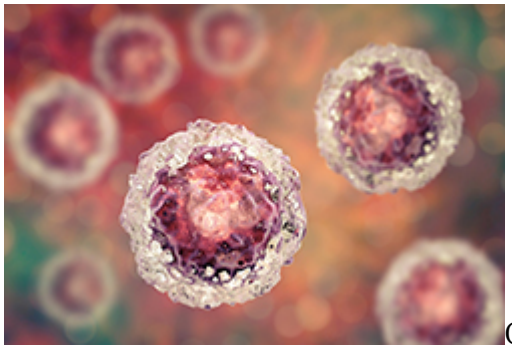
FDA Issues Guidance for Cell and Gene Therapy Manufacturers to Minimize Potential Transmission of SARS-CoV-2

 On January 19, 2021, the FDA issued **guidance** for licensed and investigational cellular and gene therapy (CGT) manufacturers during the COVID-19 pandemic. This new guidance supplements the recommendations provided in FDA's **June 2020 guidance** regarding manufacturing controls to prevent contamination in drugs, risk assessment of SARS-CoV-2 as it relates to drug safety and quality, and continuity of manufacturing operations as applied to all drug and biological product manufacturers.

The new guidance provides risk-based recommendations to minimize potential transmission of SARS-CoV-2 to patients and facility personnel with specific considerations relating to, among other things, the assessment of donors, cellular and tissue source materials, manufacturing processes, manufacturing facility control, material testing, and the number of patients that can be treated with the product. While FDA acknowledges in the guidance that is not aware of any CGT products that have been contaminated with SARS-CoV-2 or of information indicating transmission of SARS-CoV-2 via CGT products, FDA notes that "CGT manufacturers are expected to evaluate whether [the virus] poses new risks in the context of their specific products, facilities, processes, and manufacturing controls."

FDA recommends that CGT manufacturers review the current good manufacturing practice requirements and recommendations and perform a risk assessment that identifies, evaluates, and mitigates factors that may allow for transmission of SARS-CoV-2 to patients and facility personnel and include a description of the risk assessment and mitigation strategies in any investigational new drug application (IND), biologics license application (BLA), or master file. Since this is an evolving area, manufacturers should look to scientific literature to provide justification and support for their risk assessment and mitigation strategies.

CGT manufacturers should evaluate their manufacturing operations for SARS-CoV-2 risks and be sure that all risk assessments of production controls, including any follow-up and changes, are approved by their quality unit and appropriately documented within their quality management system.

FDA Announces Temporary Review Timelines

for Responses to Facility Assessment-Related Complete Response Letters Due to COVID-19

 As follow-up to our October **post** on pre-approval and pre-licensure inspections impacting U.S. Food and Drug Administration (FDA) drug and biologic approvals, this blog post discusses FDA's recently announced temporary policy set forth in its **December 2020 guidance** on review timelines for company responses to a Complete Response letter (CRL) for applications requiring the conduct of manufacturing or bioresearch monitoring (BIMO) program site facility inspections prior to approval. This guidance augments FDA's **August 2020 guidance**, which described FDA's intent to issue a CRL or defer action on an application until an inspection can be completed.

FDA acknowledges in its recent guidance that it is "facing difficulties" in conducting inspections during the COVID-19 pandemic. Industry has felt the impact of this with delayed approvals of new therapies in 2020 as a result of these inspection delays. While FDA has sought to use alternative tools to mitigate the need for in-person inspections (*e.g.*, requesting records and other information directly from facilities and requesting existing inspection reports from trusted foreign regulators), FDA indicated in its December 2020 guidance that these inspection-alternatives "can be as resource intensive as inspections, if not more," thereby presenting a challenge to timely completion of required pre-approval and pre-license inspections during the application review period.

To provide greater transparency on expected timeline impacts for company complete responses where FDA issued a CRL either (a) due to its inability to perform a required inspection because of COVID-19, or (b) where the inspection involves the use of time- and resource-intensive alternative tools, the Agency provides the below timeline expectations in its December 2020 guidance for the review of applicant responses to CRLs:

- NDAs & BLAs: Resubmissions of original applications and efficacy supplements for NDAs and BLAs will be subject to a Class 2 review timeline of 6 months, which is "consistent with existing policies and practices when a facility inspection is required."
- Biosimilars & NDA & BLA manufacturing supplements: There will be no changes in the review timelines for resubmissions of original applications, supplements with clinical data, and manufacturing supplements for biosimilars, or for resubmissions of manufacturing supplements for NDAs and BLAs.
- ANDAs: Regardless of whether the CRL contains a major deficiency, amendments to original ANDAs and amendments to prior approval supplements for approved ANDAs will be treated as major amendments, subject to the timelines provided in FDA's **July 2018 guidance** on Generic Drug User Fee Amendments (GDUFA).

