“FDA Regulations Decoded: A Practical Workshop for Researchers and Clinical Trialists”

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Disclosure and Conflict of Interest Declaration

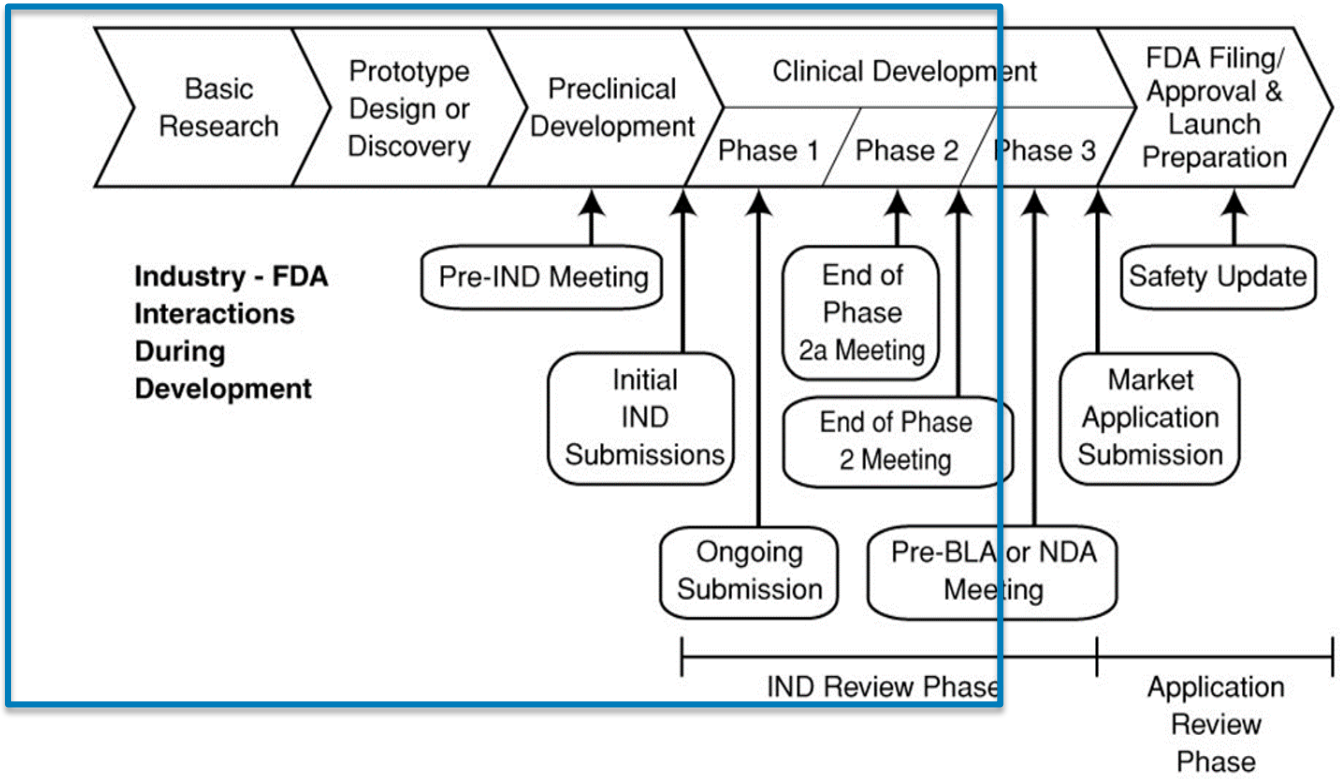
- I have no financial disclosures regarding pharmaceutical drug products.
- I have no conflicts of interest to disclose.
- The views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Lecture Outline

- Early phase drug development: filing an Investigational New Drug (IND) application as an academic investigator
  - Safety
  - IND exemptions
  - Forms and procedures
  - Review process

- Late phase drug development:
  - Evidentiary standard for new drug approvals
  - Traditional vs Accelerated approvals
    - Biomarker Development for approvals

Drug Development: from Bench to phase 2a *(proof-of-concept study)*



Requesting a Pre-IND meeting

IND Application Procedures: Interactions with FDA

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Sponsors of IND applications may obtain advice and guidance from FDA at any stage of IND development. A sponsor may consult with the Agency before formal submission of an IND application and send a pre-IND meeting request (PDF - 145KB) to an appropriate Review Division responsible for overseeing products in the therapeutic area relevant to the IND application

A pre-IND meeting may be requested for issues related to data needed to support the rationale for testing a drug in humans; the design of nonclinical pharmacology and toxicology studies including design and potential uses of any proposed treatment in animal models; data requirements for an Investigational New Drug (IND) application; initial drug development plans, regulatory requirements for demonstrating safety and efficacy and other aspects of the development program.

Sponsors of IND applications may request formal face-to-face meetings (PDF - 95KB) that can be scheduled throughout the development program.

Other interactions with FDA may occur via a variety of communication means including written correspondences, submission of IND Application Amendments, Dispute Resolutions, and e-mail and telecommunications with project management staff in the appropriate Review Division.

