



Working with FDA: Biological Products and Clinical Development

An Introduction to FDA's Clinical Trial Review

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NATIONAL INSTITUTES OF HEALTH



RAID Investigator Training (March 2007): Clinical Trial Section

- Clinical Trial Review
 - What is FDA looking for?
 - Influence of phases of clinical development on trial design
 - Projects as outlined in Exploratory IND guidance – CDER products only.
 - Unique issues pertaining to tumor vaccines, cell therapies and gene therapies
- What are GCP?



Outline

- Hypothetical Case
- What is FDA looking for
 - IND process
 - Clinical protocol and clinical review process
 - Hold reasons for INDs
 - Common clinical reasons for Clinical Hold by citations
- Some unique Issues related to OCTGT regulated products
- Good Clinical Practice
- Discussion of the hypothetical case



Hypothetical Case

An investigator discovers a gene therapeutic agent 008⁰⁰⁰⁰⁸. *In vitro* testing shows that this agent has “superactivity” in lysing a wide variety of tumor cells. In particular, the agent kills pancreatic cancer cells **more efficiently**. Intratumoral injection of this agent to a human pancreatic tumor implanted in one SCID mouse causes an **incredible** tumor regression.



Hypothetical Case

The investigator decides to move this agent to 1st in human testing.

- Patient population: anybody with pancreatic cancer
- Intratumoral injection (the only description of the treatment procedure without specifying the dose and schedule, procedure for injection, site of injection etc.)
- Document in medical record “RTC” in 2 months (the only description in the monitoring and patient follow-up without specifying items and schedule for followup etc).
- Plans to write to FDA after treating 3 patients to check whether an IND is needed



Questions for this Hypothetical Case?

- Is the patient population appropriately identified?
- Is the treatment plan adequately described?
- Are the plans for monitoring and reporting adverse events adequately described?
- Is the required regulatory procedure appropriately followed?



What is FDA Looking for (in INDs)

- IND process
- Clinical protocol and review process
- Hold reasons for IND submission
- Common clinical reasons for Clinical Hold by citations



IND

Investigational New Drug Application



The IND Application

- Preclinical testing/investigation
 - *In vitro* tests/animal testing
 - “reasonably safe” determination (21 C.F.R. § 312.23)
 - Pharmacological data
 - Toxicity testing

- “Good Laboratory Practice” (GLP) (21 C.F.R. Part 58)
 - Governs preclinical testing conduct
 - Organization, personnel, facilities, study conduct, and records retention



The IND Process Application Components

- Cover sheet Form 1571 (21 C.F.R. § 312.23(a)(1))
- Table of contents (21 C.F.R. § 312.23(a)(2))
- Introductory statement and general investigational plan (21 C.F.R. § 312.23(a)(3))
 - Brief 2-3 page summary
 - Helps FDA anticipate sponsor needs



