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October 27, 2023

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

Re: Docket No. FDA-2023-D-2436, Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the draft guidance titled **Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO welcomes new regulatory guidance by FDA to help cell and gene therapy (CGT) product sponsors to efficiently navigate the regulatory aspects of improving their manufacturing processes. While some CGT developers have extensive experience with life cycle management of biological products, other CGT developers have limited experience and will especially benefit from a clear explanation of the regulatory expectations for reporting manufacturing process changes provided in this guidance.

Changes in manufacturing processes throughout the lifecycle of a CGT product, such as scaling up the manufacturing process to ensure production of sufficient CGT product for all patients, are both inevitable and desirable, and the industry will benefit from better understanding how they can meet FDA's regulatory requirements for implementing such changes. FDA notes in this draft guidance that prior comparability guidances (ICH Q5E (2005) and FDA guidance on comparability for biologics (1996)) provide some useful principles for sponsors but do not directly address CGT products. FDA acknowledges the necessity of making manufacturing changes and highlights some of the unique challenges in the manufacture of CGT products, which are important for our industry to continue to consider and evaluate.

Risk-Based Approach to Evaluating Manufacturing Changes

A risk-based approach for managing post-approval CMC changes was codified in Section 116 of the Food and Drug Administration Modernization Act (FDAMA) and in biologics regulations

under 21 CFR 601.12. Risk-based regulatory processes for product lifecycle management were also introduced to the global regulation framework through the ICH Q12 guideline. This regulatory approach to encourage improvement is fundamentally important for the development of CGT products, especially in the early stage of development. A risk-based approach allows for timely and efficient implementation of CMC changes that are important for drug quality, safety, efficacy, and availability. BIO recommends that FDA consider a risk-based approach for CMC changes for CGT products throughout this guidance, particularly to support how to leverage risk-based approaches to demonstrate comparability given how the CGT field is rapidly evolving. In this regard, we also request that the Agency include a reference to the ICH Q9 (R1) guideline for quality risk management in the final guidance.

Final Guidance Needs to Recognize Differences in CGT Product Modalities and the Phases of Development

The draft guidance addresses all types of CGT product modalities together, with unique considerations only articulated for tissue-engineered medical products (TEMPs) in Section VI. This broad approach may lead to confusion regarding how the elements of the guidance apply to different CGT modalities. It would, for example, be helpful to distinguish between considerations that may apply to *in vivo* gene therapies (e.g., nucleic acid-based or viral vector-based) versus *ex-vivo* cell-based gene therapies. We therefore suggest the inclusion of additional sections to address the considerations for different CGT modalities. Since CGT products include a broad range of modalities with widely different properties, it would be valuable to acknowledge that fit-for-purpose approaches may be needed to assess their comparability when manufacturing changes are made. Providing examples for each major modality may be helpful.

The draft guidance emphasizes the need to demonstrate the absence of impacts on product quality, safety, or efficacy. Setting such expectations may sometimes overestimate the current understanding and abilities in the field to predict and demonstrate the impact of planned manufacturing changes. It also fails to recognize the significance of the phase of drug development in the assessment of manufacturing changes, and how the capability to conduct rigorous studies changes with each phase. It also does not explicitly acknowledge that positive impacts on quality, safety or efficacy may be beneficial for patients (see next section).

Within the draft guidance, the expectations and recommendations for licensed products and products in early- and late-stage development are all presented together. It is not feasible to apply the same rigor for comparability assessments at all of these stages due to, for example, limited manufacturing experience and product characterization in the early stages of development. We ask that the final guidance recognize that comparability exercises during development stages may not be as extensive as those for approved products, and, as the product moves towards late stages of development, the comparability exercise becomes more comprehensive.

Encouraging Process Changes That Improve Product Safety and Effectiveness

Through this draft guidance, it is apparent that FDA aims to support the CMC lifecycle management needs of CGT products. This should include supporting product quality improvements. The draft guidance also highlights reasons why manufacturers may seek to improve CGT products through a manufacturing change. However, the guidance also explicitly states that if comparability studies demonstrate that the quality of a product has improved in a way that will provide a "significant benefit in effectiveness and/or safety," FDA would consider the improved product to be not comparable with the previous product. This position is inconsistent with the approach taken in ICH Q5E and in the FDA guidance on comparability for biologics (1996), which state that there should be no *adverse* impact on product quality, safety, or efficacy.

