The Active IND and Available Development Programs

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FDA Disclaimer

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Active IND
Sponsor's responsibilities

- Protocol amendments
- Information amendments
- Safety Reporting
- Pediatric Study Plans
- Annual Reports
- Inactivation of an IND
- Withdrawal of an IND

Protocol Amendments

21 CFR 312.30

- New Protocol
- Change in Protocol
- New Investigator

Protocol Amendments

- **New Protocol**
  - FDA Form 1571
    - 11. **Protocol Amendment**/New Protocol
  - Copy of the new protocol
  - Brief description of the most clinically significant differences between the new and previous protocols
- Study may begin provided that
  - The Sponsor has submitted the New Protocol to FDA
  - The Protocol has been approved by the Institutional Review Board (IRB)

Protocol Amendment
Change in Protocol (1)

- **Change in Protocol**
  - FDA Form 1571
    - 11. **Protocol Amendment** /Change in Protocol
  - Phase 1-Any change that significantly affects the safety of the subjects
  - Phase 2 and 3- Any change that significantly affects the safety of the subjects, the scope of the investigation, and/or the scientific quality of the study

Protocol Amendment
Change in Protocol (2)

- Increase in drug dosage or duration of exposure
- Any significant increase in the number of subjects under the study
- Any significant change in the design of the protocol (control group)
- Addition of a new test or procedure intended to improve the monitoring or reduce the risk of a side effect or adverse event

Protocol Amendment
Change in Protocol (3)

- Change may be implemented when
  - The Sponsor has submitted the revised Protocol to FDA
  - The Protocol has been approved by the Institutional Review Board (IRB)
- A protocol change intended to eliminate and apparent immediate hazard to subjects may be implemented immediately provided that
  - FDA is subsequently notified by protocol amendment
  - IRB is notified according 21 CFR 56.104 (c)

Protocol Amendment
Best practice

- Cover letter
  - Study Phase
  - Statement as to whether the study is intended to support a marketing application/labeling change
  - Study objective
  - Population
  - Brief description of study design
  - Specific concerns for which you anticipate the Division might have comments

Protocol Amendment-Best practice

- For changes in protocol
  - Brief description of the change and reference (date and number) to the submission that contained the original protocol
    - Track changes and clean version of the protocol change
  - Other significant changes
  - Proposed implementation date

Protocol Amendment
New Investigator

- **New Investigator**
  - FDA Form 1571
    - 11. **Protocol Amendment** /New Investigator
  - Once the Investigator is added, the investigational drug can be shipped and the investigator may begin participating in the study
  - Notification to FDA shall be made within 30 days of the investigator being added to the study

Protocol Amendment
New Investigator

- Investigators name
- Qualification to conduct the investigation
- Reference to previously submitted protocols
- Other information as requested by 21 CFR 312.23 (a) (6)(iii)(b)
- Information Sheet Guidance for Sponsor's, Clinical Investigators, and IRBs
  - https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

Protocol Amendments Timelines

- **New Protocol and Protocol Change** submitted before implementation
- **New Investigator and/or Update information on investigator** can be submitted at 30-day intervals

Information Amendments
21 CFR 312.31

Any essential information not within the scope of a protocol amendment, IND safety report or annual report

- Chemistry/Microbiology
- Pharmacology/Toxicology
- Clinical
- Statistics
- Clinical Pharmacology

Information Amendments

- FDA Form 1571
  - 11. **Information Amendment**
- Statement of the nature and purpose of the submission
  - New toxicology, chemistry or other technical information
  - Discontinuation of investigation
  - Request for comment
  - Specific questions

IND Safety Reporting Regulations

- IND Safety Reporting (21 CFR 312.32)
  - Requirements for expedited reporting under an IND
- Investigator Reports (21 CFR 312.64)
  - Reporting requirements from investigators to sponsors
- Applicability of requirements regarding an IND application (21 CFR 320.31)
  - Requirements for bioavailability/bioequivalence expedited reporting

Pediatric Study Plans (PSP)

- Food and Drug Administration Safety and Innovation Act (FDASIA), 2012
- Initial Pediatric Study Plan (iPSP) with 60 days of an End-of-Phase 2 meeting
  - Guidance for Industry: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf .

Pediatric Study Plan

- Outline of pediatric studies
- Request for deferral, partial waiver or full waiver
- Supporting documentation
- Previously negotiated pediatric plans with other regulatory authorities
- Failure to include and agreed iPSP with a marketing application could result in a refuse to file action.

Pediatric Study Plan

- Division of Pediatric and Maternal Health
  - 301-796-2200
  - Pedsdrugs@fda.hhs.gov
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

Annual Report

21 CFR 312.33

- Report of the progress of the investigation
  - Individual Study Information-Summary of the status of each study in progress during the previous year
    - Title of the Study(ies), purpose, brief description of the patient population and indication if the study(ies) is/are complete
    - Total number of subjects initially planned for inclusion, number of subjects included to date, number of subjects who dropped from the study, etc.
    - If study has been completed, a summary of interim results or description of results

Annual Report (2)

- Summary Information obtained in the previous year's clinical and non clinical investigations
  - Narrative or tabular summary showing most frequent and serious adverse experiences by body system
  - Summary of all IND safety reports submitted the past year
  - List of subjects who died, with cause of death
  - List of subjects who dropped out in association with any adverse events

Annual Report (3)

- Brief description of any information deemed to further understanding of the drug's actions
- List of preclinical studies completed or in progress
- A summary of any significant manufacturing or microbiological changes during past year

Annual Report (4)

- A description of the general investigational plan for the coming year
- Change made to a Phase 1 study not yet reported to the IND
- Summary of significant foreign marketing
- Log of outstanding issues for which the sponsor expects a reply, comment or meeting (not mandatory)