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-interactions-fda

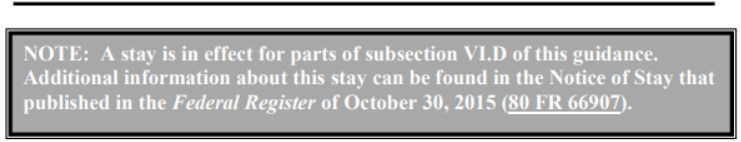
General Principles for FDA's Review of IND Application

- Primary objectives of FDA's review:
  - Assure the safety and rights of human subjects
  - Help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety
- Upon the IND application submission, FDA:
  - Assesses the general investigational plan and protocols for specific human studies
  - Assesses the safety of Phase 1 clinical investigations

Source: https://www.ecfr.gov/current/title-21/section-312.22

What is contained in an IND?

1. Standard electronic forms and a cover letter
2. CMC data-chemistry, manufacturing and controls
3. Non-clinical data—aspects of toxicology related to drug-development, e.g. NOAEL data (no-obvious adverse event level), to calculate safety margins. Important in first-in-human (FIH) study design.
4. Sponsor or investigator brochure
5. Clinical research protocol along with
    - Curriculum Vitae of the medical monitor or PI
    - Informed Consent as will be submitted to an IRB



NOTE: A stay is in effect for parts of subsection VI.D of this guidance. Additional information about this stay can be found in the Notice of Stay that published in the *Federal Register* of October 30, 2015 (80 FR 66907).

Guidance for Clinical Investigators, Sponsors, and IRBs

Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Food Safety and Applied Nutrition (CFSAN)

September 2013
Clinical/Medical

Not all clinical research requires an IND

https://www.fda.gov/media/79386/download

A clinical investigation of a marketed drug is exempt from the IND requirements if all the criteria for an exemption in § 312.2(b) are met

1. The drug product is lawfully marketed in the United States.
2. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
6. The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

https://www.fda.gov/media/79386/download

Caveats to IND exemptions: DHN (1)

- Patient Population: The acceptability of known and unknown risks can vary across different treatment populations (see § 312.2(b)(1)(iii)). The population chosen for study could be at increased risk compared to the approved use population for a variety of reasons, such as increased age, different disease or stage of disease, concomitant illness, **decreased** renal or **hepatic function**, or concomitant therapy.

  For example, a drug with significant toxicity can be approved for use in a population with a life threatening or severely debilitating disease because the risk of toxicity is acceptable in that population. Use of that drug in a clinical investigation in a population that is not so ill (e.g., to evaluate the drug for prevention of disease or symptomatic relief), however, would present a different risk-benefit situation in which the known risks might not be acceptable.

- When use of the drug in a specific patient population decreases the acceptability of the known risks, the study would have to be conducted under an IND as required under 21 CFR part 312

https://www.fda.gov/media/79386/download

Caveats for IND exemption: DHN (2)

"Generally, it seems reasonable to infer that any well-controlled trial of a marketed drug (e.g., a study of a new indication) sponsored by the manufacturer of the drug would be intended to be used to influence labeling or promotion in some significant way and would have to be conducted under an IND. ….similar studies of marketed drugs conducted by an entity that Contains Nonbinding Recommendations and does not have an independent ability to change a drug's labeling – e.g., a study conducted by a sponsor-investigator in an academic setting or Government agency sponsor – would *not generally be intended* to be submitted to FDA *to support a new indication or to otherwise influence the drug's labeling* or promotion. However, *data from such studies may subsequently be submitted to FDA for that purpose and, therefore, FDA has an interest in helping to ensure that these studies are designed to yield data adequate to support a labeling change*".

https://www.fda.gov/media/79386/download

Which of these projects is IND exempt?

1. Joe PI is awarded an R01 to study mechanisms of how fenofibrate reduces endoplasmic reticular stress. He wants to compare exosomal deep sequences of MASLD subjects exposed to fenofibrate or a comparator agent. The NIDDK SRO recommends the PI file an IND. Is the project IND exempt or does it require and IND?

2. Sara Jean at Southern Methodist University is awarded a K24. In one of the specific aims she plans to study a lawfully marketed product in the United States to determine whether it improves glucose control in subjects with hemochromatosis who have cardiac and hepatic disease. The NIDDK SRO indicates that since the product is previously marketed the study is IND exempt. Is the SRO correct?

Scenario 1 Joe PI

Joe PI does not need to submit an IND, and the project is IND exempt because

1. The drug product (**fenofibrate**) is lawfully marketed in the United States.
2. The investigation is not intended to be reported to FDA as a well-controlled study *in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug*. *Joe PI is conducting an experiment using human subjects research for the intent of gaining new knowledge and not necessarily for any efficacy findings.*
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for **fenofibrate**.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
6. The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize **fenofibrate**).

Scenario 2 Sara Jean PI

Sara Jean does need to submit an IND, and the project is not IND exempt even though

1. The drug product is lawfully marketed in the United States.
2. The investigation is not intended to be reported to FDA as a well-controlled study *in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug. Joe PI is conducting an experiment using human subjects research for the intent of gaining new knowledge and not necessarily for any efficacy findings.*
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for **the product**.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)). #4 does not apply. The product is being tested in a patient population that likely has hepatic (and cardiac) impairment which increases the risk associated with the lawfully marketed product.
5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
6. The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize **the product**).

Table of Contents
Cover Letter
Table of Contents
Introductory Statement and General Investigational Plan
Investigator Brochure
Clinical Protocol
Informed Consent Form
Informed Assent Form
Monitoring Plan
Chemistry, Manufacturing, and Control (CMC) Information
Pharmacological and Toxicological Data
Previous Human Experience
Additional Information
Relevant Information
Form FDA 1571
Form FDA 1572
Form FDA 3674

IND Application Is Submitted before Clinical Trials Begin

Preclinical Phase

1) Sponsor develops a drug

2) Drug is tested for its toxicity in animal models or via an alternate method to animal models (e.g., in vitro)

3) Sponsor submits IND Application with *all relevant information* (sometimes, that includes human data, information from the literature or other sources)

IND Review

IND submission reviewed by FDA to ensure that the proposed clinical trials do not place human subjects at unreasonable risk.

