Market Application & Incentives for Drug Commercialization in North America & Europe

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 marketing applications and respective incentives put in place. 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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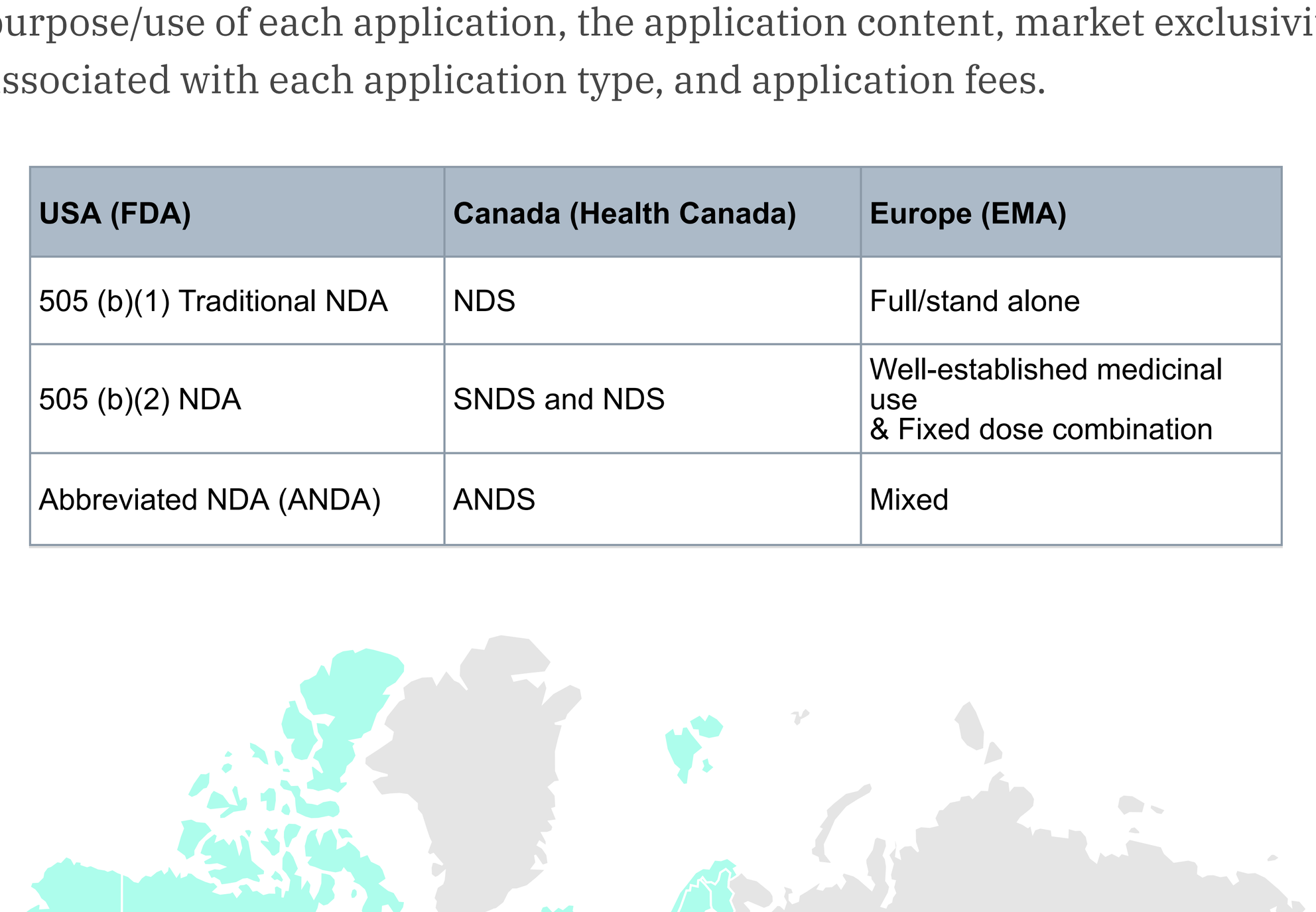
Marketing *applications*

If the results of all the preclinical and clinical studies show that a drug's potential therapeutic benefit outweighs its risks (side effects, toxicity, etc.), and the chemistry and manufacturing dossier is complete, then the sponsor may decide to file a marketing application - referred to as legal basis in Europe - to be granted authorization to sell the drug.

