Use of Consensus Standards in the Regulatory Approval of Tissue Engineered Medical Products (TEMPs)

David S. Kaplan, PhD

Office of Science & Engineering Laboratories

Center for Devices and Radiological Health

Scaffold

- **A support, delivery vehicle, or matrix for facilitating the migration, binding, or transport of cells or bioactive molecules used to replace, repair, or regenerate tissues**
  - ASTM (F04 Terminology)
- **Ideal scaffold**
  - Biocompatible, biodegradable, promote cellular interactions and tissue development and possess proper mechanical and physical, biological and chemical properties

Scaffold Properties/Attributes

- **Permanent vs. absorbable/bioresorbable**
- **Support**
  - Cell seeding, proliferation and 3-D tissue formation
- **Stimulate biological response**
  - e.g., Osteoconductive or osteoinductive
- **Reference materials (NIST)**
  - Inter-laboratory studies and cell seeding

Product Areas involving Scaffolds

- **Cartilage repair**
- **Bone repair**
  - Critical size gaps
  - Bone void fillers
  - Bioactive agents (i.e., BMP's) on sponges
  - $CaS0_4$ beads/pellets – bone voids secondary to osteomyelitis
- **Dental applications**
- **Wound dressing**
- **Skin**
- **Ligament and hernia repair – synthetic/biologic mesh**

Scaffolds – Regulatory Questions

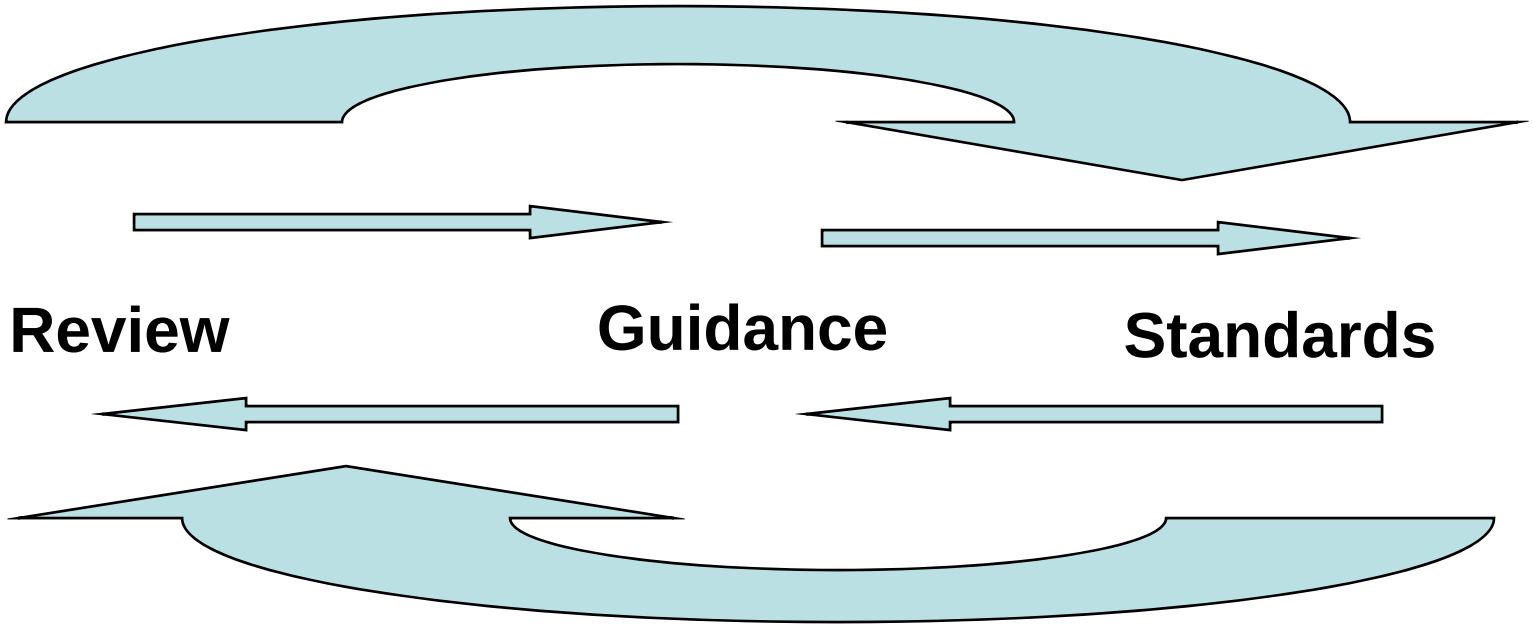
- **Purpose of scaffold**
- **Mode of interaction of scaffold with ECM or seeded cells/tissues**
- **Does the scaffold help the overall product to achieve its intended mode of action?**
- **Does the scaffold degrade or other significant changes which could affect the biological, mechanical, physical or chemical properties?**

