The New Drug Approval Process: New Drug Research and Development

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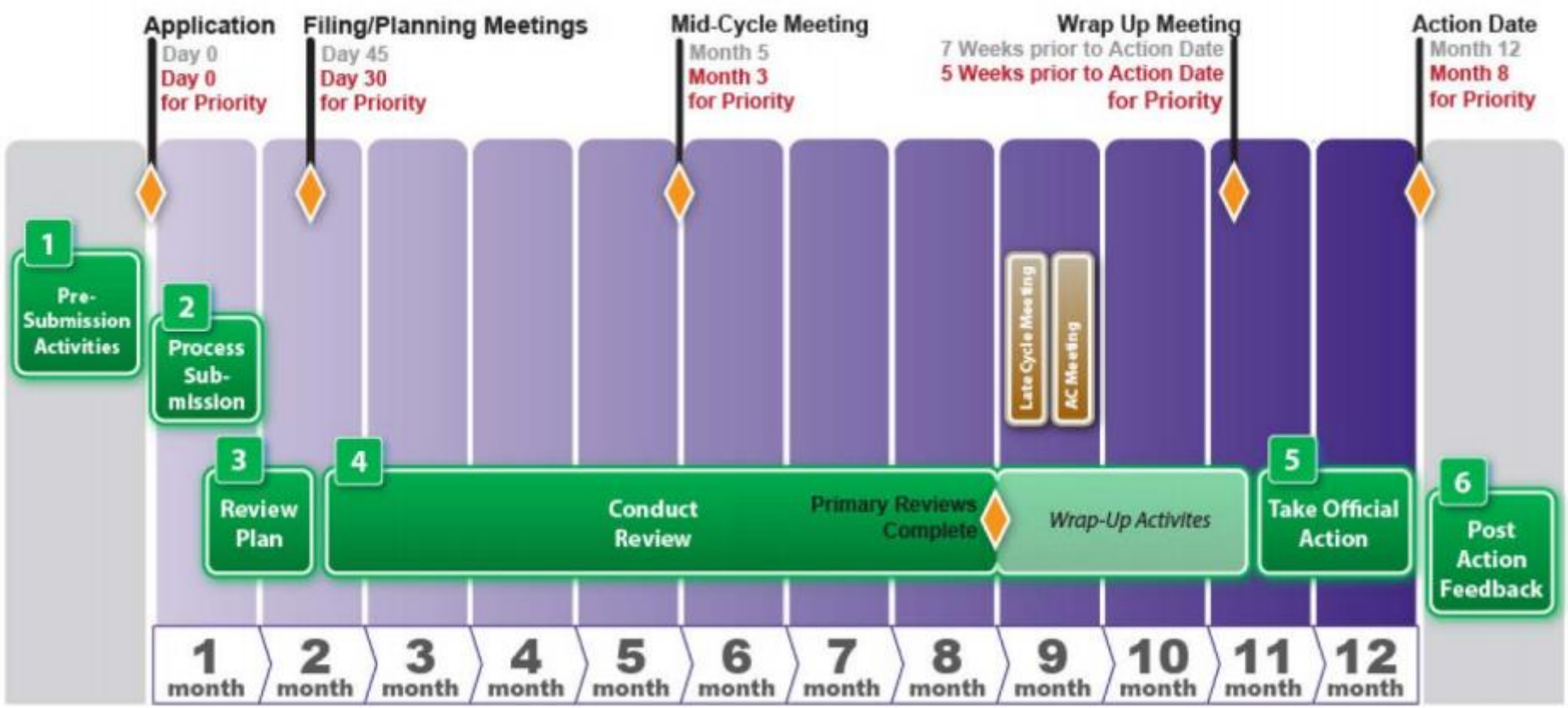
Overview

- Brief intro of content of NDAs (full session on NDA submission and review later today)
- FDA Approval Standards
- FDA Approval Pathways
- Good Laboratory Practices
- Investigational New Drug Applications
- Clinical Trials
- Expedited Review
- Meeting with FDA

FDA Review Timeline



Content of NDA- 21 CFR § 314.50

- Summary
- Chemistry, Manufacturing, and Controls (CMC)
- Nonclinical pharmacology and toxicology
- Human pharmacokinetics and bioavilability
- Microbiology
- Clinical Data
- Statistical

Content of NDA- 21 CFR § 314.50 continued

- Pediatric use
- Samples, packaging, and labeling
- Case reports
- Patent information
- Investigator disclosures and certifications
- Cover letter

What Does FDA Approval Mean?