Below is a summary of the similarities that can be made between the marketing application types among three main regulatory authorities: Health Canada, the Food and Drugs Administration (FDA), and the European Medicines Agency (EMA). This whitepaper will explore the different application types in-depth, including the corresponding regulations, the purpose/use of each application, the application content, market exclusivity associated with each application type, and application fees.

USA (FDA)	Canada (Health Canada)	Europe (EMA)
505 (b)(1) Traditional NDA	NDS	Full/stand alone
505 (b)(2) NDA	SNDS and NDS	Well-established medicinal use & Fixed dose combination
Abbreviated NDA (ANDA)	ANDS	Mixed



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FDA *Marketing applications*

505 (b)(1) *Traditional NDA*

505 (b)(1) Traditional New Drug Application (NDA)

FD&C Act

Section 505 (b)(1)

Purpose: used for novel drugs that have not previously been studied or approved.

Content: (full eCTD)

- Chemistry, Manufacturing and Controls (CMC) information
- Nonclinical pharmacology and toxicology study reports
- Human pharmacokinetics and bioavailability study reports
- Clinical data (from phase 3 trials)
- Statistical evaluation
- Case report forms and tabulations
- Labeling
- Patent information
- Establishment description (biologics)
- All information outlined in 21 CFR 314.50

Incentive: 5-year market exclusivity

505 (b)(2) *NDA*

505 (b)(2) New Drug Application (NDA)

FD&C Act

Section 505 (b)(2)

Purpose:

- Used for combination products that consist of at least one API or device that has been previously approved. In this case, since existing data is available, it is not necessary to reconduct research studies. However, if the Sponsor does not have the right of reference for these studies, testing is required to meet these safety and efficacy requirements.

Content: full reports of safety and effectiveness. These can be literature reviews if available (i.e., clinical review, CMC review, labeling review, administrative review, etc. posted by the FDA).

Incentive: 3-year market exclusivity

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Original/Biosimilar *BLA*

Originial Biologics License Applications (BLA)

FD&C Act

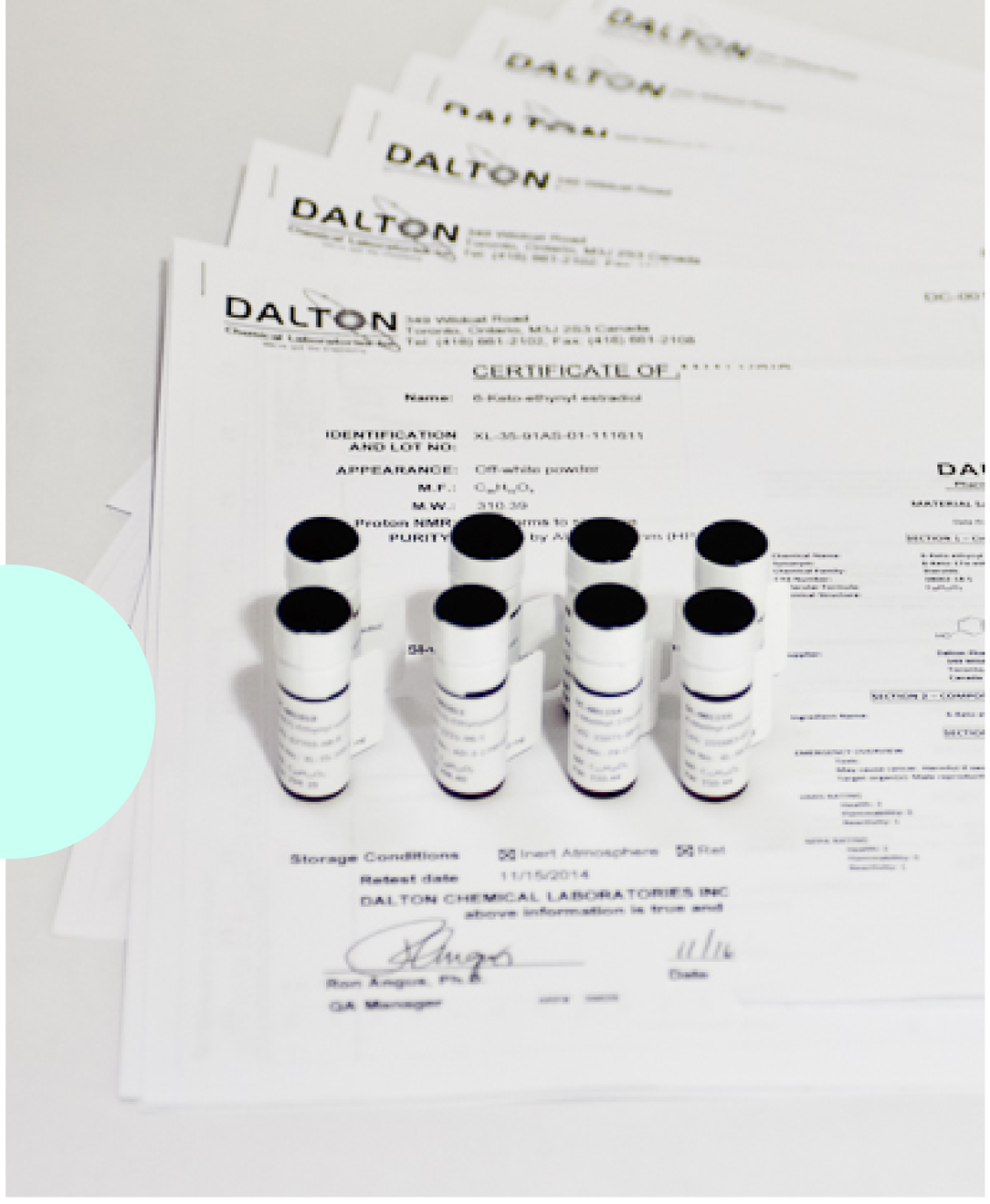
Section 351 (a)