The IND Application Components

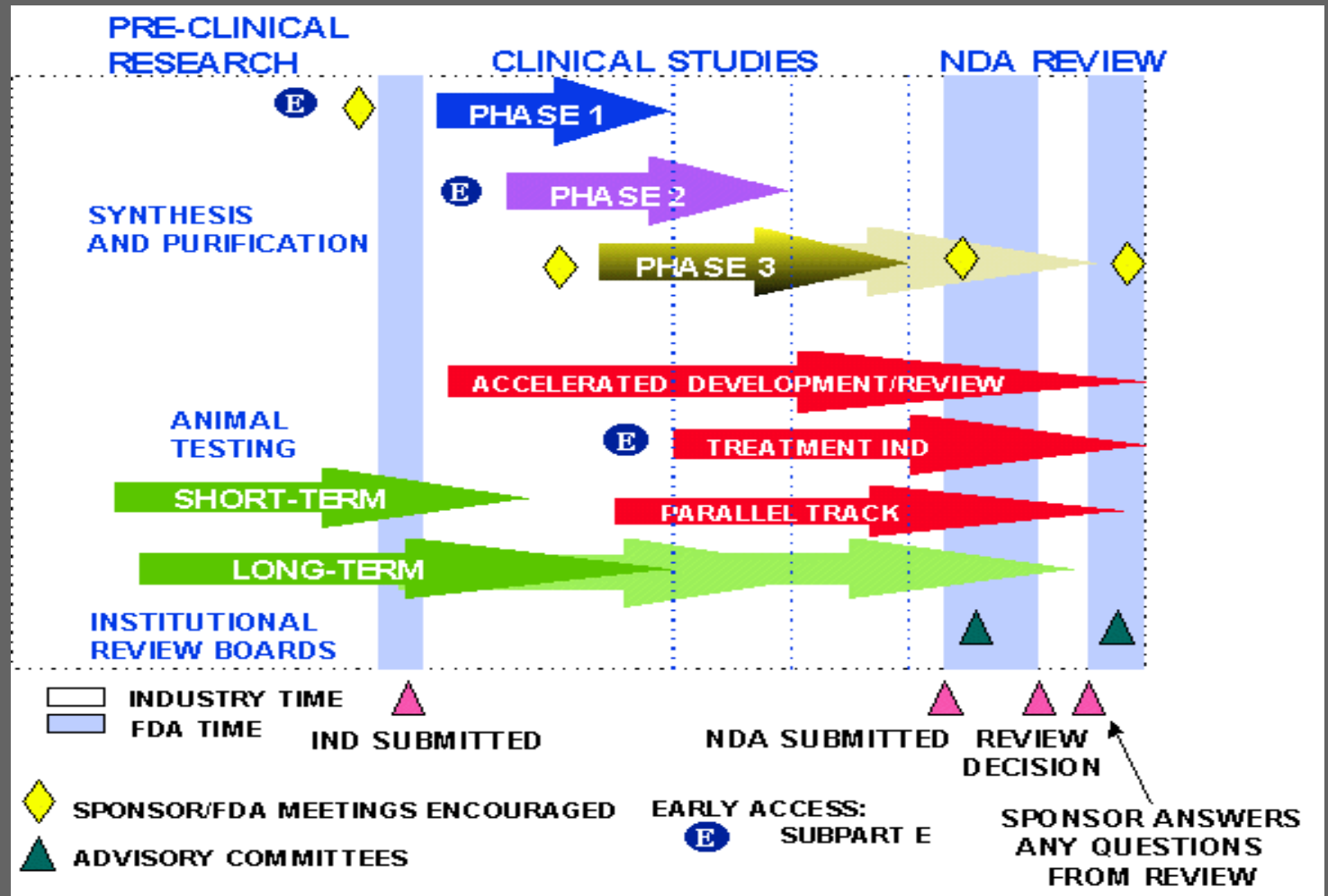
- Investigator's brochure (21 C.F.R. § 312.23(a)(5))
 - Compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects
 - Facilitates investigator understanding of rationale of key features of the protocol (dose frequency/interval, methods of administration)
- Protocols (21 C.F.R. § 312.23(a)(6))
- Chemistry, Manufacturing, and Control (CMC) information (21 CFR § 312.23(a)(7))
 - Information on drug substance, drug product (preparation, manufacturer, components, etc.)



The IND Application Components

- Sponsor's pharmacological and toxicological studies (21 C.F.R. § 312.23(a)(8))
 - Description of pharmacological effects, ADME
 - Integrated summary of toxicological effects in animals and *in vitro* studies
 - Study reports should be available to FDA within 120 days of the start of the human study
- Previous human experience summaries (21 C.F.R. § 312.23(a)(9))
 - previous human experience should be presented in an integrated summary

Phases of Clinical Product Development





FDA IND Review Process

Team Approach

- Communication
- Multidisciplinary
- Consensus building

Decision Making

- Evidence-based
- Safety-dependent
- Phase-dependent



Phase 1 Studies

- Initial administration of drug to humans
- Assessment of human toxicology
- Determine Maximum Tolerated Dose (MTD) or Optimal Biological Dose (OBD)



