FDA Investigational New Drug Application

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 FDA's investigational new drug application process and requirements. 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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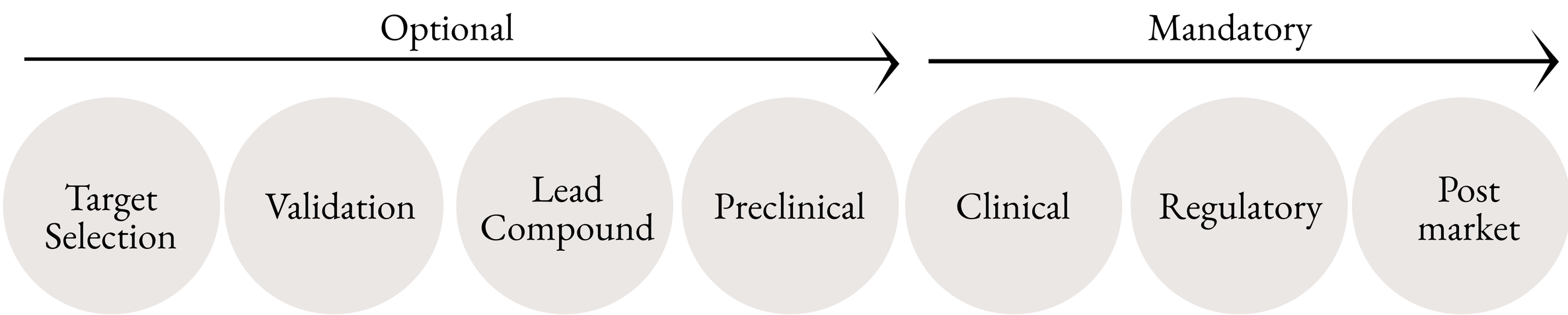
When to Start Interacting with FDA?



Interaction with the FDA begins at the clinical trial stage of the drug development process to obtain authorization for an investigational new drug (IND).

Drug Development Process

8 Steps to Launch

1

Preclinical testing

3.5 years; assesses safety and biological activity

2

IND filing

1 year; determines safety and dosage

3

Phase I

1-2 years; evaluates efficacy and safety

4

Phase II

1-4 years; verifies effectiveness/ monitors long term adverse reactions

5

Phase III

1-4 years; verifies effectiveness/ monitors long term adverse reactions

6

Marketing application

1-2 years

7

FDA review

1-2 years

8

Phase IV

Post market testing required by FDA

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

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Investigational New Drug Application

An **investigational new drug** is a potential therapy a sponsor would like to use in human clinical trials. An Investigational New Drug Application (INDA or IND) is a request to the FDA for authorization to administer an investigational drug to humans.

- In the US, the IND must be updated continually – this means you can update the same application after each phase.
- Note that the type and amount of information varies depending on the phase of the investigation.
- 21CFR, Sec. 312.1 to Sec. 312.32 contains procedures and requirements governing the use and submission of INDs to the FDA.

IND Exemptions

(FDA, 2015)

Not all clinical investigations using investigational drugs require an IND. You may be exempt from requiring an IND if all of the following exemption criteria are met:

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

IND Types

(FDA, 2021)

Investigator IND

An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Emergency Use IND

Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

Treatment IND

Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted, and the FDA review takes place.

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IND Content

(FDA, 2021)

The IND application must contain information in three broad areas:

1. **Nonclinical**: requires animal pharmacology and toxicology studies to permit an assessment as to whether the product is reasonably safe for initial testing in humans
2. **Quality**: requires chemistry, manufacturing, and controls (CMC) information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. *At Dalton, we help document CMC development projects for your investigational drug*
3. **Clinical** protocols and investigator information – requires detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks

1 Nonclinical

Pharmacology and Toxicology studies demonstrate reasonable safety to conduct clinical study and estimate the safe starting dose. The pharmacology section of the application requires:

- A description of the pharmacologic effects and mechanism(s) of action of the drug in animals,
- Pharmacokinetics data (absorption, distribution, metabolism, and excretions of the drug), and
- Safety pharmacology studies to assess vital organ function: central nervous system, cardiovascular system, and respiratory system

The toxicology section of the application requires:

- Safety information based on the toxicological effects of the drug in animals and/or in vitro. Usually includes individual reports for each animal.
- Note that Good Laboratory Practice (GLP) studies are required to support the final marketing application for a drug, potentially including carcinogenicity, reproductive and chronic toxicity studies.