BIO suggests that the guidance provide more nuanced provisions for how developers should consider the changes in product quality, such as risk assessments that consider the extent of the change (e.g. magnitude of change in the level of a product-related impurity) and the type of change (e.g. reduced level of process residual vs. change in a product quality attribute that may impact potency). We also request that FDA explain the implications of a post-change product being considered not comparable with the pre-change product, following an improvement on the manufacturing process and improvement on one or more specific quality attribute(s), depending on the phase of development; and how the Agency would consider "bridging" the development if the change only provided a significant benefit (and no adverse impact on quality or safety).

In the event that FDA intends to require full new clinical studies (as opposed to a small bridging clinical study or adding a small comparability arm/cohort in a study) for the improved post-change product, BIO is extremely concerned that this policy will discourage innovation that would otherwise generate safer and more effective CGT products available to patients in a timely manner. Sponsors may become reluctant to make further improvements to their products as such improvements could result in a requirement to effectively restart their clinical development programs. Such an approach by FDA will add significant time and cost to the development of cell and gene therapy products, which runs counter to the commitment articulated by CBER leadership to "lean in" to advancing these therapies to serve patients in need. Ultimately, this will not benefit patients, particularly those who currently lack any treatment options such as many patients with serious rare diseases or certain cancers.

The final guidance should encourage manufacturing changes that lead to quality improvements that benefit patients and recognize that not all changes will result in the creation of a new product. It further needs to clarify that bridging clinical studies (or an arm/cohort in a clinical study) can be used to support the clinical development of the post-change improved product when there is no adverse impact of the change and that sponsors do not need to restart their clinical development programs in these instances. It is clear that sponsors may need to restart their clinical development program with the "new product" when a new IND is required as

described in the specific cases of Section IV.A (p.7). In this case, the sponsors should still be encouraged to leverage prior knowledge as applicable.

Relying upon prior data from the pre-change product, where appropriate, could expedite the development and regulatory processes for the improved post-change "new product", making these medicines available to patients in a more expedited fashion. BIO recommends the Agency address the points above in Section III.

Comparability and the Utility of Nonclinical Studies

It would be beneficial for the final guidance to provide greater clarity regarding the types of nonclinical studies that FDA regards as informative for comparability studies – in particular, whether there is an expectation that sponsors include a comparator arm of the pre-change manufacturing material. Nonclinical studies may be helpful if the availability and capabilities of analytical tests used for any comparability studies are limited, or if there is limited understanding of the product complexity and of the relationship and strength of the association or correlation of quality attributes with safety and efficacy. For example, such studies may include comparability of expression/functional assessments in animal models. Alternatively, for cell-based therapies, the guidance should acknowledge that there may not be good nonclinical *in vivo* models for safety or efficacy, and that introducing human cellular products into animals may not provide meaningful comparability results. We suggest that, where there is not an appropriate animal model, *in silico* or other *in vitro* studies be considered.

Comparability and the Utility of Clinical Studies

We urge CBER to provide more nuanced guidance on the potential need for clinical comparability assessments and clarify that this needs to be assessed on a case-by-case basis. This includes consideration for when it may be valuable to evaluate a post-change product in a new bridging arm/cohort of a clinical study, or conducting a new bridging clinical study, or including additional outcome measures in the patients treated with the post-change product. Demonstrating clinical comparability may not be feasible or appropriate in all cases. Such cases may include CGT products for slowly progressing diseases, where clinical effects could take years to be observed, or for treating ultra-rare diseases, where the recruitment of sufficient patients for a rigorous study would be challenging. When clinical bridging data are needed to evaluate comparability of pre-change and post-change product, there are longer timelines with possible delays to the initiation of pivotal trials or approval of market applications and this should be considered in the context of the existing unmet medical need for the target patient population.

Appropriate Application of Statistics for Comparability Studies

The draft guidance emphasizes the use of statistical analyses to assess comparability. However, the characterization of CGT products is generally not yet as comprehensive as for

traditional biologics (i.e. recombinant protein products), and this is especially the case for cell-based products. Sponsors should be encouraged to continue to develop techniques to better characterize CGT products and to improve structure-function understanding. An overreliance on statistical analyses could lead to an inappropriate focus on a subset of product quality attributes, thus leaving gaps in potentially meaningfully impact to product quality, safety or efficacy while imposing a high burden on CGT sponsors/manufacturers. The appropriate application of statistics should take into account the inherent variability of cell-based products and the assays used to measure their quality attributes, as well as the dynamic behavior of living cells. In addition, it is common for CGT products to involve small data sets, such as few batches of product with few patients for rare diseases, and this can greatly limit the statistical power of the studies. The final guidance should acknowledge the limits of statistical analyses and provide more specific guidance on how to assess comparability in the absence of robust statistics, with a greater emphasis on a comprehensive wholistic assessment of the scientific information available about the manufacturing process and the product.