- Benefits outweigh known and potential risks for the intended patient population
- How are drugs reviewed?
  - Analysis of the target condition
  - Assessment of benefits and risks
  - Strategies for managing risks

Standards for Approval of New Drugs

- Safety and Effectiveness
- Substantial Evidence
- Risk/Benefit Analysis

Safety and Effectiveness

- Preclinical and clinical data showing that the drug is safe and effective for the proposed use
- Information about components
- Information about the drug's formulation
- Discussion of manufacturing methods and facilities
- Proposed labeling

Substantial Evidence

- FDA cannot approve an NDA if:
  - The FDA determines that the application does not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling
  - Lack of substantial evidence that the drug is effective
- "Substantial evidence"
  - Means evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling
- Federal Food, Drug, and Cosmetic Act Section 505(d)

Adequate and Well-Controlled Investigations

- The “gold standard”
  - Double-blind
  - Randomized
  - Controlled
- 21 CFR § 314.126

Risk/Benefit Analysis

- Analysis takes into account:
  - Safety and effectiveness
  - Nature and severity of the condition the drug is intended to treat or prevent
  - Benefits and risks of other available therapies for the condition
  - Risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks
- Can change over time
  - Post-approval pharmacovigilance
  - Approval of other products and affect risk/benefits for the approved product

