Alliance for Regenerative Medicine

March 27, 2024

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2023-D-4299 for *Potency Assurance for Cellular and Gene Therapy Products*

Dear Sir/Madam:

The Alliance for Regenerative Medicine (ARM) is pleased to submit comments to the US Food and Drug Administration (FDA) in response to recently released draft guidance titled *Potency Assurance for Cellular and Gene Therapy Products.*

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

General Comments

ARM appreciates the continuing engagement with the Agency around this important topic of cell and gene therapy (CGT) potency, building upon our joint Scientific Exchange Meeting in October 2022 and the white paper that followed that interaction. We are pleased that following that meeting, FDA determined the need for additional prioritization and updated draft guidance, issued in 2023.

We appreciate that this draft guidance, *Potency Assurance for Cellular and Gene Therapy Products,* addresses the following regulatory challenges that sponsors identified during the Scientific Exchange Meeting and described in the white paper ARM and ASGCT published on this meeting:

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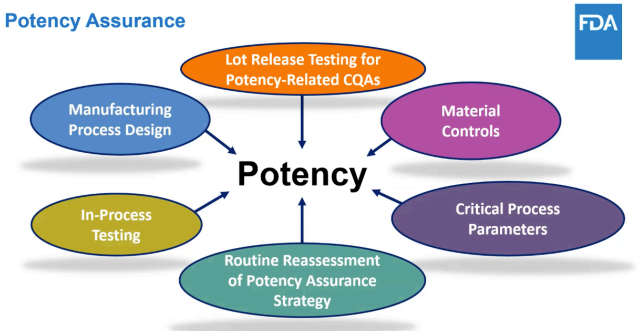
- Elimination of the term "assay matrix," used in the January 2011 guidance on potency tests since it was creating significant developer confusion.
- Reduction of redundant requirements to measure multiple steps of a biological cascade, as stated in lines 658 – 662: "... if a later step in the chain of biological activities is completely dependent on the earlier steps, then a bioassay at the later step that adequately ensures the product's biological activity at that step will typically be sufficient to also ensure the biological activities at the earlier steps."

In addition, ARM welcomes the following portions of this new draft guidance and recommends retaining them in the finalized version:

- The intent of FDA to potentially issue additional guidance documents that provide further advice about potency assays for specific classes of CGT products (lines 58 – 59).
- Acceptance of additional data sources to guide the design of a potency assurance strategy (e.g., published information and established scientific principles, lines 223 – 227), in addition to prior knowledge/experience with a specific product class, since CGT sponsors are often developing a CGT product for the first time.
- Acknowledgement of the potency assay challenge for autologous therapies that potency assay performance when using healthy volunteers may differ vastly from assay performance in donors with disease (lines 233 – 237).

However, we recommend this guidance, when finalized, address the additional issues described below to facilitate more fully the efficient development of quality CGT products.

The rationale for the potency assurance strategy approach is unclear. The need for, and potential benefit of, a new approach to assuring potency is not sufficiently clear to ARM members within the guidance document. It would be helpful to state early in the document that the benefit of using a broader potency assurance strategy, vs. using potency assays alone, is to provide more flexibility. We suggest making the statement that was made in the webinar on this guidance document, that if there are limitations in one aspect of a potency assurance strategy, other aspects may be able to compensate for those limitations. The following graphic may be instructive (from the time point of 10:30 in the archived copy), potentially labeled, "Tools That Support Assurance of Product Potency:"



ARM recommends removal of new documentation requirements and clarification that there are no other new regulatory requirements with a potency assurance approach. While ARM appreciates the potential added flexibility of a potency assurance strategy to ensure and support CGT product potency, aspects of the description of the approach lack clarity on whether the Agency intends to add new requirements for potency through the approach. In addition, it is unclear how this strategy fits into existing standardized approaches, such as ICH Q9(R1).

ARM believes the intent is to encourage integration of potency assurance into overall product quality risk management and not to request duplicative efforts, as reflected in CBER's webinar on this guidance document. We recommend explicitly stating the Agency is not expecting sponsors to develop an additional quality system specific to potency, but rather to ensure sponsors address potency as a component of the existing quality system, as many sponsors may already do.

