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Client Alert

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FDA's Much Anticipated New Cell and Gene Therapy Guidance Outlines a Conservative Approach to Manufacturing Changes

Biologics have long been defined by their processes, raising complicated questions about how to assess the effect of manufacturing changes on product quality[1]—*i.e.*, whether pre- and post-change products are comparable. This issue is particularly acute for cell and gene therapies ("CGTs"), which are often characterized by complex manufacturing processes, limited knowledge of product quality attributes, variable starting materials, and more.

At the same time, small-scale production can necessitate multiple changes in short order, and the commercial viability of CGTs, particularly for rare diseases, may hinge on the ability to nimbly update manufacturing processes for these products. As Dr. Peter Marks, Director of the Food and Drug Administration's ("FDA" or the "Agency") Center for Biologics Evaluation and Research has explained, the goal is for CGT manufacturers to "spend most of the time worrying about the actual constructs … and less time [worrying] about the manufacturing."[2] Dr. Marks has suggested that advances in manufacturing might be the answer to this problem, likening ultimate gene therapy platform technologies to soda dispensers, "very much like one of these Coke dispensers that can make 100 or 1,000 different Cokes."[3]

The Agency seemed to move in a slightly more conservative direction than these comments may have implied when it published a Draft Guidance for Industry, Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products ("*Draft CGT Changes Guidance*").[4] The *Draft CGT Changes Guidance* echoes many of FDA's longstanding positions regarding comparability, but with a specific focus on CGT products and a distinctly conservative flavor. The guidance fulfills a promise to focus in on FDA's thinking regarding the management and reporting of manufacturing changes for CGTs, but its warnings against

manufacturing changes and suggestion that FDA may require clinical studies for changes to CGTs may end up compounding difficulties scaling up CGT manufacturing.

FDA'S CAUTIOUS APPROACH TO CGT CHANGES

In 1996, FDA issued its Guidance, Demonstration of Comparability of Human Biologics Products, Including Therapeutic Biotechnology-derived Products ("*1996 Comparability Guidance*"), which recognized the historic difficulties with characterizing many biologics, while also acknowledging that advances in analytical testing and improvements in production methods meant that clinical trials will not always be needed to demonstrate product comparability.[5]

As with biologics of 30 years ago, today's analytical methods have not fully caught up with CGTs, resulting in unique challenges related to CGT manufacturing changes, as recognized in the *Draft CGT Changes Guidance*.[6] FDA cautions, therefore, that CGT manufacturers that seek to implement manufacturing changes should proceed by balancing the potential need for changes against the "risk that a manufacturing change may adversely impact product quality."[7] For example, according to FDA, "while improvement of product quality is always desirable and encouraged," if an improvement would significantly change the product, the result of an improvement in safety or effectiveness could be the creation of a "different product[]" that is "not comparable."[8]

ASSESSING RISK FOR CGT MANUFACTURING CHANGES

FDA's recommended approach to risk assessment for CGT products echoes that for most biological products. The *Draft CGT Changes Guidance* recommends that the risks be assessed before designing comparability studies. As clinical and product development progresses to later stages, so does the extent of the analytical evaluation needed to adequately assess a manufacturing change, which should be supported by knowledge of critical quality attributes ("CQAs"), accumulated manufacturing experience, and further understanding of the mechanism of action ("MOA"). If the manufacturer's risk assessment indicates that a proposed change may adversely affect product quality, FDA recommends that the manufacturer perform comparability studies to evaluate the impact of the proposed manufacturing change.[9]

The guidance veers to the conservative when describing the kinds of studies that may be able to support manufacturing changes for CGT products. For biologics generally, FDA has accepted that comparability studies may be heavily analytical, and may not require clinical studies at all.[10] However, because some CGTs may be difficult to "fully characterize" based solely on analytical methods, the *Draft CGT Changes Guidance* explains that FDA may require clinical studies to the extent that nonclinical data cannot fill any such gaps.[11]

A "LIFECYCLE APPROACH" TO MANUFACTURING CHANGES

In the context of licensed products, FDA emphasizes that if comparability cannot be demonstrated by analytical, nonclinical, and/or pharmacokinetic and pharmacodynamic ("PK/PD") data, FDA will not approve a manufacturing change. Alternative approaches, such as a new clinical study with the post-change product, will be considered on a case-by-case basis.[12]

Importantly, FDA's thinking on this point, which departs from the *1996 Comparability Guidance* with its suggestion that, for CGT products, comparability is more likely to require clinical data, applies to both licensed and investigational products.[13] The Agency notes that not only will changes to approved products need to go through the rigorous change process outlined in the *Draft CGT Changes Guidance*, but also that sponsors of investigational CGTs will need to provide "sufficient" chemistry, manufacturing, and control ("CMC") information to assess impacts on product safety, identity, quality, purity, and strength.[14] FDA explains that CGT product manufacturers should "ensure that the pace of product development is aligned with the stage of clinical development" (*e.g.*, initiating clinical studies using a product generated by a manufacturing process designed for scalability).[15]

