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

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Draft Guidance for Industry and Food and Drug Administration Staff

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov/. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2017

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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to describe the recommendations of the Center for Biologics Evaluation and Research (CBER) on the use of standards in product development and the use of such standards in CBER's managed review process. CBER recognizes the value of standards and encourages the use of appropriate standards in the development of CBER-regulated medical products. Sponsors' use of standards can facilitate product development and a more efficient evaluation of regulatory submissions. This guidance does not endorse the activities of specific Standards Development Organizations (SDOs) or recommend specific standards for use in regulatory submissions.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Federal Government's policies on the use of standards developed by voluntary consensus standard bodies 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. 1). The policies outlined in Circular A-119 were codified in the National Technology Transfer and Advancement Act of 1995 (NTTAA) (Ref. 2).

The NTTAA authorizes the National Institute of Standards and Technology to coordinate standards activities for Federal agencies.

CBER's use of, and CBER's acceptance of sponsors' use of, voluntary consensus standards do not constitute a delegation of CBER's regulatory responsibilities. Whether or not standards are used, CBER retains the ability to set, and the responsibility for setting, appropriate regulatory criteria for CBER-regulated products.

III. DEFINITIONS

A. What is a Standard?

For purposes of this guidance, and as set forth in Circular A-119, the term "standard" (or "technical standard") includes all of the following: (1) common and repeated use of rules, conditions, guidelines or characteristics for products or related processes and production methods, and related management systems practices; (2) 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 practices; test methods and sampling procedures; formats for information and communication exchange; or descriptions of fit and measurements of size or strength; and (3) terminology, symbols, packaging, marking or labeling requirements as they apply to a product, process, or production method (Ref. 1).

B. How do Standards Differ from Regulations?

Federal regulatory agencies such as FDA are authorized by Congress to promulgate regulations to interpret and/or enforce 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.

Standards are frequently developed outside of the federal government by a Standards Development Organization. The use of a standard is voluntary unless mandated by regulation or statute.

C. What is a Standards Development Organization (SDO)?

For purposes 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 voluntary consensus standards bodies (Ref. 3). Examples of SDOs include the American Society for Testing and Materials International (ASTM) and International Organization on Standardization (ISO).

D. What is a Voluntary Consensus Standards Body?

A voluntary consensus standards body is one kind of SDO. For purposes of this guidance, and as set forth in Circular A-119, it is a type of association, organization, or technical society that plans, develops, establishes, or coordinates voluntary consensus standards using a voluntary consensus standards development process that includes the following attributes or elements:

1. Openness: The procedures or processes used are open to interested parties. Such parties are provided meaningful opportunities to participate in standards development on a non-discriminatory basis. The procedures or processes for participating in standards development and for developing the standard are transparent.

2. Balance: The standards development process should be balanced. Specifically, there should be meaningful involvement from a broad range of parties, with no single interest dominating the decision-making.

3. Due process: Due process shall include documented and publically available policies and procedures, adequate notice of meetings and standards development, sufficient time to review drafts and prepare views and objections, access to views and objections of other participants, and a fair and impartial process for resolving conflicting views.

4. Appeals process: An appeals process shall be available for the impartial handling of procedural appeals.

5. Consensus: Consensus is defined as general agreement, but not necessarily unanimity. During the development of consensus, comments and objections are considered using fair, impartial, open, and transparent processes (Ref. 1).

Circular A-119 also explains that voluntary consensus standards bodies often have intellectual property rights (IPR) policies that include provisions requiring that owners of patented technology incorporated into a standard make that intellectual property available to implementers of the standard on nondiscriminatory and royalty-free or reasonable royalty terms (and binding subsequent owners of standards-essential patents to the same terms) (Ref. 1).

E. What are Voluntary Consensus Standards?

For purposes of this guidance, voluntary consensus standards are standards developed or adopted by a domestic or international voluntary consensus standards body.

In order to qualify as a voluntary consensus standard for the purposes of Circular A-119, a standard that includes patented technology needs to be governed by intellectual property

rights policies, as described above, put into place by the voluntary consensus standards body. Circular A-119 states that such policies should be easily accessible, set out clear rules governing the disclosure and licensing of the relevant intellectual property, and take into account the interests of all stakeholders, including the IPR holders and those seeking to implement the standard (Ref. 1).

F. What are Written or Documentary Standards?

For purposes of this guidance, written or documentary standards include documents that set forth performance characteristics, testing methodology, manufacturing practices, product standards, scientific protocols, compliance criteria, ingredient specifications, labeling, and terminology.

G. What are Reference Materials or Physical Standards?

For purposes of this guidance, reference materials or physical standards are typically highly characterized reagents or substances that are distributed to assure consistency, quality, and safety of regulated products. Reference materials are materials that are considered to be sufficiently homogeneous and stable with respect to one or more specified attributes, and that have been established to be suitable for their intended use in a measurement process (for example, measurement of potency or product consistency).

