Standards Coordinating Body

Cell and Gene Therapy Consensus Standards - A Shared Path Forward

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STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

Cell and Gene Therapy Consensus Standards - A Shared Path Forward

Why are consensus standards needed?

How do consensus standards fit into the regulatory process?

What is the Standards Coordinating Body (SCB) and how does it accelerate standards development?

- SCB Consensus Standards Efforts
- How to get involved

How is SCB aiding and simplifying the community to find and implement consensus standards?

- SCB Standards Portal
- ANSI Packages
- Standards Implementation Courses

The Need for Regenerative Medicine Standards

Regenerative medicine/advanced therapies present unique challenges related to product testing, scientific protocols, product quality and specifications, performance characteristics, and compliance criteria.

Standards, Regulations, and Guidances

Regulations:
Have the force and effect of law and are usually mandatory, setting out specific requirements that regulated products and organizations must meet. In the United States, regulations are written in the Code of Federal Regulations and published in the Federal Register.

Guidances:
Formal documents issued by a government agency **to clarify** the agency's **thinking on existing laws or regulations** and offer guidelines for how industry **can comply with these regulations**.

Standards:
Voluntary rules, conditions, characteristics, or physical materials that an organization can adopt to make a process safer, more efficient, or better aligned with the practices of other organizations in their industry.

Different standards types include:

- **Documentary Standards**
- Standard Reference Material
- Standard Reference Data

Legal Basis for the Use of Standards in the Regulatory Process

The legal basis of the federal use of consensus standards is found in the:

1. National Technology Transfer and Advancement Act (NTTAA)
2. Federal Food, Drug, and Cosmetic Act (FD&C)

It is further clarified in two FDA guidances,

1. *Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research*
2. *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices*

This stance across the federal government is well summarized by the Office of Management and Budget (OMB) as follows:

> *"Agencies shall use existing voluntary consensus standards, both domestic and international, in their regulatory and procurement activities as a means of carrying out policy objectives or activities determined by the agencies, unless use of such standards would be inconsistent with applicable law or otherwise impractical.* ***Agencies shall use such voluntary consensus standards for test methods, procurement guidelines, management systems, sampling procedures, or protocols to determine whether established regulatory limits or targets have been met."***

Consensus Standards in the Regulatory Process

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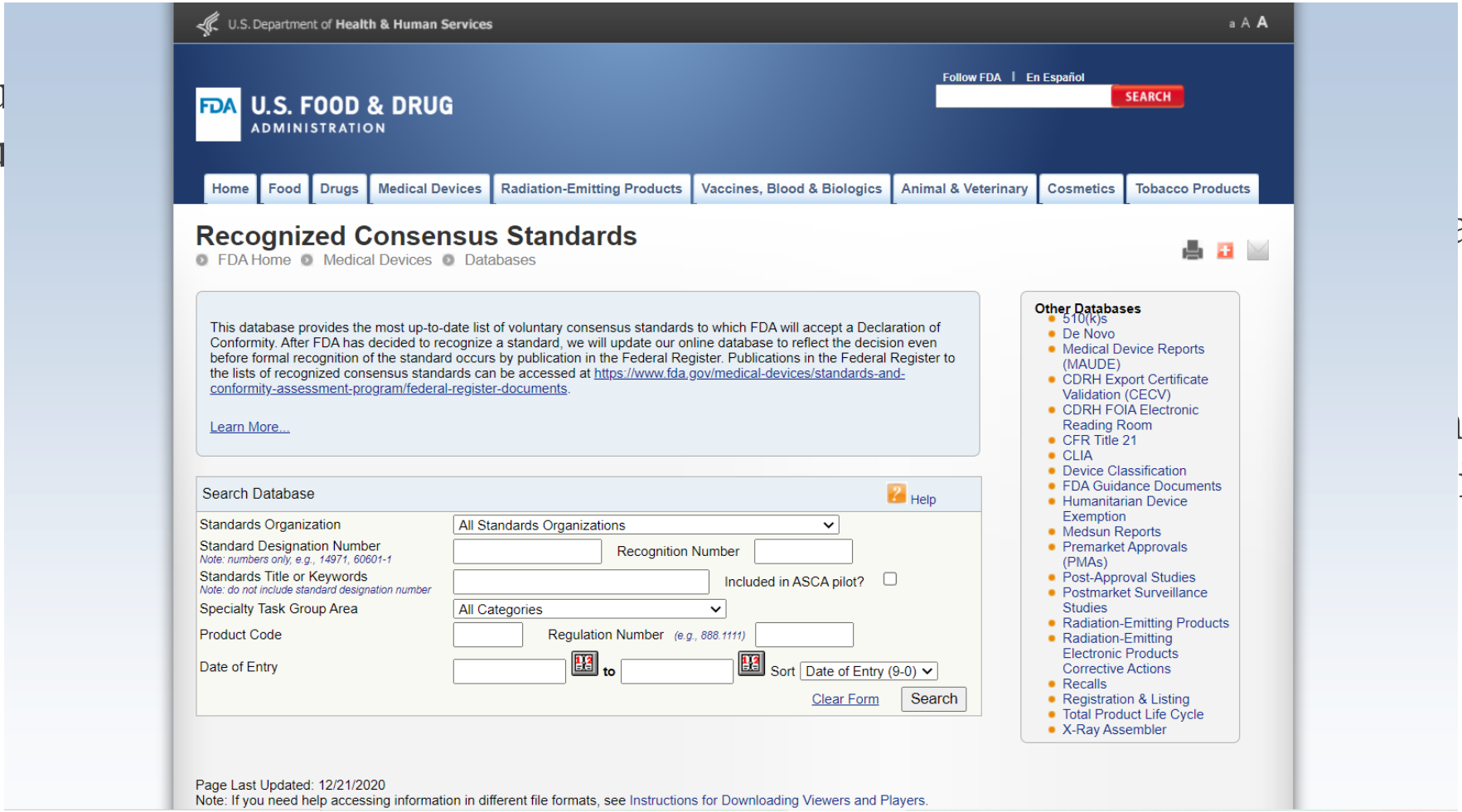