Purpose: used for novel biologic drugs that have not previously been studied or approved.

Content:

- Non-clinical and clinical and clinical studies conducted to demonstrate the drug's safe and effective use
- All information outlined in 21 CFR 601.2

Incentive: 12-year market exclusivity



Biosimilar

FD&C Act

Section 351 (k)

Purpose: used for a biological product that is demonstrated to be biosimilar to or interchangeable with an FDA-licensed biological product. A biosimilar drug is "highly similar" to the original BLA, except for "minor differences in clinically inactive components." This means it must have the ***same*** mechanism of action (if known), route of administration, dosage form, strength, and labeling. The biosimilar must also be interchangeable, meaning that there must be no risk in switching between the reference product and the biosimilar.

Content: requires (unless waived) analytical, animal, and one or more clinical studies that indicate no clinically significant differences between the biological product and the reference product.

Incentive: 1-year market exclusivity (if no other biosimilar has been approved thus far).

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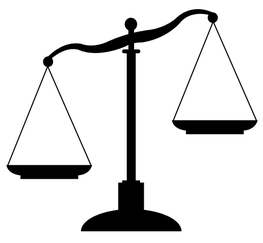
Abbreviated *(ANDA)*



Abbreviated New Drug Application (ANDA)

FD&C Act

Section 505 (j)

Purpose: used for the approval of generic drugs. Note: you cannot apply for an ANDA until the patent and marketing exclusivity of the innovator product has expired.

Incentive: 180-day market exclusivity for the ***first*** generic on the market.

Content:

- Chemistry and bioequivalence data to show the proposed product is identical in **active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use** to the previously-approved reference listed drug (RLD). See Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for RLDs.
- Nonclinical and clinical data is generally not required.

Market Exclusivity *& Fees*

Additional data protection:

- Pediatric approval leads to an additional 6 months of market exclusivity.
- As mentioned above, applications for new indications (505 (b)(2)) provide a 3-year market exclusivity period. ***Regulatory strategy*:** Delay studies for new/other indications until the end of the 5 year period to receive an additional 3 years of market exclusivity.
- To search drugs that have been granted 505 (b)(2) approval, click here (search drug > approval dates and history > letters/ reviews).

Fees:

NDA

Requiring clinical data	$2,875,842
Not requiring clinical data	$1,437,921
Program	$336,432
Abbreviated new drug application	$196,868

BLA

Requiring clinical data	$1,746,745
Not requiring clinical data	$873,373
Program	$304,162

Fee **reductions and waivers** are available.