H. What are Data Standards?

For purposes of this guidance, data standards are defined rules, formats and terminologies that provide structure and consistency for exchange and utilization of data.

I. What are Performance Standards?

For purposes of this guidance, and as set forth in Circular A-119, performance standards state requirements in terms of required results without stating the methods for achieving those results. A performance standard may define the functional requirements for the item, operational requirements, and/or interface and interchangeability characteristics. (In contrast, a prescriptive standard may specify design requirements such as materials to be used, how a requirement is to be achieved, or how an item is to be fabricated or constructed.) (Ref. 1).

IV. HOW ARE STANDARDS DEVELOPED?

SDOs develop or sponsor the development of voluntary standards that can be used by a person involved in the manufacture, distribution, sale or use of products or services or in the legal regulation of such products and services. SDO standard-setting activities include the

development of performance characteristics, testing methodology, manufacturing practices, product standards, scientific protocols, compliance criteria, ingredient specifications, labeling, and terminology.

Participants in the standards development process are individuals who represent stakeholders and possess expertise in the particular area for which a standard is under development. Although standards development procedures vary among SDOs, the process typically begins with identifying the need for a written/documentary standard or a reference material/physical standard and gathering experts to develop the standard. Drafts of written standards are circulated for comment, voting, editing and publishing. Reference materials/physical standards may be distributed for testing and certification to ensure that they serve their intended purpose.

CBER staff often participate in the development of standards. CBER participation in the development of a particular standard does not constitute endorsement of that standard.

V. WHAT ARE THE BENEFITS OF USING STANDARDS?

In line with OMB Circular A-119 (Ref. 1) and the NTTAA (Ref. 2), the use of existing standards minimizes the need for government-unique standards. By leveraging stakeholder efforts to develop standards, FDA can eliminate the costs to the Federal Government associated with the development of government-unique standards, and promote international harmonization of standards acceptable to FDA.

CBER participates in SDOs in order to become familiar with standards as they are developed and to help ensure that standards developed are not in conflict with FDA regulations or policies. CBER's participation also increases the likelihood that the standards under development will ultimately be suitable for products regulated by CBER during individual reviews.

CBER encourages the use of appropriate standards in the development of CBER-regulated medical products. Sponsors' wider use of existing relevant voluntary consensus standards can facilitate development by reducing the need to develop unique methods and/or reference materials for individual products. The use of standards can facilitate product design and contribute to a more efficient evaluation of regulatory submissions, ultimately improving time to market.

VI. WHAT IS CBER'S POLICY ON ACCEPTING STANDARDS USED IN REGULATORY SUBMISSIONS?

A. What is CBER's Policy on Use of Standards in Regulatory Submissions?

FDA encourages sponsors of regulatory submissions and manufacturers to use appropriate voluntary consensus standards. Furthermore, FDA intends to preferentially use internationally harmonized standards (standards developed by organizations typically

involving representatives from many countries) in their processes, when those standards represent the most appropriate standards for a specific purpose and are not in conflict with U.S. law (Ref. 3).

Guidance documents published by FDA may reference standards, including test methods, practices, guides, and material specifications, developed through voluntary consensus processes with the regulated industry and other interested parties. For example, the CBER/Center for Devices and Radiological Health (CDRH) joint guidance, "Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage" (Ref. 4) references ASTM F2451-05, "Standard Guide for in vivo Assessment of Implantable Devices Intended to Repair or Regenerate Articular Cartilage," reapproved by ASTM in 2010. In that guidance, the Agency recommends consulting the ASTM standard for the development of animal models and the testing of implantable devices (cartilage repair products).

Sponsors are advised to discuss the proposed use of a particular standard or portion of a standard with CBER prior to implementation in order to determine if the standard is appropriate for the intended regulatory purpose. Sponsors should contact the relevant CBER office responsible for regulatory oversight (e.g., the Office of Biostatistics and Epidemiology (OBE), Office of Blood Research and Review (OBRR), Office of Tissues and Advanced Therapies (OTAT), Office of Compliance and Biologics Quality (OCBQ), or Office of Vaccines Research and Review (OVRR)). The Office of Communication, Outreach and Development (OCOD) may be contacted at industry.biologics@fda.hhs.gov for advice on which office is responsible for the review of a particular product.

CBER recommends the following to those considering the use of a standard in support of their regulatory application.

1. When using a standard, the sponsor should provide a complete reference for the standard in the regulatory submission.

2. Note that, once CBER has determined that a version of a standard is acceptable, the sponsor should not implement a new version of that standard before discussing with the product office.

3. Written/Documentary Standards: A sponsor may use appropriate written/documentary standards that describe a process or assay used to assess a manufacturing intermediate or final product.

4. Reference Materials/Physical Standards: A sponsor may also utilize an appropriate physical standard or reference material in the development and testing of their product. Examples of reference materials include commercially supplied reference standards obtained from a reputable commercial source; other materials of documented purity certified by an analytical laboratory or other noncommercial establishment; and a well-characterized lot of the product itself.

