The Role of Standards in U.S. FDA Regulation of Cellular Therapy Products

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Scope of Presentation

- FDA Policy for Standards Activities
- Terminology Used for Standards
- Examples of Standards for Cell Therapy Products
FDA Policy on Standards Activities

• FDA’s Staff Manual Guide (SMG 9100.1) establishes Agency-wide policies and procedures related to standards management to assure a unified approach to standards within the FDA

• Regulations governing participation in standard setting activities, 21 CFR 10.95 (a), “FDA encourages employee participation in outside standard-setting activities that are in the public interest”
Agency Expectations for Employees

• Individuals who interact with Standards Development Organizations (SDOs) must do so clearly on behalf of the Center, the Agency, and the Department, and in a manner that assures all information or input provided reflects the positions of the Center, the Agency, and the Department.

• Provide routine updates on SDO engagement to the leadership in Center/Office
Benefits of Standards Development

• Address issues not covered by FDA Guidance
• Facilitate the development and maintenance of FDA Guidance
• Facilitate product design
• Improve time to market
• Leverage industry efforts
• May lead to international harmonization
Possible Areas for Standard-setting Activities

- Developing performance characteristics
- Testing methodology
- Manufacturing practices
- Product standards
- Scientific protocols
- Compliance criteria
- Ingredient specifications
- Labeling, and other technical or policy criteria
Terminology Used for Standards
Definition: Standard

“Common and repeated use of rules, conditions, guidelines, or characteristics for products or related processes and production methods, and related management systems practices.”

OMB Circular A-119
Regulations vs. Standards

• Regulations
  – Government implementation of statues that have the force of law
  – Define specific requirements for safety
  – Provide accurate information to health professionals and consumers

• Standards
  – Voluntary
  – Frequently developed outside of the government
  – Written standards describe how manufacturers might meet regulatory requirements
  – Physical standards provide “benchmark” materials
Types of Standards

• Voluntary Consensus
• Non-consensus
• Physical Standards/Reference Materials
• Accreditation Standards
• Harmonization Standards
  – ICH
  – WHO
Definition: Voluntary Consensus Standard

- Standards developed or adopted by voluntary consensus standards bodies, both domestic and international.

- Voluntary consensus standards “include provisions requiring that the owners of relevant intellectual property agree to make that intellectual property available on a non-discriminatory, royalty-free or reasonable royalty basis to all interested parties.”
Definition: Standards Development Organization

“An SDO is an entity that develops or sponsors the development of voluntary standards for the use of information by any person involved in the manufacture, distribution, sale, or use of products or services or legal regulation of such products and services.”

SMG 9100.1
SDO Accreditation

• American National Standards Institute (ANSI)
• Provides interested US parties with a neutral venue to work towards common agreements
• Process guided by consensus, due process, and openness
• Ensures access to the standards including an appeals mechanism for interested parties.
Non-Consensus Standards

• Standards developed in the private sector, not with consensus
  – e.g. industry standards, company standards, professional practice standards

• Government unique standards
  – Developed by the U.S. government for its own use

• Standards mandated by law
  – e.g. Prescription Drug User Fee Act (PDUFA V)
Definition: Physical Standards/Reference Materials

• Highly characterized reagents that are distributed to assure consistency, quality and safety.

• Reference materials are materials that are sufficiently homogeneous and stable with respect to one or more specified properties, and have been established to be fit for its intended use in a measurement process.
Accreditation Standards

“Accrediting organizations” that are not accredited by ANSI (do not meet the definition of a voluntary consensus SDO)

– AATB (tissue banking)
– AABB (blood and tissue banking)
– FACT (cellular therapy)
– ICCBBA (blood, tissue identification & labeling)
Harmonization Standards

- **World Health Organization (WHO)**
  - Written standards “WHO Requirements, Recommendations and Guidelines”
  - Physical Standards for manufacture and control of biological products
  - WHO standards are applicable to US FDA products and may be used at various stages of product development
Harmonization Standards (continued)

• International Conference on Harmonisation (ICH)
  – Q4B “Pharmacopoeial Harmonisation” Interchangeable pharmacopeia methods-identified in FDA Guidance
  – Joint Initiative on SDO Global Health Informatics- electronic standards
Standards Recognition/Use

• “Recognition”- a term proscribed by the medical device legislation (FD&C ACT 514(c)) describing the process used by FDA Center for Devices and Radiological Health (CDRH) for the identification of standards that manufacturers of medical devices may cite to meet relevant regulatory requirements

• “Use”- citation of standards in a regulatory application, regulation, guidance, or incorporation into policy statements
Standards Use in CBER

• Manufacturers of medical devices regulated in CBER may use standards “recognized” by CDRH to support regulatory submissions to CBER.

• “Non-recognized” standards may also be used. Consultation with the Review Office is recommended.

