

Preparing an IND Application: CMC

Principles & Content Outline

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Dalton Pharma Services

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Company Profile

Leading cGMP contract service provider that accelerates projects to market while saving our clients time and money

- Over 100 employees
- 30 years of experience
- 2 successful FDA and Health Canada inspections
- EU approved through MRA
- Emphasis on quality, speed and flexibility
- Research molecules catalogue of over 3000 fine chemicals
- Full range of services in-house all at one location (Toronto)

Mission Statement

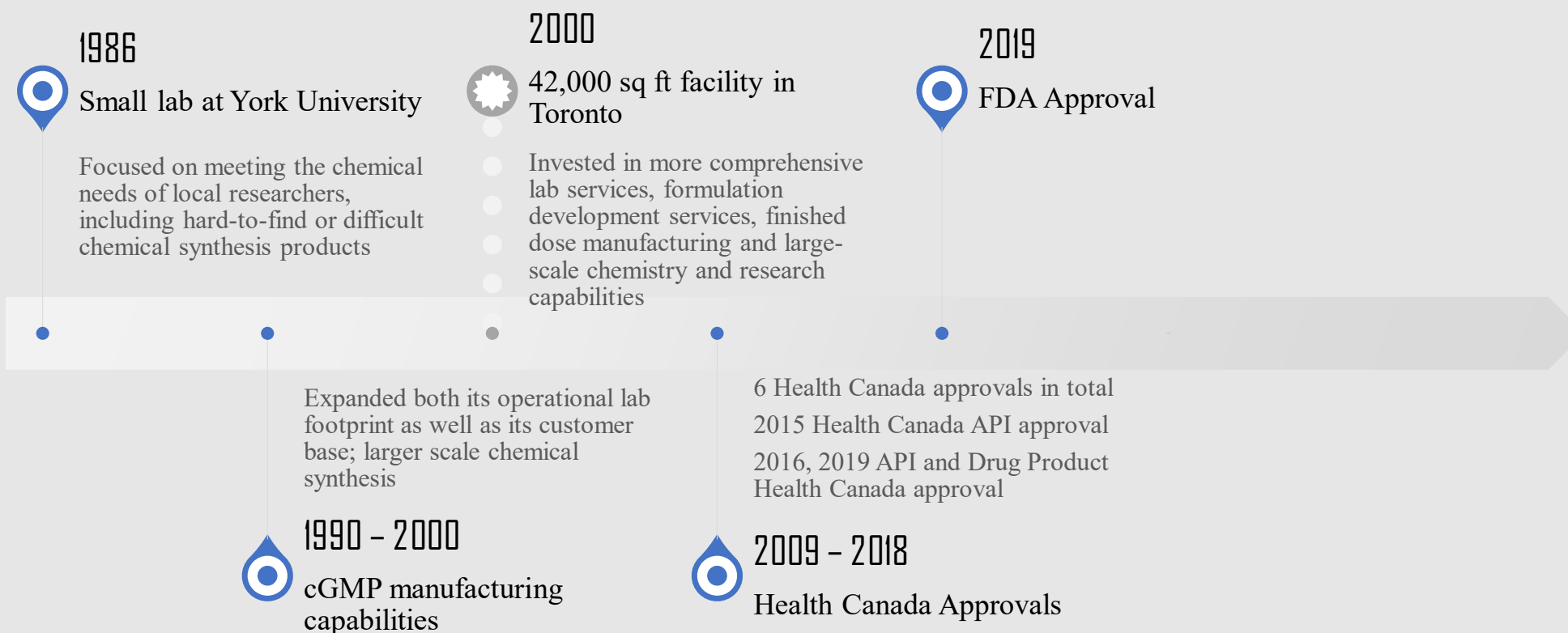
“To make the impossible possible. Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality.”

