Hogan Lovells

New Drug Development Under an IND

FDLI: Intro to Drug & Device Law & Regulation for Patient Organizations

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A little bit about me…

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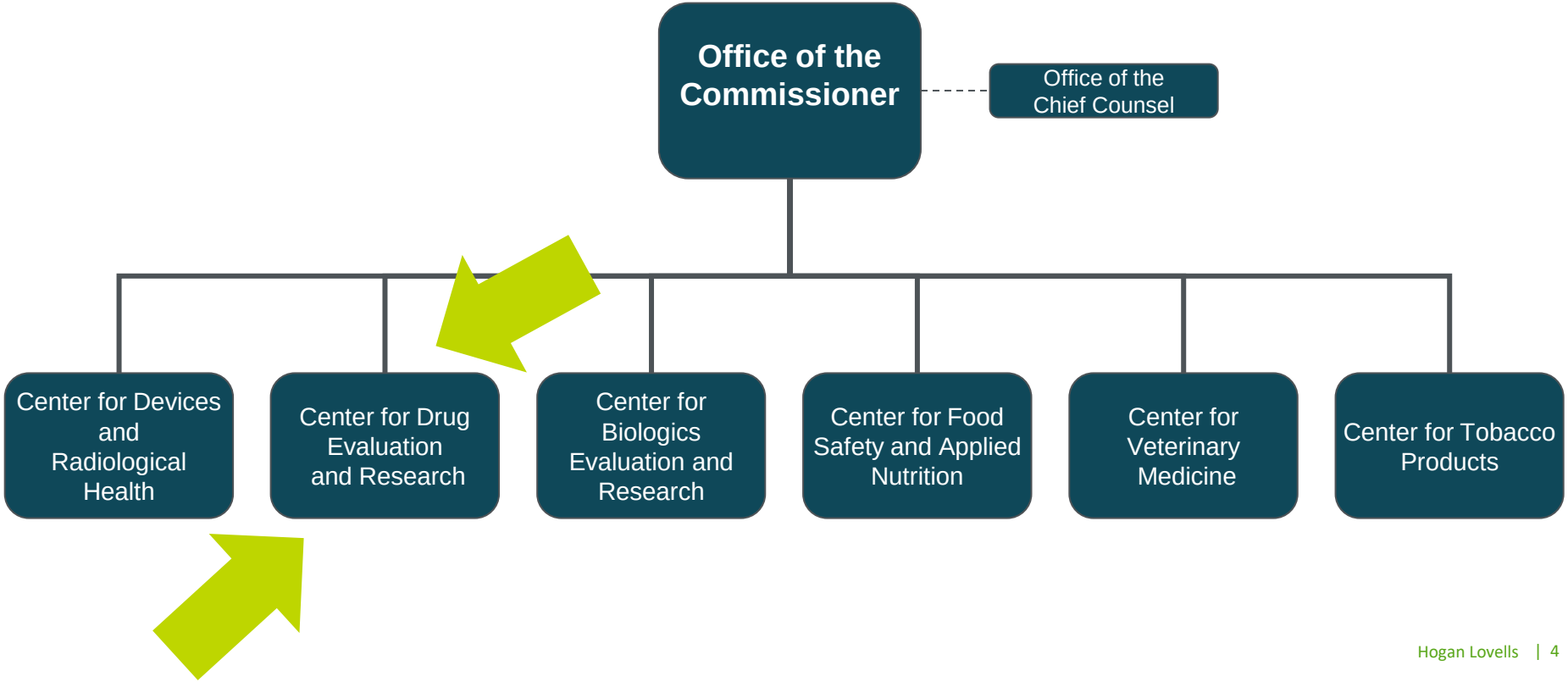
- 13 years experience at FDA's Office of the Chief Counsel
- 6 years at Hogan Lovells
- 24 years working on research/bioethics issues
- 3 years of formal bioethics training
- 13 years of IRB membership
- Experience in all aspects of clinical research/INDs
  - IND/IDE requirements
  - Research Design
  - Strategic FDA interactions
  - Compliance
  - Federal Inspections and Enforcement
  - Human Subjects Protections
    - Common Rule
    - 21 CFR Parts 50 and 56
      - Informed Consent
      - IRB Function and Operation
      - IRB Review

