FDA Perspective/Review of Cell Scaffold Products

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FDA/NIST Sponsored Workshop on In Vitro Analyses of Cell/Scaffold Products

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NTSB, Washington, D.C.

Outline

- Introduction
  - Overview of Workshop and Goals
  - How FDA develops policy/guidance
- Cell/Scaffold characterization: pathways and gaps

FDA Mission

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

Promises and Challenges

- Promising areas of scientific development may pave the way for novel therapeutics
- Characterizing these products is a key early challenge for sponsors
- Developing/assessing the tools for characterization is a common interest for FDA, NIST, and the scientific community

Background on Regulations and Policy Development

- Constitution
- Statutes
- Regulations
- Guidance

Statutes

- Federal Food, Drug and Cosmetic Act
- Other Statutes
  - e.g. Administrative Procedure Act
  - Federal Advisory Committee Act
- Public Health Service Act
  - licensing provisions
  - prevent communicable disease

Regulations

- Regulation- “an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy
- Has binding effect
- We create rules under statutory authorities (PHS Act and FDC Act)
- Opportunity for public participation by written comments

Guidance Documents

(21 CFR 10.115(b))

- A document prepared for FDA staff, applicants/sponsors, and public that:
  - Describes FDA's interpretation of or policy on a regulatory issue; or
  - Relates to
    - The design, production, labeling, promotion, manufacturing, and testing of regulated products;
    - The processing, content, and evaluation or approval of submissions; and
    - Inspection and enforcement policies.

Examples

- Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs) 7/23/07
  - http://www.fda.gov/cber/gdlns/pbsc.htm
- Draft Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage 7/6/07
  - http://www.fda.gov/cber/gdlns/kneecart.htm

FDA, Review Science, and Policy Development

- Workshops (like this one!)
- Advisory Committee input
- FDA Research/Research collaborations
- Standards committees
- Critical Path Initiative
- Review experience
- Scientific exchanges at meetings

The FDA Critical Path Initiative

http://www.fda.gov/oc/initiatives/criticalpath/

Established to modernizing the evaluation of safety, efficacy and quality of medical products as they move from product selection and design to mass manufacture

- A key goal is to improve product safety and efficacy and speed products to the patients who need them and the consumers who use them.
- Involves collaborative efforts among government, academia, industry and patient groups.

FDA Critical Path Goals

- Get more innovative products to patients through development pathways that are efficient and predictable.
- Develop new toolkits that bring scientific advances into the product development process.
- Perform research on tools that remove specific identified obstacles in product development.

Critical Path Research at FDA

- Examples at CBER:
  - Markers predictive of cell fate, cell death, cell function
  - Analyze interaction of product cells with environment
  - Develop improved measurement technologies (quantitative flow cytometry, collaborations with NIST)
- Examples at CDRH
  - Identification of unanticipated mechanical problems related to the mechanical behavior or materials and devices in their intended environments
  - Development of standard test methodology for evaluating materials and devices

Biomarkers Consortium

Public-private biomedical research partnership managed by the Foundation for the National Institutes of Health (FNIH).

The Biomarkers Consortium involves government, industry, patient advocacy groups, and other non-profit private sector organizations. In addition to the Foundation for NIH, founding members include:

- NIH
- FDA
- PhRMA
- Centers for Medicare and Medicaid Services (CMS)
- Biotechnology Industry Organization.

•www.biomarkersconsortium.org

Outreach/Collaborations

- **Liaison meetings**
  - **ISCT**
  - **TERMC**
  - **AATB**
  - **EBAA**
- **Standards organizations**
  - **ASTM**
  - **AAMI**
  - **ISO**
- **Government organizations**
  - **NIST**
  - **MATES**
  - **NINDS**
  - **NCI**
  - **CDC**

