Response to a request for comments Docket No.FDA-2023-D-4299 Potency Assurance for Cellular and Gene Therapy Products

Comments submitted by the International Society for Pharmaceutical Engineering (ISPE), regulatorycomments@ispe.org

GENERAL COMMENTS ON THE DOCUMENT
Strength, potency assay, and bioassay are used throughout the document including as footnotes to specific sections, which makes it difficult to identify and clearly understand the distinctions. Also, in some instances, the defined terms appear to be used interchangeably. Please consider including a glossary including comprehensive definitions. It is crucial for the understanding of the nuances in the guidance to clearly distinguish the terms (and their interchangeability), such as e.g. bioassay, potency, strength, and assay.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or Line Number	Current Text	Proposed Change	Rationale or Comment
98	…support the stability of the drug substance (DS) and drug product (DP)...	…support the stability of the drug product substance (DS) and drug product (DP) **(if applicable)**	Both DS and DP are called out whereas there may be cases where we do not have a true DS.
93-95 versus 97-99	…the degree of potency assurance for a product should be appropriate for the phase of clinical investigations and should progressively increase during the course of clinical development, as described in more detail in section IV.G of this guidance. versus During all phases of clinical investigation, your IND must contain sufficient data to support the stability of the drug substance (DS) and drug product (DP) during planned clinical investigations.	During all phases of clinical investigation, your IND must contain sufficient data to support the stability of the drug substance (DS) and drug product (DP) during planned clinical investigations. It is recognized that in early development potency assay may require further development and will be used for release.	The recommendations of potency assurance for release potentially conflict with stability expectations. It could be understood that a higher assurance of potency is expected for stability compared to release testing: i.e. "*the degree of potency assurance for a product should be appropriate for the phase of clinical investigations and should progressively increase during the course of clinical development"* versus "*during all phases of clinical investigation, your IND must contain sufficient data to support the stability of the drug substance (DS) and drug product (DP) during planned clinical investigations".*

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155-156	Phase-appropriate assays and acceptance criteria for potency should be established, and lots that fail to meet acceptance criteria should be rejected.	and lots that fail to meet acceptance criteria ~~s~~hould be fully reviewed. In order to assess such a batch a fully justified, risk-based justification should be produced using a multi-disciplinary team. The assessment should be discussed with the agency, otherwise the batch should be rejected.	ISPE suggests more guidance is included on handling in such exceptional circumstances batches that fail proposed acceptance criteria. In limited cases, OOS products may have some clinical benefit and allowances for the tending physician to decide if the product is administered. For example, for autologous products in the last line of care.
184-187	At all stages of the product lifecycle, you should use quality risk management to assess risks to product potency and to reduce those risks to acceptable levels. We recommend that you consider the following concepts when designing a potency assurance strategy for your product	Please include a reference to part G "Progressive implementation of a potency assay assurance strategy". Please consider including a figure illustrating the start, progression, and finalization of aspects highlighted in the bullet points	It may be beneficial to have the phase-appropriate approaches to be highlighted in the introduction.
204-205	…all CQAs within appropriate pre-determined limits.	ISPE suggests changing this text to read "all CQAs ~~within~~ **meet** appropriate pre-determined limits."	Text change is recommended as not all CQAs have two-sided limits.
256-261	Nonclinical studies bullet point	Suggest adding a sentence such as "Non-clinical studies may include in vitro approaches such as in silico modelling or organs-on-a-chip in lieu of in vivo nonclinical studies to assess the MoA."	For many CGT products, especially cell-based therapies, animal studies may not be informative
277	…,nonclinical studies,...	Please consider including consideration for in silico models or organs-on-a-chip approaches using a sentence such as that given for the comment on lines 256 – 261.	Same as the comment above.
278-282	For products that have MOAs that are not fully understood, evidence of a statistical	Consider replacing 'statistical' with **'correlative'**.	Correlative analysis of a product attribute and clinical outcome should be evaluated, but demonstration of a

