# REGULATORY CONCERNS IN CELLULAR THERAPY

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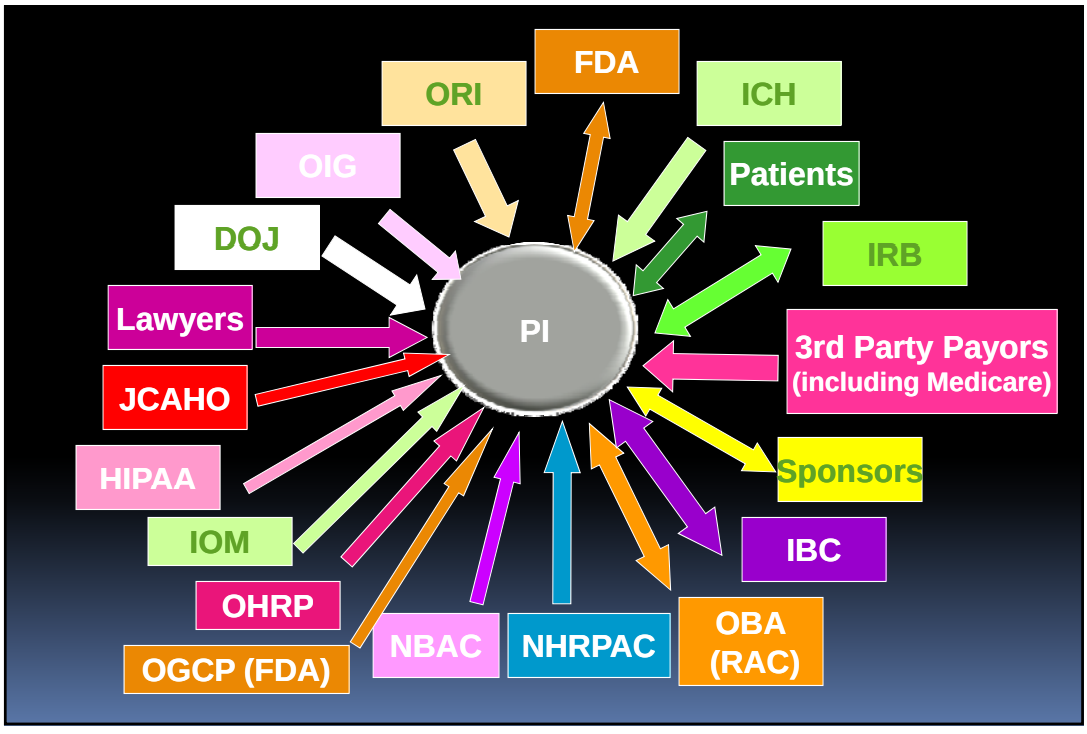

