The New Drug Approval Process

New Drug Research and Development

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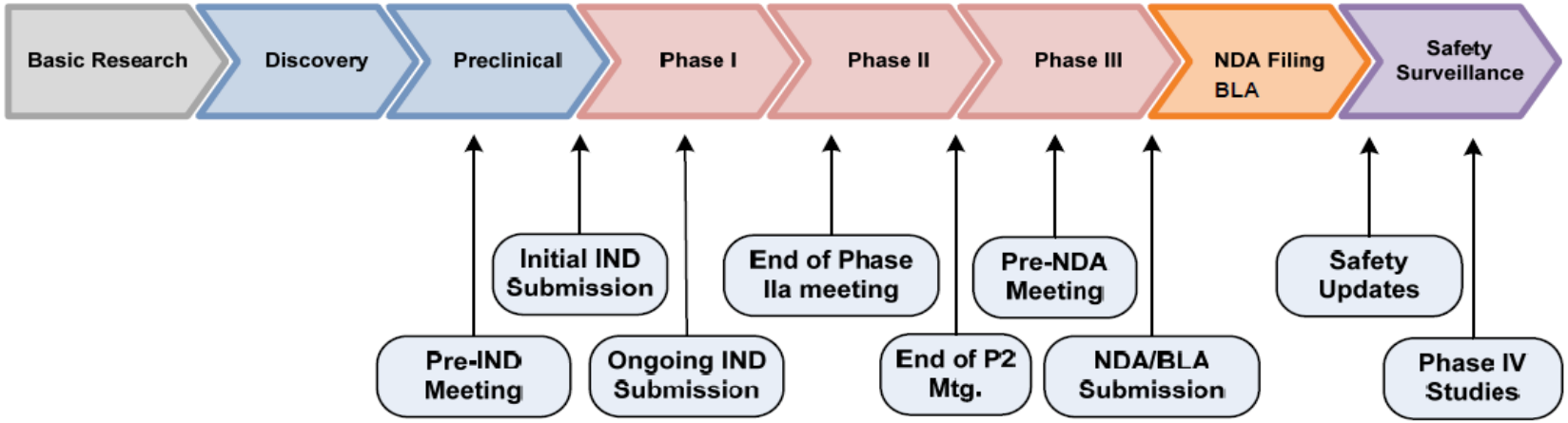
FDLI

Drug Development Process



Source: FDA

Preclinical Studies

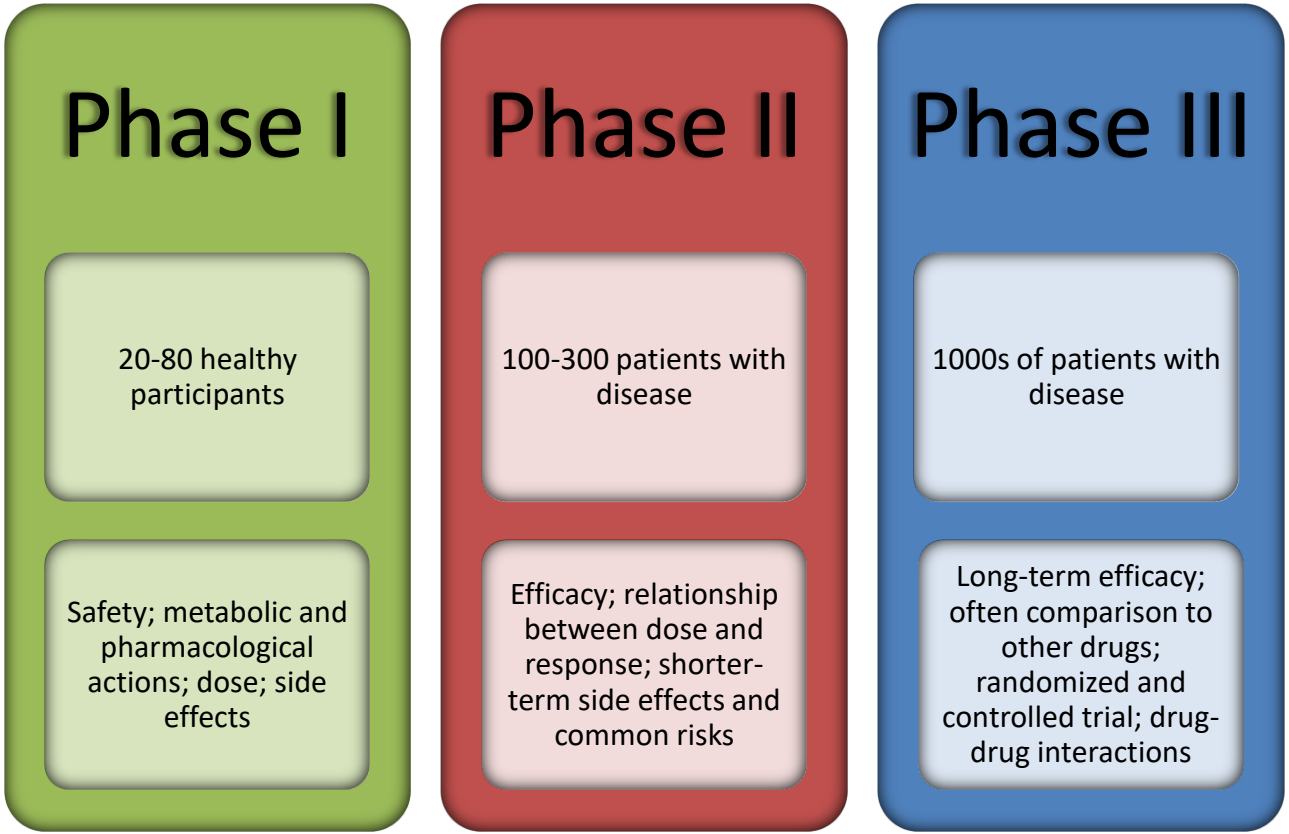
Purpose:

