U.S. FOOD & DRUG ADMINISTRATION

Standards for Regenerative Medicine Therapies
Alignment of Regulatory and Technical Requirements

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FDA/CBER/OFFICE OF TISSUES AND ADVANCED THERAPIES

Food and Drug Law Institute
Regenerative Medicine: Regulatory, Legal, and Compliance Challenges for Cell and Gene Therapies Conference
June 8, 2021

Outline

Introduction to Standards

- US Government Policy on Standards
- FDA Policy on Standards
- Definitions

21st Century Cures Act

- FDA-NIST collaborations
- Contract with Nexight/SCB
- CBER Standards Guidance

U.S. Government References for Standards Use and Development

- **National Technology Transfer and Advancement Act of 1995**. Pub. L. 104-113, March 1996, Including Amendment by Pub. L. 107-107, section 1115, December 2001, https://www.nist.gov/standardsgov/national-technology-transfer-and-advancement-act-19953.
- **OMB Circular A -119: Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities**, January 2016, https://obamawhitehouse.archives.gov/sites/default/files/omb/inforeg/revised_circular_a-119_as_of_1_22.pdf

FDA Policy for Standards

FDA Staff Manual Guide (SMG) 9100.1 https://www.fda.gov/media/79684/download

- Standards use is voluntary
- Use of voluntary consensus standards that do not conflict with US statute or regulation is encouraged
- Sponsors of product applications and manufacturers may cite appropriate voluntary consensus standards in support of their applications and manufacturing process documents
- FDA staff may participate in the development of documentary standards and reference materials
- FDA may reference standards in guidance documents

“Standard”- The Definition

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

U.S. National Technology Transfer and Advancement Act of 1995, Public Law 104-113

https://www.nist.gov/standardsgov/national-technology-transfer-and-advancement-act-1995

Regulations vs. Standards

Regulations

- Developed by U.S. regulatory agencies (FDA) to implement and/or enforce legislation enacted by Congress
- Mandatory, have the force and effect of law
- Set out specific requirements that regulated entities must meet

Standards

- Use is voluntary
- Frequently developed outside of the government
- Written/documentary standards describe how manufacturers might meet regulatory requirements
- Physical standards (reference materials) with accepted reference value(s) for “benchmarking”

Regulatory Standards

Requirements defined in regulation

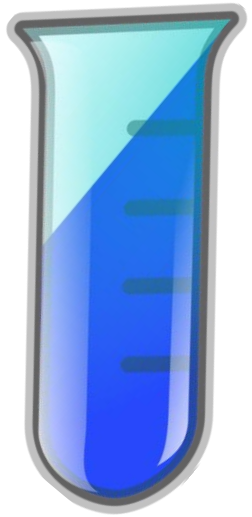
Example: 21 CFR 610 General Biological Products Standards

Subpart	Section	Requirement
A Release Requirements	610.1	Release testing
B General Provisions	610.10	Potency
B General Provisions	610.13	Purity
G Labeling Standards	610.60	Container label

Types of Standards: (1) Written or Documentary Standards

- Performance characteristics
- Testing methodology
- Manufacturing practices
- Scientific protocols
- Ingredient specifications
- Data standards
- Terminology/nomenclature
- Others

Types of Standards: (2) Reference Materials or Physical Standards



- Certified Reference Material (CRM)
- NIST Standard Reference Material (SRM)
- In-house reference material*

*ISO Guides on Reference Materials: 31, 32, 33, 34, 35

www.iso.org

WHY STANDARDS FOR REGENERATIVE MEDICINE THERAPIES?

Benefits of Standards Use for Regenerative Medicine Therapies

- Facilitate product development by reducing the need to develop unique methods or reference materials for individual products
- Establish a common language for therapeutic areas through information models, concepts, and controlled terminologies
- Enhanced the ability to perform complex analyses
- Build a foundation for broader benefits to clinical research, premarket analysis, and safety signal detection.

Role of Standards in Meeting Regulatory Requirements

Alignment of regulatory and technical requirements

- **Product Testing** (ex. assays for assessing potency, sterility, identity, etc.)
- **Development of performance characteristics** (ex. cell characterization, methods to detect off-target effects of genome editing)
- **Testing methodologies** (ex. cell counting, cell viability, quantification of nucleic acids, quantification of vector copy numbers)
- **Scientific protocols** (ex. vector manufacturing, cell processing, viral titer determination, etc.)
- **Compliance criteria** (ex. accreditation standards)
- **Terminology** (ex. gene editing, tissue engineered products, cell therapy)

21st Century Cures Act Section 3036

STANDARDS FOR REGENERATIVE MEDICINE THERAPIES (RMT)

21st Century Cures Act Section 3036

Directs FDA to work with NIST* and FDA stakeholders to "facilitate an effort to coordinate and prioritize the development of standards and consensus definition of terms, through a public process, to support regulatory predictability, the development, evaluation, and review of regenerative medicine therapies, with respect to manufacturing processes and controls of such products".