Scaffolds and New Technology

- **Increasing use of more sophisticated technology**
  - Cell-loaded, drug-loaded or biologic
  - Absorbable/bioresorbable
  - Chemical modification
  - Tethering
  - DNA/genetic sequences
- **TEMPs subcommittees develop standards to foster new technology**

Needs for Medical Device Standards

- **Wide spectrum of technical/scientific concepts**
- **Materials of diverse origin and properties**
- **High rate of innovation**



Examples of Motivating Factors

- Test methods for design attribute verification
- Guides for performance/ safety evaluation in emerging device areas
- Need to detect known post-market issues early and design for it
- Variable methods to evaluate same or similar device attribute
- Consistency in performance/ safety evaluation

Standards Utilization

- **Is this the right standard?**
- **Are we working in the right area?**
- **What does the program need?**
  - **Premarket workload**
  - **Postmarket issues to be resolved**
  - **Harmonization needs**

Standards Process

- **Voluntary consensus process**
- **Criteria include:**
  - Openness
  - Balance of interest
  - Due process
  - An appeals process
  - Consensus
- **Voting members designation varies by organization**

Specialty Task Groups (STGs)

- Anesthesia
- Biocompatibility
- Cardiology/Neurology
- Dental/ENT
- General
- General Hospital/ General Plastic Surgery
- IVDs
- Materials
- OB-BYN/Gastroenterology
- Ophthalmic
- Orthopedics/Physical Medicine
- Radiology
- Software
- Sterility
- Tissue Engineering

Standards Organizations & FDA

- **FDA liaisons to each subcommittee/ working group**
  - Input on document content
  - Priorities of work items
  - Technical expertise
  - Bridge to FDA recognition

Use of Standards in CDRH

- **Review documents**
  - 510(k)s, IDEs, PMAs, HDEs, 513(g)s, Reclassification petitions
- **Guidance documents**
- **Compliance documentation**
- **GMPS, QSRs**
- **CDRH has a standards recognition process**

Standards Recognition

- **Nominated for recognition to CDRH Standards Technical Groups**
- **Reviewed and Supplemental Information Sheet (SIS) identifying limitations prepared**
  - Can recognize some, all, or none of a standard
- **SIS Published in Federal Register**
- **Where: Lists available in FR and CDRH Web Page**
- **Recognized over 750 since 1997**

Utility of Standards to CDRH & Industry

- Knowledge of the “level” playing field
- Focus in and emphasize what is important for safely implanting these medical products
- Conformance with recognized standards can help provide reasonable assurance of safety & effective
- Promote best science
- Conformance is voluntary

Example: Standards for TEMPs

- **Both ASTM and ISO**
  - ASTM F04.41 – F04.46
  - ISO TC150/SC7/WG 1-3
- **Scope of ASTM TEMPs**
  - Components or combinations of medical products to repair, replace, or regenerate tissue
  - Biological cells, tissue, cell products
  - Biomolecules
  - Biomaterials: synthetic or natural

Osteocel Plus,
Osiris/Nuvasive,
hBMSCs in CaP putty

Atala et al 2006, The Lancet

Activities in ASTM TEMPs

- **Over 30 published standards, 30% recognized by CDRH**
- **CBER involvement in groups significant**
- **~ 25 current work items**
  - Biomaterial characterization (scaffolds, raw materials)
  - Animal models (cartilage repair, muscle defect)
  - TEMPs performance assessment (vascular grafts)
  - SG for tissue specific repair (muscle, meniscus)

Example TEMPs Documents

- **Published**
  - ASTM F2027: SG Characterization & Testing of Raw or Starting Biomaterial
  - ASTM F2451: SG for in vivo assessment of implantable devices intended to repair or regenerate articular cartilage
  - ASTM F2064, F2259, F2605: series on characterization and use of alginate
- **Work Item**
  - WK 31014: TM Goat model for in vivo testing of articular cartilage repair or regeneration
  - WK 28890: SP in vitro osteoblastic differentiation

Summary & Closing Remarks

- **Standards used extensively by FDA & industry**
- **Beneficial for device development**
- **Extensive opportunity to become involved**
  - TEMPs: David Kaplan (david.kaplan@fda.hhs.gov)
  - Devices containing scaffolds: