Regulatory Roadblocks & Expeditions for Global Clinical Trials

WITH DALTON

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This technical whitepaper will dive into the regulatory differences in clinical trials across the U.S, Canada, Australia, and China – some of the top countries with clinical trial registrations. It will highlight the processes and elements from each corresponding regulatory authority that aid in expediting clinical trials or reducing regulatory roadblocks, such as application fees and reporting requirements.

Company Vision

"To make the impossible possible, Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

Disclaimer

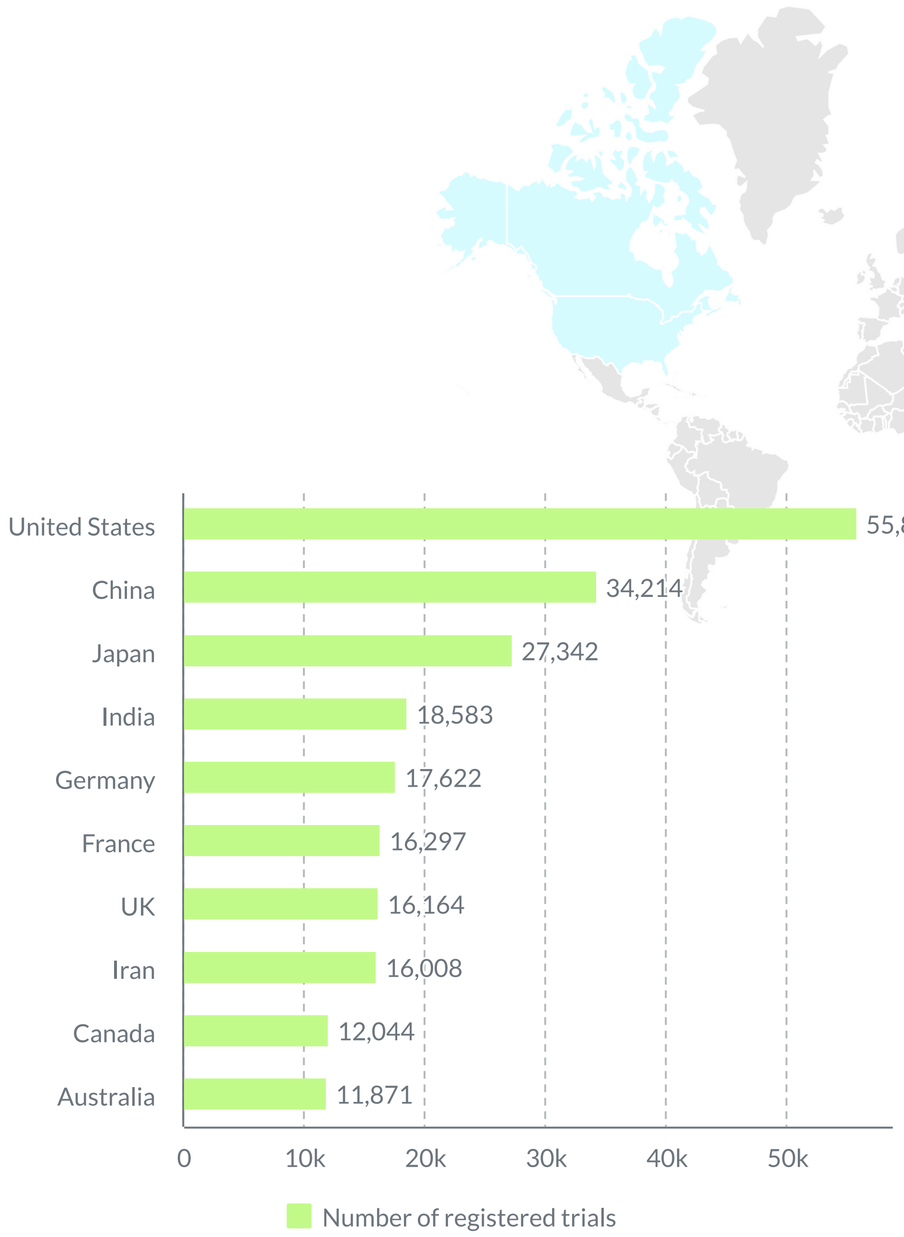
This technical report is intended to provide information to quality and regulatory correspondents on the regulatory requirement differences among various regulatory authorities in the US, Canada, China, and Australia. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