Similarly, the process of developing a potency assurance strategy (e.g., Sections IV. C – F) includes process development and control strategies that sponsors who are experienced in CGT development routinely use currently. We appreciate the Agency providing this information to guide newer developers of CGTs, but we suggest clarifying that these are not new recommendations by identifying them as best practices that will assist CGT sponsors in meeting Agency expectations.

New documentation requirements are described in lines 423 – 445, which ARM does not believe are necessary. Rather, in instances in which other elements of a potency assurance strategy (in addition to potency assays) may be supportive of assuring potency, sponsors could provide that additional information on an optional basis.

Increased differentiation of requirements by phase of development is needed. ARM appreciates CBER's acknowledgment that the amount of information a sponsor has on potency differs among phases of clinical investigations (lines 92 – 94) and that some aspects of a potency assurance strategy may not be fully mature during the early stages of product development (lines 415 – 416). A phase-appropriate approach is indicated in other areas of the guidance document, as well. For example, we agree that assays used in characterization studies do not necessarily need to be qualified (lines 269 – 270).

However, significantly more differentiation needs to be identified within the guidance document between early-phase and later-phase requirements for potency testing and assurance. For example, some control strategies are not typically performed in early-phase development or even at the initiation of pivotal trials, but rather are BLA-enabling. It is especially important that the guidance consistently states that one potency assay may be acceptable for lot release, as reflected in line 539, which indicates "one or more" potency assays are required for lot release.

We note additional examples in the line-by-line comments of several places in which further phase-differentiated guidance is necessary. ARM also requests guidance on the requirements for first-in-human studies that may be phase 1/2 pivotal trials.

ARM provides in-line comments in the table below to address these issues and more specific technical recommendations. ARM appreciates your consideration of these comments.

Sincerely,

Michael Lehmicke
Senior Vice President, Science and Industry Affairs

Specific Line-by Line Comments: Section/Line	**Guidance Text**	**Rationale for Change or Comment**	**Proposed Change**
I. Introduction			
Lines 27-29	"Potency assays remain an important part of assuring the potency of CGT products, but the comprehensive strategy described in this draft guidance document also includes complementary approaches to help assure potency."	To better identify expectations regarding use of complementary approaches, we suggest providing here the clarification similar to CBER content in its webinar on this guidance, as stated to the right. Without such clarification throughout the document, there are areas that may seem to imply that all aspects of a potency assurance strategy are always required to be documented.	"Potency assays remain an important part of assuring the potency of CGT products, but the comprehensive strategy described in this draft guidance document also includes complementary approaches to help assure potency. Since developing potency assays for cell and gene therapy products can be challenging, this new approach provides adaptability. It is not intended to increase sponsor requirements. Rather, when there are limitations in one aspect of a potency assurance strategy, other aspects, illustrated below, may be able to compensate for those limitations."
Footnote 1	"As defined in 21 CFR 600.3(s), the word potency is interpreted	The guidance document does not address the role	

	to mean 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."	clinical data may have in determining potency. We recommend adding this information. For example, it would be helpful to indicate what practical approach could be taken to use clinical data to demonstrate that a product effects a given result in a CGT setting.	
III. Regulatory Framework			
A. Licensed CGT Products			
Lines 73 – 75	CBER "may permit an alternative approach to the requirements for lot release testing for potency in Title 21 Code of Federal Regulations (CFR) 610.1 and 21 CFR 610.10 ..."	As written, the reference to the regulation citation that permits an alternative approach, 21 CFR 610.9 is provided as a footnote. ARM recommends providing this in the text for greater visibility along with the other 21 CFR citations.	"As stipulated in Title 21 Code of Federal Regulations (CFR) 601.9, the Center for Biologics Evaluation and Research (CBER) may permit an alternative approach to the requirements for lot release testing for potency in 610.1 and 21 CFR 610.10 ..."
Lines 80 – 83	"Before introducing a change to the manufacturing or testing of an approved biologic, you must assess the effects of the change, and you must demonstrate that the change does not adversely affect the potency of the product as it may relate to the safety or effectiveness of the product."	The comparability strategy will depend on the significance of the manufacturing change (see footnote 30); demonstration of comparability (e.g., supported by data) may not be warranted for a small change. We also suggest adjusting wording to align with the scope of the guidance, which is on CGT products vs. biologics more broadly.	"Before introducing a change to the manufacturing or testing of an approved ~~biologic~~ CGT product, you must assess the effects of the change, and you must demonstrate, as appropriate, that the change does not alter ~~adversely affect~~ the potency of the product as it may relate to the safety or effectiveness of the product."
B. Investigational CGT Products			
Lines 99 – 100	"Stability studies should include assessments of potency, as described in more detail in section V.A of this guidance."	We suggest noting that the phase of study affects this.	"Stability studies should include assessments of potency, in a phase-appropriate manner, as described in more detail in section V.A of this guidance.

