

The Investigational New Drug (IND) *Part 2*

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>> The IND Process: *Part 2*

□ Session Objectives

▪ Attendees will learn

- Clinical Holds
- Protocol Amendments
- Information Amendments
- Annual Reports
- Overview of IND Safety Reporting Requirements
- Review the responsibilities of both sponsors and investigators conducting studies under an IND
- Review of expedited drug development programs for serious conditions

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>> Clinical Holds

❑ Clinical Holds

- A clinical hold is an order by the FDA telling a Sponsor (or Investigator) not to start a new study or suspend an existing study
- The clinical hold can apply to one or all studies being conducted under an IND
- If a study is placed on clinical hold, no new patients can be entered into the study
- For ongoing studies, patients should be taken off investigational drug (unless the FDA allows ongoing patients to remain on study drug for safety reasons)
- FDA can notify Sponsor by phone, facsimile, or email
- Written reasons (clinical hold letter) for the clinical hold are sent to Sponsor within 30 days



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>> Clinical Holds

❑ Clinical Holds (cont'd)

- Reasons for a clinical hold:
 - Subjects would be subject to an unreasonable and significant risk of illness or injury
 - The clinical investigator(s) are not adequately qualified
 - The Investigators' Brochure is misleading or erroneous
 - The IND lacks sufficient information to assess the risks of the study
 - Inadequate design of the clinical study to meet its objectives
 - There have been one or more adequate and well-controlled studies where the investigational drug was ineffective



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>> Clinical Holds

❑ Clinical Holds (cont'd)

▪ Resumption of studies on a clinical hold

- If a study is placed on clinical hold, the Sponsor must address all the deficiencies raised in the clinical hold letter by submitting a “Complete Response to Clinical Hold” amendment to the IND
- The FDA will respond within 30 days notifying the Sponsor that all deficiencies have been addressed or identifies those deficiencies that have not yet been adequately addressed by the Sponsor
- Studies on clinical hold can only be resumed following written notification from the FDA



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>> Initiation of Studies under IND

❑ Initiation of Studies under an IND

- If the clinical study was not placed on clinical hold, the Sponsor may initiate the study after 30 days following the submission of the IND, and
- The initiation of the study also requires local institutional review board (IRB)/Ethics Committee (EC) approval of the protocol
- Once the 30 day review period has passed, the IND is said to be “in effect” (or active)
- *Note Well:* The 30 day wait only applies to the initial IND submission, not to new protocols (or amended protocols), submitted to the IND



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>> Protocols

☐ Protocol Amendments

- New protocols
- Amendments to existing protocols

☐ New Protocols

- In order for a new protocol to be started, the protocol must be submitted to the IND and the protocol must have received IRB/EC approval (in either order)

☐ Amendments to Existing Protocols

- Changes that significantly affect the safety of subjects or the scientific quality of the study should be submitted to the IND as a protocol amendment

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>> Protocols

☐ Amendments to Existing Protocols (cont'd)

- A significant change would be:
 - Increase in drug dose or duration of exposure
 - A change in the design of the study (e.g., adding or dropping a control arm)
 - The addition of a new test or procedure
 - Increase (or decrease) in the age inclusion criterion
- In order for an amendment to a protocol to be initiated, the protocol amendment must be submitted to the IND and the protocol amendment must have received IRB/EC approval (in either order)
- Note that the above suggests that not all changes to a protocol (for example, an administrative change) have to be submitted to the IND as a protocol amendment; however, most Sponsors do so (and it is good regulatory practice)

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>> Protocols

❑ Amendments to Existing Protocols (cont'd)

- Note that adding new investigators to a multi-center study is considered a protocol amendment
- For practical reasons, the FDA allows Sponsors to group or batch new investigators together into single submissions
 - Within 30 days of the investigator beginning participation in the study
 - Participation is generally defined as having received investigational drug
 - Most Sponsors submit new investigator documentation (Form FDA 1572/CV) to the IND monthly for those investigators who have received investigational drug



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>> Information Amendments

❑ Information Amendments

- Information amendments are submissions to an effective IND that provide new pharmacology/ADME/toxicology, CMC, clinical, clinical pharmacology, or statistical information
- Oftentimes, an information amendment supports a protocol amendment
 - CMC: New dosage strength
 - Toxicology: New toxicology study to allow for longer duration of exposure
- So, if the Sponsor is submitting a new protocol that uses a new dosage strength and for a greater duration of exposure, the Sponsor would submit a new protocol amendment and an information amendment (CMC/tox) to the IND