• CBER does not have a formal standards recognition (as does CDRH).
Standards Use for Cellular Therapy Products

• Sponsor can cite a standard in their regulatory application

• Sponsor can use a reference material in the development and testing of their product.
Examples of SDOs and Standards for Cell Therapy Products
American Society for Testing Materials International ASTM International

Committee F04: Medical and Surgical Devices

Subcommittees for TEMPS

F04.41 Classification and Terminology
F04.42 Biomaterials and Biomolecules
F04.43 Cells and Tissue Engineered Constructs
F04.44 Assessment – preclinical evaluation of TEMPs
F04.45 Adventitious Agent Testing
F04.46 Cell Signaling
Examples of ASTMi Standards for Cell Therapy Products

• F2315-11 Standard Guide for Immobilization or Encapsulation of Living Cells or Tissues in Alginate Gels

• F2944-12 Standard Test Method for Automated Colony Forming Unit (CFU) Assays—Image Acquisition and Analysis Method for Enumerating and Characterizing Cells and Colonies in Culture

• F2383-11 Standard Guide for Assessment of Adventitious Agents in Tissue Engineered Medical Products (TEMPs)
ISO Tissue Engineering Technical Committees

- TC150 SC7 Implants for Surgery, Tissue Engineered Medical Products
  - WG 1 Management of Risk
  - WG 2 General Guideline of Safety Test
  - WG 3 Tissue-Engineered Medicinal Products for Skeletal Tissues

- TC194 SC1 Biological Evaluation of Medical Devices, Tissue Products Safety
  - WG 1 Risk assessment, terminology and global aspects
  - WG 2 Sourcing controls, collection and handling
  - WG 3 Elimination and/or inactivation of viruses and TSE agents
  - WG 4 TSE Elimination
Examples of ISO Standards for Cell Therapy Products

• ISO 10993.xx (Biocompatibility)
• AAMI/ISO 13022:2012 Application of Risk Management to Viable Materials of Human Origin Used for the Production of Medical Products
• AAMI/ANSI/ISO 13408(R2011) Aseptic Processing of Health Care Products
American Type Culture Collection (ATCC)

- **ATCC Biological Resource Center**
  - **Mission:** To acquire, authenticate, preserve, develop, standardize, and distribute biological materials and information for the advancement and application of scientific knowledge

- **ATCC ANSI accredited SDO**
  - **Mission:** To develop best practices (standards) in life science laboratory testing and to promote their use globally, using a consensus-driven process that balances the viewpoints of industry, government, academic and clinical professions.
  - **Goal:** To develop written standards for life science products and methods
  - **ATCC® published standards are recognized by the American National Standards Institute (ANSI) and are compatible with requirements of the International Organization for Standardization (ISO).**
ATCC Standards

• Written Standard:
  – ASN-0002-2011 Authentication of Human Cell Lines: Standardization of STR Profiling

• Reference Materials/Physical Standards
  – ATCC VR-1516 Adenovirus Type 5
  – ATCC VR-1616 Adenovirus Type 2
  – CRM-CCL-2™ HeLa cells for lab competency testing
  – Ca Ski – positive control for HPV
Clinical Laboratory Standards Institute (CLSI)

Accredited by ANSI

• CLISI Consensus Committees
  – Automation and Informatics
  – Clinical Chemistry and Toxicology
  – Evaluation Protocols
  – Hematology
  – Immunology and Ligand Assay
  – Microbiology
  – Molecular Methods
  – Point-of-Care Testing
  – Quality Systems and Laboratory Practices
Examples of CLSI Standards for Cell Therapy Products

• H42-A2 Enumeration of Immunologically Defined Cell Populations by Flow Cytometry; Approved Guideline- Second Edition

• H43-A2 Clinical Flow Cytometric Analysis of Neoplastic Hematolymphoid Cells
Standards Use for Characterization
# Examples Standards for Characterization

<table>
<thead>
<tr>
<th>Standard</th>
<th>Title</th>
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<tr>
<td>ASTM 2027</td>
<td>Standard Guide for Characterization and Testing on Raw or Starting Materials for TEMPs</td>
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<tr>
<td>ASTM 2064</td>
<td>Standard Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical or TEMPs</td>
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<tr>
<td>ASTM F2150</td>
<td>Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in TEMPs</td>
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<td>ISO 10339</td>
<td>Biological Evaluation of medical devices</td>
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<tr>
<td>ICH Q5E</td>
<td>Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process</td>
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Summary

• Written standards complement regulations by describing how manufacturers might meet the regulatory requirements for a particular product.

• Standards can complement FDA guidances by providing an alternate approach or an acceptable technology.

• Standards address numerous topics such as design, manufacturing, professional practices, nomenclature, and testing.

• Standards can be useful tools throughout the life cycle of a product in many disciplines.
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OCTGT Learn Webinar Series:
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Public Access to CBER

CBER website:  
http://www.fda.gov/BiologicsBloodVaccines/default.htm

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