Recognizing the Value of Understanding Manufacturing Process

The draft guidance fails to address the importance of controlling the manufacturing process in detail. Process characterization and in-process controls can be valuable in predicting when a manufacturing process change may impact process performance and, ultimately, CGT product quality. The guidance would benefit from additional recognition of the value of understanding and monitoring the manufacturing process, particularly given the limited characterization of the more complex CGT product modalities (e.g., cellular products) at this time.

Greater Opportunities for Communication with CBER

The draft guidance indicates a willingness by FDA staff to meet with CGT product sponsors regarding changes to manufacturing processes for CGT products. The guidance would benefit from examples of how a sponsor could obtain timely feedback from FDA on detailed comparability plans, such as requesting a Type C or Type D meetings or submitting an IND amendment with request for feedback. For IND amendments submitted to obtain feedback on comparability plans/protocols, BIO Members urge the Agency to review these within 30 days as often as feasible, as obtaining this feedback is often gating for the development of CGT products.

BIO members welcome opportunities to engage with the CBER Super Office of Therapeutic Products (OTP) on comparability, especially given the complexity of manufacturing CGT products, the nuanced nature of changing and comparing manufacturing processes, and the wide variety of different product modalities with rapid innovation that fall under the CGT “umbrella”. BIO would appreciate FDA providing greater detail on their thinking for how CGT product sponsors might use these opportunities to ensure that changes in manufacturing processes do not unnecessarily delay the development of CGT products. For example, CBER/OTP could develop a Standard Operating Procedure and Policy on how to evaluate

proposed manufacturing changes or provide examples of using comparability protocols for CMC changes during product development.

BIO looks forward to the publication of the final guidance on manufacturing changes and comparability for cell and gene therapy products and is available to answer any questions you may have on our comments.

Sincerely,

/s/
Derek T. Scholes, Ph.D.
Senior Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

LINE-BY-LINE RECOMMENDED EDITS

SECTION/ LINE	ISSUE	PROPOSED CHANGE
I.	**Introduction**	
II.	**Background**	
35-40	"CGT products are regulated under the existing framework for biological products. Manufacturing and control of CGT products can often be affected by unique factors, including limited knowledge of product quality attributes, limited manufacturing experience, limited and variable starting materials, limited amount of product, complex manufacturing processes, and limited product shelf life. These aspects of CGT products may make the management of manufacturing changes more challenging than for other biological products."	It's difficult to reconcile this statement with that of text throughout this guidance that appears to establish that comparability studies be initiated for virtually all manufacturing changes. In addition, current guidance on post approval changes provides for a more flexible and yet specific framework for which changes should be reported to the Agency.
46-49	"We note that while improvement of product quality is always desirable and encouraged, if the results of comparability studies indicate an improved product quality suggesting a significant benefit in effectiveness and/or safety, the pre- and post-change products may be different products and, therefore, not comparable."	It would be helpful to define comparability up front and explain (at a high level, considering this is the background section) the scientific and regulatory basis for determining that two products are not comparable when the post-change product has an improved quality, suggesting a significant benefit in safety and/or efficacy. It appears these lines are inconsistent with others in the draft Guidance that state that comparability is focused on an adverse effect/impact on product quality, which is more aligned with ICH Q5E and Q9 and other FDA Guidance on comparability.
54-57	This is a very broad statement compared with ICH Q5E. There is limited discussion in this document about factors or situations that would indicate that nonclinical or clinical data are required.	We suggest that additional guidance similar to that outlined in ICH Q5E Section I.D (1.4) apply, i.e., quality attributes should be compared, risk to safety and efficacy should be assessed, and the need for a targeted "bridging" nonclinical or clinical study (or clinical cohort within a study) should be determined based on the risk assessment.