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Recognized Consensus Standards

FDA Home › Medical Devices › Databases

This database provides the most up-to-date list of voluntary consensus standards to which FDA will accept a Declaration of Conformity. After FDA has decided to recognize a standard, we will update our online database to reflect the decision even before formal recognition of the standard occurs by publication in the Federal Register. Publications in the Federal Register to the lists of recognized consensus standards can be accessed at https://www.fda.gov/medical-devices/standards-and-conformity-assessment-program/federal-register-documents.

Learn More...

Search Database — Help

Standards Organization: All Standards Organizations

Standard Designation Number (Note: numbers only, e.g., 14971, 60601-1) | Recognition Number

Standards Title or Keywords (Note: do not include standard designation number) | Included in ASCA pilot?

Specialty Task Group Area: All Categories

Product Code | Regulation Number (e.g., 888.1111)

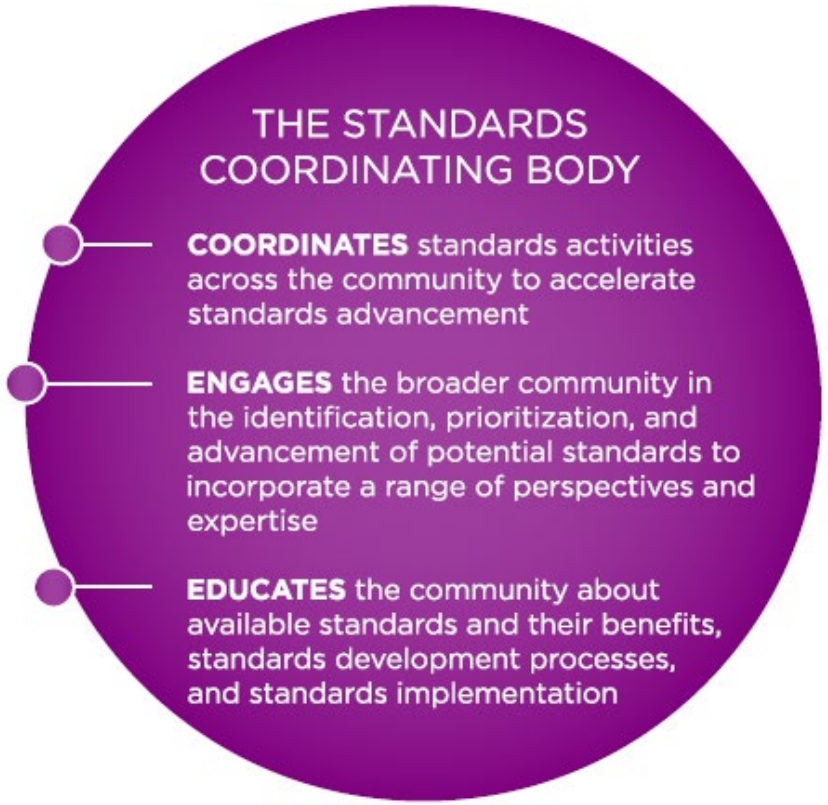
Date of Entry: to | Sort: Date of Entry (9-0)