Phase 2 Studies

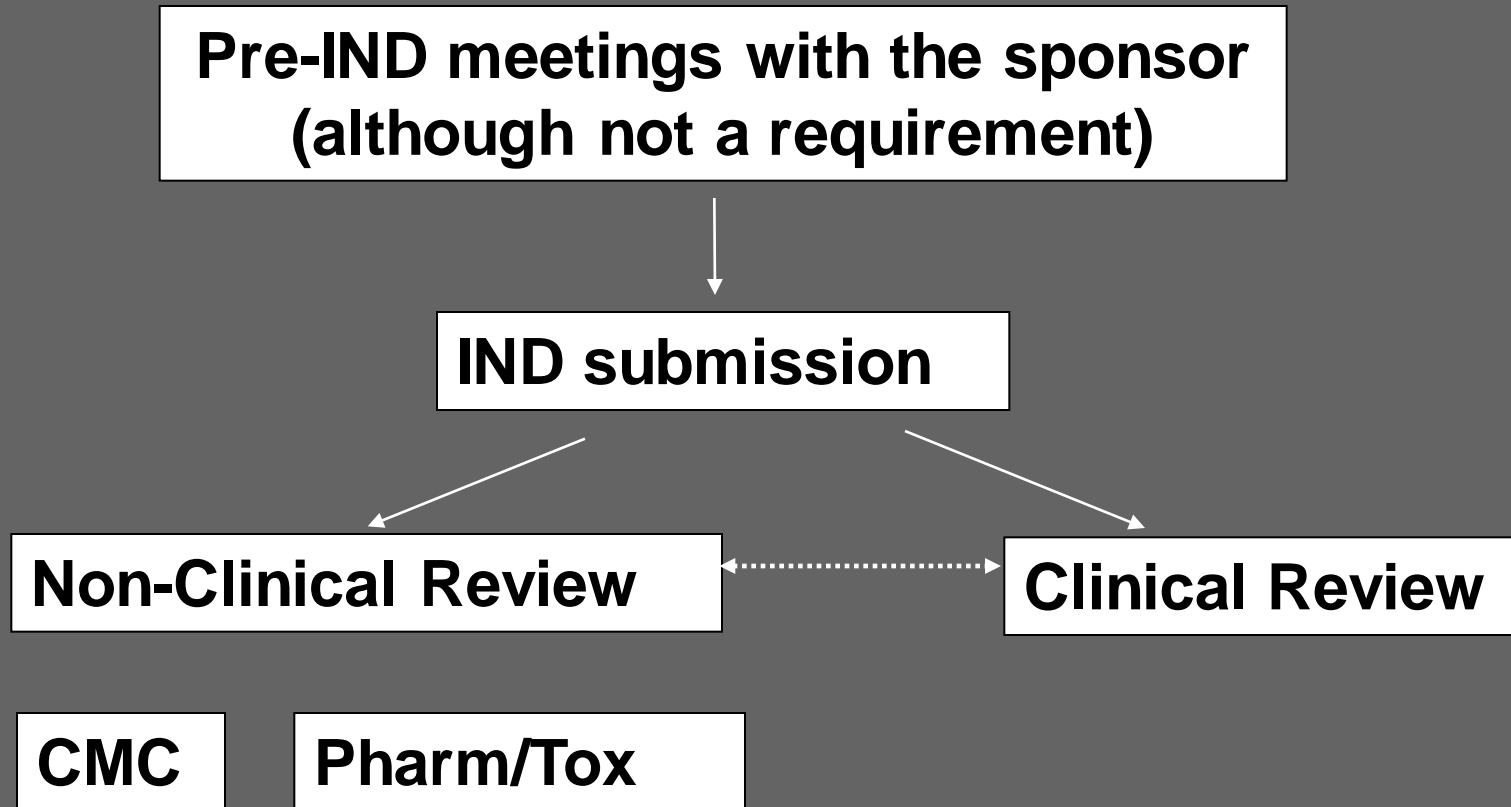
- Begin if Phase 1 studies do not reveal unacceptable toxicity.
- Primarily focus on collection of preliminary data on
 - whether the drug has effect in a defined patient population
 - the relationship between dose and effectiveness.
- **Continue to evaluate safety and short-term side effects.**
- For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment -- usually a placebo or a different drug.



