FDA Perspective on the Preclinical Evaluation of Biological Therapies for Cancer

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Presentation Outline

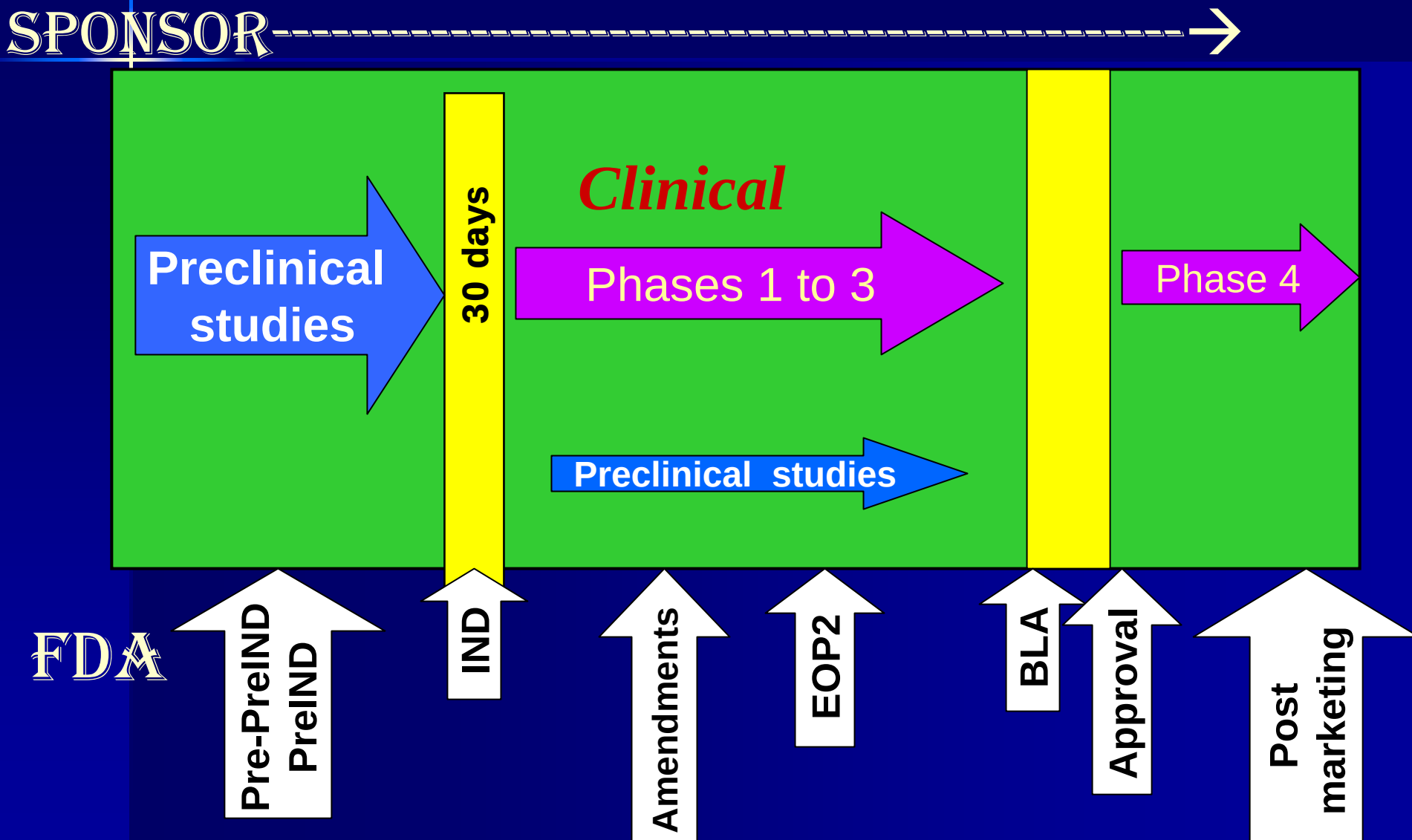
- Introduction
- Biological therapies for cancer regulated by FDA
- Rationale for conducting preclinical studies
- Pharmacology studies
- Toxicology studies
- Translating preclinical data to the clinical trial

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)]

Product Development Timeline



Expectations for Preclinical Studies

Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or *in vitro*, on the basis of which the sponsor has concluded that it is reasonable safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.