Overview

- FDA/CDER Organization
- Product Development Considerations
- Pre-clinical Testing/GLP
- INDs
  - When you need one
  - Content
- Clinical Hold
- Sponsor and Investigator Obligations

- GCP, Informed Consent and IRB Review
- Financial Disclosure
- Meetings with FDA
- Expanded Access
- Right to Try
- ClinicalTrials.gov
- Disqualification and Debarment

FDA Organization



CDER—Office of New Drugs (OND)

- **Office of New Drugs** – Immediate Office
  - **Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)**
  - **Office of Immunology and Inflammation (OII)**
  - **Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)**
  - **Office of Infectious Diseases (OID)**
  - **Office of Neuroscience (ON)**
  - **Office of Nonprescription Drugs (ONPD)**
  - **Office of Oncologic Diseases (OOD)**
  - **Office of Specialty Medicine (OSM)**
  - **Office of Therapeutic Biologics and Biosimilars (OTBB)**

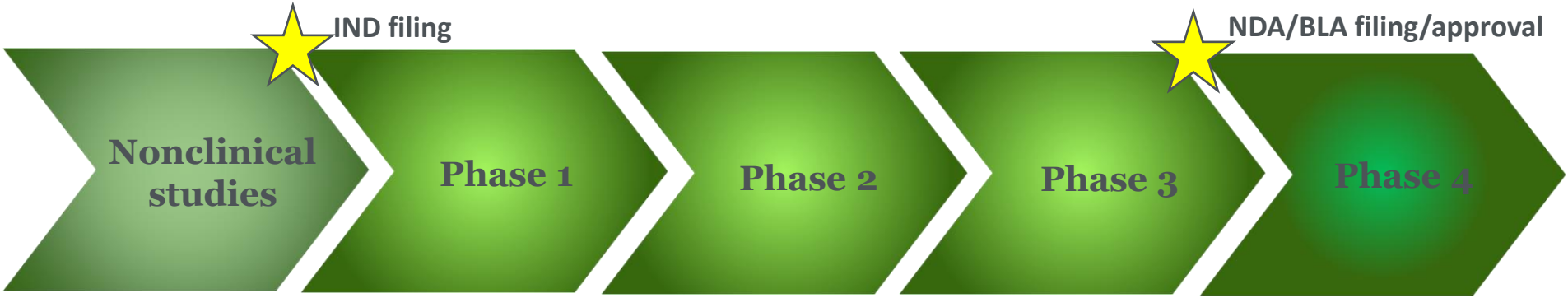
- **9 Offices, 27 Divisions**

Key Considerations During Medical Product Development

- Product composition—active and inactive ingredients
- How will the product be used clinically? Intended use?
- Funding for product development
- What is the competition doing?
- What are the regulatory hurdles?
- Study design
- What is the data burden?
- Likely timeline for approval

Developing Drugs & Biologics

Overview of Drug Development Process



- For a novel drug or biological product, development typically requires many years and is costly
- Many opportunities to engage with FDA during development process (e.g., pre-IND, end of Phase II, pre-NDA)

Engaging with FDA

Too often we have folks come in with [investigational new drug applications] and they haven't started their natural history study yet, and they haven't started thinking about what their outcome measures are going to be for Phase III … I mean when you first start to do preclinical studies, think about what is the target. The target is not getting into clinical trials … the target is getting a product on the market that's of use to patients.

