Designation: F3368 – 19

Standard Guide for Cell Potency Assays for Cell Therapy and Tissue Engineered Products[1]

This standard is issued under the fixed designation F3368; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide is intended as a resource for individuals and organizations involved in the development, production, delivery, and regulation of cellular therapy products (CTPs) including genetically modified cells, tissue engineered medical products (TEMPs) and combination products where cell activity is a functional component of the final product.

1.2 This Guide was developed to include input derived from several previously published guidance documents and standards (section 2.4). It is the intent of this Guide is to reflect the current perspectives for CTP potency assays.

1.3 CTPs can provide therapy by localized or systemic treatment of a disease or pathology.

1.4 The products may provide a relatively short therapy, may be transient, or may be permanent and provide long-term therapy.

1.5 The products may be cells alone, cells combined with a carrier that is transient, or cells combined with a scaffold or other components that function in the overall therapy.

1.6 Potency assays may be *in-vitro* or *in-vivo* assays designed to determine the potency of a specific product. *In-vivo* assays are likely to be particularly useful to study the mechanism of action (MOA) of the therapy, but may not be desirable for final product quality control where they may be time-consuming and expensive, and where *in-vitro* assays may be preferable.

1.7 It is likely that multiple assays, and possibly both *in-vitro* and *in-vivo* assays, will be required to provide a broad measure of potency. However, *in-vitro* assays are likely to be preferred as release assays for products, and so studies to identify potency assays should emphasize *in-vitro* assays that are correlative or predictive of preclinical or clinical results.

1.8 Potency assays should be developed during the product development cycle and therefore are likely to be more comprehensive at the end of that cycle compared to the beginning of product development and testing. It is recommended that potency assays be developed as early as possible in the product development cycle (Figs. 1 and 2).

1.9 Potency measurements are used as part of the testing for cell and cell-based products to demonstrate that product lots meet defined specifications when released for clinical use.

1.10 Shelf life specifications should be developed during the product development process to include potency measurements.

1.11 This standard guide is not intended to apply to drug or gene therapy products. However, genetically modified cell therapies, for example the chimeric antigen receptor-T (CAR-T) cell therapy, which the United States FDA classifies as gene therapy, are applicable.

1.12 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.13 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

F2312 Terminology Relating to Tissue Engineered Medical Products

2.2 *ISO Document:*[3]

ISO 17025 General Requirements for the Competence of Testing and Calibration Laboratories

[1] This guide is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.44 on Assessment for TEMPs.

Current edition approved May 15, 2019. Published July 2019. DOI: 10.1520/F3368-19

[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

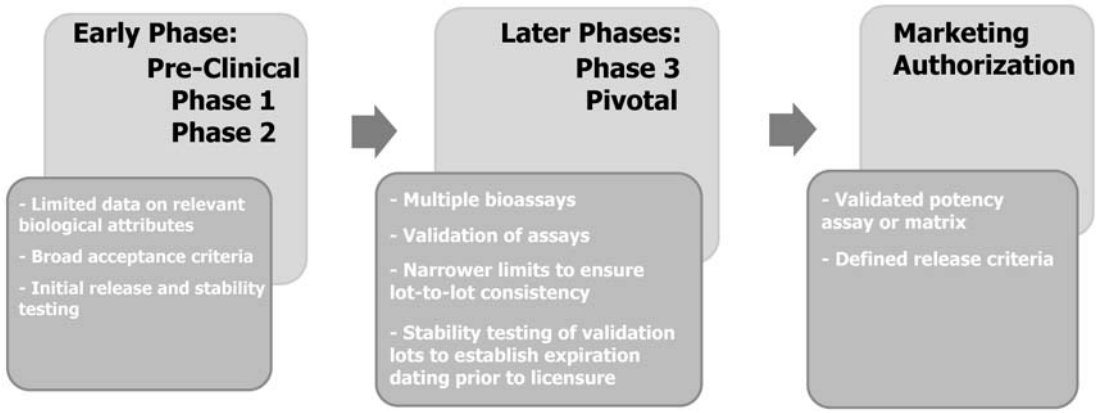

FIG. 1 Progressive Implementation of Potency Assays

2.3 *U.S. Regulations:*[4]

