Guidance for Industry

Potency Tests for Cellular and Gene Therapy Products

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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I. INTRODUCTION

We, FDA, are issuing this guidance to provide you, manufacturers of cellular and gene therapy (CGT) products, with recommendations for developing tests[1] to measure potency.[2] These recommendations are intended to clarify the potency information that could support an Investigational New Drug Application[3] (IND) or a Biologics License Application[4] (BLA). Because potency measurements are designed specifically for a particular product, this guidance does not make recommendations regarding specific types of potency assays, nor does it propose criteria for product release. This guidance is intended to supplement related documents (Refs. 1 through 11, and 15) and does not replace or supersede any existing documents.

This guidance applies only to CGT products[5] reviewed by FDA's Office of Cellular, Tissue and Gene Therapies (OCTGT), CBER under Section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) (Refs. 1 and 2). This guidance does not apply to human cells, tissues, and cellular and tissue products (HCT/Ps), which are regulated solely under section 361 of the PHS Act (42 U.S.C. 264) as described under 21 CFR 1271.10 or to products regulated as medical devices under 21 CFR Part 820. This guidance also does not apply to biological products reviewed by CDER or by CBER's Office of Vaccine Research and Review (OVRR) or Office of Blood Research and Review (OBRR).

[1] For the purpose of this document, "tests" are used interchangeably with "assays" and "measurement."
[2] As defined in 21 CFR 600.3(s), and discussed in Section II.A of this guidance.
[3] See 21 CFR Part 312.
[4] See 21 CFR Part 601.
[5] Information pertaining to the transfer of some of the therapeutic biological products that had been reviewed and regulated by the Center for Biologics Evaluation and Research (CBER) to Center for Drug Evaluation and Research (CDER) can be found at: http://www.fda.gov/cber/transfer/transfer.htm.

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II. BACKGROUND

A. What Are the Regulatory Requirements for Potency of Licensed Biological Products?

All biological products must meet prescribed requirements of safety, purity and potency for BLA approval (42 U.S.C. 262, Federal Food, Drug and Cosmetic Act, (FDC Act) (21 U.S.C. 321 et seq.); 21 CFR 601.2). For CGTs, product conformance testing (21 CFR 601.20(a)) and control of the manufacturing process (21 CFR 601.20(c)) are required to comply with FDA's Current Good Manufacturing Practice (CGMP) For Finished Pharmaceuticals regulations (21 CFR Parts 210 and 211[6]) as well as the biologics regulations (21 CFR Part 600 et seq.). No lot of any licensed product may be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product, (21 CFR 610.1), which include tests for potency, sterility, purity, and identity (21 CFR Part 610, Subpart B). These requirements apply to all biological products, including autologous and single patient allogeneic products, where a lot may be defined as a single dose.

Potency is defined as "the specific ability or capacity of the product, as indicated 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." (21 CFR 600.3(s)). Strength[7] is defined as "potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data. . . ." (21 CFR 210.3(b)(16)(ii)). Regulations stipulate that "[t]ests for potency shall consist of 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 definition in § 600.3(s) of this chapter." (21 CFR 610.10).

FDA regulations allow for considerable flexibility in determining the appropriate measurement(s) of potency for each product. Potency is determined based on individual product characteristics; therefore, the adequacy of potency assays is evaluated on a case-

[6] The drug CGMP regulations contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that the drug meets the requirements of the FDC Act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

[7] For purposes of this guidance, strength is the equivalent of potency.

by-case basis. All potency assays used for release testing of licensed biological drug products must comply with applicable biologics and CGMP regulations including:

- Indicate potency (biological activity/activities) specific to the product (21 CFR 600.3(s) and 610.10; and 21 CFR 210.3(b)(16)(ii));
- Provide test results for release of the product (21 CFR 610.1; 21 CFR 211.165(a))
- Provide quantitative data (21 CFR 211.194; see also 21 CFR 600.3(kk); 21 CFR 211.165(d); 211.165(e););
- Meet pre-defined acceptance and/or rejection criteria (21 CFR 211.165(d); see also 21 CFR 600.3(kk); and 21 CFR 210.3(b)(20));
- Include appropriate reference materials, standards, and/or controls (see; 21 CFR 210.3(b)(16)(ii) and 211.160);
- Establish and document the accuracy, sensitivity, specificity and reproducibility of the test methods employed through validation (21 CFR 211.165(e) and 211.194(a)(2));
- Measure identity and strength (activity) of all active ingredients (21 CFR 211.165(a); see also 21 CFR 210.3(b)(7));
- Provide data to establish dating periods (see 21 CFR 600.3(l) and 610.53(a))
- Meet labeling requirements (21 CFR 610.61(g)(3) and 610.61(r))

