

# Regulation of Tissue Engineered Products by the FDA

Pre-clinical trials, Safety, Efficacy, Clinical end-points

Robert T. McNally, Ph.D.  
CEO – Cell Dynamics, LLC

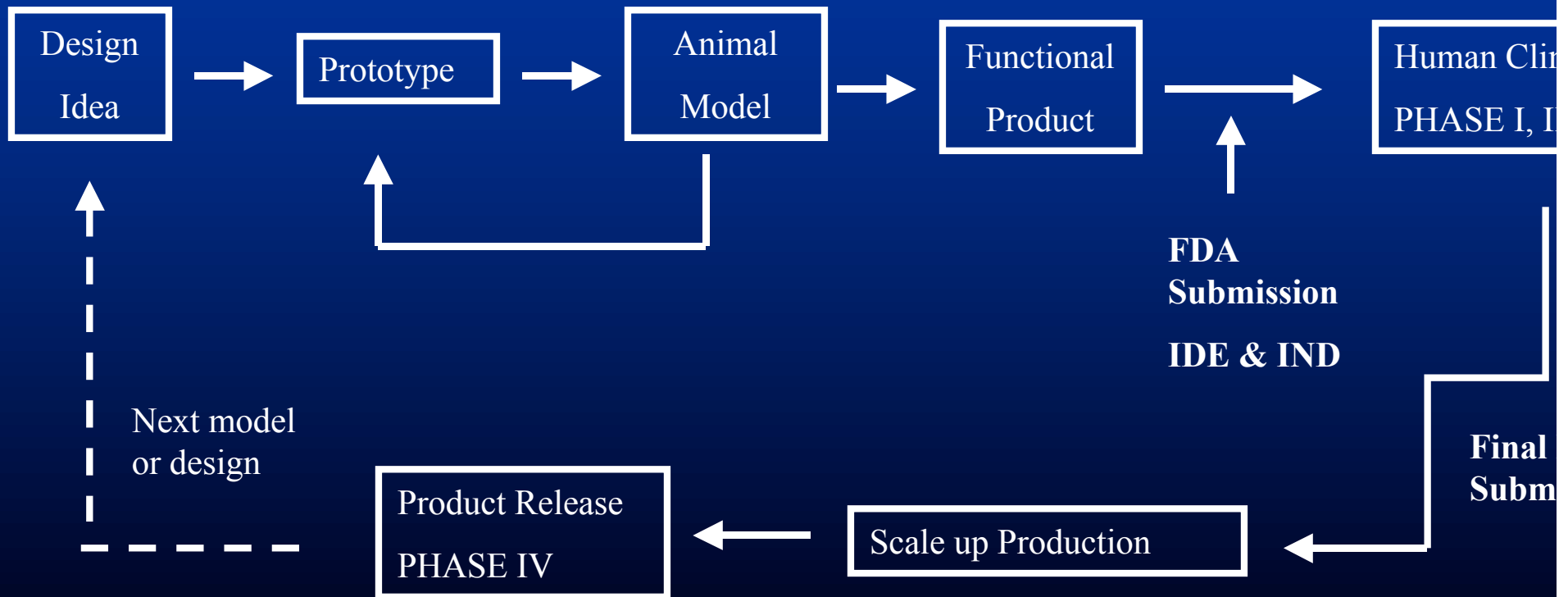
# GLOSSARY OF TERMS

- Pre-clinical Trials
  - Normally, animal trials designed to mimic the human condition the tissue engineered product is designed to correct
- Safety
  - DO NO HARM
  - Toxicology - Non-clinical safety study
  - Sometimes determined in pre-clinical trial
  - Definitely part of human (clinical) trials

# GLOSSARY OF TERMS

- Efficacy
  - Does it function for the intended purpose?
  - Does it function better than current clinical products?
- Clinical End-points
  - What is measurable to supply a statistically relevant observation to support safety and/or efficacy?