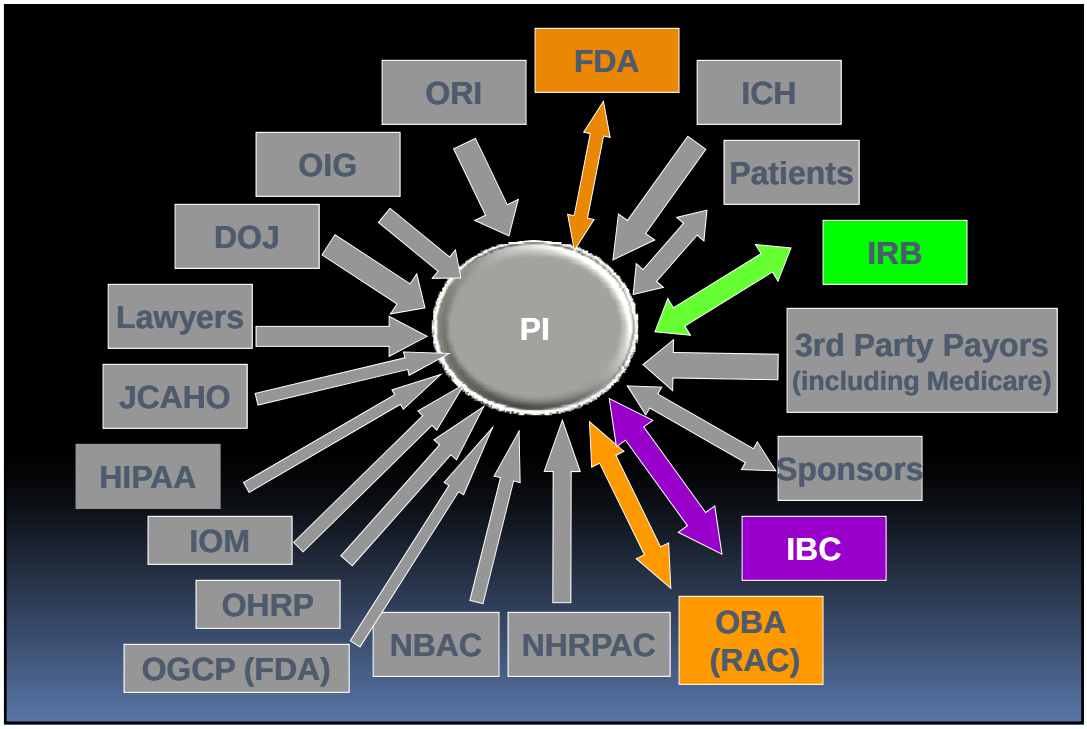
FDA
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(including Medicare)
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(RAC)
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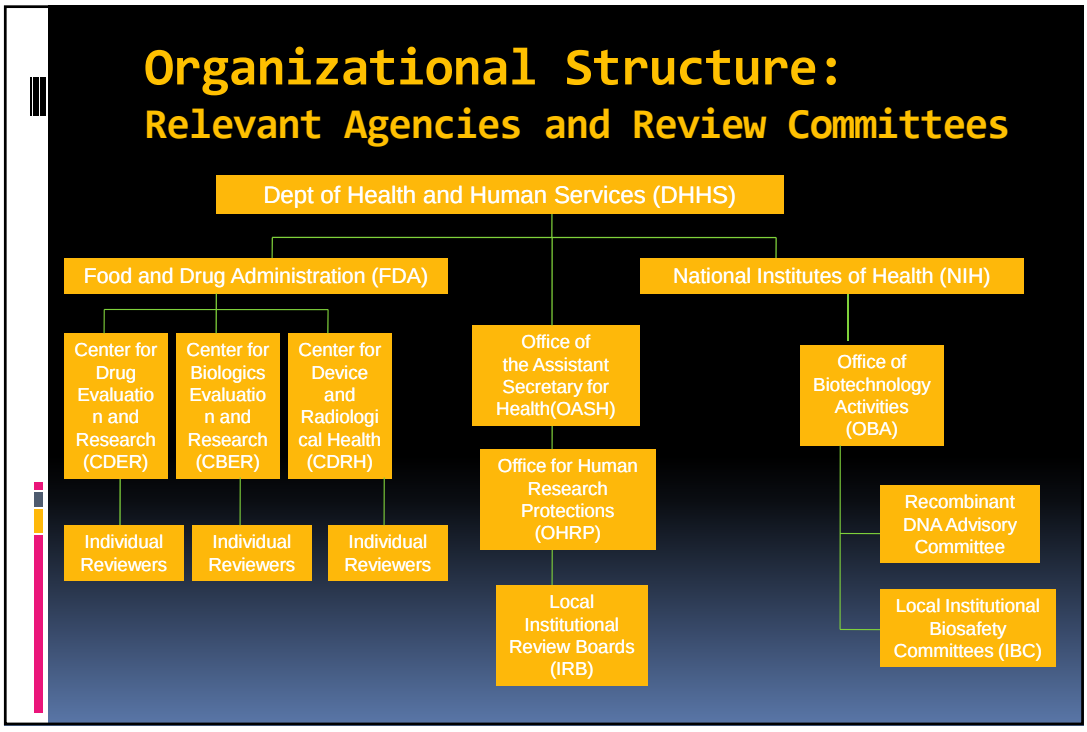

Organizational Structure:
Relevant Agencies and Review Committees
Dept of Health and Human Services (DHHS)
Food and Drug Administration (FDA)
National Institutes of Health (NIH)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Device and Radiological Health (CDRH)
Office of the Assistant Secretary for Health(OASH)
Office of Biotechnology Activities (OBA)
Individual Reviewers
Individual Reviewers
Individual Reviewers
Office for Human Research Protections (OHRP)
Recombinant DNA Advisory Committee
Local Institutional Review Boards (IRB)
Local Institutional Biosafety Committees (IBC)