- Collect data on safety and toxicology
- Determine safe initial dosing for human studies (in clinical phase)
- Determine whether sufficiently effective against a disease target in chemical assays or animal models

Subject to GLP regulations [21 C.F.R. Part 58]

- Ensure quality and integrity of preclinical data on safety and toxicology
- Applies to nonclinical lab studies: in vivo and in vitro experiments of test articles (e.g., drugs) in test systems
- Minimum requirements for study conduct, personnel, facilities, equipment, written protocols, operating procedures, final reports, and quality assurance oversight

Main Phases of Clinical Testing [21 C.F.R. § 312.21]



Investigational New Drug (IND) Application [21 C.F.R. § 312]

Purpose

- Notifies FDA of intent to conduct human studies
- Ensures that subjects will not face undue risk of harm

FDA Review

- Determines whether safe to proceed with human studies or to impose clinical hold
- FDA comments are advisory unless accompanied by clinical hold

Approval

- IND becomes effective 30 days after receipt by FDA unless FDA notifies investigator otherwise, meaning human studies may commence

Studies Requiring an IND Application [21 C.F.R. § 312.2]

Research involves a "drug," as defined in FDCA (21 U.S.C. 321)

- Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or
- Intended to affect the structure or function of the body, but not regulated as food

Research is clinical investigation

- Drug will be administered to human subjects for an experimental use

Clinical investigation is not exempt from IND requirements

- Exemption only applies to approved drugs meeting certain criteria (see next slide)

Exemptions from IND Requirement [21 C.F.R. § 312.2]

To be exempt, investigation must satisfy **all** of the following criteria:

- Drug product is **lawfully marketed** in the U.S.
- Investigation must **not**:
  - Be intended to be reported to FDA as a well-controlled study for a **new indication** or a **labeling change**
  - Be intended to support a significant **change in advertising**
  - Involve a route of administration, dose, or patient population, or other factor that **significantly increases risk** (or decreases acceptability of risk)
- Investigation must be conducted in compliance with:
  - IRB and informed consent requirements (21 C.F.R. Parts 50 & 56)
  - Prohibition on promoting or commercializing investigational drug (21 C.F.R. § 312.7)

IND Contents

- Animal pharmacology, toxicology studies, and previous experience with drug in humans (e.g., outside the U.S.)
  - Pivotal nonclinical studies conducted in compliance with GLP; and if not, reason for noncompliance
- Chemistry, manufacturing, and control (CMC) – identification, quality, purity, and strength of investigational drug
  - Possible safety risks; any differences between the drug planned for clinical studies and the drug used in animal toxicology studies
- Investigator's brochure
- Clinical protocols and investigator qualifications
- Special topics: drug abuse potential, plans for pediatric studies
- Commitments to obtain informed consent, review by IRB, and adhere to IND regulations

INDs Submitted to CDER

	2020	2019	2018	2017
Commercial	1253	928	852	836
Research	929	750	742	836
Unknown	2182	1678	1894	1672

*Excludes Biosimilar Biologic INDs, Expanded Access INDs, and Unknown INDs.
**Unknown refers to INDs where the designation of Commercial or Research had not been made at the end of the calendar year.

