Dalton Pharma Services:

Orphan Drugs

Who we are

“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.”

1986

Small lab at York University

Focused on meeting the chemical needs of local researchers, including hard-to-find or difficult chemical synthesis products

1990 – 2000

cGMP manufacturing capabilities

Expanded both its operational lab footprint as well as its customer base; larger scale chemical synthesis

2000

42,000 sq ft facility in Toronto

Invested in more comprehensive lab services, formulation development services, finished dose manufacturing and large-scale chemistry and research capabilities

2009 – 2018

Health Canada Approvals

6 Health Canada approvals in total

2015 Health Canada API approval

2016, 2019 API and Drug Product Health Canada approval

2019

FDA Approval

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What are Orphan Drugs?

- Drugs that are intended to treat either a rare disease or conditions that are not developed by the pharmaceutical industry for economic reasons

- Monetary incentives and regulatory relaxations have been introduced in recent years

Orphan Drug Statistics

Orphan Diseases

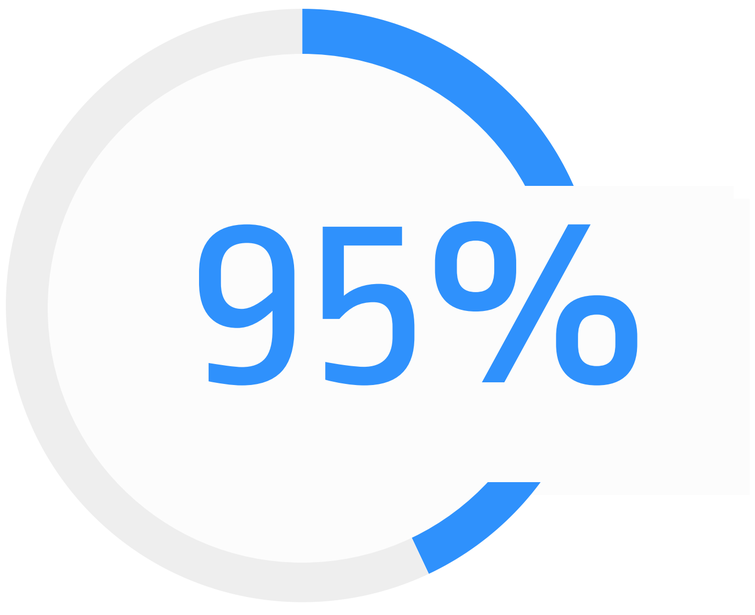
There are approximately 7,000 orphan diseases affecting an estimated 25 to 30 million people in the United States (Gupta & Ryu, 2020)

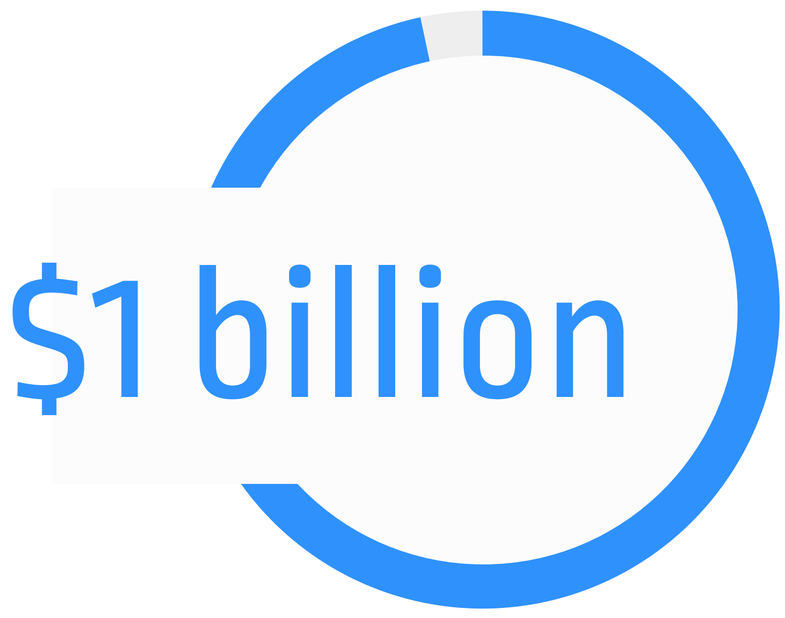
- AIDS
- Thalassaemia
- Paediatric malaria
- Tuberculosis
- Blinding trachoma
- Paediatric Crohn’s disease
- Juvenile idiopathic arthritis
- Pemphigus vulgaris
- Huntington's disease

(Kontoghiorghe et al., 2014)

Orphan Drug Demand

95% of 7,000 rare diseases still lack treatments (Yehia, 2020)





Orphan Drug Sales

The average annual sales of orphan drugs exceeded $1 billion USD between 2013 and 2019 (Yehia, 2020)

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Problem

- Malaria is a life-threatening parasitic disease caused by Plasmodium (P.) parasites that are transmitted by Anophles mosquito bites to humans
- It is a prominent threat to service members, one of the reasons being because of drug-resistant malarial parasites
- The annual number of cases of Malaria reported in the United States has increased in recent years

Dalton's Solution

- As a supplier of low volume complex pharmaceuticals, Dalton provided cGMP sterile powder filling, aseptic liquid filling, quality control release testing, and ICH stability services for an anti-malarial drug development program with United States Army Medical Materiel Development Activity (USAMMDA)
- The FDA approved the orphan drug Artesunate for the orphan disease malaria in 2020

- Dalton Pharma Services is a Health Canada approved and FDA registered cGMP contract service provider of integrated chemistry, drug development, and manufacturing services to the pharmaceutical and biotechnology industries
- We offer cGMP API manufacturing and sterile or solid finished dose manufacturing all at a single location
- For our full range of in-house services including cGMP sterile fill/finish services please visit https://www.dalton.com/

Dalton has years of experience with orphan drug development

- AB569 for the orphan disease chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) with Arch Biopartners
- Rare and ultra-rare diseases with Cerium Pharmaceuticals

Key drivers to orphan drug development are seen on the right (Bouwman et al., 2020).

