The FDA Approval Process for Drugs

Lee H. Rosebush
BakerHostetler

Overview

- Submission & Filing of NDAs/BLAs
- Approval Standards
- The Review Process
- Expedited Review
- Meeting with FDA
- Approval or other options

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

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

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

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

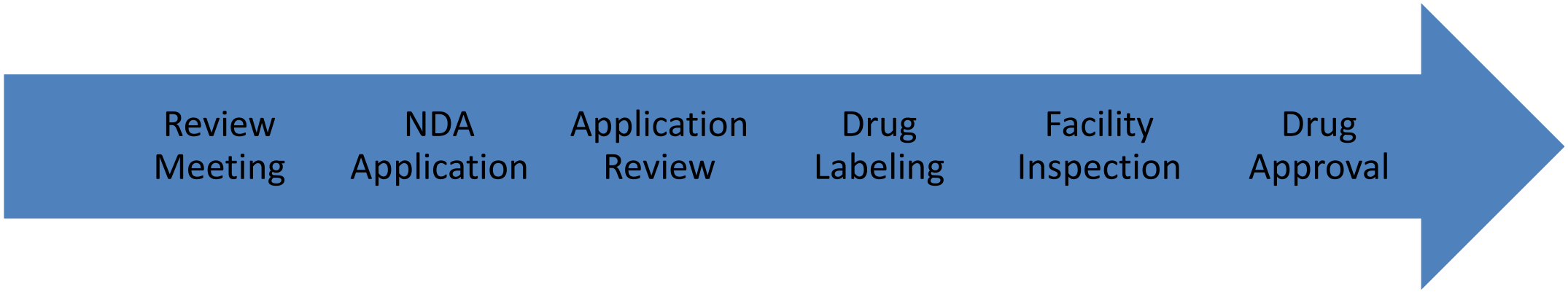
Quick Review on Standards for Approval

- 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

NDA Review


Review Meeting
NDA Application
Application Review
Drug Labeling
Facility Inspection
Drug Approval

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

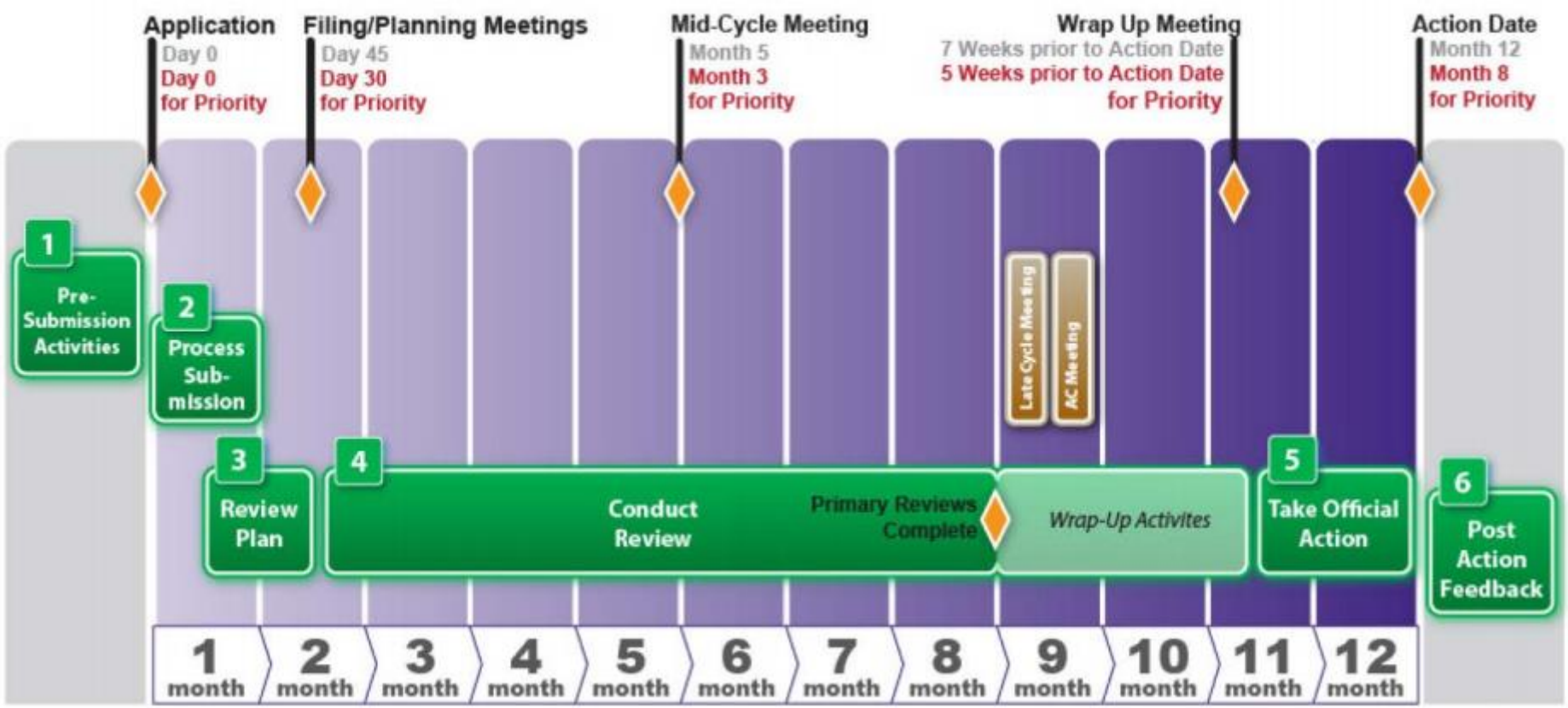
Content of NDA- 21 CFR § 314.50 continued

