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>> The IND Process: *Advanced II*

❑ Session Objectives

▪ Attendees will learn

- Responsibilities of sponsors and investigators conducting studies under an IND
- FDA's expedited drug development programs for serious conditions

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The IND Process: *Advanced II*

☐ 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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Responsibilities of Investigators

□ Responsibilities of Investigators

- Control of the investigational drug
 - An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator
 - The investigator shall not supply the investigational drug to any person not authorized to receive it



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Responsibilities of Investigators

❑ Responsibilities of Investigators (cont'd)

▪ Investigator recordkeeping and record retention

- An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
- If the study is terminated, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor or dispose of the unused supply of drug
- An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug
- Case histories include the case report forms and supporting data including, signed and dated consent forms and medical/hospital records
- The case history for each individual shall document that informed consent was obtained prior to participation in the study
- An investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug or until 2 years after the investigation is discontinued and FDA is notified

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Responsibilities of Investigators

❑ Responsibilities of Investigators (cont'd)

▪ Investigator reports

- The investigator shall furnish reports to the sponsor so that the sponsor can submit an Annual Report
- An investigator must immediately report to the sponsor all serious adverse event, and include an assessment of relatedness
- The investigator must record non-serious adverse events and report them to the sponsor according to the protocol
- An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation
- The investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements
- The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study

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Responsibilities of Investigators

❑ Responsibilities of investigators (cont'd)

▪ Assurance of IRB review

- An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study
- The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others
- The investigator will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects



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Responsibilities of Investigators

❑ Responsibilities of investigators (cont'd)

▪ Inspection of investigator's records and reports

- An investigator shall permit any authorized officer or employee of FDA to have access to, and copy and verify any records or reports made by the investigator
- The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained

▪ Handling of controlled substances

- If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug 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 Investigators

❑ Responsibilities of Investigators (cont'd)

▪ Disqualification of a clinical investigator

- If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the IND, informed consent, or IRB requirements or has submitted to FDA or to the sponsor false information, the investigator's participation in a study can be terminated and the investigator can be disqualified participating in future clinical studies
- For completed studies, the FDA can require the sponsor re-evaluate the study results with the data from the investigator in question removed
 - ✓ Note: If the removal of an investigator's data results in the study no longer being positive (statistically significant) the FDA may withdraw the approval of a marketing application (NDA/BLA) that relied on such data

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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 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
- Requested 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)



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The IND Process: *Advanced II*

☐ Next session: Orphan Drug Products

☐ Questions?



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