Phase 3 Studies

- Begin if preliminary evidence of effectiveness is shown during phase 2.
- Gather more information about safety and effectiveness in a defined population.
- May form the primary basis of an efficacy claim

Review for Phase 1 Trials





Regulatory Considerations

- The product manufacturing and characterization?
- The level of safety assurance needed for beginning clinical trials
- Clinical study design




Clinical Review

- **Clinical Protocol**
- Protection of human subjects




What is a Clinical Protocol

- Written plan for how the drug is to be studied and the procedures to be followed by each investigator



Contents of a Clinical Protocol (21 C.F.R. § 312.23 (a) (6))

1. A statement of the objectives and purpose of the study.
2. The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.
3. A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.
4. The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.



Contents of a Clinical Protocol (21 C.F.R. § 312.23 (a) (6)) (cont.)


5. A description of the observations and measurements to be made to fulfill the objectives of the study.
6. A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.
7. The name and address and a statement of the qualifications of investigators (Form 1572); the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board

Details of the clinical protocol depend on the phase of the study



Major Review Elements for a Phase 1 Clinical Protocol

- Patient population
- Dose, schedule and administration
- Dose escalation
- Dose Limiting Toxicity (DLT) definition and Optimal Maximum Dose determination



Major Review Elements for a Phase 1 Clinical Protocol (cont.)

- Stopping rules
- Safety monitoring and evaluation
- Safety Reporting
- Case Report Form
- Informed consent
- Investigator's brochure if applicable (21 C.F.R. § 312.23(a)(5))



Clinical Review

- Clinical Protocol
- **Protection of human subjects**



Protection of Human Subjects

- **Informed consent (21 C.F.R. Part 50)**
 - Ensures voluntary participation
 - Required disclosures:
 - Risks, benefits, and alternative treatments
 - No contracting out of liability
 - “No more than minimal risk”
- **“Institutional Review Boards” (IRBs) (21 C.F.R. Part 56)**
 - Composed of at least 5 members from the health care community and public
 - Approve and monitor protocol
 - Authority to approve, require modifications, or disapprove research



Protection of Human Subjects (cont.)

- IRBs should review proposed clinical trial within a reasonable time
- IRBs should provide dates for the following
 - Approval/favorable opinion;
 - Modifications required prior to its approval/favorable opinion;
 - Disapproval/negative opinion; and
 - Termination/suspension of any prior approval/favorable opinion



Obligations of Sponsors and Investigators in the Conduct of Clinical Trials

- **Sponsor obligations (21 C.F.R. § 312.50)**
 - Management of IND
 - Safety reports
 - Transportation/shipment of drug
 - Collection of unused drug
 - Records: maintenance and retention

- **Investigator obligations (21 C.F.R. § 312.60)**
 - Assure IRB review and informed consent
 - Adherence to protocol
 - Adverse event reporting
 - Trial supervision
 - Records: maintenance and retention



FDA Review and Decision-Making

- FDA inaction in 30 days triggers the study under the IND to “proceed”
or
- FDA issuance of “clinical hold”



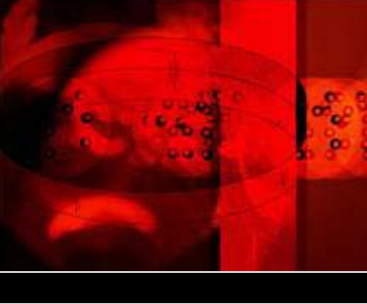
“Clinical Hold” (21 C.F.R. § 312.42)

- A clinical hold is an order issued by FDA to the sponsor of an IND to delay or to suspend a clinical investigation
- Partial or complete clinical hold
 - Partial
 - A delay or suspension of only part of the clinical work requested under the IND
 - Complete
 - A delay or suspension of all clinical work requested under an IND
- Can occur during phase I, II, or III



Hold Reasons (21 C.F.R. § 312.42)

1. Human subject exposure to an unreasonable and significant risk of illness or injury;
2. Incomplete information to assess the risk to subjects;
3. Deficient plan or protocol (additional for Phase 2 or 3);
4. Misleading, erroneous, or materially incomplete investigator brochure; or
5. Unqualified clinical investigators.