FDA inspected, HC approved, & MRA with EMA

DALTON Pharma Services

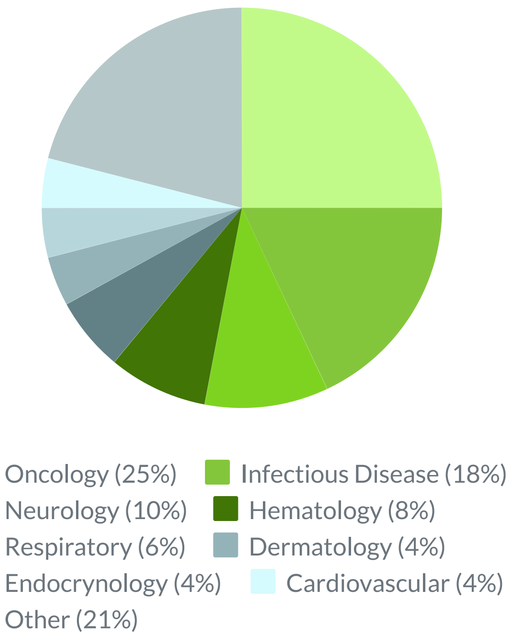
Clinical Market

The highest number of registered clinical studies worldwide from 1999-2020 is in the U.S (147,213). However, most clinical studies are registered in countries outside of the U.S (nearly 200 thousand clinical studies are registered in non-U.S countries, with most of these studies being in China (57,150) followed by Japan (53,385). Most clinical studies are registered in countries outside of the U.S because there are often fewer regulatory roadblocks to conduct trials in these locations. (14, 18)



DID YOU KNOW?

One quarter of clinical drug trials started worldwide in 2020 were for the field of oncology. Below are the clinical drug trials started worldwide in 2020, by key therapeutic area. (13)



This technical whitepaper will focus on the regulatory roadblocks, along with regulatory expeditions, commonly found during clinical trial applications in the US, Canada, Australia, and China. The regulatory aspects covered will include programs, exemptions, application fees, application approval timelines, whether regulatory & ethics committee (EC) review can be performed simultaneously, clinical data registration and other requirements, safety reporting, progress reporting, insurance, compensation, whether in-country sponsor presence is required, export and imports requirements, and GMP requirements. For further details on each regulatory element please view pages 5-8.

	USA	*Canada*	*Australia*	*China*
Programs	✔ Interact and pre-investigational new drug application consultation program. Also, investigator INDs and emergency and treatment applications.	✔ Pre-CTA consultation meeting	N/A	N/A
Exemptions	✔ Certain studies are exempt from requiring an IND application	✔ Phase IV studies are exempt from CTAs	N/A	✔ Drugs with trial data generated overseas, before the enactment by the drug administration, do not require the same studies to enter China
Application fees	✔ No fee	✔ No fee	From 353 to 25,521 CAD	From 37,132 to 97,085 CAD
Application approval timeline	30 days	30 days *Temporarily extended to 45 days*	✔ 5 to 7 days	60 days
Simultaneous Reg authority & EC review	✔ Yes	✔ Yes	✔ Yes	✔ Yes
Clinical data requirements	Registration to clinicaltrials.gv database required	✔ No registration to a database required	Registration to a database (i.e., Australian New Zealand clinical trials registry) required	Registration to chinadrugtrials.org database required. Also, data must include Chinese subjects.
Safety reporting	Disclose any severe adverse reactions (SAR)/ adverse reactions (AR) that are both serious and unexpected	Disclose any adverse reactions that are serious, unexpected, and have a suspected causal relationship	Disclose all adverse events	Provide a periodic safety update report

	USA	*Canada*	*Australia*	*China*
Progress reporting	Responsibility of the investigator **and** the sponsor	Responsibility of the investigator **and** the sponsor	Responsibility of the investigator	Responsibility of the investigator
Insurance	✔ Insurance coverage is not required	✔ Insurance coverage is not required	Institution and investigator are responsible for appropriate insurance coverage	Sponsor is required to provide legal and economic insurance
Compensation	✔ Not required to offer compensation	✔ Not required to offer compensation	Sponsor is required to offer compensation	Sponsor is required to offer compensation
In-country sponsor presence required	✔ No	Yes	Yes	Yes
Specimens export allowed	✔ Yes	✔ Yes	✔ Yes	✔ Yes, with Chinese research institutions
Manufacturing & import	An investigational product may be imported into the US if it is subject to an IND that is in effect	Canadian importer(s) must be located within Canada and Health Canada's authorization i.e., the no objection letter (NOL) is required	✔ The importer doesn't require approval from TGA prior to importation of the IP, but the trial must be notified to the TGA through the CTN scheme prior to supply of the IP to the trial sites	Prior to investigational product (IP) import or manufacture, a NMPA import drug license must be obtained for each IP
Good manufacturing practices (GMP) regulations	There are regulatory requirements on ensuring that products are manufactured in accordance with GMPs	There are regulatory requirements on ensuring that products are manufactured in accordance with GMPs	✔ There are no explicit regulatory requirements, but rather ICH guidelines, on ensuring that products are manufactured in accordance with GMPs	There are regulatory requirements on ensuring that products are manufactured in accordance with GMPs

