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FDA's New Guidance on Cell and Gene Therapy Recommends Assessment of COVID-19 Transmission Risks

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FDA'S New Guidance on Cell and Gene Therapy Recommends Assessment of COVID-19 Transmission Risks

The U.S. Food and Drug Administration ("FDA") recently published guidance[1] to assist manufacturers of licensed and investigational cell and gene therapy ("CGT") products in minimizing the potential transmission of the novel coronavirus, SARS-CoV-2. In this Guidance, FDA recommends that CGT manufacturers conduct a risk assessment to identify and evaluate factors that may allow SARS-CoV-2 to be transmitted by the CGT product and to implement appropriate strategies to mitigate the risk. The evaluation should include, as appropriate, donor assessment, cell and/or tissue source materials, and certain manufacturing processes, such as cell expansion and viral reduction steps, which can affect viral spread.

This CGT Guidance is intended to supplement FDA's prior June 2020 guidance[2] for responding to COVID-19 infection in employees involved in drugs and biologics product manufacturing. The new Guidance builds upon FDA's prior recommendations by providing updated considerations specific to development and manufacturing of CGT products, which may be susceptible to viral contamination.

Risk Assessment and Mitigation Strategies

FDA notes that it is not aware of any CGT products known to have been contaminated with SARS-CoV-2 or of transmission of SARS-CoV-2 through CGT products. Furthermore, FDA at this time is not providing specific recommendations for testing source materials, intermediates, or final CGT products for SARS-CoV-2. The CGT Guidance makes clear, however, that manufacturers should carefully evaluate whether the novel coronavirus poses new risks to the safety and quality of their CGT products. Such an evaluation aligns with FDA's understanding of current Good Manufacturing Practice ("cGMP") requirements. Thus, even if it is determined that the risk is minimal, it is important for CGT developers and manufacturers to document a thorough risk assessment that can be provided to FDA or other regulators upon request, such as during an inspection. The risk-based approach should consider, among other things, the number of patients expected to be treated with the CGT product, since a product manufactured from a cell bank and used to treat a large number of patients would have a higher contamination risk than a product intended for autologous use.

FDA recommends that manufacturers of CGT products derived from human cell, tissue, or cellular or Tissue-based Products ("HCT/P") include COVID-19 risk factors in their donor eligibility screening. Specifically, manufacturers should consider whether, in the 28 days prior to HCT/P collection, the donor had close contact with individuals diagnosed with or suspected of having COVID-19, had been diagnosed with or suspected of having COVID-19, or had a positive test result from a diagnostic test but never developed symptoms. At this time, FDA does not recommend screening asymptomatic donors for SARS-CoV-2; however, CGT manufacturers considering testing as a risk mitigation strategy should use viral testing methods previously authorized by FDA for this purpose.

In assessing source materials, manufacturers should consider, for example, the ability of the coronavirus to infect and replicate in the source cells and tissues, as well as the risk of infection of the specific organ system (e.g., the respiratory system) from which the materials are sourced. In addition to evaluating source materials, however, manufacturers should also focus on the "manufacturing process used to control viral spread (e.g., cell expansion in culture, viral reduction steps, producer cell lines, controls for open systems), and contamination risk during manufacturing." This is especially important, given that SARS-CoV-2 has been found to be capable of infecting or replicating in cells often used for vector propagation, such as HEK293 and Vero cells. The manufacturer's quality unit should review and approve any risk assessments. If the risk assessment indicates the need to address specific risks related to SARS-CoV-2, manufacturers may consider product testing as a potential risk mitigation strategy.

These assessment activities are in addition to FDA's expectations that manufacturers prevent or mitigate the potential for contamination from a sick employee engaged in product manufacturing. Manufacturers should ensure that employees practice good sanitation and health habits. Further, as detailed in FDA's June 2020 guidance, manufacturers should confirm appropriate implementation of policies restricting infected employees from production areas and ensure that adequate cGMP controls are in place to prevent transmission among employees and contamination of product. This earlier guidance also provides specific recommendations on manufacturing controls to prevent contamination and ensuring continuity of manufacturing operations.

Next Steps

CGT manufacturers should submit a description of their risk assessment and mitigation strategies in their Investigation New Drug Application, Biologics License Application, or master file with FDA. For currently marketed products or for pending applications subject to pre-approval inspections, FDA may also confirm through inspections or record requests that the assessment has been completed and appropriate viral control strategies are in place. It is critical that risk assessments be clearly documented and conclusions well supported by technical and scientific data. For example, risk assessments may need to include review of existing cleanroom process and microbiological controls to prevent or minimize contamination. Manufacturers may need to consider their current product testing procedures. Relevant questions may include "What qualification or validation data supports the detection of SAR-CoV-2, if present, in your final product?," "Would your current cell bank and harvest testing and related controls detect the coronavirus if present in the source materials?," and "How can existing data regarding the removal of adventitious viral agents and other impurities be applied under the current risk assessment?" Manufacturers should also consider revisiting their risk assessments as they gain more knowledge about their CGT products and manufacturing processes and as additional information about SARS-CoV-2 becomes available.

The publication of this new CGT Guidance is only one of almost a dozen guidance documents in this rapidly developing area that FDA has published in the last year. CBER's 2021 guidance agenda also

includes a number of other important CGT topics that are expected to be the subject of guidance this year.

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If you have any questions concerning these developing issues, please do not hesitate to contact any of the following Paul Hastings lawyers:

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[1] FDA Guidance for Industry: Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency (January 2021), available at: https://www.fda.gov/media/145301/download (hereinafter, "CGT Guidance" or "Guidance").

[2] FDA Guidance for Industry: Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing (June 2020), available at: https://www.fda.gov/media/139299/download.