57-58	"Otherwise, additional clinical studies may be warranted."	We suggest revising the statement to: "**If the analytical and nonclinical studies are inconclusive**, additional clinical studies **(or cohort(s) within a clinical study)** may be warranted."
83-85	This is a subjective statement for which internationally recognized guidance still provides the agreed upon framework for comparability assessment of biotechnology products. It may minimize the value and create confusion for industry and health authorities in situations where the principles of ICHQ5E are still applicable to CGT products. For example, viral vectors are highly purified and characterized biologics using manufacturing processes and analytical methods very similar to those used for protein therapeutics. Production, control and characterization of in vivo viral vectors such as adeno-associated virus (AAV) are much more similar to therapeutic proteins than other CGT product classes such as cell therapies. Because viral vectors have more similarities to protein therapeutics than cell therapies, it may be more appropriate for viral vectors to fall under the ICH Q5E guidelines.	
III. Considerations for the Management of Manufacturing Changes		
A. **Risk Management**		
101-103	"A robust framework for managing manufacturing changes is especially valuable for CGT products because of the complexity of these products and their manufacturing processes."	We recommend adding a sentence: "Manufacturing process understanding is important for evaluating the potential impact of a process change on subsequent steps in the process or product quality."
114-116	"Defining acceptable ranges for CQAs and establishing operating ranges for CPPs prior to making a manufacturing change facilitates	Acceptable ranges for CQAs and operating ranges for CPPs and acceptable quality for critical raw materials for early-phase/late-stage

	conducting a risk assessment and evaluating the change."	development may not be well defined due to many factors including limited manufacturing experience and rareness of the disease.
120-122	"Factors such as product and process knowledge, qualification/validation of methods, and the stage of clinical development should be considered when assessing the risk of the manufacturing change."	We suggest that platform data should be included as a potential source of supporting information for risk assessment (e.g., impurities from a different product using the same manufacturing process and route of administration).
132-138	It may not be possible to make all "major" manufacturing changes prior to phase 3, especially for programs working on accelerated timelines or rare diseases. Well-understood and characterized process changes such as scale-up or changing/adding manufacturing sites using the same manufacturing process during late-stage development should be a low risk if accompanied by a strong analytical comparability package.	We suggest clarifying and providing examples.
143-147	Please clarify whether this recommendation is for investigational products or for products in all stages of development. There may not be sufficient data to perform data trend and analyses for early development investigational products or in rare disease areas where few manufacturing batches are made.	We suggest revising the statement to: "For licensed products, we recommend that you ~~must~~ evaluate data at least once a year to determine if changes in product specifications or manufacturing or control procedures are needed to maintain the quality standards of the product, even when no manufacturing changes are undertaken (21 CFR 210.2, 211.180(e) and 601.2(d))."
B. **Stability and Delivery Device Compatibility**		
156-157	Please revise the wording to reflect significant changes that are expected to impact DP stability.	We suggest revising the statement to: "DP stability should be thoroughly assessed after changes to the container closure system, formulation, product concentration, **storage temperature** or shipping conditions **that could impact the stability profile of the DP**."
158-159	Examples of changes that could impact device compatibility should be included (e.g., formulation or DP concentration).	We request clarification by providing examples of manufacturing changes that would impact device compatibility

C. **Nonclinical studies**		
179-185	The level of detail in the nonclinical studies section is much less than that of other sections.	We request that FDA provide additional guidance on the use of nonclinical studies (i.e., animal and cell-based). It would also be helpful for FDA to provide examples of the types of changes it anticipates would require nonclinical studies. This is especially applicable given variation by modality type (e.g., in-vivo AAV, gene editing, ex-vivo LVV, CAR-T), and limitations to nonclinical study material throughout development. It would be helpful for FDA to provide an example where non-clinical evidence would suffice to support a post-approval change.
D. **Clinical studies**		
187-209	The draft guidance provides an emphasis on clinical studies in the absence of adequate analytical comparability data, or where variability is seen which may be inherent to some types of CGT products. However, there is a lack of guidance on how to judge whether and when analytical and/or nonclinical comparability studies are insufficient. For some types of CGT products, clinical studies may be complex; for this reason, it would be helpful for the guidance to provide more specific direction regarding the expectations for such data/studies.	We suggest adding some examples or typical cases where analytical and/or nonclinical comparability studies are insufficient, or providing a decision tree. We suggest retaining the constructive recommendations regarding considering " … broadening the scope of the adverse events of special interest, staggering enrollment of subjects, modifying study stopping rules, and conducting additional dose-finding studies." In general, when considering potential impact on product effectiveness, we suggest focusing on potency/bioactivity assays before escalating to *in vivo* studies (nonclinical or clinical).
231-233	If you wish to pool clinical data from subjects treated with the post-change product and subjects treated with the pre-change product, you should demonstrate that the products are comparable and justify that the clinical study designs are appropriate for pooling.	This paragraph would benefit from additional guidance on the aspects of clinical study designs (e.g., extrapolation criteria from previous clinical studies pre-change) to be considered to justify that the design is appropriate for pooling.
IV. Regulatory Reporting of Manufacturing Changes		
251-252	"Applicants must notify FDA of manufacturing changes through a BLA supplement or annual report in accordance with 21 CFR 601.12 (Ref. 6)."	We suggest revising the statement to: "For licensed products, applicants must notify FDA of manufacturing changes through a BLA supplement or annual report in accordance with 21 CFR 601.12 (Ref. 6)."

