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Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852
[submitted at www.regulations.gov]

Re: Docket No. FDA-2008-D-0520, CBER 200721; Draft Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products; Federal Register October 9, 2008 (Volume 73, Number 197, pp. 59635-59636)

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on FDA's *Draft Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products.* BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

The draft guidance is a comprehensive document that consolidates and describes in some depth information provided by the Agency over the past several years at scientific meetings, particularly the need to start product and assay characterisation early in development. BIO agrees that the adequacy of potency assays should be evaluated on a case-by-case basis and that an incremental approach to product characterization testing, including the development of potency assays, is needed. We offer the following general and specific comments.

GENERAL COMMENTS

Assay Development

- As methods and science develop, potency tests may evolve. While this process is referenced at IV. C. 4, it may bear mentioning earlier in the guidance (specifically as a part of section III. E – Progressive Potency Assay Implementation) to emphasize the iterative nature of potency test method development.

- The section on the assay validation plan, IV. C, is organized differently from the International Conference on Harmonisation (ICH) and United States Pharmacopeia (USP) guidance documents on this subject, although both of these documents are referenced by FDA (i.e., Refs 10 and 11). This may give rise to a misunderstanding that a new approach to method validation is being proposed. We ask that the terminology associated with validation parameters, the usage of those terms, and the organization of section IV. C align with the existing guidance documents. We provide more detail in our Specific Comments, below.

Statistics

- The terms “correlated” and “correlation” are used in Section II. C and in later sections in a non-statistical sense to mean an association between two or more factors. Correlation in a statistical sense is a measure of the strength of the relationship between variables; correlation measures near 0 are often interpreted as a lack of relationship, yet there are still correlations. In our Specific Comments we provide recommendations for revising the definition for correlation and utilizing this definition throughout the document.

Regulatory Issues

- Multiple references are made in the draft guidance to timely discussions with the Center for Biologics Evaluation and Research (CBER) review team concerning the design, evaluation and validation of potency measures. To allow these timely interactions, we ask CBER to consider offering an opportunity, parallel to the end of Phase 2a meeting proposed by CDER, in which these interactions could occur.

SPECIFIC COMMENTS

Citation Location Section/Page	Relative Impact *	SPECIFIC Concern (short explanation)	Proposed Change (if applicable)
II. C / page 4	C	For some products it may be difficult to establish the true relationship between the potency assay and the clinical response, both because of the variability in the clinical response and the variability of the potency assay. As many of these products are being developed for orphan indications or small markets it may not be possible to have a large enough sample in clinical trials to achieve this relationship.	Suggested alternative wording for sentence 4: Rather, the potency test should be designed by using information from preclinical studies to develop a scientific rationale to justify the product properties to be measured. The potency assay or matrix of assays is used for lot release, stability and/or comparability studies. Data from the clinical studies may be used to evaluate correlation between potency and clinical efficacy.
II. C. footnote / page 4	M	Footnote 9: The word "correlation" appears to be used throughout the document with this same meaning. Because this is not the meaning some readers may think of without reading the footnote (i.e., not linear statistical correlation or the Pearson correlation coefficient), we recommend expanding the footnote to indicate that the definition is intended throughout the document.	Suggested alternative wording: *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 order. *This definition is intended throughout this document.*

III. A Paragraph 3 / page 5 (see also III. B. 2 / page 6)	M	A specific example of two relevant biological activities is provided for a gene therapy vector. Is the intention to require that these two tests be performed throughout the product lifecycle for gene therapy products? We suggest that it may be possible eventually to substitute a quantitative analytical procedure that has been demonstrated to completely correlate with biological activity. In the case of a gene therapy product, the product might be completely described by confirming the amount of DNA, the correctness of the primary sequence, the extent of supercoiling and clipping, and the presence of all excipients in the expected quantities. If correlation of these attributes with biological activity were established, we do not believe it would be necessary to continue performing biological activity tests for product release.	Please clarify that the example presented is not meant to establish a requirement for all gene therapy vector products, and is not meant to apply throughout the product lifecycle.
III. A Paragraph 4 / Page 6	M	The meaning of "(strength)" after "biological activity" in the third sentence is not completely clear. Is the intent to indicate that both the amount and biological activity should be determined for each active ingredient?	Suggested alternative wording: "For products that contain more than one known active ingredient, you should design potency measurement(s) to determine the biological activity as well as the amount of all active ingredients (see 21 CFR 211.165(a)).
III. A paragraph 4 / page 6	C	We request clarification of "Additionally, when designing your assay(s), you should also consider the potential for interference or synergy effects between active ingredients." Interference and synergy are two specific terms used when evaluating combination effects; there are other synonyms and concepts that could be considered as well.	Suggested alternative wording: Additionally, when designing your assay(s), you should also consider the potential for non-additive effects between active ingredients, such as interference or synergy.

