# Global Expedited Review Programs & Incentives

WITH DALTON

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## 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 global regulatory incentives put in place for drug applications. 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

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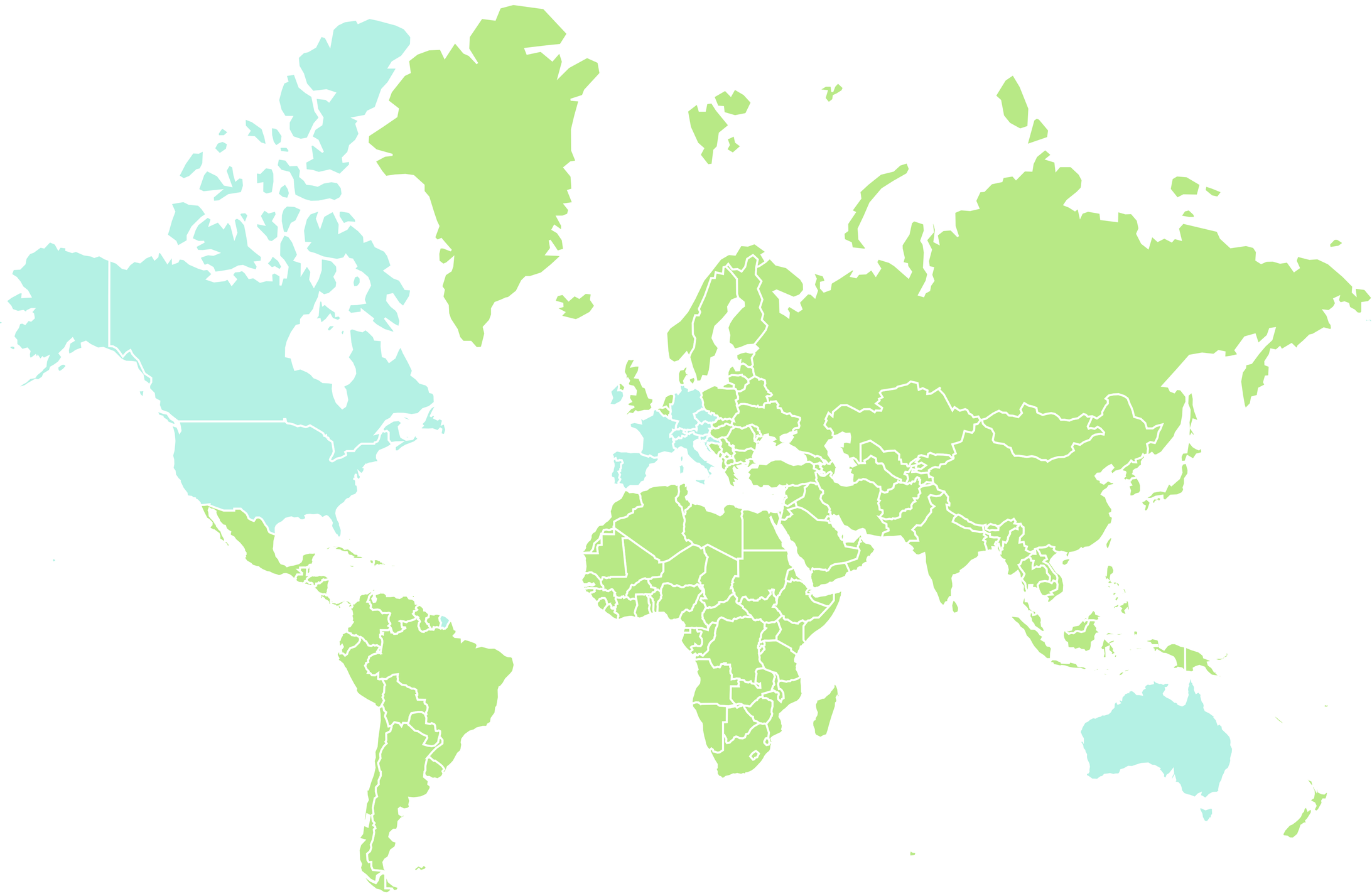
# Expedited Review Program

## What is an Expedited Review Program?



Expedited review programs have been developed by regulatory authorities to help expedite and support drug development and review.

These programs are intended to help ensure that therapies are approved and available to patients as early as possible while ensuring that the therapies' benefits justify their risks.

These programs have several incentives such as enhanced interaction and early dialogue with the corresponding regulatory authority to improve clinical protocols and shorten evaluation and review periods.