*NIST: National Institute for Standards and Technology

Activities under Section 3036

- Collaborations between FDA and NIST
- Collaborations FDA, NIST and Regenerative Medicine stakeholders
  - FDA contract with Nexight/Standards Coordinating Body (SCB)
- CBER Guidance on Standards

Leveraging NIST and FDA Expertise in Standards Development for RMT

- NIST expertise in measurement sciences addresses specific analytical challenges
- FDA scientific and regulatory expertise ensures that standards that are developed do not conflict with FDA regulation and policy and ensures that standards developed address significant regulatory challenges that recur across the field of regenerative medicine therapies

FDA-NIST Collaborations Supporting Standards Development for RMT

Laboratory Collaborations

Examples:

- Cell counting
- Cell viability
- Flow cytometry

Co-Hosting Workshops

Past topics:

- Cell counting
- Flow cytometry
- Genome editing
- Cell characterization
- Others

Standards Development

- US Technical Advisory Group ISO TC 276 Biotechnology
- ASTM F04 Tissue Engineered Medical Products

NIST Consortia

- Genome Editing
- Rapid Microbial Methods
- Flow Cytometry

FDA Contract with Nexight & Standards Coordinating Body (SCB)

- *Annual Landscape Report*
- *Needed Standards Report*
- Regenerative medicine standards portal (searchable)
  - Existing standards, Standards needed, Standards under development
- Conduct feasibility assessments- evaluate if an identified needed standard is ready for standardization

www.standardscoordinatingbody.org

Additional Nexight/SCB Activities

- Facilitate and coordinate expert working groups, collect comments on standards under development
- Curricula on the implementation of specific standards
  - Cell counting
  - Nucleic acid synthesis
- Conduct workshops and webinars on standards-related topics

CBER Guidance Document on Standards

"Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research" March 2019

CBER Guidance: https://www.fda.gov/media/124694/download

Describes:

- Policy for staff participation in standards development activities
- Encourages the use of standards by sponsors/applicants of INDs, BLAs, NDAs
- Documentation of standards use in a regulatory submission
- Standards use for CBER-regulated devices IDEs, 510(k), HDEs, PMAs
  - CDRH/CBER joint guidance documents on standards for medical devices https://www.fda.gov/media/71983/download; https://www.fda.gov/media/71995/download

Citation of a Standard in a Regulatory Submission

- A complete reference for the standard should be provided
  - Name of the Standards Development Organization (SDO)
  - Title of the standard
  - Version of the standard
- Specify how the standard was used
- Attestation that you used a standard as published OR
- Describe deviations from the published standard if applicable

Example for Documentation of the use of a Standard in a Regulatory Submission

Standard*: GTX 1234:Quantification of Nucleic Acids in a Biological Sample; 2021**

Possible sponsor statements in a submission:

Methods used to quantify nucleic acids in the final product were conducted according to GTX 1234; 2021 without deviation.

OR

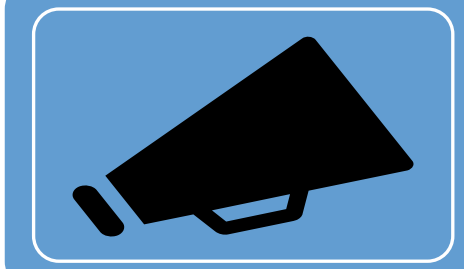
Standard GTX 1234; 2021 was utilized for the quantification of nucleic acids except that the method of sample preparation was modified to be more suitable for our manufacturing conditions.

*The standard referred to in this example is hypothetical

Summary

- Standards use is voluntary
- The use of standards allows for the alignment of scientific and regulatory requirements for RMT
- CBER Standards Guidance describes standards use for CBER-regulated products

Contact Information



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International Harmonization and Standards Development Lead for Regenerative Medicine Therapies

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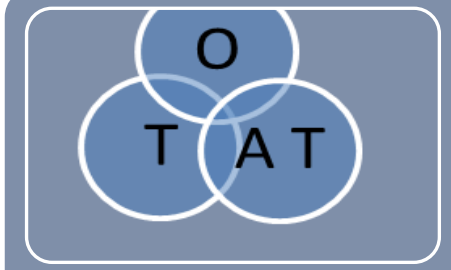


Office of Tissues and Advanced Therapies

- Regulatory Questions: 240 402 8190
- Email: OTATRPMS@fda.hhs.gov

Center for Biologics Evaluation and Research

- www.fda.gov/BiologicsBloodVaccines/default.htm
- Consumer Affairs: OCOD@fda.hhs.gov
- Manufacturers Assistance and Technical Training: industry.biologics@fda.hhs.gov