21 CFR 600.3(s)

21 CFR 3.2(k)

21 CFR 1271 Current Good Manufacturing Practice for Human Cells, Tissues, and Cellular and Tissue-Based Products

2.4 *Other Documents:*

FDA Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products. January 2011

Europeans Medicines Agency, Committee for Medicinal Product for Human Use, Guideline on human cell-based medicinal products. Doc. Ref. EMEA/CHMP/410869/2006, 2008

ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology

ICH Q6B Note for guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products (CPMP/ICH/365/96)

Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use FDA CBER, February 1997

EMEA/CHMP Guideline on potency testing of cell-based immunotherapy medicinal products for the treatment of cancer (CHMP/BWP/271475/06 rev.1)

USP 1034 Analysis of Biological Assays

3. Terminology

3.1 Unless provided otherwise in 3.2, terminology shall be in conformance with Terminology F2312.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *mechanism of action (MOA), n*—the means by which a product achieves its intended therapeutic effect or action, as defined in 21 CFR 3.2(k).

3.2.2 *potency, n*—the specific ability or capacity of the product, as demonstrated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result. (CFR 600.3(s))

3.2.3 *potency, n*—may also be the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties and functions. The assay demonstrating the biological activity should be based on the intended biological effect that should ideally be related to the expected clinical response. (ICH Q6B)

3.2.4 *strength, n*—the potency, or therapeutic activity of the product.

3.2.5 *tests for potency, n*—either *in-vitro* or *in-vivo* tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in 21 CFR 600.3(s).

3.2.6 *validation, n*—the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled ISO 17025:2005 (5.4.5.1).

4. Summary of Guide

4.1 It is the intent of this guide to provide a compendium of information that may be related to the potency assays used in the development and post-approval use of CTPs where activity(s) of the cell are related to function of the product. It is expected that for many products multiple assays will be required to provide a comprehensive assessment of potency. It is also possible that the potency assays for a particular product will continue to develop through the product development cycle.

4.2 CTPs are complex and their therapeutic effectiveness is dependent on multiple features and characteristics of the cell, and it is likely that these can only be assessed using multiple assays. These assessments preferably will be related to mechanism of action.

4.3 It is important to note that a potency assay is not a measure of clinical efficacy. The only way to measure clinical efficacy in humans is through a human clinical trial. Potency assays evaluate the article's biological activity based on the hypothesized MOA (see 3.2.1 and 3.2.2). Ideally, potency assays are a measurement of the biological activity of a product based on the hypothesized MOA (see 3.2.1 and 3.2.2);

[4] Available from U.S. Government Printing Office, Superintendent of Documents, 732 N. Capitol St., NW, Washington, DC 20401-0001, http://www.access.gpo.gov.

