7-day target timeline for BE studies. 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, FDA 1572, Financial Disclosure Form, IB acknowledgment by Principal Investigator, Debarment Certification)
- 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 consistency in timelines and conduct of clinical trials.

Figure 1. CTA Process

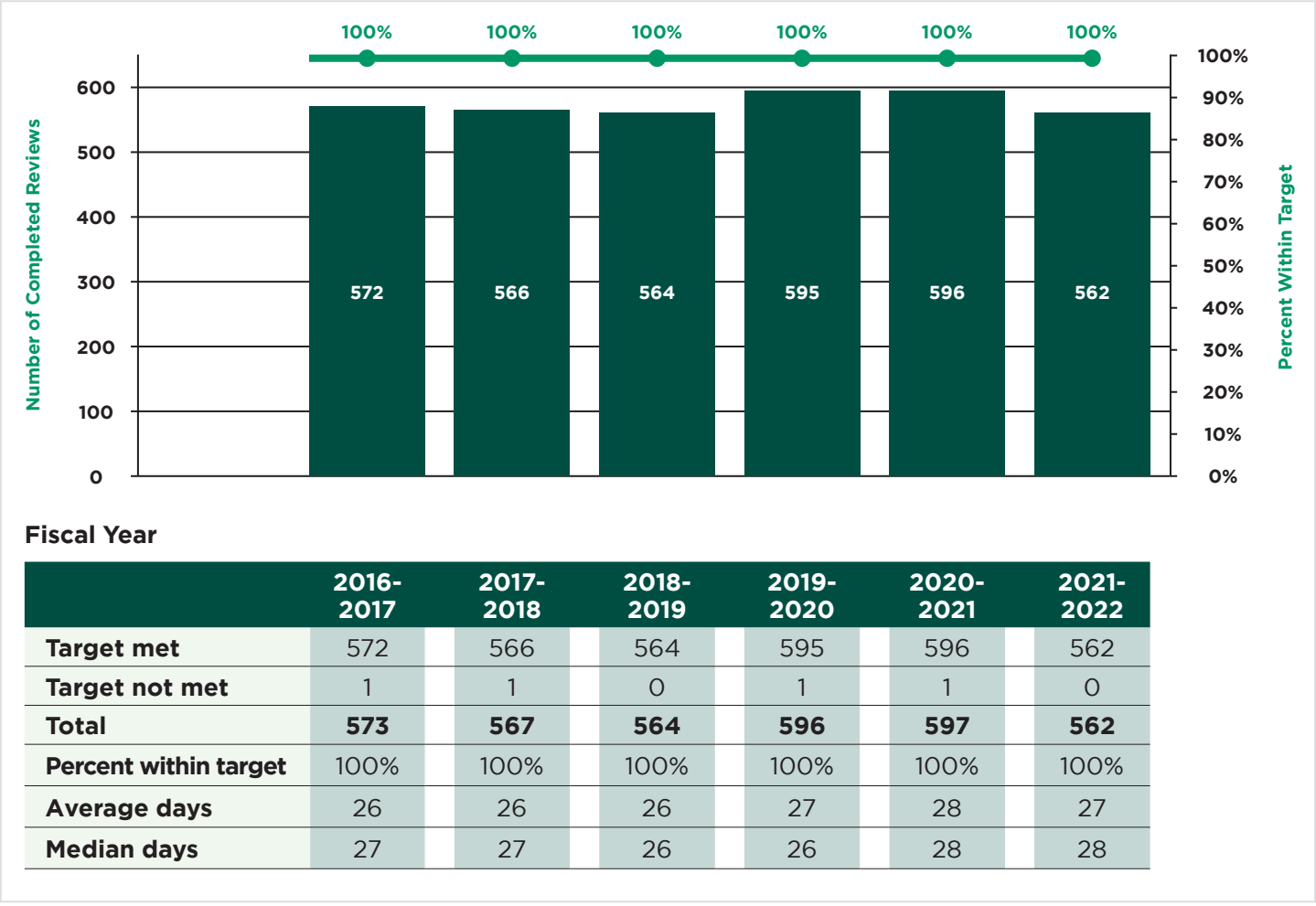


In the Canadian Therapeutic Product Directory (TPD) Annual Drug Submission Performance Report[2] for the year-end 2022, the TPD reported an average of 524 submissions with a 30-day target reviewed in Canada per year since 2016. Of those submissions, only one received a non-satisfactory notice, and an 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)