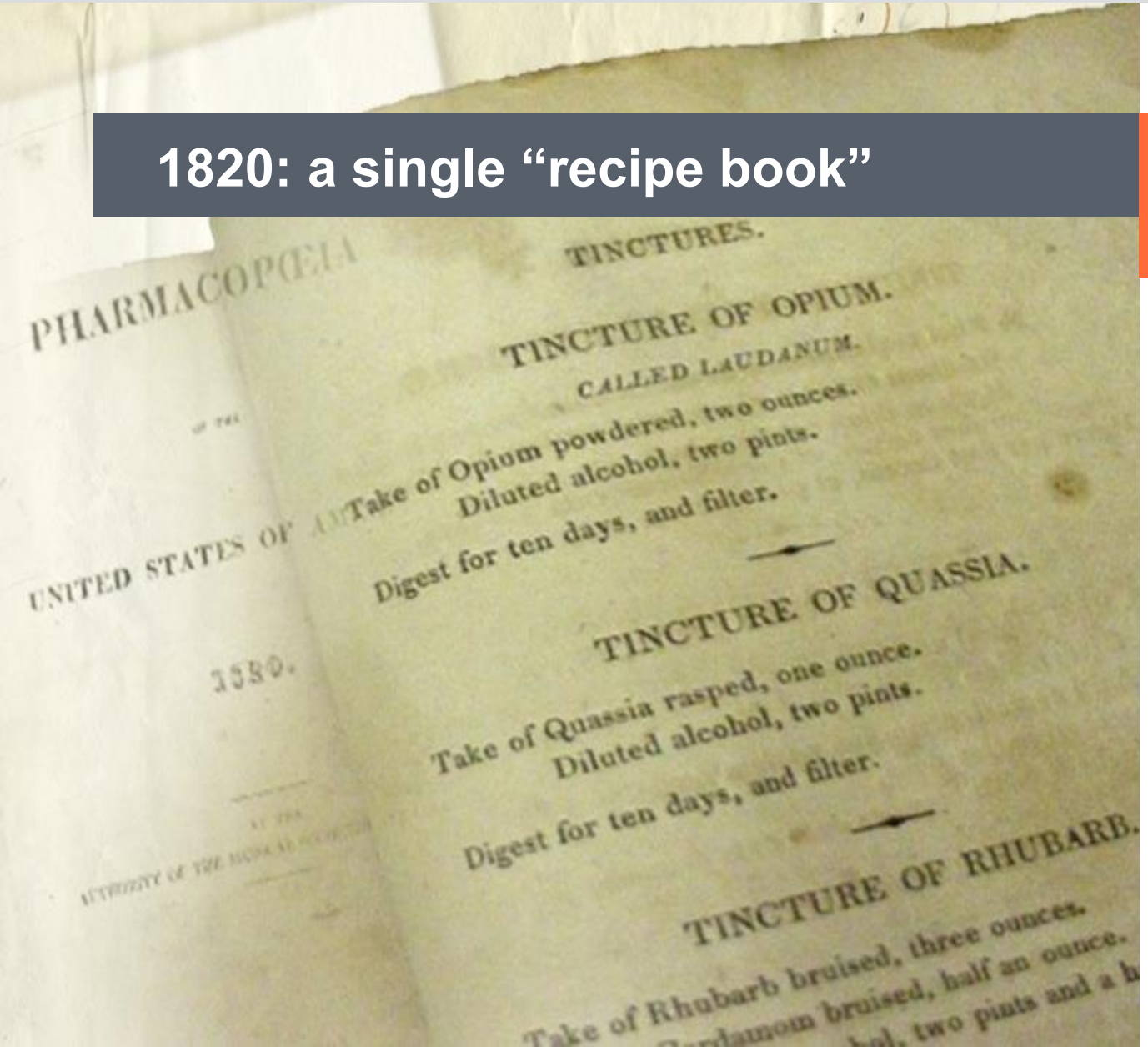
Public Standards to Support Quality of Advanced Therapies

Fouad Atouf, Ph.D.
Vice President, Global Biologics

FDLI Regenerative Medicine Conference
June 8-9, 2021| Virtual Event

200 Years of building trust in the US and well beyond

1820: a single “recipe book”



2021: Procedures and acceptance criteria to support medicinal articles in the marketplace

Heparin Sodium

DEFINITION
Heparin Sodium is the sodium salt of sulfated glycosaminoglycans present as a mixture of heterogeneous molecules varying in molecular weights that retains a combination of activities against different factors of the blood clotting cascade.