Lines 102 - 125	This section indicates that FDA may place investigations on clinical hold if potency is not adequately assured at any phase if there is risk to subjects, and in phase 2 or 3 if lots are not consistently potent.	Because the emphasis of phase 1 studies is on safety vs. efficacy, it is our understanding that a potency assay is not required for phase 1. We request the Agency clarify that a clinical hold at phase 1 would relate to delinquency in safety control, if that is the intent, and to provide some examples of what is needed for potency assurance at phase 1.	
C. Current Good Manufacturing Practice			
Lines 130 - 131	"The facilities and methods used for manufacturing CGT products must comply with current good manufacturing practice (CGMP), and many aspects of CGMP help to assure product potency."	As noted in lines 331 – 333, process development studies and process design do not need to be performed under CGMP conditions. We recommend stating this exception here for clarity. We also suggest using the word "process" instead of "methods" to distinguish from analytical methods.	"The facilities and process ~~methods~~ used for manufacturing CGT products must comply with current good manufacturing practice (CGMP), and many aspects of CGMP help to assure product potency. Note that product and process development studies do not need to be performed in accordance with cGMP."
Lines 139 - 141	"The materials used for manufacturing may affect the product's potency. Materials should meet suitable specifications before being used in the manufacturing process."	ARM recommends adding a reference related to suitable specifications.	"The materials used for manufacturing may affect the product's potency. Materials should meet suitable specifications before being used in the manufacturing process. For example, guidance for ancillary material qualification is provided in USP chapter <1043>."
Lines 149 – 153	"Potency assays used for lot release should be verified to be suitable for their intended purpose (able to measure potency with sufficient specificity, accuracy and/or	We request indication of whether the word "verified" is synonymous with the word "qualified," and if so, using "qualified" for clarity.	

	precision over the reportable range of the assay)."		
Lines 158 – 159	"To further facilitate compliance with CGMP, you should develop an effective pharmaceutical quality system."	It would be helpful to discuss further a phase-appropriate approach to developing a quality system. We also suggest a footnote referencing the phase 1 and phase 2/3 GMP guidance documents.	
IV. Developing a Potency Assurance Strategy			
Lines 172 – 174	"Finally, potency assurance strategies should include lot release testing that confirms that potency-related quality attributes meet appropriate acceptance criteria."	Early-stage products might not have enough product-specific information to generate acceptance criteria. We recommend noting this, as stated to the right.	"Finally, potency assurance strategies should include lot release testing that confirms that potency-related quality attributes meet appropriate acceptance criteria in later development, when there is sufficient product-specific information to develop acceptance criteria."
Lines 174– 176	"Lot release testing for most CGT products should include at least one bioassay that measures a biological activity related to the intended therapeutic effect of the product, as described in more detail in section V of this guidance."	ARM requests clarification: • That cell lines or other cells may be used in lieu of the target cell type if justified based on an understanding of potential differences in the test results. • That a lot release bioassay is only needed beyond FIH studies, since there is often not enough information on the product until after that point.	"Beyond FIH studies, lLot release testing for most CGT products should include at least one bioassay that measures a biological activity related to the intended therapeutic effect of the product, as described in more detail in section V of this guidance.
Lines 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	The information listed below this statement is very limited in early development (e.g., at initial IND submission). We suggest noting these phase considerations here.	"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. However, since the information available is