Outreach/Collaborations, cont'd

- **Research collaborations**
  - **NIST**
  - **NCTR**
  - **NIH**
  - **CDC**
  - **Academic Institutions**
- **International activities**
  - **WHO**
  - **ICH**
- **Workshops**
  - **In Vitro Analyses of Cell/Scaffold Medical Products (with NIST)**
  - **FDA/NCI Workshop on Cancer Vaccines**
  - **Processing of Orthopedic, Cardiovascular, and Skin Allografts (with CDC)**
  - **US-Japan Cellular and Gene Therapy Workshop**

Workshop Goal

- Explore recent scientific advances to improve understanding of cell/scaffold constructs within the framework of a product under consideration for clinical evaluation
- Two Sessions:
  - In Vitro/Bench Top Characterization
  - Systematic and High Throughput Analyses

Questions for Speakers

- What questions should be addressed when evaluating cell/scaffolds in preparation for the first human studies?
- What test methods are available and what analytical procedures need to be researched developed and/or standardized for these products?

FDA Organization

- Office of the Commissioner
  - Office of Combination Products
- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cells, gene therapy, screening tests for blood safety
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CDER (Center for Drug Evaluation and Research): drugs, monoclonal antibodies, therapeutic proteins)
- CVM
- CFSAN
- NCTR

Regulatory Pathways

- Biologic (IND, BLA)
- Device (IDE, 510k, HDE, PMA)
- Combination Product

Cell Scaffold Products

- Guidances for Cellular, Gene Therapies, and Devices
- Leveraging existing guidances to support specific areas of tissue engineered medical products
  - CMC guidances for cellular products
  - General (CT and GT) preclinical guidances
  - Guidances for devices may be applicable to scaffolds
  - Many clinical guidances cross-cut product areas

Cell Therapy: Chemistry, Manufacturing, and Controls

Cells: Examples of Indications/Sources

- Pancreatic islets for diabetes
- Stem and skeletal muscle progenitor cells for ischemic cardiac
- Hematopoietic reconstitution in treatment of malignancies
- Stem cells for metabolic storage diseases
- Stem cells for CNS indications (Parkinson’s disease)
- Expanded autologous cartilage for joint repair

Cell Therapy Guidances

- FDA 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
- Guidance for Human Somatic Cell Therapy and Gene Therapy- 3/30/1998 http://www.fda.gov/cber/gdlns/somgene.pdf
- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)-8/8/2007 (http://www.fda.gov/cber/gdlns/tissdonor.pdf
- PTC in the Characterization of Cell Lines to Produce Biologicals, CBER, FDA, 1993.

Cells- Cell Source

- Starting Cells or Tissues
  - Cell source (tissue & cell type)
  - Infectious Disease Screening/Testing
    - Donor Screening and Testing (see rule, guidance)
  - Collection method (mobilization, surgery, leukapheresis, devices used)
- Cell Banks
  - Testing for adventitious agent contamination (microbial, viral)
  - Identity/stability/activity of the cell line

Cells- Component and Reagents

- Reagents used in manufacture
- Vendor/supplier/reagent quality (COAs)
- Source (animal: tissue, age and country of origin for bovine)
- Qualification programs
- Final concentration
- Removal from final product
- Use of antimicrobial agents
  - Effect on sterility testing
  - Allergy responses in patients

Cells- Manufacturing Procedures

- Manufacturing process and controls
  - Method of cell selection
  - Culture components (human serum, antibiotics, growth factors)
  - Irradiation (for certain tumorigenic cells)
    - cells are replication incompetent
    - calibration of cell irradiator source
  - Intermediate storage
  - Final harvest (if cells washed or cryopreserved)
  - Final formulation (excipients)
- Characterization of process residuals
- Prevention of product contamination
  - Terminal sterilization not feasible for live cells

Cells- Testing

- Testing to assure safety and quality
  - Safety Tests (sterility, mycoplasma)
  - Cell number
  - Viability
  - Identity (e.g. morphology, cellsurface markers)
  - Purity
    - Residual contaminants – cells, proteins, cytokines, antibiotics
    - Pyrogens/Endotoxin
  - Potency
    - Measure of biological function