## The Drug Development Process

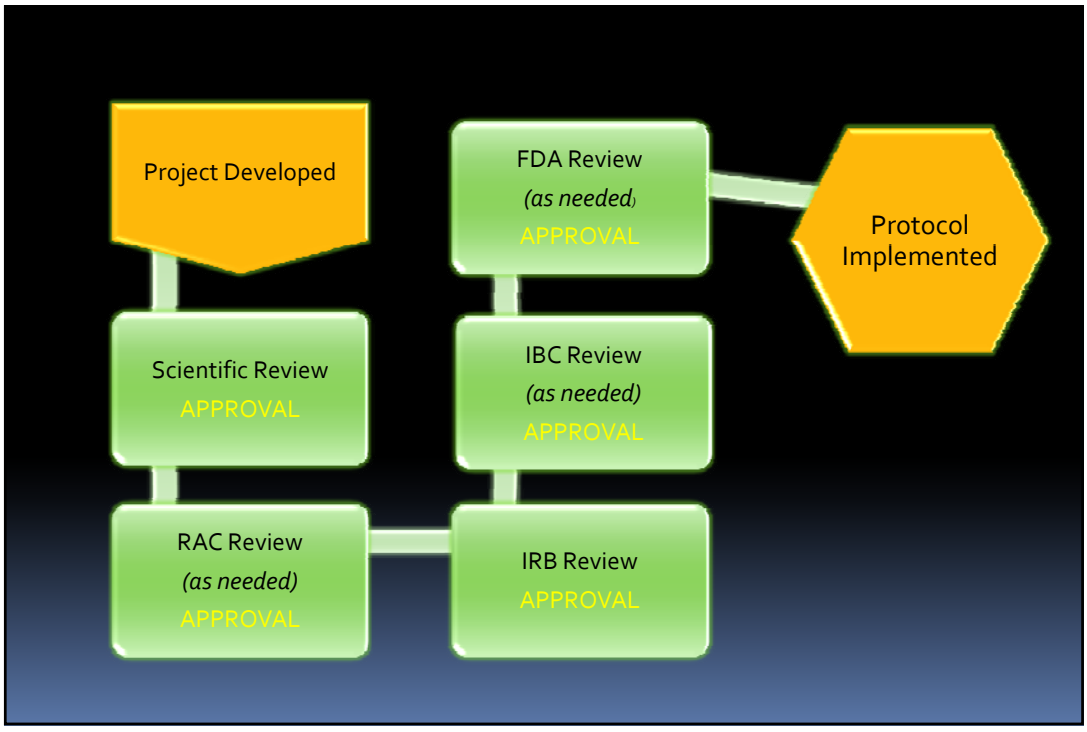
- Pre-clinical Investigations
- IND
- Clinical Trials
  - Phase I
  - Phase II
  - Phase III
- NDA
- Phase IV Trials

## Components of a Protocol

- Objectives
- Background and Rationale
- Drug Information
- Patient Eligibility Criteria
- Treatment Plan
- Monitoring of Patients
- Criteria for Response Assessment
- Statistical Considerations
- Adverse Reaction Reporting
- Consent Form

## Consent Form

- Should provide enough information for the subject to understand and evaluate:
  - Purpose of the study
  - Procedures involved in the study
  - Risks and benefits
  - Alternatives
  - Reason for participation



## Recombinant DNA Advisory Committee (RAC)


- The goal of the Recombinant DNA Advisory Committee is to consider the current state of knowledge and technology regarding DNA recombinants, their survival in nature, their transferability to other organisms, and their societal impact.

## Included in the RAC Submission

- Scientific Abstract
- Non-Technical Abstract
- Response to Appendix M-II through M-V
- Clinical Protocol
- Approved Informed Consent
- Curricula Vitae
- Institutional Biosafety and Institutional Review Board (IRB) Approvals

## RAC submissions should be done for:

- New Protocols
- Serious Adverse Events
- Protocol Amendments
- Annual Reports

## Institutional Biosafety Committee (IBC)

- Reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with the *NIH Guidelines* as specified in Section III, *Experiments Covered by the NIH Guidelines*, and approving those research projects that are found to conform with the *NIH Guidelines*.