2 Quality

Information regarding the chemical makeup of the product, its manufacturing, and testing is required in this section. The purpose of this section is to ensure the proper identity, strength or potency, quality, and purity of the drug substance and drug product.

- Drug Substance
  - Raw Materials
  - Manufacturing Process (i.e., chemical synthesis, simple purification)
  - Analytical Testing (in-process and release)
  - Certificate of Analysis (CoA)
- Drug Product
  - Manufacturing Process
  - Analytical Testing and Specifications
  - Release Criteria and CoA
- Stability
- Container Closure
- Labeling

For more detailed information on CMC information required for an IND click here

3 Clinical

Any information of previous human experience is required. To do so, you may refer to published literature, reference an approved label, or obtain a letter of authorization.

- You may reference an approved label by cross referencing the package insert of an FDA approved drug for off label use.
- You may obtain a letter of authorization (LOA) from a company to reference information in their IND or drug master file (DMF) for their drug that has been FDA approved to undergo investigation.

Clinical protocols which describe exactly how a study will be carried out and how results will be analyzed is also required.

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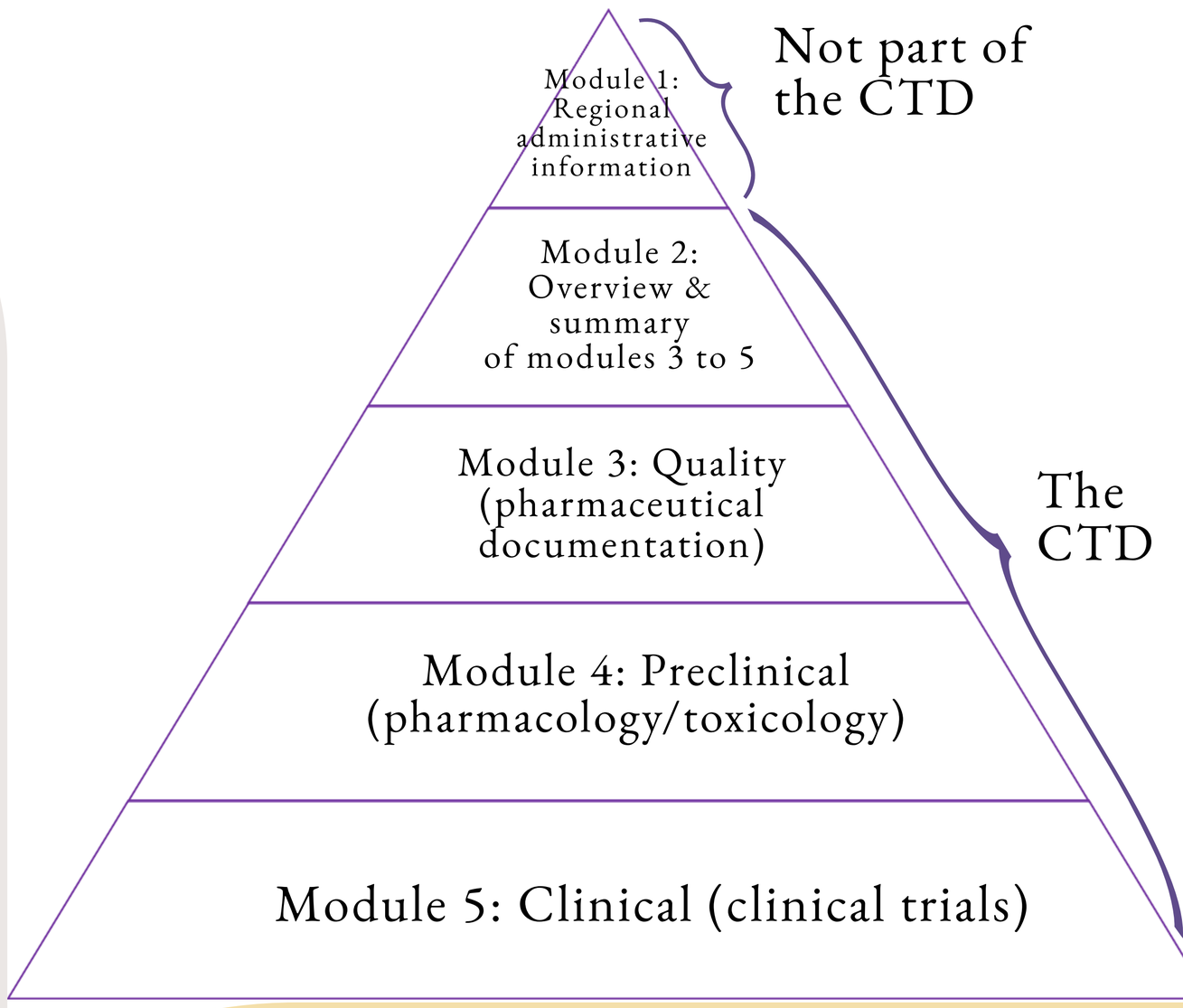
IND Format Requirements