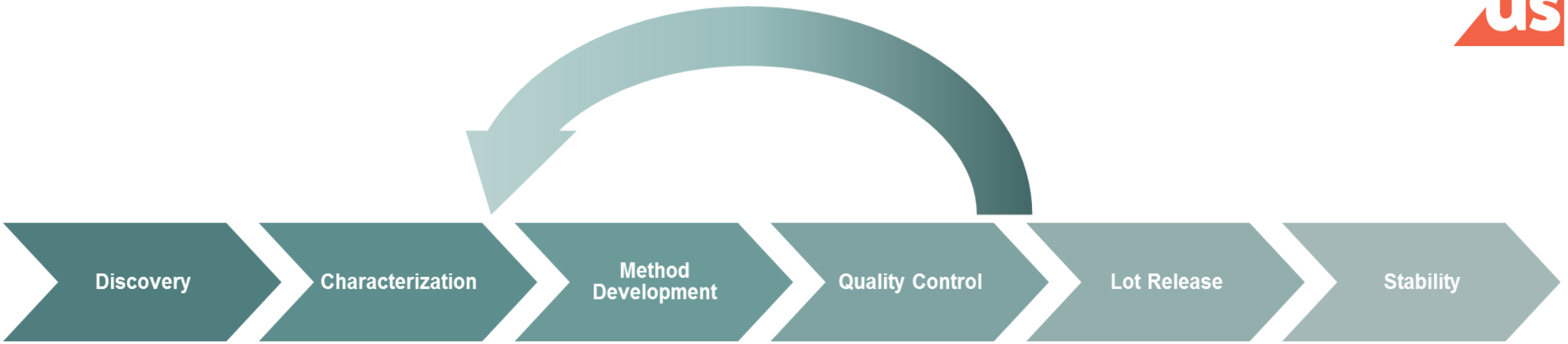
IDENTIFICATION
- **A. ^{1}H NMR Spectrum**
- **B. Chromatographic Identity**
- **C. Anti-Factor Xa to Anti-Factor IIa Ratio**
- **D. Molecular Weight Determinations**
- **E.** A solution of Heparin Sodium imparts an intense yellow color to a nonluminous flame.

Filgrastim

DEFINITION
Filgrastim is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor.

IDENTIFICATION
- **A.** It meets the requirements in the *Assay*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained as directed in the test for *Organic Impurities, Related Compounds*.
- **C. Peptide Mapping**
  (See *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩.)

USP Biologics strategy—
Evolving standards to enable a culture of quality



- USP Biologics is expanding standards development to cover quality testing throughout the overall biopharmaceutical product lifecycle.
  - Early engagement of stakeholders to identify common bottlenecks and identify solutions
  - Focus on **analytical tools, performance standards** and alignment with global norms
  - Support **raw materials** qualification and biomanufacturing
  - Standards to support **emerging therapies** based on new technologies

Advanced Therapies
Challenges in standardization

- As compared to manufacturing of other large molecule products like monoclonal antibodies, advanced therapy manufacturing presents unique challenges
- Manufacturing viral vectors and cell therapies requires several discrete manufacturing activities, each with requirements for raw materials, production, purification, release and stability testing
- A variety of analytical methodologies are in use for assessing CQAs and there is limited harmonization or use of common standards used across products/developers
  - For example – AAV genome quantitation (see 2018 FDA workshop)
- The diversity of cell types and patient variability complicate broad-based standard development
- Defining one or more specific standards that suit developer's needs across a diverse range of product types and indications remains difficult

Advanced therapies—examples of USP standards

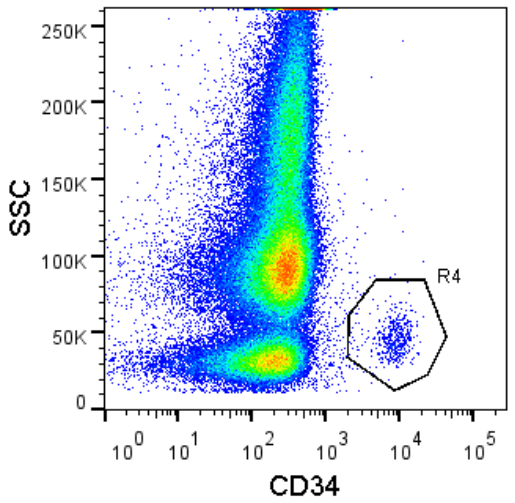
Documentary standards – General chapters

<1046> *Cell-Based Advanced Therapies and Tissue-Based Products*
<1047> *Gene Therapy Products*
<1043> *Ancillary Materials for Cell, Gene, and Tissue-Engineered Products*
<1027> *Flow Cytometry*
<1024> *Bovine Serum*
<90> *Fetal Bovine Serum--Quality Attributes and Functionality Tests*
<89> *Enzymes Used as Ancillary Materials in Pharmaceutical Manufacturing*
<92> *Growth Factors and Cytokines Used in Cell Therapy Manufacturing*
<127> *Flow Cytometric Enumeration of CD34+ Cells*

Reference Standards

Physical RS associated with ancillary material monographs (FBS, Trypsin, Collagenase)
Freeze-dried cells as Reference Standards (e.g., CD34+ Cells)

Existing standards for method performance—USP <127> Enumeration of CD34+ Stem Cells



USP CD34+ Cell Enumeration System Suitability Reference Standard is used to calibrate instruments, assess reagents and ensure correct gating for data acquisition and analysis

CD34+ CELL ENUMERATION SYSTEM SUITABILITY

USP Catalog No.:	1084292
USP Lot No.:	F045V0

Additional Information:

USP CD34+ Cell Enumeration System Suitability Reference Standard is made from mobilized peripheral blood collected by apheresis of a G-CSF mobilized donor. The reference standard contains human leukocytes, erythrocytes and CD34+ cells that have been fixed and lyophilized.