Wilson Bryan
Director, Office of Tissues and Advanced Therapies, CBER
October 17, 2017

Preclinical Testing

- Purpose: **To initially evaluate an investigational drug's safety profile to establish that it is reasonably safe to conduct proposed clinical investigations in humans**
  - Determine safe starting dose
  - Understand which organs may be susceptible to toxicity
  - Estimate the margin of safety between a clinical and toxic dose
- *In vitro* and *in vivo* studies
- Generally, in vivo testing conducted in two or more species (one rodent, one non-rodent) because a drug may affect species differently
  - Pharmacology
  - Pharmacokinetics (absorption, distribution, metabolism, excretion)
  - Toxicology: acute and chronic
- No pre-notification to FDA, but agency may inspect

FDA Good Laboratory Practices (GLP)

- GLP requirements apply to preclinical safety studies in an application to FDA
  - IND or NDA must include statement that each applicable study was conducted in compliance with GLP (or a brief statement of the reason for noncompliance)
- **GLP regulations at 21 CFR Part 58**
  - Personnel/study director
  - Quality assurance unit
  - Facilities (including animal separation)
  - Equipment design, maintenance, and calibration
  - Facility operation (SOPs)
  - Characterization and handling of test and control articles
  - Protocols
  - Recordkeeping and reporting

Investigational New Drug Application (IND)

- An IND is a request for an exemption from the prohibition on introduction or delivery for introduction into interstate commerce of an unapproved drug
  - FDCA § 505(i); 21 CFR Part 312
- IND becomes effective 30 days after receipt by FDA, unless FDA issues clinical hold

When is an IND required?

- In general, the IND regulations in 21 CFR Part 312 require that clinical research be conducted under an IND if the following conditions exist:
  - The research involves a drug (defined in section 201(g)(1) of the FD&C Act);
  - The research is a clinical investigation (defined at 21 CFR 312.3), and;
  - The clinical investigation is not otherwise exempt from the IND regulations, Part 312.

What is a drug?

- Includes "articles intended for use in the **diagnosis, cure, mitigation, treatment, or prevention** of disease . . ." and "articles (other than food) intended to **affect the structure or any function of the body** of man or other animals."
- Biological products are considered drugs within the meaning of the FD&C Act and INDs are needed to study biologics, too.
- **What is a new drug?**
  - Essentially, it's an unapproved drug (this could be use of an approved drug outside it's labeling—for a different population, indication, etc.)

Clinical investigation v. the practice of medicine

- …an experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of the IND regulations, an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug **in the course of medical practice** (21 CFR 312.3(b))
- As a general matter, if randomization of a marketed drugs is involved, FDA would **not** consider this activity to constitute use in the course of medical practice.

When do you need an IND?

Generally, if you are using an unapproved product or using an approved product in a manner that is outside its approved labeling, it's considered investigational, and an IND is required.

IND Exemptions

- 21 CFR 312.2(b)
- A clinical study is IND-exempt if
  - Drug product is lawfully marketed in the United States
  - Study is not intended to support a significant labeling or advertising change
  - No significant risk (e.g., due to route of administration, dosage level, or patient population)
  - Compliance with IRB and informed consent requirements
  - No pre-approval promotion or commercialization (21 CFR 312.7)
- Other types of studies exempted by regulation include
  - Certain bioavailability studies (21 CFR 320.31)
  - Drug intended solely for in vitro or animal tests
  - Studies involving certain in vitro diagnostic biological products (blood grouping serum, reagent red blood cells, anti-human globulin) for use in a diagnostic procedure that confirms the diagnosis made by another, medically established diagnostic procedure

