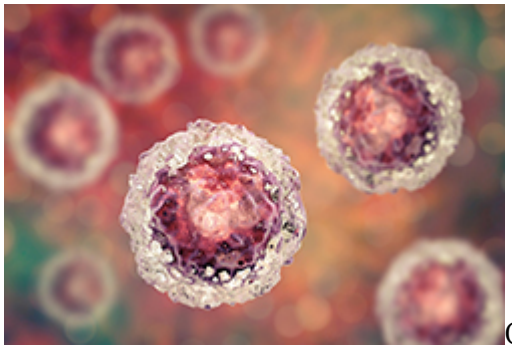
FDA Issues Guidance for Cell and Gene Therapy Manufacturers to Minimize Potential Transmission of SARS-CoV-2

 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.

Pressing the Accelerator on Growth

 **What is an accelerator**? An accelerator is an entity that provides a fixed-term, cohort-based program designed to accelerate growth and support disruptive and innovative early-stage businesses. They can be generalist or specialist and are located all around the world.

Who are they? Probably the most well-known accelerator is Y Combinator (US), which is active in most sectors, including life sciences. Other particularly active biotech and life science accelerators include JLabs (US), Startup Health (US), BioCity (UK) and Illumina (US). Closer to home of the authors are Accelerate@Babraham (Cambridge, UK) and Start Codon (Cambridge, UK), which debuted its first cohort in 2020. Not all accelerators are the same though, so it is important to do the research to ensure they are the best 'fit' for the business (stage, location, specialism, oversight and financing level).

What do they do? There are many reasons why founders are attracted to an accelerator program. They provide an intense and immersive education in the life of a start-up, covering strategy, sales, marketing, communication, risk management, finance and legal matters. Perhaps the most popular reason is mentorship from experienced practitioners, investors and entrepreneurs, whose advice and relationships can be vital as the company grows. Although the level of financing is not normally substantial, it is nevertheless welcome and participation in a program can sometimes make future fundraising easier, as supported by the statistics. Therefore, it is crucial to maintain and leverage new connections with angel and institutional investors during and after the program.

Why are they important? Starting any business is difficult and can be isolating. As a result of lockdown and social distancing measures, isolation is a key concern for many and so building a business and developing relationships is even more challenging. Accelerators do not guarantee success and are not the only route, but they can provide valuable access to a community of entrepreneurs and mentorship and drive a business forward in a protected environment.

Tensions in University Start-up Life Science Licensing Agreements

 University tech transfer offices (TTOs) and venture capital firms (VCs) work closely together to advance certain technologies and discoveries from the lab to the market. However, because there are different motivations and incentives for TTOs and VCs while negotiating licensing agreements, tensions often arise during these negotiations.

At a meeting between certain TTOs and VCs, important deal terms were highlighted as especially sensitive**[1]**, such as equity, royalties, success-based milestones, and windfall success payments. In addition, board seat requests by the university to understand how the company is progressing also creates tension because some VCs see this as a potential conflict-of-interest with respect to adjacent technologies.

Outside of these financial and governance terms, the biggest tensions arise when negotiating intellectual property (IP) encompassing the invention, specifically negotiating points about patent(s), know-how, and development. With regards to patents, tension exists in the management and payment of patent prosecution and who has ultimate control and decision making authority. With regards to know-how, one of the most difficult clauses to negotiate is what is considered an enabled product from which the university would receive royalties and milestone payments. Discussion surrounding the scope of the ongoing collaboration between the university and the company can be complex. A clear understanding of the role of the university's employees at the company, along with ongoing discussions regarding active development projects could aid in understanding the scope and what would be considered enabled products.

Lastly, there are also tensions during the negotiation regarding the economics of sublicensing. Sublicensing of the licensed IP is typically agreed upon by both parties. However, despite this agreement, the specific terms and parameters surrounding the sublicensing can lead to friction, especially around the sharing of non-royalty sublicensing income.

Reflecting upon the perspectives and friction points of both parties can hopefully lead to a more productive and collaborative drafting and negotiating experience, which hopefully leads to a long-term productive relationship for the specific agreement and other technologies the university may be willing to license.

---

[1]
https://techventures.columbia.edu/term-sheet-recommendations-for-launching-university-startups

---

Highlights for SaMD Developers: FDA's

January 2021 Artificial Intelligence/Machine Learning Action Plan

 On January 12, 2021, the U.S. Food and Drug Administration (FDA) published its **Action Plan** for further development of the Agency's framework for regulatory oversight of artificial intelligence (AI) and machine learning (ML) based Software as a Medical Device (SaMD). The Action Plan identifies several opportunities for SaMD developers to engage the FDA as its regulatory framework for AI/ML-based SaMD oversight evolves:

- **Predetermined Change Control Plans:** FDA remains committed to refining a regulatory framework that would allow for some post-market SaMD modifications based largely on the establishment and utilization of SaMD Pre-Specifications (SPS) and an Algorithm Change Protocol (ACP) set forth in a "Predetermined Change Control Plan." SaMD developers can expect, and be ready to submit comments on, a draft guidance in 2021 addressing a Predetermined Change Control Plan.
- **Real-World Performance:** Real-world data collection and monitoring is another key concept in FDA's proposed regulatory framework for oversight of modifications to AI/ML-based SaMD. FDA plans to advance real-world performance monitoring pilots with stakeholders on a voluntary basis, and use the learnings from these activities to develop a framework for gathering and validating relevant real-world performance parameters and metrics.
- **Algorithm Transparency:** To identify types of information that FDA may recommend SaMD developers include in the labeling of their AI/ML-based devices, FDA intends to hold a public workshop to elicit input from the broader community on how device labeling supports transparency to users.

