Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies

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Guidance for Industry

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Table of Contents

Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance describes a standards recognition program for regenerative medicine therapies (SRP-RMT) at FDA's Center for Biologics Evaluation and Research (CBER) designed to identify and recognize Voluntary Consensus Standards[1] (VCS) to facilitate the development and assessment of regenerative medicine therapy (RMT) products regulated by CBER when such standards are appropriate. CBER encourages the use of appropriate standards in the development of CBER-regulated products. The use of recognized VCS can assist stakeholders in more efficiently meeting regulatory requirements and increasing regulatory predictability for RMT products. This program is modeled after the formal standards and conformity assessment program or S-CAP for medical devices (Ref. 1).[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

[1] In this guidance, the phrase *voluntary consensus standard* refers to

> a standard that is developed or adopted by domestic and international voluntary consensus standards bodies . . . . These bodies often have . . . policies that include provisions requiring that owners of relevant patented technology incorporated into a standard make that intellectual property available to implementers of the standard on non-discriminatory and royalty-free or reasonable royalty terms.

(See Ref. 2 at 16)

[2] FDA has a formal recognition program for device standards under the Food and Drug Administration Modernization Act of 1997. Public Law 105-115. Under the device standards recognition program, the term "recognize" refers to FDA's formal identification of a standard under section 514(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act after the determination that the standard is appropriate to meet relevant requirements in the FD&C Act, Public Health Service (PHS) Act, and Title 21 of the Code of Federal Regulations (21 CFR).

II. BACKGROUND

The Federal government's policies on the use of VCS are described in the Office of Management and Budget (OMB) Circular A-119, "Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities" (Ref. 2). The policies outlined in Circular A-119 were codified in the National Technology Transfer and Advancement Act of 1995 (NTTAA) (Ref. 3). CBER's recommendations on the use of standards in product development and control, as well as the use of such standards in CBER's managed review process, are described in a guidance document entitled "Standards Development and Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research; Guidance for Industry" March 2019 (CBER Standards guidance) (Ref. 4).

Title 3, section 3036 of the 21st Century Cures Act[3] adds section 506(g) to the FD&C Act. This section directs FDA, in consultation with the National Institute of Standards and Technology (NIST) and stakeholders, to "facilitate an effort to coordinate and prioritize the development of standards and consensus definitions of terms, through a public process, to support, through regulatory predictability, the development, evaluation, and review of regenerative medicine therapies and regenerative advanced therapies, including with respect to the manufacturing processes and controls of such products." (Ref. 5).

RMTs are defined in section 506(g)(8) of the FD&C Act and include cell therapies (allogeneic and autologous), therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products except those regulated solely under section 361 of the PHS Act (42 U.S.C. 264) and 21 CFR part 1271. Based on FDA's interpretation of section 506(g), human gene therapies, such as genetically modified cells that lead to a sustained effect on cells or tissues, and xenogeneic cell products may meet the definition of RMT products (Ref. 6).

In accordance with section 3036 of the 21st Century Cures Act of 2016, facilitation of standards development and their use in regulatory submissions are ongoing priorities in CBER's effort to promote the development and streamline the review of RMT products. The scientific and manufacturing novelty of many RMT products present unique challenges for meeting regulatory requirements with respect to product testing, product characterization, testing methodologies, manufacturing processes, product quality, and specifications. Increased development and use of standards has the potential to contribute to regulatory predictability and facilitate the overall development of safe and effective RMT products.

For the purpose of this guidance and as set forth in Circular A-119, the term "standard" (or "technical standard") includes all of the following:

- Common and repeated use of rules, conditions, guidelines or characteristics for products or related processes and production methods, and related management systems practices;
- The definition of terms; classification of components; delineation of procedures; specification of dimensions, materials, performance, designs, or operations; measurement of quality and quantity in describing materials, processes, products, systems, services, or

[3] Pub. L. 114-255.

practices; test methods and sampling procedures; formats for information and communication exchange; or descriptions of fit and measurements of size or strength; and
- Terminology, symbols, packaging, marking or labeling requirements as they apply to a product, process, or production method (Ref. 2).