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>> Annual Reports

❑ Annual Reports

- Required to be submitted within 60 days of the anniversary date the IND went into effect
 - IND submitted 1 May 2021
 - IND goes into effect 31 May 2021
 - IND Annual Report due no later than 31 July 2022
- If IND was put on Clinical Hold for three months
 - IND submitted 1 May 2021
 - Clinical Hold lifted 1 August 2021
 - IND Annual Report due no later than 1 October 2022



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>> Annual Reports

❑ Annual Reports (cont'd)

- The Annual Report should contain:
 - A brief summary of the status of each study in progress or completed during the previous year to include:
 - ✓ Title of the study
 - ✓ Number of subjects planned/enrolled, completed/dropped out (by age, gender, and race)
 - ✓ If the study has completed, a brief description of the results/key findings
 - Summary information obtained during the previous year
 - ✓ Narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
 - ✓ A summary of all IND Safety Reports submitted during the previous year
 - ✓ A list of subjects who died during participation in the investigation (including cause of death)

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» Annual Reports

❑ Annual Reports (cont'd)

▪ The Annual Report should contain (cont'd):

➤ Summary information obtained during the previous year (cont'd)

- ✓ A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related
- ✓ A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability
- ✓ A list of the preclinical studies completed or in progress during the past year and a summary of the major preclinical findings
- ✓ A summary of any significant manufacturing or microbiological changes made during the past year

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» Annual Reports

❑ Annual Reports (cont'd)

▪ The Annual Report should contain (cont'd):

- A description of the general investigational plan for the coming year to replace that submitted one year earlier
 - If the Investigators' Brochure has been revised, a description of the revision (tracked changes version) and a copy of the new brochure
 - A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment
 - A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country
 - If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting
- FDA now accepts the Development Safety Update Report (DSUR) in lieu of the Annual Report (helpful for international studies)

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>> IND Safety Reporting

❑ IND Safety Reporting

- Surprisingly, safety reporting is the least understood and poorly practiced IND regulation (in my view)
- Most (nearly all) sponsors over-report serious adverse events (SAEs) to health authorities
- There are subtle, but important differences, between FDA regulations and ICH guidance
 - Remember, Sponsor must follow IND regulations, not guidelines
- Reporting SAEs globally is more challenging than reporting solely to the FDA



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>> IND Safety Reporting

❑ IND Safety Reporting (cont'd)

- 15- and 7-Day Reports (SUSARs)
 - 15-day reports: The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its IND) in an IND safety report, of all suspected (i.e., considered related) adverse reactions that are both serious and unexpected no later than 15 calendar days of the sponsor's initial receipt of the information.
 - 7-day reports: Unexpected fatal or life-threatening (serious) suspected (i.e., related) adverse reaction reports should be sent to the FDA and all participating investigators as soon as possible but in no case no later than 7 calendar days after the sponsor's initial receipt of the information.



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» IND Safety Reporting

❑ IND Safety Reporting (cont'd)

- There are subtle differences between the IND Regulations and ICH guidelines on safety reporting
 - Definition of suspectedness/causality/relatedness:
 - ✓ ICH guidelines: The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, *i.e., the relationship cannot be ruled out.*
 - Determination of relatedness
 - ✓ IND regulations: Silent on this issue, but FDA guidance encourages the sponsor to make the determination
 - ✓ ICH guidelines: Either the sponsor or investigator can make the determination
 - Following ICH guidance results in nearly all serious and unexpected AEs being reported

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» IND Safety Reporting

❑ IND Safety Reporting (cont'd)

- FDA: "Safety Reporting Requirements for INDs and BA/BE Studies" (2012)
 - Emphasizes the US regulatory definitions of serious, suspected (related), and unexpected
 - FDA believes that the sponsor is better positioned than the individual investigator to assess causality (relatedness)
 - Encourages the breaking of the blind (reduces over reporting)

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The IND Process: *Part 2*

☐ **Questions?**



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The IND Process: *Part 2*

☐ **Responsibilities of Sponsors and Investigators**

- **21 CFR 312.50 to 21 CFR 312.70**

- **Note: It is the requirements under 21 CFR 312.50-312.70 that establish the parameters for FDA inspections**