For changes to investigational products impacting safety, the *Draft CGT Changes Guidance* explains that if analytical and nonclinical data is insufficient to assure against adverse impacts from the manufacturing change, the sponsor should consider conducting new clinical studies and/or incorporating additional safeguard measures and safety evaluations in their ongoing clinical studies (*e.g.*, broadening the scope of adverse events of significant interest, staggering enrollment, modifying stopping rules, or conducting additional dose-finding studies).[16] For changes impacting efficacy, if comparability studies are insufficient to exclude an adverse impact on effectiveness, 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," prompting another warning from FDA that sponsors should "critically evaluate" implementing manufacturing changes with the potential to affect effectiveness after the initiation of studies intended to provide substantial evidence of effectiveness.[17]

According to the *Draft CGT Changes Guidance*, undertaking manufacturing changes for investigational products later in product development "without adequate comparability data" can result in a clinical hold.[18] The guidance explains that a negative impact on efficacy could be the basis for a clinical hold in the absence of comparability data, because it might be evidence of a study that is clearly deficient in design to meet its stated objectives, *e.g.*, it lacks adequate statistical power to demonstrate effectiveness because it includes pre-change product. Similarly, such a study may expose subjects to an unreasonable and significant risk of illness or injury, as there may be insufficient reason to believe that the post-change product could provide a clinical benefit.[19] And, for certain pediatric studies, even evidence demonstrating a direct benefit from the pre-change product may not be adequate to support a post-change product.[20]

The *Draft CGT Changes Guidance* also emphasizes that pooling data across clinical trials using products manufactured with different processes will require a sufficient demonstration of comparability. The Agency recommends that sponsors seek FDA's advice on the design of any pooled analysis, preferably before conducting last-phase studies.[21]

REPORTING MANUFACTURING CHANGES

The *Draft CGT Changes Guidance* emphasizes the obligations of Investigational New Drug Application ("IND") sponsors and Biologics License Application ("BLA") holders to notify FDA of manufacturing changes.[22] For licensed products, FDA reiterates that when reporting manufacturing changes, the supplement or annual report should include a risk assessment and data from appropriate studies to evaluate the effect of the change on product quality.[23]

For investigational products, the guidance contends that certain changes are simply not appropriate for an IND amendment.[24] For example, changes that can "fundamentally alter the design or nature of the product" result in a new product, requiring a separate IND, as do changes in the cellular starting material (*e.g.*, allogenic versus autologous donor), changes in a viral vector capsid or envelope that changes the tropism or serotype of a viral vector used for *in vivo* gene therapy, and changes in the target gene for genome editing products, including addition of a target gene.[25] For manufacturing changes that do not warrant a new IND, the *Draft CGT Changes Guidance* explains that manufacturing changes that could affect product quality are "essential information" that must be submitted in an information amendment to the IND prior to use of the post-change product in clinical investigations.[26]

COMPARABILITY ASSESSMENT AND REPORT

The *Draft CGT Changes Guidance* contains broad and general advice to consider when designing a comparability study and analyzing comparability data. In general, the guidance reminds the reader that, due to the complexity of these products, the effects of manufacturing changes can be difficult to predict, so a thorough understanding of the product, process, and analytical method performance is necessary to properly evaluate the risk of changes.[27]

This begins with the risk assessment. As described above, FDA cautions that, although the process and tools for conducting a risk assessment for a CGT manufacturing change may be similar to those for other types of drugs,

conducting the assessment may be more challenging for CGT products, and more extensive comparability data may be needed (particularly where there are gaps in product knowledge that raise risk levels). Critically, the guidance emphasizes that relying exclusively on release and process testing is not enough to evaluate the impact of a manufacturing change.[28] Instead, the guidance recommends evaluating additional attributes, the need for further characterization studies, and, for changes that may affect high risk attributes, the potential use of more than one assay to measure the attribute.[29] The guidance also emphasizes that when multiple changes are to be implemented simultaneously, the risk assessment must evaluate both the individual and potential cumulative effects.[30]

The risk assessment will also inform the study design, including the selection of the relevant set of quality attributes, appropriate test methods, and the comparability acceptance criteria.[31] In particular, factors that should be considered when designing a comparability study include:

- **Selection of Product Lots.** Comparability studies should generally be performed using lots that have been manufactured at full scale and with a sufficient number of lots to ensure adequate statistical power. FDA recognizes that these recommendations are not always feasible for CGT product developers, as the number of lots may be very small due to limited manufacturing for rare diseases, rapid development timelines during clinical studies, or difficulty in obtaining cellular starting material from adequate donors—but still notes that an insufficient number of lots may render the study inadequate to demonstrate comparability. For pre-change product lots, reliance on historically-generated data may be acceptable, presuming equivalency in analytical methods;[32] it seems likely, however, that FDA would expect sample reanalysis given the Agency's view that such methods often change during CGT product lifecycle.[33]
- **Special considerations for product derived from variable cellular starting material.** Given inherent variability in these products, the number of lots required for a statistically valid comparability study could be very large, or even infeasible. The *Draft CGT Changes Guidance* provides some recommendations to address this limitation, including using a split-source study design or a scientifically-justified wider acceptance criteria (*e.g.*, when there is sufficient knowledge that CQAs can vary widely without an adverse impact on product quality). FDA also acknowledges the possibility of using alternative cellular source material (*e.g.*, from healthy donors), if scientifically appropriate.[34]
- **Special considerations for vectors used for *ex vivo* cell modification.** CGT product developers must carefully evaluate manufacturing changes of gene therapy vectors on the quality of not just the vector but also the *ex vivo* gene-modified cells. Given the difficulties in implementing vector manufacturing changes, which "can cause delays in clinical studies or shortages in licensed products," FDA recommends a risk management strategy that ensures sufficient vector lots will be available for future comparability studies.[35]
- **Assessment of potency.** The Agency recommends assessing potency using analytical methods, which, for some products, may be supplemented with animal models. However, the *Draft CGT Changes Guidance* notes that CGT products have multifaceted MOAs, which complicate the development of assays to measure relevant biological activities of CGT products. Because potency assays are generally developed in later clinical stages, FDA recommends retention of samples from all lots to facilitate future potency comparisons.[36] The guidance does not clarify whether such retention would be in addition to existing requirements for retain samples per lot. Accommodating additional retain samples may present a challenge for sponsors of products for which yield is critical for efficacy, such as some cell therapy products that have sourcing limitations. The guidance, however, does not offer advice for these situations.
- **Comparability acceptance criteria.** The measurements from CQAs need not always be identical pre- and post-change, but the acceptance criteria should be defined prior to initiating the study. Whether a quality range or

equivalence margin approach is used will depend on the risk of the change, with equivalence margins generally used for higher risk changes.[37] The Agency also notes that the criteria should "ideally" be based on understanding the potential effect of the attribute on the safety and effectiveness of the product[38]—though it is challenging to reconcile that recommendation with the guidance's emphasis that CGT product manufacturing changes can have unpredictable effects on CQAs.[39] Potentially in recognition of this tension, the *Draft CGT Changes Guidance* acknowledges that the acceptance criteria can be based on a statistical analysis of historical, pre-change data, presuming adequately justified.[40]

The *Draft CGT Changes Guidance* emphasizes that interpretation of the comparability test results depends on the suitability of the analytical methods used. FDA references its existing, generally applicable guidance to assist with assay validation,[41] but also identifies what it perceives as specific challenges for CGT products, *e.g.*, the importance of analytical method precision given the potential for small changes to have a "profound" impact on quality.[42] The guidance underscores that, consistent with comparability for all biological products, appropriate statistical methods should be used to assess comparability and such methods should be predefined. Similar to the challenges with designing a comparability study for CGT products, the guidance emphasizes the difficulties with selecting a statistical approach when there are limited numbers of samples, quality attributes are highly variable, and/or data is not normally distributed.[43]

SPECIAL CONSIDERATIONS FOR TISSUE-ENGINEERED MEDICAL PRODUCTS ("TEMPS")

The *Draft CGT Changes Guidance* includes a section devoted exclusivity to TEMPs, which commonly incorporate viable cells and scaffolds, with cells either seeded onto the scaffold's surface or embedded within the scaffold. As explained by FDA, even more so than with other CGTs, there exists limited understanding of TEMPs' product quality, posing additional challenges for manufacturing changes. The guidance provides additional recommendations for conducting risk assessments and evaluating manufacturing changes, including expectations for evaluating the impact of manufacturing changes on the drug product (even if a manufacturing change is made only to the scaffold or cells, prior to combining the components) and on product quality post-administration.[44]

OUR ANALYSIS

Manufacturing changes for CGT products certainly raise complicated scientific issues, and many of the potential work-arounds (such as leveraging platform technologies in BLAs) raise difficult legal issues, to boot. Even so, the approach outlined in the *Draft CGT Changes Guidance* risks effectively freezing the manufacturing process—or, for some products, elevating the bar for manufacturing changes past the point of commercial viability. Indeed, the guidance's recommendation to align manufacturing changes with clinical trial timing disregards the reality that CGT developers cannot always predict these changes in advance. Similarly, FDA's recommendations on retention samples lack practical applicability, given that patients often need as many cells as they can get.