## Institutional Biosafety Committee (IBC) Submissions


- Institution Specific

## Institutional Biosafety Committee (IBC) Submission Updates

- Institution Specific

## Institutional Review Board (IRB)

- Federally mandated committee of reviewers that evaluates the ethical implications of a clinical study protocol

## The Role of the Institutional Review Board (IRB)

The IRB is responsible for reviewing and approving all human subject research with consideration given to:

- The risk to the subjects
- Anticipated benefits to the subjects and others
- The importance of the knowledge that may be reasonably expected to result
- The informed consent to be employed

## Institutional Review Board (IRB) Submissions

- Institution Specific

## Institutional Review Board (IRB) Submission Updates

- Amendments
- Unanticipated Problems Involving Risk to Subjects or Others (this includes adverse events but can include other scenarios as well)
- Annual Reports

## Food and Drug Administration (FDA)

- Authorized by Congress to enforce the Federal Food, Drug, and Cosmetic Act and several other public health laws, the agency monitors the manufacture, import, transport, storage, and sale of drug and medical devices in this country.
- FDA ensures that the medicines and medical devices sold in this country are safe and effective

## Included in the IND

- Cover sheet (form 1571)
- Table of contents
- Introduction
- General Investigational Plan
- Investigator's Brochure
- Clinical Protocol
- Chemistry, Manufacturing, and Control data (CMC)
- Pharmacology and toxicology data
- Previous human experience
- Additional information
  - 1572
  - 3454
  - 3455
  - 3674

## FDA Form 1571

- Prepared by IND Sponsor
- Contains the following types of information:
  - Sponsor demographics
  - Type of study
  - Type of submission
  - Serial number of submission
- Included with each submission to the FDA
- Available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html

## FDA Form 1572

- Prepared by PI
- Contains the following types of information:
  - PI Information
  - Site information
  - IRB information
  - Lab information
  - Co-Investigator list
- Submitted to the FDA by the IND sponsor when new sites are added or when information changes
- Available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html

## Financial Disclosure

- The sponsor is also required to obtain the investigator's commitment to promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study. By collecting the information prior to study start, the sponsor will be aware of any potential problems, can consult with the agency early on, and take steps to minimize the potential for bias.

## Financial Disclosure Forms

- **Form 3454 (PI)**
- **Form 3455 (co-investigator)**
- **These forms don't have to be submitted to the FDA until the NDA is filed BUT you do need to have them on hand**

## Documentation of submission to ClinTrials

- The ClinicalTrials.gov Protocol Registration System (PRS) is a web-based tool developed for submitting clinical trials information to ClinicalTrials.gov.
- Web address: https://register.clinicaltrials.gov
- Documented in the IND submission through completion of FDA form 3674
- Responsibility lies with the "responsible party" who can be defined as the PI or the Sponsor

## The IND should be amended for:

NOTE: All submissions are made by the IND sponsor

- Protocol Amendments
- Information Amendments
- IND Safety Reports
- Annual Reports

## ICH and FDA
## Definition of a Serious Adverse Event

- A *serious adverse event (SAE)* is one that:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of an existing hospitalization
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly or birth defect.

## ICH : Definition of a Serious Adverse Drug Reaction

- A *serious adverse drug reaction* is one that meets at least one of the five categories specified above and in which a causal relationship between the medicinal product and the adverse event is a reasonable possibility (i.e. it cannot be ruled out).

## FDA : Definition of a Serious Adverse Event or Serious Suspected Adverse Reaction

- A *serious adverse reaction* is one that meets at least one of the five categories specified above and in which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event This implies that the event should be ruled in as a possibility

## ICH and FDA: Definition of an Unexpected Adverse Reaction

- An *unexpected adverse drug reaction* is an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

## FDA Guidelines for Reporting Adverse Reactions (ARs)

- Serious and unexpected Adverse Reaction:
  - Fatal or life-threatening unexpected adverse reactions should be reported to regulatory agencies by phone, fax, or in writing within 7 calendar days after the sponsor is first notified of the event.
  - A complete report should be submitted to the regulatory agencies within 8 additional calendar days (total of 15 calendar days).