Meetings with the FDA [21 C.F.R. § 312.47]

- Often held at critical points in drug development process
  - Pre-IND: discuss chemistry, manufacturing, and controls (CMC) issues relating to safety of IND
  - End-of-Phase II: evaluate CMC plans and protocols to ensure meaningful data generated during Phase III
  - Pre-NDA/BLA: discuss filing and format issues
- Recommended, but not mandatory

Meetings with the FDA: Process

Meeting request	• States specific objectives/desired outcomes of meeting • Includes draft list of questions to be addressed
Information package	• Contains brief summary of relevant CMC information, developmental status, plan and timeline for future drug development
Meeting formats	• Multidisciplinary with FDA representatives from clinical, microbiology, statistics, other disciplines • CMC-specific (supplemental or in lieu of multidisciplinary)
Focus	• Address questions identified in information package

Clinical Study Protocol [21 C.F.R. § 312.23]

- Describes study objectives, design, methodology, schedule, and organization of clinical trial
- Used to obtain ethics approval by IRBs or local ethics committees
- Generally contains the following information:
  - Background information
  - Trial objectives and purpose
  - Trial design
  - Selection, treatment, and withdrawal of subjects
  - Assessment of efficacy and safety
  - Statistics
  - Source data and documentation
  - Quality control and assurance
  - Ethics
  - Data handling and recordkeeping
  - Financing and insurance
  - Publication policy

Informed Consent: Overview [21 C.F.R. Part 50]

- Required for all IND research, subject to very few exceptions
  - Informed consent must be obtained from subject (or legally authorized representative)
  - With sufficient opportunity for subject to consider whether to participate (no coercion or undue influence)
  - In plain language
  - Without any exculpatory language

Informed Consent: Necessary Disclosures [21 C.F.R. § 50.25]

- To obtain informed consent, must describe:
  1. Research context, purposes, expected duration, procedures to be followed
  2. Reasonably foreseeable risks or discomforts to the subject
  3. Reasonably expected benefits from the research
  4. Appropriate alternative procedures or treatments
  5. Confidentiality of medical records, possibility that FDA may inspect the records
  6. Any compensation or treatments available to address injuries or risks of injury from the clinical trial
  7. Contact information for questions regarding research, participant rights, and research-related injuries
  8. Voluntariness of participation, no retaliation for refusal to participate, subject's right to end participation at any time

Informed Consent: Additional Disclosures [21 C.F.R. § 50.25]

- Where appropriate, disclosure of:
  1. Potential unforeseeable risks (including to fetus if subject becomes pregnant)
  2. Circumstances in which researcher may terminate participation
  3. Potential costs to the participant resulting from the research
  4. Consequences of a decision to withdraw and procedures for withdrawing from study
  5. Statement of significant new findings developed from research that may relate to subject's willingness to continue to participate
  6. Approximate number of study participants
  7. For Phase 2 or 3 clinical trials, disclosure about ClinicalTrials.gov:

     "A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Website at any time."

Clinical Testing: Roles and Responsibilities [21 C.F.R. Part 312, Subpart D]

- **Sponsor**
  - Overall responsibility for study
  - Designs study goals and protocol
  - Selects qualified investigators
  - Ensures proper monitoring of investigation
  - Submits safety reports and annual reports
  - Submits protocol and information amendments
  - Ensures proper review and approval by FDA and IRB
- **Contract Research Organizations (CROs)**
  - Sponsor may outsource some or all aspects of clinical trials to CROs on a contract basis, but sponsor retains ultimate responsibility

Clinical Testing: Roles and Responsibilities [21 C.F.R. Part 312, Subpart D]