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EMA
Marketing applications

STAND ALONE/FULL

Directive 2001/82/EC

Article 8 (3)

Content:

- Pharmaceutical (physico-chemical, biological or microbiological) tests
- Nonclinical (toxicological and pharmacological) tests
- Clinical trials

MIXED

Directive 2001/82/EC

Article 8 (3)

Content:

- Nonclinical and/or clinical studies carried out by the applicant
- Nonclinical and/or clinical literature

GENERIC PRODUCTS

Directive 2001/83/EC

Article 10 (1)

Definition: a generic product must have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product.

Content:

- Bioavailability studies to demonstrate bioequivalence with the reference medicinal product.
- Nonclinical and clinical data is generally not required.

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WELL ESTABLISHED MEDICINAL USE

Directive 2001/82/EC

Article 10 (a)

Definition: a well established medicinal product is a product that has ten years of recognized efficacy and an acceptable level of safety.

Content: reference to published literature on preclinical and clinical studies.

HYBRID APPLICATION

Directive 2001/82/EC

Article 10 (3)

Purpose: for products where the strict definition of a ‘generic product' is not met.

Content:

- Additional clinical or preclinical studies
  - where bioavailability studies cannot be used to demonstrate bioequivalence (for example where the new product is supra-bioavailable or for locally applied/locally acting medicinal products);
  - where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form **or** route of administration of the generic product compared to the reference product
- Rely in parts on dossier of the reference medicinal product and results of appropriate own non-clinical and/or clinical studies.

FIXED DOSE COMBINATION

Directive 2001/82/EC

Article 10 (b)

Purpose: used when you combine two well established drugs.

Content: clinical studies for the combination.

BIOSIMILARS

Directive 2001/82/EC

Article 10 (4)

Content: comparative non-clinical, clinical, and quality studies to demonstrate similarity.

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The type of legal basis (application) depends on the amount of data available:

- Is there well-established medicinal use for at least 10 years in the proposed therapeutic indication for the active substance? → Article 10a
- Is there a reference medicinal product? → Articles 10(1), 10(3), and 10(4)
- Is the drug a development of a medicine (i.e., new indication)? → Article 8(3)

Market Exclusivity *& Fees*

Market exclusivity:

- Reference medicinal products authorised through the centralised procedure for which the initial submission was made ***before*** November 20, 2005, benefit from the previous market exclusivity period which is 10 years.
- Innovative medicinal products authorised through the centralised procedure for which the initial submission was made ***after*** November 20, 2005, have an 8 year market exclusivity period.
- Orphan drugs have a 10 year market exclusivity period
- New indications of well-established substances receive a 1 year market exclusivity period.
- A change of classification results in a 1 year market exclusivity period.

Fees:

Marketing-authorisation application	From €296,500
For an application for a marketing authorisation pursuant to Article 10(4)	€188,700
For applications for a marketing authorisation pursuant to Article 10(1)	€113,300

- These fees are for a single strength associated with one pharmaceutical form and one presentation. Additional fees apply for:
  - each additional strength or pharmaceutical form including one presentation, submitted at the same time as the initial application for authorisation.
  - each additional presentation of the same strength and pharmaceutical form, submitted at the same time as the initial application for authorisation.
- Note: fees are adjusted every year for inflation.
- Fee **reductions and incentives** are available for micro, small and medium-sized enterprises (SMEs), designated orphan medicines, multiple applications on usage patent grounds and other classes of application.

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Health Canada
Marketing applications

New Drug Submission *(NDS)*

Purpose: used for a drug product that meets the definition of a “new drug” as found in the Food and Drug Regulations. The definition of a new drug includes new drug substances as well as “new” indications, dosage forms, or combinations of drugs, which have not yet been sold in Canada.

Content:

- Preclinical and clinical studies
- Details regarding the production of the drug
- Packaging and labelling details
- Information regarding therapeutic claims and side effects
- Stability and validation procedures

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Abbreviated New Drug Submission *(ANDS)*

Purpose: used to obtain marketing approval of a generic product.

Content: bioequivalence studies to demonstrate safety and efficacy against the innovator drug which is known as the ‘Canadian Reference Product.’ The ANDS submission is filed with the Canadian reference product with NOC/ status.