	you consider the following concepts when designing a potency assurance strategy for your product: …"	We also suggest a footnote referencing the phase 1 and phase 2/3 GMP guidance documents.	limited in early development, the following recommendations are primarily aimed at later stages of development."
A. Quality Risk Management and Assurance of Potency			
Lines 203 – 205	"Your manufacturing process should consistently produce lots that have all CQAs within appropriate predetermined limits."	We suggest rewording to reflect that not all CQAs may be tested during production but may be deemed under control without the need for testing, as part of the defined control strategy.	"By later phases of development, ~~Your~~ the performance of the manufacturing process and other measures should ~~consistently produce lots that have~~ assure suitable control of all CQAs ~~within appropriate predetermined limits~~."
Lines 212 – 213	"You should identify risks to potency-related CQAs, analyze the probability and severity of these risks, and evaluate their significance."	We suggest alignment with ICH Q9, as indicated to the right.	"You should identify risks to potency-related CQAs, analyze the probability, ~~and~~ severity and detectability of these risks, and evaluate their significance."
B. Applying Prior Knowledge and Experience			
Lines 226 – 227	"Prior knowledge and experience with a specific product class can also help you to identify potency-related CQAs and assays to measure and control these CQAs."	ARM comment: Since CQAs can only be measured, not controlled, we suggest rewording.	"Prior knowledge and experience with a specific product class can also help you to identify potency-related CQAs and assays to measure ~~and control~~ these CQAs."
C. Gaining Product and Process Understanding			
Lines 250 – 261	"If available, information from nonclinical studies should be used to inform your initial potency assurance strategy, including selecting potency-related CQAs and identifying appropriate acceptance criteria."	ARM requests indicating whether nonclinical studies could also be used to inform the QTPP and clarifying how to leverage or cross-reference nonclinical information.	"If available, information from nonclinical studies should be used to inform your initial potency assurance strategy, including selecting potency-related CQAs and identifying phase-appropriate acceptance criteria."
Lines 265-268	"Starting from the earliest stages of	It may be clearer throughout the	"Starting from the earliest stages of product

	product development, we recommend that you conduct product characterization studies to better understand your product's MOA and to help identify product attributes that may be potency-related CQAs."	guidance to use the term, "potential" or "candidate potency-related quality attribute" rather than "potency-related CQAs" to indicate that the criticality (mechanistic relationship) of the attribute may not have been established in early development.	development, we recommend that you conduct product characterization studies to better understand your product's MOA and to help identify candidate potency-related quality ~~product~~ attributes ~~that may be potency-related CQAs~~."
Lines 274 - 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. However, a statistical relationship alone cannot establish a mechanistic relationship between an attribute and potency."	ARM requests clarification on what is meant by a statistical relationship We assume this refers to interrelationship analyses, though that is not necessarily statistical.	
Line 285		ARM recommends adding a bullet point to this section on the impact of product stability (and degradation pathways) on potency assurance. There are many potency attributes that are not impacted by product degradation (but other, non-potency attributes could be).	
Lines 292 – 293	"You should perform process characterization to identify CPPs in your manufacturing process…."	Identifying CPPs is typically done via process characterization prior to process finalization and as a sponsor approaches the PPQ stage.	"As you approach finalizing the commercial manufacturing process during development, you should perform process characterization to identify CPPs in your manufacturing process…."

D. Risk Assessment			
Lines 312 – 316	"Analyzing and evaluating risks to potency can be challenging if assays used to measure potency-related CQAs have not been qualified to determine whether they have adequate performance. Using unqualified assays may decrease your ability to analyze risks to potency, due to a potential for inconsistent assay performance or uncertainty about the ability of the assay to detect clinically relevant changes in product potency."	Since assays used in characterization studies do not necessarily need to be qualified (lines 269 – 270), we suggest indicating the potential benefits of qualified assays outside of characterization studies. We also recommend referencing the 2020 guidance, Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)	"Analyzing and evaluating risks to potency can be challenging if assays used to measure potency-related CQAs ~~have not been qualified to determine whether they~~ do not have ~~adequate~~ suitable performance. The ~~U~~ use of ~~ing unqualified~~ assays with confirmed ~~may decrease your ability to analyze risks to potency, due to a potential for inconsistent assay~~ performance, such as via qualification, may increase your ability to analyze risks to potency, due to consistency of assay performance or ~~un~~certainty about the ability of the assay to detect clinically relevant changes in product potency."
Lines 323 - 325	"Following evaluation of risks, any risks to potency that are unacceptably high should be mitigated or avoided through the design of the manufacturing process and the control strategy, as discussed in the following sections of this guidance."	To reflect that risk continues to be evaluated over time, we recommend describing quality risk management similarly to the wording in ICH Q9, which indicates that when control of risk is unacceptable, returning to risk assessment may be appropriate.	
E. Control Strategy			
Lines 344 – 345	"Your control strategy should mitigate any unacceptable risks to product potency. We recommend that your control strategy include the following elements, as applicable for the stage of the product lifecycle: …"	In the bulleted items that follow, we request FDA clarify what the applicable product development stages are for: (1) control of materials, (2) process parameters, and (3) in-process testing.	
Lines 351 - 353	"For example, if a manufacturing	If the growth factor is added in the process	