# Bioengineering Approach to Product Development



# Design Idea

- R&D
- Do not harm
- **Improvement over current products**
- **Can it be manufactured?**
- **End user friendly**
- **Will someone pay?**
- **FDA approvable?**

# Prototype ↔ Animal

- Toxicology
- Safety & efficacy
- Failure mode analysis
- Small vs. large animal
- Determine method of use

# Functional Product

- cGmp
- Control of:
  - Facility
  - Equipment (validation)
  - Personnel
  - Raw materials (audit)
  - Production
  - Storage
  - Documents
  - Final Product

# Human Clinicals

- Safety & efficacy
- Determine endpoints
- Clinical protocols

# Human Clinicals

## Phase I, II, III

- Gather Data



- Final FDA Submission



- Scale up production

# Product Release Phase IV

- Monitor for failure
- Determine failure modes
- Complications
- Complaints
- Generate performance statistics
- Suggest next generation product

# TISSUE ENGINEERING CONSTRUCT

Vascular Graft, Skin Sub, Valve Whatever?

Device

Prosthetic

IDE

Biologic

Likely Choice

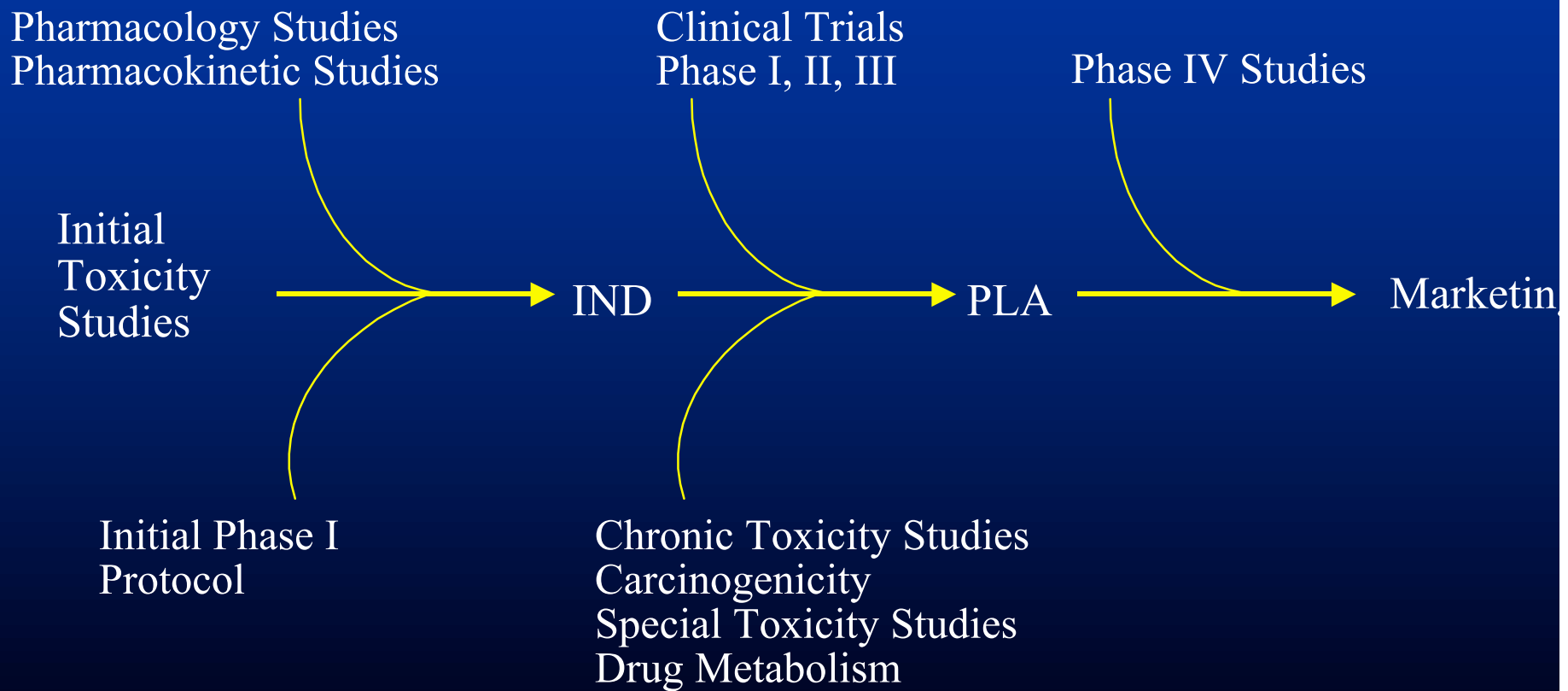
IND

Drug

Not Likely

IND

# REGULATORY APPROVAL OF NEW DRUGS/BIOLOGICS



# TISSUE ENGINEERED PRODUCTS AND THE FDA

- Tissues Regulated by the FDA
- Human Tissue as a Biologic
- 21 CFR / 1270 / 1271 Part C/210/211/820
- Proposed Legislation 1271
- FDA Proposed Regulatory Guidelines
  - Combinational Products

# REGULATED TISSUES AND CELLS

- Blood
- Human Breast Milk
- Reproductive Cells
- Bone Marrow
- Human Heart Valves
- Bone, Cornea, Vessels, Connective Tissue
- ?? Engineered and Cultured Tissues ??

# FDA NEW APPROACH

February 28, 1997

- “Proposed Approach to the Regulation of Cellular and Tissue-based Products”
  - Tiered system of regulation
  - Provides firm structure to regulations
  - Reduces restrictions on new technology development
  - Technology representing higher level of risk concerns receive greater level of review

# TIERED SYSTEM OF REGULATION

- Areas of Concern
  - Transmission of Communicable Disease
  - Processing
    - Minimal vs. more-than-minimal
  - Clinical Safety
    - Non-homologous use of cells/tissues
    - Non-tissue components in product
    - Metabolic function of cells/tissues
  - Promotion and Labeling
  - Facility / Product Registration

# TISSUE/CELL PROCESSING

- Minimal Manipulation vs. More-than-Minimal Manipulation