Clear Form | Search

Other Databases
- 510(k)s
- De Novo
- Medical Device Reports (MAUDE)
- CDRH Export Certificate Validation (CECV)
- CDRH FOIA Electronic Reading Room
- CFR Title 21
- CLIA
- Device Classification
- FDA Guidance Documents
- Humanitarian Device Exemption
- Medsun Reports
- Premarket Approvals (PMAs)
- Post-Approval Studies
- Postmarket Surveillance Studies
- Radiation-Emitting Products
- Radiation-Emitting Electronic Products Corrective Actions
- Recalls
- Registration & Listing
- Total Product Life Cycle
- X-Ray Assembler

Page Last Updated: 12/21/2020
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Founding of SCB



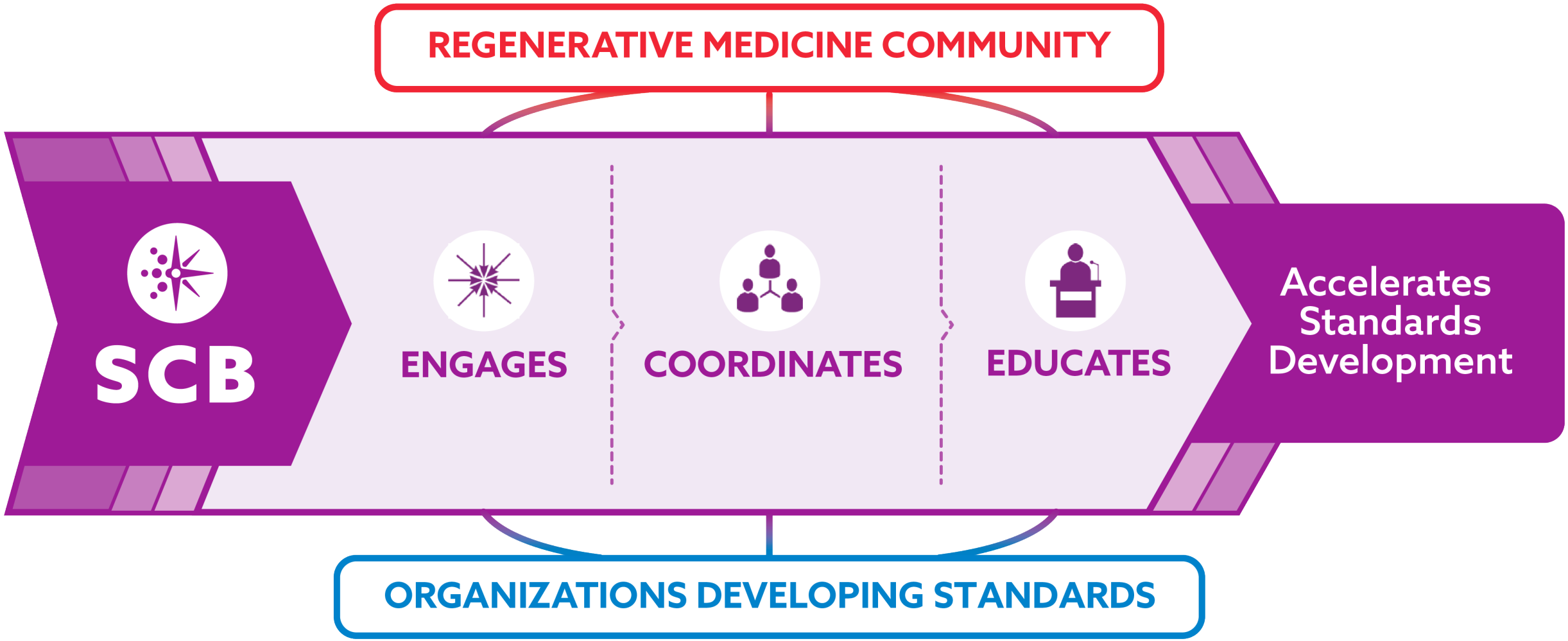
Established in 2016 and launched in January 2017, SCB is an **independent 501(c)(3)** organization