USA

(7, 8, 9, 10)

Programs:

The FDA has two programs to promote the accelerated approval of innovative medical products, **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s (INTERACT) (announced June 22, 2018) and Pre-Investigational New Drug Application (IND) Consultation Program. The FDA also allows a physician who initiates and conducts an investigation to submit an IND (Investigator IND), the use of an experimental drug in an emergency situation that does not allow time for submission of an IND (emergency IND), and submission of an experimental drug showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted.

Exemptions:

Some studies may be exempt from requiring an IND if the following exemption criteria are met:

- The study is not designed to support approval of a new indication or a change in label,
- The study is not intended to support a significant change in the advertising for the product,
- ***The study does not involve a route of administration, dosage level, patient population, or other factors that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug,***
- The study is conducted in compliance with the IRB (Institutional Review Boards) and informed consent regulations,
- The study is conducted in compliance with regulations regarding the promotion of investigational drugs.

Regulatory Fee:

The Food & Drug Administration (FDA) does not charge a fee to assess investigational new drug (IND) submissions. The FDA, however, has the authority to assess and collect user fees from companies that produce certain human drug and biological products as part of a New Drug Application (NDA). The data gathered during the animal studies and human clinical trials of an IND become part of the NDA.

Timeline of Review:

Unless the FDA notifies the sponsor that the IND is subject to a clinical hold, or the FDA has told the sponsor that the trial may begin sooner, an IND automatically enters into effect in 30 days.

Clinical Data:

- Sponsors must make phase II, III, and IV clinical trial results publicly available in the http://clinicaltrials.gov database to obtain a certification of registration (Form 3674).
- For the clinical portion of the application, reference through an approved label via a letter of authorization or published literature is acceptable.

Safety Reporting:

The sponsor must disclose any severe adverse reactions (SAR)/ adverse reactions (AR) that are both serious and unexpected, as defined by 21CFR312. An adverse event (AE) must only be reported as a SAR if there is evidence to suggest a causal relationship between the drug and the AE.

Progress Reporting:

In accordance with 21CFR312 and the US-ICH-GCPs, the investigator and the sponsor share responsibility for submitting progress reports on the status of a clinical trial and for submitting final study reports upon the trial's completion.

Insurance:

Not required but highly recommended. Guidance document available.

Compensation:

Trial participants are not by law entitled to compensation, even in the event of a trial-related injury or death.

Import:

An IP may be imported into the US if it is covered by an active IND and meets one of the following criteria: The IP consignee is the IND sponsor, the consignee is a qualified investigator named in the IND, or the consignee is a domestic agent of a foreign sponsor, and the IND describes what, if any, actions the consignee will take with respect to the IP.

Canada

(3, 4, 5, 6)

Programs:

Sponsors may request a pre-CTA consultation meeting. The pre-CTA consultation meeting provides an opportunity for the sponsor to present relevant data, discuss concerns and resolve issues regarding drug development. It also gives Health Canada an opportunity to provide guidance on the acceptability of the proposed trial(s). Requests for a pre-CTA consultation meeting should be submitted in the form of a cover letter, proposing 4 dates and times suitable for a pre-CTA consultation meeting

Exemptions:

Clinical trials involving marketed drugs where the investigation is to be conducted within the parameters of the authorized NOC or DIN application (Phase IV clinical trials).

Regulatory Fee:

Health Canada does not charge a fee to submit a clinical trial application.

Timeline of Review:

A clinical study that has been filed with HC and has not received an objection within 30 days is considered permitted. On August 13, 2020, the Minister of Health approved an order to temporarily extend the default period to review clinical trial applications and amendments by 15 days.

Safety Reporting:

The sponsor is required to expedite reporting of adverse drug reactions (ADRs) to HC that meet these three (3) criteria: serious, unexpected, and having a suspected causal relationship. ADRs that are expected or unexpected but not serious should not be reported to HC; instead, the sponsor should monitor and track them.