IND Regulations [21 CFR 312.23 (a)(8)]

Biological Therapies for Cancer Regulated by FDA

Center for Drug Evaluation and Research (CDER)

- Cytokines
- Enzymes
- Growth Factors
- Monoclonal antibodies
- Other biological immunomodulators
- Radio-labeled biologics for therapeutic use
- Recombinant proteins

Biological Therapies for Cancer Regulated by FDA

Center for Biologics Evaluation and Research (CBER)

Conventional antigen-based:

Polypeptides; fusion/conjugated proteins; anti-idiotype antibodies

Cell therapy-based:

Autologous/allogeneic somatic cells/stem cells with or without activation/expansion; tumor cells or lysates; or tumor cells fused with normal somatic cells (e.g., dendritic cells)

Gene therapy-based:

Attenuated bacteria; plasmid DNA; DNA/RNA/viral vectors; *ex vivo* genetically modified cells; yeast vectors with/without gene modification

Biological Therapies for Cancer Regulated by CBER:

Challenges:

- **Products:** Can be complex, diverse, and contain novel features in order to achieve anti-tumor effect
- Administered in combination with adjuvants (e.g., TLR agonists, cytokines), immunomodulators, monoclonal antibodies, growth factors, chemotherapy or radiation therapy

Rationale for Conducting Preclinical Studies

- Mechanism of action
- Pharmacological or biological activities
- Target or off-target toxicities
- Preliminary risk/benefit assessment
- Guide clinical trial(s) design

Pharmacology Studies Proof-of-Concept (POC)

Goal:

Provide the scientific basis to support the rationale and feasibility for conducting the clinical trial

Pharmacology Studies

In vitro or *in vivo* studies conducted to determine:

- Functional response (i.e., anti-tumor activity)
- The nature of immunological responses
- Permissive cell populations or cell lines for further testing
- Biologically responsive animal species for further testing
- Pharmacologically effective dose(s) and dose response
- Optimization of the route of administration (ROA)
- Optimization of the dosing regimen

Toxicology Studies

Goal:

Selection of a safe starting dose and dose escalation scheme for the clinical trial

Toxicology Studies

Conducted to identify:

- Potential toxicities to organs/tissues, cells/proteins/genetic elements
- Delayed toxicities/reversibility of toxicities
- Dose/exposure (NOAEL)
- Subject Selection
- Parameters for clinical monitoring

FDA Approach to Preclinical Study Designs for Biologics

- Data-driven
- Question-based
- Based on the best available science, technology to date
- Follow FDA guidances, ICH guidelines and the CFR

Animal Species

- Biological relevance
  - Anatomy and pathophysiology
  - Biological activity & toxicity
- Animal numbers/sex/age
- Healthy animals vs. disease models
  - Healthy: toxicology endpoints
  - Disease:
    - Pharmacology endpoints
    - Pharmacology-toxicology endpoints

Control and Test Articles

- **Control article**:
  - Clinical vehicle/diluent/buffer
  - Provides background/baseline information
- **Test article:**
  - Intended clinical product or product comparable to clinical product

Route of Administration

Mimic the intended clinical route of administration as closely as possible

Dose Levels and Dosing Schedule

- Do the dose levels used in the toxicology study support a safe clinical starting dose and the planned clinical dose escalation scheme?
- Does the dosing schedule used in the toxicology study support the safety of the proposed clinical dosing schedule?

Study Duration

- Is the study duration sufficient to characterize the pharmacological/ biological activity profile?
- Is the study duration sufficient to characterize the toxicology profile?

Toxicology Study Endpoints

- Mortality
- Clinical signs/physical exams
- Body weights, food consumption
- Clinical pathology (hematology, chemistry, coagulation, urinalysis)
- Gross pathology
- Histopathology
- Immunological responses
- Other* (local tolerance, ophthalmology, neurological, developmental/reproductive, etc…)

* Some endpoints may be evaluated during later phase clinical trials

‘Pharmacokinetic’ Assessment

- Sensitive, specific and reproducible assays
- *In vitro* and *in vivo* studies
  - **Biodistribution**: vector-based products
  - **Cell trafficking/migration**: cellular-based products
  - **Tissue distribution**: antigen-based products
  - Binding specificity, binding affinity, cellular location or genetic integration, if applicable

Good Laboratory Practice

The toxicology studies should be conducted in compliance with Good Laboratory Practice (GLP) as per 21 CFR Part 58.

Sources of Preclinical Data to Support Clinical Trials

- Pharmacology/toxicology assessment in animals or *in vitro* conducted by the IND sponsor
- Cross reference to identical/similar products in previously submitted MFs/INDs
- Published data in peer-reviewed journals

Translating Preclinical Data to the Clinical Trial

- To what extent will data obtained from preclinical studies in the current animal models ‘predict’ the biological activity (immunological, anti-tumor, etc..) and/or the potential toxicities in human subjects?
- What *in vitro* studies and other new technologies can provide information that will bridge the *in vivo* preclinical data?

[Some] FDA Guidance Documents

Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events -11/28/06

Nonclinical Safety Evaluation of Drug or Biologic Combinations - 3/14/06

Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use - 2/28/97

Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications - 10/29/07

Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients - 5/18/05

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Thank you