Occupies unique niche within field with **no vested interests in specific scientific, commercial, clinical or policy approaches**

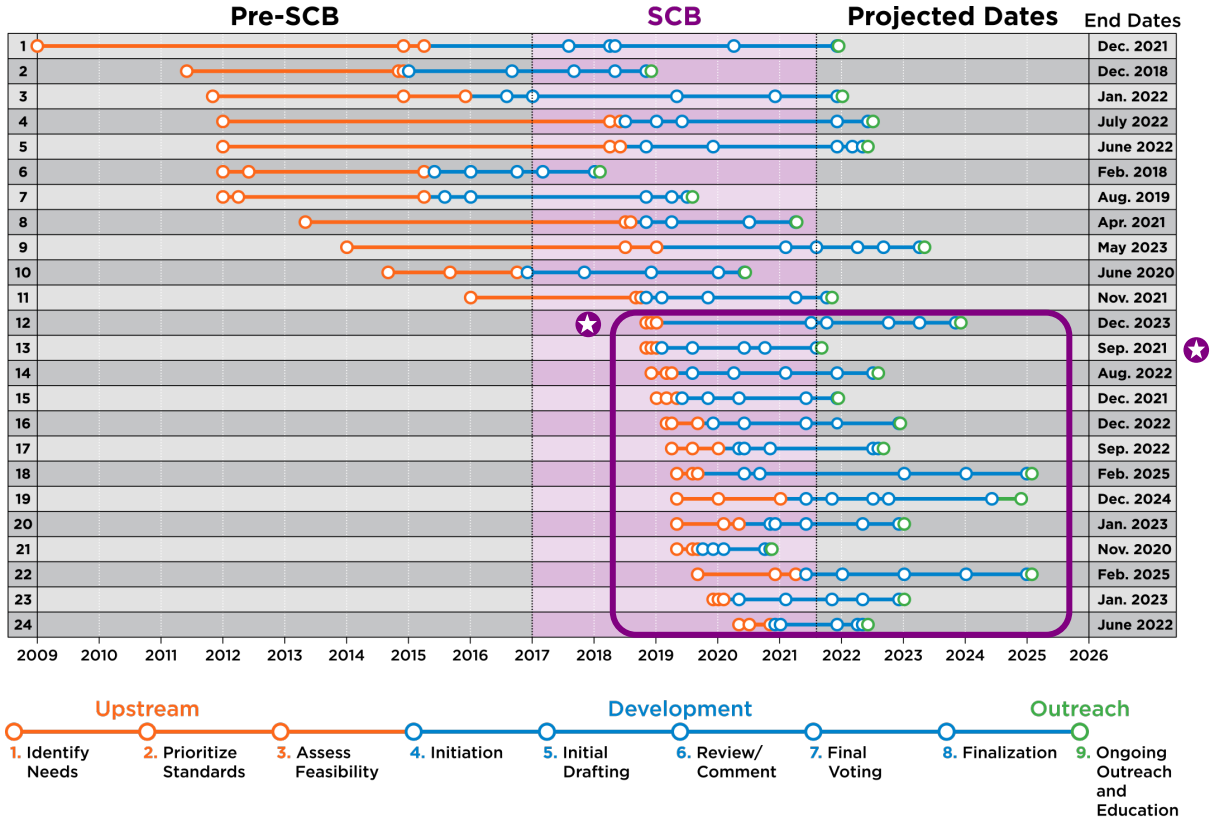
SCB is **not an SDO**, but rather **coordinates** the standards development process

Serves as **communication vehicle** among all stakeholders, including government agencies, critical to the development of standards

The Standards Coordinating Body (SCB)