Values

- Honesty, integrity and accountability
- Respect and a professional approach in all of our interactions
- Perseverance and initiative on the part of all contributors
- A customer-oriented focus and a commitment to quality in products and services
- A spirit of innovation, a desire to achieve, a CAN DO attitude

Business Strategy

“The objective is to focus on offering pharmaceutical services that meet our customer's evolving needs and add value by making their supply choices simpler”



Company Facilities

- GMP Manufacturing and Aseptic Filling Area
 - GMP Suites (3 API suites)
 - Aseptic Filling Area
 - Autoclave Room
- Water System
- cGMP Encapsulation Suite
- QA Sampling Room
- Laboratory Services
- Synthetic Laboratories (R&D Area)



Services

- Contract Research
- Custom Synthesis
- Medicinal and Flow Chemistry
- API Process Development
- Formulation Development
- cGMP API Manufacturing
- cGMP Sterile Filling
- Analytical and Microbiology Services



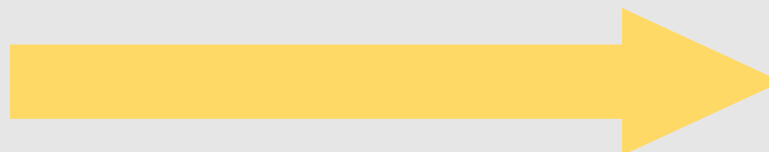
Products

- Building Blocks
- Coelenterazines
- Drugs & Metabolites
- Giltazones
- Heterocycles
- Labelled Compounds
- Metabolites & Impurities
- Natural Compounds
- Nucleic Acids
- Organometallics
- Peptides
- Cannabinoids
- Controlled drugs
- GMP APIs, Excipients & Diagnostic Reagents

Drug Development Support



- SAR Elucidation
- Small Focused Libraries
- Bulk Intermediates & Impurity Standards
- Process Optimization & Scale Up
- Lead Optimization
- Prodrug Synthesis
- API Manufacturing (GMP)
- Sterile Filling (GMP)



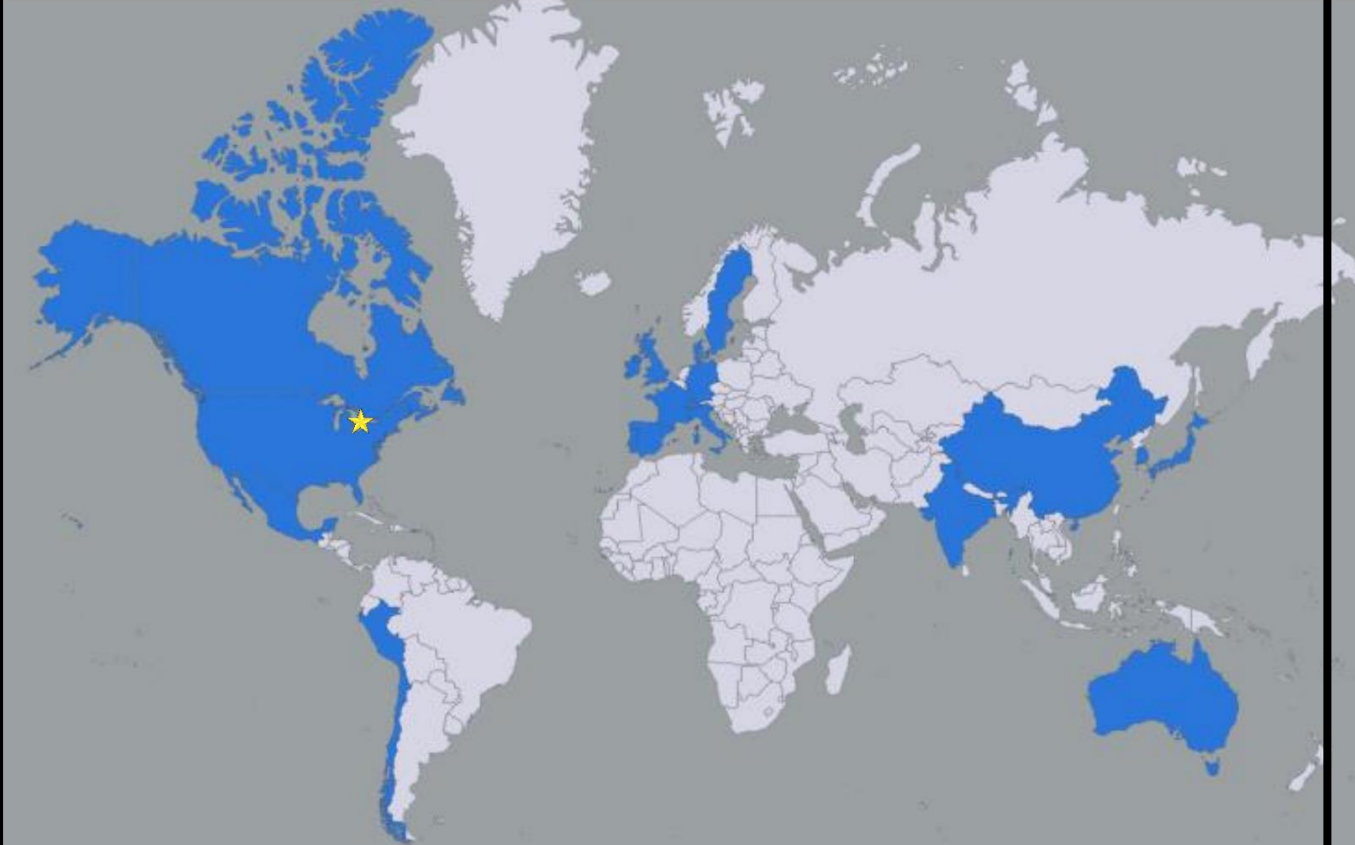
- Batch Records
- Analytical
 - Method Development
 - Method Validation
 - Stability Programs
 - Impurity Identification
- Regulatory Support
 - CMC
 - IND
 - NDA