Analysis of IND Review Decisions in OCTGT between October 1, 2002 and December 31, 2004




Common Deficiencies Leading to Clinical Hold

- Citations for Pharmacology, Toxicology and or CMC
 - Refer to other sessions of this course
- Most common clinical deficiencies were related to unreasonable and significant risk with need for change to the eligibility criteria, safety monitoring plan and stopping rules
- The second most common citations were related to insufficient information to assess the risk to subjects



Common Clinical Reasons for Clinical Hold by Citations

- Patient population:
 - Eligibility and/or exclusion criteria inappropriate
 - Number of subjects not specified or unreasonable
- Starting dose:
 - Insufficient data to support the intended starting dose
 - Product preparation or formulation inadequately described




Common Clinical Reasons for Clinical Hold by Citations

- Dose regimen:
 - Administration of product risky or inadequately described
 - Proposed dose increases too aggressive
 - Failure to stagger enrollment of new product with unknown risks
 - Dose modification plan unreasonable
 - Repeat treatment plan unreasonable or not supported
 - Reporting



Common Clinical Reasons for Clinical Hold by Citations

- Safety monitoring:
 - Anticipated toxicities inadequately monitored
 - Lack of appropriate Toxicity Scale
 - Individual Patient Treatment Discontinuation Criteria absent or unreasonable
 - Study Stopping Rules absent or unreasonable
 - Withdrawn subjects not adequately followed
 - Long term follow up for patients absent or inadequately described
 - Adverse event



Some Unique Issues Related to OCTGT Regulated Products

- Cancer vaccines
- Cell therapies
- Gene therapies



Some Unique Issues Pertaining to Cancer Vaccines, Cell Therapies and Gene Therapies

- Product manufacturing and characterization, especially autologous products
- Unique aspects of early phase studies
 - Metabolism does not follow standard pharmacokinetics and/or pharmacodynamics
 - Distinct product mechanism of action requires different trial design
 - Defining optimal biologic dose (OBD) rather than maximum tolerated dose (MTD)
 - Consideration of unique toxicity profiles and monitoring
 - Long term follow-up issues



Considerations for Early Cancer Vaccine Trial Designs

- **Patient eligibility**
 - Consider enrolling patients with a single tumor histology in phase I trials
 - Safety, feasibility and optimal dose regime
 - Consider evaluating the product in later phase trials in different histologies if promising



Considerations for Early Cancer Vaccine Trial Designs (cont.)

■ Eligibility


For some cancers, if the standard treatment has low expectations for patient benefits or has severe toxicity

- Consider enrolling patients before such treatment
- Proceed to standard treatment if disease progresses with the investigational treatment



Considerations for Early Cancer Vaccine Trial Designs (cont.)

- Dose Escalation
 - Cancer vaccines in general have a favorable toxicity profile
 - Consider other alternative approaches for dose escalation in early phase cancer vaccine trials such as accelerated titration designs
 - Not to sacrifice the evaluation of the toxicities
 - Reduce the chances that subjects receive suboptimal doses of cancer vaccine
 - Shorten the time interval before late phase trials start