Accelerating Standards Development



1. Characterization of Human Cells for Therapeutic Use
2. Ancillary Materials Used in Cellular Therapy Production (3-Part TS)
3. Requirements for Cell Therapy Manufacturing Equipment
4. Rapid Microbial Testing Method Design and Validation Framework
5. Sampling Methods of Tissue Engineered Medical Products for Sterility Assurance
6. General Guidance on Cell Counting Part 1
7. General Guidance on Cell Counting Part 2
8. Characterization of Fiber-Based Scaffolds
9. Cell Collection Standards for Cell Therapies
10. Transportation Requirements of Cells for Therapeutic Use
11. Bioink Printability Test Method
12. Evaluating Pre-existing Immunity to Adeno-Associated Viruses
13. Cryopreservation of Cells (PDA-led project)
14. Bioprinter Hardware
15. Ancillary Materials used in Cellular Therapy Production (IS)
16. Bioprinter Software/Data Governance
17. ASME Thermal Medicine Tissue Properties
18. Base Requirements for Digital Platforms for Providers
19. Viral Vectors (Lenti/AAV) for Gene Therapy
20. Microphysiological Systems
21. Base Labeling Requirements for Regenerative Medicine Product
22. Cell Viability
23. Tissue Engineering Lexicon
24. Chain of Custody (COC)/Chain of Identity (COI)

Key: Prioritized for Coordination Feasibility Reports Both

**Availability dates are estimates only. Development of a standard depends on SDO timelines, which can be time intensive and may vary significantly (particularly for reference materials).

KEY TAKEAWAY

SCB involvement has significantly reduced the time spent on upstream steps, allowing needs to be addressed more quickly.

STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

Cell Therapy & Crosscutting

Efforts recently advanced:

- **ISO Cell Characterization**: Cell characterization document has been published
- **ISO Requirements for Cell Therapy Manufacturing Equipment**: Published
- **PDA Cryopreservation of Cells**: Public Comment completed and revised draft to be released shortly
- **ISO Ancillary Materials**: International Standard ballot opened
- **PDA Cell Collection**: Initiation with PDA and Task Force formed
- **RMTM Framework and validation**: Draft is currently open for comment period before a DIS ballot
- **ISO Cell Processing Management System**: Working group to provide feedback on this effort has begun

Cell Therapy* Working Group

Assess potential standards that could improve the safety, quality, and efficacy of cell therapy products and enable more efficient product development processes, such as by establishing common methods to measure cells' functional response to their environment.

* Cell therapy products use living cells as a means of replacing or repairing damaged cells to treat disease.

PDA - Apheresis Cell Collection Standard Description

Variation in apheresis cell collection requirements for cell and gene therapy products set by product manufactures/sponsors **needs to be reduced.** The current variations cause **undue burden in the apheresis centers** and can lead to errors in the collection process.

This goals of this standard effort are to:

1. **Give best practices/recommendations** for procedures and collection requirements.
2. **Creating a standard template for** product manufactures/sponsors' **leukapheresis manuals/SOP** to **minimize the variations in communication** of procedures and requirements.

PDA®
Parenteral Drug Association
Connecting People, Science and Regulation®

Gene Therapy

Efforts recently advanced:

- **Pre-Existing Immunity to AAV**: Ongoing discussion on titer comparability and analysis standard with UK leadership within ISO and the British Standards Institution
- **Titration Assays for Viral Vectors**: Ongoing discussion on the Lexicon and Considerations for Titration Assays standard with ISO and UK leadership
- **Gene editing methods framework**: Off-target effects working group is drafting

Gene Therapy* Working Group

Evaluate the potential for standards that can help improve the safety and efficacy of gene therapy treatments, such as by improving screening for pre-existing immunity to common viral vectors.

* Gene therapy involves the use of a vector, such as an inactivated virus, to insert a new copy of a gene or relevant nucleotide sequence into a patient's cells to treat a genetic health condition.

AAV Pre-existing Immunity Working Group

Scope:

Why it's needed: Consensus is needed in the measurement and analysis of preexisting immunity in order to leverage data from the literature to improve and encourage the sharing of data from individual laboratories and different assays. There is currently no common language or standard process for evaluating pre-existing AAV immunity prior to attempting treatment. There are also issues with validation of the appropriate characterization assays to determine quality and consistency for gene therapy usage. There are also issues with comparability in AAV associated assays.