R&D related drivers	Commercial-related drivers
Tax credits	Lower hurdles to approval
R&D grants	Longer exclusivity
Waived fees	Lower market costs
Shorter development times	Faster uptake
Greater regulatory success	Premium pricing
	Favorable reimbursement

Clinical trials on rare diseases are easily identifiable and searchable through the ICTRP and Orphanet database

- Includes rare disease of concern, the category of clinical trial, and the medicinal product in development

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Comparison of Legal Framework

ORPHAN DRUG ACT IN U.S.A (FDA)
1983

FDA Regulations Title 21 eCFR part 316
Subpart A — General provisions
Subpart B — Written recommendations for investigations of orphan drugs
Subpart C — Designation of an orphan drug
Subpart D — Orphan-drug exclusive approval
Subpart E — Open protocols for investigations
Subpart F — Availability of information

ORPHAN DRUG ACT IN SINGAPORE (HSA)
1991

Medicines Act Chapter 176, Section 9 &
The Rare Disease and Orphan Drug Act

ORPHAN DRUG REGULATION IN JAPAN (PMFA)
1993

Pharmaceutical Regulations and Association in Japan Chaptetr 2, 4.6

ORPHAN DRUG POLICY IN AUSTRAILIA (TGA)
1997

Therapeutic Good Act Part 3B—Designated orphan drugs
16H — Application to designate medicine as orphan drug
16J — Designation of medicine as orphan drug
16K —Period during which designation is in force
16L — Extension of designation
16M —Revocation of designation

ORPHAN DRUG REGULATION IN EUROPE (EMA)
2000

Regulation (EC) No 141/2000 (the Orphan Regulation)
Regulation (EC) No 847/2000
Regulation (EC) No 726/2004
Regulation (EC) No 507/2006
Regulation (EC) No 1901/2006
Regulation (EC) No 2049/2005

There is currently no regulatory framework for orphan drugs in Canada

Health Canada addresses therapeutic products, which are considered to be orphan drugs from the patient access perspective, through the **Special Access Program**

The regulations for the special access program for drugs can be found under sections C.08.010 and C.08.011 of the Food and Drugs Regulations

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Comparison of Regulatory Application Requirements

FDA

- Discussion of rare disease
- Prevalence documentation
- ROI discussion
- Scientific rationale
- Current regulatory status of the drug

PMFA

- Description of the condition
- Prevalence documentation
- Comparison against registered therapeutic goods for diagnosis, prevention, or treatment
- Stage of development

TGA

- Data on the number of patients and medical needs
- Theoretical rationale
- Development plan

EMA

- Discussion of rare disease
- Prevalence documentation
- ROI discussion
- Other methods of diagnosis, prevention, or treatment
- Stage of development

Comparison of Development Incentives

FDA

- Market exclusivity: 7 years
- Communication with FDA
- Tax credit of 50% of the costs of conducting clinical trials
- Medicaid coverage & reimbursement policies favourable (varies state to state)
- Fast-track development and approval
- Waived drug application fees
- Federal grants for clinical testing
- Smaller clinical trials

EMA

- Market exclusivity: 10 years (+2 if pediatric)
- Protocol assistance
- Fee reductions (100% for small and medium-sized enterprises)
- EU- funded research

PMDA

- Market exclusivity: 10 years
- Financial subsides
- Tax credits
- Corporate tax deductions
- User fee waivers
- Priority review
- Fast track approval
- Free protocol assistance

TGA

- Market exclusivity: 5 years
- Fee reduction for marketing authorization approval
- Pre-licensing access
- Regulatory assistance

(Bouwman et al., 2020), (Kontoghiorghe et al., 2014)

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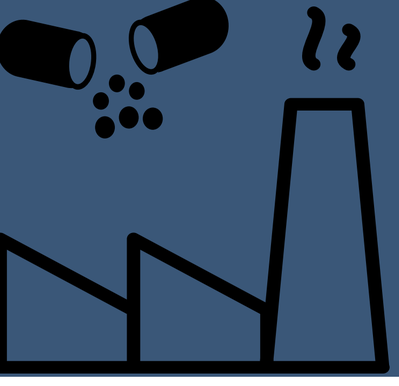

ORPHAN DRUGS

Orphan Drugs FAQs

01

What is an orphan designation and a priority review designation?

An orphan designation qualifies the sponsor of the drug for various development incentives of the orphan drug act.

A priority review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

02

Is there a general list (besides OOPD database) of specific conditions considered to have prevalence of <200,000?

The NIH Genetic and Rare Diseases Information Center (GARD) provides a rare disease list. NOTE: OOPD will not accept the fact that a disease is listed as a rare disease on a website as evidence of prevalence of <200,000.

03

What information is required for an orphan drug designation request? How should the request be formatted?

The content and format of a request for an orphan drug designation are described in 21 CFR 316.20(b).

04

What guidance documents can I refer to?

- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations
- Draft Guidance for Rare Pediatric Disease Priority Review Vouchers
- Guidance for Industry Clarification of Orphan Designation of Drugs and Biologics for Pediatrics
- Rare Diseases: Common Issues in Drug Development Guidance for Industry
- Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations
- Guidance for Industry, Researchers, Patient Groups and FDA Staff on Meetings with OOPD
- Guidance for Industry and FDA Staff - Humanitarian Use Device (HUD) Designations

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#DaltonPharmaServices

bd@dalton.com

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