Top Markets

- United States
 - Sales share = 40.4%
- China
 - Sales share = 11.1%
- Japan

<https://bit.ly/32wC92d>

Dalton Serves Global Markets



Disclaimer

- Views presented here are provided to illustrate the general process and issues of preparing for an IND
- Each therapeutic development program may differ in the details particular to that drug
- Be sure to consult all laws, regulations, and guidance's that apply to your situation

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Investigational New Drug Application

- An investigational new drug (IND) application grants permission to start human clinical trials and to transport or distribute the drug before marketing approval
- IND regulations aim to balance protection of the public with the need to introduce new therapies
- Title 21, [§312.1 to §312.32](#) of the eCFR contains procedures and requirements governing the use and submission of INDs to the FDA



Investigational New Drug Application

An IND application consists of 3 parts:

1. Preclinical data – Animal pharmacology and toxicology studies to assess safety for initial human testing
2. **Chemistry, manufacturing, and controls (CMC) information** – Composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product to ensure that the company can adequately produce and supply consistent batches of the drug
3. Clinical Protocols and Investigator Information – Protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators

IND Application Guidance Documents

Refer to the guidance document “[Investigational New Drug Applications \(INDs\) - Determining Whether Human Research Studies Can Be Conducted Without an IND](#)” to determine if an IND application is required for your situation

Refer to the guidance document “[Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators](#)”

Refer to the guidance document “[Investigational New Drug Applications for Positron Emission Tomography \(PET\) Drugs](#)”

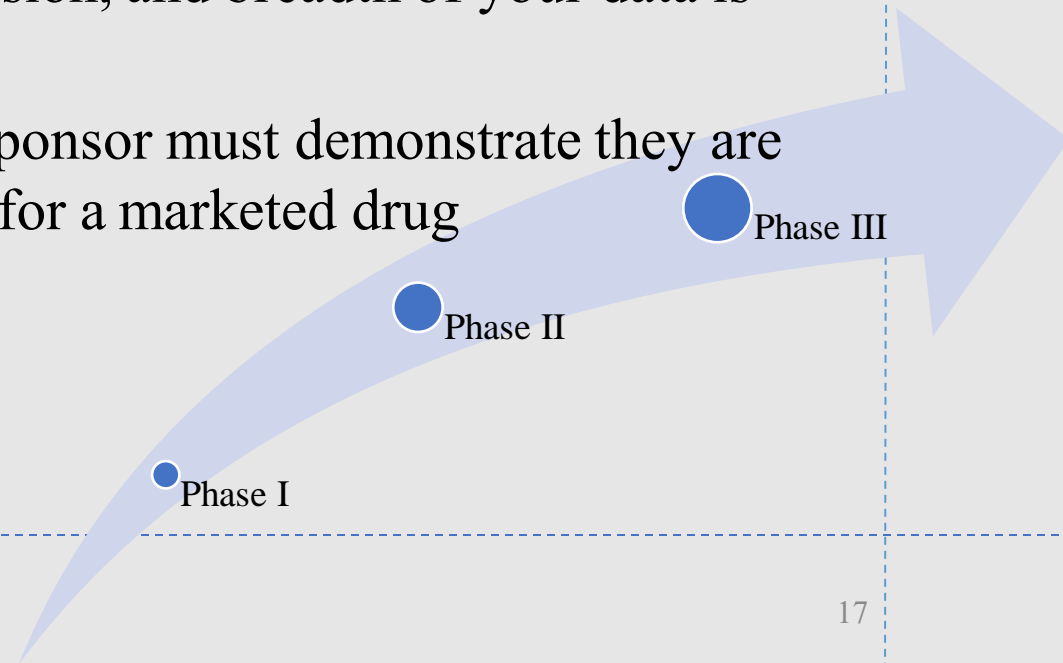
Refer to the guidance document “[Preparation of Investigational New Drug Products \(Human and Animal\)](#)”

