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The IND Process: *Advanced I*

☐ **Session Objectives**

- **Attendees will learn**
 - **Clinical Holds**
 - **Protocol Amendments**
 - **Information Amendments**
 - **Annual Reports**
 - **Overview of IND Safety Reporting Requirements**



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>> Clinical Holds

❑ Clinical Holds

- A clinical hold is an order by the FDA 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” letter
- 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
- 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 have 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



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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 2020
 - IND goes into effect 31 May 2020
 - IND Annual Report due no later than 31 July 2021
- If IND was put on Clinical Hold for three months
 - IND submitted 1 May 2020
 - Clinical Hold lifted 1 August 2020
 - IND Annual Report due no later than 1 October 2021



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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 (including animal 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 1 year earlier
 - If the Investigators' Brochure has been revised, a description of the revision 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 Drug 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
- 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
 - 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 suspectendess/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
 - 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: *Advanced I*

☐ Next Session: The Investigational New Drug (IND) Process: *Advanced II*

- Review the responsibilities of both sponsors and investigators conducting studies under an IND
- Review of expedited drug development programs for serious conditions
 - Fast Track
 - Breakthrough Therapies
 - Accelerated Approval
 - Priority Review

☐ Questions?



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