INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

13 November 2023

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Re: Docket No. FDA-2023-D-2436, Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry

To whom it may concern:

The International Society for Stem Cell Research (ISSCR) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance for Manufacturing Changes and Comparability for Human and Cellular Gene Therapy Products.

The ISSCR is an independent, global, nonprofit organization that promotes excellence in stem cell science and applications to human health. ISSCR represents 4,700 scientists, educators, ethicists, and business leaders across 80 countries. Our vision is a world where stem cell science is encouraged, ethics are prioritized, and discovery improves understanding and advances human health.

ISSCR commends FDA's desire to share their current thinking on management and reporting of manufacturing changes for CGT products based on a life-cycle approach, and comparability studies to assess the effect of manufacturing changes on product quality. Additional guidance from the FDA will help our members, who are at the forefront of research and innovation, in their work. To complement FDA's initiatives and foster progress in this field, we offer the following comments and recommendations:

I. General Comments

1. **Document structure and organization.** ISSCR suggests that FDA make two adjustments to the document's structure: 1) group the Risk Management section closely with the Comparability Assessment and report; and 2) incorporate Risk Assessment into the Risk Management section. We believe that implementing these changes would improve the clarity and readability of the document by enhancing the cohesion among closely related topics.

2. **Specific Considerations for Different Therapies.** ISSCR requests that FDA clarify the distinctions between different cell and gene therapies. Moreover, ISSCR urges FDA to highlight specific manufacturing and comparability considerations for each type, including gene-modified cell therapy, viral vector/gene-edited hematopoietic stem cells, and induced pluripotent stem cells derived. We recommend adding a dedicated section towards the end to address these differences.

3. **Provision of Examples.** ISSCR also requests that FDA include examples throughout the document especially in demonstrating in vitro testing sufficiency for comparability and outlining required preclinical and clinical testing for comparability. Offering examples

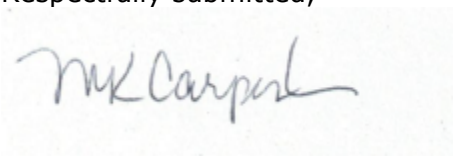
is essential to establish clear standards for meeting the FDA's expectations in terms of understanding and implementing the guidance requirements.

4. **Defining and Achieving Comparability**. ISSCR requests that FDA provide a clear definition of the term "comparable" and discuss the consequences of failure to statistically "pass" comparability, outlining specific outcomes. ISSCR also requests the provision of clear guidelines to address cases when additional nonclinical studies might or might not be required. Additionally, ISSCR urges FDA to provide principles for evaluating product development with small clinical trial populations and manufacturing batches, emphasizing the impact of science-based decision-making on demonstrating comparability. Lastly, we offer the following suggestions to help in clarifying the expectations for comparability at different stages of clinical development:
    a. A table can be created to outline the level of comparability required based on the different stages of development, emphasizing phase-appropriate changes.
    b. A section can be added to describe the expectations for comparability concerning identity, strength, quality, purity, and potency.

5. **Frequently Asked Questions (FAQ) Document.** ISSCR recommends that FDA generate a FAQ document to address questions arising from the draft guidance. We understand that not all comments and suggestions will be addressed in the final guidance, having an FAQ document could be valuable. It can effectively address recurring questions without the need to incorporate them directly into the final guidance while still ensuring clarity and understanding for stakeholders.

Thank you for considering our views on the draft guidance for Manufacturing Changes and Comparability for Human and Cellular Gene Therapy Products. If the ISSCR can clarify any of these views or be of assistance, please contact Tyler Lamb, ISSCR's Director of Policy at tlamb@isscr.org or Denise de Villa, ISSCR's Manager of Policy at ddevilla@isscr.org.

Respectfully submitted,



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Chair, Manufacturing, Clinical Translation, and Regulatory Committee

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II. Specific Comments

Section (Line)	Issue	Proposed Change
II. Background		
46 – 49	The draft guidance indicates that improved product quality is desirable, but 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." The definition of significant as it applies to benefit is unclear. While examples like increased purity have been given, it is concerning that such improvements could inadvertently classify the product as a 'new product. This may disincentivize manufacturers from providing improved treatments to their patients since doing so means the manufacturer may not be able to rely on previous data or experience to support the use of the product.	ISSCR requests clarification on the definition of "significant benefit."
132 – 134	The draft guidance states: ". . . we recommend that any extensive manufacturing changes be introduced prior to initiating clinical studies that are intended to provide evidence of safety and effectiveness in support of a BLA." This statement could have broad and unintended implications. For rare diseases with limited patient population this implies that a commercially viable manufacturing process should be in place prior to initiation of the first study, since it will likely provide "evidence of safety and effectiveness in support of a BLA."	ISSCR requests that FDA dedicate a section to discuss manufacturing challenges with respect to rare diseases and accelerated approval.