Key Components of an IND

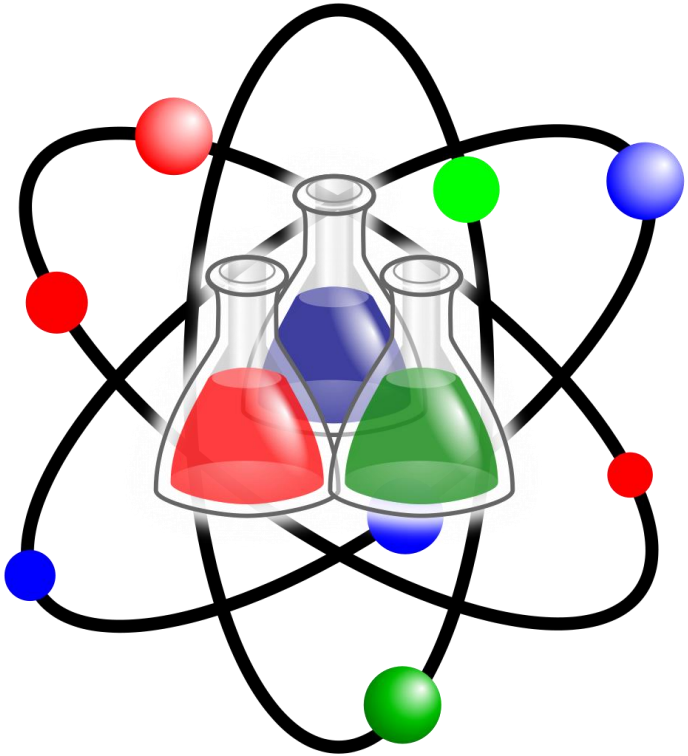
- Cover sheet (Form FDA-1571)
- Introductory statement and general investigational plan
- Investigator's brochure
- Study protocols
- Chemistry, manufacturing, and control (CMC) information
- Labeling ("Caution: New Drug—Limited by Federal Law to Investigational Use")
- Pharmacology and toxicology information
- Previous human experience with the drug (e.g., ex-US, literature)
- Pediatric plan
- Drug dependence/abuse potential

Investigator's Brochure

- Contents
  - Brief description of drug substance
  - Summary of pharmacology & toxicology
  - Safety & effectiveness summary
  - Anticipated risks & side effects
- Updated as new information becomes available
- Serves as basis of labeling submitted in NDA/BLA

Study Protocol

- Statement of objective and purpose
- Criteria for study subject selection and estimated number of patients
- Study design
- Dosage
- Observations and measurements
- Clinical procedures and laboratory tests
- Information regarding investigators, sub-investigators, research sites and IRBs



Phases of Clinical Investigation

- Safety, metabolism, pharmacology
- Usually healthy volunteers
- 20-80 subjects

- Safety, initial effectiveness, dose-finding
- Patients with disease
- Usually several hundred subjects

- Pivotal trials to establish safety and efficacy
- Up to several thousand patients in target condition

Clinical Hold

- FDA order to delay a proposed clinical study or suspend an ongoing clinical study
- Reasons for clinical hold
  - Unreasonable or significant risk of illness or injury
  - Unqualified clinical investigators
  - Deficient investigator brochure
  - Protocol design clearly deficient to meet stated objectives
  - Insufficient information to assess risks to subjects

- In general, subjects may not be given the investigational drug
  - No new subjects should be recruited and placed on the investigational drug
  - Enrolled patients should be taken off therapy unless specifically permitted by FDA in the interest of patient safety

Sponsor Obligations

- **Select qualified investigators**
  - Education/training
  - Investigator information & financial disclosure
  - Form FDA 1572
- **Control drug shipments**
- **Provide investigators with adequate information**
- **Disposition of unused study drug**
- **Monitoring**
  - Compliance with protocols
- **Inform FDA & investigators of significant new adverse events or risks**
- **Recordkeeping & reporting**
- **May transfer responsibilities to CRO**
  - All or in part
  - Specified in writing

Investigator Obligations

- Personally conduct or supervise the investigation
- Ensure that colleagues know their obligations
- Understand the Investigator Brochure
- Conduct the study in accordance with the protocol