For drugs for which an IND submission is required, clinical investigations cannot proceed without written authorization from FDA. Written authorization will be provided 30 days (or earlier) after FDA receives the IND.

Clinical Phase

Phase 1—Safety
Testing drug in healthy volunteers for the evaluation of metabolic and pharmacologic actions of the drug and sometimes early evidence of effectiveness; *approximately 20–80 people*

Phase 2—Efficacy
Gathering preliminary data on effectiveness for particular indications in the target population(s); *approximately 100s of people*

Phase 3—Safety & Efficacy
Gathering additional information about effectiveness and safety to evaluate overall benefit versus risk; *approximately 1,000s of people*

Sources: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda
https://www.fda.gov/drugs/investigational-new-drug-ind-application/drug-development-and-review-definitions

IND Application Review Process

Sponsor submits IND with:

- Animal pharmacology and toxicology studies

During the 30 days after IND submission:

- FDA reviews IND for safety to assure that

30 days after FDA receives IND submission, the application is:

In effect and clinical

Sources: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
https://www.ecfr.gov/current/title-21/part-312/subpart-C

IND Application Goes into *Effect*

- An IND goes into effect:
  - 30 after FDA receives the IND application unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold
  - On earlier notification by FDA that the clinical investigations in the IND may begin
    - FDA will notify the sponsor in writing of the date it receives the IND

When an IND goes into effect, a sponsor may ship an investigational new drug to investigators named in the IND application.

Source: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-C

Changes to an IND Application *in Effect*

- Once an IND is in effect, a sponsor can amend it as needed to ensure that clinical investigations are conducted according to protocols included in the application
- Sponsors are expected to submit protocol amendments for new protocols or changes to existing protocols before implementation of the respective changes
- Changes may include the following:
  - A new study that is not part of any protocol in the IND in effect
  - Modifications to a protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study

Sources: https://www.ecfr.gov/current/title-21/section-312.30

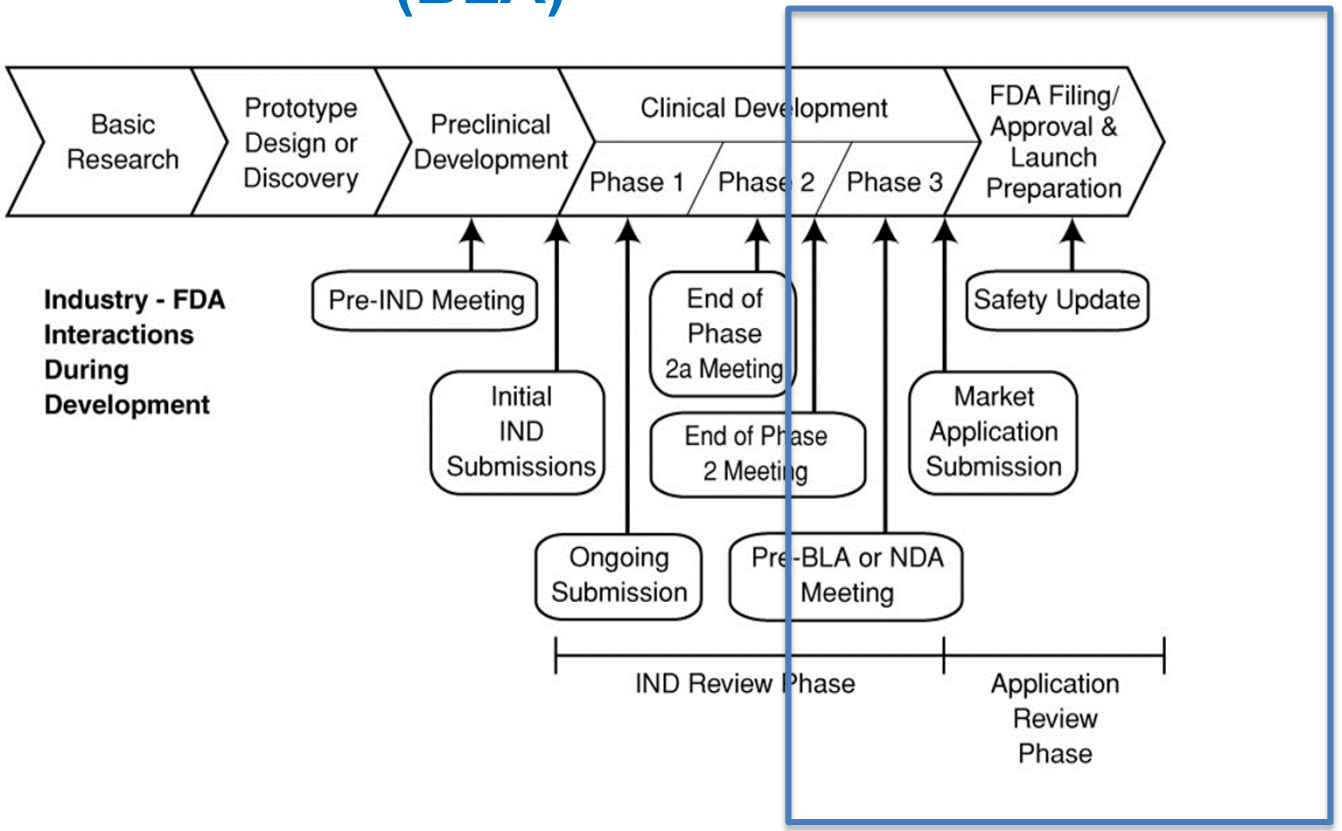
https://www.ecfr.gov/current/title-21/section-312.31