  - Alteration of biologic or functional characteristics of tissue or cell
- Less than Minimal Manipulation
  - Follow “GTPs” with no S&E Submission
- More-than-Minimal Manipulation
  - Follow GMPs with controls to address S&E concerns

\*Safety and Efficacy

# CLINICAL SAFETY

## IND or IDE for Safety/Effectiveness Data, if...

- More-than-minimal Manipulation
  - Alteration of biologic and functional character
- Non-homologous Use
  - Does not replace an analogous structural function
- Combination with a Non-tissue Component
- Tissue/Cell Used for Metabolic Purpose
  - Except reproductive or autologous tissue

# STEPS IN PRODUCT DEVELOPMENT

- Concept
  - Vascular Graft
- Design Review (Testing/Efficacy/End-points)
  - Xenograft Collagen & Mammalian Cells
- Prototype (Design Lock)
  - 5mm x 10cm
- *In-vitro* Feasibility
  - Hemodynamics
- *In-vivo* Feasibility
  - 3 Animals Carotid

# PRECLINICAL TESTING

- Selection of Animal Species
  - Rat
    - Large #
    - M&F
- Mode of Delivery
  - Dog
    - More likely to mimic human delivery
- Immunogenicity - Probably a Big Issue with Tissue Engineering Constructs
  - Measurement of antibodies

# STEPS IN PRODUCT DEVELOPMENT

- Analysis of Raw Materials/Supplies
  - Purity, Identity, Strength, Sterility, Stability
- CMC (Validation/Viral Assay Development)
  - ID By-products and Interaction of All Components
- Documentation Process
  - SOP/cGMP/GLP
- Toxicology
  - Acute, Subacute/Subchronic, Chronic
- Pre-clinical Testing (Animal Efficacy/Safety)
  - Define Human Protocol/End-points

# PRODUCT DETAIL

- Product
  - List of all components
  - Manufacturing and packaging
  - Limits to identify, strength, quality, purity
  - Stability
- Labeling
  - Pharmacology and toxicology
  - Previous human experience

# PRODUCT DETAIL

- CMC
  - Chemistry Manufacturing and Control
  - Assure proper identification of quality, purity, and strength of product
  - Product made from impure components, chemical structures which are toxic, and chemical instability
  - Poorly characterized cell bank
  - Starting with source of supply, is it consistent and work towards current product?
  - How is it made? Identity, strength, quality, purity

# SAFETY PHARMACOLOGY

- Effects on Cardiovascular, Respiratory, Central Nervous System, Renal System, etc.