III. Considerations for the Management of Manufacturing Changes		
B. Stability and Delivery Device Compatibility		
156 – 157	Drug product stability should be thoroughly assessed after changes to the container closure system, formulation, product concentration, or shipping conditions.	ISSCR requests that FDA describe alternate options for autologous products where sufficient material does not exist to conduct comprehensive stability studies – what criteria should be considered when designing an autologous product study that has material constraints?
C. Nonclinical Studies		
183 – 185	The draft guidance states: "If analytical studies alone are insufficient to determine the impact of the manufacturing changes on CGT product quality, then nonclinical studies may contribute to a demonstration of comparability."	ISSCR requests that FDA include precautions about the overall usefulness/relevance of animal models for CGT products (separate from classic PK/PD small molecule benefits) for evaluating dose/efficacy, in particular. ISSCR requests that FDA provide examples of nonclinical studies that may contribute to demonstrating comparability.
D. Clinical Studies		
200 and 238	What is the rationale for including *Investigational Products* and *Licensed Products* under Clinical studies section?	
210 – 222	The draft guidance states: "If comparability studies demonstrate that the manufacturing change does not adversely affect product safety but are insufficient to exclude an adverse impact on product effectiveness, then the sponsor will need to evaluate the effectiveness of the post-change product in clinical studies to support a BLA for the post-change product." It is unclear when and in what situations this would happen in the application. Moreover, can *Investigational Products* and *Licensed Products* be sufficiently disassociated?	ISSCR requests that FDA provide examples of what data would indicate no effect on safety but insufficient to support efficacy, such that another clinical study would be required.

218 – 222	The draft guidance states: ". . . evidence demonstrating a prospect of direct benefit of a pre-change investigational CGT product to pediatric subjects, as required for studies conducted in accordance with 21 CFR 50.52, may not be adequate to demonstrate prospect of direct benefit with respect to the post-change product."	ISSCR requests that FDA clarify how the direct benefit requirement for pediatric studies differs from evaluating the impact on effectiveness as part of comparability analysis.
233	The draft guidance states: ". . . justify that clinical study designs are appropriate for pooling."	ISSCR requests that FDA provide examples of the kinds of designs that are appropriate for pooling.
IV. Regulatory Reporting of Manufacturing Changes		
A. CMC Changes Requiring a New IND Submission		
265	Can it be concluded that if the comparability assessment is supportive then the example changes could be implemented, and product manufactured via the new method would not be considered a new product?	ISSCR requests that FDA provide examples for cases where the specified criteria are met, but the product is not considered new. Conversely, provide examples for situations where the same criteria are satisfied, resulting in the product being categorized as new.
273 – 287	The examples provided focus on somatic cell sources.	ISSCR requests clarification on the impact of changing PSC cell lines used as starting material for cell products.
273 - 274	The draft guidance states: "Change in the cellular starting material of a cellular product (e.g., allogeneic vs. autologous donor; adipose-derived cells vs. umbilical cord-derived cells)" It is unclear whether this change in cellular starting material is also applicable when considering the specificity of the treatment type, specifically in the context of iPSC banking.	ISSCR requests that FDA elaborate what constitutes a change in starting material for iPSC.
286 – 287	The draft guidance states:	ISSCR requests clarification on whether individual guides to target distinct mutations in the same gene each warrant a new IND submission. We also suggest

	"Change of target gene for genome editing products, including addition of a target gene" Is targeting a different mutation within the same target gene basis for a new IND?	that FDA provide a criterion for defining comparability when switching guides.
B. Reporting Manufacturing Changes to an IND		
306	The standard for determining whether a manufacturing change has the potential to adversely affect safety is unclear.	ISSCR requests that FDA provide examples of specific manufacturing changes that the Agency believes has the greatest potential to adversely affect safety.
310 – 311	There is no distinction between analytical comparability and other analytical data relevant to safety.	ISSCR requests that FDA provide examples of analytical data relevant to safety.
310-312	The draft guidance states: "Evidence may be provided as an amendment. . . If these data do not allow for conclusive determination"	ISSCR suggests removing "conclusive" as it is not clear what the difference is between a conclusive determination and a regular determination.
335 – 336	It is unclear whether, even if a comparability study shows consistent results, there might still be cases where the change is considered to potentially impact the product's effectiveness.	ISSCR recommends the following edit: "If you make a manufacturing change that could adversely affect the effectiveness of the investigational product ~~without demonstrating~~ **and do not demonstrate** comparability, then the **benefit/risk assessment** ~~capacity~~ of the post-change product ~~to provide a potential benefit to subjects~~ **may change** ~~be in doubt~~."
V. Comparability Assessment and Report		
364	Raw materials frequently change labels, and it would be helpful to understand which modifications would require a comparability study. For instance, if the ingredients of the raw material remain unchanged or are altered to be less xenogenic or purer, is a comparability study necessary, or would a risk assessment suffice?	ISSCR suggests that FDA create a flow chart or decision tree describing how to assess changes implemented to improve product quality that could lead to a change in effectiveness or safety would be helpful.

396 – 399	The draft guidance states that, "if a product quality attribute does not meet the pre-defined acceptance criterion for comparability, but you still consider the pre- and post-change products to be comparable, you should provide justification and/or additional scientific information..." It is unclear what level of additional information is required to deem process changes to be comparable.	ISSCR requests that FDA provide guidance on what additional information is needed for a complementary data package, including the relevance/importance placed on the use of nonclinical study data as part of the overall comparability package.
A. Risk Assessment		
401	The draft guidance discusses Risk Assessment towards the end of the document, but there is extensive discussion in the beginning and middle of the document where they reference the analytics being utilized. It would enhance the quality of the analytics requested if there were detailed descriptions in those sections.	ISSCR requests that FDA provide information about the quality of analytics used for release, in-process and characterization testing should be included.
431 – 435	The draft guidance states: ". . . assign a score to each attribute based on the probability, severity, and detectability of the risk. The assigned score can be used to determine the overall risk for each attribute. 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 approach." This statement is vague and may lead to under or over estimating risk.	ISSCR requests that FDA provide a table of low-risk and high-risk manufacturing practices. This framework would help standardize the rating system requested.
441 – 444	Requesting additional comparability data, beyond what is essential for ensuring the safe release of a product batch, appears excessive. It extends beyond the requirements for establishing product quality, encompassing aspects such as identity, strength,	ISSCR requests that FDA provide examples of quality attributes that are not regularly assessed through release tests and process controls. Alternatively, specifying what additional comparability data is required

	quality, purity, and potency. Clarifying the specific necessity for this additional data could improve the process and ensure a more efficient quality assessment.	beyond what is necessary for product release would also be helpful. ISSCR also request that FDA provide examples of additional characterization studies. .
453 - 455		ISSCR requests that FDA provide examples of statistical approaches that would apply to higher risk attributes.
B. Analytical Comparability Study Design		
490 – 492	See above comment. (L. 441 – 444) The draft guidance states: "To adequately evaluate the impact of the manufacturing change on product quality, a comparability study will frequently need to include measurement of attributes that are not routinely used for product release."	See above comment. (L. 441 – 444) ISSCR requests that FDA specify whether "attributes that are not routinely used for product release" are the same as characterization data.
499 – 500	The draft guidance states: "A comparability study should generally be performed using lots that have been manufactured at full scale." The interpretation of "full scale" varies based on the stage of development. It would be beneficial to provide a clear explanation or definition for the term to avoid confusion and ensure consistent understanding and application.	ISSCR requests that FDA provide an explanation or definition of the term "full scale." Many comparability studies will be conducted to assure no change in safety/efficacy during scale up from lots used in nonclinical or early clinical development to those used in registrational studies.
522 – 524	The draft guidance states: "An insufficient number of lots could compromise statistical power and be insufficient to demonstrate comparability"	ISSCR requests that FDA provide recommendations on how to design studies that account for the limitations of small sample sizes, which are not uncommon, and that will not reach the multiples necessary to achieve statistical power.

566	The draft guidance states: "GT vectors used for ex vivo cell modification *must* be manufactured in compliance with good manufacturing practices…" However, the FDA GFI for Human Gene Therapy Products Incorporating Human Genome Editing, does not mandate the use of specific vectors in ex vivo cell modification. Thus, the requirements of the two documents do not match up perfectly. Aligning these guidelines could enhance clarity and ease of application.	ISSCR suggests removing the term "must" in the guideline to align with the FDA GFI for Human Gene Therapy Products Incorporating Human Genome Editing.
611 – 614	The draft guidance states: ". . . we recommend that samples be retained from all lots to facilitate future analysis of potency to support comparability."	ISSCR requests that FDA provide recommendations on how to implement potency testing for fresh products when determining the correct assay(s) is hampered by the understanding of MOA versus safety and effectiveness. Retention of samples for testing is not always possible for fresh products since freezing or otherwise storing DP inherently changes the product, rendering testing suspect.
E. Statistics		
771 – 775	The draft guidance states: ". . . appropriate number of lots should be considered early. . . lack of sufficient numbers of samples may impede comparability analysis. . . "	With products used to treat rare diseases or where product consumption for treatment is minimal versus batch size, a limited number of products will be manufactured – consider a separate section in the guidance dedicated to comparability studies that rely on limited numbers of product lots
VI. Special Consideration for Tissue-Engineered Medical Products		
816	These products are highly complex, with limited availability for conducting comparability assessments with significant statistical power. It may be beneficial to address this topic in a separate GFI.	ISSCR suggests removing this section from this GFI. Instead, we recommend that FDA consider drafting a GFI on the development of tissue-engineered medical products, which includes a section on comparability.