The December 2020 guidance enables applicants to better plan for approval timeline delay contingencies as they proceed through FDA's review process. Comments on the December 2020 guidance may be submitted to the docket for Agency consideration **here**.

Are Pre-Approval and Pre-Licensure Inspections Limiting Approvals During COVID-19?

 In this post, we discuss FDA's conduct of inspections of manufacturing facilities for new drugs and biologics during the COVID-19 pandemic. These inspections, known as pre-approval and pre-licensure inspections (PAIs/PLIs, respectively), are performed to give FDA assurance that a manufacturing site named in a new drug or biologics license application is capable of manufacturing the product according to current good manufacturing practices (cGMPs) and producing the product at commercial scale.

In **July**, FDA resumed limited domestic on-site inspections after temporarily postponing all domestic and foreign routine surveillance facility inspections in March. Since **June**, FDA had conducted only mission-critical domestic inspections. Currently, domestic on-site inspections are pre-announced and are prioritized on a newly developed rating scale that uses real-time data on the number of COVID-19 cases in a local area to qualitatively determine when and where it is safest to conduct inspections. Foreign PAIs/PLIs continue to be temporarily postponed unless deemed mission-critical. FDA may deem an inspection mission-critical based on a variety of factors including, but not limited to, whether the product has received breakthrough therapy or regenerative medicine advanced therapy designation.

In response to COVID-19, FDA has used, on a limited basis, various tools to conduct alternative inspections. These tools include the use of FDA's authority under Section 704(a)(4) of the FD&C Act, which enables the Agency to request records directly from facilities "in advance of or in lieu of" drug inspections. In addition, FDA has indicated that it may also look to records of recent inspections and information shared by foreign regulatory partners through mutual recognition agreements. And while the concept of virtual inspections has been floated, it remains to be seen if video-based or other virtual inspection strategies can be used to fulfill PAI/PLI requirements and how long such proposals may take to implement.

Worryingly, FDA explains in its **August 2020 guidance** that should the Agency determine that a PAI/PLI is necessary, and such an inspection cannot be completed during the review cycle due to restrictions on travel or other COVID-19-related risks, FDA generally intends to issue a Complete Response letter or may defer action. The guidance, along with a number of concerns raised quietly by sponsors regarding delayed inspections leading or potentially leading to Complete Response letters, paints a potentially ominous picture for drug and biologic approvals and the advancement of the public health over the coming months. Sponsors submitting marketing applications in the near-term would be wise to proactively prepare for discussion of alternative inspection approaches during the review of their applications.

Real-World Evidence: Challenges and Opportunities During COVID-19

The urgent needs of the COVID-19 pandemic have more squarely brought into focus the role real-world evidence (RWE) can play in analyzing and informing product development and clinical and public health decisions. Specifically, the U.S. Food and Drug Administration (FDA) is participating in the COVID-19 **Evidence Accelerator**, in partnership with Friends of Cancer Research and the Reagan-Udall Foundation, to bring leading experts together to share insights and use RWE to help answer the most pressing research questions raised by the pandemic.

The FDA believes that RWE can play an informative role in analyzing potential therapies, vaccines, and diagnostics for COVID-19. At the recent "Establishing a High-Quality Real-World Data Ecosystem" **workshop** hosted by the Duke Margolis Center for Health Policy, Amy Abernethy, the Principal Deputy Commissioner of Food and Drugs and Acting Chief Information Officer at the FDA, highlighted the work of the Evidence Accelerator initiative, noting that RWE allows the FDA to constantly update its understanding of COVID-19 and recurrently analyze data to address changing needs. Amongst the other presenters, the general discussion focused on the many hurdles industry needs to address to establish a robust and more accurate RWE data ecosystem, including efficient capture of reliable data at the source. While internet access, smartphones, and wearable technology enable consumers and patients to keep meticulous records of their biometric data, the vast amount of collected data does not necessarily lead to efficient or fruitful analysis currently. FDA noted during the workshop that, to be more insightful, RWE stakeholders must narrowly tailor their collection to what is actually useful and relevant to clinical endpoints, fit for purpose, rather than merely what is easily accessible. Eric Perakslis, a Rubenstein Fellow at Duke University, noted that stakeholders must balance the usefulness of RWE collection against the risk of over-surveillance for each data point collected. While not discussed during the workshop, collecting massive data sets must also be weighed against the ever-present risk of data breach. Finally, speakers also discussed patient-generated health data (PGHD) and the need for aligned stakeholders who are motivated to collect this data and understand the process for doing so, including a plan for handling outlier data which is unavoidable with PGHD.

In the context of the COVID-19 pandemic, RWE presents an opportunity for real-time learnings toward quicker identification and development of treatments and vaccines. As a result, the pandemic has only strengthened the importance of RWE in product development and, if deployed well, could help support more efficient and expedited product development plans.

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contributed to this post.