III. B. 1 / page 6	M	We request clarification of "... to develop a quantitative biological assay …" Not all biological assays are quantitative.	Suggested alternative wording: …to develop a quantitative or semiquantitative (eg, titration) biological assay…"
III. B. 2 / page 6	C	The wording used seems to emphasize the technical difficulty of developing a bioassay, but not some other issues that are also important. For some products the potency assay result may not be available before the product needs to be released or the potency of the product cannot be determined without destroying all of the product. In these cases the process can be qualified to produce the product or indirect surrogate assays can be validated by data collected during clinical development.	Suggested alternative wording: Development of a quantitative bioassay for some CGT products may be complicated by properties of the product and/or technical limitations (see Table 1). Development of a suitable bioassay may not be feasible, or a bioassay might consume too much of the batch or take too long to perform before the batch needs to be released. In these cases, it may be necessary to identify a surrogate of biological activity.
III. C paragraph 1 / page 7	M	We request clarification of "show that the assay can detect an inactive or degraded product". An assay should not only be able to detect an inactive or degraded product, it must be able to discriminate from active.	Suggested alternative wording: "show that the assay can discriminate between active product and an inactive or degraded form of the product"
III. E / page 9	C	This section should address or refer to evolution of potency assay after approval (see language in section IV. C. 4)	We suggest adding a section III. E. 4 (Assay evaluation and modification) containing the information provided in IV. C. 4.

III. E. 2 & III. E. 3 / page 9	C	The potential for using multiple assays (assay matrix) to adequately characterize potency was introduced in III. B. 3. This approach may be necessary for many of these products. To avoid confusion about the acceptability of this approach, it would be helpful to reiterate the concept in sections dealing with late phase development and BLA.	Suggested alternative wording: III. E. 2., paragraph 1, sentence 3: "Therefore, your potency assay *or assay matrix* design and acceptance criteria should be sufficient…" III. E. 2., paragraph 2, sentence 1: "In addition, you should use a well-characterized potency assay *or assay matrix* with established limit*(s)* during stability testing..." III. E. 3. paragraph 1, sentence 1: "To market a biological product, a validated potency assay *or assay matrix* with defined acceptance criteria must be described…"
IV. A / page 9 - 10	M	Some sources of variability, even when reduced, are unavoidable and should be accounted for in the design.	Suggested alternative wording: Modify the existing sentence: Therefore, you should consider sources of variability in the assay and take steps to limit *and account for* them in your assay design. Insert a sentence before the last sentence: Some sources of variability, even when reduced, are unavoidable and so should be balanced, measured and modelled.
IV. B paragraph 3 / page 10-11	M	Requirements for novel reference materials vary according to stage of development, and it is not clear to us at what stage these novel reference materials should be evaluated for possible implementation. There is no indication whether the Agency would welcome the development of new "common" reference materials.	Please indicate the stage of development when novel reference materials should be evaluated for possible implementation. Please also indicate whether FDA would welcome the development of new "common" reference materials, and under what circumstances.

IV. C. 1 / page 11	M	Detection Limit and Quantitation Limit are useful parameters to evaluate aspects of the procedure for a potency test method. However, neither is included in the ICH list of parameters required for validating a potency method. We request that this section be written in a way that makes it clear that FDA is not proposing a change to the ICH guideline on method validation.	Suggested alternative wording for sentences 3 – 5: The validation process requires evaluation of both the component processes that comprise the measurement method as well the reliability of the final potency result that is reported. Numerous resources are available for analytical methods validation (Refs. 9 through 11). You should determine the appropriate assay parameters to evaluate to quantify potential sources of errors within the method and the impact of these on the potency value. Parameters that may be analysed include:
IV. C. 1 / Page 11	M	The list of assay parameters to validate does not exactly align with the ICH definitions and recommended approach. Precision is typically addressed at the level of Repeatability, Intermediate Precision and Reproducibility. The USP uses the same terminology, adding "Ruggedness" as a synonym for "Intermediate Precision." The same usage should apply here. Also, we suggest that the order of assay parameters stay the same as in both the ICH guideline and USP chapter.	Suggested change to bulleted list: • Accuracy • Precision (Repeatability, Intermediate Precision, Reproducibility) • Specificity • Detection Limit • Quantitation Limit • Linearity • Range • Robustness

*** Relative Impact** **C** = A critical concern that must be addressed
M = A minor concern that should be addressed
E = Editorial comment to text (change not necessarily required)

Once again, we appreciate the opportunity provide comment on FDA's *Draft Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products*. We would be pleased to clarify or expand our comments, as needed.

Respectfully submitted,

/s/

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