Potential Scope for Guide for assays used in assessment of Preexisting Humoral Immunity to AAV: This document provides best practices for anti-AAV total binding antibody (TAb) and cell-based assays measuring the neutralization transduction n (hereafter referred to as transduction inhibition or TI) assays, assays and on the reporting and the analysis of the data collected from these assays. This document is intended to be used by researchers in academia and industry and by clinicians in therapy development from the bench, to preclinical, to clinical studies, as well as the regenerative medicine communities for biomedical research. This standard will have immediate relevance for those evaluating the safety and efficacy of AAV based genomic medicines with respect to pre-existing immunity. The cellular immune response and assays used to measure cellular immunity are outside of the scope of this standard.

This standard is applicable to the detection of anti-AAV antibodies to determine preexisting immunity and the emerging immune response after the administration of the AAV based genomic medicine. Preexisting immunity may be derived from previous exposure to the capsid of interest or other closely related capsid serotypes and variants capable of inducing cross reactive antibodies. There is also the potential that these assays could be used to aid in the development and the assessment of the effectiveness of immune modulation strategies.

Titration Methods for Viral Vector

Scope:

Why it's needed: Consensus is needed due to the current lack of consistency between data from different companies and labs. Transferring products from a client to a manufacturer while maintaining quality is difficult and often requires a change in methodology. Currently, companies are relying upon comparability studies, which are insufficient. Additionally, due to needed changes in methodology for the assessment and quantification viral vectors, historical data is often lost unless the historical titrations methods are continued. The current system is inefficient and difficult for manufactures. If there was comparability and consistency with functional titer measurements it would speed up the manufacturing and development process, lower the cost, and result in better characterized products.

Potential Scope for methods for the assessment and quantification of viral vector functional titer: This document provides guidance on methods for the assessment and quantification of the critical quality attributes, functional titer and physical titer of viral vectors. This guidance can be used by producers and consumers of viral vectors, CDMOs, researchers in academia and industry, and by companies pursuing clinical studies.

This standard will be used to improve the comparability between functional titers of viral vectors measured in different labs and different manufactures. This will help ease tech transfer and support assay validation. Improved comparability will also help determine accurate dosing and determine dosing strategies that will allow the titer/dose to be measured using a different assay. This document will increase the consistency of data across the product life cycle.

White Paper - Off Target Effects

Scope:

This article is concerned with the effects to genome edited cells resulting from unintended edits to edited cells termed here off-target effects, with specific focus on what the main issues are and how we can move forward with them.

1. Why are we writing this (needs/gaps)?
    - What does off-target effect mean?
    - Why does the possible presence of off-target effects matter? (what is the concern?)
2. What are the currently used genome editing systems?
3. What are the types of off-target nucleic acid sequence changes that can result from use of genome editing systems?
4. What is current state-of-the-art for predicting, modeling and detecting the nucleic acid sequence changes
    - Challenges of interpreting between naturally occurring variation and genome editing induced off-target editing
    - Data interpretation
    - Needs/gaps
5. What are types of off-target effects beyond nucleic acid sequence changes and the state-of-the-art for detecting these effects?
6. How does the physical sample you are editing and measuring impact the challenge of understanding off-target effects?
7. What is the current state-of-the-art for trying to understand the biological relevance of the off-target effect and risk of harm?

Seeking Subject Matter Experts

- **Titration Assays for Viral Vectors** — Lexicon and Considerations for Titration Assays: To join contact CZander@regenmedSCB.org 