A. **CMC Changes Requiring a New IND Submission**		
255-257	"For amendments containing extensive changes, we recommend that you provide a "Reviewer's Guide" or a comprehensive summary of the changes in Common Technical Document (CTD) sections 1.2 or 1.11.1, respectively."	We request that FDA provide greater clarity on expectations for 'Reviewers Guide' or process summaries, and whether the Agency will support requests for discussion on submission and manufacturing change scope on a case-by-case basis, to align on the scope of the module 3 update. There is an opportunity to discuss these changes in flexible or novel meetings (e.g., Type D) to expedite development and limit the potential of a clinical hold. Please clarify for a licensed product if an M.2.3 section is acceptable rather than a Reviewer's Guide or 1.11.1 section.
265	"CMC Changes Requiring a New IND Submission"	It would be helpful if the Agency could provide modality specific examples, similar to pg. 11 of the January 2020 Guidance on "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)", where specific examples are provided for viral-based gene therapies, microbial-based gene therapies, and ex vivo genetically modified cell-based gene therapies. For commercial CGT products, post-approval changes to raw materials, starting materials, and manufacturing processes (Drug Substance and Drug Product) are routine as sponsors need to scale-up and/or scale-out processes to meet global demand. To expedite the change management process and associated regulatory filings, a post-approval guidance for viral-based gene therapies, microbial-based gene therapies, and ex vivo genetically modified cell-based gene therapies is needed to help align expectations across the Agency and with product sponsors. This may also help harmonize international expectations. We recommend that FDA hold an OTP CMC Town Hall and/or Listening Session with sponsors to better understand the challenges faced by sponsors when they need to conduct comparability. This could include work to streamline future filing approaches, potentially reducing the workload for Agency review staff. Based on the OTP Town Hall/Listening Session feedback, the Agency could define future steps

		to assure consistency in the C&GT post-approval space, including a guidance document, additional sponsor interactions, and/or regulatory convergence activities (WHO, ICH, etc.).
272-287	The draft guidance provides several examples of changes that could result in a new IND. However, there may also be changes that would not result in a new IND. In certain situations, a manufacturing change could alter the cell type ratio but not alter the types of cells within a cellular product.	We recommend that the final guidance acknowledge that some changes do not result in new IND. We request that consideration be given/and distinction be made in the guidance for early development stages where a change may be in line with the guidance "Studying multiple versions of a CGT product in an early-phase clinical trial." We request that the FDA clarify whether a separate IND needs to be filed for changes in expression control elements of a viral vector (e.g., change from a tissue-specific to a ubiquitous promoter, or vice versa). We request that the final guidance clarify if a manufacturing change results in a different ratio of cells in a post-change cellular product whether a new IND is inherently required and/or if the product is considered a new product. We suggest clarifying whether changes in ratios of the same scaffold components will also be considered a new product or only if alternative scaffold components are introduced. We suggest adding greater clarity on changes to the sequence of a transgene and expression control elements that would require a new IND. e.g., a change in the transgene that does not translate into the sequence but increases fidelity of transcription should be possible under the same IND; similarly for a control element where the new element enables increased efficiency targeting the same tissue. We suggest revising lines 275-276 to: "Change in the design of a cellular product to target different types of cells (e.g., mixture of CD4+ and CD8+ T cells instead of solely CD4+ T cells)."
B. **Reporting Manufacturing Changes to an IND**		
	There is a strong emphasis on circumstances likely to result in a clinical hold.	It would be useful to see some guidance on how developers can mitigate the risk of such holds.