Pre-IND Consultation Program

- The Centre for drug Evaluation and Research (CDER's) provides an opportunity for the sponsor to present relevant data and discuss concerns regarding drug development to new drug review divisions
- New drug review divisions provide guidance on the data necessary to warrant IND submissions

CMC Information for INDs

- Balancing protection with investigation leads to a graduated, “bootstrapping” approach
 - Early studies provide limited data to assess the risk vs. benefit, therapeutic potential, toxicity, safety, efficacy, and dosage of the IND
 - As the program develops, the accuracy, precision, and breadth of your data is expected to improve
 - By the time of a marketing application, the sponsor must demonstrate they are ready and able to meet the full requirements for a marketed drug



CMC Clinical Holds

- According to [21 CFR §312.23\(a\)\(7\)](#), a clinical hold based on the CMC section results if there is a safety concern or insufficient data. This includes:
 - Unknown or impure components
 - Chemical structures of known or highly likely toxicity
 - Product that cannot remain chemically stable throughout the testing program proposed
 - Product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard
 - Poorly characterized master or working cell bank

Basic CMC Strategy for IND

- Develop pre-clinical data or cite research to answer these two questions:
 1. Does the chemistry of either the drug substance or the drug product present any signals of potential human risk?
 2. Does the manufacturing of either the drug substance or the drug product present any signals of potential human risk?

Continue to address these questions throughout your development program!

Good Manufacturing Practices (GMP)

- **Good Manufacturing Practices (GMP)** is a system for ensuring that products are consistently produced and controlled according to quality standards
- **Current Good Manufacturing Practises (cGMP)** uses modern technologies and innovative approaches to ensure GMP
- Information provided in the IND that supports GMP is the CMC portion of the file
 - The [ICH](#) offers documents that are intended to provide guidance regarding GMP for the manufacturing of Active Pharmaceutical Ingredients (APIs) under an appropriate system for managing quality
 - Extractables and leachable (E&L) impurities are excluded from the scope of the general ICH impurity guidelines. Thus, a new [guideline](#) on the assessment and control of E&L is currently being proposed

Extractables and Leachables at Dalton

- Extractable and leachable studies are essential for the identification and quantitation of toxic leachable impurities that can migrate from pharmaceutical container closure systems, process equipment, and packaging, resulting in adulterated products
- Dalton Pharma Services now offers consultation services and customized testing capabilities for determining extractables and leachables on container closure systems

eCFR - Title 21 - Chapter 1 - Subchapter C

“Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act provides that a drug (including a drug contained in a medicated feed) shall be deemed to be **adulterated** if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with **current good manufacturing practice** to assure that such drug meets the requirement of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”

“The regulations set forth in this part ([§210](#)) and in parts [§211](#), [§225](#), and [§226](#) of this chapter contain the minimum **current good manufacturing practice** for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.”

cGMP Legal Principles

- cGMP non-compliance deems the drug “adulterated” under the law
- cGMP non-compliance can lead to:
 - Risk to public safety
 - Inaccurate label claims
 - Contamination
 - Misbranding
 - Inaccurate bioavailability studies
 - Warning advisories
 - Recalls
 - Lawsuits

cGMP Scope

- Applies to any ingredient (including excipients)
- Applies to finished dosage forms administered to humans and/or animals
 - OTC, Rx products
 - Biologics, veterinary drugs
 - Drugs undergoing study (IND)
- cGMP involves adequate control of manufacturers, test laboratories, packagers (including pharmacies), and warehouses