CBER prepares, calibrates, holds and distributes certain official U.S. reference standards and reagents to assist firms holding approved biologics license applications (BLAs) or investigational new drug applications (INDs). The sponsor should provide information on the reference standards or reference materials used for testing the drug substance or drug product in the submission. CBER recommends providing the source and lot number, expiration date, certificates of analyses when available, and/or internally or externally generated evidence of identity and purity for each reference standard. In cases where the sponsor would be using a well-characterized lot of their product, CBER recommends that the sponsor reserve and maintain a sufficient supply of the product to serve as a reference material.

An in-house standard should be maintained in accordance with the regulated reference standard to which it is traceable, unless a sponsor demonstrates that maintaining the in-house standard otherwise is appropriate. However, please note that changes to the way an in-house standard is maintained must be reported to the Agency, in accordance with FDA regulations in Title 21 of the Code of Federal Regulations (CFR) 312.31 for INDs; 21 CFR 314.70 for New Drug Applications (NDAs); or 21 CFR 601.12 for BLAs.

If the sponsor has questions about whether the use of a particular standard is appropriate, the sponsor should discuss its use with the appropriate product office or CBER's OCBQ Division of Biological Standards and Quality Control, as appropriate, before using that standard in a regulatory submission.

5. Data Standards: Data standards can help promote effective and efficient review of regulatory submissions. Examples of data standards include Structured Product Labeling (SPL), Health Level 7 (HL7) Stability Standard, etc. For more information, see the FDA Data Standards Catalog, available at: https://www.fda.gov/ForIndustry/DataStandards/default.htm.

B. What if a Product is Regulated by CBER as a Device?

Section 514(c) of the Federal Food, Drug, and Cosmetic Act (FD&C) (21 U.S.C. 360d(c)) authorizes FDA to recognize certain standards for which a person may submit a declaration of conformity, certifying that a device is in conformity with the standard, in order to meet a premarket submission requirement or other requirement under the FD&C Act. In accordance with the Food and Drug Administration Modernization Act (FDAMA) of 1997, CDRH maintains a list of recognized Consensus Standards that can be found at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. Standards referenced in the CFR can be found in the Standards Incorporated by Reference (SIBR) Database at https://standards.gov/sibr/query/index.cfm. The database

includes voluntary consensus standards, government-unique standards, private industry standards, and international standards referenced in the CFR. For additional information on the standards recognition program refer to relevant CDRH guidance documents (Refs. 5-7).

C. Does CBER take Accreditation Standards into Consideration when Assessing Compliance with CBER Regulatory Requirements?

Accreditation standards are set forth by accreditation organizations to ensure that certain criteria are met for a specified process or system. Note that these organizations generally do not meet the definition of a voluntary consensus standards body. CBER may, when it deems it appropriate, take accreditation standards established by these organizations into consideration when assessing compliance with CBER regulatory requirements. Examples of accreditation organizations include AABB (transfusion medicine and cellular therapies), Foundation for the Accreditation of Cellular Therapy (cellular therapy), International Council for Commonality in Blood Banking Automation (identification and labeling of blood and tissues), and American Association of Tissue Banks (tissue banking). CBER has, for example, recognized certain blood donor history questionnaires developed by AABB as acceptable for use by blood collection establishments to collect donor history information from donors of blood and blood components.[1]

D. Can Standards Developed by the World Health Organization (WHO) be used to Support a CBER Regulatory Submission?

Although the WHO does not meet the definition of an SDO, the WHO and the standards it develops have a role in the development, manufacturing, and use of certain medical products.

WHO develops both written standards and physical standards/reference materials that, when appropriate, can be used to support a regulatory submission. Written standards are published on the WHO website as recommendations and guidelines. WHO also provides biological reference materials for the manufacture and control of certain manufactured products.

[1] "Implementation of Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Blood and Blood Components; Guidance for Industry" dated May 2016 can be found via the following link: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM273685.pdf.

VII. REFERENCES

1. OMB Circular A-119: Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities. https://obamawhitehouse.archives.gov/sites/default/files/omb/inforeg/revised_circular_a-119_as_of_1_22.pdf

2. National Technology Transfer and Advancement Act of 1995. https://standards.gov/NTTAA/agency/index.cfm?fuseaction=home.main

3. FDA Staff Manual Guide 9100.1 Common Standards, Development and Use of Standards; June 2012. https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM240278.pdf

4. Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage; December 2011. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM288011.pdf

5. Frequently Asked Questions on Recognition of Consensus Standards; September 2007. https://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm074973.htm

6. Guidance for Industry and FDA Staff - Recognition and Use of Consensus Standards; September 2007. https://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm077274.htm

7. Guidance for Industry and for FDA Staff: Use of Standards in Substantial Equivalence Determinations; March 2000. https://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073752.htm