As used in this guidance, the term standards refer to standards developed outside of the Federal government. CBER intends to consider recognition of standards developed by VCS bodies[4] that adhere to the following five elements mentioned in the revised OMB Circular A-119[5]:

1. Openness

The procedures or processes for participating in standards development are transparent and open to interested parties. Such parties are provided "meaningful opportunities to participate in standards development on a non-discriminatory basis."[6]

2. Balance

A broad range of stakeholders engage in meaningful involvement in the standards development process of the VCS body, with no single interest dominating the decision making.

3. Due Process

The standards development process of the VCS body contains a due process provision where (1) that body's standards development policies and procedures are documented and publically available, (2) all stakeholders are provided adequate notice of that body's meetings and standards development activities, "sufficient time to review drafts and prepare views and objections, access to views and objections of other participants, and (3) a fair and impartial process for resolving conflicting views."[7]

4. Appeals Process

The standards development process of the VCS body contains an appeals provision, which allows that body to impartially handle any procedural appeals.

[4] *Voluntary consensus standards bodies* refer to any "association, organization, or technical society that plans, develops, establishes, or coordinates voluntary consensus standards using a voluntary consensus standards development process that includes [specific] attributes or elements." (See Ref. 2) VCS are defined as bodies as having policies that include provisions requiring that owners of relevant patented technology incorporated into a standard make that intellectual property available to implementers of the standard on non-discriminatory and royalty-free or reasonable royalty terms. Id.
[5] OMB Circular A-119 defines consensus as a "general agreement, but not necessarily unanimity". (See Ref. 2)
[6] Id.
[7] Id.

5. Consensus

During the development of consensus[8] on standards, comments and objections are considered using fair, impartial, open, and transparent processes.

The policies of OMB Circular A-119 are intended to: (1) encourage Federal agencies to benefit from the expertise of the private sector, (2) promote Federal agency participation in voluntary consensus standards bodies to ensure the creation of standards that are usable by Federal agencies, and (3) reduce reliance on Government-unique standards when an existing voluntary standard would suffice. CBER's program for informal recognition of VCS is consistent with the policies of OMB Circular A-119 (Ref. 2).

The use of standards is strictly voluntary unless mandated by statute or regulation. Federal regulatory agencies, such as FDA, are authorized by Congress to promulgate regulations to implement legislation enacted by Congress. Regulations have the force and effect of law and are generally mandatory, setting out specific requirements that regulated products and entities must meet (Ref. 4).

For the purpose of this guidance, a Standards Development Organization (SDO) is an entity that develops or sponsors the development of voluntary standards for use or information by any person involved in the manufacture, distribution, sale, or use of products or services or the legal regulation of such products or services. This definition includes but is not limited to VCS bodies.

III. SCOPE

This guidance describes a program at CBER for recognition of VCS relevant to RMT products regulated in CBER. This guidance also describes how CBER intends to review for recognition in the SRP-RMT. This program will not apply to: statutory and regulatory standards that are legally binding, such as certain provisions of the FD&C Act (21 U.S.C. 301-et seq.) and PHS Act (42 U.S.C. ch. 6A); to standards developed by SDOs that do not follow consensus mechanisms; or to electronic data exchange standards for submissions to CBER.[9,10]

[8] The revised OMB Circular A-119 defines *consensus* as a "general agreement, but not necessarily unanimity." OMB Circular A-119 Revised. See footnote 3.

[9] Electronic data exchange standards for submissions to CBER can be found in the FDA Data Standards Catalog. For more information, see the FDA Data Standards Catalog, available at the FDA Resources for Data Standards website: https://www.fda.gov/ForIndustry/DataStandards/default.htm.

[10] The program also does not apply to non-recognized standards that product sponsors and applicants are seeking to use in regulatory submissions.

IV. PURPOSE OF THE PROGRAM

The use of existing VCS minimizes the need for government-unique standards consistent with the OMB Circular A-119 and the NTTAA (Refs. 2 and 3). By leveraging stakeholders' efforts to develop standards, FDA can eliminate costs to the Federal government associated with the development of government-unique standards and promote international harmonization of standards that are acceptable to FDA.