306-310	The draft guidance states that an IND may be placed on clinical hold if evidence is not submitted to support acceptable safety of the post-change product. It is unclear if there are options for sponsors to avoid a clinical hold due to insufficient evidence of comparability by staying with the pre-change process, aside from seeking Agency feedback in a meeting, in which a definitive answer may not be given as to the acceptability of the change until review is complete.	While mechanisms to avoid a hold would not be limited to CGT products, clinical studies of CGT products may be more likely to be placed on hold due to the unique factors, such as those outlined in the background of the draft guidance. As such, details about any mechanisms FDA may be able to use to avoid imposing a clinical hold in the setting of insufficient evidence of comparability would be helpful to CGT product developers. For example, can sponsors request in the cover letter for an amendment regarding a proposed change to stay with the current pre-change process if the FDA does not determine the post-change product is comparable? This could help to encourage efforts for continuous improvements in product quality by providing a mitigation against a clinical hold, allowing sponsors to continue with the cleared pre-change process while gathering more evidence to support the change or making improvements to the change to address FDA concerns.
311-315	This text indicates that a toxicology study should be conducted which could be interpreted as an animal study. We recommend aligning with the other sections in the guidance and refer to using the broader terminology of "nonclinical study" as other nonclinical studies, such as in-vitro, in-silico, could also be applicable.	We suggest revising lines 311-315 to: "If these data do not allow for a conclusive determination that the manufacturing change has no adverse effect on product quality as it relates to safety, then you should consider performing a nonclinical study(ies) to evaluate whether the post-change product has an acceptable safety profile."
320-324	FDA should clarify that if a comparability protocol is submitted via an IND amendment requesting feedback, and the change has not yet been implemented, then a clinical hold will not be issued. As the change is not yet implemented, there is no risk to patient safety.	We suggest to either delete this or to clarify FDA's expectations in issuing a clinical hold for a protocol when implementation/supporting data have not yet been generated. If data are insufficient to establish comparability, then a clinical hold may be warranted, but not if the comparability protocol (which is not yet implemented) is deficient.
325-331	"If, for example, a phase 3 study intended to provide substantial evidence of effectiveness to support a BLA for a post-change product uses lots of both pre- and post-change product, but those products are not comparable, then the study may lack statistical	We suggest the Agency add the following sentence after "post-change products": "**Sponsors are encouraged to work with the FDA on an agreeable approach to progressing with a phase 3 study using both pre- and post- change product. Comparability protocols may be submitted as an amendment to the IND to gain alignment with**

	power to demonstrate effectiveness of the post-change product. Such a study may be considered clearly deficient in design to meet its stated objectives and placed on clinical hold if the IND submission does not provide evidence demonstrating comparability of the pre- and post-change products."	**the FDA on the study design prior to execution. The comparability study report should be submitted as a subsequent amendment**."
C. **Reporting Manufacturing Changes to a BLA**		
346-347	The text implies that annual report changes need to be supported by a risk assessment.	We suggest revising the statement to: "When reporting these changes, your supplement or annual report should include a risk assessment report **if appropriate**…" We propose using a risk-based approach for the inclusion of risk assessment report and studies performed to evaluate the effect of the changes on product quality, i.e., include for PAS and CBE-30; AR and CBE-0 information will be available upon request or available during inspection.
351-353	"To facilitate management of post-approval manufacturing changes, you may submit one or more comparability protocols to your BLA for FDA review, as described in 21 CFR 352 601.12(e)."	We suggest revising the statement to: "To facilitate management of post-approval manufacturing changes, you may **choose to** submit one or more comparability protocols to your BLA for FDA review, as described in 21 CFR 352 601.12(e)."
V. Comparability Assessment and Report		
381-383	"Further, to aid FDA review of your study, we recommend that you provide a short summary of your current relevant manufacturing and clinical experience."	It's not clear what information is requested here. We request greater clarity.
387	Manufacturing process consistency is usually only demonstrated in late development.	We suggest revising the statement to: "You should provide a summary of relevant previous manufacturing changes and their effect on process ~~consistency~~ **repeatability** and product quality."
391-392	"Comparability study reports should be submitted to CTD sections 3.2.S.2.6 or 3.2.P.2.3 of the BLA or IND, as appropriate"	We suggest revising the statement to**: "**Comparability study reports should be submitted to CTD sections 3.2.S.2.6 or 3.2.P.2.3 of the BLA or IND, as appropriate, **along with updates to other relevant quality**

