CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FDA Expectations for INDs for Cellular and Gene Therapy

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Scope of Talk

Focus on Products Regulated Under Section 351 of PHS Act (Products needing IND/IDE)

- Introduction
- Chemistry, Manufacturing, and Controls (CMC)
- Preclinical Testing
- Clinical Trials

CBER Mission Statement

The mission of CBER is to protect and enhance the public health through regulation of **biological** and related products including blood and diagnostics, vaccines, biological therapeutics and of related drugs and devices, according to statutory authorities. The regulation of these products is founded on **science and law** to ensure their purity, potency, safety, efficacy and availability.

Safety is Always Primary

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.

IND Regulations [21 CFR 312.22 (a)]

Safety of a Biological Product is Relative

"The relative freedom from harmful effects of the recipient when a product is prudently administered, taking into consideration the characteristics of the product in the relationship to the condition of the recipient at the time; thus the property of safety is **relative**."

21 CFR, Subchapter F

FDA Review is Product-based

- Parallels prudent product development
- Dependent on characteristics of specific product
- Preclinical studies designed to support use of specific products
- Clinical trial design supported by manufacturing, preclinical data
- Supported by science, framed by regulations

Early Communication ("pre-pre-IND")

- Non-binding, informal scientific discussion between FDA and sponsor
  - Via telecons
  - Via scientific meetings/workshops
  - Via outreach presentations (*i.e.*, this meeting)
- Provide pre-read materials to FDA
- Discuss specific issue (s) of interest
- A two-way communication to allow for information exchange

Pre-IND Meeting

- Submit a pre-IND package to include:
- Product development/characterization
  - Chemistry, Manufacturing and Controls (CMC)
  - Summary of device information (if applicable)
    - Bench and/or *in vivo*
- Summary of preclinical information
    - Pharmacology/Toxicology - *in vitro* and/or *in vivo*
- Proposed clinical protocol

Chemistry, Manufacturing, and Controls (CMC)

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Ensuring a Safe Product

- Controlled manufacturing process
- Product Testing

Basic elements of each must be in place from initiation of phase 1 trials

Controls increase during product development

Control of the Manufacturing Process

- Defined manufacturing procedures
  - Follow written procedures
  - Keep records for each product lot
- Segregation and tracking procedures
  - Prevent cross-contamination and mix-ups
- Facility conditions to support aseptic processing
- Ensure quality of all ancillary materials used
- Trained personnel

Product Characterization

- Safety
- Identity
- Purity
- Potency
- Stability
- Development of Specifications
  - test methods and criteria

Product Testing During Clinical Development

- Safety testing is required on each lot from phase 1
  - Infectious agents
  - Microbiological safety
  - Mycoplasma (if cells are cultured)
  - Endotoxin (if open system)
  - Cell viability
- Recommend early implementation of other characterization testing
  - Identity, purity, potency, additional characterization

Additional product characterization

- Characterization of cell populations
  - Morphology
  - Immunophenotype
  - Proliferative potential
  - Colony formation
  - Cytokine production
  - Gene and protein expression
- Define product and develop specifications for product release
- Product Stability

For guidance on preparation of CMC section of IND, please refer to:

- Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (2003) at http://www.fda.gov/cber/gdlns/cmcsomcell.pdf

- Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2004) http://www.fda.gov/cber/gdlns/gtindcmc.pdf

Preclinical Testing

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Phase 1 Preclinical Expectations

- Scientific basis for conducting clinical trial
  - Feasibility/establishment of rationale
  - Establish pharmacologically effective dose(s)
  - Optimize ROA/dosing regimen
  - Rationale for species/model selection for further tests
- Recommend initial safe dose & dose escalation scheme in humans
  - Identification of potential target tissue(s) of toxicity/activity
  - Identification of parameters to monitor clinically
  - Identification of patient eligibility criteria

Ideal Animal Model for Cell and Gene Therapies

- Similar pathophysiology to humans
  - Improves predictability of human risks
- Similar anatomy to humans
  - Allows modeling of device use with clinical device
  - Allows for dose exploration
- Immune tolerance to human cells
  - Allows use of clinical cellular product

Ideal Animal Model for Cell and Gene Therapies

- Ideal model does not exist
- Should understand abilities and limitations of each available model and weigh each in assessment of the overall suitability of a model to provide support for clinical trial

Potential Animal Study Designs

- Pharmacology or “proof of concept” studies in animal model of disease
- Toxicology studies in healthy animals
- Hybrid pharmacology-toxicology study design
  - Animal model of disease
  - Toxicology endpoints

Toxicology Study Design

- Appropriate controls
- Mimicking clinical treatment as closely as possible
  - Product, ROA, formulation, device, dose regimen, etc…
- Reasonable group size
  - n = >5/sex/group/time point for small animals
  - n = >3/sex/group/time point for large animals
- Endpoints
  - Mortality, clinical observation,cardiac function, hematology, serum chemistry, gross pathology, histopatholgy, body weights, food consumption etc…

IND Regulations

- 21CFR312.23 (8)(ii)(b)
  - For each toxicology study that is intended **primarily to support the safety** of the proposed clinical investigation, a **full tabulation of data** suitable for detailed review…..

Sources of Data to Support Initiation of Clinical Trials

- Safety Assessment in Animal Model
  - GLP-compliant toxicology studies
  - Well-controlled studies conducted “in house”
- Published data in peer-reviewed journals
- Cross reference to identical/similar product in previously submitted MF/INDs
- *In vitro* studies

Perils of Using Published Animal or Human Studies as Sole Support for Initiation of Clinical Trials

- Often they were ***not designed to answer a toxicologic*** question, and therefore, adequate toxicology endpoints may not have been incorporated into the design
- Published reports ***must provide sufficient information for independent review***
- Products must be comparable

Clinical Trials

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Clinical Trial Review

- Biologic and device components considered in the context of their use in the proposed clincial trial
- Early communication with FDA is helpful
  - Enhance similarities among animal studies, bench studies, previous studies and proposed clincial trial
  - Define target populations
  - Discuss innovative clinical trial designs

Clinical Trial Review

- Primary focus is subject safety in all phases of investigation
- Phase 2 and 3 Trials
  - Quality of trial design and conduct is adequate to generate sufficient data to permit an evaluation of a product's effectiveness and safety

Common Clinical Issues that Delay Initiation of Human Trials

- Plan for monitoring safety of subjects inadequate to detect important adverse events in a timely manner
- Eligibility criteria that are vague or allow enrollment of especially vulnerable patients
- Rate of subject enrollment not specified
- Insufficiently detailed description of the administration procedure

Subject Safety Monitoring

- Usually based on toxicities predicted from animal studies or product class
- These products are in early stage and are rapidly evolving
- Generally ask for frequent early noninvasive monitoring
- Duration of product activity unclear (some intended to have life long effects)

Eligibility Criteria Considerations

- Include screening procedures and/or criteria to precisely identify eligibility
- Consider exclusion of subjects who are at special risk from product administration or protocol specified procedures
- In exploratory studies do not enroll subjects if participation excludes them from receiving conventional beneficial therapy

Staggering Subject Enrollment

- Time between **subjects** within a dose cohort should be sufficient to allow assessment of important acute toxicities
- Time between **dose cohorts** should be sufficient for observation of potential adverse effects based on the pharmacodynamic effects observed in preclinical studies

Administration Procedure

- FDA can not assess risk of administration procedure or other protocol specified procedures unless they are adequately explained
- In general, the procedures must be detailed enough so that someone unfamiliar with the trial would perform them as intended from the description

Conclusion

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