Scaffold Characterization and Safety

Examples of Scaffold Materials

- *Resorbable and Non-Resorbable Polymers*
  - Polylactic acid (PLA), Polyglycolic acid (PGA), Nylon, Vapor-Sensitive Polymers
- *Physiological Materials*
  - Collagen, Hyaluronic acid, Processed Human Tissue

Surgical Mesh Considerations

- Manufacture
  - Starting materials
    - Synthetic material
      - Purity
      - Contaminates (e.g., organic solvents, heavy metals, cross-linking reagents)
    - Animal tissue
      - species and tissue
      - health of herd
      - health of each animal
      - tissue collection and transport

"Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh"
http://www.fda.gov/cdrh/ode/116.html

Surgical Mesh Considerations

- Manufacturing Processes
  - Reagents Used
  - Processes involved
  - Consistency of process
  - New contaminates introduced

- Sterilization Methods and Validation
  - Bacteria
  - Fungi
  - Viruses
  - Prions

Surgical Mesh Considerations

- Testing
  - Biocompatibility
    - Cytotoxicity
    - Sensitization
    - Irritation or Intracutaneous reactivity
    - Systemic toxicity (acute)
    - Genotoxicity (long term carcinogenicity)
    - Implantation (with histology of the surrounding tissue)
    - Hemolysis
    - Pyrogenicity

For material in the body for greater than 30 days:

- Subchronic toxicity
- Chronic toxicity

Surgical Mesh Considerations

- Surgical mesh characterization
  - Thickness (dimensions)
  - Pore size
  - Scaffold density
  - Tensile strength
  - Scaffold stiffness
  - Suture pullout strength
  - Burst strength and tear resistance
  - Pyrogenicity
  - Shelf-life

For resorbable material:

- How do properties change as a function of time?

Surgical Mesh Considerations

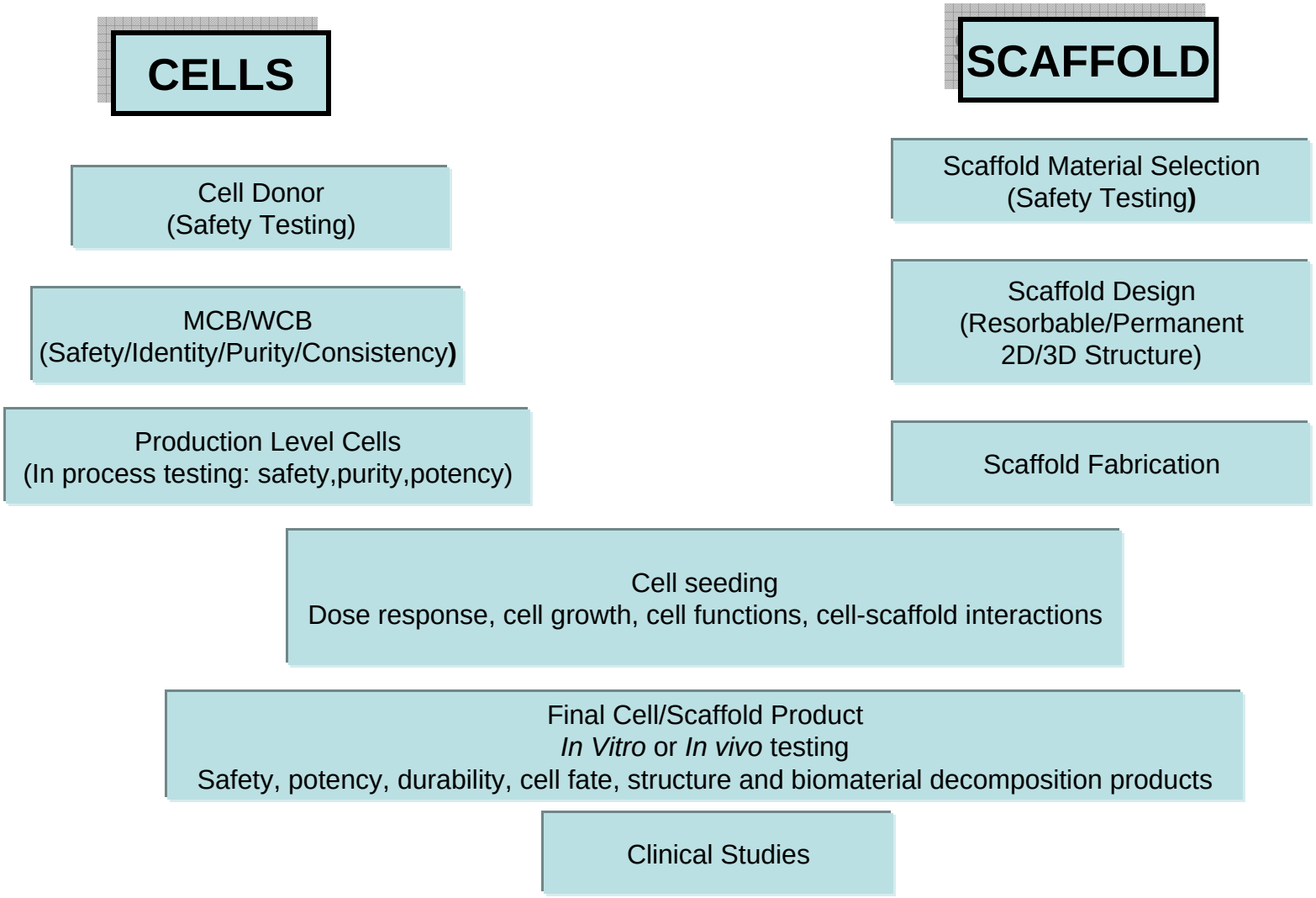
- Preclinical & Clinical Evaluations
  - The extent of animal and human studies of product performance and effectiveness are determined by the proposed clinical use.