	process for a cellular product includes a growth factor, the potential influence of the growth factor on the potency of the DP should be assessed."	but not expected to be in final product, it is more appropriate to treat it as a residual/impurity and confirm clearance.	
Lines 363 – 365	"…the duration of the culturing step is a CPP that should be assigned a limit based on prior knowledge and/or data from process development studies, process characterization studies, or process performance qualification studies."	This requirement applies only to the appropriate phase of development.	"…the duration of the culturing step is a CPP that should be assigned a limit at the appropriate phase of development, based on prior knowledge and/or data from process development studies, process characterization studies, or process performance qualification studies."
Lines 367 – 368	"In-process samples should be tested to monitor quality attributes that may influence or predict product potency."	Use of the word "monitor" may seem to imply testing within the process that has acceptance criteria. We suggest clarification.	"In-process samples should be tested to monitor or assess quality attributes that may influence or predict product potency."
Lines 376 – 380	"For potency testing of licensed products, potency release assays must be performed using a sample collected after completion of all manufacturing steps that may affect potency. For example, if cryopreservation of a cellular product poses a high risk to the product's potency, then this risk should be mitigated by performing the potency assay on a sample taken after cryopreservation."	The FDA guidance, *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*, refers to the option to provide a rationale to perform testing on either DS or DP if in some cases repeat testing may not be feasible. We recommend this flexibility also apply at the BLA stage and for the licensed product.	
Lines 391 – 392	"…potency assurance may also be improved by including additional	We recommend clarifying that additional testing during continued	"…potency assurance may also be improved by including additional characterization testing or

	testing as part of continued process verification."	process verification is for characterization or monitoring.	monitoring as part of continued process verification."
Lines 396 – 397	"… we recommend that you also initiate one or more potency bioassays immediately after manufacturing the DP and evaluate the results when they become available post-release."	We suggest indicating how batch release testing should be performed before the correlation can be made between the physicochemical assay and the bioassay.	
Lines 403 - 410	"If one aspect of the potency assurance strategy cannot adequately mitigate a risk to product potency, then you should mitigate the risk by strengthening other aspects of the potency assurance strategy. ... In these cases, other aspects of the potency assurance strategy (such as process design and process control) will take on increased importance and should therefore be more stringent and extensive."	ARM appreciates Agency flexibility in certain circumstances. However, while other aspects of the potency assurance strategy may be supportive of the assurance of potency, these aspects should not need to be more stringent and extensive. If this requirement is maintained, ARM would suggest providing examples of how to demonstrate other aspects of the potency assurance strategy more stringently.	"If one aspect of the potency assurance strategy cannot adequately mitigate a risk to product potency, then you could consider mitigating the risk by ~~strengthening~~ providing support of potency testing with other aspects of the potency assurance strategy. … In these cases, other aspects of the potency assurance strategy (such as process design and process control) may provide support to the assurance of potency ~~will take on increased importance and should therefore be more stringent and extensive~~."
F. Progressive Implementation of a Potency Assurance Strategy			
Lines 423 - 431	"To document that the potency assurance strategy will ensure an adequate level of potency for conducting early-phase clinical investigations and to obtain feedback on your plans for strengthening potency assurance, you should include the following information about your potency	ARM recommends not requiring additional documentation of a potency assurance strategy. We also suggest stating the recommendations are for beyond phase 1 (i.e., for trials in phase 2 and beyond) since some recommendations are not feasible for phase 1 studies. In addition, at the time of an IND submission, there is likely to be uncertainty	"~~To document that the potency assurance strategy will ensure an adequate level of potency for conducting early-phase clinical investigations and to obtain feedback on your plans for strengthening potency assurance,~~ When factors in addition to potency assays may support the assurance of potency, you ~~should~~ may provide an overview of ~~include~~ the following information about your potency assurance