The SRP-RMT is expected to promote the visibility and use of standards applicable to FDA's public health mission by:

- Using Agency expertise to evaluate and recognize voluntary consensus standards related to RMT products that are potentially useful to industry and CBER staff. Specifically, this process will allow CBER to:
    - Receive a candidate VCS, with relevant information (e.g., the scope of the standard and the purpose), from FDA staff or external stakeholders for informal recognition.
    - Determine whether to recognize a standard in whole or in part following an internal scientific evaluation.
    - List the recognized standards in a publicly searchable database on CBER's website, accompanied by an information sheet describing the scope and the extent of CBER's recognition of that standard and any other relevant information about the standard.
- Providing transparency to industry and other stakeholders regarding CBER's thinking about a particular method or approach, thereby increasing regulatory predicitability.

CBER encourages the use of appropriate standards in the development of CBER-regulated products. Increased use of existing relevant VCS can facilitate product development by reducing the need to develop unique methods for individual products. In addition, when used appropriately, VCS will typically reduce the amount of documentation that a submitter needs to provide and may reduce FDA review time.

V. PROCEDURES FOR EVALUATING VCS FOR RECOGNITION IN THE SRP-RMT

Existing published VCS relevant to RMT products may be identified internally by FDA or externally by stakeholders for evaluation and potential recognition in the SRP-RMT. FDA subject matter experts (SMEs) in the Office of Therapeutic Products (OTP) in CBER generally intend to consider multiple factors in assessing the standard, including that:

- The standard does not conflict with the FD&C Act , the PHS Act, applicable regulations, or current policies;
- The standard is scientifically sound;
- The standard can assist in the assessment of a regulatory submission for RMT products; and;
- Use of the standard may facilitate the ability of a sponsor to meet regulatory requirements for RMT products reviewed in CBER.

CBER will assign a recognition number to recognized standards. The recognition of a standard will include a Standard Recognition Summary (SRS). This SRS, developed by CBER/OTP, is intended to assist stakeholders should they elect to use standards in their development, manufacturing, or for other purposes. The SRS includes the standard's scope and other helpful information. (See Appendix 1).

FDA intends to maintain a list of VCS that have been recognized (either whole or in part) by CBER/OTP) on the FDA Regenerative Medicine website at https://www.fda.gov/vaccines-blood-biologics/standards-development-regenerative-medicine-therapies. CBER intends to update information on the website at least twice annually.

Any stakeholder can request recognition of a specific VCS by email to SRP-RMT by submitting the following information to SRP-RMT@fda.hhs.gov:

1. Name and electronic or mailing address of the requester;
2. Name of the SDO;
3. Title of the VCS;
4. The VCS reference or SDO designation number and publication date (e.g., Q1234-2019);
5. Proposed list of products for which the standard could apply routinely;
6. Rationale for request; and
7. A brief description of the testing, performance, or other characteristics of the RMT product(s) or process(es) that would be addressed by the proposed standard.

CBER intends to decide on recognition (complete or partial) or non-recognition within 180 days from the date the request is received, as resources permit. CBER intends to send to the submitter a response by email acknowledging receipt of the request. CBER intends to begin to accept requests for recognition of specific standards when this draft guidance is published as a final guidance.

VI. DOCUMENTING THE USE OF A STANDARD RECOGNIZED BY CBER UNDER THE SRP-RMT IN A REGULATORY SUBMISSION

The documentation of use of a standard is described in the CBER Standards guidance (Ref. 4) Briefly, the sponsor should provide the name of the SDO, title and version of the standard. The sponsor should also state if the standard was used as written or describe deviations from the standard and the rationale for the deviation. When using a standard that has been recognized by

CBER, the sponsor should also provide the recognition number for the specific standard. (Note that use of recognized standards is not required.)

VII. QUESTIONS AND ANSWERS

1. **What if I want to use a standard that has not been recognized in the SRP-RMT?**

   Recognition in the SRP-RMT is not required for a submitter to reference a standard in a regulatory submission. Sponsors may seek to utilize and reference any standard not recognized in the SRP-RMT in any regulatory submission. However, the use of recognized and non-recognized standards in a regulatory submission is subject to FDA's assessment of whether the standard is fit for the intended purpose.

