IND "202" Clinical Perspective

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Topics Covered

- IND activity for somatic cell therapies in CBER OCTGT
- Pre-IND meeting
- IND Processing
  - Document preparation
  - Review Team Assignments
  - Review Process
- Clinical Review
  - Priorities
  - Common Clinical Hold Issues
- IND Annual Report Review

What is an IND?

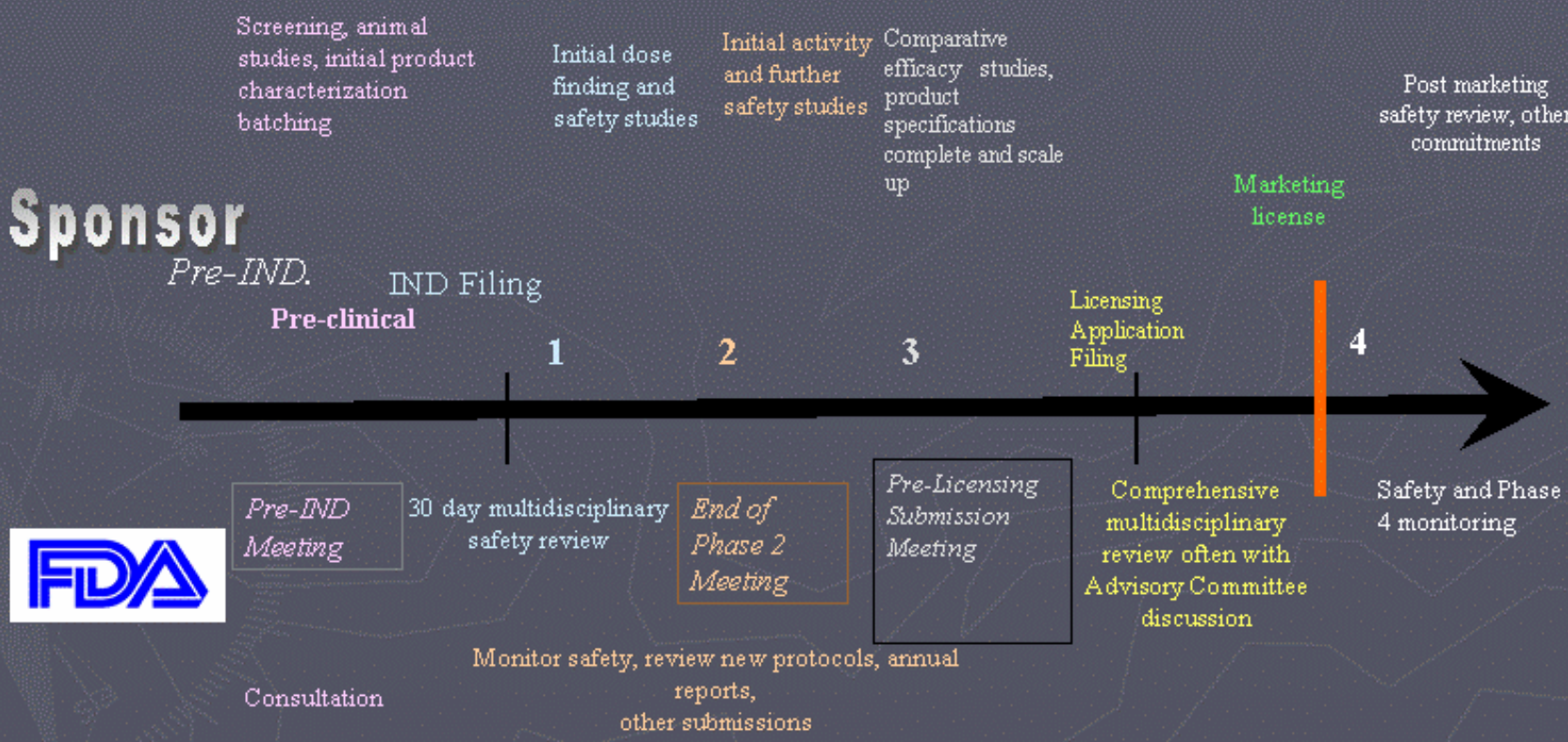
- Investigational New Drug application
  - Mechanism to allow interstate transport of investigational agents for clinical research
  - Provide patient protection through Federal oversight

- Authority for IND mechanism comes from Food, Drug & Cosmetic Act Section 505
- IND regulations may be found in the Code of Federal Regulations (CFR) Title 21 Part 312