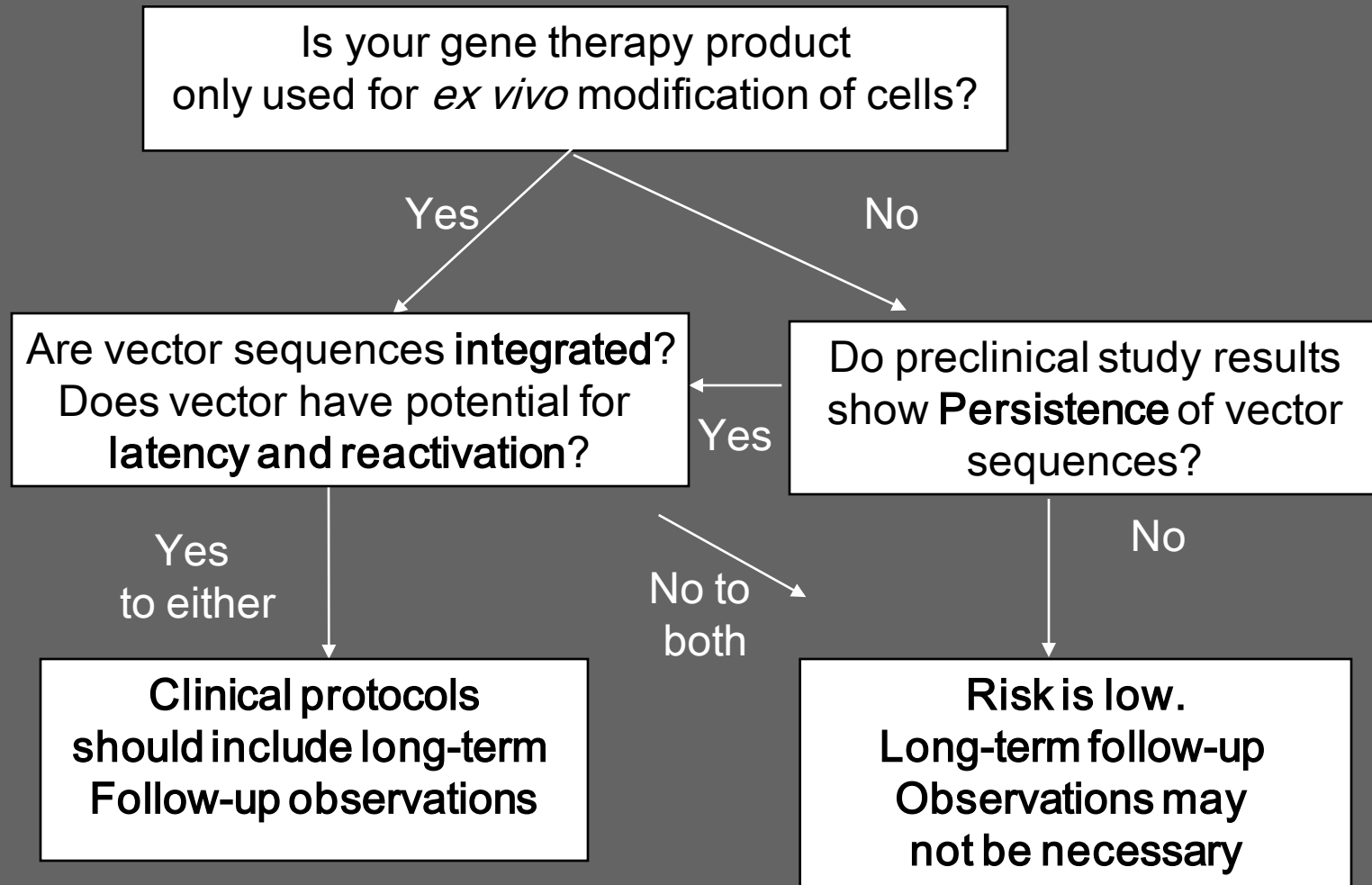


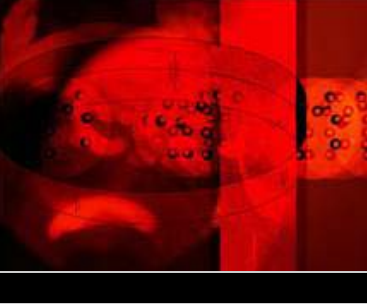
Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events

How does one determine whether long-term observations should be performed in a particular clinical trial?

Guidance for industry: <http://www.fda.gov/cber/gdlns/gtclin.pdf>

Criteria to Assess Potential Delayed Risks of Gene Therapy





Good Clinical Practice (GCP)



GCP

- Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
 - See Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance (April 1996)

<http://www.fda.gov/cder/guidance/959fnl.pdf>



Principles of ICH GCP

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.



Principles of ICH GCP (cont.)