# TOXICOKINETICS AND PHARMACOKINETICS (ADME)

- Absorption
- Distribution
  - Labeled studies
- Metabolism
  - Sophisticated detection method chromatographic
- Execution
- Immunotoxicity
- Reproduction performance
- Genotoxicity
- Carcinogenicity
- Local Tolerance

# NON-CLINICAL SAFETY

- General Purpose is to Evaluate Negative Effects of Large Dosing a Product in Small Animal Models and to Help Determine the Limits to Safety of the Product (e.g., How Much Can be Used Before the Product Induces a Negative Effect?).
- Safety Pharmacology - Effect on Vital Function (e.g., CV, Central Nervous System, or Respiratory System).

# GENERAL CONSIDERATIONS

<u>Duration of Human Exposure</u>	<u>Phase of Clinical Trial</u>	<u>Duration of Animal Toxicity Studies</u>
1-3 Days	I, II, III, PLA	2 Species; 2 Weeks
Up to 2 Weeks	I	2 Species; 2 Weeks
	II	2 Species, Up to 4 Weeks
	III, PLA	2 Species; Up to 3 Months
Up to 3 Months	I, II	2 Species; 4 Weeks
	III	2 Species; 3 Months
	PLA	2 Species; Up to 6 Months
6 Months to Unlimited	I, II	2 Species; 3 Months
	III	2 Species; 6 Months or Longer
	PLA	2 Species; 12 Months (Non-rodent) 18 Months (Rodent)

# STEPS IN PRODUCT DEVELOPMENT

- Human Protocol
  - Phase I
    - Not Applicable for A/V Shunt
  - Phase II
    - Safety/Efficacy
    - 3 Sites x 10 Patients on Dialysis
    - Develop Statistics for Phase III
  - Phase III
    - Efficacy
    - 10 Sites x 30 Patients on Dialysis

# CLINICAL TRIAL EXAMPLE

- Vascular Graft A/V Shunt for Kidney Dialysis Versus PTFE
  - Safety (Do No Harm)
    - Prions Test: Blood Test
    - Microbiology Test: Blood Test
    - No Aneurysm Test: Doppler
    - Occlusion Test: Doppler
  - Efficacy (Functional Parameters)
    - Flow Test: Doppler
    - # of Punctures Test: Measurement
  - End-points (Label Claims)
    - Immunogenic Test: Blood Test
    - Flow Test: Doppler
    - Patency Test: Doppler
    - Hematoma Test: Measurement

# CLINICAL TRIAL EXAMPLE

- Skin Graft Versus Porcine Patch for Burn Patients with  $>50\%$  Burn
  - Safety (Do No Harm)
  - Efficacy (Functional Parameters)
  - End-points (Label Claims)

# GENERAL CONSIDERATIONS FOR HUMAN CLINICAL TRIALS

- *Phase I:* Healthy Volunteer (10-50 pts)
  - Single dose
  - Dose escalation
  - Repeated dose

# GENERAL CONSIDERATIONS FOR HUMAN CLINICAL TRIALS

- *Phase II: Small Scale*  
(3 Hospitals Doing 10 Procedures for the Indicated Condition)  
—Objectives:
  - Work on surgical technique
  - Refine end-points
  - Reassured about doing NO HARM (Safety)
  - Helps define the statistical difference between the control group and experimental product to determine the number of patients required for Phase III

# GENERAL CONSIDERATIONS FOR HUMAN CLINICAL TRIALS

- *Phase III:* Large Scale Statistically Relevant Studies  
(Typically 10 Sites Doing 20 or More Patients per Site)

# STEPS IN PRODUCT DEVELOPMENT

- Product License Application/FDA Submission
- Approval (3-5 Years After Initial Concept)
- Post-Marketing Surveillance

# DRUG DEVELOPMENT IN THE UNITED STATES