Expedited review programs are seen among various regulatory authorities, including Health Canada, the Food and Drugs Administration (FDA), the European Medicines Agency (EMA), the Therapeutic Goods Administration (TGA), and Swissmedic.


At Dalton, we can help you with your drug development needs, from small/medium clinical trial batches to commercialization.

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# HC's Expedited Review Program

Health Canada (HC) has developed two expedited review programs to expedite the development and review of drugs:

## Priority Review

### Eligibility

The New Drug Submission (NDS) or Supplemental New Drug Submission (S/NDS) must be for a serious, life-threatening, or severely disabling illness or condition for which the drug shows sufficient evidence of clinical effectiveness: effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada

### Features/ Incentives

Shortened review target of 180 calendar days.

### Request

Sponsors seeking Priority Review status are encouraged to deliver a brief pre-NDS or pre-S/NDS presentation to the directorate review staff, prior to submitting a written request for Priority Review status.

## &

## NOC/c

### Eligibility

The NDS and SNDSs must be for a serious, life-threatening, or severely disabling disease or condition for which there is promising evidence of clinical benefit based on available data, such as:

- effective treatment, prevention, or diagnosis of an illness or condition for which there is currently no medicine on the market in Canada; or
- a significant gain in efficacy and/or a significant decrease in risk over existing therapies, preventatives, or diagnostic agents for an illness or condition that is not adequately managed by a drug marketed in Canada, resulting in a better overall benefit/risk profile.

Or, an ANDS and SANDS where the Canadian Reference Product still holds an NOC/c status.

### Features/ Incentives

Provides patients suffering from serious, life-threatening, or severely debilitating diseases or conditions with earlier access to promising new drugs.

### Request

The sponsor is required to deliver a pre-NDS or pre-SNDS presentation to the appropriate directorate outlining the evidence of effectiveness to be provided in the submission. Sponsors should also submit a pre-submission meeting information package to the appropriate directorate in advance of the meeting.

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# FDA's Expedited Review Program

The Food and Drug Administration (FDA) has developed four expedited review programs to expedite the development and review of drugs:

## Fast Track

### Eligibility

The drug must treat a 1) serious condition and 2) demonstrate clinical or non-clinical potential to address an unmet medical need.

The term " serious condition" refers to a condition that:

- Has an effect on day-to-day operations
- If not addressed, can develop into a serious condition
- AIDS, Alzheimer's, heart failure, cancer, epilepsy, depression, and diabetes are examples of significant conditions

The term " unmet need" refers means:

- There is no available therapy, or
- There is available therapy, however the proposed medicine may be better than what's available because it:
  - Demonstrates superior effectiveness or a greater impact on severe outcomes.
  - Avoids the serious side effects that are common with current treatments.
  - Improves the diagnosis of a serious condition in which early detection leads to a better outcome.
  - Reduces the clinically significant toxicity of a commonly used drug that leads to treatment termination.
  - Addresses a public health need that has arisen

For a list of drugs granted fast track designation click here.

### Features/ Incentive

A drug that receives fast track status may be eligible for one or more of the following:

- More frequent meetings and communication with the FDA to discuss the drug's development plan
- Eligibility for accelerated approval and priority review
- Rolling review, which permits review of data as it becomes available from ongoing studies versus waiting until the study phase is complete

### Request

- The sponsor must request fast-track designation. This can be done at any time during the drug development process.
- The FDA will review and make a final decision of the fast track request within 60 days.

## Accelerated Approval

### Eligibility

- There is a surrogate or intermediate endpoint, and the drug demonstrates significant advantages over current therapies.
- A "clinical benefit" is a favourable treatment result that is clinically significant in the context of a certain condition. Within this context, a surrogate or intermediate endpoint is a marker such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.
- If granted accelerated approval, the sponsor is subject to post market commitments. This includes phase 4 confirmatory trials to confirm rather than predict the clinical benefit.

### Features/ Incentive

A drug that receives accelerated therapy designation is eligible for all fast-track designation features.

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# FDA's Expedited Review Program

## Priority Review

### Eligibility

The drug demonstrates significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition when compared to standard applications.

Significant improvement may be demonstrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of condition
- Elimination or substantial reduction of a treatment-limiting drug reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes evidence of safety and effectiveness in a new subpopulation

### Features/ Incentive

Priority review designation means that the FDA's goal is to take action on an application within 8 months (compared to 12 month) for a new chemical entity, or to take action on an application within 6 months (compared to 10 months) if it is not a newchemical entity.