Store USP CD34+ Cell Enumeration System Suitability Reference Standard in a freezer. Allow the vial to warm up to room temperature. Reconstitute the entire contents of the vial with 500 µL of water, use immediately as a system suitability standard as described in <127> Flow Cytometric Enumeration of CD34+ Cells. After reconstitution in 500 µL of water, the concentration range is 16-34 CD34+ cells/µL.

Advanced therapies and USP standards to be developed

- Lentiviral **Vector Copy Number** Standard
  - Genomic DNA from cells with defined numbers of lentiviral vector genomes per cell equivalent
  - Standard will be used to calibrate VCN assays as well as processes for transduction
- Standards for mRNA-based therapies
  - Roundtable held in November 2018
  - Potential standards
    - Standard for T7 RNA polymerase activity
    - mRNA size standards
- Standards for AAV
  - Roundtable- March 2019 cosponsored with NIH
  - Potential standards
    - AAV9 vector as a new standard
    - **AAV empty capsids standards**
    - AAV plasmid standards with multiple AAV specific targets as a broad PCR standard
    - Raw materials e.g., **plasmid DNA**
  - Best practices and general chapters

For quality standards to be impactful, they must be…

Aligned with
Public health and patient safety priorities

Developed by
Independent experts

Adapted & Improved
For technology and evolution of healthcare

Practical for
- Users of the standard
- Enforcers of the standard

Measured by
Public health impact indicators

Informed by
Real world implications for patients and practitioners

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Empowering a healthy tomorrow

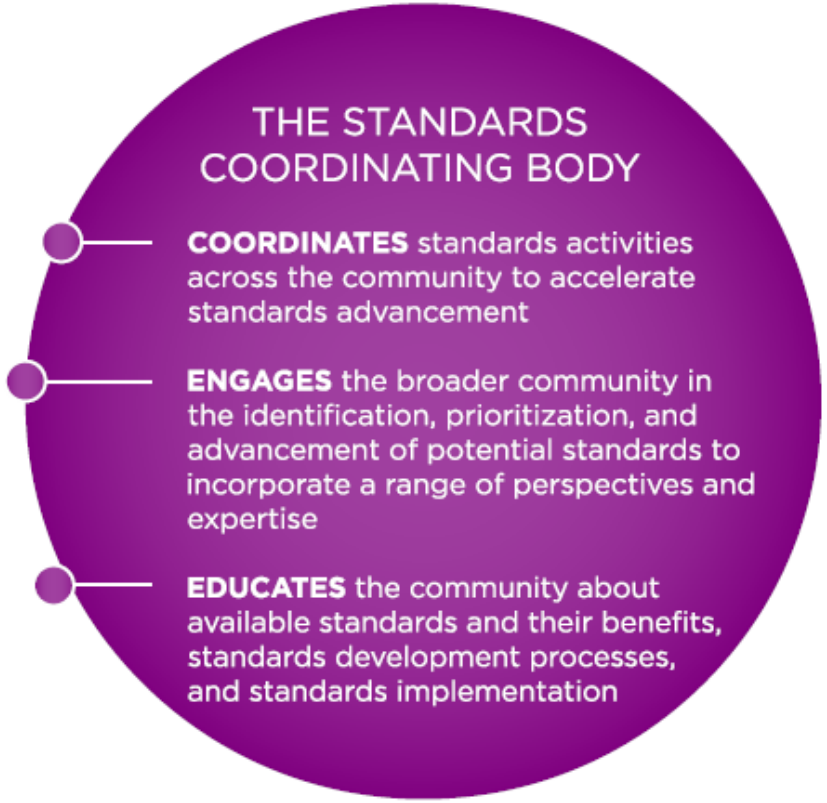
Standards Coordinating Body for Regenerative Medicine