Excluded from cGMP

- A list of the conditions that must be met for a compounded drug product to be exempt from cGMP are stated in section 503A of the FD&C Act and in the guidance document [“Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act.”](#)
- Homeopathic drug products are exempt from cGMP [§211.137 Expiration dating](#)
- New drug products for investigational use are exempt from cGMP [§211.137 Expiration dating](#)
- An active ingredient in an OTC drug product is exempt from cGMP [§211.137 Expiration dating](#)
- Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt from cGMP [§211.166 Stability testing](#)

cGMP Implementation

- Prepare, review, approve and distribute SOPs
- Ensure adequate qualifications, training, and experience for personnel operating under cGMP
- Follow SOP and MBR
- Review MBR and executed BR
- Evaluate all deviations, investigate and resolve critical deviations
- Ensure sanitary facilities
- Calibrate and maintain equipment and facilities. Document the maintenance
- Review and approve validation protocols and reports
- Establish a change control process



General Quality Principles

- Quality is ***built*** into a product and not tested at the finished product stage
- Quality is assurance that the product not only meets the final specifications but that it has been made by the same procedures under the same conditions each and every time it is made; ***Consistency***
- Quality is everyone's job
 - Quality of facilities and equipment
 - Quality of personnel
 - Quality of components and drug product containers and closures
 - Quality of the production at all stages
 - Quality of the packaging & labeling
 - Quality of the testing of the product
- Sponsors must establish a quality system
- Real-time quality records
- Investigate all deviations
- Quarantine before release

Office of Pharmaceutical Quality (OPQ)

- CDER established the [Office of Pharmaceutical Quality \(OPQ\)](#) to ensure a uniform drug quality program across *all* sites of manufacture and across *all* human drug product areas
- As part of an application to make a drug, applicants are expected to show that they can consistently produce a quality product
- Quality Related Guidelines
 - ICH-Quality
 - Chemistry, Manufacturing, and Controls (CMC)
 - Microbiology
 - Current Good Manufacturing Practice (CGMP)

Content & Format of IND

1. Cover sheet
2. Table of contents
3. Introductory statement and general investigational plan
4. [Reserved]
5. Investigator's brochure
6. Protocols
- 7. Chemistry, manufacturing, and control (CMC) information**
8. Pharmacology and toxicology information
9. Previous human experience with the investigational drug
10. Additional information
11. Relevant information

For Phase I INDs, refer to “[Content and Format of INDs for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products.](#)”

Content & Format of IND

Item 7: CMC

[21 CFR
312.23 (a)
(7)]

Item 7 of the IND: CMC

- (7) (i-iv) Introduction
- (7) (a) Drug Substance
- (7) (b) Drug Product
- (7) (c) Placebo
- (7) (d) Labeling
- (7) (e) Environmental Analysis

CMC information: CFR 312.23 (7)(i-iv)

- A section describing the composition, manufacture, and control of the drug substance and the drug product
- Sufficient information to assure the proper identification, quality, purity, and strength of the investigational drug
 - This will vary based on the scope of the proposed clinical investigation
- Stability data required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical trial
- The sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation

Drug Substance: CFR 312.23 (7)(b)

- A description of the drug substance, including its physical, chemical, or biological characteristics
- The name and address of its manufacturer
- The general method of preparation of the drug substance
- The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance
- Information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies

Reference to USP-NF may satisfy certain requirements

Drug Product: CFR 312.23 (7)(c)

- A list of all components used in the manufacture of the investigational drug product
- The quantitative composition of the investigational drug product
- The name and address of the drug product manufacturer
- Brief description of manufacturing and packaging procedures
- The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product
- Information sufficient to assure the product's stability during the planned clinical studies

Reference to USP-NF may satisfy certain requirements

Placebo: CFR 312.23 (7)(c)

- A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial

NB: Placebo lots require the same care as active lots and consume similar time and resources!

Labelling: CFR 312.23 (7)(d)

- A copy of all labels and labelling to be provided to each investigator
- Investigational labels in USA must carry a caution statement as required by [§21 CFR 312.6 \(a\)](#) that reads “Caution: New Drug - Limited by Federal (or United States) law to investigational use.”