### Request

- For every application the FDA decides if a priority review designation is applicable. However, the sponsor may request priority review as described in the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics.
- The FDA will inform the applicant of a priority review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement.

## Breakthrough Therapy

### Eligibility

- The drug should demonstrate preliminary clinical evidence that indicates a substantial improvement over available therapy, on a clinically significant endpoint(s), for a serious condition
- A **clinically significant endpoint** is a specific treatment that has a high correlation with a real clinical endpoint and may guarantee a relationship; a confirmatory study

### Features/ Incentive

- All fast-track designation features
- Intensive guidance on an efficient drug development program, starting in Phase 1
- Organizational commitment involving senior managers

### Request

- The sponsor should submit a request for breakthrough therapy designation with the submission of a new IND, or as an amendment to an active IND.
- However, FDA may suggest that the sponsor consider submitting a request based on their initial review of the clinical evidence.
- The FDA will review and make a final decision of the breakthrough therapy designation request within 60 days.

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# SwissMedic's Expedited Review Program

SwissMedic has developed three expedited review programs to expedite the development and review of drugs:

**Article 13** – reduces the routine 330-day approval process by one third (~220 days)

Allows expedited reviews of products approved by countries with comparable control systems.

Countries include Australia, Canada, Japan, New Zealand, Singapore, US and EU

- Thus, a common regulatory straategy is to submit an applicaction through EMA first, and then get it approved by Swissmedic.

Oncology products cannot be registered under this procedure.

**Fast-track** – approval timeframe = 140 days

Ensures faster access to innovative medicines to treat life-threatening conditions.

Oncology products may be registered under this procedure if justifiable.

This procedure is subject to higher submission fees.

**Simplified**

The types of products that may be registered under the simplified procedure include orphan drugs and oncology products.

- Orphan drugs are mentioned in the Swiss Therapeutic Products Act. However, no specific orphan drug legislation exists.

This procedure has reduced submission fees.

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# EMA's Expedited Review Program

The European Medicines Agency (EMA) has developed five expedited review programs to expedite the development and review of drugs:

| | | |
|---|---|---|
| **PRIME** | **Eligibility** | The medicine has to show its potential to benefit patients with unmet medical needs based on ***<u>early clinical data (i.e., phase 1).</u>*** A drug that meets an unmet medical need provides a significant therapeutic advantage over existing medicines or benefits patients who have no other treatment alternatives.<br>Click here for a list of prodcuts granted eligibility to PRIME. |
| | **Features/ Incentives** | Early and proactive assistance to drug developers to optimise development plans and accelerate evaluation so that these treatments can reach patients sooner. |
| | **Request** | The sponsor must submit a request for PRIME. |
| **Conditional Approval** | **Eligibility** | • The medicine addresses an unmet medical need<br>• The medicine is aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases (includes orphan medicines)<br>• The benefit of <u>immediate</u> availability of the medicine outweighs the risk of less comprehensive data than normally required (i.e., For products intended for use in public health emergencies such as Covid-19)<br>• It is likely that the applicant will eventually be able to provide comprehensive data<br><br>These approvals are valid for a renewable ***<u>one-year</u>*** period. Once the pending studies are provided, it can become a "normal" marketing authorization |
| | **Features/ Incentives** | • In a public health emergency, it can be combined with a rolling review of data during the development of a promising medicine, to further expedite the evaluation.<br>• Click here for a list of conditional approvals. |
| | **Request** | The sponsor should indicate a request for conditional approval in their notification of intention to submit a marketing authorisation application. This should be submitted 6 to 7 months before submitting the application. |
| **Accelerated Assessment** | **Eligibility** | The medicinal product is expected to be of major public health interest, particularly from the point of view of therapeutic innovation. |
| | **Features/ Incentives** | Reduced review timeframe (150 days instead of 210 days). |
| | **Request** | Any request for accelerated assessment should be made at least two to 2 to 3 before submitting the marketing-authorisation application. |