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	relationship between a product attribute and nonclinical or clinical outcomes may suggest that the attribute is relevant to potency. However, a statistical relationship alone cannot establish a mechanistic relationship between an attribute and potency.		statistical relationship would often be premature given the limited knowledge of the MOA as well as product attributes.
278-280	For products that have MOAs that are not fully understood, evidence of a statistical relationship between a product attribute and nonclinical or clinical outcomes may suggest that the attribute is relevant to potency.	For products that have MOAs that are not fully understood, evidence of a statistical relationship between a product attribute and nonclinical or clinical outcomes may suggest that the attribute is relevant to potency. **In some cases, additional data may warrant revisions to the MOAs and potency assays under lifecycle management.**	Suggest adding additional text. There could be a "not potent but efficacious" therapeutic that is effective due to an MOA that is not the proposed MOA. The therapeutic is truly *not potent* for its proposed MOA, but the therapeutic is truly effective in treating the intended indication. It could be that the proposed MOA was incorrect, and the product is effective due to an alternate MOA (perhaps an unknown biological activity). For example, the potency of a CAR T-cell therapy may not be due to its ability to secrete IFN-γ upon binding to target cells but instead could be due to the secretion of IL5 upon binding to target cells or the ability of the CAR T-cells to kill target cells via perforin-granzyme or Fas-Fas ligand interactions. [Janeway CA Jr, Travers P, Walport M & Shlomchik MJ. T cell-mediated cytotoxicity. In Immunobiology: The Immune System in Health and Disease, 5th edition. New York: Garland Science; 2001. T cell-mediated cytotoxicity. Accessed March 14 2024 https://www.ncbi.nlm.nih.gov/books/NBK27101/.]
318-319	Risks to potency should be reassessed as you increase your understanding of your product and manufacturing process.	Risks to potency should be reassessed as you increase your understanding of your product**,** manufacturing process**, and analytical method maturity**.	Risk assessments are required to be used at all stages of the product life cycle (see line 184), however, maturity of the potency assay at early stages may not

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			allow a comprehensive assessment of the potency risks.
380-384	For products such as tissue-engineered medical products that are not amenable to destructive sampling, we recommend that you conduct potency release testing on an additional unit of the lot that is manufactured in parallel for the specific purpose of providing a representative sample.	For products such as tissue-engineered medical products that are not amenable to destructive sampling, ISPE recommends that you conduct potency release testing on an additional unit of the lot **or other surrogate material** that is manufactured in parallel for the specific purpose of providing a representative sample.	Some tissue-engineered medical products are manufactured as a lot of one.
395-399	For both investigational and licensed products, such post-release testing will help to verify that the manufacturing process is continuously capable of producing potent lots. In addition, for investigational products with an extremely short shelf life, you should initiate one or more potency bioassays immediately after manufacturing the DP and evaluate the results when they become available post-release, with the goal of confirming product potency and manufacturing process reliability. Post-release potency bioassays should also be part of potency assurance for licensed products that have an extremely short shelf life, if the bioassays add value to continued process verification and reduce risks to potency.	ISPE recommends removing the word "testing" and replace with "characterization assays" "For both investigational and licensed products, such post-release ~~testing~~ **characterization assays** will help to verify that the manufacturing process is continuously capable of producing potent lots." In addition, for investigational products with an extremely short shelf life, you should initiate one or more potency **characterization** bioassays immediately after manufacturing the DP and evaluate the results when they become available post-release, with the goal of confirming product potency and manufacturing process reliability. Post-release potency **characterization** bioassays should also be part of potency assurance for licensed products that have an extremely short shelf life, if the bioassays add value to continued process verification and reduce risks to potency.	Please consider providing more clarity on post-release testing as characterization assay since the product was already released.

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430-431	Your product's MOA and QTPP, a list of your product's initial CQAs, and an explanation of how potency-related CQAs were identified.	Suggest changing the text to clarify that at this early stage, it is likely to be potential CQAs and initial information on MOA which may be limited at this stage of development. Your product's **proposed** MOA and QTPP, a list of your product's initial CQAs, and an explanation of how potency-related CQAs were identified.	The text refers to "initial IND submission" and states that MOA information is needed along with a list of CQAs. It is important to make this clarification.
487-488	We recommend that you evaluate the utility of these assays in parallel during early clinical investigations.	We recommend that you evaluate the utility of these assays in parallel during early clinical investigations **and through the lifecycle.**	MOAs may not be fully understood, and additional post-marketing data may require lifecycle management of the MOAs and potency assays.
582-583	…your potency assurance strategy should typically include multiple release assays…	…your potency assurance strategy ~~should typically~~ **may** include multiple release assays…	The current language could be interpreted to mean that multiple assays are always needed, and this may not be possible or required.
678-756	*Approaches to Potency Assay Selection and Design* Section	ISPE recommends adding a section on individualized gene therapy products.	This section would benefit from guidance on strategy for individualized products where a unique vector or unique combination of vectors is included
731-741	Bullet point on vector-transduced patient-specific cellular products	ISPE suggests adding a sentence: . ***"Assurance of potency for vector and transduced cells may be achieved using different approaches".***	It is worth noting that the current text is missing an important distinction between the potency expectations for vectors and those for the transduced cells. One could argue that the vector's potency can be demonstrated by its ability to infect the cells with transgene using transduction efficiency and/or infectivity, while the transduced cell's potency can be demonstrated by its ability to engage with the antigen of interest and to kill the antigen-presenting tumor cells using cell killing assays. However, current expectations to have similar potency assays for both vector and

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			transduced cells may pose an unnecessary burden on the developers. The guidance should clearly state the flexibility in showing potency assurance of each component that corresponds to its particular activity biologically.

End of Comments