IND Application Placed on Clinical Hold

- Definition of clinical hold (21 CFR 312.42)
  - An order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation
  - Order may apply to one or more of the investigations covered by an IND
- Human subjects in those clinical investigations placed on hold may not be given the investigational drug

Source: https://www.ecfr.gov/current/title-21/section-312.42

Late-stage development to support a new drug application (NDA) or a biologic license application (BLA)



Evidentiary Standard for Approval

Substantial evidence of effectiveness/**clinical benefit** – Typically: Requires two adequate and well-controlled clinical studies and studies that have been designed "to distinguish the effect of a drug from other influences, such as spontaneous change, placebo effect, or biased observation".

FDA Modernization Act (FDAMA), 1997 – If FDA determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, FDA may consider such data and evidence to constitute substantial evidence.

Regulatory flexibility – FDA can "exercise its scientific judgment" in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs.

21 CFR 314.50
21 CFR 314.126
21 CFR 312.80
21 CFR 314.105(c)

Adequate and Well-Controlled Trials (1)

- Trials designed to show that a new drug is safe and effective for treatment
  - Effective: benefit that patients experience (cure, improvement)
  - Safe: the risk of side effects
- FDA and clinicians weigh the benefits and risks of new drugs for treatment

Adequate and Well-Controlled Trials (2)

Drugs approved must meet the statutory standards for effectiveness and safety

- Section 505(d) of the FD&C Act
- Section 115(a) of the Modernization Act allows for one trial

Substantial evidence from adequate and well-controlled clinical trials (21 CFR 314.126)

- Placebo concurrent control
- Dose-comparison concurrent control
- No treatment concurrent control
- Active treatment concurrent control
- Superiority or non-inferiority*
- Historical control – e.g., historical experience = high mortality

* Treatment effect over placebo of the active control drug must be known for non-inferiority

Traditional Approval

- When a sponsor has completed work in both phase 1 and phase 2 studies, it will want to proceed with a marketing, or registration, trial,
- This consists of a phase 3 clinical study which is an adequate and well-controlled study includes randomization, double-blinding, along with a placebo-controlled comparator.
- Typically for marketing approval (or registration) two trials are submitted for review in a new drug application (NDA) or a biologic licensing application (BLA).
- For traditional approval, the studies can examine a clinical effect as a clinical outcome directly or with a validated surrogate endpoint (e.g., blood pressure, HIV-RNA). That is the effectiveness of a new drug should demonstrate how it improves how a patient *"feels, functions, or survives*."

The Accelerated Approval Pathway

Requirements:

(1) A drug that treats a serious condition AND generally provides a meaningful advantage over existing therapies

AND

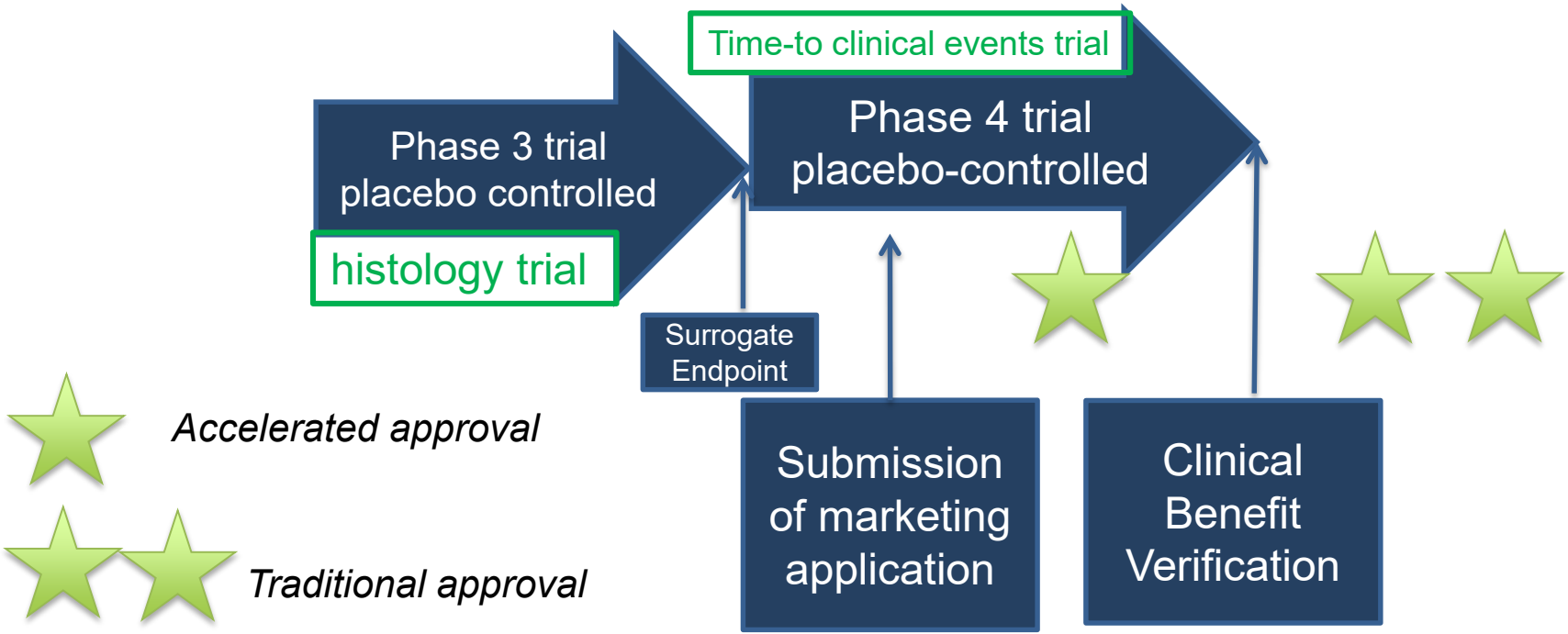
(2) Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit; or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality that is also reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit (i.e., an intermediate clinical endpoint).