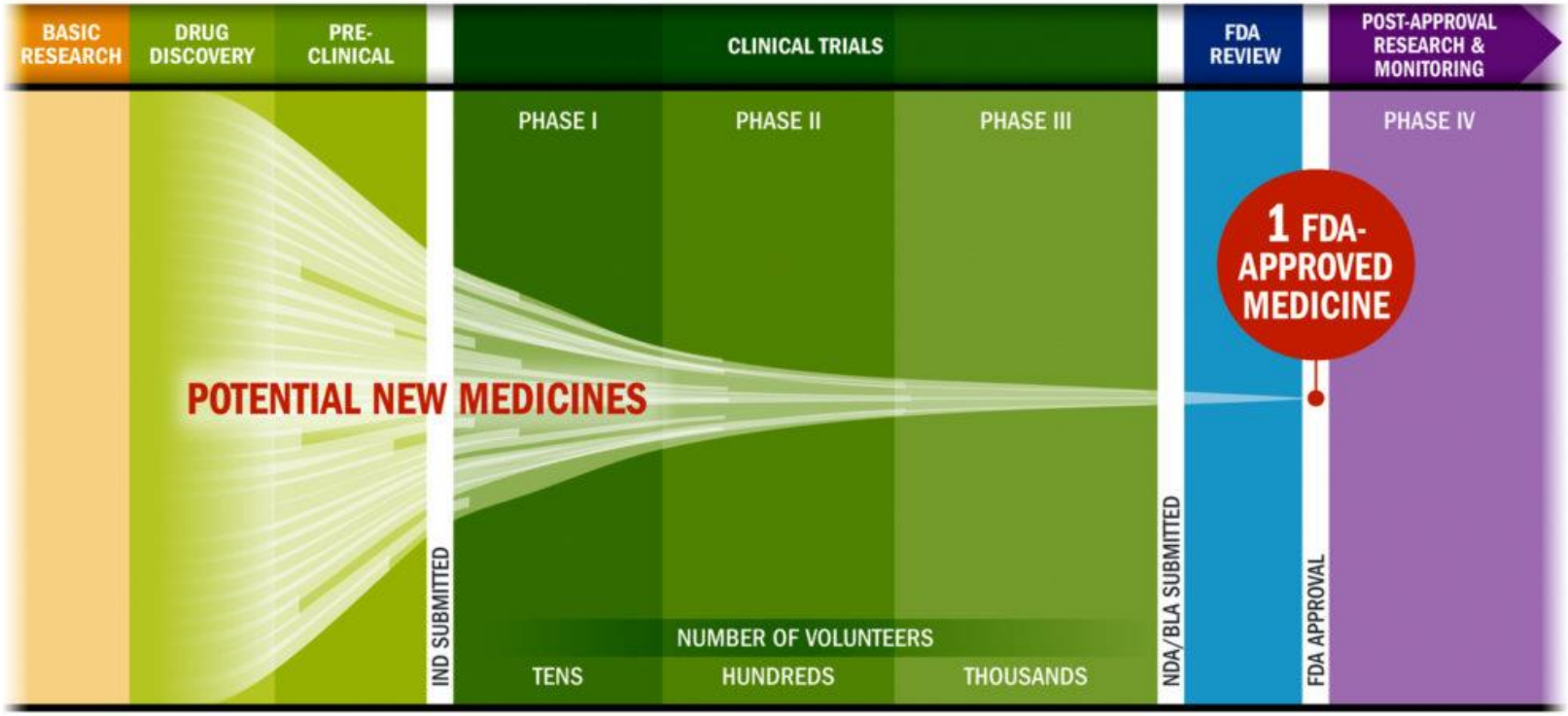
Quick Review on Standards for Approval

- No efficacy threshold
- No requirement that new drugs be “better” than drugs that are already approved
- Price ($) is not considered by FDA

New Drug Approval Pathways

- Section 505 of the Federal Food, Drug, and Cosmetic Act describes three types of new drug applications:
  - New Drug Application (NDA)— an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1));
  - Abbreviated New Drug Application (ANDA)— an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j))
  - A hybrid of NDA/ANDA— an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2))
- Relatedly, for Biologics
  - Regulated as a drug under the Federal Food, Drug and Cosmetic Act
  - Approved under the Public Health Services Act

Every step is regulated



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf (accessed Jan. 20, 2015).

Source: Phrma http://www.phrma.org/images/main/Clinical-Trial-Chart.jpg

"Good Laboratory Practice" (GLP) Regulations

- 21 CFR Part 58
- Describes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA
- Compliance with this part is intended to assure the quality and integrity of the safety data
- Includes:

• Personnel • Facilities • Equipment • SOPs	• Protocols • Controls • Records and Reports • Disqualification

Preclinical Studies

- Safe to begin testing in humans
- Starting dose and range
- In vitro- “within glass”
- In vivo- “within the living”

Preclinical Data Requirements

- Preclinical data is about basic safety
- Preclinical safety testing should consider:
  - Selection of the relevant animal species;
  - Age;
  - Physiological state;
  - The manner of delivery, including dose, route of administration, and treatment regimen; and
  - Stability of the test material under the conditions of use
- In some cases, lack of full GLP compliance does not necessarily mean that the data from these studies cannot be used to support clinical trials and marketing authorizations.

Investigational New Drug Application (IND)

- Requests that the FDA authorize administration of an investigational new drug to humans
- IND approval is required prior to shipping interstate
- Exemptions for off-label use

Investigational New Drug (IND) Applications

- 21 CFR Part 312
- IND= a request for FDA for authorization to administer an investigational drug to humans.
- Must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application.
- Developers must include:
  - Animal study data and toxicity (side effects that cause great harm) data
  - Manufacturing information
  - Clinical protocols (study plans) for studies to be conducted
  - Data from any prior human research
  - Information about the investigator