- **Investigator**
  - Ensures that study is conducted according to the investigational plan and applicable regulations
  - Personally conducts or supervises research
  - Protects study subject rights, safety, and welfare under investigator's care
  - Controls the investigational drugs
  - Recordkeeping and retention of case histories and disposition of drug
  - Reporting to sponsor of adverse events
  - Reporting to IRB of all unanticipated problems involving risk to human subjects or others
- **Institutional Review Board (IRB)**
  - Responsible for protecting the interests and well-being of study participants
  - Reviews study protocol
  - Ensures proper monitoring

Monitoring [21 C.F.R. §§ 312.50, 312.53]

- Purpose
  - Quality control measure to ensure integrity of trial data and protection of rights and well-being of study participants
- Selection
  - Monitor appointed by sponsor and must have requisite scientific and technical expertise
- Role
  - Monitor ensures compliance of clinical trial with protocol, GCP, standard operating procedures (SOPs), and regulatory requirements

Adverse Event Reporting: Requirements [21 C.F.R. § 312.32]

- Sponsors are required to notify FDA in a written safety report of:
  - any **adverse events** associated with the use of the drug that is *both* **serious** *and* **unexpected**
  - any findings from tests in lab animals that suggest a **significant risk** for human subjects including reports of mutagenicity, teratogenicity, and carcinogenicity

- **Adverse event**:
  - any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related

Adverse Event Reporting: Definitions [21 C.F.R. § 312.32]

- **Unexpected**: adverse event or reaction that is:
  - not listed in the **investigator's brochure**;
  - not listed at the **specificity or severity** that has been observed; or
  - not consistent with the risk information described in the **general investigational plan** or elsewhere in the **current IND application**
- **Serious:** adverse event that results in:
  - death or is life-threatening (i.e., places patient in immediate risk of death);
  - in-patient hospitalization;
  - a persistent or significant incapacity or substantial disruption to ability to conduct life functions; or
  - a congenital anomaly or birth defect

Reporting Responsibilities of Investigators under 21 CFR 312.64(b) and Sponsors under 21 CFR 312.32(c)(1)(i) for Serious and Unexpected Suspected Adverse Reactions

Term	Investigator Responsibility	Sponsor Responsibility	Final Determination Responsibility
Serious (or life-threatening)	Yes (Investigator must report all serious adverse events to the sponsor immediately)	Yes	An event is considered serious or life-threatening, based on ***either*** the investigator's or sponsor's opinion.
Unexpected	No (No requirement to assess "expectedness")	Yes	The **sponsor** is responsible for determining whether event meets the definition of "unexpected," based on whether the event is listed in the investigator brochure; or if an investigator brochure is not required or available, is not consistent with the risk information described elsewhere in the general investigational plan or elsewhere in the current application.
Suspected Adverse Reaction – (causality assessment standard - "reasonable possibility")	Yes (Investigator must provide sponsor with an assessment of causality)	Yes (Sponsor's assessment determines reportability, regardless of investigator's assessment)	The ***sponsor*** is responsible for determining whether there is a reasonable possibility that the drug caused the adverse event, taking into consideration the investigator's assessment.

↓

The *sponsor* reports serious and unexpected suspected adverse reaction to the FDA and all participating investigators.

FDA Guidance, Safety Reporting Requirements for INDs and BA/BE Studies (Dec. 2012)

Financial Disclosures: Overview [21 C.F.R. Part 54]

- Sponsor must identify all clinical investigators and identify which are employees of the sponsor
- For each clinical investigator who is *not* an employee of the sponsor, must submit financial disclosure form for studies submitted in a marketing application to establish effectiveness or in which a single investigator makes a significant contribution to a study that demonstrates safety
  - Form FDA 3454 – certifying the absence of any financial arrangements listed in 21 C.F.R. § 54.4, or
  - Form FDA 3455 (where such financial arrangements exist) – disclosing the nature of those interests and the steps to minimize bias resulting from those interests

Financial Disclosures: Disclosable Interests

- Compensation affected by outcome of clinical trials
  - Applies to any compensation from sponsor where outcome *could* affect value
- Significant financial interest in the sponsor entity
  - Ownership interest, stock options, or other financial interest
  - If sponsor is publicly held company, applies if interest is >$50,000
  - Covers period of study and continues for one year after study completion
- Proprietary interest in the tested product
  - E.g., patent, trademark, copyright, or licensing agreement
- Significant payments of other sorts
  - Cumulative value of >$25,000
  - Covers period of the study and continues for one year after study completion