Cell Scaffold Characterization

Cell Scaffold Examples

- Autologous or allogeneic cells on collagen or synthetic resorbable matrix for wound repair
- Cell seeded scaffolds for cardiovascular repair
- Encapsulated pancreatic islet cells
- Expanded autologous cells on a matrix for collagen repair

Developing Cell Scaffold Products



Cells- Combination with a Device

- Impact of the device upon the biologic
  - Genotypic or phenotypic changes in cells/tissues
  - Survival of cells/tissue within the device
  - Potential benefits to be evaluated
    - Barrier to immune rejection
    - Barrier to transmission of adventitious agents
- Impact of the biologic upon the device
  - Degradation – changes in rate of breakdown of biodegradable materials
  - Other biocompatibility issues

Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage

- CBER/CDRH Joint Guidance
  - Reflects CBER AC input
    - CDRH participated
    - March 2005
- Leverages ASTM document
  - Written by ASTM subcommittee
  - FDA staff participation according to FDA policy and ASTM process

Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage

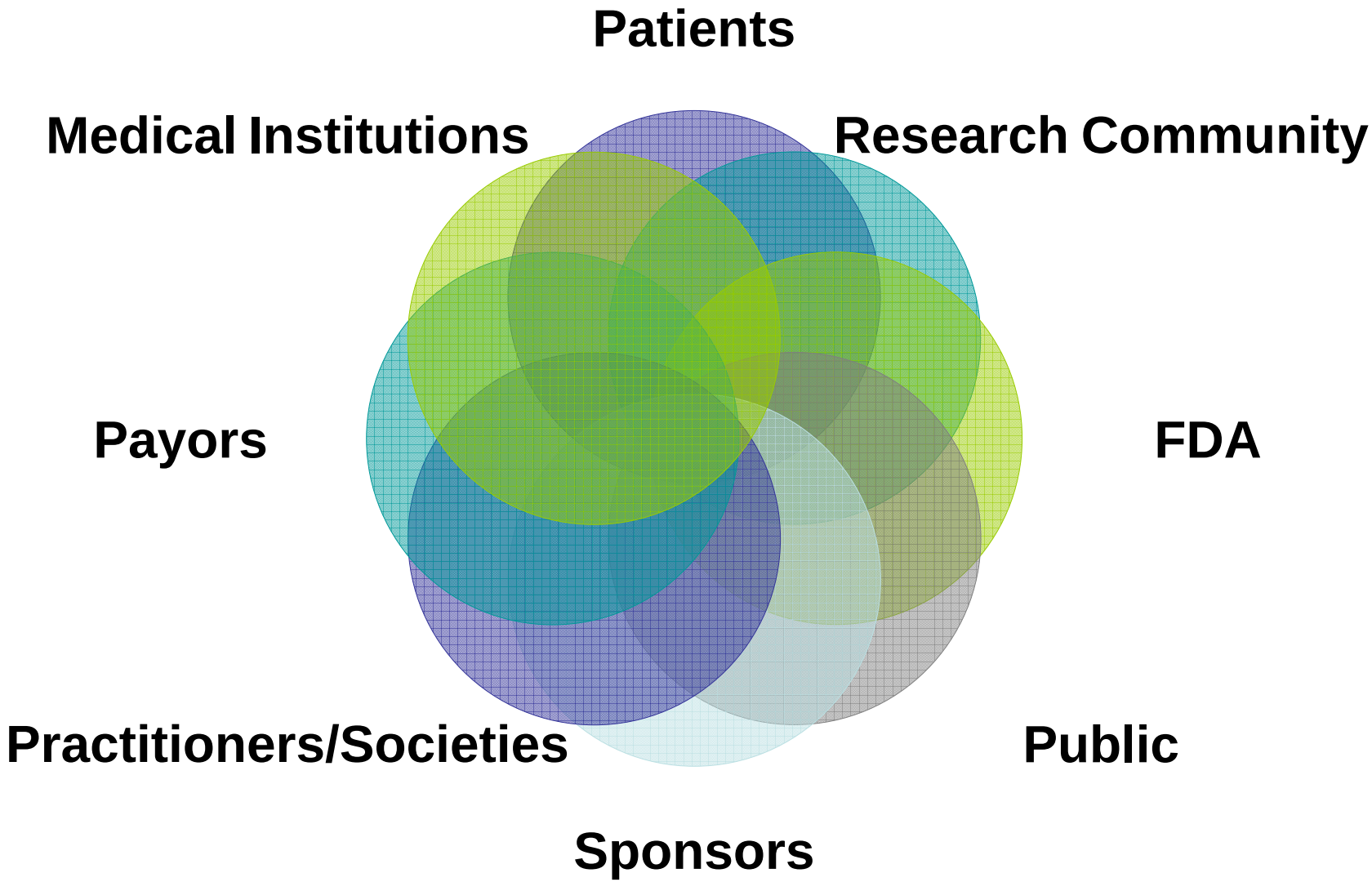
- Scope
  - IND/IDE products to repair or replace articular cartilage of the knee
    - Devices
    - Biologics
    - Combinations Products
  - Excludes
    - Unicondylar and total knee implants
    - Meniscus replacement products
    - “361” HCT/P products

Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage

- "Manufacturing and CMC Information"
  - Brief explanation of requirements for
    - Devices
    - Biologics
    - Combination Products
  - Tailored for specifics of product composition
- "Nonclinical Data and Testing"
  - Leverages ASTM document Purposes of Animal Studies
  - Mechanical Testing
  - Biocompatibility
- Clinical Study Design
  - Expectations of Exploratory versus Confirmatory Trial Design
  - Endpoints
  - Adverse Event and Follow-up Considerations

Workshop Planning Committee

- CDRH, FDA
  - Jiyoung Dang
  - Charles Durfor
  - David Kaplan
  - Suzanne Malli
- NIST
  - Anne Plant
- CBER, FDA
  - Rabia Ballica
  - Kimberly Benton
  - Deborah Hursh
  - Bernadette Kawaley
  - Richard McFarland
  - Brenton McCright
  - Celia Witten
  - Leslie Wheelock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