Annual Report (5)

- Submitted within 60 days of the anniversary date that the application went into effect.
- Submitted annually
- Include FDA Form 1571
- Development Safety Update Report (DSUR) can be submitted to meet IND application annual report requirements
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073109.pdf

IND Inactivation

21 CFR 312.45

- May be inactivated at the Sponsor's or FDA's request
  - No subjects entered in clinical trial(s) for 2 years or longer
  - The IND application is on hold for 1 year or longer
- No requirement to submit IND annual reports
- An IND that remains on inactive status for 5 years may be terminated by FDA

IND Withdrawal

21 CFR 312. 38

- Requested at any time
  - Notify FDA
  - All clinical investigations conducted under the IND are ended
  - All investigators are notified
  - All stocks of the drug returned to the Sponsor or disposed
  - Provide reasons if withdrawn for safety reasons

Status Change:
From Hold to Inactive

21 CFR 312.42(g)

- If an IND remains on clinical hold for greater than 1 year the IND may be placed on inactive status by the FDA under 21 CFR 312.45.
- A sponsor is not required to submit annual reports to an IND on **inactive** status. An **inactive** IND is, however, still in effect for purposes of the public disclosure of data and information under 312.130.

Status Change:
From Inactive to Terminated

21 CFR 312.45(e)

- An IND that remains on **inactive** status for 5 years or more may be terminated under 312.44.

Expedited Programs for Serious Conditions-Drugs and Biologics

- Programs intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life threatening condition
  - Fast Track Development
  - Breakthrough Therapy Designation
  - Accelerated Approval

Expedited Programs
Fast Track

- Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)
  - To treat a serious condition **and** nonclinical and clinical data demonstrate the potential to address an unmet medical need or
  - Drug that has been designated as a Qualified Infectious Disease Product

Expedited Programs
Fast Track

- Submitted with IND or after
- Ideally, no later than pre-NDA or pre-BLA meeting
- Allow the opportunity for frequent interactions
- Eligible for Rolling submission
- May be Priority Review
- Designation may be rescinded if it no longer meets fast track qualifying criteria

Expedited Programs
Breakthrough Therapy

- Food and Drug Administration Safety and Innovations Act of 2012 (FDASIA)
  - Serious Condition **and**
  - Preliminary clinical evidence that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies

Expedited Programs
Breakthrough Therapy

- Submitted with IND or after
- Ideally, no later than the End-of-Phase 2 meeting
- Similar designation features as Fast Track
- Intensive guidance on efficient drug development
- Designation may be withdrawn if no longer meets the criteria
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/ucm373559.htm

Expedited Programs
Accelerated Approval

- 21 CFR 314, subpart H
- 21 CFR 601, subpart E
- Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)

Expedited Programs
Accelerated Approval

- Serious condition **and**
- Generally provides meaningful therapeutic benefit over available therapies **and**
- Demonstrates an effect on a surrogate endpoint that is reasonable likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit

Expedited Programs
Accelerated Approval

- Sponsor should discuss the possibility of accelerated approval with the review Division
- Conduct any required post-approval trials to verify and describe the anticipated clinical benefit or effect on irreversible morbidity or mortality
- Can be withdrawn

Title VIII-Generating Antibiotic Incentives Now (GAIN)

- Provides incentives for the development of certain antibacterial and antifungal drug products designated as Qualified Infectious Disease Products (QIDP)
  - Additional 5 years marketing exclusivity
  - Priority Review Status
  - Fast Track Designation Eligibility

Qualified Infectious Disease Product (QIDP) Designation

- QIDP refers to an **antibacterial** or **antifungal** drug for human use intended to treat **serious or life-threatening infections**, including those caused by
  - Qualifying pathogens listed by the Secretary under section 505E(f) of the FD&C Act or
  - An antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens.
- Designation applies to a specific drug product from a specific sponsor for a specific use being studied.
- Granted only to the sponsors making request; does not apply to the drug substance or beyond specified indications.

Requesting QIDP

- Sponsor may request QIDP designation at any time before submission of a marketing application for the drug
- Clear cover letter stating QIDP request
- Intended serious or life-threatening condition
- Justification that supports the role of the drug as an antibacterial or antifungal drug
- FDA will respond within 60 days of receipt of request
- Once granted, QIDP designation cannot be revoked by FDA unless
  - the request is found to have contained an untrue statement of material fact
- QIDP Guidance published January 2018 [see Resources]

Special Protocol Assessment (SPA)

- The following protocols* are eligible for a SPA Request:
  - Animal Carcinogenicity protocols
  - Clinical Trial Protocols
  - Drug substance and Drug product stability protocols
  - Animal Rule Efficacy studies (animal rule)
  - Protocols for clinical or animal trials of bioequivalence or bioavailability that will form basis of efficacy claim
  - Protocols for any necessary clinical study or studies to prove biosimilarity and/or interchangeability
- To qualify* sponsor must have held an end-of-phase 2/pre-phase 3 meeting; or an end-of-phase 1 meeting for biosimilar biologic product development, Type 2 or Type 3 meeting.

*see SPA Guidance for Industry (April 2018)

Resources

- Investigational New Drug (IND) Application
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm
- Expedited Programs for Serious Conditions-Drugs and Biologics
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf
- Qualified Infectious Disease Product Designation Q & A Guidance for Industry
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm594213.pdf
- List of Qualifying Pathogens
  - https://www.federalregister.gov/articles/2014/06/05/2014-13023/establishing-a-list-of-qualifying-pathogens-under-the-food-and-drug-administration-safety-and#h-47
- Pediatric Study Plans
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf
- Special Protocol Assessments – Guidance for Industry
  - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm498793.pdf

Questions?

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