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).



Principles of ICH GCP (cont.)

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting Interpretation, and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.



FDA Regulations Relating to Good Clinical Practice and Clinical Trials

- Electronic Records; Electronic Signatures (21 CFR Part 11)
- Human Subject Protection (Informed Consent) (21 CFR Part 50)
- Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products (Interim Rule) (21 CFR Part 50, subpart D)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Institutional Review Boards (21 CFR Part 56)
- Investigational New Drug Application (21 CFR Part 312)
- Forms 1571 (Investigational New Drug Application) and 1572 (Statement of Investigator)
- Applications for FDA Approval to Market a New Drug (21 CFR Part 314)
- Applications for FDA Approval of a Biologic License (21 CFR Part 601)
- Investigational Device Exemptions (21 CFR Part 812)
- Premarket Approval of Medical Devices (21 CFR Part 814)
- <http://www.fda.gov/oc/gcp/regulations.html>



Discussion of the Hypothetical Case

- What were the problems?
 - Rationale
 - Objective
 - Patient eligibility
 - Trial design
 - Treatment: dose, schedule, route etc.
 - Safety monitoring and follow up
 - Informed consent
 - IRB approval
 - IND submission



Discussion of the Hypothetical Case

■ Solutions

- Follow regulations
- Follow GCP
- Interactions with FDA
 - Early interactions with FDA are critical
 - Know your guidance documents
 - Consider early in translational research the questions that will be asked at the clinical trial phase
 - Phone, face to face; formal or informal: dialogue is encouraged



Quiz Questions

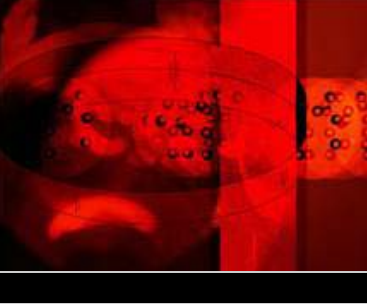
Choose the most appropriate answer for questions 1-3



Question 1. In developing a clinical protocol, the following should be considered

- I. Objectives and purposes of the study
- II. Inclusion and exclusion criteria
- III. Design of the study including the dose, schedule and the route of administration
- IV. Plans for evaluation and monitoring of the trial subjects

- A. I, II, III
- B. I, III
- C. III
- D. II, IV
- E. I, II, III, IV

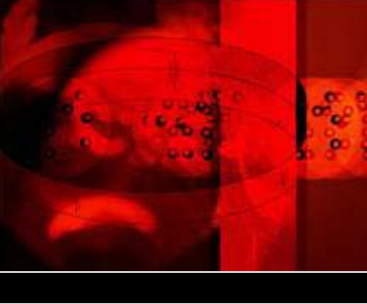


Answer to question 1: E



Question 2. All of the following are true regarding IB and its contents **except**

- A. A brief description of the drug substance and the formulation, including the structural formula, if known. A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
- B. A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.
- C. A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)
- D. A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.
- E. All clinical studies require IB.

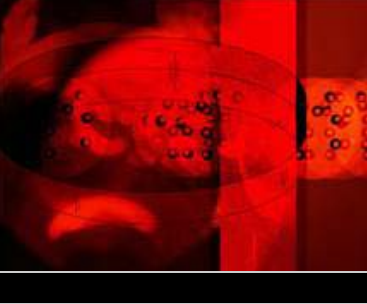


Answer to question 2: E



Question 3. Which of the following constitutes a reason that FDA may use to put a study on clinical Hold?

- A. The sponsor did not have a pre-IND meeting with FDA before IND submission.
- B. One of associate investigators is not a dentist.
- C. The investigator brochure is misleading, erroneous, or materially incomplete.
- D. The sponsor complains that the 30-day IND review is too slow.



Answer to question 3: C



Choose true or false for the following statements (questions 4-5):

Question 4. All human subjects who are exposed to gene therapy products must be followed for life to observe the delayed adverse events.

Question 5. Safety evaluation remains top priority in all phases of clinical studies.



Answer to question 4: False

Answer to question 5: True