NB: Label production and use are regulated!

NB: Other nations have different rules for labels!

Environmental Analysis: CFR 312.23 (7)(e)

- A claim for categorical exclusion under [§25.30](#) or [§25.31](#) or an environmental assessment under [§25.40](#)
- Refer to the guidance document “[Categorical Exclusions for Certain Classes of Actions Involving Tobacco Products](#)”

Other CMC Considerations

- Investigator's brochure references CMC information
- Integrate the toxicology and clinical protocols with CMC via the Pharmacy Manual
 - Storage, handling, and disposal of the drug
 - If required, preparing/compounding the drug for administration (e.g., reconstitution with Diluent)
 - Specifications and stability limits for any contact materials (e.g., IV bags, catheters, syringes, pumps, etc.)—often overlooked, risking clinical timeline
- Combination products are governed by additional rules. Refer to the guidance document “[Current Good Manufacturing Practice Requirements for Combination Product](#)”

Electronic IND Submissions

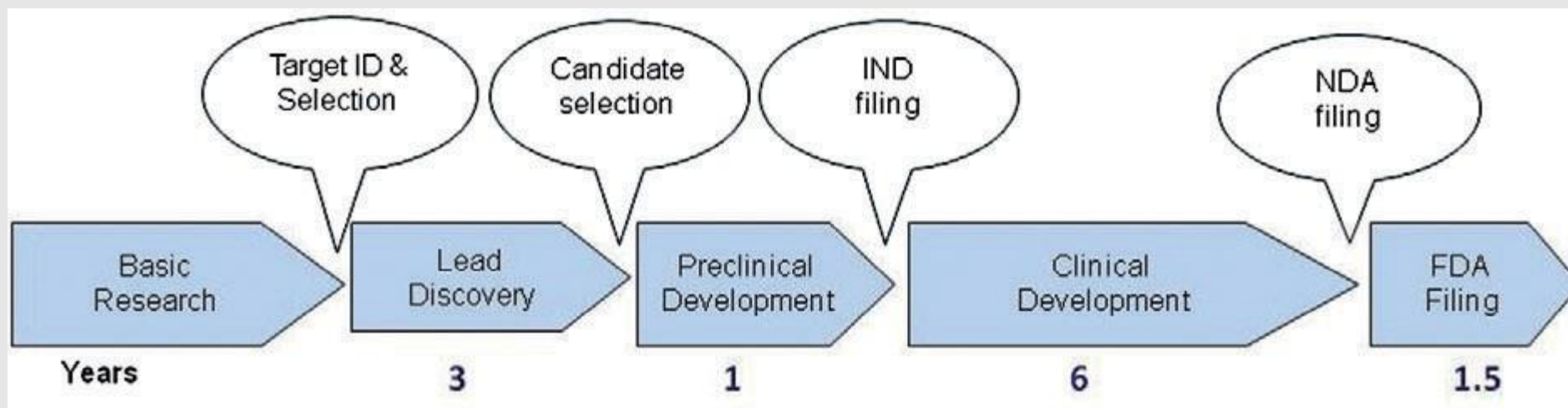
- **Electronic Common Technical Document (eCTD)** is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER)
- Refer to the guidance document “[Providing Regulatory Submissions to CBER in Electronic Format — Investigational New Drug Applications \(INDs\)](#)”