(FDA, 2021a), (ICH, 2021)
(FDA, 2015a), (FDA, 2015b)

1. Paper Submission in Legacy Format, or
2. Electronic Submission in CTD Format

The Common Technical Document (CTD) was developed by the International Council on Harmonization (ICH) and sets of specifications for a collection of documents used in the registration of pharmaceuticals.

- This format enables electronic CTD (eCTD) submissions to FDA via the Electronic Submissions Gateway (ESG)
- FDA requires the following submission to be done via the eCTD format:
  - Marketing applications –5/5/2017
  - Commercial INDs –5/5/2018



Paper Submission

VS

eCTD

Form 1571	
Table of Contents	equivalent to module 2 of eCTD
Introductory Statement	equivalent to module 2 of eCTD
General Investigation Plan	equivalent to module 1 of eCTD
Investigator's Brochure - Compilation of the clinical and nonclinical data on the investigational product that provides investigators and study teams with the information to understand key features of the protocol and the drug (i.e., expected adverse effects)	equivalent to module 1 of eCTD
Protocols	equivalent to module 5 of eCTD
Chemistry, Manufacturing and Control Data (CMC)	equivalent to module 3 of eCTD
Pharmacology and Toxicology Data	equivalent to module 4 of eCTD
Previous Human Experience	equivalent to module 5 of eCTD
Additional Information	
Biosimilar User Fee Cover Sheet	equivalent to module 1 of eCTD
Form 3674 (Certification of registration at http://clinicaltrials.gov) - Registration of clinical trial details allows studies to be easily accessible to the public. Failure to register results in a fine.	equivalent to module 3 of eCTD

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Review Process and Timeline

(FDA, 2021), (FDA, 2015c)

Once the IND is submitted, wait 30 calendar days. If after 30 days, you do not hear from the FDA it means that there has been no clinical hold and you have received the green light to initiate any clinical trials.

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 toxic compounds
- 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

IND Amendments

(FDA, 2015d)

"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." Sec. 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." Sec. 312.31

Formal Meetings with FDA

(FDA, 2021)

Type A

Examples of type A meetings relevant to the IND process:

- Meetings to discuss clinical holds
- Special Protocol Assessment (SPA) meetings requested by sponsor after evaluation of protocol by FDA

Type B

Examples of type B meetings relevant to the IND process:

- Pre-IND meetings
- Certain End-of-phase 1 meetings (EOP1)
- End-of-Phase 2/Pre-Phase 3 meetings (EOP2)
- These meeting are meant to discuss the format and content of the application and address any questions regarding your project:
  - Clinical protocol design i.e., study endpoints, duration of studies, and number of studies
  - Manufacturing information/changes
  - Preclinical testing adequacy/effectiveness or additional studies
  - General product development questions (i.e., post-marketing commitments, status of pediatric studies)
  - Regulatory questions

Type C

Any meeting type other than a Type A or Type B meeting regarding the development and review of a product in a human drug application

Pre-IND Meeting with FDA

A pre-IND meeting provides an opportunity for the sponsor to present relevant data, discuss concerns and issues regarding drug development, and gives FDA an opportunity to provide guidance on the acceptability of the proposed trial(s). Therefore, a pre-IND meeting can help:

- Prevent clinical holds
- **Reduce time to market**
- **Minimize costs**
- Ensure more efficient drug development

Pre-IND meeting request packet	VS	Pre-IND meeting background packet
Meeting objective		Overall program synopsis
Proposed agenda with estimated times needed for each agenda item		Whether the animal efficacy rule is being considered
List of questions categorized by discipline (i.e., CMC, pharmacology/toxicology)		Clinical study synopsis
List of sponsor participants		Results for *in vitro* and early *in vivo* toxicology
List of requested CDER participants		Rationale for safety, based on toxicological profile and safety margin using dose regimen and exposure
Quantitative composition of the drug proposed for use in the study		Brief description of the manufacturing scheme for the API and formulation for clinical study
Proposed indication		Brief assay descriptions
Dosing regimen: concentration, amount dosed, and frequency and duration of dosing		Full description of the development plan
Proposed meeting date (must be 6-8 weeks in the future)		Copy of the meeting request with updates to reflect the most current information
Availability of the background packet (must be at least 4 weeks before the proposed meeting date)		