	assurance strategy in Module 3 of the Common Technical Document (CTD) of your initial IND submission, and you should summarize this information in Module 2 of the CTD submission: • Your product's MOA and QTPP, a list of your product's initial CQAs, and an explanation of how potency-related CQAs were identified.	regarding the product's MOA and a limited definition of the QTPP (which is developed based in part on an understanding of the product's MOA). When sponsors optionally want to provide additional information to support assurance of potency, we suggest sponsors should then provide an overview of the potency assurance strategy in 3.2.S.2.6 or 3.2.P.2.	strategy in Module 3.2.S.2.6 or 3.2.P.2~~. Module 3~~ of the Common Technical Document (CTD) of your initial IND submission~~, and you should summarize this information in Module 2 of the CTD submission~~: • Your product's postulated MOA ~~and QTPP, a list of your product's initial CQAs,~~ and an explanation of how potential potency-related CQAs were identified.
Lines 439 – 441	"If your control strategy does not include potency testing for lot release, you should explain how other aspects of your process design and control strategy provide adequate potency assurance for a product in early-phase clinical investigations."	ARM requests FDA to provide examples of other aspects of process design and control strategy.	
Lines 443 – 445	"General descriptions of your plans for additional product characterization, plans for potency assay development, and plans for further strengthening your potency assurance strategy during product development."	Providing plans for the future does not align with ICH M4Q. Plans should be aligned at the pre-IND meeting, rather than submitted in the IND dossier.	~~"General descriptions of your plans for additional product characterization, plans for potency assay development, and plans for further strengthening your potency assurance strategy during product development."~~
Lines 447 - 450	"Throughout early-phase clinical investigations, you should reassess and refine your product's QTPP, CQAs, CPPs, and potency assurance strategy.	This information is not available in phase 1 of development. We suggest revising as indicated to the right.	"In ~~Throughout~~ early-phase clinical investigations, you should begin developing ~~reassess and refine~~ your product's QTPP, CQAs, CPPs, and potency assurance strategy. By later stages of

	By later stages of clinical development, you should have developed a comprehensive potency assurance strategy that includes potency assays with appropriate acceptance criteria."		clinical development, you should reassess and refine these elements to obtain ~~have developed~~ a comprehensive potency assurance strategy that includes potency assays with appropriate acceptance criteria."
Lines 453 – 457	"Before beginning clinical investigations that involve significant risk … the manufacturing process and the control strategy should provide phase-appropriate assurance that each lot of the product will be potent."	We suggest providing examples of what constitutes significant risk.	
Lines 457 – 460	"Your control strategy for a product used in such investigations should include at least one physicochemical assay or bioassay that is performed on a suitable sample for lot release and that quantitates a potency-related CQA."	We request clarification of whether "a test that measures a potency-related CQA" is referring to a potency assay. Provision of examples may be instructive.	
Lines 462 – 464	"Potency assays for products used in these types of clinical investigations should be qualified to demonstrate that the performance characteristics of the assays are fit for the intended purpose of the assay."	We recommend indicating that the requirements for qualification depend upon the phase of development.	"Potency assays for products used in these types of clinical investigations should ~~be qualified to~~ demonstrate that the performance characteristics of the assays are fit for the intended purpose of the assay, appropriate to the phase of development."
Lines 469 – 470	"Assays used for lot release and in-process testing must be validated."	We recommend differentiating the differences in requirements between lot release and in-process testing.	"Assays used for lot release ~~and in-process~~ testing must be validated." Assays used as in-process controls must be qualified (type I validation),