Electronic IND Submissions

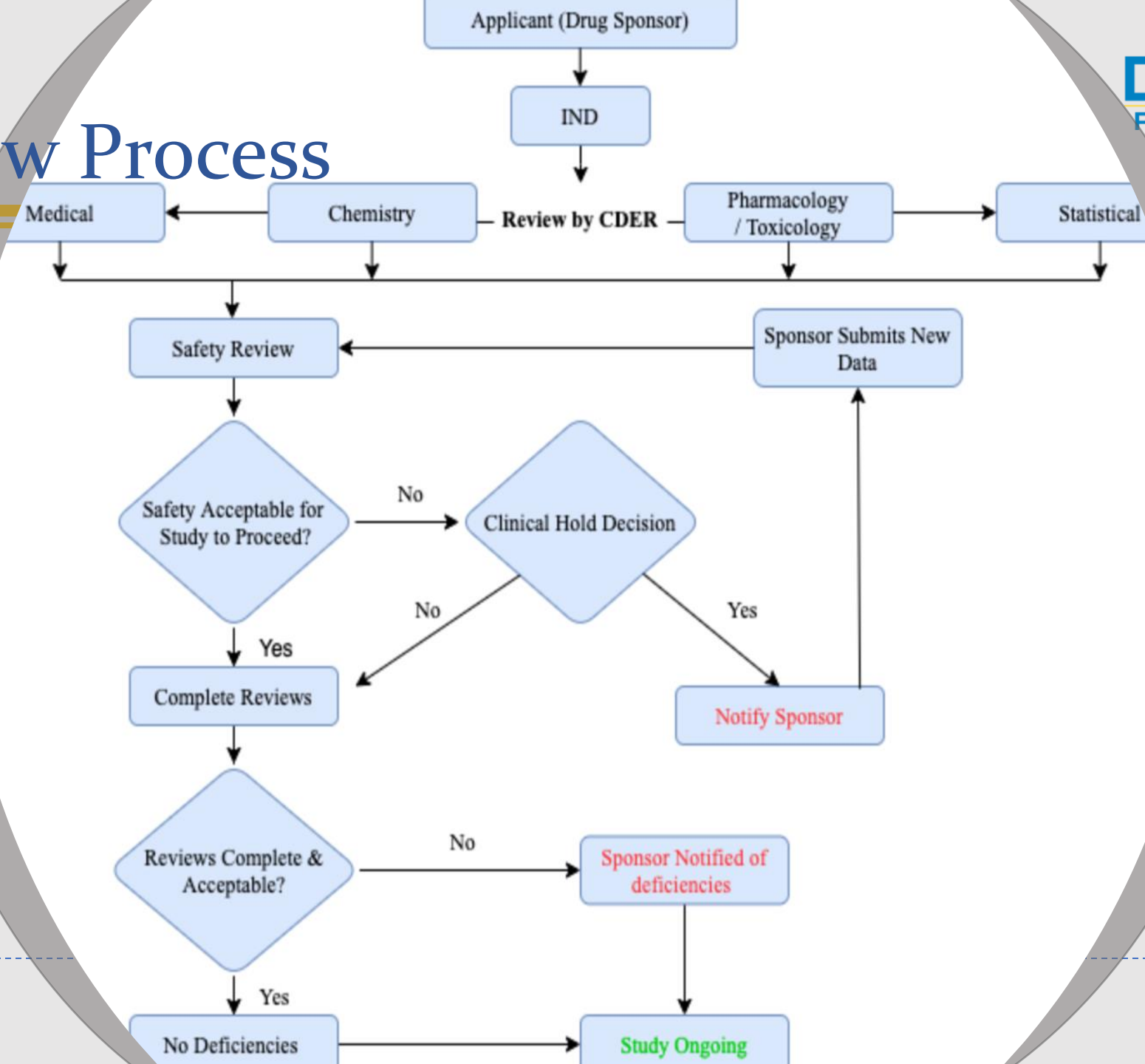
- Effective May 5, 2018 mandatory use of eCTD format only for the following:
 - New Drug Applications (NDAs)
 - Abbreviated NDAs (ANDAs)
 - Biologics License Applications (BLAs)
 - Commercial Investigational New Drug Applications (INDs)
 - Master Files
- Electronic submission standards will be optional but encouraged for the following categories:
 - Noncommercial INDs, such as investigator-sponsored INDs and expanded-access INDs
 - Submissions for blood and blood components, including source plasma
 - Submissions for promotional materials for human prescription drug

IND Review Timeline

- Reviewed by the Division of Manufacturing and Product Quality (DMPQ) in 30 calendar days
- Drug development process: 12-15 years
- Possibly > \$1 billion