B. What are the Potency Requirements for Investigational CGT Products?

In early clinical phase investigations, it may not be possible to meet all of the requirements described above for licensed biological products (Refs. 3, 4, 8). Nonetheless, you must submit data to assure the identity, quality, purity and strength (21 CFR 312.23(a)(7)(i)) as well as stability (21 CFR 312.23(a)(7)(ii)) of products used during all phases of clinical study. "[T]he amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available." (21 CFR 312.23(a)(7)(i)).

Potency measurements are necessary for product characterization testing,[8] comparability studies (Ref. 6), and stability protocols (Ref. 7), which are used to establish that a consistently manufactured product is administered during all phases of clinical investigation. However, the complexity of CGT products can present significant challenge(s) to establishing potency assays (see Table 1). To facilitate the development of CGT products, we recommend an incremental approach to product characterization testing, including the development of potency assays. General recommendations for progressive potency assay implementation are outlined in Section III.E. As described in

[8] For the purpose of this guidance, product characterization testing includes in-process, drug substance and final product tests that measure product attributes associated with product consistency and quality in order to assure identity, purity, strength (potency) and stability of products used during all phases of clinical study.

Sections III.A, III.E, and IV.C.4 of this document, your potency measurement will evolve and may change significantly as you develop your product.

Table 1:

Challenges to Potency Assay Development for CGT products:	**Examples:**
Inherent variability of starting materials	• Autologous and allogeneic donor variability • Cell line heterogeneity • Error-prone replicating viruses
Limited lot size and limited material for testing	• Single dose therapy using autologous cells suspended in a small volume
Limited stability	• Viability of cellular products
Lack of appropriate reference standards	• Autologous cellular material • Novel gene therapy vectors
Multiple active ingredients	• Multiple cell lines combined in final product • Heterogeneous mixtures of peptide pulsed tumor and/or immune-modulatory cells • Multiple vectors used in combination
The potential for interference or synergy between active ingredients	• Multiple genes expressed by the same vector • Multiple cell types in autologous/allogeneic cell preparations
Complex mechanism of action(s)	• Multiple potential effector functions of cells • Multiple steps required for function such as infection, integration, and expression of a transgene • Vectors containing multiple genes
In vivo fate of product	• Migration from site of administration • Cellular differentiation into the desired cell type • Viral or cellular replication • Viral vector infection, uncoating, and transgene expression

C. What Is the Relationship Between Potency and Clinical Effectiveness for CGT Products?

There is no single test that can measure adequately those product attributes that predict clinical efficacy. Clinical effectiveness is demonstrated by adequate and well-controlled clinical investigations conducted with a consistently manufactured quality product. Clinical effectiveness may be correlated to product potency, but clinical study data is not a practicable quantitative measure of potency to release a lot. Rather, clinical study results may be used to establish a correlation(s) [9] between the product's clinical efficacy and a potency measurement(s), which can be used for lot release, stability, and/or comparability studies (see Section III.C for more details related to correlation studies).

[9] *Correlation* means a statistical relationship between two or more variables such that systematic changes in the value of one variable are accompanied by systematic changes in the other.

III. RECOMMENDATIONS FOR POTENCY MEASUREMENTS

A. How to Determine What to Measure for Potency?

Because of the complexity of CGT products, you need to acquire an appropriate understanding of the biological properties of your product in order to develop relevant and meaningful potency measurements. You should collect sufficient data throughout preclinical and clinical development to inform and refine your approach to measuring potency.