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# EMA's Expedited Review Program

| | | |
|---|---|---|
| Compassionate Use | **Eligibility** | The unauthorized medicine is for patients with life-threatening, long-term, or severely disabling conditions who cannot be treated satisfactorily with any currently permitted treatment or who are unable to participate in relevant clinical studies.<br><br>The medicine must be:<br>• Undergoing clinical trials and while early studies will generally have been completed, its safety profile and dosage guidelines may not be fully established, or<br>• Have entered the marketing-authorization application process and while early studies will generally have been completed, its safety profile and dosage parameters may not be fully established |
| | **Features/ Incentives** | Allows the use of an unauthorized medicine if elegibility criteria are met. |
| | **Request** | • National competent authorities can seek advice from EMA for an opinion on how to administer, distribute and use certain medicines for compassionate use. The Committee for Medicinal Products for Human Use (CHMP) also identifies which patients would benefit, and Member States should take consider these recommendations when making decisions.<br>• Manufacturers and marketing-authorisation applicants should not contact EMA to request an opinion. |
| Exceptional Circumstances | **Eligibility** | • The sponsor is unable to offer comprehensive data on the efficacy and safety of a medical product under typical conditions of usage, because the condition to be treated is rare or because collection of full information is not possible or is unethical.<br>• Consequently, the authorization under exceptional circumstances is granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product,communication of any incident relating to its use, and actions to be taken.<br>• Reviewed annually to reassess the risk-benefit balance, in an annual re-assessment procedure |
| | **Features/ Incentives** | Leniency on providing comprehensive data on the efficacy and safety of a medicinal product. |
| | **Request** | The sponsor should submit a statement on the appropriateness of granting exceptional circumstance authorization in the notification to the EMEA submitted in advance of the Marketing Authorisation Application. |

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# TGA's Expedited Review Program

The Therapeutic Goods Administration (TGA) has developed two expedited review programs to expedite the development and review of drugs:

## Provisional Approval

*implemented on March 20, 2018*

Eligibility
- New prescription medicine or new indications medicine
- For the treatment of a serious condition
  Favorable compared to currently available therapies
  A significant therapeutic breakthrough
- Evidence of a plan to submit comprehensive clinical data

Features/ Incentives
- Expedited through accepting early data where the benefit of availability outweighs the risk
- Target timeframe: 220 working days

Request
- Sponsors are strongly encouraged to organize a pre-submission meeting with the TGA to discuss planned applications for provisional determination.
- For more information on the application process, see the guidance document "Provisional approval determination process and provisional registration process."

## Priority Review

*implemented on July 1, 2017*

Eligibility
- New prescription medicine or new indications medicine
  - For the treatment of a serious condition
  - Comparison against registered therapeutic goods
  - Major therapeutic advance

Features/ Incentives
- Expedited target timeframe of 150 working days.

Request
- Sponsors must first apply for a priority determination before lodging a registration application.
- For more information on the application process, see the guidance document "Priority determination process and registration process."

## Similarities Between Programs

| | Canada | USA | Europe | Australia |
|---|---|---|---|---|
| **Program** | NOC/c | Accelerated Approval | Conditional Approval | Provisional Approval |
| | | Fast Track | PRIME | |
| | Special Access Program | Treatment IND | Compassionate Use | |
| | Priority Review | Priority Review | | Priority Review |

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# Orphan Drug Programs

Another program with regulatory incentive is the orphan drug desingation.

## USA

Eligibility
- Drug treats conditions with less than 200,000 cases per year in the US. Approved drugs can be designated orphan drugs

Features/incentives
- FDA works closely with sponsor
- Marketing applications fees are waived
- Sponsor receives 7-years marketing exclusivity
- Rare Pediatric Disease Priority Review Vouchers allows expedited review

## Europe

Eligibility
- The medicine must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating
- The prevalence of the condition in the EU must not be more than 5 in 10,000
- Has an unmet medical need

Features/incentives
- Protocol assistance
- Fee reduction. Fees are waived id the company is small or medium sized.
- Sponsor receives 10-years marketing exclusivity and an additional 2 years if the medicinal product is for a pediatric population.

## Australia

Eligibility
- A medicine, including vaccines or in vivo diagnostic agents, may be eligible for orphan drug designation if all orphan criteria in the linked table are satisfied (regulation 16J of the Therapeutic Goods Regulations 1990).
  - A pathway to obtain orphan status for innovative dosage form drugs is available in addition to the regular orphan designation. Eligibility for new dosage form medications is intended to encourage sponsors to register medicines on the Australian Register of Therapeutic Goods (ARTG) that introduce a new dosage form that would be financially unviable without a fee waiver from the TGA.

Features/incentives
- Sponsor receives 5-years marketing exclusivity.
- Fee reduction.

For more on global regulatory frameworks of orphan drugs and to discover how Dalton can help with rare disease innovations view our orphan drug technical report.