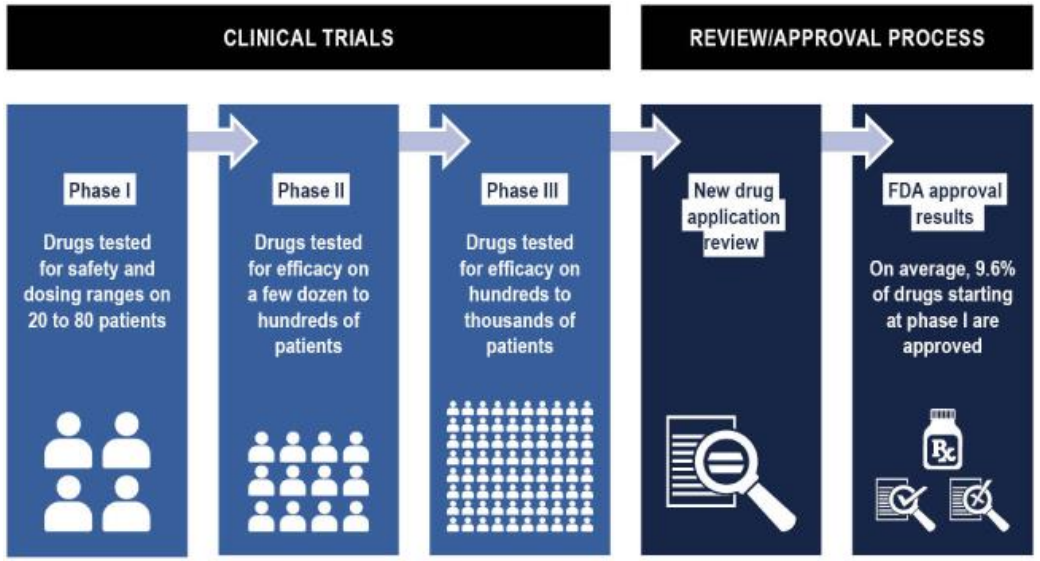
IND Content and Format

- Cover Sheet (Form FDA 1571)
- Table of Contents
- Introductory Statement
- General Investigational Plan
- Investigator's Brochure
- Protocol
- Chemistry, Manufacturing and Control Information
- Pharmacology and Toxicology Information
- Previous Human Experience with the Investigational Drug

Regulatory Resources

21 CFR Part 201	Drug Labeling
21 CFR Part 312	Investigational New Drug Application
21 CFR Part 314	NDA and ANDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21 CFR Part 316	Orphan Drugs
21 CFR Part 50	Protection of Human Subjects
21 CFR Part 54	Financial Disclosure by Clinical Investigators
21 CFR Part 56	Institutional Review Boards
21 CFR Part 58	Good Lab Practice for Nonclinical Laboratory Studies
21 CFR Part 11	Electronic Records; Electronic Signatures

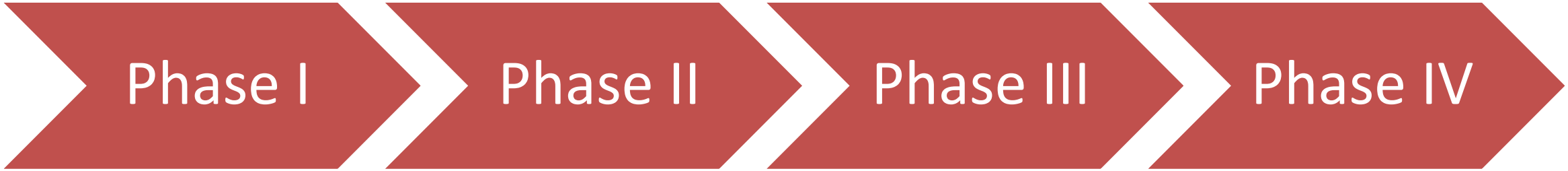
Clinical Trials



Source: GAO analysis of FDA data. | GAO-17-564

Note: According to FDA officials, there can be wide variation in the number of patients involved in the different clinical trial phases, and when a new drug is being tested for a life-threatening ailment, the drug development process may be expedited by going through only one or two phases of clinical trials before an application is submitted to FDA for marketing approval.

Clinical Trials



Designing Clinical Trials

- Who qualifies to participate (selection criteria)?
- How many people will be part of the study?
- How long the study will last?
- Whether there will be a control group and other ways to limit research bias?
- How the drug will be given to patients and at what dosage?
- What assessments will be conducted, when, and what data will be collected?
- How the data will be reviewed and analyzed?

Phase I

- Study Participants: 20 to 100 healthy volunteers or people with the disease/condition
- Length of Study: Several months
- Purpose: Safety and dosage
- According to FDA: Approximately 70% of drugs move to the next phase

Phase II

- Study Participants: Up to several hundred people with the disease/condition
- Length of Study: Several months to 2 years
- Purpose: Efficacy and side effects
- According to FDA: Approximately 33% of drugs move to the next phase

Phase III

- Study Participants: 300 to 3,000 volunteers who have the disease or condition
- Length of Study: 1 to 4 years
- Purpose: Efficacy and monitoring of adverse reactions
- According to FDA: Approximately 25-30% of drugs move to the next phase