- Obtain informed consent
- Comply with IRB requirements
- Report adverse events to sponsor
- Comply with FDA requirements for clinical investigators (record-keeping, reports, control of investigational drug)

Good Clinical Practices (GCP)

- Standards for design and conduct of clinical trials
  - Protect rights, safety, and welfare of human subjects
  - Assure integrity of clinical data on which product approvals are based
- GCPs are embedded in FDA regulations
  - 21 CFR Parts 50, 54, 56, 312
  - Guidance documents

Informed Consent: Key Principles

- 21 CFR Part 50
  - Required for IND and IND-exempt studies
- Understandable language
- Voluntary choice to participate
  - Minimize possibility of coercion or undue influence
  - If payment is offered for participation
    - Payment should not be conditioned upon completion of study
    - Payment installments as study progresses, not lump sum at end of study
- No exculpatory language requiring waiver of legal rights
- Informed consent forms must be reviewed by IRB

Informed Consent: Key Elements

- Explanation of research (e.g., nature, duration, procedures)
- Description of risks and benefits
- Disclosure of available alternatives
- Description of confidentiality of records
- Compensation
- Whether medical treatment is available in case of injury
- Contact information for questions or in case of injury
- Participation is voluntary

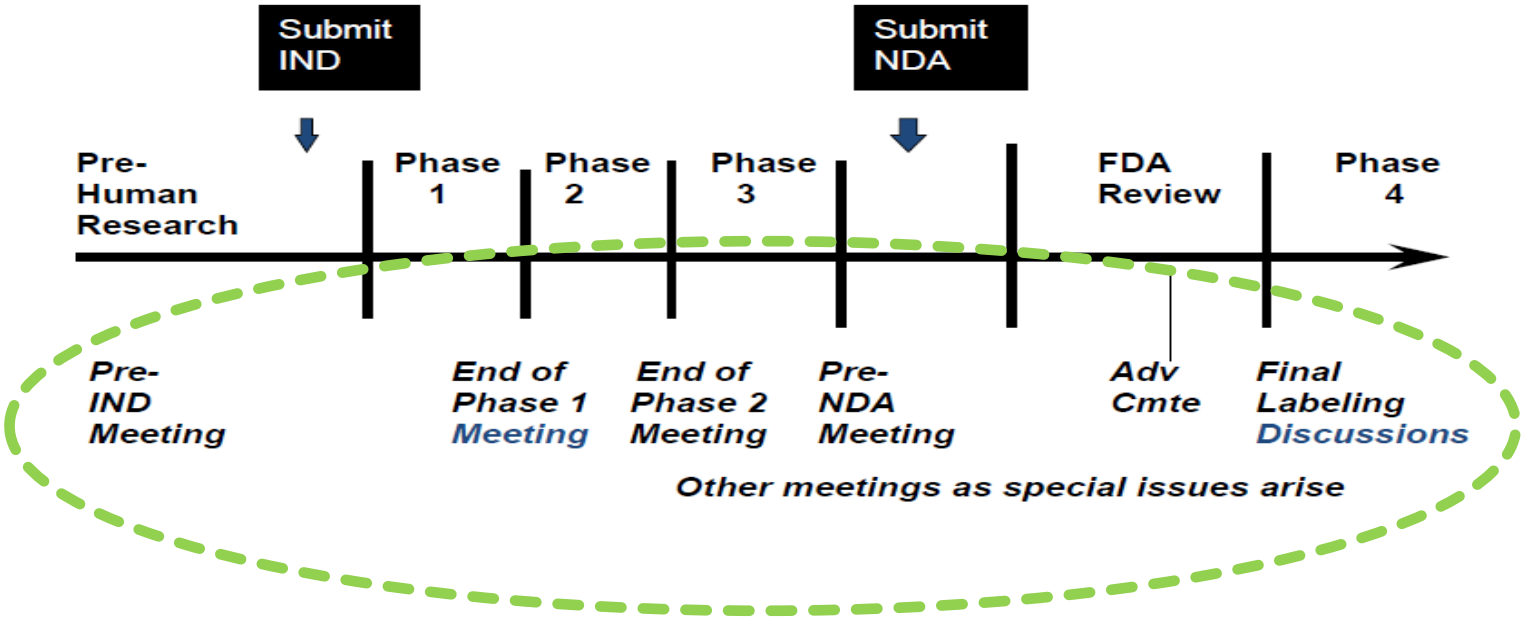
Institutional Review Boards (IRBs)