When initially determining the biological activity or activities that will guide your potency assay design, you should consider relevant pre-clinical investigations, proof of concept studies, early clinical studies, available historical experience, and available reference materials and controls (see Section III.C). This information may provide you with a basic understanding about product characteristics and biological activities that contribute to function. Characterization data obtained during product development may provide support for the potency assay that you choose initially, or it may lead to an improved potency measurement as you prepare to market your product (see Sections III.E and IV.C.4). As you develop your product(s), you should measure a wide range of product properties in addition to those performed for routine lot release. This may help you to assess which product attribute(s) best correlate(s) with potency. Although some of the assays you evaluate may not be practical for lot release (e.g., difficult to consistently obtain quantitative results, time-consuming), most properly designed assays (see Section IV.A) have the potential to provide valuable information about product attributes related to biological activity or clinical effectiveness, or both.

CGT products may present challenges for developing assays to measure specific biological attributes that quantitatively demonstrate potency (see Table 1). CGT products often have complex and/or poorly defined mechanism(s) of action (i.e., relevant therapeutic or clinical functional activity), making it difficult to determine which product attribute is most relevant to measuring potency. Nonetheless, potency measurements should reflect the relevant biological attributes. For example, a gene therapy vector should rely on at least two biological activities for its potency: the ability to transfer a genetic sequence to a cell and the biological effect of the expressed genetic sequence. Therefore, the potency assay should incorporate both a measure of the gene transfer frequency and the biological effect of the transferred gene.

In addition, the proposed mechanism(s) of action for CGT products may be dependent on more than one active ingredient[10] (e.g., multiple cell types, multiple vectors, multi-epitope vaccines). For some complex products (e.g., cellular tumor vaccine) there could be ambiguity about which ingredients contribute to potency. For products that contain

[10] *Active ingredient* means any component that is intended to furnish pharmacologic activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals (21 CFR 210.3(b)(7)).

more than one known active ingredient, you should design potency measurement(s) to determine the biological activity (strength) of all active ingredients (see 21 CFR 211.165(a)). Thus, if your product contains more than one active ingredient you might need more than one assay to measure potency of the product because one assay might be insufficient to measure the activity of each of the active ingredients (Section III.B.3). Additionally, when designing your assay(s), you should also consider the potential for interference or synergy between active ingredients.

B. What Methods May be Used to Measure Potency?

1. Biological assays

The traditional approach for assessing the potency of biological products is to develop a quantitative biological assay (bioassay) that measures the activity of the product related to its specific ability to effect a given result, and that also meets the criteria listed in Section II.A. Bioassays measure potency by evaluating a product's active ingredients within a living biological system. Bioassays can include in vivo animal studies, in vitro organ, tissue or cell culture systems, or any combination of these. You may use in vitro or in vivo assays; however, we encourage the responsible limitation of animal use whenever possible (Ref. 12).

2. Non-biological analytical assays[11]

Development of a quantitative bioassay for some CGT products may be complicated by properties of the product and/or technical limitations (see Table 1). In cases where bioassay development is not feasible, it may be necessary to identify a surrogate of biological activity. For example, you may need to use an analytical assay(s) that is practical and reliable for lot release. Analytical assays can provide extensive product characterization data by evaluating immunochemical, biochemical, and/or molecular attributes of the product. These attributes may be used to demonstrate potency if the surrogate measurement(s) can be substantiated by correlation to a relevant product-specific biological activity(s) (see Section III.C, Refs. 13 and 14). To establish meaningful correlations, you should conduct rigorous product characterization testing, as recommended throughout this document.

[11] To distinguish traditional bioassay methods (performed in a living system) from non-bioassay methods (performed outside of living system), we use "analytical assay" to refer to methods that measure immunochemical (e.g., quantitative flow cytometry, enzyme-linked immunosorbant assay), molecular (e.g., reverse transcription polymerase chain reaction, quantitative polymerase chain reaction, microarray) or biochemical (e.g., protein binding, enzymatic reactions) properties of the product outside of a living system. Furthermore, we acknowledge that in other contexts a bioassay may be considered an analytical assay.

3. Multiple assays (assay matrix)

In many cases, a single biological or analytical assay may not provide an adequate measure of potency. The following are some potential reasons:

- Product has complex mechanism of action
- Product has multiple active ingredients and/or multiple biological activities
- Limited product stability
- Biological assay is not quantitative, not sufficiently robust, or lacks precision

If one assay is not sufficient to measure the product attribute(s) that indicates potency, then an alternative approach could be used to develop multiple complementary assays that measure different product characteristics associated with quality, consistency and stability. When used together and when results are correlated with a relevant biological activity, these complementary assays should provide an adequate measure of potency. Such a collection of assays (referred to as an assay matrix) might consist of a combination of biological assays, biological and analytical assays, or analytical assays alone (Refs. 13 and 14). The assay matrix may include assays that give a quantitative readout (e.g., units of activity) or qualitative readout (e.g., pass/fail). If qualitative assays are used as part of an assay matrix to determine potency for lot release, stability or comparability studies, they should be accompanied by one or more quantitative assays (see Section II.A).

C. What is Necessary to Correlate an Analytical Assay with Biological Activity?

To demonstrate potency using an analytical assay as a surrogate measurement of biological activity, you should provide sufficient data to establish a correlation between the surrogate measurement(s) and the biological activity(ies) that is related to potency. The relationship between the surrogate measurement and biological activity may be established using various approaches, including comparison to preclinical/proof of concept data, in vivo animal or clinical data, or in vitro cellular or biochemical data. If you choose to use an analytical assay as a surrogate measurement of biological activity to meet the potency requirements for licensed biological products, you should meet criteria listed above in Section II.A. This could necessitate that you stress the product (i.e., show that the assay can detect an inactive or degraded product) and perform sufficiently controlled studies (see Section IV.).

The suitability of data used to support surrogate assays for biological activity is evaluated on a case-by-case basis and depends on or is influenced by the following:

- Type and relevance of the correlation(s) being made;
- The amount of product information you have accumulated;

- How well the biological activity of the product is understood; and
- How well the surrogate measurement(s) reflects biological activity.

If you intend to demonstrate potency by correlating a surrogate assay(s) to a relevant biological activity, you should start collecting product and assay characterization data during early investigational phases.

D. When Should Potency Assay Development Initiate?

As discussed throughout this document, thorough product characterization is necessary to understand the product parameter(s) that affect quality, consistency, and stability. Moreover, understanding and controlling these parameters will be necessary to demonstrate consistency between production lots, to assess comparability of different manufacturing processes and/or various assays, and may also be necessary to allow you to determine which product attributes are related to an effective product. Thus, because the ability to measure potency is essential to product characterization, you should initiate potency assay development during preclinical and early clinical investigations to obtain as much product information as possible.

In addition, measuring potency during early product development has a number of advantages, such as allowing you to:

- Demonstrate product activity, quality and consistency throughout product development;
- Generate a collection of data to support specifications for lot release;
- Provide a basis for assessing manufacturing changes;
- Evaluate product stability;
- Recognize technical problems or reasons a different assay might be preferable;
- Evaluate multiple assays; and
- Collect sufficient data to support correlation studies, if necessary.

E. What is Progressive Potency Assay Implementation?

1. Early product development:

For some products in pre-clinical, Phase 1 and early Phase 2 studies, limited quantitative information on bioactivity may be sufficient. Potency assays performed on product lots used for early clinical studies are likely to have wider acceptance ranges than assays used in later phase investigations. Nevertheless, as clinical studies progress and product knowledge increases, you should develop and implement improved potency measurement(s) that quantitatively assesses relevant biological product attribute(s) (see 21 CFR 312.23(a)(7)).

2. Later phase product development:

The primary objective of later phase investigational studies (i.e., Phase 3, pivotal[12]) is to gather meaningful data about product efficacy. Efficacy is determined by adequate and well-controlled clinical study(ies). Therefore, your potency assay design and acceptance criteria should be sufficient to assure that a well-characterized, consistently manufactured product was administered during your pivotal study(ies). Conformance to established limits for potency should thus provide reasonable confidence that future product lots will perform as expected at a given dose in patients.

In addition, you should use a well-characterized potency assay with established limits during stability testing of conformance lots used to establish expiry dating for licensure (see 21 CFR 610.53; Ref. 7).

3. Biological License

To market a biological product, a validated potency assay with defined acceptance criteria must be described and justified in the BLA (21 CFR 601.2(a) and 211.165(e), see also Section II.A). The acceptance criteria should be based on knowledge gained through manufacturing experience and data collected from assays performed during all phases of product development and clinical investigation (Ref. 5). As you evaluate product conformance lots or lots manufactured explicitly for use in your pivotal clinical studies, acceptance criteria should be refined to reflect these data.