June 7th, 2021

Robert Shaw
Executive Director

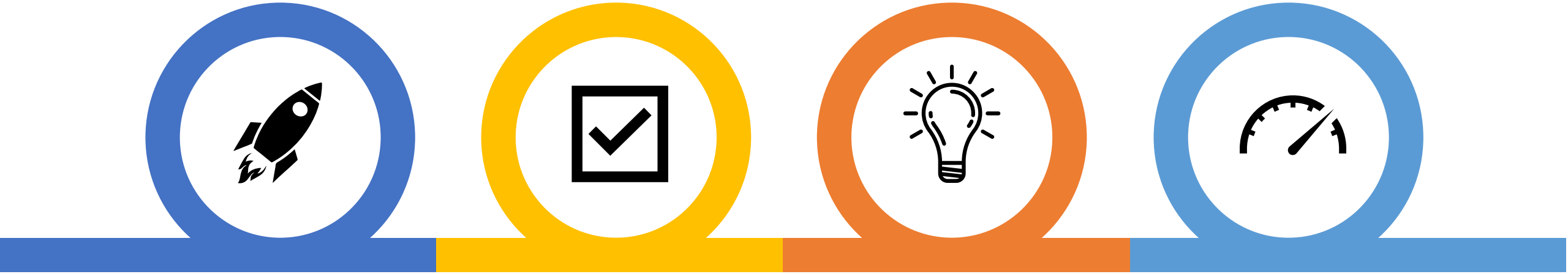
STANDARDS COORDINATING BODY
REGENERATIVE MEDICINE

SCB Background – We Work for the Regenerative Medicine Community



- 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 a Standards Development Organization (e.g. ISO)**, but rather **coordinates** standards development in order to ***accelerate*** the process
- **No** membership/fees to participate
- We serve as **communication catalyst** among all stakeholders, including government agencies, critical to the development of standards

SCB is Focused on Accelerating Standards Processes



Unleash

Standards help unleash the full potential of regenerative medicine and advanced modalities and accelerate innovation

Protect

Standards help ensure the highest degree of quality and safety for patients

Educate

SCB educates the field on the importance of standards and prioritizes what standards are needed

Catalyze

SCB brings stakeholders together to catalyze development, harmonization and adoption of standards

Why Should We Care About Standards?

We work directly with FDA and Regulatory Authorities

We can save time - map processes where standards can impact

We can save money - Implement phase appropriate

The Regenerative Medicine Standards Landscape for CMC Development – Reference and Searchable Portal

Reference Information for all standards relevant to Regen Med (available on the SCB website*).
Portal https://portal.standardscoordinatingbody.org/

- Overview of existing standards by sector
  - Cell Therapy
  - Gene Therapy
  - Tissue Engineering
- Overview by application area (bioprocessing → clinical trials)
- Identifies potential standards gaps or needs

*https://www.standardscoordinatingbody.org/publications

A number of organizations have started to move the needle on standards development in CGT

CGT standards overview

250+

Published standards relevant to CGT products, including over 100 for cell therapies and over 50 for gene therapies

20+

SDOs involved in standards development for CGT. Leaders include ASTM International, ISO, USP, PDA, and a range of others

Example standards already developed

Cell therapy standards

- Quality testing methodologies, including assessment of potency, viability, etc.
- Use of ancillary materials (e.g., trypsin, cytokines) throughout manufacturing
  - Reference material for specific ancillary materials (e.g., cytokines, FBS)
- Collection, transportation, and storage of cell therapies

Gene therapy standards

- Assessment of product quality (e.g., host-cell protein concentration)
- Reference material for various viral vectors (e.g., AAV5, AAV8)
- Best practices for manufacturing of gene therapy products

Example standards in development

Cell therapy standards

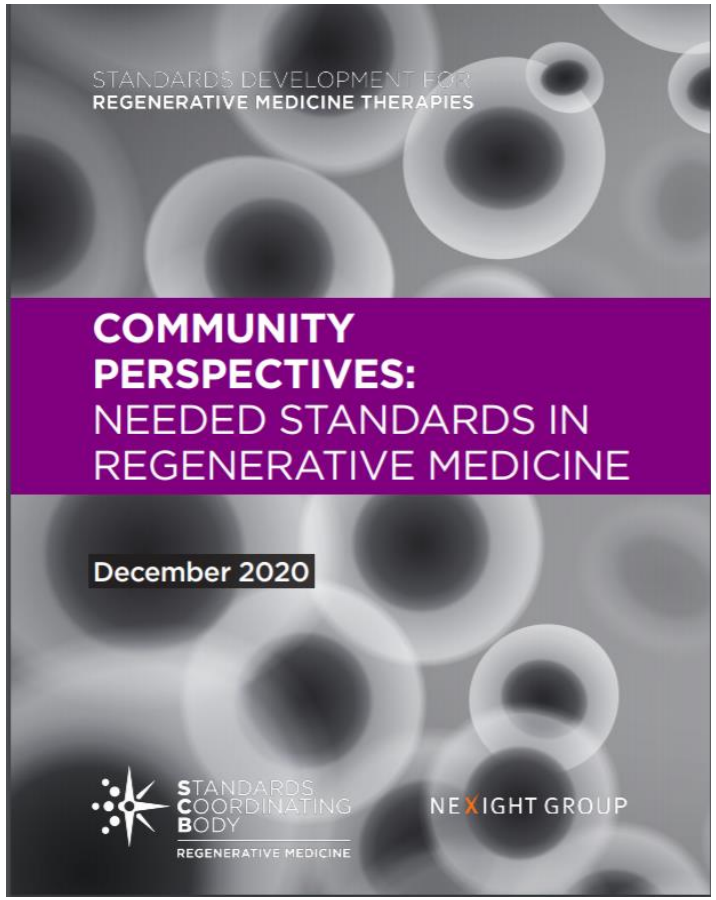
- Cell collection (e.g., apheresis) methods, including best practices for collection, documentation, etc.
- Rapid microbial testing method validation and implementation
- Maintenance of chain of custody / chain of identify for cell therapies