Financial Disclosures: Agency Actions

- FDA may refuse to file an application that omits requisite disclosures or certifications
- If FDA determines that financial interest of any clinical investigator raises a **serious question** about the integrity of the data, FDA may take action to ensure reliability of data, including:
  - Initiating agency audits of data received from the investigator in question
  - Requesting applicant to submit further analyses of data (e.g., to evaluate overall effect of investigator's data on overall study outcome)
  - Request applicant to conduct additional independent studies to confirm results of questioned study
  - Refuse to treat covered clinical study as providing data that can be basis for an agency action (e.g., basis for FDA marketing approval)

Clinical Holds [21 C.F.R. § 312.42]

Definition	Phase 1 grounds	Phase 2 and 3 grounds
• An order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation • Can be issued at any time	• Unreasonable risk to human subjects • Unqualified investigators • Insufficient, erroneous, misleading, or incomplete information to assess risks • Treatment for life-threatening disease that affects both genders, and exclusion by gender because of reproductive/developmental toxicity	• Any of the previous reasons • Protocol deficient in design to meet stated objectives

Use of Foreign Studies [21 C.F.R. § 312.120]

- IND foreign study
  - Sponsor may conduct foreign study under an IND, in which case all IND requirements must be met unless waived
- Non-IND foreign study
  - FDA will accept a well-designed, well-conducted foreign study *not* conducted under an IND if:
    - The study was conducted in accordance with GCP; and
    - FDA is able to validate the data from the study through an onsite inspection, if necessary

Investigator Disqualification / Debarment [21 C.F.R. § 312.70]

- FDA may initiate disqualification proceedings if investigator has repeatedly or deliberately:
  - Failed to comply with applicable regulatory requirements
  - Caused false information to be submitted to sponsor or in any required report to FDA

- Disqualified investigator:
  - Ineligible to receive investigational new drugs or to conduct any clinical investigation that supports application for IND or NDA/BLA
- Restricted investigator:
  - If FDA determines lesser sanctions sufficient to protect public health
  - Still eligible to receive investigational products if conducts regulated studies in accordance with restrictions specified in restriction agreement

Pediatric Testing: Pediatric Research Equity Act (PREA) [21 U.S.C. § 355B]

- Requires sponsors of NDAs and BLAs to submit data to assess safety and effectiveness of the drug for the indication(s) under review, and to support dosing and administration in pediatric populations (unless the sponsor has a waiver or deferral)
- Applies to applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration
- Total number of products studied under PREA since 2012 = 312
- Resource: Final Guidance, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (July 2020)

PREA (cont'd)

- Exemptions and Waivers:
  - Orphan indications
  - Disease does not exist in pediatric patients
  - Studies are impossible or highly impracticable
  - Evidence strongly suggests that drug/biologic would be ineffective or unsafe
  - Drug/biologic does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by substantial number of pediatric patients
  - Reasonable attempts to produce pediatric formulation have failed
- Deferral: May be eligible for study deferral until specified date after approval

Pediatric Testing: Pediatric Exclusivity

- Best Pharmaceuticals for Children Act (BPCA) provides a financial incentive to companies to voluntarily conduct pediatric studies
- Section 505(A) of the FDCA enables FDA to issue Written Requests for pediatric studies of approved and/or unapproved indications
  - (1) Prior to approval of an NDA
  - (2) To holders of approved applications
- Sponsors also can request FDA to issue a Written Request

- As an incentive to conduct studies requested by the FDA → grant of 6-month period of marketing exclusivity
  - The additional exclusivity is extended to the **entire drug**, not just pediatric uses (all uses and formulations with the same active ingredient)

Expanded Access [21 C.F.R. § 312.305]

- Pathway to gain access to investigational medical product outside of clinical trial
  - For the treatment of a serious or immediately life-threatening disease or condition when there is no comparable or satisfactory alternative therapy
  - Potential patient benefit justifies the risks
  - Primary purpose is not the collection of safety and effectiveness information about the drug

Expanded Access (cont'd)

- Types: individual patient/emergency use; intermediate-size patient population; widespread treatment use
- Requests: Firm submits request to FDA, or otherwise provides access to necessary information
- Approvals: FDA approves request; IRB reviews expanded access protocol and consent
- Reports: Sponsor submits IND safety report and annual report to FDA
  - For individual expanded access, sponsor submits summary of results, including adverse effects