Phase IV

- Post-approval
- Study Participants: Several thousand volunteers who have the disease/condition
- Purpose: Safety and efficacy

Before beginning clinical trials

- Sponsor must have submitted IND
- IND must be “in effect”
  - 30 days after FDA receives the application, unless FDA notifies the sponsor that the investigations described in the application are subject to a Clinical Hold; or
  - on earlier notification by FDA that the clinical investigations in the IND may begin.
- Sponsor and clinical investigator must comply with:
  - Informed Consent (21 CFR 50)
  - Institutional Review Board (21 CFR 56)

Informed Consent

- No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent (21 CFR 50)
- Circumstances must provide the subject the opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence
- Information must be given in a language understandable to the subject
- No waiving of any of the subject's legal rights or release investigator or sponsor from liability for negligence

Informed Consent is More than a Signature

- Informed Consent Information Sheet, Draft Guidance for IRBs, Clinical Investigators, and Sponsors (July 2014)
- Informed consent involves providing a potential subject with
  - Adequate information to allow for an informed decision about participation in the clinical investigation
  - Facilitating the potential subject's comprehension of the information
  - Providing adequate opportunity for the potential subject to ask questions and to consider whether to participate
  - Obtaining the potential subject's voluntary agreement to participate
  - Continuing to provide information as the clinical investigation progresses or as the subject or situation requires

Institutional Review Board (IRB)

- IRB= administrative body established to protect the rights and welfare of human research subjects recruited to participate in research
- Protects the welfare, rights, and privacy of human subjects
- At least five members, with varying backgrounds

Responsibilities of Sponsors

- Selecting investigators: A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.
- Control of drug: A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

Responsibilities of Investigators

- Investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations
- Protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.
- Obtain the informed consent of each human subject to whom the drug is administered
- Reports:
  - Progress
  - Safety
  - Final
  - Financial disclosure

FDA Form 1572

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

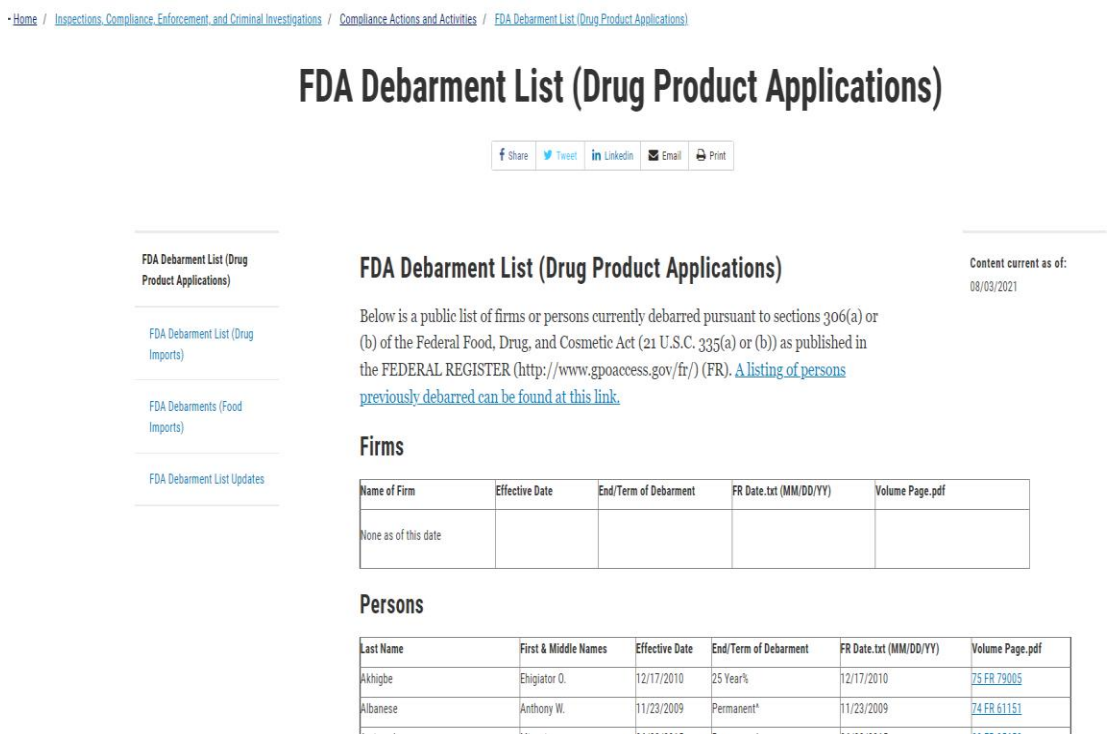
I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)