Of additional note, FDA's approach could end up deterring incremental *improvements* in CGT product safety and effectiveness.[45] For example, FDA acknowledges that, consistent with other biological products, stability and/or delivery device comparability studies may be needed to assess the effect of a manufacturing change on product quality.[46] However, in focusing on CGT products in particular, the Agency notes they are often frozen for significant periods of time, and their shelf life must be based on real-time stability data obtained at the long-term storage condition—accelerated stability studies will not suffice. Applicants seeking to make manufacturing changes—regardless of whether they could enhance product quality—are thus warned that "[g]enerating real-time long-term stability data can delay product development, especially when manufacturing changes that have the potential to adversely affect stability are implemented during late stages of product development."[47] Indeed, generating the

necessary data to support a post-licensure change "could severely delay the implementation of the manufacturing change."[48]

Although the guidance seems conservative in the recommendations presented, the underlying theme seems to be "if you cannot meet these recommendations, reach out to us for discussion." Of course, as the guidance points out throughout the document, these discussions should be data driven.

It will be particularly important for CGT firms to carefully review the *Draft CGT Changes Guidance*, and to submit comments to FDA before the comment period expires on September 12, 2023.

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King & Spalding LLP regularly counsels biologics companies on all issues related to cell and gene therapies. Please let us know if you have any questions or concerns regarding this draft guidance, or if we can be of any assistance developing your comments.

[1] As applicable here, "product quality" refers to the identity, strength, quality, purity, and potency of a product, as these factors may relate to the safety and effectiveness of the product. *See* 21 C.F.R. § 601.12; *see also* U.S. Food & Drug Admin., *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products* at 1 n.5 (July 2023), *available at* https://www.fda.gov/media/170198/download.
[2] Jonathan D. Grinstein, *Peter Marks Outlines FDA's Commitment to Advancing Gene Therapies*, GEN (Oct. 13, 2022), *available at* https://www.genengnews.com/gen-edge/peter-marks-outlines-fdas-commitment-to-advancing-gene-therapies/.
[3] Derrick Gingery, *Could US FDA Move Gene Therapy Regulation To Device Center In Years To Come?*, PINK SHEET (Nov. 25, 2022), *available at* https://pink.pharmaintelligence.informa.com/PS147228/Could-US-FDA-Move-Gene-Therapy-Regulation-To-Device-Center-In-Years-To-Come.
[4] Notice of availability, Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry; Availability, 88 Fed. Reg. 45,222 (July 14, 2023).
[5] *See generally* U.S. Food & Drug Admin., *Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products* (1996), *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstration-comparability-human-biological-products-including-therapeutic-biotechnology-derived.
[6] *See Draft CGT Changes Guidance* at 2 (referring to management of CGT product manufacturing changes as "more challenging").
[7] *Id.*
[8] *Id.*

[9] *See id.*
[10] *See 1996 Comparability Guidance* § 2.
[11] *See Draft CGT Changes Guidance* at 2.
[12] *See id.* at 6.
[13] *See id.* at 2, 5-6.
[14] *See id.* at 3.
[15] *Id.* at 4.
[16] *See id.* at 6.
[17] *See id.*
[18] *Id.* at 2.
[19] *See id.* at 8-9.
[20] *See id.* at 6.
[21] *See id.*
[22] *See id.* at 7 (For BLA holders, referencing 21 C.F.R. § 601.12(a)(2) and for IND sponsors, referencing 21 C.F.R. § 312.23(a)(7)(i).).
[23] *See id.* at 9.
[24] *See id.* at 7 (referencing 21 C.F.R. § 312.20).
[25] *Id.*
[26] *See id.* at 8.
[27] *See id.* at 10.
[28] *See id.* at 11 ("Please note that relying solely on established release tests and in-process controls is generally insufficient to assess the impact of manufacturing changes.").
[29] *See id.* This seems particularly advisable if the method has limitations, and aligns with FDA's advice elsewhere in the guidance regarding the use of "several analytical methods" to assess potency if the routine assay is imprecise or otherwise lacking in ability to measure all aspects of a product's MOA that could be affected by the change. *See id.* at 14-15.
[30] *See id.* at 10-12.
[31] *See id.* at 12.
[32] *See id.* at 12-13.
[33] *See id.* at 17.
[34] *See id.* at 13-14.
[35] *See id.* at 14.
[36] *See id.* at 14-15.
[37] *See id.* at 15-16.
[38] *See id.* at 16.
[39] *See id.* at 10.
[40] *See id.* at 16.
[41] *See id.* at 16-17.
[42] *See id.* at 17.
[43] *See id.* at 18-19.
[44] *See id.* at 20-21.
[45] *See id.* at 2 ("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.").
[46] *See id.* at 4-5.
[47] *Id.* at 5.
[48] *Id.*