	Could a detailed, comprehensive summary (including the data) be presented, if the sponsor/manufacturer did not want to generate reports geared toward submission in an IMA/BLA.?	**sections as appropriate."** We recommend considering an allowance for an appropriate summary, rather than a "requirement" for reports.
392-394	Reviewing the comparability results in scope of the totality of the drug product development may be challenging. While this is appropriate for some comparability strategies, it should not be a recommendation for all comparability study design and reports	We request that FDA provide clarification on "totality" of data.
396-399	Previously in line 360 it is stated that all predefined acceptance criteria must be met. If this is a distinction at different phases of product development, it should be stated directly.	We recommend revising the statement to: "…product quality attribute does not meet **or exceeds** the pre-defined acceptance criterion..." We recommend clarifying the apparent conflict with line 360.
A. Risk Assessment		
423-424	"Performing a thorough risk assessment, including consideration of method equivalence and CPPs, is essential when transferring a manufacturing process to a new facility."	We suggest revising the statement to: "Performing a thorough risk assessment, including consideration of method equivalence and **potential impact to** CPPs, is essential when transferring a manufacturing process to a new facility."
436	The term "more focused approach" for low-risk changes is unclear.	We request revising the statement to " Manufacturing changes that are determined to have a high risk to product quality should be supported by an extensive analytical comparability study, while it may be possible to evaluate low-risk changes using a more focused **analytical** approach or **justification by risk assessment alone**."
443-450	"…consider the potential impact of manufacturing changes…product quality."	Clarify at which clinical phase this is required
453	"Your risk assessment should also inform the statistical approach to comparability."	We request revising the statement to: "Your risk assessment should also inform the statistical approach to comparability **when sufficient amounts of data are available**."

		Some guidance for situations where quantity of data is limited for high-risk attributes would be useful regarding what type of assessment would be acceptable when statistical approaches provide low resolving power.
455-457	"Side-by-side or graphical presentations (such as dot plot) to allow visual comparison, in lieu of statistical analysis, may be sufficient for characterization of attributes at low risk of being impacted by a manufacturing change."	Revise the statement to "Side-by-side or graphical presentations (such as dot plot) to allow visual comparison, in lieu of statistical analysis, may be sufficient for characterization of attributes at low risk of being impacted by a manufacturing change, **or in cases where limited numbers of batches are available for pre-change product or post-change product and there are not enough data to perform a statistical analysis."**
464-465	"Finally, if multiple changes are to be implemented simultaneously, we recommend that you assess the risk of each individual change and the potential cumulative effect…"	It will be often the case that major process changes will be done simultaneously with offsetting effects so that the final product quality is comparable. It may be impossible to assess the individual impacts on all quality attributes and stability, certainly not at full scale. Emphasis on studying the cumulative effect in this case is preferred.
B. **Analytical Comparability Study Design**		
499-500	"A comparability study should generally be performed using lots that have been manufactured at full scale."	It is not clear whether "….at full scale" means the current scale (approved scale) or same scale (pre-/post-) or something else. We suggest providing more clarity on what is meant by 'full scale' and examples of when a scaled down model is not adequate or acceptable. .
512-513	"You should avoid biased selection of historical data."	We suggest revising the statement to: "You should ~~avoid biased~~ **select appropriate historical data sets and provide justification**. ~~selection of historical data"~~
519-524	This paragraph correctly notes that the number of lots available for CGT products may be insufficient to evaluate using the statistics discussed in section V.E but offers no guidance on how to handle this situation. For some CGT products, the number of lots may be very small due to, for example, limited	It would be beneficial to provide recommendations on non-statistical ways to assess comparability when data sets are unavoidably small. It is often not possible to increase the number of lots to obtain statistical power.

	manufacturing for rare disease indications, rapid development timelines during clinical studies, or difficulty obtaining cellular starting materials from an adequate number of donors. An insufficient number of lots could compromise statistical power and be insufficient to demonstrate comparability, particularly if there is high lot-to-lot variability, as discussed later in section V.E of this guidance.	
530-531	" The number of lots that might be used for such products to perform a statistically valid comparability study could be quite large, or even unfeasible."	We suggest revising the statement to: The number of lots that might be used for such products to perform a statistically valid **and sensitive** comparability study could be quite large, or even unfeasible."
540-541	We suggest that the Agency include the use of paired ratio, similar to statistical approaches for bioequivalence.	We suggest revising the statement to: "Paired difference **or paired ratio** analysis can be ~~is typically~~ performed."
587	Realistically, CGT developers and risk management strategy cannot always predict future manufacturing changes to estimate retain samples and vector lots to support comparability studies. Pragmatically, vector lots are prioritized for patients and clinical supplies.	We suggest revising the statement to: "**Where possible**, your risk management strategy..."
599-602	"For some products, animal models may be used to supplement a relevant quantitative assay(s) to demonstrate that the product has the desired biological effect and to provide supportive evidence for comparable biological activity of the pre-change and post-change product."	The use of animal models should be restricted to cases where no relevant quantitative assay(s) are available. Sponsors should be able to rely on relevant, quantitative functional assays for comparability assessment.
638	"An equivalence approach is often appropriate for evaluating comparability of CQAs"	We suggest revising the statement to: "**When sufficient data are available**, an equivalence approach **may be** appropriate for evaluating comparability of CQAs." The inherent variability of many CGT products,