- If FDA has information indicating that an investigator (including a sponsor-investigator) has *repeatedly or deliberately* failed to comply with the requirements of an IND, IRB, or Protection of Human Subjects, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report, the FDA will give the investigator an opportunity to explain
- If an explanation is offered and accepted by the FDA, the disqualification proceeding ends
- If an explanation is offered but not accepted, the investigator will be given an opportunity for a regulatory hearing

Disqualification of Investigators/Debarment

- A disqualified clinical investigator is not eligible to receive investigational drugs, biologics, or devices, and is not eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA
- FDA publishes a Debarment list ("Investigator blacklist")



Home / Inspections, Compliance, Enforcement, and Criminal Investigations / Compliance Actions and Activities / FDA Debarment List (Drug Product Applications)

FDA Debarment List (Drug Product Applications)

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FDA Debarment List (Drug Product Applications)
FDA Debarment List (Drug Imports)
FDA Debarments (Food Imports)
FDA Debarment List Updates

FDA Debarment List (Drug Product Applications)

Content current as of: 08/03/2021

Below is a public list of firms or persons currently debarred pursuant to sections 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335(a) or (b)) as published in the FEDERAL REGISTER (http://www.gpoaccess.gov/fr/) (FR). A listing of persons previously debarred can be found at this link.

Firms

Name of Firm	Effective Date	End/Term of Debarment	FR Date.txt (MM/DD/YY)	Volume Page.pdf
None as of this date				

Persons

Last Name	First & Middle Names	Effective Date	End/Term of Debarment	FR Date.txt (MM/DD/YY)	Volume Page.pdf
Akhigbe	Ehigiator O.	12/17/2010	25 Year%	12/17/2010	75 FR 79005
Albanese	Anthony W.	11/23/2009	Permanent*	11/23/2009	74 FR 61151

Role of Contract Research Organizations (CROs)

- *Contract research organization* means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor:
  - Design of a protocol
  - Selection or monitoring of investigations
  - Evaluation of reports
  - Preparation of materials to be submitted to the FDA. 21 CFR § 312.3
- A sponsor may transfer responsibility for any or all of its obligations to a CRO

Clinical Hold

- A clinical hold is an order issued by FDA to the sponsor of an IND application to delay a proposed clinical investigation or to suspend an ongoing investigation.
- When a proposed study is placed on clinical hold, subjects may not be given the investigational drug.
- When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and given the investigational drug; patients already in the study are expected to be taken off therapy involving the investigational drug unless treatment continuation is specifically permitted by FDA in the interest of patient safety.

Grounds for imposition of clinical hold:

- The grounds for imposition of clinical hold for a proposed or ongoing Phase 1 investigation include the following:
  - Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury; or
  - The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND; or
  - The investigator brochure is misleading, erroneous, or materially incomplete; or
  - The IND application does not contain sufficient information needed to assess the risks to subjects of the proposed studies; or
  - The IND application is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring).
- The grounds for imposition of clinical hold for a proposed or ongoing Phase 2 or Phase 3 investigation include the following:
  - Any of the conditions described above as for Phase 1 investigations; or
  - The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

Clinical Trial Registration and Reporting

- Registration on **ClinicalTrials.gov** is required for studies that meet the definition of an "applicable clinical trial" (ACT) and either were initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007.
- ACTs, as defined in section 402(j) of the PHS Act, include the following:
  - Controlled clinical investigations (other than phase 1 investigations) of any U.S. Food and Drug Administration (FDA)-regulated drug or biological product for any disease or condition
  - Certain studies of FDA-regulated medical devices, excluding small clinical trials to determine feasibility and certain clinical trials to test prototype devices, but including FDA-required pediatric postmarket surveillances of a device product
- ACTs generally include interventional studies (with one or more arms) of FDA-regulated drug, biological, or device products that meet one of the following conditions:
  - The trial has one or more sites in the United States
  - The trial is conducted under an FDA investigational new drug application or investigational device exemption
  - The trial involves a drug, biological, or device product that is manufactured in the United States or its territories and is exported for research

Who is responsible for Clinical Trial Registration and Reporting?