Gene therapy standards

- Testing methods to enable assessment of viral vector titers and transduction efficiencies
- Documentation of assessment of pre-existing immunity to adeno-associated viruses

*https://www.standardscoordinatingbody.org/publications

Updated Community Perspectives: Needed Standards in Regenerative Medicine



Process development can be accelerated by proactively incorporating these priority areas into CMC and regulatory strategy.

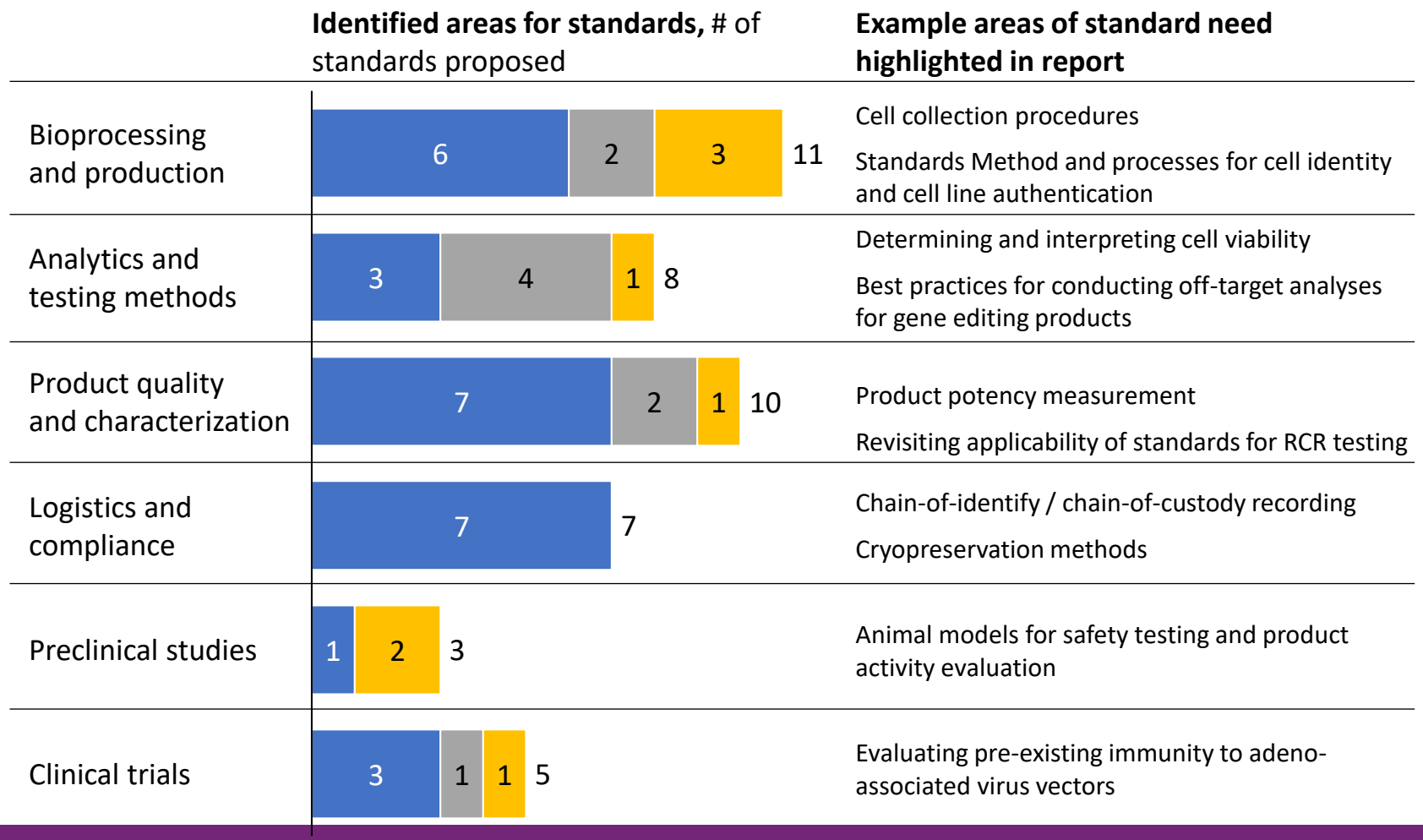
- **44 Needed Standards Identified**
- Added ***9 new needed standards*** areas
- Standards prioritized by Impact and Urgency for field
- Prioritized areas will enter feasibility studies to determine next steps
- Interactive On-Line SCB Portal - https://portal.standardscoordinatingbody.org/