		particularly cellular products, needs to be considered with any statistical analyses.
642-643	"Exceeding this margin would be interpreted as an adverse effect of the post-change manufacturing process on product quality."	This statement appears in conflict with prior statements regarding assessing adverse product quality changes, e.g., reduction of residual host cellular material. The example is very specific and may not be applicable for all scenarios. We suggest deleting.
662	In some cases, comparison of new process data to historical may be the primary justification for comparability (such as all new process data falls within existing process/clinical history), especially in cases where the connection between the magnitude of a change's impact to product quality is not clearly defined.	Add clarification regarding use of historical pre-change data.
C. Analytical Methods		
675-728		We request that the Agency provide additional guidance on method accuracy in addition to method precision.
D. Statistics		
742-814		We recommend reorganizing this section for clarity, such as including a decision tree on how which type of statistical method would be used in what situations.
762	Instead of transformations, the use of generalized linear models or generalized linear mixed models would allow for the direct computation of parametric tests for distributions other than normal, like binomial, beta, log normal and gamma.	We suggest revising the statement to: "…transformation could be useful to meet the assumption of data normality. **Statistical approaches that do not require the assumption of normality could also be used with justification."**
779-786	This section provides the only practical suggestion for cases when there are a limited number of lots. There are statistical methods for treating repeated measures data beyond simply taking the mean. If they give us more power or a	It would be beneficial to include an example to illustrate how to assess and decide on how many replicates values are required. We recommend that the text be replaced by the following: "In this case, it is inappropriate to treat each individual assay result as an independent data point in the comparability analysis, and

	better evaluation of comparability, these should be available is appropriate and pre-specified	appropriate statistical methods for repeated measures data should be prespecified and employed."
788-791	We suggest that the Agency include the use of paired ratio.	We suggest revising the statement to: "For studies that compare two cellular manufacturing processes using split-donor starting material, the product data from each donor are paired. In such cases, you could select a statistical test suitable for analysis of the difference between paired data or **a statistical test suitable for analysis of the ratio between paired data**, rather than a test that assumes an independent data structure."
792-808	In general, we agree with the statement that "The absence of a statistically significant difference between the pre- and post-change products (e.g., p-value > 0.05) does not demonstrate comparability. Indeed, a more appropriate procedure for testing comparability (of the means) is the TOST procedure. In addition, the draft guidance seems to encourage the use of the TOST even when sample sizes are small (where inferential statistics may not be appropriate).	We suggest adding guidance on how the equivalence margin (e.g., maximum allowable difference) can be pre-specified when historical data is sparse. Also, we suggest revising lines 803-804 to: "…the CQA of interest is a mean value, you may consider using **an approach based on concepts** for the 'Two-One-Sided Tests procedure' (TOST) or other appropriate statistical method to establish..."
810-813	We suggest rewording of the text for clarity	We suggest revising the statement to: "The lots selected for the comparability study should be representative of your typical manufacturing process to ensure corresponding results will have meaningful interpretation, regardless of the particular statistical methodology applied."
815	We recommend adding additional statistical examples	We suggest adding the following points: • Comparability of pre- and post-change lots may also be evaluated using Bayesian methods by constructing probability intervals for means or difference in means, as well as predictive intervals for future batches. • For quality ranges, various methods can be used to construct statistical intervals based on the distribution of the data (or the

		transformed data) such that the post-change results can be compared to expected values from the pre-change process.
VI.	**Special Considerations for Tissue-Engineered Medical Products**	
850-855	The draft guidance describes that "certain changes may have a significant impact on how the DP behaves after administration in terms of safety and performance, and therefore on product quality." The draft guidance then advises to "assess the potential impact of the change on product quality post-administration (e.g., remodeling, degradation)." It appears based on wording in the draft guidance that performance is a distinct concept from biological activity and safety (although it may impact them) and is related more closely to stability (e.g., remodeling, degradation), but it is not clear if there is a broader definition.	A definition of performance should be given or examples should be provided to clarify the Agency's thinking around product performance with respect to comparability. For instance, ICH Q8(R2) gives examples of stability and bioavailability for drug product and also describes product specifications as being based on the desired product performance.