§ 21 CFR part 314, subpart H

§ CFR part 601, subpart E

506(c) of the FD&C Act, as amended by section 901 of the FDASIA

Accelerated Approval for MASH with (F2/F3)fibrosis*



Source: *Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry*

Biomarker Endpoint Measures

- Biomarker: *A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention.*
  - Biomarkers Definitions Working Group 2001 & IOM Report 2011

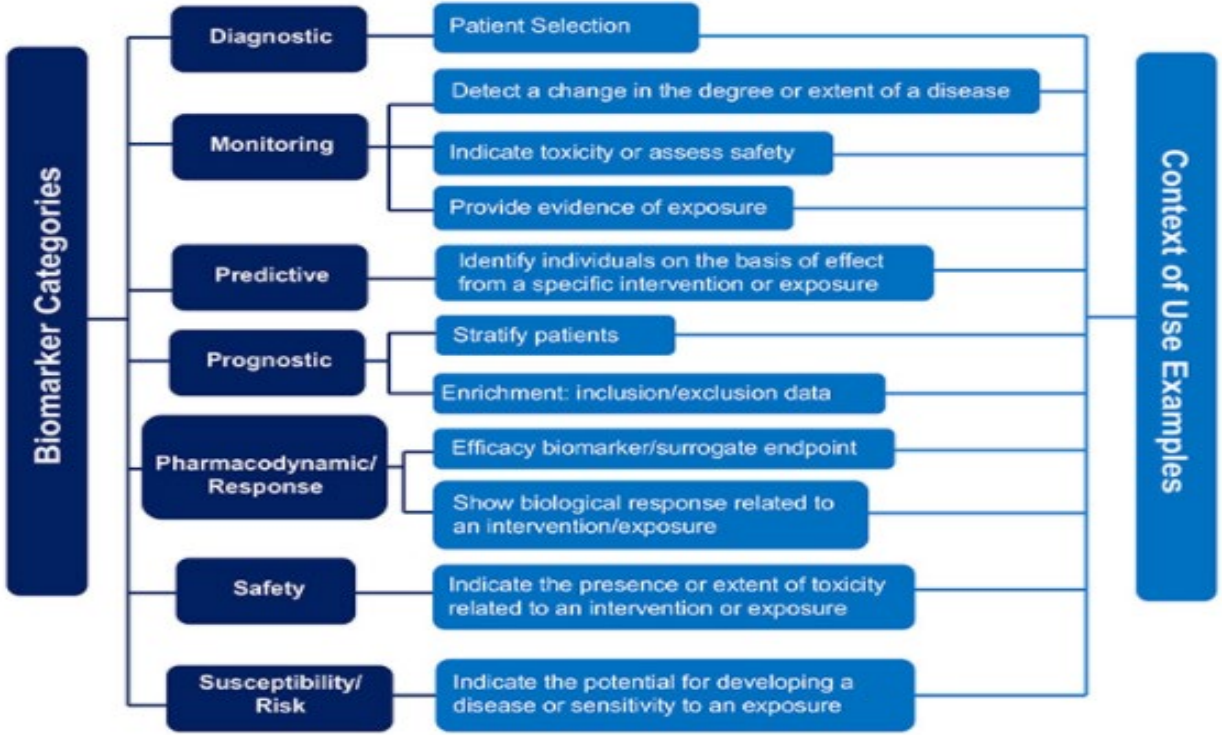
- *A surrogate endpoint, or "marker", is a laboratory measurement or physical sign that is used in therapeutic trials as a* ***substitute for a clinically meaningful endpoint*** *that is a direct measure of how a* ***patient feels, functions, or survives*** *and that is expected to predict the effect of therapy.*
  - Federal Register/Vol. 57, No.73/April 15, 1992

Surrogate Endpoints

- **Validated Surrogate Endpoint (VSE)** – can be used in place of a clinical endpoint to support **traditional** approval
- **Reasonably Likely Surrogate Endpoint (RLSE)**– can be used to support **accelerated** approval
- **Intermediate Clinical Endpoint** – can be used to support **accelerated** approval
- **Candidate Surrogate Endpoint** – *cannot* be used to support approval

BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-S

Biomarker Qualification Program (BQP) focuses on context of use (COU)



the BQP serves to validate and approve biomarkers specifically for advanced clinical trials of therapeutic drugs and biologics

If the BQP approves a biomarker for the stated COU for a clinical trial, then it becomes available to the public for use by other drug developers

www.fda.gov

Review Procedure for an NDA/BLA: Filing of NDA/BLA

CDER has 60 days to decide whether to file the NDA/BLA for regulatory review:

- Regulatory review team assigned to examine the application for filing determination
  - If decision = file, then regulatory review continues
  - If decision = refuse to file because NDA/BLA incomplete, the application process stops

Sources: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective
https://www.fda.gov/media/102796/download

Review Procedure of NDA/BLA: NDA/BLA Filed and Reviewed

Review team evaluates the NDA/BLA (initial review cycle is usually ten months unless time frame adjusted through mutual agreement between FDA and applicant, per 21 CFR 314.100(c))

FDA issues one of two letters:

Approval Letter

OR

Complete Response Letter: application is **not ready** for approval

Sources: https://www.fda.gov/media/82381/download
https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-D/section-314.100

Benefit-Risk Assessment (Efficacy-Safety Evaluation)

Efficacy

- The data are statistically significant and clinically meaningful
- Statistically significant data may represent modest efficacy
- Assess whether potential benefit is sustained if chronic use is likely
- Are existing therapies available?
- Does the new product provide benefit in a serious disease (e.g., melanoma, end stage organ failure)?

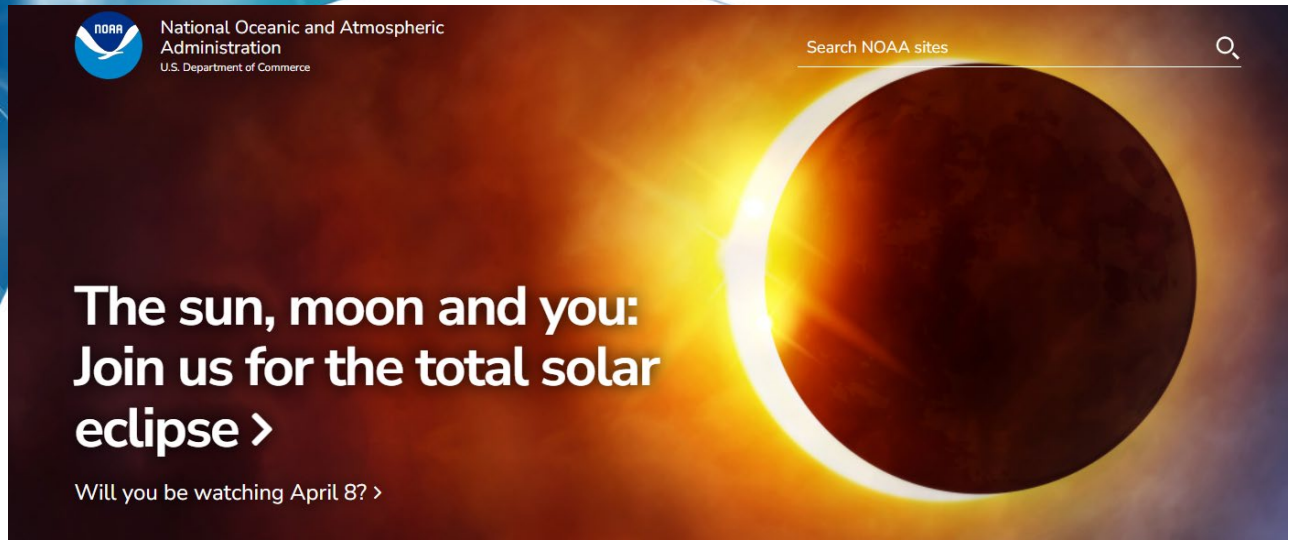
Safety

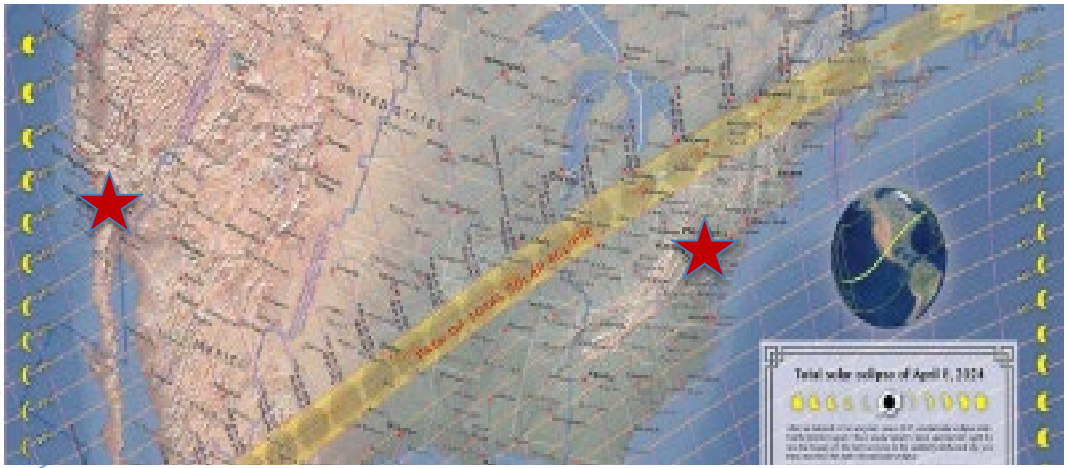
- Adverse events, adverse hepatic reactions, DILI, and off-target adverse reactions are considered based on adequate dose-exposure
- What will the long-term health outcomes be the intended-use population?
- Will the treatment be short-term or life-long?