Supplemental Drug Submission *(SNDS, SANDS)*

Purpose:

- Filed when the applicant wants to make important changes to an already approved NDS or ANDS. Supplements (also known as level I changes) are changes to a new drug that are significantly different and therefore, have the potential to impact the safety, efficacy, quality, and/or effective use of the drug.
  - Less critical changes are documented as a Notifiable Change (NC).
- SNDS and SANDS are subject to a target 90-day review period and are approved via a “letter of no objection” resulting in a 'new Notice of Compliance' (NOC). Note: the change may not be implemented by the sponsor until a NOC has been issued.

Content: changes being made shall be filed, along with the recommended supporting data.

Pre-Submission *Content*

MEETING REQUEST

- Pre-submission meetings are required for NDS, SNDS, ANDS
- Purpose:
  - To discuss the presentation of data
  - Serves as a heads up for the Health Canada review staff
  - Uncovers any major unresolved problems
  - Identifies studies the sponsor is relying on as adequate
- Submit pre-submission meeting request in writing or by fax no less than 1 month prior to the proposed meeting date
- Include agenda (purpose, product description, 3 proposed dates)

PACKAGE

- Pre-submission packages are required for pre-NDS/SNDS meetings
- In the package include a:
  - Cover letter and agenda
  - List of specific issues
  - Brief summary of the drug product (proposed strengths and dosages)
  - Overview of the market history (foreign regulatory status)
  - Summary of the development and clinical development of the product
  - Indications
  - Draft product monograph

Market Exclusivity *& Fees*

Market Exclusivity:

- The data protection period is 8 years from the date of issuance of the first NOC for an innovative drug.
  - In some cases, a drug may contain one or more medicinal ingredient(s) that is/are the same as the medicinal ingredient(s) found in an innovative drug for which a data protection period is still in effect. Consistent with the intent of section C.08.004.1 to protect new chemical entities, these drugs will benefit from the same period of data protection as the innovative drug.
- An additional 6 months of market exclusivity is granted for pediatric applications.
- There is no market exclusivity for generic drug.

Fees:

New active substance	$437,009
Submissions based on clinical or non-clinical data and chemistry and manufacturing data for a drug that does not include a new active substance	$224,242
Comparative studies (generics)	$55,737

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Orphan Drugs
Incentives

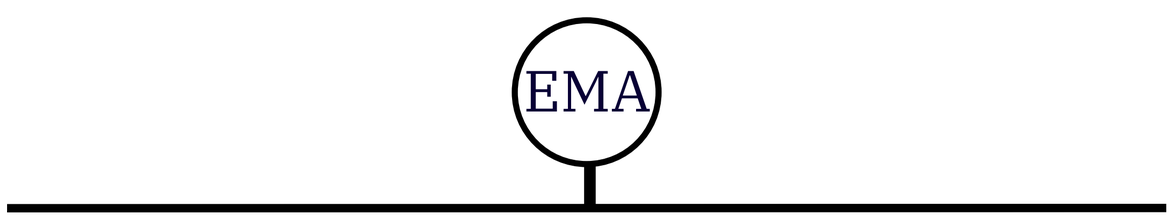
Another type of marketing application is an orphan drug application. These applications are for drugs intended to treat a rare disease. This application type does not exist in Canada.

Purpose: for drugs that treat conditions with less than 200,000 cases per year in the US.

Content: The content and format of a request for orphan drug designation is described in 21 CFR 316.20.

Market Exclusivity & Other Incentives:

- 7-year marketing exclusivity
- FDA guidance
- Application fees are waived
- Expedited review for a rare pediatric disease via priority review voucher



Purpose: for medicines intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating, has an unmet medical need, or targets a condition that has a prevalence of less than 5 in 10,000 in Europe.

Content: for guidelines on the format and content of orphan drug applications click here.

Market Exclusivity & Other Incentives:

- 10-years marketing exclusivity
  - Additional 2-years if the medicinal product is for a pediatric population
- Protocol assistance
- Fee reduction. Fees are waived id the company is small or medium sized

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.