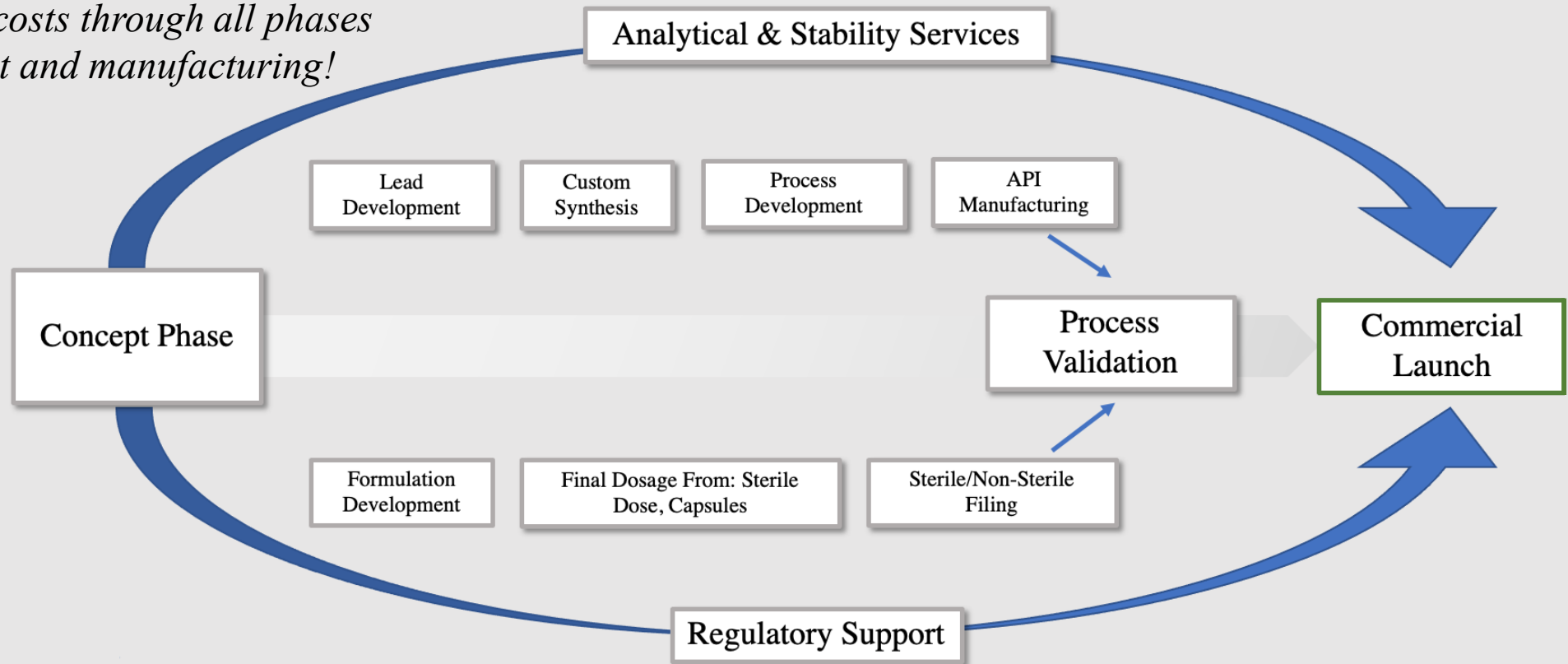


IND Review Process



IND Review Timeline

Dalton Pharma Services reduces timelines and costs through all phases of development and manufacturing!



IND- Amendment

“Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made.” [§312.30](#)

“Requirement for information amendment. A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report.” [§312.31](#)

Other Resources

- [ICH guidelines](#)
 - Brings together the regulatory authorities and pharmaceutical industry worldwide to achieve harmonization on the scientific and technical aspects of pharmaceuticals
- [CDER handbook](#)
 - Directives and documentations of internal policies and procedures that are required by law, to make CDER more transparent

Current IND processes with Dalton Pharma Services



- Dalton is currently working with VIDO-InterVac to provide aseptic formulation and sterile fill/finish towards the clinical development of an effective COVID-19 vaccine

Drug Discovery & Development at Dalton

- Recent FDA CDER and CBER new drug therapy approvals with Dalton Pharma Services:
 - CardiolRx™ with Cardiol Therapeutics Inc.
 - Anti-malaria diluent with United States Army Medical Materiel Development Activity (USAMMDA)
- Dalton Pharma Services won CMO 2016, 2017 and 2018 [Leadership Award](#) from Life Science Leader in the categories of Quality, Reliability, Capabilities, Expertise, Compatibility and Development

Thank
you

Special acknowledgement to

 [Mark Winnett](#)

&

 [Gisel Murillo](#)