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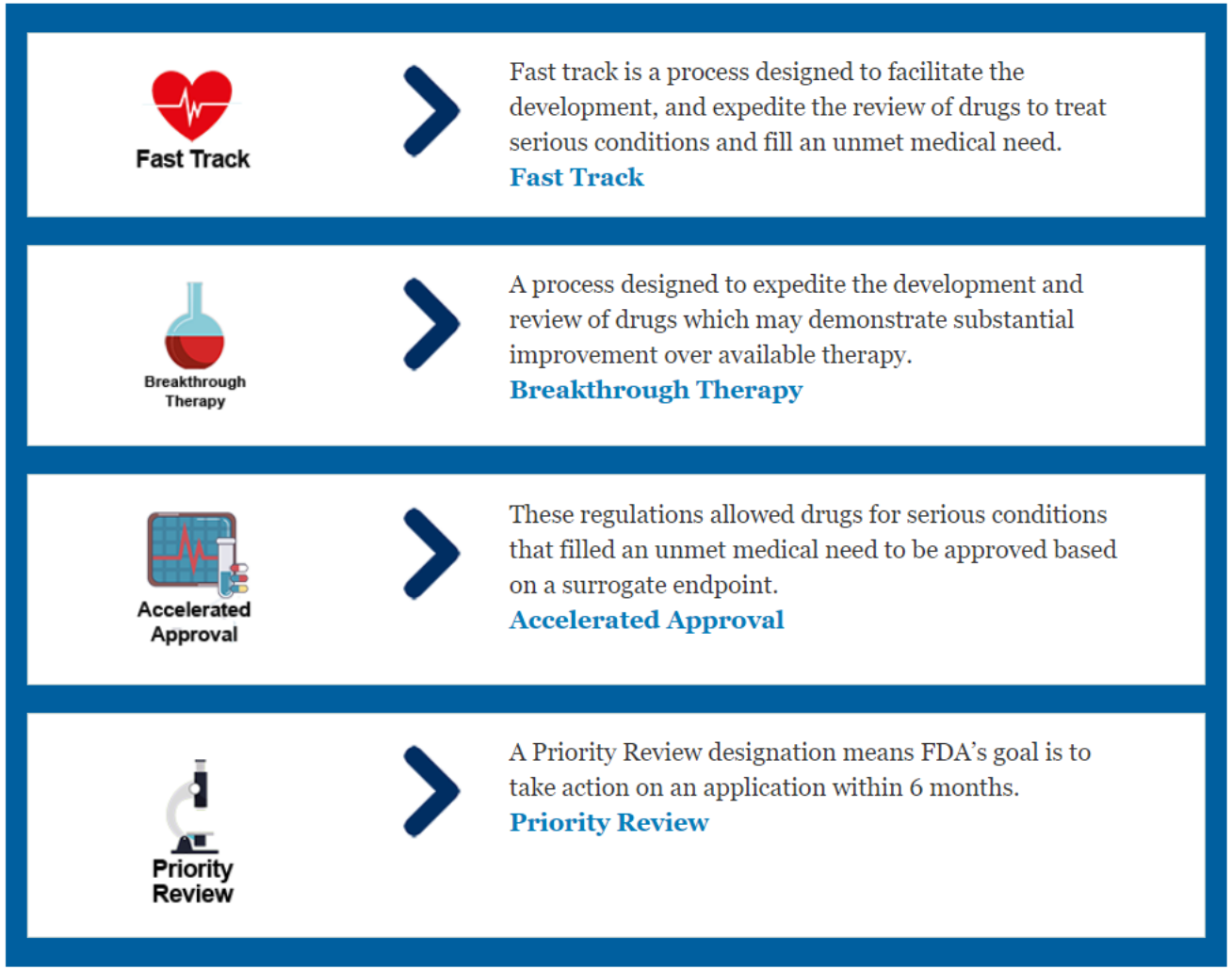
- Responsible party means, with respect to a clinical trial, the **sponsor of the clinical trial**, as defined in 21 CFR 50.3; or the **principal investigator** of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this part for the submission of clinical trial information. For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party is the entity who FDA orders to conduct the pediatric postmarket surveillance of the device product.