			scientifically sound, and fit for purpose."
Lines 478 – 481	"If you anticipate a compressed development timeline, we recommend that you thoroughly characterize the product and manufacturing process to help you rapidly establish a well-controlled manufacturing process that consistently yields a potent product."	We recommend providing examples of thoroughly characterizing the product. We also recommend noting that the typical process may not be possible for expedited development and/or rare disease.	"If you anticipate a compressed development timeline, we recommend that you thoroughly characterize the product and manufacturing process to help you rapidly establish a well-controlled manufacturing process that consistently yields a potent product. This typical process may not always be possible, however, in the case of expedited development and/or rare disease."
Lines 486 – 489	"… we recommend developing multiple assays that measure known or potential potency-related CQAs. We recommend that you evaluate the utility of these assays in parallel during early clinical investigations. Assays that are redundant may be discontinued later in development…""	One potency assay may be suitable in some cases, since out of the multiple assays developed, one may have superior utility, as discussed in greater detail in section V.A. Some examples would be helpful to assist sponsors in determining the assays best suited for various purposes.	"… we recommend developing multiple assays that measure known or potential potency-related CQAs. We recommend that you evaluate the utility of these assays in parallel during early clinical investigations. Assays that are ~~redundant~~ overlapping may be discontinued later in development… Therefore, one potency assay may be sufficient later in development, provided it is suitable for use."
G. Requesting FDA Advice on a Potency Assurance Strategy			
Lines 497 – 498	"We also recommend that you consult CBER before making major changes to your potency assurance strategy."	We request clarification of what types of changes are considered major changes, e.g., whether downgrading a CQA to a release assay or a change of a material supplier are considered major changes.	
Lines 501 – 502	"We recommend that you request feedback either by asking CBER specific questions during meetings or by	ARM believes the most effective way to obtain advice on this topic is through an interactive meeting. We also suggest indicating the	"We recommend that you request feedback ~~either~~ by asking CBER specific questions during meetings. A type D meeting is often the most appropriate

	submitting an amendment to your IND that provides relevant background information and asks questions."	most appropriate meeting type to request, with a type D meeting likely being most appropriate in most cases.	meeting type to request, if sponsors have only a few (e.g., 3-5 total) questions. ~~or by submitting an amendment to your IND that provides relevant background information and asks questions~~."
V. Potency Assays and Acceptance Criteria			
A. Uses of Potency Assays			
Lines 541 – 543	"When feasible, we recommend that you identify potency-related CQAs that are stability-indicating by using forced degradation studies, real-time studies, or prior knowledge and experience."	We request provision of examples of degradation studies for viral vector and cellular products which are cryopreserved in well-controlled temperature conditions.	
Lines 546 – 548	"If justified, acceptance criteria for potency-related CQAs in stability studies may be different from acceptance criteria used for lot release…"	We recommend clarifying that stability criteria may be wider compared to release criteria. We also suggest clarifying if the recommendation is intended for a specific modality (e.g., *in vivo* vs. *ex vivo* gene therapy). Further, it should be clarified if "potency-related CQAs" refers here to potency assays used during stability studies.	"If justified, acceptance criteria for potency-related CQAs in stability studies may be different (e.g., wider) from acceptance criteria used for lot release …"
B. Assay Selection and Design			
Lines 581-590	"Because CGT products usually have multiple potency-related CQAs that cannot be controlled adequately without release testing, your potency assurance strategy should typically include multiple release assays, each of which quantitates a potency-related CQA that is at risk. … and	ARM comments: This paragraph seems to conflict with other statements within the guidance. We recommend deleting the paragraph, or if retained, addressing ARM's view that a single assay may effectively measure potency in later development. In addition, typically only	"~~Because~~ CGT products ~~usually~~ may at times have multiple potency-related CQAs that cannot be controlled adequately without release testing.~~,~~ In these cases, your potency assurance strategy should ~~typically~~ include multiple release assays, ~~each~~ one of which quantitates a potency-related CQA that is required for the primary mechanism of action. ~~is at risk~~. …"

	it is not essential for the bioassay to mimic the product's MOA. Rather, your understanding of the MOA should help to drive selection of the product's potency-related CQAs."	one assay needs to be quantitative.	
1. Desirable Characteristics of Potency Assays			
Lines 623 - 626	"Bioassays may have substantial variability that can be difficult to eliminate. In such cases, we recommend that potency bioassays be designed to quantitate potency relative to a reference material, which will increase the precision of the reportable value for the bioassay."	ARM recommends indicating whether using cell starting material is suitable as reference material, as well as whether an assay could report a change in readout (editing, expression, function) in the drug product, rather than in the starting material.	
Lines 633 – 635	"The assay should be accurate**.** An inaccurate assay will produce biased results that do not closely match expected values. The assay should have adequate precision and accuracy across the reportable range of the assay."	Clarification would be helpful on how to test for accuracy, such as whether an orthogonal readout is expected.	
Lines 637 – 643	"When feasible, we recommend that specificity be evaluated using a very similar product (or an altered version of the product) that does not possess the potency-related attribute that is detected by the assay."	We request clarification and/or reference to guidance on the definition of "similar product." This term could refer to a product with the same process control (e.g., untransduced cells in a similar manufacturing process) or to a target antigen negative control (e.g., knockout of the target in the cell line).	