Review Decision for NDA/BLA: Complete Response (CR) Letter (CRL) for NDA/BLA vs. Approval

- Written communication to an applicant from FDA, usually describing all the deficiencies that the Agency has identified in an NDA (or BLA) that must be satisfactorily addressed before it can be approved (21 CFR 314.3 “Complete response letter”).
- The CRL is not publicly available; therefore, the FDA has no authority to disclose the contents of the CRL to the public.
- If an application is approved, then *the complete review* by the Agency will be uploaded as a public facing document along with *the final product label (USPI)* and *the approval letter* that is sent to the applicant. These can be viewed at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (Drugs@fda.gov).

Source: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314


National Oceanic and Atmospheric Administration
U.S. Department of Commerce
Search NOAA sites
The sun, moon and you: Join us for the total solar eclipse ›
Will you be watching April 8? ›



Thank you!

Questions


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Supplemental slides

IND Application Procedures: Overview

When submitting original IND applications, sponsors are expected to send their applications in triplicate (one original and two copies). Electronic submissions should be considered whenever possible (FDA Study Data Standards Resources).

Each application should be accompanied by:

- Form 1571 (PDF - 830KB) (IND application cover),
- Form 1572 (PDF - 718KB) (Investigator's statement), and
- Form 3674 (PDF - 3MB) (certification requirement & mandatory registration and reporting of results for applicable clinical trials through ClinicalTrials.gov.)

While IND application sponsors are not required to submit information regarding clinical investigators' financial interests or arrangements in the original IND applications, they are expected to collect this information before a clinical investigator participates in a clinical study. For further information refer to Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators (PDF - 165KB).

The current address for sending IND applications may be found at Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs).

Upon receipt of an IND application, FDA will notify the sponsor of the date it receives the application through an IND acknowledgment letter.

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-applications-clinical-investigations-overview

Where to find help when preparing an IND: fda.gov

Investigational New Drug (IND) Application

Emergency Investigational New Drug (EIND) Applications for Antiviral Products

IND Forms and Instructions

Investigator-Initiated Investigational New Drug (IND) Applications

Pre-IND Consultation Program

Regulatory Information for INDs

This table provides links to information for investigators about submitting Investigational New Drug (IND) applications to FDA. The resources for application reporting and applications procedures apply to IND applications for both clinical research and clinical treatment.

IND Applications for Clinical Investigations (*Product Development*)	IND Application Reporting	IND Application Procedures	IND Applications for Clinical Treatment (*Expanded Access*)
Overview	Overview	Overview	Overview
Contents and Format	Protocol Amendments	Exemptions from IND Requirements	Contents and Format
Regulatory and Administrative Components	Information Amendments	Interactions with FDA	Emergency IND Timeline (Treatment of a Single Patient in Emergency Setting)
Non-clinical Components	Safety Reports	Clinical Hold	For Physicians: A Guide to Non-emergency Single Patient Expanded Access Submissions
Clinical Components	Annual Reports	Investigator's Responsibilities	Treatment of a Group of Patients

https://www.fda.gov/drugs/investigational-new-drug-ind-application/investigator-initiated-investigational-new-drug-ind-applications

Categories of IND Applications

Commercial

- Drug sponsor (usually a corporate entity) intends to commercialize the product by eventually submitting a marketing application

Research (noncommercial)

- Drug sponsor (generally an individual investigator, academic institution or nonprofit entity) does not intend to later commercialize the product

Sources: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/research-investigational-new-drug-applications-what-you-need-know

Some Terms in Drug Development (1)

Marketing Application

An application for a new drug submitted under section 505(b) of the FD&C Act or a biologics license application for a biological product submitted under the PHS Act

Sponsor

Takes responsibility for and initiates a clinical investigation

- May be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization
- Sponsor of an IND application is the party who submits the application to FDA

Investigational New Drug

New drug or biological drug used in a clinical investigation

Sources: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-A/section-312.3
https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-applications-clinical-investigations-overview

Some Terms in Drug Development (2)

Clinical Investigation (or Clinical Trial)

Experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects

Investigator

An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject)

Subject

A human—healthy or a patient with a disease—who participates in an investigation, either as a recipient of the investigational new drug or as a control

Source: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-A/section-312.3

Investigator-Initiated IND Applications

- IND submitted by an investigator who both initiates and conducts the clinical investigation—and under whose immediate direction the investigational new drug is administered or dispensed
  - Investigator might submit an IND application to study an unapproved drug or an approved product for a new indication or in a new patient population

Investigator-initiated IND applications may be for commercial development or noncommercial, clinical research or for clinical treatment, such as in an expanded access IND.

Sources: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
https://www.fda.gov/drugs/investigational-new-drug-ind-application/investigator-initiated-investigational-new-drug-ind-applications

Administrative Actions FDA Can Issue When IND Application *in Effect* (1 of 5)

- Comment and advice
- Clinical hold
- Termination
- Inactive status

Source: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-C

Administrative Actions FDA Can Issue When IND Application *in Effect* (2 of 5)
Comment and Advice

- FDA may start communication
  - Reasons include deficiencies in the IND application or about need for more data or information
- Sponsor can also start communication
  - Reasons may include seeking advice from FDA on specific matters relating to an IND application
- All communications are advisory unless accompanied by clinical hold

Sources: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-C
https://www.ecfr.gov/current/title-21/section-312.41

Administrative Actions FDA Can Issue When IND Application *in Effect* (3 of 5)
Clinical Hold