42 CFR § 11.10(a)

When and Why must registration and reports be made to ClinicalTrials.gov?

- 21 calendar days after the first human subject is enrolled
- Failure to Register and Submit information is a prohibited act under one or more provisions of section 301(jj) of the Federal Food, Drug, and Cosmetic Act
  - Civil or Criminal Penalties
  - Grants
- 42 CFR PART 11 - CLINICAL TRIALS REGISTRATION AND RESULTS INFORMATION SUBMISSION

Expedited Programs



Fast Track

- Eligibility: Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need
  - If there are available therapies, a fast track drug must show some advantage over available therapy
- Benefits of receiving Fast Track
  - More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
  - More frequent written communication from FDA about such things as the design of the proposed clinical trials and use of biomarkers
  - Eligibility for *Accelerated Approval and Priority Review, if relevant criteria are met*
  - *Rolling Review*, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA
- *Fast Track* designation must be requested by the drug company
- The request can be initiated at any time during the drug development process. FDA will review the request and make a decision within sixty days based on whether the drug fills an unmet medical need in a serious condition

Break Through Therapy

- Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint
  - Clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality or on symptoms that represent serious consequences of the disease
- A drug that receives Breakthrough Therapy designation is eligible for:
  - All Fast Track designation features
  - Intensive guidance on an efficient drug development program, beginning as early as Phase 1
  - Organizational commitment involving senior managers
- Requested by the sponsor

Accelerated Approval

- Food and Drug Administration Safety Innovations Act (FDASIA) allows the FDA to base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint
  - Surrogate endpoint is a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit
  - Intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality
- Phase IV confirmatory trials to verify clinical benefit

Priority Review

- Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).
- A *Priority Review* designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications
  - Evidence of increased effectiveness in treatment, prevention, or diagnosis of condition
  - Elimination or substantial reduction of a treatment-limiting drug reaction
  - Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
  - Evidence of safety and effectiveness in a new subpopulation
- FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original application

Meeting with FDA

- Informal
- Formal
  - Type A
  - Type B
  - Type C

Meeting with FDA- Type A Meeting

- Dispute resolution meetings
- Meetings to discuss clinical holds in which development is stalled and a new path forward should be discussed
- Special protocol assessment meetings that are requested by sponsors or applicants after receipt of FDA evaluation of protocols under the special protocol assessment procedures
- Post-action meetings requested by the sponsor within 3 months after an FDA regulatory action other than an approval

Meeting with FDA- Type B Meeting

- Pre-investigational new drug application (pre-IND) meetings
- Certain end-of-phase 1 meetings
- End-of-phase 2 and pre-phase 3 meetings
- Pre-new drug application (pre-NDA) pre-biologics license application (pre-BLA) meetings
- Meetings regarding risk evaluation and mitigation strategies (REMS) or post-marketing requirements that occur outside the context of the review of a marketing application
- Post-action meetings requested by the sponsor 3 months or more after an FDA regulatory action other than an approval
- Meetings held to discuss the overall development program for products granted Breakthrough Therapy designation status

Meeting with FDA- Type C Meeting

- Any meeting other than a type A or type B regarding the development and review of a product
- Examples:
  - A written response to questions posed in pre-IND or Type C meeting requests may be requested by the sponsor
  - FDA may determine that a written response would be the most appropriate means for responding to a meeting request
  - FDA shall notify the requester of the date it intends to send the written response
  - FDA shall provide this notification within the specified time frame for responding to the meeting request

Tips on Requesting a Meeting with FDA

- Meeting Requests/Packages should include the following:
  - Product name and application number (if applicable)
  - Chemical name and structure
  - Proposed indication
  - Dosage form, route of administration, and dosing regimen (frequency and duration)
  - An updated list of sponsor or applicant attendees, affiliations, and titles
  - A background section that includes:
    - A brief history of the development program
    - The events leading up to the meeting
    - The status of product development
    - A brief statement summarizing the purpose of the meeting.
  - A proposed agenda
  - A list of the final questions for discussion grouped by discipline and with a brief summary for each question to explain the need or context for the question
  - Data to support discussion organized by discipline and question

Questions

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