## More about ARs

- All other serious unexpected ARs must be filed with the appropriate regulatory agencies within 15 calendar days.
- At the time of annual report (or more frequently if determined by the FDA) relevant toxicities should be summarized

## Additional Sites

- IRB approval for EACH site (unless a central IRB is used) – local PI is responsible
- IBC approval for EACH site – local PI is responsible
- One FDA submission (IND) per protocol however separate documentation is required as per next slide
- One RAC submission updated with regulatory approvals and CVs from each site

## Additional Sites

- **Sponsor must obtain:**
  - **1572 and associated documents**
    - **Medical Licenses (kept on file)**
    - **CVs (these then are submitted to the FDA)**
    - **Conflict of Interest Forms**
    - **Laboratory Normals and Certifications (kept on file)**
  - **IRB approvals of initial submissions, amendments, AEs, and renewals**
    - **These are kept on file by the Study Sponsor and are not necessarily sent to the FDA**

## To be clear

- ALL clinical research using human subjects must be reviewed and approved by an IRB prior to treating patients. For multi-institutional studies the sponsor (IND Holder) must ensure this is done at all sites.

## Other Requirements of the FDA - Study Monitoring

- Quality Assurance
  aka Monitoring
- Quality Control
  aka Establishment of Standards and Related Training
- Data Safety Monitoring (DSMB)
- This is for ALL Sites/Data

## Quality Assurance

- The FDA issued a guidance in January 1998
- Requested as part of the 3/6/00 letters to holders of gene therapy INDs
- Commonly noted as a deficiency on FDA warning letters
- QA Plan required by NIH for some applications
- Monitoring required by FDA and ICH for sponsors of multi-site studies

## Quality Assurance

- Is retrospective
- QA:
  - Ensures that SOPs for protocol development, conduct of clinical trials, and data collection/management are accurately defined and being followed
  - Reviews regulatory documents including investigational agent accountability, investigator CVs and laboratory certifications
  - Reviews selected patient charts for crucial data elements

## Quality Control

- Excerpt from FDA letter (Winter 2003):
  - "The conduct monitoring plan for your clinical trial contains several deficiencies. The request extent of study conduct monitoring is described in the FDA Gene Therapy letter of March 6, 2000…Please be aware that monitoring is the process of continuous "real-time" corroboration of completeness and accuracy of information and adherence to standard procedures. We note that your descriptions …refer to study "auditing" a retrospective monitoring…"

## Quality Control

- Is Prospective
- The QC Program:
  - Evaluates the conduct of clinical trials and the compliance of clinical research operations staff with all federal regulations, International Conference on Harmonization Good Clinical Practices (ICH GCP) and institutional standard operating procedures (SOP).
  - Provides training to new clinical research operations personnel and continuing education to all clinical research personnel.
  - Implements or improves the operational processes established in the SOPs.

## Data Safety Monitoring (DSMB)

- NIH 1979 Policy which included the concept that "every clinical trial should have provision for data and safety monitoring
- NIH 1998 Policy on Data and Safety Monitoring released
- NIH 2000 Further Guidance on DSMB released
- FDA Guidance released 2001, 2005, 2006

## Data Safety Monitoring

- The method and degree of monitoring should be commensurate with the degree of risk involved in participation in the trial as well as the size and complexity of the clinical trial
  - All Phase III trials supported by NIH must be monitored by a DSMB
  - Phase I and II studies may also use DSMBs however, smaller clinical trials may not require this level of oversight and alternative monitoring plans may be more appropriate
  - The FDA requires that the sponsor have a plan for providing Data Safety Monitoring.

## Data Safety Monitoring

- The study should be monitored for:
  - Effectiveness
  - Safety
  - Study Conduct
  - Consideration of External Data

## Data Safety Monitoring

- The DSMB should have written SOPs.
- It must have a written policy describing how AEs will be reported to the IRB, FDA, NIH, and OBA (if required)
- It may also include procedures for ensuring:
  - Safety of participants/volunteers
  - Validity and integrity of the data
  - Enrollment rate relative to expectation, characteristics of participants
  - Retention of participants, adherence to protocol
  - Data completeness

# In addition……

- For clinical research a significant infrastructure may be required
  - Regulatory Staff
  - Research Coordinators
  - Data Management
  - Investigational Drug Pharmacists
  - Laboratory Staff
  - Database Support
  - Quality Assurance
  - Quality Control
  - Administrative support
- Training and Documentation of Training is Required and must be Maintained