- Delay a proposed clinical investigation or suspend an ongoing investigation for various reasons—human subjects exposed to an unreasonable risk, protocol for the investigation is deficient, and other reasons
- Once an investigation is placed on clinical hold:
  - Subjects may not be given the investigational drug
  - No new subjects may be recruited to the study
  - Subjects should be taken off therapy involving the investigational drug unless treatment continuation is specifically permitted by FDA in the interest of patient safety

Sources: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-C
https://www.ecfr.gov/current/title-21/section-312.42

Administrative Actions FDA Can Issue When IND Application *in Effect* (4 of 5)
Termination of IND Application

- Termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond
- FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in 21 CFR Part 312.42
- Termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND
- Upon termination, sponsor shall end all clinical investigations under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug

Sources: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-C
https://www.ecfr.gov/current/title-21/section-312.44

Administrative Actions FDA Can Issue When IND Application *in Effect* (5 or 5)
Inactive Status

- Issued when no subjects are entered into clinical studies under an IND for 2 or more years
- Issued if all investigations under an IND remain on clinical hold for 1 year or more

Sources: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-C
https://www.ecfr.gov/current/title-21/section-312.45

Meetings Between FDA and Sponsor When IND Application *in Effect* (1 of 3)

- General principles
  - Free, full, and open communication about any scientific or medical question that may arise during the clinical investigation
  - Aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit

Source: https://www.ecfr.gov/current/title-21/section-312.47

Meetings Between FDA and Sponsor When IND Application *in Effect* (2 of 3)

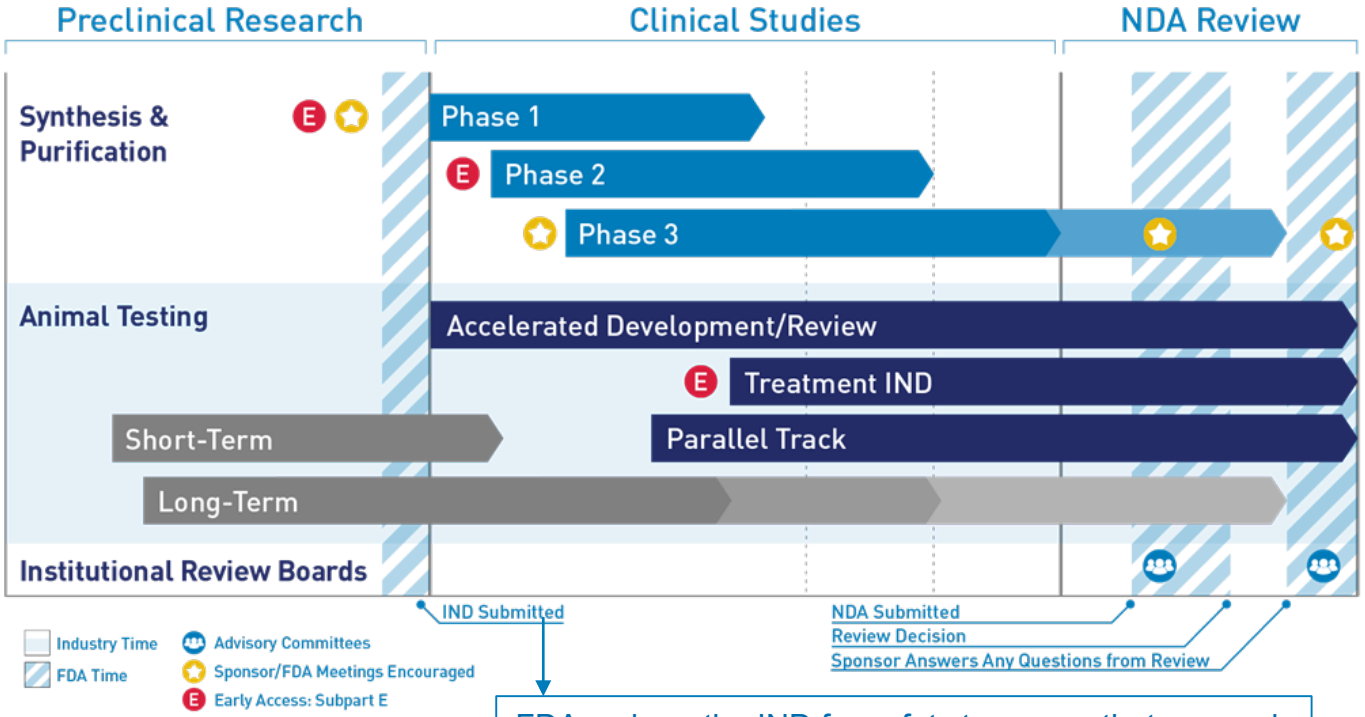
- End-Of-Phase 2 meetings
  - Determine the safety of proceeding to phase 3
  - Evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness
  - Identify any additional information necessary to support a marketing application for the uses under investigation

Source: https://www.ecfr.gov/current/title-21/section-312.47

Meetings Between FDA and Sponsor When IND Application *in Effect* (3 of 3)

- Near completion of Phase 3: pre-NDA or pre-BLA meetings
  - Uncover any major unresolved problems
  - Identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness
  - Identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness
  - Acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information)
  - Discuss appropriate methods for statistical analysis of the data
  - Discuss the best approach to the presentation and formatting of data in the marketing application

Source: https://www.ecfr.gov/current/title-21/section-312.47



FDA reviews the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

Source: https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/new-drug-development-and-review-process