- 21 CFR Part 56
  - Required for IND and IND-exempt studies
- Purpose: Protect rights, safety, and welfare of human subjects
  - Approve and monitor clinical trials at particular study site(s)
  - Review informed consent and protocol
  - Continuously evaluate whether risks to subjects are reasonable in light of benefits

Investigator Financial Disclosures

- 21 CFR Part 54
- FDA reviews disclosures and measures to minimize bias to assess reliability of clinical data
- Requires disclosure of certain investigator financial interests for covered studies
  - Efficacy studies and studies that make a significant contribution to demonstration of safety
- Disclosable interests
  - Compensation affected by outcome
  - Significant payment of other sorts by sponsor (> $25K)
  - Proprietary interest in tested product
  - Significant equity in sponsor (ownership interest in private company, >$50K in public company)
- Investigator must provide updated information for 1 year after study completion

Meetings with FDA



Source: CDER presentation

Meetings with FDA (continued)

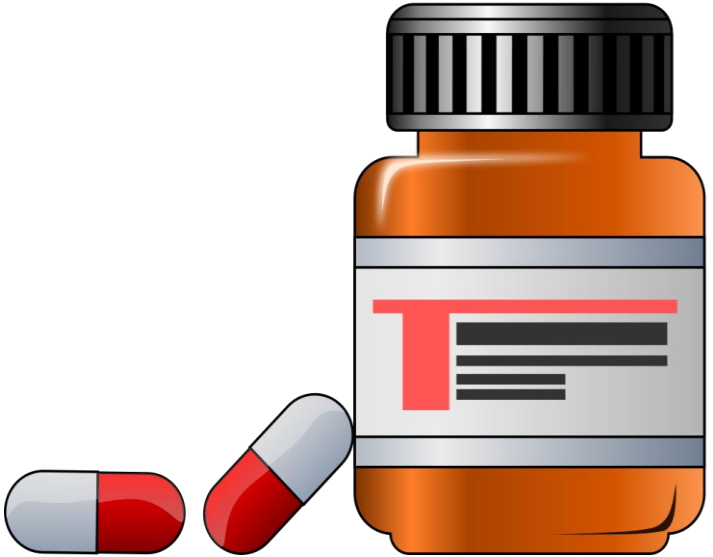
- Pre-IND meeting
  - Discuss scope and design of phase 1 studies, plans for pediatric studies, presentation and format of IND
- End-of-phase 1 meeting
  - Review and reach agreement on design of phase 2 studies
  - Discuss need for and design and timing of pediatric studies
- End-of-phase 2 meeting
  - Determine safety of proceeding to phase 3
  - Evaluate phase 3 plan and protocols
  - Adequacy of current studies and plans to assess pediatric use
  - Identify any additional information needed to support NDA/BLA

Meetings with FDA (continued)

- Pre-NDA/pre-BLA meeting
  - Familiarize FDA with information to be submitted in application
  - Discuss statistical methods
  - Identify any major unresolved problems
  - Discuss presentation and format of application

Expanded Access

- Primary purpose: treatment, rather than to obtain safety or efficacy data
- Conducted under an IND, and subject to IRB review and informed consent requirements
- Required findings:
  - Serious or immediately life-threatening disease or condition; no comparable or satisfactory alternative therapy
  - Potential benefit justifies the potential risks, and potential risks are not unreasonable, and
  - Will not interfere with clinical investigations that could support marketing approval of, or otherwise compromise potential development of the expanded access use
- 3 types: **individual patient, intermediate-size, treatment IND**