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

Application Review

- FDA has 60 days to review application
- Review application for completeness
- If complete, FDA will “file” NDA
  - Review team is assigned to evaluate research on the safety and effectiveness
    - Review teams composed of:
      - Project manager
      - Medical Officer
      - Pharmacology/Toxicology Specialist
      - Statistician
      - Clinical Pharmacology/Biopharmaceutics
      - Chemists/Biologists/Microbiologists

FDA Review Timeline



NDA or ANDA

NDA	ANDA
“Substantial Evidence”	Reference to an approved drug
Safety data	Sameness
Full reports on clinical studies	Bioequivalence

Abbreviated New Drug Application (ANDA)

- "Section 505(j) application"
- Application shows that the generic drug is comparable to the reference listed drug (RLD)
- Certification for each patent that claims the RLD
  - Paragraph IV Patent Certification
- Suitability petition (in some cases)
- "Sameness"

ANDA — Sameness

- Generic drug applicant must show that it is the same as the RLD
- Identical with respect to:
  - Active ingredient
  - Dosage form
  - Strength
  - Route of Administration
  - Conditions of use

ANDA — Suitability Petition

- Certain differences between a RLD and a proposed generic drug product may be permitted in an ANDA if these differences are the subject of an approved suitability petition submitted under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act, and pursuant to 21 CFR 314.93.
- An applicant may submit a suitability petition to the FDA requesting permission to submit an ANDA for a generic drug product that differs from a RLD in its:
  - Route of administration,
  - Dosage form,
  - Strength, or
  - If it has one different active ingredient in a fixed-combination drug product.
- A generic applicant cannot submit an ANDA for such a product that differs from the RLD until FDA has approved the suitability petition

ANDA — Bioequivalence

- Evidence demonstrating that the drug product is bioequivalent to the RLD
- Bioequivalence means:
  - The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (21 CFR 320.1(e))
- In Bioequivalence studies, the exposure profile of a test drug product is compared to that of a reference drug product
- A complete study report must be submitted for the bioequivalence study upon which the applicant relies for approval

Hybrid application: 505(b)(2) Pathway

- A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted“
- Applications typically rely on:
  - Published literature
  - FDA’s finding of safety and effectiveness for an approved drug

Examples of 505(b)(2) Applications

- Change of Dosage form
  - Such as a change from a solid oral dosage form to a transdermal patch, that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug
- Change of Strength
- Different Route of Administration
  - Such as a change from an intravenous to intrathecal route
- Substitution of an active ingredient in a combination product

Drug Master Files (DMFs)

- DMFs are submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products
- May be referenced by DMF holder or authorized persons
- Types of DMFs:
  - Type II Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation; or Drug Product
  - Type III Packaging Material
  - Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
  - Type V FDA-Accepted Reference Information

Biologics (BLAs)

- Biologics are approved under Section 351 of the Public Health Service Act
- *See* FDLI's introductory courses or webinars on biologics for more information
- Brief overview of biologics
  - Biologics are drugs but not all drugs are biologics

A biological product is any of the following applicable to the prevention, treatment, or cure of a disease or condition of human beings			
Virus	Therapeutic serum	Toxin	Antitoxin
Vaccine	Blood	Blood component or derivative	Allergenic product
Protein	Analogous product	Arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound)	

Approval Standards of BLAs

- The product, the manufacturing process, and the manufacturing facilities meet applicable requirements to ensure continued **safety, purity and potency**
  - Safety means the relative freedom from harmful effects, direct or indirect, when a product is prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time
  - Purity means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances
  - Potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests, to yield a given result (including effectiveness 21 CFR § 600.3(s))

Compare Drug Approval to Biologic Licensure

Drug Approval	Biologic Licensure
Approved under the Federal Food Drug and Cosmetic Act	Licensed under the Public Health Service Act
NDA – 505(b)(1)	BLA – 351(a)
505(b)(2)	Biosimilar application under section 351(k)
ANDA – 505(j)	