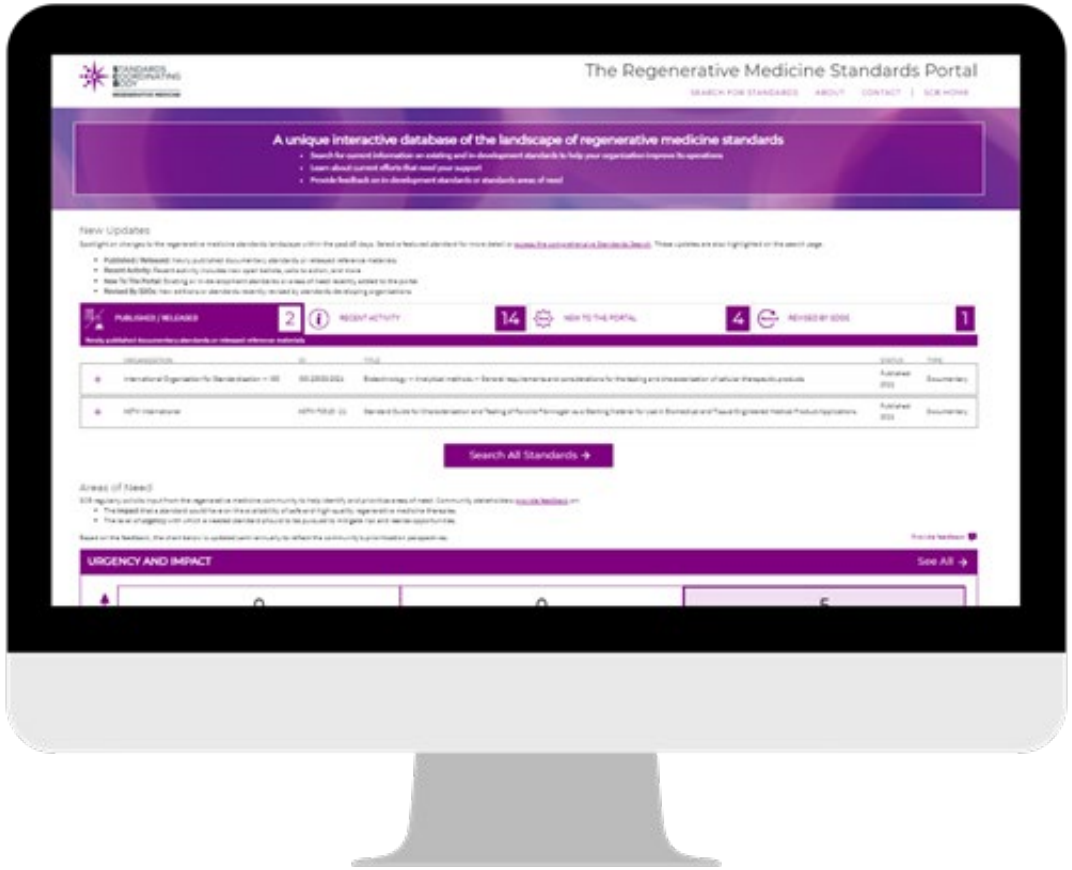
- **ISO/WD 20688-2** Nucleic Acid Synthesis — Part 2: General definitions and requirements for the production and quality control of synthesized gene fragment, gene, and genome
- **Pre-existing Immunity to AAV** — Titer Comparability and Analysis: To join contact CZander@regenmedSCB.org
- **ISO/PWI 24480** Biotechnology — Validation of database used for nucleotide sequence evaluation
- **ISO Stem Cell Data Interoperability** 

