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
• **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
- Prototype
- Animal Model
- Functional Product
- Human Clinical PHASE I, II, III
- FDA Submission
- IDE & IND
- Final FDA Submission
- Scale up Production
- Product Release PHASE IV
- Next model or design
Design Idea

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

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

- Pharmacology Studies
- Pharmacokinetic Studies
- Initial Toxicity Studies
- Initial Phase I Protocol
- Clinical Trials
  - Phase I, II, III
- Chronic Toxicity Studies
  - Carcinogenicity
  - Special Toxicity Studies
  - Drug Metabolism
- Phase IV Studies
- Marketing
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

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

Average Time Required

- Discovery
  - Synthesis
  - Laboratory
  - Preclinical (Animal) Pharmacology
  - Toxicology
  - IND Filing
  - Clinical
    - IND Filing
    - Phase 1
    - Phase 2
    - Phase 3
    - Phase 3 (Cont.)
    - Phase 4
  - PLA Submission
  - PLA Approval
  - Manifested

3.5 years 6 years 2 years

(?)