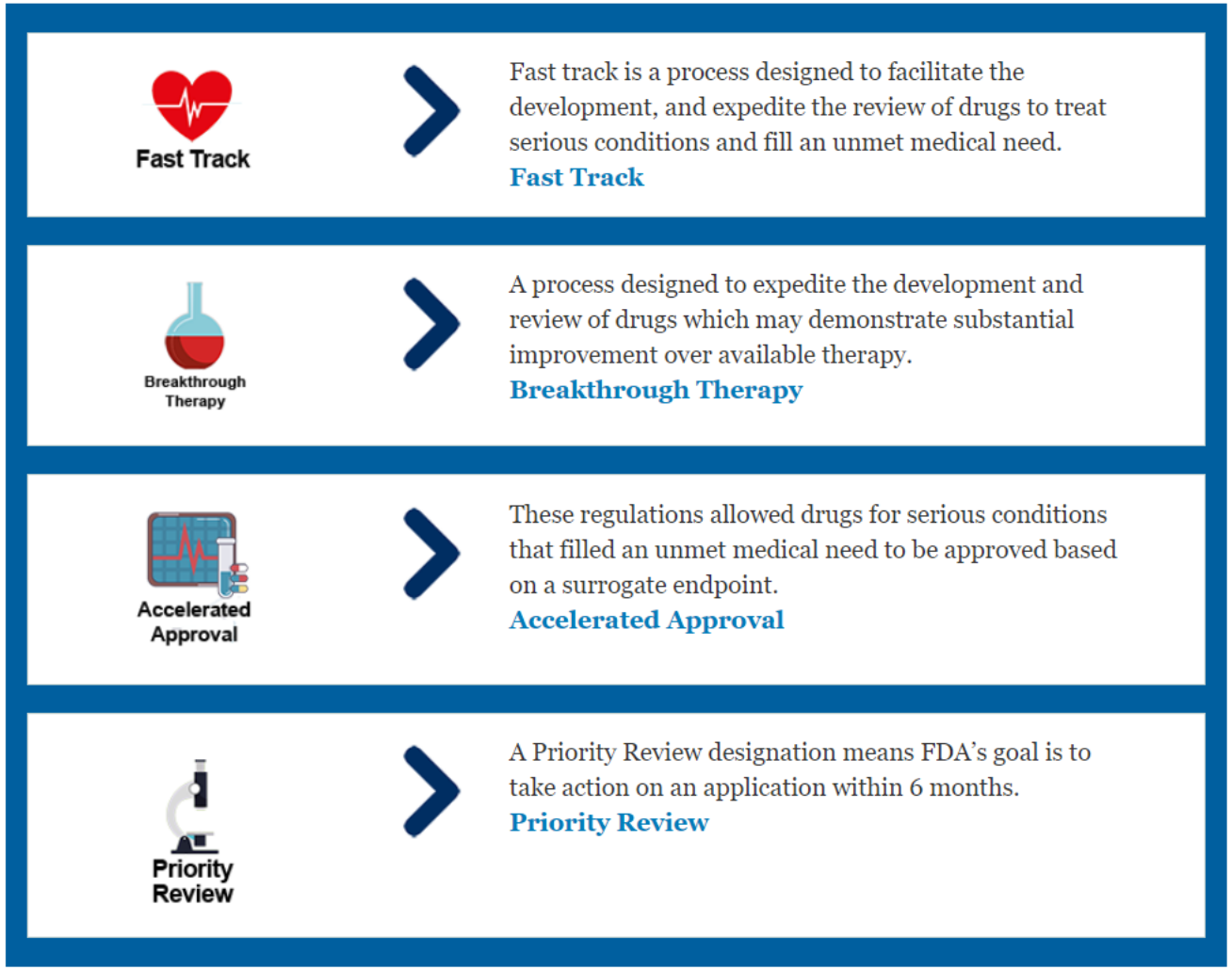
Biosimilar Application

- Demonstrate that the biological product is biosimilar to a single reference product (BLA)
  - The biological product is **highly similar to** the reference product notwithstanding minor differences in clinically inactive components; and
  - **No clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product
- Reference product is a single biological product, licensed under section 351(a) of the PHS Act, against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.

Biosimilarity (remember Sameness for ANDAs)

- Biosimilar to a reference product
- Same mechanism of action for the proposed condition of use
- Same Condition of use proposed in labeling as previously approved for the reference product
- Same route of administration
- Same dosage form
- Same strength as the reference product
- Manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent

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/Pacakges 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

FDA Approval

- If FDA determines that application drug is safe and effective, it approves the application
- Otherwise, FDA issues a complete response letter

Complete Response Letter

- FDA will send the applicant a complete response letter if the agency determines that it will not approve the application or abbreviated application
  - Description of specific deficiencies
  - Based o a complete review of data submitted in an original application or abbreviated application
  - Recommendation of actions for approval
- Applicant actions *a*fter receiving a complete response letter
  - Resubmission
  - Withdrawal
  - Request opportunity for hearing
- Failure to take action - FDA may consider an applicant's failure to take any of such actions within 1 year after issuance of a complete response letter to be a request by the applicant to withdraw the application, unless the applicant has requested an extension of time in which to resubmit the application

Questions

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