Individual Patients

- Requirements set forth at 21 CFR 312.310
  - General expanded access criteria, plus:
  - Probable risk from investigational drug must not exceed probable risk from disease or condition
  - Patient cannot obtain drug under another IND or protocol
- Generally limited to a single course of therapy for a specified duration unless FDA authorizes multiple courses or chronic therapy
- Physician or sponsor must provide FDA with a written summary of results, including adverse effects
- In an emergency, FDA may authorize use by telephone, with written submission from physician or sponsor within 15 working days

Intermediate-Size Patient Populations

- Circumstances
  - Drug not being developed (e.g., inability to recruit patients for clinical trial)
  - Patients not able to participate in clinical trial (e.g., geographically inaccessible)
  - Drug product is approved but no longer marketed for safety reasons or failure to meet conditions of approval
  - Consolidation of significant number of requests for individual patient access
- Requirements set forth at 21 CFR 312.315
  - General expanded access criteria, plus
  - Sufficient safety evidence to justify a clinical trial in the number of patients expected to receive the drug, and
  - At least preliminary evidence of efficacy or plausible pharmacologic effect to make expanded access a reasonable therapeutic option

Treatment Use

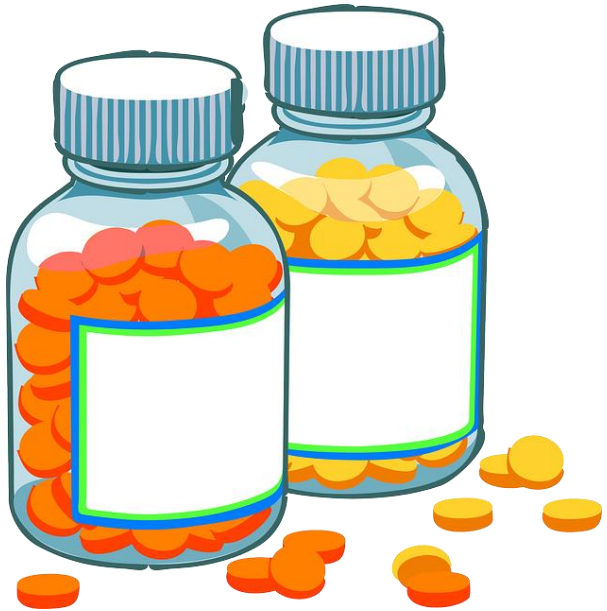
- For widespread treatment use
- Requirements set forth at 21 CFR 312.320
  - General expanded access criteria, plus:
  - Clinical trial for the expanded access use is underway or all clinical trials are complete
  - Sponsor is pursuing marketing approval with due diligence, and
    - *For a serious disease or condition*: Sufficient clinical evidence of safety and effectiveness to support the expanded access use (e.g., phase 3 data or compelling data from phase 2 trials)
    - *For an immediately life-threatening disease or condition*: Reasonable basis to conclude that investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk (generally phase 3 or phase 2 data, but could be more preliminary clinical evidence)

Federal Right to Try Act—Public Law 115-176 (May 2018)

- The Right to Try Act permits/allows eligible patients to have access to eligible investigational drugs
- An eligible patient is a patient who has:
  - Been diagnosed with a life-threatening disease or condition
  - Exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug (this must be certified by a physician who is in good standing with their licensing organization or board and who will not be compensated directly by the manufacturer for certifying)
  - And has provided, or their legally authorized representative has provided, written informed consent regarding the eligible investigational drug to the treating physician

