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

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Guidance for Industry

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Contains Nonbinding Recommendations

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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 control as well as 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 and control of CBER-regulated medical products. Sponsors' use of standards can facilitate product development and provide a more efficient evaluation of regulatory submissions, including investigational new drug applications (INDs), biologics license applications (BLAs), new drug applications (NDAs), investigational device exemptions (IDEs), premarket approval applications, and premarket notifications, supplements, and amendments. This guidance does not endorse the activities of specific Standards Development Organizations (SDOs) or recommend specific standards for use in regulatory submissions. This guidance finalizes the draft guidance of the same title dated December 2017.

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 guidance means that something is suggested or recommended but not required.

II. BACKGROUND

The Federal Government's policies on the use of voluntary consensus standards 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 (NIST) to coordinate standards activities for federal agencies. Neither CBER's use of nor CBER's acceptance of sponsors' use of voluntary consensus standards constitutes a delegation of CBER's regulatory responsibilities. Whether or not standards are used, CBER retains both the ability to set and the responsibility for setting appropriate regulatory criteria for CBER-regulated products.

III. DISCUSSION

A. What Is a Standard?

For purpose 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 an SDO. The use of a standard is voluntary unless mandated by regulation or statute.

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

For purpose of this guidance, an 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). Additional information on SDOs can be obtained from NIST at https://www.nist.gov/ and the American National Standards Institute at https://www.standardsportal.org/usa_en/resources/sdo.aspx.

D. What Is a Voluntary Consensus Standards Body?

A voluntary consensus standards body is one kind of SDO. For purpose 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 publicly 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 purpose 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 purpose of Circular A-119, a standard that includes patented technology needs to be governed by intellectual property

rights policies, as described in section III.D. of this guidance, 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 purpose 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 purpose 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 purpose of this guidance, data standards are defined rules, formats, and terminologies that provide structure and consistency for exchange and utilization of data. Data standards may describe the data elements and relationships necessary to achieve the unambiguous exchange of information between disparate information systems.

I. What Are Performance Standards?

For purpose 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 VOLUNTARY STANDARDS DEVELOPED?

SDOs develop or sponsor the development of voluntary standards that can be used by a person involved either 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 voluntary standards. CBER participation in the development of a particular standard does not constitute endorsement of that standard. Guidelines for FDA participation in standards development activities are outlined in the FDA Staff Manual Guide for the Development and Use of Standards, SMG 9100.1 (Ref. 3).

V. WHAT ARE THE BENEFITS OF USING VOLUNTARY 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 stakeholders' efforts to develop standards, FDA can eliminate the cost to the Federal Government associated with the development of government-unique standards and promote international harmonization of standards that are acceptable to FDA.

CBER participates in SDOs to become familiar with standards as they are developed, updated, or withdrawn. CBER participation facilitates the development of standards that are not in conflict with or duplicative of FDA regulations or policies. CBER's participation also increases the likelihood that the standards under development will ultimately be suitable for use in regulatory submissions reviewed by CBER.

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 development and reduce the amount of documentation needed in a regulatory submission, thus contributing to a more efficient submission evaluation and, 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?

CBER encourages sponsors of regulatory submissions and manufacturers to use appropriate voluntary consensus standards. Further, CBER intends to preferentially use

internationally harmonized standards (standards developed by organizations typically involving representatives from many countries) when those standards represent the most appropriate standards for a specific purpose and are not in conflict with U.S. law (Refs. 3, 4).

Sponsors should confirm that the standard was used as published or state how they deviated from the assay described in the standard. 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 the standard is revised and the sponsor chooses to use the updated version of the standard, then the sponsor should provide an amendment to the regulatory file, stating the version of the standard that is currently in use.

For example, a sponsor utilizing a differentiation assay to measure the potential of progenitor stem cells per a relevant standard (e.g., Standard ABC, Version X, Date Y) would note that it either used the standard as written or describe how it deviated from the assay described in the standard.

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. 5) 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, Office of Blood Research and Review, Office of Tissues and Advanced Therapies, Office of Compliance and Biologics Quality, or Office of Vaccines Research and Review. OCOD may be contacted at industry.biologics@fda.hhs.gov for advice on which office is responsible for the review of a particular product. When referencing a standard in a regulatory submission, sponsors should provide the name of the SDO, the title of the standard, and the version of the standard. The use of voluntary standards is not mandatory.

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. Once CBER has determined that a version of a standard is acceptable, the sponsor should implement a new version of that standard after the sponsor qualifies and validates the changes and the Agency determines it is acceptable. The sponsor should submit the information requesting implementation of a new version as an amendment or supplement to the regulatory file.

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 BLAs, NDAs, or INDs.

   The sponsor should provide information on the reference standards or reference materials used for testing the drug substance or drug product in the regulatory 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 is otherwise 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 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. Compendial Standards: Compendial standards may be used to support a regulatory submission once CBER reviews and determines it is appropriate.

6. Data Standards: Data standards can help promote effective and efficient review of regulatory submissions. Examples of data standards include Structured Product Labeling, Health Level 7 Stability Standard, etc. Submission data standards are listed in the FDA Data Standards Catalog established in the Standardized Study Data Guidance (Ref. 6). 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.

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

The use of consensus standards is not mandatory for medical device regulatory submissions unless the consensus standard has been incorporated by reference into a regulation. For devices regulated by CBER, a sponsor or manufacturer of a medical device may use either standards that have been "recognized" by CDRH or non-recognized standards to support regulatory submissions for medical devices. In accordance with the Food and Drug Administration Modernization Act 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://www.nist.gov/standardsgov/what-we-do/federal-policy-standards/sibr. For additional information on the standards recognition program, refer to the CDRH/CBER joint guidance, entitled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices; Guidance for Industry and Food and Drug Administration Staff" (Ref. 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 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

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3. FDA Staff Manual Guides, Volume IV – Agency Program Directives, Common Standards, Development and Use of Standards, SMG 9100.1, June 2012, https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM240278.pdf
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