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» Responsibilities of Sponsors

□ Responsibilities of Sponsors

▪ General responsibilities of sponsors (21 CFR 312.50)

- Selecting qualified investigators
- Providing investigators with information needed to conduct the study
- Ensuring proper monitoring of the study
- Ensuring that the study is conducted in accordance with the protocol
- Maintaining an effective IND
- Ensuring that FDA and investigators are promptly informed of significant new adverse effects or risks with respect to the drug

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» Responsibilities of Sponsors

□ Responsibilities of Sponsors (cont'd)

▪ Transfer of Obligations

- A sponsor may transfer responsibility for any or all of the obligations to a contract research organization (CRO)
 - ✓ Any such transfer shall be described in writing
 - ✓ All or selected obligations can be transferred
 - ✓ Any obligation not covered by the written description shall be deemed not to have been transferred
- A CRO that assumes any obligation of a sponsor shall
 - ✓ Comply with the specific regulations applicable to this obligation
 - ✓ Be subject to the same regulatory action as a sponsor for failure to comply
- FDA does expect there to be oversight of the CRO by the Sponsor

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» Responsibilities of Sponsors

❑ Responsibilities of Sponsors (cont'd)

▪ Selecting investigators and monitors

➤ Selecting investigators

- ✓ A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug
- ✓ A sponsor shall ship investigational new drugs only to investigators participating in the investigation
- ✓ Before study start, the sponsor shall obtain the following:
 - A signed investigator statement (Form FDA-1572)
 - Commits the investigator to follow FDA regulations
 - Curriculum vitae/resume
 - Financial disclosure information

➤ Selecting monitors

- ✓ A sponsor shall select a monitor qualified by training and experience to monitor the progress of the study
 - Medical monitor, not a CRA

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» Responsibilities of Sponsors

❑ Responsibilities of Sponsors (cont'd)

▪ Informing investigators

- Provide each participating clinical investigator an Investigator Brochure
- As the investigation proceeds, keep each participating investigator informed of new observations, particularly with respect to adverse effects

▪ Review of ongoing investigations

- The sponsor shall monitor the progress of clinical studies under its IND
- If an investigator is not complying with regulations, the sponsor shall either secure compliance or discontinue drug shipments and end the investigator's participation in the study.
 - ✓ If participation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug and notify FDA
- The sponsor shall review safety and effectiveness data as it is obtained from the investigator and make reports to FDA regarding safety (IND Safety Reports) and annual reports
- If the study drug presents a significant risk, the sponsor shall discontinue the study(ies), notify FDA, all IRBs, all investigators, and assure the disposition of unused drug

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Responsibilities of Sponsors

□ Responsibilities of Sponsors (cont'd)

▪ Record keeping and record retention

- A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug.
 - ✓ To include, the name of the investigator, date, quantity, and batch of each shipment
- A sponsor shall maintain complete and accurate records showing any financial interest in the study paid to clinical investigators
- A sponsor shall retain the records for 2 years after a marketing application (NDA/BLA) is approved; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug is discontinued and FDA has been notified
- A sponsor shall retain reserve samples of any test article and reference standard used in any bioequivalence or bioavailability studies for a period of 5 years from NDA/BLA approval

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Responsibilities of Sponsors

□ Responsibilities of Sponsors (cont'd)

▪ Inspection of sponsor's records and reports

- A sponsor shall, upon request from an authorized officer or employee of the FDA, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under the IND
- Upon written request by FDA, the sponsor shall submit records or reports (or copies of them) to FDA
- The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation
- If an investigational drug is a controlled substance (for example, narcotics) records concerning shipment, delivery, receipt, and disposition of the drug, shall be made available by the investigator or sponsor to whom the request is made, for inspection and copying
- The sponsor shall assure that the storage of the controlled drug is in a securely locked, substantially constructed cabinet or enclosure, access to which is limited, to prevent theft or diversion

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» Responsibilities of Sponsors

❑ Responsibilities of Sponsors (cont'd)

▪ Disposition of unused supply of investigational drug

- The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated
- The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug
- The sponsor shall maintain written records of any disposition of the drug



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» Responsibilities of Investigators