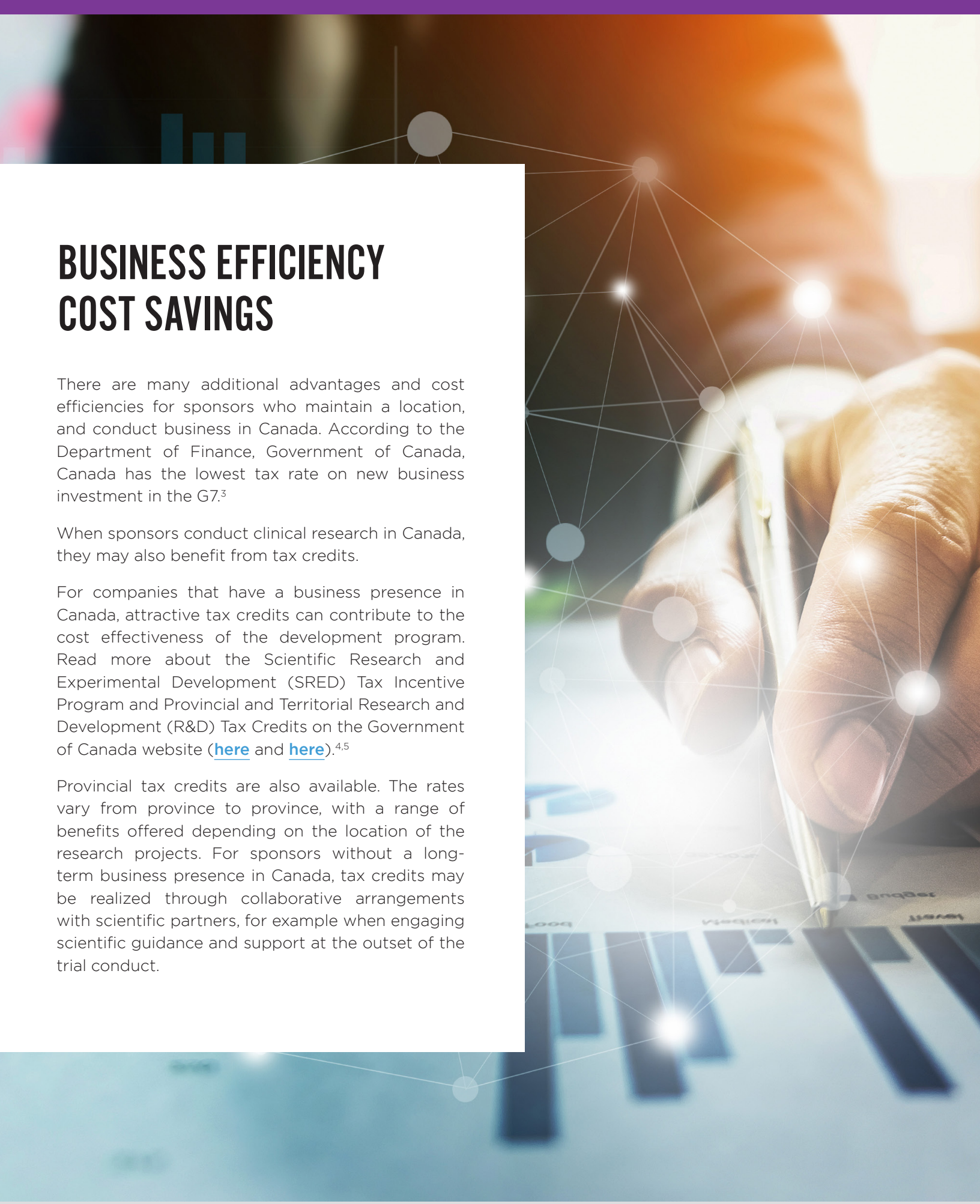
Document Type	2016-2017	2017-2018	2018-2019	2019-2020	2020-2021	2021-2022
No objection letter	540	519	535	549	563	442
Cancelled by company during review	33	50	32	52	42	22
Cancelled by company at processing	4	10	9	13	10	22
Not satisfactory notice	0	0	1	0	0	0

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]