2. **What does it mean when CBER recognizes a VCS?**

   CBER's recognition of a VCS communicates to FDA staff and external stakeholders that FDA has evaluated a VCS and has generally found it, in whole or in part, appropriate for the development and review of RMT products. Even if a submitter decides to use one of CBER's recognized voluntary standards, CBER may request that the submitter provide additional information to support an application when appropriate. As indicated previously, an applicant's use of such recognized consensus standard is voluntary.

3. **Are electronic data exchange standards included in this recognition program?**

   Electronic data exchange standards are not included in the SRP-RMT. These types of standards are outside of the scope of the SRP-RMT.[9]

4. **How often will VCS standards be reviewed for recognition and where will recognized standards be posted?**

   FDA intends to review voluntary consensus standards for recognition throughout the year. FDA intends to update its list of recognized consensus standards twice a year on the FDA Regenerative Medicine website https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/framework-regulation-regenerative-medicine-products. Each recognized standard will be accompanied by an SRS, which outlines the scope and extent of recognition.

5. **When an SRP-RMT recognized standard is updated by an SDO, will the updated standard automatically be recognized or will the standard be re-reviewed for recognition?**

   Standards are typically reviewed by the SDOs every 5 years to ensure that the standard continues to be relevant and to assess whether the standard needs to be updated because of advances in technology. If an SRP-RMT recognized consensus standard is revised and an updated version is published by an SDO, FDA will typically review it using the

internal process and criteria described in section V of this guidance to determine if the new changes affect the recognition status in the SRP-RMT program. Unless and until the new version is recognized, the earlier version will generally remain recognized in the SRP-RMT.

VIII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The time required to complete this information collection is estimated to average 3 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave., Bldg. 71, Rm. 7301
Silver Spring, MD 20993-0002

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0338. To find the current expiration date, search for this OMB control number at https://www.reginfo.gov).

IX. REFERENCES

1. Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices; Guidance for Industry and Staff, September 2018, https://www.fda.gov/media/71983/download.

2. 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.

3. 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-1995.

4. Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research; Guidance for Industry, March 2019, https://www.fda.gov/media/124694/download.

5. 21st Century Cures Act of 2016 (Pub. L. 114-225), https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.

6. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry, February 2019, https://www.fda.gov/media/120267/download.

APPENDICES

Appendix 1: Sample Standards Recognition Summary

CBER-Recognized Standards for Regenerative Medicine Therapies
Standards Recognition Summary (SRS)

Recognition Number (CBER Assigned) **Date of Recognition:**
Standard Information
ISO XXXX, Edition YEAR
Title of Standard

Scope/Abstract

Extent of Recognition (Full or Partial)
(For partial recognition CBER intends to identify the parts of the standard that are not recognized.)

Rationale for Recognition
(Ex. This standard is relevant to the characterization of CAR T cells and supports existing regulatory policy, name of guidance document or Federal Register notice, etc.)

Standards Development Organization
(Ex. ISO International Organization for Standardization)
https://www.iso.org

Appendix 2: Acronyms

1. SRP-RMT: Standards Recognition Program for Regenerative Medicine Therapies
2. CBER: Center for Biologics Evaluation and Research
3. VCS: Voluntary Consensus Standards
4. RMT: Regenerative Medicine Therapy
5. OTP: Office of Therapeutic Products
6. CDRH: Center for Devices and Radiological Health
7. S-CAP: Standards and Conformity Assessment Program
8. FD&C Act: Federal Food, Drug, and Cosmetic Act
9. PHS Act: Public Health Service Act
10. CFR: Code of Federal Regulations
11. OMB: Office of Management and Budget
12. NTTAA: National Technology Transfer and Advancement Act of 1995
13. NIST: National Institute for Standards and Technology
14. SDO: Standards Development Organization
15. SME: Subject Matter Expert
16. U.S.: United States
17. SRS: Standard Recognition Summary
18. USP: United States Pharmacopeia
19. WHO: World Health Organization