The potency assay acceptance criteria defined in your BLA, which are intended for subsequent lot release testing, should depict the potency limits established for product lots used in the pivotal clinical studies demonstrating clinical effectiveness (see FDC Act, Section 505(d), 21 U.S.C. 351).

IV. ASSAY DESIGN AND VALIDATION

A. What Should be Considered During Assay Design?

In accordance with CGMP regulations, assay design should allow you to collect data that will permit you to evaluate your assay(s). This includes incorporating a sufficient number of replicates to allow for statistical analysis, using sample randomization to reduce biases (e.g., sources of bias associated with placement in a 96-well plate), and including appropriate controls. Assay design should also reflect knowledge of the factors that influence assay variability. Therefore, you should consider sources of variability in

[12] For the purpose of this document the term "pivotal" study is used to represent any clinical study where the data obtained from that study will be used to support a clinical efficacy claim for the biologics license application (BLA).

the assay method and take steps to limit them in your assay design. General principles for reducing variability include using well-defined reagents, well-calibrated equipment, and adequately trained operators. Assay variability can also be substantially reduced by following detailed standard operating procedures (SOPs) and having appropriate controls in place. Assay-specific controls will depend on the product being analyzed as well as the assay used. You should also consider the long-term availability of critical reagents, including reference materials and controls. Manufacturers may refer to several resources for a more detailed discussion of assay design strategies (e.g., Refs. 13 through 20).

B. How Should Reference Materials and Controls be Utilized?

As with all well designed experiments, developing a potency assay should include appropriate controls and a comparison to an appropriate reference material, when available. Running a reference material and/or control samples in parallel with the product helps ensure that the assay is performing as expected. In addition, controls help establish that the equipment and reagents are working within established limits. A well designed set of control samples can substantially increase confidence that results are meaningful and reproducible.

Reference materials and standards can help with assay development and can be used to develop and qualify more relevant "in house" reference materials and/or controls. A number of reference materials, standards, and controls are available or are being developed for characterizing biologics. For instance, there are fluorescent bead/antibodies and particle size standards[13] and guidelines[14] available to help calibrate equipment and help define acceptable parameters for quantitative flow cytometry analysis (Ref. 18). Reference materials are also currently available for adenovirus type 5 (Ref. 19)[15] and retrovirus[16] vectors. A reference material for adeno-associated virus type 2 vectors[17] is under development. Standard materials and controls for lentivirus vectors have also been described (Ref. 20).

In the event that a universal standard or reference material is not available, you should develop your own "in house" reference material(s) (Refs. 9 through 11). These may include well characterized clinical lots or other well characterized materials prepared by you or another resource (e.g., a well characterized cell line with a profile similar to your product). There should be a clear rationale for how and why the reference material

[13] National Institute of Standards and Technology. Available at http://ts.nist.gov/MeasurementServices/ReferenceMaterials/232.cfm.
[14] Fluorescence Calibration and Quantitative Measurement of Fluorescence Intensity; Approved Guideline. NCCLS: ILA24 Vol 24 No 26. Available at http://www.nccls.org.
[15] Adenovirus Type 5 Reference Material (ARM) available at http://www.atcc.org/common/documents/pdf/VR-1516text2.pdf.
[16] Retrovirus Reference Material. Available at http://www.atcc.org/common/catalog/numSearch/numResults.cfm?atccNum=VR-1450.
[17] Information related to the Adeno-Associated Virus Reference Material is available at http:\\www.wilbio.com\ReferenceMaterials\aav2.htm.

(including "in house" reference material/control) was developed. We encourage you to consult with your CBER review team when developing or obtaining reference materials.

Because you will use reference materials at various stages of product development and characterization, you should subject them to stability studies in parallel with your product stability studies (Ref. 7). Moreover, you should appropriately characterize each new batch of reference material, compare it with the original, and establish appropriate procedures to qualify and eventually validate new reference materials. When possible, you should retain samples (Refs. 6 through 8) of each lot of reference material for comparison with newly manufactured reference material and prepare in advance for depletion or expiration of reference materials.