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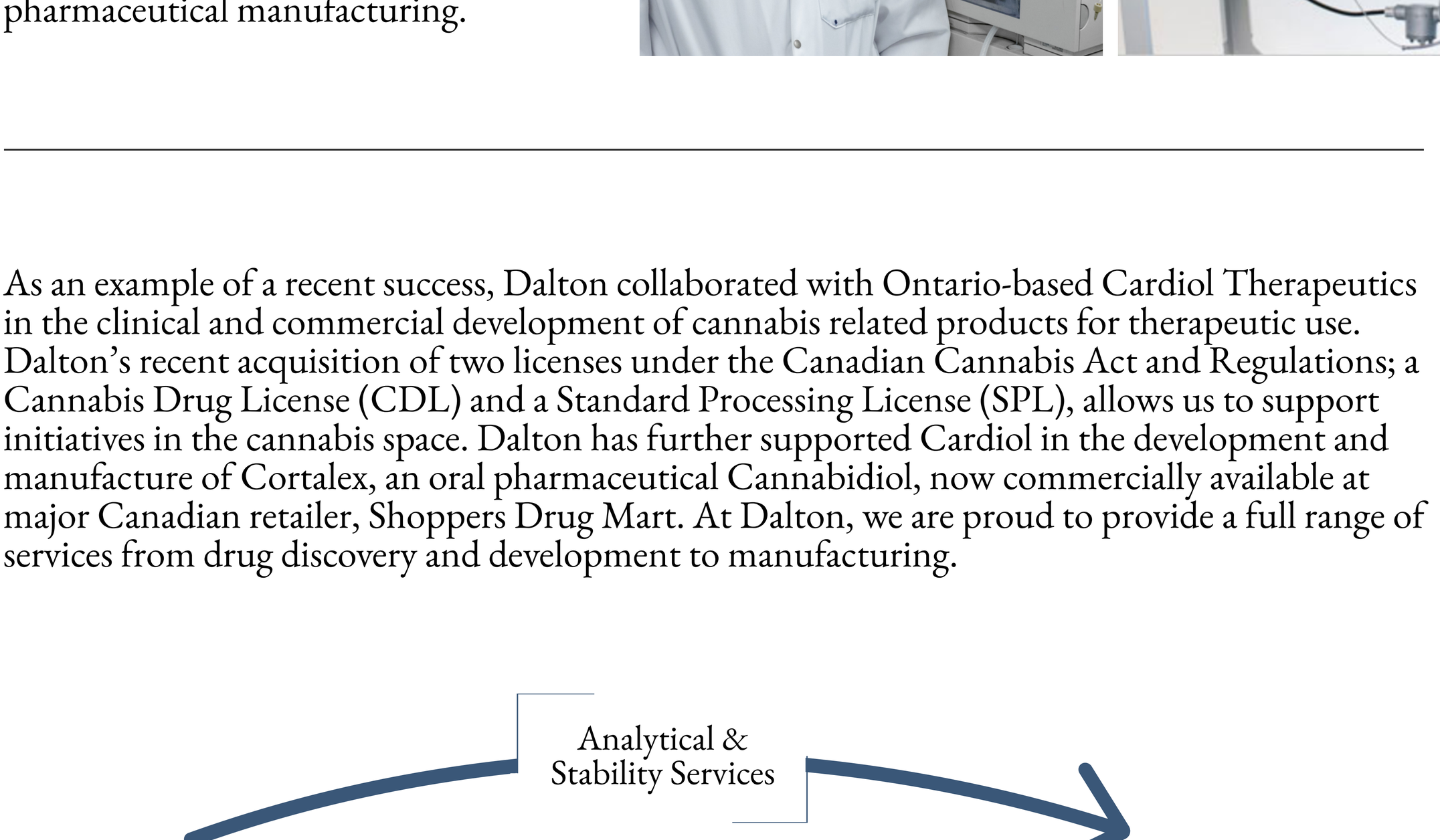
# Dalton's Services

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. Health Canada is known for being among the world's most stringent regulators, and pharmaceuticals manufactured in Canada are well regarded in the global market. 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.


As an example of a recent success, Dalton collaborated with Ontario-based Cardiol Therapeutics in the clinical and commercial development of cannabis related products for therapeutic use. Dalton's recent acquisition of two licenses under the Canadian Cannabis Act and Regulations; a Cannabis Drug License (CDL) and a Standard Processing License (SPL), allows us to support initiatives in the cannabis space. Dalton has further supported Cardiol in the development and manufacture of Cortalex, an oral pharmaceutical Cannabidiol, now commercially available at major Canadian retailer, Shoppers Drug Mart. At Dalton, we are proud to provide a full range of services from drug discovery and development to manufacturing.

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