❑ General Responsibilities of Investigators

▪ An investigator is responsible for

- Compliance with the signed investigator statement (Form FDA 1572)
- Adhering to the investigational plan (protocol)
- Following applicable regulations for protecting the rights, safety, and welfare of subjects under the investigator's care
- The control of drugs under investigation
- Obtain the informed consent of each human subject to whom the drug is administered



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>> Expedited Drug Development Programs

❑ Expedited Drug Development Programs

▪ Purpose

- To establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists
 - ✓ “life-threatening” means: (1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival
 - ✓ “severely debilitating” means diseases or conditions that cause major irreversible morbidity



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>> Expedited Drug Development Programs

❑ Expedited Drug Development Programs (cont'd)

- **FDA Guidance: *Expedited Programs for Serious Conditions – Drugs and Biologics* (2014)**
 - Fast Track
 - Breakthrough Therapy
 - Accelerated Approval
 - Priority Review
- All four expedited programs represent efforts to address an unmet medical need and require that the investigational drug is intended to treat a serious condition



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Expedited Drug Development Programs

❑ Expedited Drug Development Programs (cont'd)

▪ Unmet medical need:

- No therapy exists
- Therapy exists but new drug
 - ✓ Has impact on outcomes where existing therapies treat symptoms
 - ✓ Is superior to existing therapy
 - ✓ Is effective in patients who failed previous therapy
 - ✓ Has comparable efficacy but an improved safety profile
 - ✓ Has comparable efficacy and safety but offers improved patient compliance



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Expedited Drug Development Programs

❑ Expedited Drug Development Programs (cont'd)

▪ A serious condition

- A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one



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» Expedited Drug Development Programs

❑ Expedited Drug Development Programs (cont'd)

▪ Fast Track

- Requires that a drug be intended to treat a serious condition, AND
 - ✓ Nonclinical or clinical data demonstrate the potential to meet an unmet medical need
- Best to make request early in the IND process
 - ✓ FDA will respond within 60 days
- Provides for
 - ✓ Frequent meetings with the FDA
 - ✓ Priority review
 - FDA reviews NDA/BLA within six months
 - ✓ Allows for “rolling review” of NDA/BLA
 - Can submit NDA/BLA sections when they become available
- Can be rescinded

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» Expedited Drug Development Programs

❑ Expedited Drug Development Programs (cont'd)

▪ Breakthrough Therapy

- Requires that the drug is intended to treat a serious condition, AND
 - ✓ There is preliminary clinical evidence the drug demonstrates improvement on a clinically significant endpoint(s) over available therapies
- Best to request with IND or prior to End-of-Phase 2 Meeting
 - ✓ FDA will respond within 60 days
- Provides for
 - ✓ Intensive guidance from FDA
 - ✓ FDA will involve senior and experienced reviewers
 - ✓ Rolling review
 - ✓ Priority review
- Can be rescinded

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» Expedited Drug Development Programs

❑ Expedited Drug Development Programs (cont'd)

▪ Accelerated Approval

- Requires that a drug treats a serious condition AND
 - ✓ Provides a meaningful advantage over available therapies, AND
 - ✓ Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit
- Best to request early during development process
 - ✓ FDA response time is not specified
- Provides for approval based on a surrogate endpoint or an intermediate clinical endpoint that is likely to predict a drug's clinical benefit
- Conditions of accelerated approval
 - ✓ Sponsor must submit promotional material during NDA/BLA review
 - ✓ FDA is likely to require a confirmatory trial
 - ✓ Marketing approval is withdrawn if confirmatory trial is negative

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» Expedited Drug Development Programs

❑ Expedited Drug Development Programs (cont'd)

▪ Priority Review

- Requires that a drug treats a serious condition, AND
 - ✓ Would provide a significant improvement in safety or effectiveness, OR
 - ✓ An NDA/BLA supplement for a pediatric claim, OR
 - ✓ Is for a drug designated as a qualified infectious disease product, OR
- Sponsor requests Priority Review at time of NDA/BLA (or supplement) submission
 - ✓ FDA responds within 60 days
- Provides for shorter clock for review of marketing application (6 months compared with the 10-month standard review)
- Note that FDA can also consider Priority Review at the time of NDA/BLA submission

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The IND Process: Part 2

❑ Questions?



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