Right to Try Act of 2017

- Right to Try is one pathway for patients diagnosed with life-threatening diseases or conditions who have exhausted all approved treatment options and are unable to participate in a clinical trial to access certain unapproved drugs
- Eligible patients can request that a company provide access to certain investigational drugs/biologics – without involving FDA in the process
- FDA does not review or approve Right to Try requests
- Proposed Rule (July 2020): Would require submission to FDA of annual summary of doses and use, number of patients treated, and serious adverse events from use of drugs under Right To Try

Orphan Drugs: Designation [21 C.F.R. Part 316]

- Designation provides orphan status to drugs and biologics for the treatment, prevention, or diagnosis of a rare disease or condition
  - Rare disease: affecting < 200,000 people in the U.S.
- Qualifies the sponsor for various development incentives of the Orphan Drug Act (ODA)
  - Tax credits and grants
  - Waiver of user fee for NDA/BLA
  - Potential exemption from Pediatric Research Equity Act (PREA) requirements
  - Protocol assistance

Orphan Drugs: Exclusivity

- Exclusivity:
  - FDA may not approve another application for the **same drug** for the **same condition** for **seven years**, subject to exceptions
- Exceptions: Exclusivity may be revoked or overridden if:
  - FDA later determines that the request for designation was materially defective;
  - The applicant is unable to secure sufficient quantities of the drug to meet the needs of patients with the rare disease or condition following approval; or
  - Another drug is the same drug and for the same condition, but is shown to be safer, more effective, or makes a major contribution to patient care

Orphan Drugs: FDA Assistance in Study Design

- Orphan drugs are subject to the same requirements as any other drug seeking NDA/BLA approval
- FDA acknowledges challenges of small population clinical trial development for rare diseases
  - Provides guidance to assist sponsors of orphan drugs in conducting more efficient and successful drug development programs
- FDA Public Meeting, Rare Disease Day 2021 (March 4, 2021) agenda:
  - Rare disease partnerships and collaborations
  - Product development during COVID-19
  - Scientific advancements

Clinical Trials Registry

- ClinicalTrials.gov is a registry and results information database of publicly and privately supported clinical studies of human participants conducted around the world
- Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801) established the registration and reporting of information on "applicable clinical trials" on ClinicalTrials.gov
    - Earlier version of registry focused on NIH-funded studies
- NIH has implementation responsibilities; FDA has compliance and enforcement responsibilities

Clinical Trials Registry: Regulatory Requirements

- Final Rule for Clinical Trials Registration and Results Information Submission (42 C.F.R. Part 11)
  - In 2016, HHS issued a regulation to expand the information about clinical trials and clarify FDAAA 801
  - Final Rule describes requirements for registering and submitting summary results information for certain clinical trials to ClinicalTrials.gov

Clinical Trials Registry: Requirements

- The responsible party for an applicable clinical trial must register the trial and submit information about the results
- Responsible party:
  - Sponsor or sponsor's designee (e.g., principal investigator, CMO)
- Applicable drug clinical trial:
  - Controlled clinical investigations (other than Phase 1 investigations) of any drug or biologic as defined in Section 505 of the FDCA or Section 351 of the Public Health Service Act

Clinical Trials Registry: Requirements

- **When?** The responsible party must submit the required clinical trial information no later than 21 days after enrollment of the first participant
- **Which Trials Must Have Results Information Submitted?** All applicable clinical trials of approved or licensed products that reach their primary completion date
- **When to Submit Results Information?** In general, results information must be submitted by the responsible party no later than 12 months after the primary completion date

Clinical Trials Registry: FDA Compliance

- To certify compliance with ClinicalTrials.gov requirements, FDA requires that applicants complete and submit Form FDA 3674
- The following statement must be included in the informed consent documents of "applicable clinical trials":
  - "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Clinical Trials Registry: Penalties

- Final Guidance, Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank (August 2020)
  - Reviewing evidence collected during inspections and evaluation of complaints
  - Applying risk-based approach to determine enforcement actions
  - Maximum penalties
    - $10,000 for violations adjudicated in a single proceeding
    - Plus $10,000/day for any violation that is not corrected within 30 days following notification of the violation

21st Century Cures Act [Pub. L. 114-255, December 2017]