DID YOU KNOW?

Serious, Unexpected ADR *– A serious ADR that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.*

Progress Reporting:

Investigators and sponsors share responsibility for producing interim and annual reports on the status of a clinical trial under the Canadian FDR.

Insurance:

The sponsor is not required to offer insurance coverage to investigators, institutions, or trial participants under the Canadian FDR. The International Council for Harmonisation (ICH), however, advises sponsors on how to provide insurance. Here, the ICH guidance precedes HC guidelines.

Compensation:

The Canadian regulations do not require compensation for trial participants in the event of trial-related injuries or death. ICH guidelines can be used by sponsors for providing compensation to research participants in the event of trial-related injuries or death.

Import:

In accordance with Health Canada, the sponsor can be authorized to import an investigational product (IP), if they arelocated within Canada. A sponsor who is not located in Canada must appoint a representative (senior medical or scientific officer) in Canada to oversee the import process. In addition, a copy of HC's authorization (i.e., the No Objection Letter (NOL)) must be provided at the port of entry. Specific requests to import IPs should be directed to the Health Product Border Compliance Program, if 30 days have passed and a NOL has not been issued. Note that a sponsor does not need to submit a clinical trial application for authorization to import an IP used in a Phase IV clinical trial.

China

(1, 2, 11, 12)

Exemptions:

For overseas clinical trial data completed before the enactment of NMPA-No35-2017, NMPA will consider approval of these drug registrations exempted from conducting clinical trials, with the condition.

Regulatory Fee:

According to the Drug Regulation Registration (DRR), the applicant must pay a charge in line with the applicable regulations. The National Medical Products Administration (NMPA) levies the following drug registration fees as part of the drug registration process:

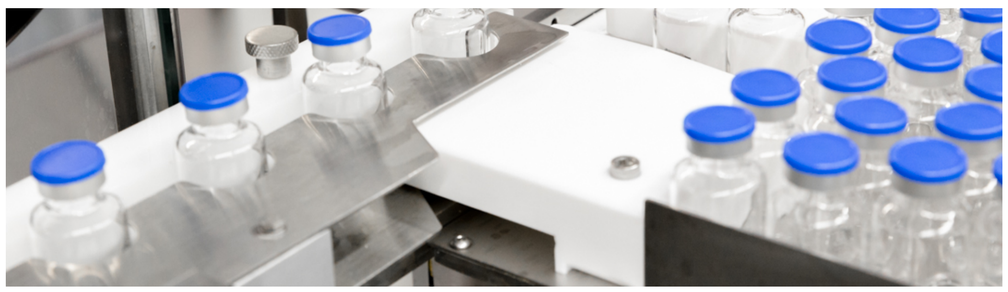
- New drugs made in China: 192,000 Renminbi
- New drugs made outside China: 376,000 Renminbi
- Generic drugs made in China: 318,000 Renminbi
- Generic drugs made outside China: 502,000 Renminbi

Timeline of Review:

A clinical trial application will be considered approved after 60 working days if the applicant does not receive a rejection or an inquiry for clarification from the NMPA. These procedures do not apply in every situation.

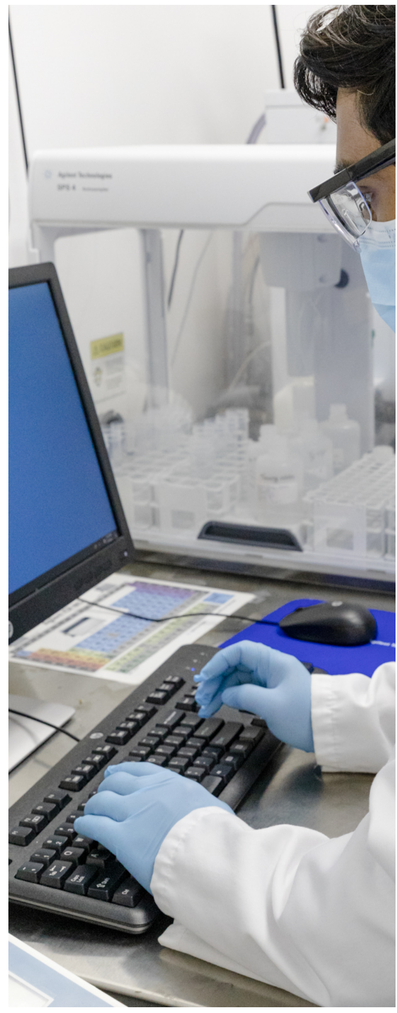
Clinical Data:

Clinical data should include statistical analysis reports and a database of all clinical studies that include Chinese subjects. Japan, South Korea, and China established (in 2007) a tri-partite cooperation agreement regarding pharmacokinetic clinical trial collection and analysis, with an aim to share and streamline pharmacokinetics (PK) requirements specifically for the north Asian population.