Right to Try—eligible investigational drug

- An **eligible investigational drug** is an investigational drug:
  - For which a Phase 1 clinical trial has been completed
  - That has not been approved or licensed by the FDA for any use
  - For which an application has been filed with the FDA or is under investigation in a clinical trial that is intended to form the primary basis of a claim of effectiveness in support of FDA approval and is the subject of an active investigational new drug application submitted to the FDA
  - Whose active development or production is ongoing, and that has not been discontinued by the manufacturer or placed on clinical hold by the FDA



Right to Try—how to access…

- Patients interested in Right to Try should discuss this pathway with their licensed physician
- Ultimately, **sponsors** developing drugs for life-threatening diseases or conditions **are responsible for determining whether to make their products available to patients who qualify for access under the Right to Try Act**
- **FDA's role** in implementation of the Right to Try Act is limited to receipt and posting of certain information submitted regarding Right to Try use

ClinicalTrials.gov

- 1997: FDAMA section 113 required NIH to create a clinical trial registry for studies of investigational drugs for "serious or life-threatening diseases or conditions"
- 2000: NIH launched ClinicalTrials.gov
- 2007: FDAAA expanded submission requirements (PHSA 402(j))
- 2016: HHS published final rule implementing FDAAA section 801 (42 CFR Part 11)
- Many purposes
  - To help patients find trials for which they might be eligible
  - Enhance the design of clinical trials and prevent duplication of unsuccessful or unsafe trials
  - Improve the evidence base that informs clinical care
  - Increase the efficiency of drug and device development processes
  - Improve clinical research practice
  - Build public trust in clinical research

NIH U.S. National Library of Medicine

ClinicalTrials.gov

ClinicalTrials.gov Disclosure Requirements

- Applicable drug clinical trial
  - Interventional
  - Other than phase 1, and
  - At least one of the following:
    - At least one facility for the clinical trial is in the U.S. or a U.S. territory,
    - Drug is manufactured in and exported from the U.S. for study in another country
    - The clinical trial has an IND number
- Register trial within 21 days after enrollment of first subject
- Results information must be submitted regardless of whether product is approved, unless waiver is granted (extraordinary circumstances)
  - Within 1 year of primary completion date (2-year delay for new use or initial approval)

Investigator Disqualification

- 21 CFR 312.70
- Grounds for disqualification
  - Repeated or deliberate failure to comply with GCP or IND requirements
  - Submission of false information
- Procedure
  - FDA written notice to investigator and investigator response
  - Opportunity for hearing if FDA doesn't accept investigator response
  - FDA must provide statement of basis for any disqualification
- Disqualified investigator ineligible to receive test articles or to conduct any investigation that supports an application an NDA/BLA

Debarment

- FFDCA section 306
- **Mandatory**
  - Entities: Convicted of federal felony for conduct relating to development or approval of an ANDA (1-10 years for first debarment; permanent for second debarment within 10 years)
  - Individuals: Convicted of federal felony for conduct relating to development or approval of any drug product or otherwise relating to the regulation of any drug product (permanent)
- **Permissive** (up to 5 years)
  - Conviction for certain criminal offenses if underlying conduct "undermines the process for the regulation of drugs"
- **Consequences**
  - Entities: Cannot submit or assist in submission of a marketing application
  - Individuals: Cannot provide services to a person with a pending or approved drug product application

Patient Engagement at FDA

"Patients are at the heart of what the FDA does and are vital to our work protecting the public health by ensuring the safety and efficacy of drugs, biological products, and medical devices. Your experience can help inform our understanding of your medical condition, as we move from early stages in research to the later stages of approving new products."

(FDA patient engagement webpage, accessed 11/12/2020)

- Patient Affairs Staff in the Office of the Commissioner
  - Email: patientaffairs@fda.gov
  - Phone: 301-796-8460
- Patient Engagement
  - Website: https://www.fda.gov/patients/learn-about-fda-patient-engagement
    - Patient Representative Program
    - Patient Listening Sessions
    - Patients Matter Video series
    - Patient Engagement Collaborative


Your questions &
discussion