Lines 664 – 671	”In such cases, we recommend that you evaluate whether a bioassay that adequately controls one of these biological activities might also mitigate risks to the other linked biological activities, potentially in conjunction with relevant physicochemical assays. If so, a separate bioassay to measure each biological activity may not be necessary for assuring potency of the active ingredient.”	The wording of this recommendation is unclear. We propose to reword as indicated to the right.	”In such cases, if feasible, one bioassay, potentially in conjunction with relevant physicochemical assays, may be sufficient, provided that it measures all ~~we recommend that you evaluate whether a bioassay that adequately controls one of these biological activities might also mitigate risks to the other linked biological activities, If so, a separate bioassay to measure each biological activity may not be necessary for assuring potency of the~~ active ingredients.”
C. Assay Control and Change Management			
1. Suitability			
Lines 762 – 763	“Potency assay protocols should include pre-defined acceptance criteria for sample suitability and system suitability.”	“Potency assay protocols” can be confused with qualification or validation protocols, so we suggest clarifying.	“Potency analytical procedures ~~assay protocols~~ should include pre-defined acceptance criteria for sample suitability and system suitability.”
2. Reference Materials			
Lines 783 – 784	“It is often appropriate to designate a well-characterized lot of DP as a reference material.”	This can be particularly challenging for autologous cellular products due to the limit of batch size. ARM would suggest providing guidance on how reference materials can be provided for autologous products or indicating if there are situations in which doing so is not appropriate.	
Line 803		ARM recommends the addition of a discussion of when and how healthy donor cells	

		could be used for reference materials.	
3. Qualification and Validation			
Lines 833 – 835	"If unacceptable risks are identified, you should reduce these risks to acceptable levels by either changing the design of the assay or improving control of the assay, for example by including additional control materials."	We suggest providing an additional example to indicate that increasing the number of replicates can be used to improve control of the assay.	"If unacceptable risks are identified, you should reduce these risks to acceptable levels by either changing the design of the assay or improving control of the assay, for example by including additional control materials and/or increasing the number of the replicates."
4. Assay Changes and Transfers			
Lines 837 - 848	"When replacing or changing a validated potency assay…"	This section only addresses validated assays; we request guidance on changing and transferring assays for early-stage programs which have not been validated. This section describes the two situations of changing a validated potency assay and transferring a potency assay to a new laboratory, which may require different considerations. For example, assay changes might be able to be justified by further understanding of MOA and clinical data from different trial phases.	
Lines 845 - 848	"We recommend using equivalence testing to evaluate whether results from the new potency assay or new laboratory are sufficiently similar to results from the original assay or original laboratory."	We recommend clarifying whether equivalence testing is based on performing comparability analysis as prescribed in recent draft guidance (i.e., historical data vs. side-by-side testing, split source testing, etc.)	
D. Acceptance Criteria			

Lines 862-866	"If your product has biological activities that pose potential safety risks (or if it is unclear whether a product with high potency will be safe), you should also use available manufacturing data, nonclinical studies, and/or clinical experience to set an appropriate quantitative upper limit to confirm that the potency of each lot will not be in a potentially unsafe range."	Because there are typically only one or two nonclinical toxicology lots, ARM suggests adding that the appropriate acceptance criteria will be set at a wider range in early clinical studies.	
Lines 874 - 875	"For a licensed product, acceptance criteria for potency release assays should link product potency to evidence of clinical effectiveness from clinical investigations."	There may not be sufficient data to ensure that a potency method developed under clinical investigations will be consistent for lots distributed under license despite the method's reproducibility and robustness. Expansion of patient populations may need to be taken into consideration. It is not always possible to establish the correlation between potency and clinical effectiveness.	"For a licensed product, acceptance criteria for potency release assays should link product potency to evidence of clinical effectiveness from clinical investigations, when feasible."