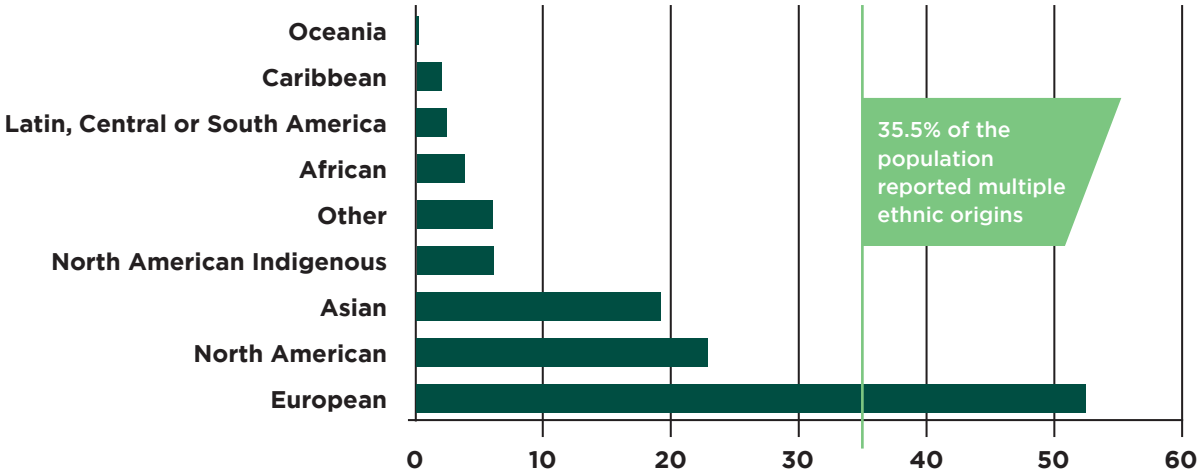
Provincial tax credits are also available. The rates vary from province to province, with a range of benefits offered depending on the location of the research projects. For sponsors without a long-term business presence in Canada, tax credits may be realized through collaborative arrangements with scientific 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 of the 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 which provides easy access to the clinical pharmacology units facilitates patient/healthy participant screening and return visits.

CANADIAN CTA FREQUENTLY ASKED QUESTIONS

If we conduct Phase I studies in Canada, will they be acceptable by the U.S. FDA in support of NDA, 505(b)(2), or ANDA regulatory pathways, or do we need to do any additional bridging studies in the U.S.? Similarly, can Canadian Phase I studies support marketing authorization by the EMA?

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). Canadian Phase I studies are also permitted in support of EMA marketing authorizations.

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

The CTA requirements in Canada are lighter than for a U.S. IND, or a CTA in the EU. If you have the documents ready to support your IND, the CTA process will be straightforward. The documentation is specified in the ICH M series guidance.

Are CMC requirements for drug manufacturing process less extensive for Phase I trials in Canada?

Yes. For EMA and IND packages, the sponsor is required to build an extensive Investigational Medicinal Product Dossier (IMPD) that contains more detailed CMC information on the drug manufacturing process, for example validation of analytical procedures, and specifications for Drug Substance and Drug Product. This information is not required for Phase I trials in Canada.

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

As we have reviewed above, yes, the Canadian process allows sponsors to get to first dose administration more quickly, and with less administrative burden, than either the U.S. FDA or the EMA.

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 3 to 5 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 HC 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, the Clinical Study Report (CSR) will be tailored for the agency you are targeting for submission. HC does not review CSRs that are not intended to be submitted in Canada. However, the CSRs should be made available if requested by HC.

CANADIAN CTA FREQUENTLY ASKED QUESTIONS (CONT'D)

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 HC of the end of the trial. Annual Reports (e.g., DSUR) are not required by HC.

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

HC 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 Europe?

No. In fact, it's the opposite. When the process is properly understood, and the sponsor or the representatives have established contacts with HC, the clinical trial application 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?

An important feature to look for in CRO capabilities is horizontal integration. Working with a CRO that, in addition to designing, conducting, and reporting on clinical trials, also has a reputable presence in the preclinical, bioanalytical, data management, and biostatistics space can bring additional efficiencies and savings. Integrated offerings in manufacturing are also a benefit, as the 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 Offers:

- 25-year history and over 2,850 clinical trials conducted
- 265-bed unit and over 200 clinical trial experts
- Central location across from public transport
- 15-minute drive to Altasciences' bioanalytical laboratory for small/large molecule analysis, PD biomarkers, and flow cytometry
- Proven recruitment with an active participant database > 50K
- Large database of 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
- Access to specialty physicians for protocol-specific needs
- And more!

REFERENCES

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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 November 1, 2022.

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6 Statistics Canada 2021 Canadian Census. https://www12.statcan.gc.ca/census-recensement/2021/ref/98-500/008/98-500-x2021008-eng.cfm. Accessed November 1, 2022.

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 25 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.