Safety Reporting:

According to the DRR, the sponsor is required to submit a safety update report to the National Medical Products Administration's (NMPA) Center for Drug Evaluation (CDE) at the Applicant's Window on a regular basis. During the research and development stage, the safety update report shall be submitted once a year, and within two (2) months of the complete year following the approval of the medication clinical study. Based on the review circumstances, CDE may compel the sponsor to change the reporting cycle.



Progress Reporting:

Investigators must provide clinical trial progress reports annually to the ethics committee (EC).

Insurance:

The sponsor is responsible for providing legal and economic insurance to the investigator and clinical trial institution or a guarantee related to the clinical trial, which must be compatible with the nature and degree of risk of the clinical trial. Damage caused by the investigator and the clinical trial facility itself should not be covered by this insurance. Sponsors are guided on how to provide insurance by the International Council for Harmonisation's Guideline for Good Clinical Practice E6(R2).

Compensation:

The sponsor must take adequate efforts to guarantee that the participants and researchers are rewarded in compliance with the NMPA. The sponsor is responsible for the costs of diagnosis and treatment, as well as compensation, if a participant is injured or dies as a result of the clinical trial. In addition, the sponsor is responsible for providing free trial medications to participants as well as paying for medical testing associated with clinical studies.

Australia [15, 16, 17]

Regulatory Fee:

The sponsor must pay a charge to the Therapeutic Goods Administration (TGA) to submit a clinical trial notification (CTN) or clinical trial approval (CTA) for evaluation, according to the Therapeutic Goods Regulations (TGR). The following are the fees for the fiscal year 2021-2022:

- 380 AUD for unapproved medicine CTN and for each notification of one or more additional trial sites
- 1,810 AUD for unapproved medicine CTA for a 30-day evaluation
- 22,500 AUD for unapproved medicine CTA for a 50-day evaluation
- 380 AUD for unapproved biological CTN and for each notification of one or more additional trial sites
- 27,400 AUD for unapproved biological CTA

Timeline of Review:

The TGA's target period for processing online CTNs is 5-7 working days. When the trial has been submitted to the TGA and the relevant notification fee has been paid, CTN studies can begin. The TGA no longer distributes acknowledgment letters through email, because this information may now be seen and printed via the web portal.

Safety Reporting:

The investigator is responsible for recording and assessing all adverse events (AEs) that occur at the site. Within 24 hours of becoming aware of the occurrence, the investigator must notify the sponsor of all serious adverse events (SAEs) and all urgent safety measures implemented by the site. Furthermore, all important safety issues and Suspected Unexpected Serious Adverse Reactions (SUSAR) emanating from the local site must be reported to the university within 72 hours of becoming aware of the event.

DID YOU KNOW?

Serious Adverse Event (SAE) – *Any adverse event/adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect*

Suspected Unexpected Serious Adverse Reaction (SUSAR) – *An adverse reaction that is both serious and unexpected*

Progress Reporting:

The investigator(s) is responsible for sending progress reports to the ethics committee (EC) (known as Human Research Ethics Committee in Australia) annually, or more frequently if required. The investigator shall make a written report to the sponsor, the EC, and, if relevant, the institution if there are significant changes in trial conduct or safety. The investigator must also submit a final clinical trial report to the EC and the sponsor should make the final report available to the TGA upon request.

Insurance:

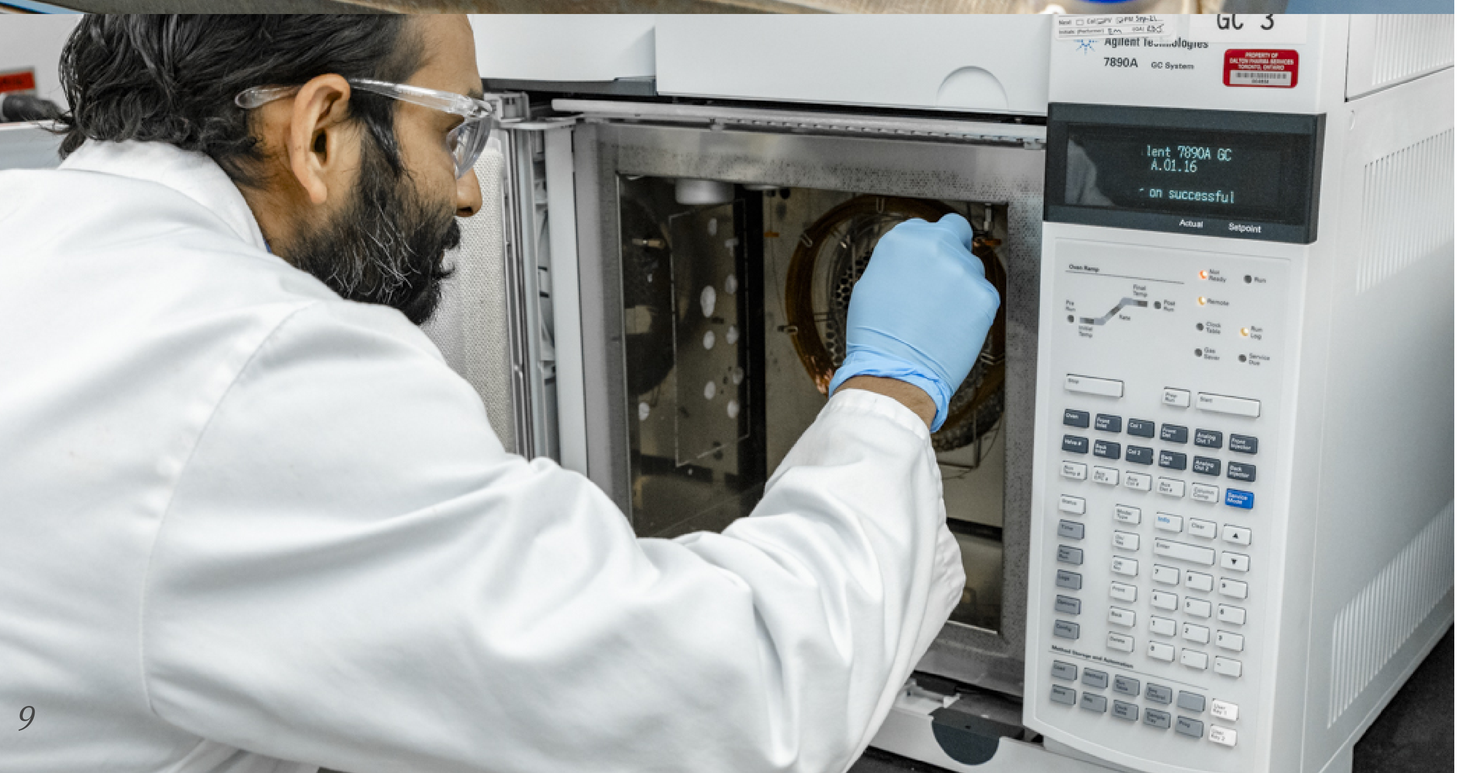
The institution and investigator are responsible for managing risks of any proposed research, including appropriate insurance coverage. In the private sector, sites that conduct clinical trials will usually purchase clinical trials insurance from a commercial insurer. In the public sector, each state or territory provides indemnity or insurance coverage in relation to its clinical trial activities. Click here for more details on each state and territory scheme.

Compensation:

The TGR instructs the sponsor to follow the obligations set out in the ICH GCPs and The National Statement on Ethical Conduct in Human Research Guidance, which indicate that the sponsor must compensate trial participants in line with applicable regulatory requirements. The ethics committee (EC) reviewing the research should consider any proposal for payment of participants.

Import:

Investigational products (IPs) may be imported and held under the importer's direct control until they are included in a notification made to the TGA through the CTN scheme. The IPs must be stored in a warehouse or other secure location.



Dalton's Services

At Dalton, we offer both contract drug development and manufacturing services ranging from early-stage research and development through to developing material for both clinical trials and commercial production. As a CDMO, we enhance our customers production efforts through expertise from highly qualified chemists and researchers to accelerate the end-to-end process, while ensuring regulatory standards are met throughout. Given that Dalton is Health Canada approved and an FDA inspected facility, quality control is essential to meeting these strict regulatory standards for pharmaceutical manufacturing.

Dalton Pharma Services is a leading cGMP contract service provider of integrated drug discovery, development and manufacturing services to the pharmaceutical and biotechnology industries.

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- API Process Development
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