- **ISO Cell Viability** 

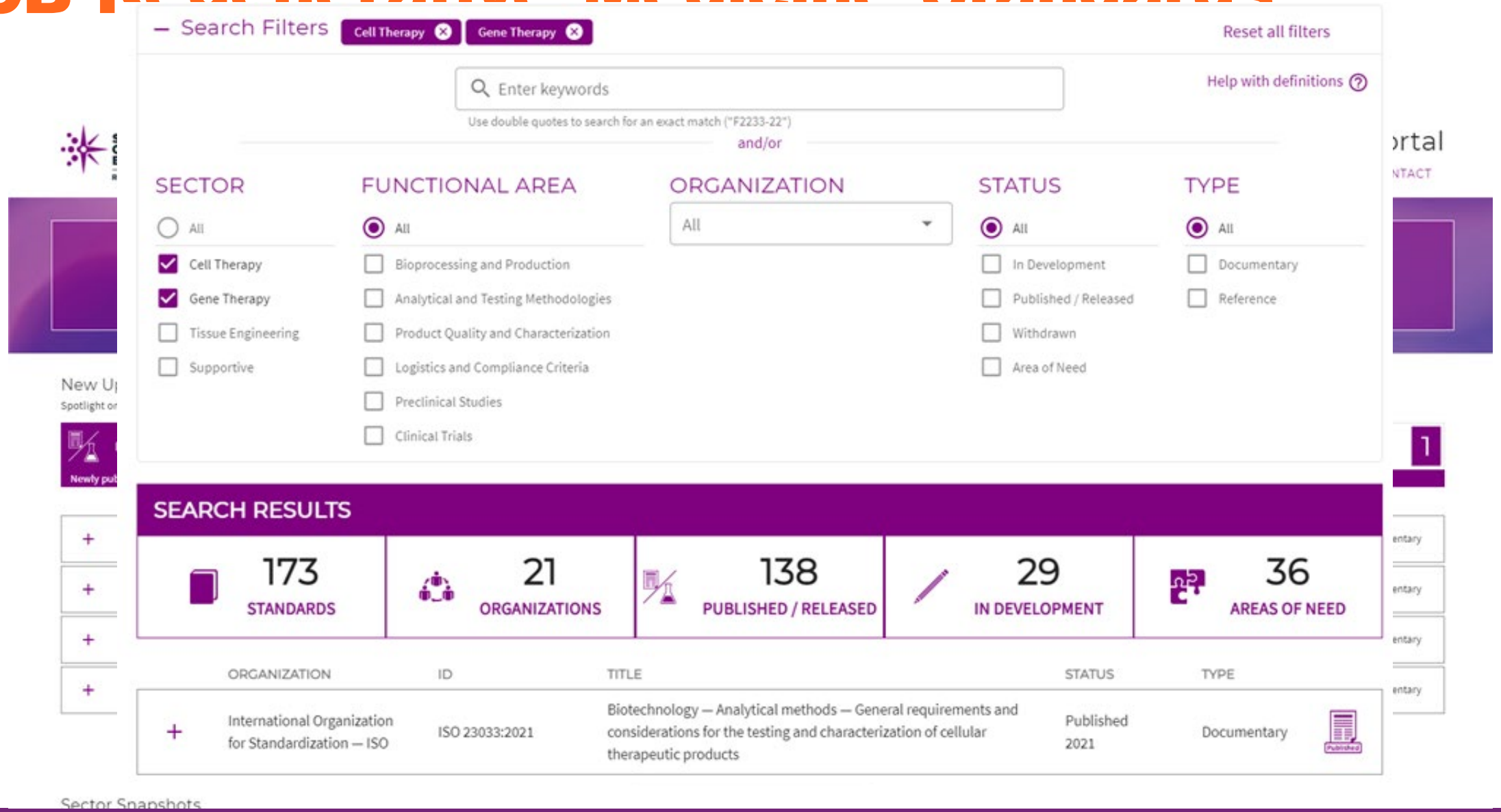
- **ISO/CD 23511** General Requirements for Cell Line Authentication
- **ISO/PWI 20460** Quality Management System for Cell Processing

SCB Regenerative Medicine Standards Portal

- Helps stakeholders more easily see **which standards relate to their operations**
- **Increases community awareness** and discoverability of:
  - Available standards
  - Open ballots
  - Working groups for in-development standards
- **Highlights high-priority standards needs** and identifies in-development standards relevant to those needs
- Shows a **more up-to-date snapshot** of standards and needs (updated monthly)



SCB Regenerative Medicine Standards



ANSI Standards Package Agreement

SCB teamed up with the American National Standards Institute (ANSI) to develop standards packages tailored to specific regenerative medicine application areas. Each package bundles existing ANSI-accredited standards from multiple standards developing organizations (SDOs) relevant to a specific application area and offers them at a **discounted rate**.

Highlights:

- Held **Standards Development Forum with 8 SDOs** (e.g., ASTMF04, ISO TC/276, ASME, PDA) to discuss necessary ANSI packets
- Sought feedback on smaller packages (e.g., cell viability, apheresis/blood, cellular differentiation, devices and matrixes, and contamination)
- SCB hosted industry focus group meeting in November to identify potential process packages

Contact us to help identify potential standards packages!

Standards Implementation Courses

SCB is developing Standards Implementation Courses. Upon successful completion of each course participants will receive an **ANSI certified SCB training certificate** that is intended to be recognized industry wide.

These courses will greatly benefit the regenerative medicine community as **they will make implementation of standards easier** and will, over time, **significantly improve the workforce** through the **stackable credentials**.

Three standards implementation courses have been identified to help manufacturers to avoid/minimize many of the **common front-end issues** of the manufacturing process

- ISO Cell Counting (parts 1 and 2)
- ISO Ancillary Materials (ISO 20399)
- ISO Cell Characterization Standard

Additional standard implementation courses in development include:

- ISO Nucleic acid synthesis (part 1) 20688-1:2020

Questions?

Thank you!

FOR MORE INFORMATION VISIT

www.standardscoordinatingbody.org

OR CONTACT

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