- Key objectives:
  - Accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently
  - Incorporate patient voices into product development and FDA decision-making
  - Modernize clinical trial designs, including use of real-world evidence and clinical outcome assessments
  - Enable FDA to recruit and retain scientific, technical, and professional experts
- Implementation by FDA:
  - Cures Act appropriated $500 million over 9 years toward FDA implementation
  - FDA developed a work plan and publicly tracks deliverables required by the Cures Act against statutory deadlines

The Cures Act: Patient-Focused Drug Development

- Section 3001: Requires FDA to publish a brief statement explaining how patient experience data and related information was taken into account in the review of a marketing application
- Section 3002: Requires FDA to issue guidance on incorporating patient experience data:
  - Impact of disease, condition, or therapy on patients' lives, and patient preferences regarding treatment
  - Resources: Final Guidance, Patient-Focused Drug Development: Collecting Comprehensive and Representative Input (June 2018); Draft Guidance, Methods to Identify What is Important to Patients (October 2019)
- Section 3004: Directs FDA to issue reports at specific intervals assessing the use of patient experience data in regulatory decision-making

The Cures Act: Real-World Evidence

- Emphasizes use of **real-world data** and **real-world evidence** to support regulatory decision making, including approval of new indications for approved drugs
- Real-world evidence: data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than clinical trials
- Real-world data sources: electronic health records; claims and billing activities; product and disease registries; patient-generated data; data gathered from other sources that can inform on health status, such as mobile devices
- Resources: Framework for FDA's Real-World Evidence Program (December 2018); Draft Guidance, Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry (May 2019); Final Guidance, Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry (July 2018)

The Cures Act: Novel Clinical Trial Designs

- Section 3021: Directs FDA to promote incorporation of complex adaptive designs and other novel trial designs into proposed clinical protocols and NDA/BLAs
  - Adaptive design: allows for planned modifications to aspects of the design based on accumulating data from subjects in the study
  - "Complex" adaptive design: often uses multiple adaptations (e.g., to treatment arm and sample size); adaptations to scientific aspects; simulations to determine operating characteristics
- Resource: Final Guidance, Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products (December 2020)

The Cures Act: Qualification of Drug Development Tools

- Section 3011:
  - Requires FDA to establish a qualification process for DDTs (e.g., biomarkers, clinical outcome assessments) for proposed contexts of use
  - Once a DDT is qualified under this new process, sponsor may use it to support NDA or IND application
- Resource: Final Guidance, Qualification Process for Drug Development Tools (November 2020)
  - Taxonomy for biomarkers and other DDTs
  - Processes for drug sponsors and other requestors to seek qualification of a DDT

Coronavirus Treatment Acceleration Program (CTAP)

- Comprehensive public-private approach to bring coronavirus treatments to market as fast as possible
- Redeploying medical and regulatory staff to serve on review teams dedicated to COVID-19 therapies
- Streamlining processes and operations for developers and scientists to send inquiries and requests
- Providing resources to health care providers and researchers to help them submit emergency requests to use investigational products
- Partnering in public and private sectors to collect and analyze information in areas such as illness patterns and treatment outcomes
- Collaborating with federal partners, developers, and researchers to create protocols that can be used across institutions and programs to streamline efforts

CTAP Update

600+

Drug development programs in planning stages[1]

440+

Trials reviewed by FDA[2]

10

COVID-19 treatments currently authorized for Emergency Use[3]

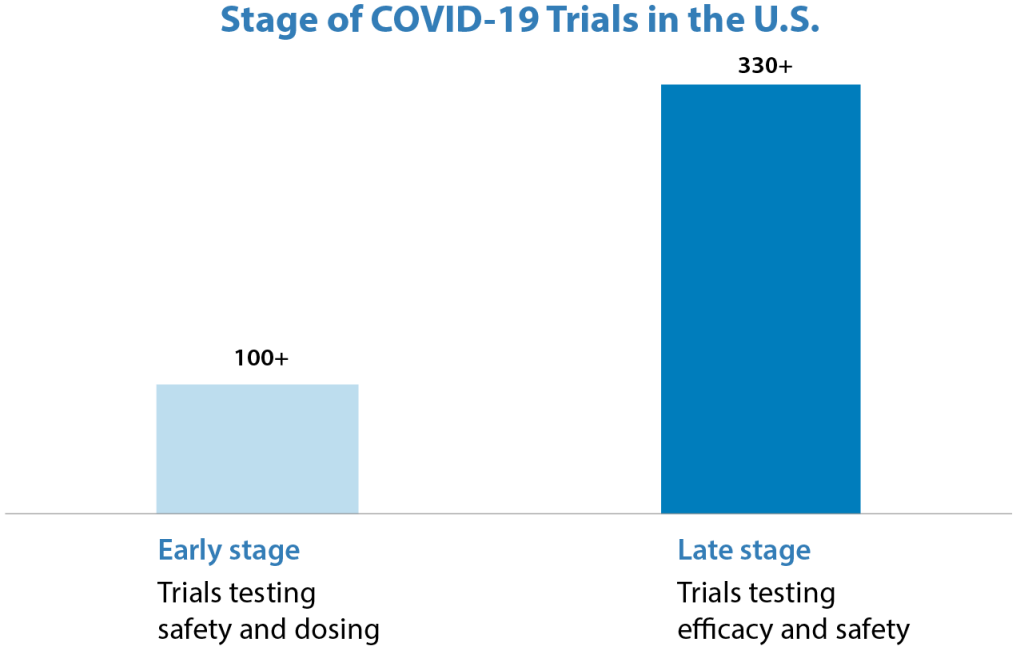
1

Treatments currently approved by FDA for use in COVID-19

*Excludes INDs related to vaccines

**FDA data as of March 31, 2021

CTAP Update



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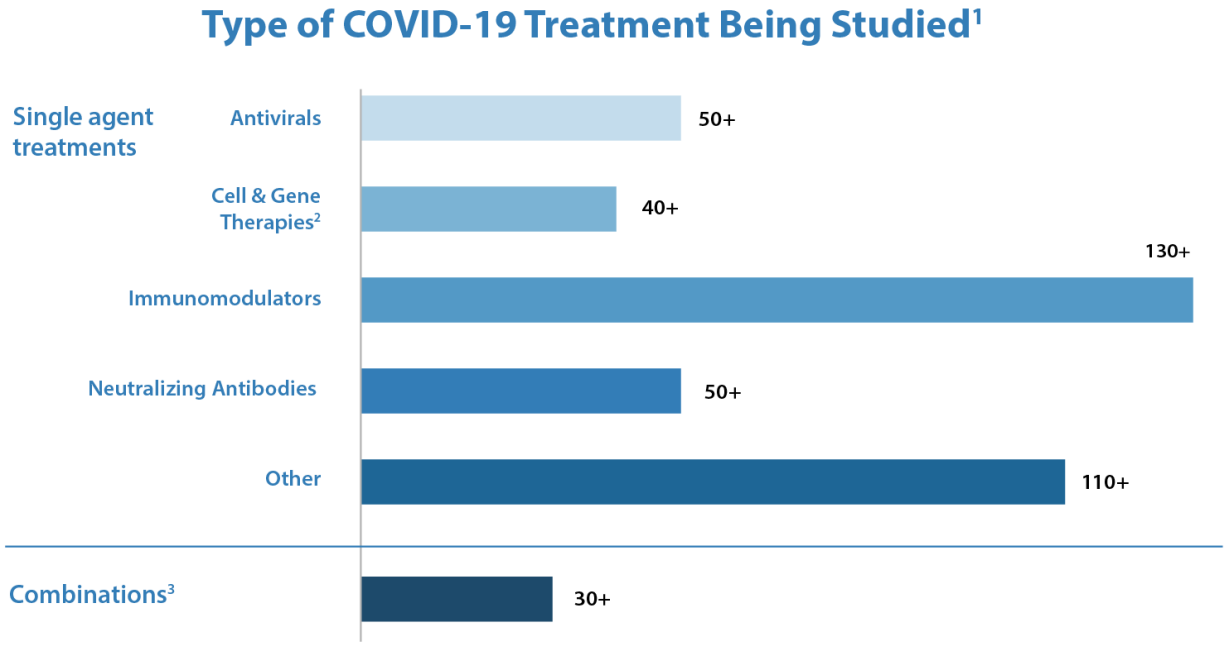
**FDA data as of March 31, 2021

CTAP Update


Type of COVID-19 Treatment Being Studied[1]
Single agent treatments
Antivirals
50+
Cell & Gene Therapies[2]
40+
130+
Immunomodulators
Neutralizing Antibodies
50+
Other
110+
Combinations[3]
30+

Thank you

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