Document available on website https://www.standardscoordinatingbody.org/needed

SCB has identified 44 areas for standards development in CGT

Multiple modalities
Cell therapy only
Gene therapy only
Tissue engineering only

Source: SCB: Needed standards in Regenerative Medicine Report (December 2020)



Key takeaways

Standards continue to be needed across the CGT value chain (e.g., logistics, preclinical trials, testing)

Majority of identified areas will impact multiple CGT modalities, although a number of gene therapy or tissue engineering specific

Needs for a variety of standards types were identified (e.g., best practices, process standards)

SCB has identified prioritized areas of need *and is assessing feasibility of standards development*

How standards development can be accelerated

- **Focus on developing standards in pre-competitive areas** to avoid impacting innovation and limit resistance to standards adoption
- **Industry (biotech, big pharma or CDMO) stakeholders to effectively prioritize standards** based on impact and feasibility
- **Ensure compatibility of standards across geographies** to enable broad adoption
- **Encourage transparency across all stakeholders** involved in the standards development process

How Should Companies Think About Standardization

Standardization embedded in **business strategy – aligned with regulatory strategy**

Map processes to business strategy and identify areas where standards should be developed

Identify resources responsible for implementation of standards

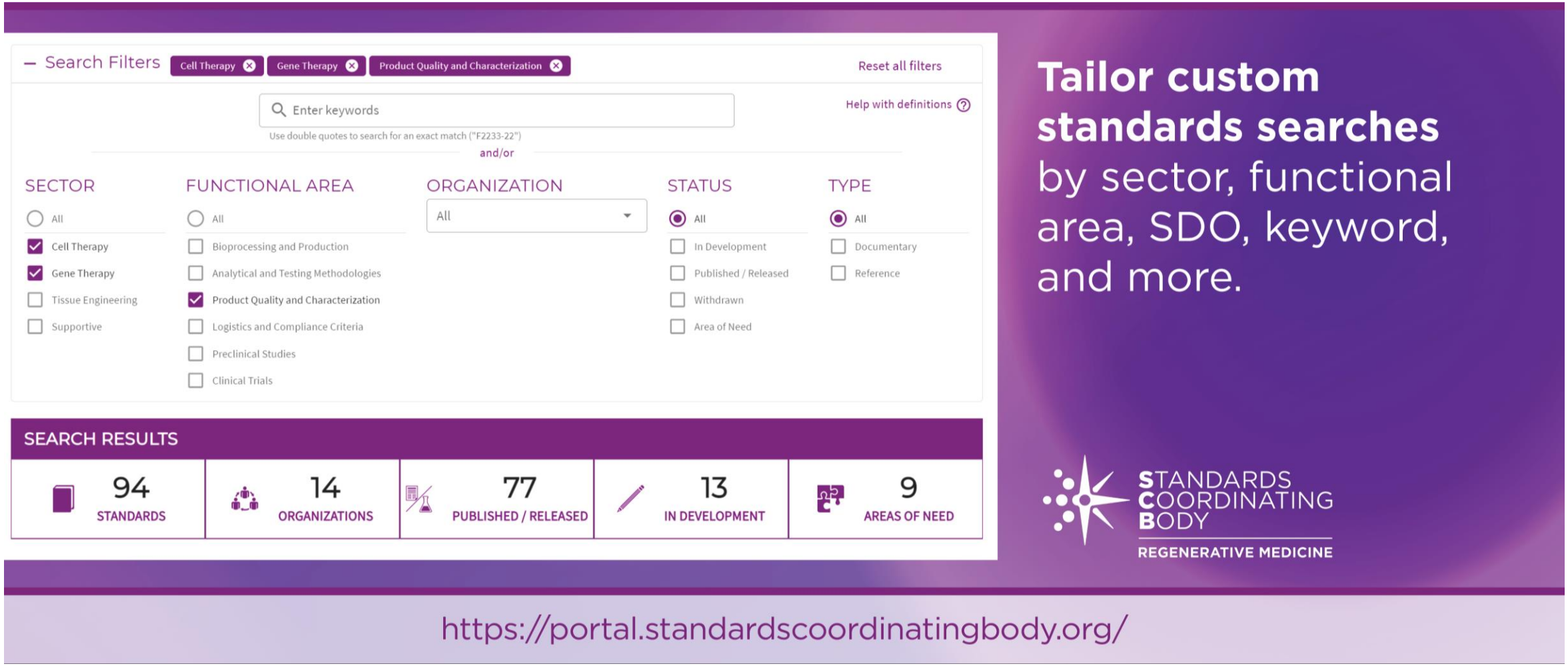
www.standardscoordinatingbody.org

And/Or Contact

rshaw@regenmedscb.org

Backup

SCB Regenerative Medicine Portal interactive tool for standards information



https://portal.standardscoordinatingbody.org/


Patient
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