Dalton's
Services

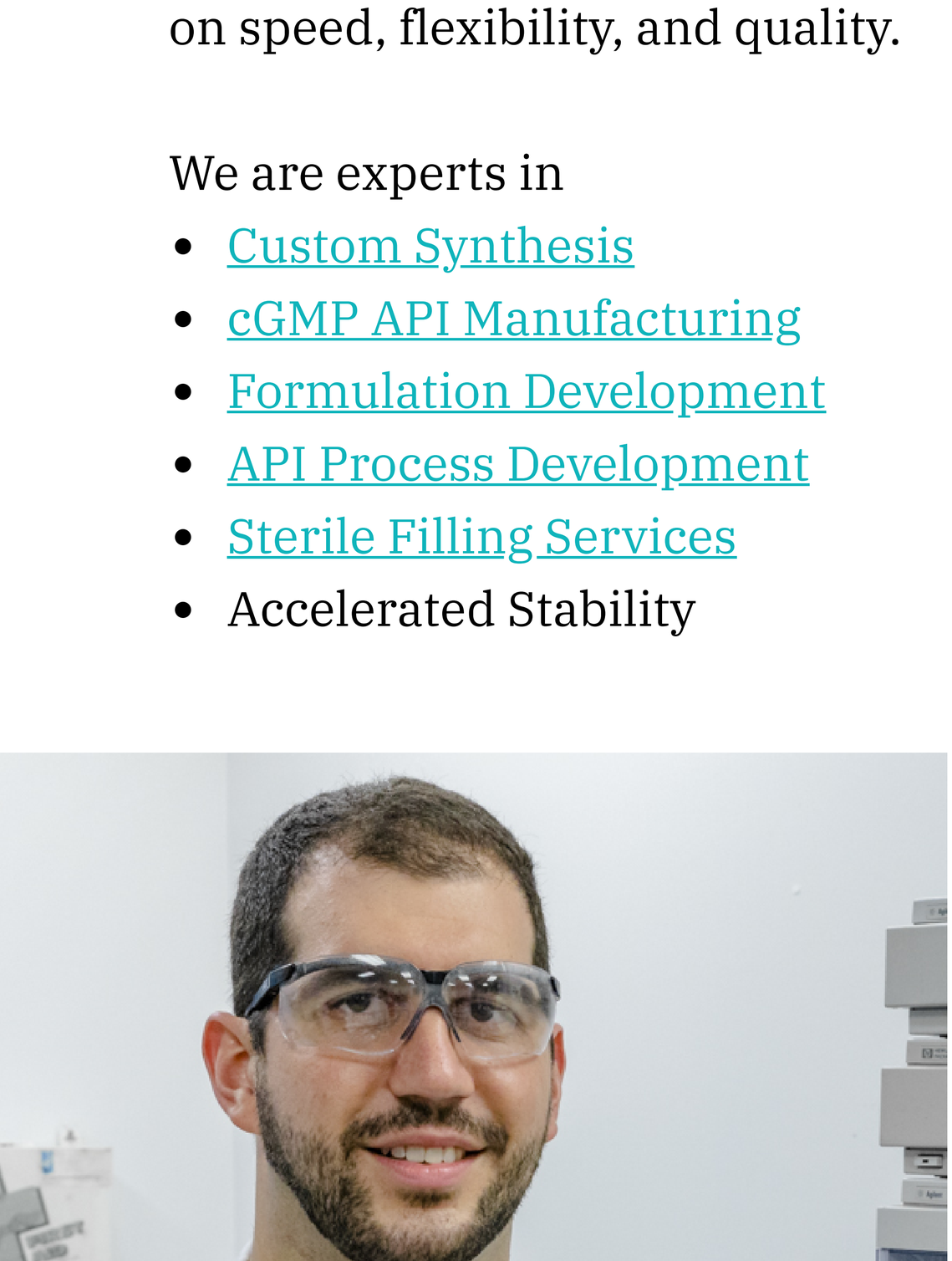
Dalton Pharma Services is a leading cGMP contract service provider of integrated drug discovery, development and manufacturing services to the pharmaceutical and biotechnology industries.

We are FDA inspected and Health Canada approved.

We deliver fully integrated solutions with emphasis on speed, flexibility, and quality.

We are experts in

- Custom Synthesis
- cGMP API Manufacturing
- Formulation Development
- API Process Development
- Sterile Filling Services
- Accelerated Stability



We deliver:

- High quality
- Shorter timelines
- Minimized cost
- Regulatory compliance

For more information on services we provide, visit our website.

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