C. What Should be Considered for an Assay Validation Plan?

1. Regulations

To obtain a biologics license, you must submit data in your BLA demonstrating, among other things, that your product meets prescribed requirements of potency (21 CFR 601.2), which requires that you validate your potency assay with predefined acceptance criteria (see 21 CFR 211.165(e)). The validation process identifies potential sources of errors and quantifies them within the assay method. Numerous resources are available for analytical methods validation (Refs. 9 through 11). You should perform analysis and validation of all relevant assay parameters (Refs. 9 through 11), including:

- Accuracy
- Precision (Repeatability, Reproducibility)
- Sensitivity (Limit Of Detection/Quantitation)
- Specificity
- Linearity and Range
- System Suitability
- Robustness/Ruggedness

2. Statistical design and analysis

It is critically important to apply sound and appropriate statistical methods to the design and analysis of laboratory experiments for potency measurements. Otherwise, inferences drawn from such experimental data might not be valid. Potential sources of assay variability and variations from replicates should be taken into account when reporting results. You should fully describe your methods of analysis, including your justification and rationale. These descriptions should be sufficiently clear to permit independent statistical analysis and evaluation of the results presented in the study reports. Data collected from potency assay validation studies, when provided in electronic format, can facilitate statistical evaluations by the CBER review committee. The results of

validation studies should address the targeted validation parameters and their conformance to acceptance criteria. We encourage you to initiate early discussions with the review team to receive feedback on the design and analysis of potency experiments. (See 21 CFR 211.194 for requirements pertaining to the laboratory records you must keep.)

3. Validation of qualitative assays

As discussed in Section III.B.3, qualitative assays may be used as part of an assay matrix to assess potency, provided that you conduct suitable correlation studies. You should validate all parameters relevant to your qualitative assay and provide a rationale for those parameters that you determine are not relevant. For example, although certain assay validation parameters (e.g., linearity) may not be applicable to a qualitative assay with a pass or fail readout, appropriate control samples should be used to characterize the assay for specificity and sensitivity as well as for other features of acceptable performance (e.g., robustness, system suitability).

Without quantitative data, demonstrating accuracy and precision could be challenging; however, with proper assay design (e.g., sufficient replicates), you might be able to demonstrate reproducibility. For semi-quantitative assays (assays with highly variable quantitative readout, e.g., response in an animal model), broader acceptance ranges may be considered for determining assay robustness and reproducibility. Also, limits of detection and/or quantitation may be built into the assay design suitability criteria. For example, if a reasonable amount of the control or reference material does not exhibit the desired activity with sufficient statistical justification, the assay would not generally be considered acceptable. Importantly, because of the complex nature of CGT products, specific circumstances for determining assay suitability will vary from assay to assay. Therefore, we encourage you to discuss planned experiments with your CBER review team before you initiate specific assay designs and/or detailed experimental analyses of potency measurements.

4. Assay evaluation and modification

Manufacturing and testing practices evolve during product development or post-licensure, or both, making it necessary and/or beneficial to re-evaluate your potency assay. If you plan to modify an assay that is used in an approved application or propose a new assay, you must perform validation studies to demonstrate that the modified/new assay continues to be an appropriate measure of potency (21 CFR 211.165(e)). These changes must be submitted as a supplement to an approved application (21 CFR 601.12(b)(3)(vi)).

The quantity of data needed to support changes to potency measurements(s) will depend upon a number of factors, including:

- Stage of product development
- Type of change within an existing assay
- Whether the assay is being used to measure a different product attribute(s)
- Whether the proposed assay meets assay criteria outlined above (see above and Section II.A)

If you modify the potency measurement used during an investigational study, you should qualify the assay and provide justification for the proposed change(s) (e.g., more relevant, more practical, more quantitative).

These recommendations further emphasize the importance of maintaining retention samples (e.g., product, reference materials, critical reagents) whenever possible. It will be difficult to compare assays or determine if new assays are performing appropriately without analyzing appropriate retention samples.

As this guidance indicates, a considerable amount of data might be necessary to develop a suitable measurement of potency for your product (see also Ref. 14), and your assay(s) might change over time as you develop your product and learn new information and methods. We recommend that you have timely discussions with your review team as you design, evaluate and validate your potency measurement.

V. REFERENCES

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* When finalized, this guidance will represent FDA's current thinking on this topic.

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