21CFR312.22

- *(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.*

Overview of Therapeutic Development



Pre IND Meeting

- Non-binding advice provided as courtesy
- Request is made to FDA.
- Meeting is scheduled.
- At least 30 days prior to scheduled meeting potential IND applicant submits to FDA a meeting package consisting of
  - background information
  - list of questions grouped by type (Product, Preclinical, Clinical and Regulatory)

Pre IND Meeting

- FDA review team with members from each discipline will review package and hold an internal meeting to responses to the submitted questions
- Draft responses to the questions are usually communicated to the potential applicant prior to the scheduled meeting
- Potential applicant has option to
  - cancel meeting if draft answers are satisfactory *or*
  - hold meeting but focus only on selected issues *or*
  - hold meeting and discuss all questions and responses

IND Processing

- IND Package arrives at FDA and is processed .
- Following processing, review assignments are made for relevant disciplines. Usual are product (CMC), preclinical pharmacology/toxicology, and clinical. As needed a statistical review is requested

IND Processing

- Legal requirement for 30 day review based on calendar (no holidays allowed!) beginning when the submission is logged into document control
  - Food Drug & Cosmetic Act Section 505
- FDA internal reviews are based on standardized templates
- Clarifications from the IND sponsor are usually sought during the review process with the goal of avoiding clinical hold as noted in 21CFR312.42(c)

Clinical Hold Criteria

- Risks are unreasonable and significant
- Investigators not qualified
- Investigator brochure false or misleading
- Insufficient information to assess risk
- Gender exclusion for a condition that occurs in both men and women

Clinical Hold criteria are described in 21CFR312.42

IND Review Completion

- Approximately one week prior to the due date the review team makes a preliminary determination if a clinical hold may be necessary
- If no clinical hold is issued, sponsor may begin clinical investigation after 30th day with IRB approval.
- No formal communication from FDA is necessary to activate an IND.

Clinical Hold Issuance

- If deficiencies cannot be resolved FDA will issue a clinical hold
- IND applicant is informed by telephone prior to or on Day 30 following IND submission
- A letter from the FDA is sent to the IND applicant within 30 days of the telephone call
  - listing the clinical hold issues
  - Stating what is expected to remove the clinical hold
- Sponsor may reply at any time following the telephone call with a Complete Response to Clinical Hold

Clinical Hold

- A clinical hold may be issued at any time
  - For ongoing studies usually adverse events trigger the clinical hold
- If only some and not all studies under an active IND are placed on clinical hold, the IND is under *Partial Hold*
- If all investigations under an IND remain on clinical hold for more than one year, the IND is automatically converted to inactive status

Clinical Review Elements

- All elements as outlined in 21CFR 312.23 are included in IND submission
- Adequate rationale and preclinical data to justify starting dose and schedule
- Appropriate patient population
- Acceptable dose escalation schema
- Staggered enrollment for new agents
- Adequate safety monitoring based on patient population and anticipated toxicities

IND Requirements based on 21CFR312.23

- Cover sheet of a Form 1571 filled out by the sponsor. Each Associate investigator must have an additional Form designated as 1572. Both forms are available at http://forms.psc.gov/forms/FDA/fda.html
- Table of contents
- Introductory statement and summary of general investigational plan
- Product information including chemistry, manufacturing and control information

IND Requirements based on 21CFR312.23

- Pharmacology and toxicology information
- Summary of prior human experience with the product, if applicable.
- Clinical protocols. Specific listings and requirements are noted in the regulations for various protocol types.
- Special topic information such as dependence or abuse potential, radioactive information, and plans for pediatric studies.

Clinical Review Elements

- Adverse event reporting consistent with 21CFR312.32
- Patient withdrawal criteria
- Study stopping criteria
- Adequate informed consent procedure
- Study conduct monitoring in compliance with Good Clinical Practice (ICH E6)

Investigator Brochures

- An Investigator's Brochure is required
  - if the planned investigation will occur at multiple sites and
  - the sponsor is not a sponsor-investigator.
- Most academic investigator initiated studies that file for an IND are considered sponsor-investigator studies and will not require an Investigator's Brochure unless the product is supplied by a third party.
- The IND regulations refer to the requirements for Investigator Brochure in two complementary sections and both sections apply
  - 21CFR312.23 (a) (5)
  - 21CFR312.55.

Common Clinical Reasons for Clinical Hold

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

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

Common Clinical Reasons for Clinical Hold

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 reporting procedures inadequate