Questions to ask at a pre-IND meeting

1. What available designation or methods applicable to enhance or expedite development?
2. What is the difference between submitting a 505(b)(1) or 505(b)(2) application?
3. Does the agency agree that the proposed approach will establish clinical safety?
4. What nonclinical studies does the agency recommend to support an IND?
5. What is the level of method validation required for a phase 1 product?
6. Are the animal model(s) used for the toxicology study relevant and is the study design is acceptable?
7. How to set specifications for an unstable drug substance drug product?

Be sure to ask specific well-phrased questions, adhere to the agenda, and obtain clear and concise information!

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Expedited Programs and IND

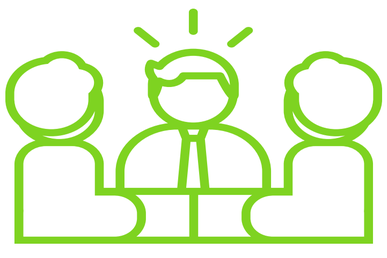
(FDA, 2020)

Fast track and breakthrough therapy designation are often submitted with an IND, and can also be submitted thereafter.

- Submissions are made to the appropriate review division or office in CDER or CBER

Breakthrough therapy designation requests should not be submitted until preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints. Therefore, breakthrough therapy designation requests are often submitted as an amendment to the IND.

Features of Fast Track Designation include meetings with FDA, including IND meetings such as end-of-phase 1 meetings, and end-of-phase 2 meetings to discuss study design.



IND Application Guidance Documents

1. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products
2. Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products. Questions and Answers
3. Preparation of Investigational New Drug Products (Human and Animal)
4. Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application
5. Safety Reporting Requirements for INDs (Investigational New Drug Applications) and BA/BE (Bioavailability/Bioequivalence) Studies
6. Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND
7. Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators
8. Good Laboratory Practice Regulations Management Briefings, Post Conference Report, Aug 1979
9. Formal Meetings with Sponsors and Applicants for PDUFA Products

View more here.

Dalton's Services

We are committed to working with you to create an API that meets your needs for your investigational new drug. We offer a variety of finished dosage forms and with our Sterile API Manufacturing and our *Steriles Made Simple* SM program we can manufacture your sterile liquid in a vial for Phase I/II clinical supplies in around 4 months.

Learn more about our cGMP sterile manufacturing and fill/finish capabilities:

- Aseptic Vial Filling - Sterile Liquid Injectables
- Lyophilization services
- Sterile Lyophilized Vials
- Sterile Powder Filling in Vials

Dalton's drug development services include:

- Custom Synthesis from mg to multi-kilogram scale including controlled drug classes (i.e., Steroids, Opioids and Cannabinoids), nucleotides, natural products and many more
- Optimization of existing synthetic routes
- Development of GMP friendly alternative synthetic routes
- Isolation of active ingredients from natural sources
- Transfer of process into GMP
- Troubleshooting
- Documentation of CMC development projects
- Synthetic feasibility
- Scale up
- Lead optimization
- Drug analog synthesis
- Structure activity optimization
- Medicinal Chemistry research

With our fully equipped custom synthesis laboratories and over 30 years of experience we deliver fully integrated solutions with an emphasis on quality, speed, and flexibility.

For a full list of our services please visit here.

VIDO

Dalton provided aseptic formulation and sterile fill/finish for VIDO-InterVac's COVID-19 vaccine to be used in early phase clinical trials. For more on sterile API development, view our technical report on guidelines for GMP of APIs.

ALGERNON PHARMACEUTICALS™

Algernon Pharmaceuticals selects Dalton Pharma Services to synthesize DMT for its clinical stage pharmaceutical development for stoke studies. For more on API development and finished product formulation, view our API and dosage form technical report.

CARDIOL™ THERAPEUTICS

With Dalton's manufacturing expertise, Cardiol Therapeutics achieved commercialization of Cortalex™ from small clinical trial batch development.

A dedicated Project Management Team is charged with the responsibility of keeping a project on time and on budget by proactively identifying and resolving any potential issues before they arise.

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