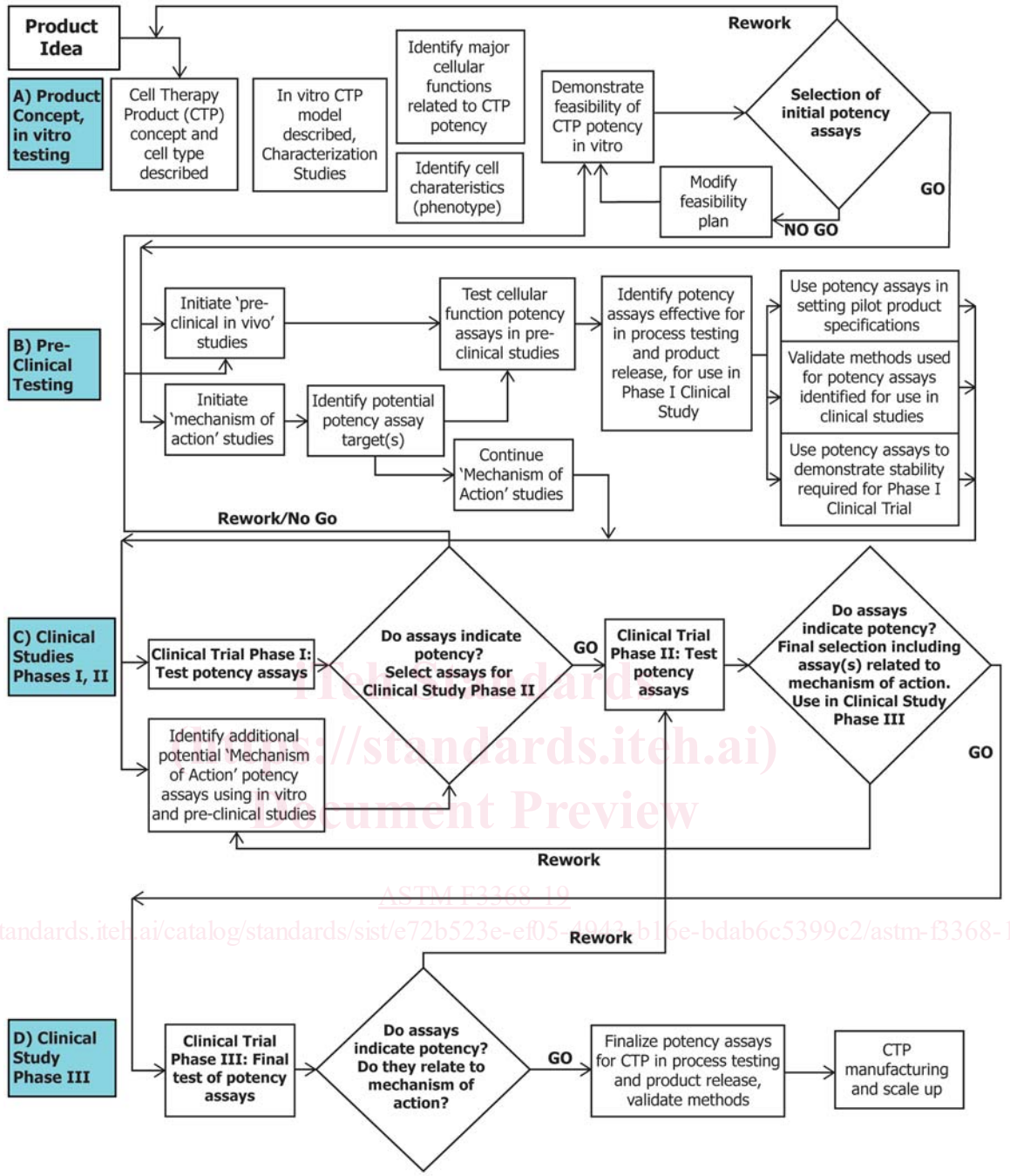

FIG. 2 Flow Chart for Stages in Product Development Showing When Potency Assays Will Be Developed and Introduced

however, the MOA may not be completely understood or there may be multiple MOAs.

4.4 The described MOA should consider what is known about the action of the product at various levels including molecular, cellular, tissue, organ and whole body.

4.5 Assays used to assess potency may become critical assessments in determining product release specifications, and ensuring lot-to-lot consistency in product manufacture. They may also become a critical feature for assessing product stability.

4.6 The potency test may be validated using cell-based tests, animal tests or other measurements. The use of clinical data is the ideal way to validate a potency assay.

4.7 It is desirable that the potency test results are predictive of clinical outcomes (efficacy), but this is not a requirement. The level of correlation between the potency test and efficacy that is acceptable will depend upon many factors and careful consideration of the risks-versus-benefits ratio.

4.8 The development of potency assays should begin as early as possible during the pre-clinical stage of product