FDA also will continue to participate in global working groups focused on harmonizing principles of Good Machine Learning Practice (GMLP) as well as expand upon the Agency's efforts to develop methods for evaluating and addressing algorithmic bias.

The Agency recognizes that continued stakeholder engagement will be crucial for the formation of a sensible regulatory framework for oversight of AI/ML-based SaMD. SaMD developers seeking to inform the development of FDA's regulatory framework are strongly encouraged to participate in the specific opportunities outlined in the Action Plan.

Hedging COVID-19 Pandemic Risks in Early-

Stage Financings

 In recent posts, we reviewed **"down-rounds"** and **hedging COVID-19 pandemic risks in M&A**. This post complements them and focuses on early-stage life sciences companies and their potential investors.

While the customary development timelines for life sciences companies may seem less prone to risks associated with COVID-19, the pandemic still resulted in delays and required adjustment to development plans and budgets, and, consequently, made evaluation of investments challenging.

There are several potential structures that companies can use to get investors "off the fence" and commit funds without lowering their valuation. Companies can offer warrant coverage, to allow investors to purchase shares at the lower price contingent upon additional financing (or failure to obtain it).[1] Alternatively, investors may prefer to spread or stagger their investments, such that capital commitments would be tied to achievement of milestones, which is already common in many life sciences financings, but can be further spread or staggered to address COVID-19 specific concerns. These solutions provide companies with sufficient funds for short-term development runway, and prospective future funds, while allowing investors to validate their evaluations and mitigate risk of overpaying. A similar solution is financing through convertible notes or simple agreements for future equity (SAFEs), with a conversion price or exchange price that is based on future financings and/or contingent upon achievement of milestones. The above alternatives are easier to implement than potential, yet unorthodox means, such as post-Closing price adjustment (which raises anti-dilution concerns).

In addition to mitigation through transaction structures, investors can also seek enhanced discretion with respect to a company's development plan and budget, access rights and other covenants and rights, or a combination thereof, such that investors could get comfortable without undermining the company's ability to progress.

Striking the right balance is not always an easy task, in particular during a time of unprecedented uncertainty, but, as long as investors and companies are aligned on the core strategy and goals, there are multiple ways to find it, including those reviewed in this post.

---

[1] Lower price can be accomplished by either offering the right to purchase additional shares of the same class at a lower price for shares in the then-current round or by offering the same price or a discount on the price per share for shares in a future financing with a higher price per share.

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

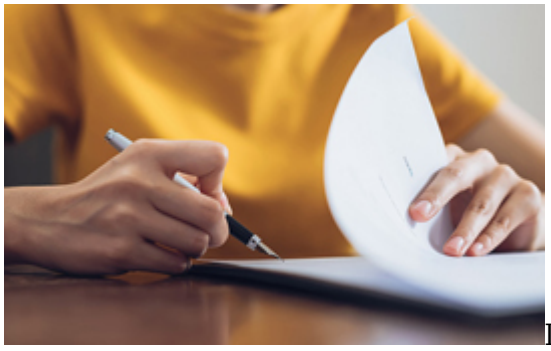
contingencies as they proceed through FDA's review process. Comments on the December 2020 guidance may be submitted to the docket for Agency consideration **here**.

Congress Enacts Amendments Affecting The Regulation Of Generic Drugs And Biosimilars

 On December 27, 2020, the President signed into law the "Consolidated Appropriations Act, 2021" (the "Act"). Included within this omnibus legislation are several provisions (in Division BB, Title III, Subtitle C) that affect the regulation of generic drugs and biosimilar medicines by the U.S. Food and Drug Administration (FDA).

Read the Alert >>

Hedging COVID-19 Pandemic Risks in M&A: PPP Loans

 During the COVID-19 pandemic, M&A counsel and their respective life science clients have attempted to navigate the new normal of an unprecedented situation.**[1]** In addition to impacts on due diligence, material adverse effects clauses, termination provisions, contingent payment mechanics and representations, warranties and covenants, potential acquirers have also had to hedge specialized risk associated with target companies engaged in the Paycheck Protection Program ("PPP").

Financially healthy life science companies have often been cautious of being associated with PPP loans during the COVID-19 pandemic, especially with the increased scrutiny surrounding the

“necessity” analysis by the U.S. Small Business Administration (“SBA”) and, in the case of public companies, the disclosure requirements to shareholders. Consequently, target companies with outstanding PPP loans have been required to address potential risks. Prominent means to hedge such risks include the use of escrow funds and covenants obligating target companies to seek forgiveness of some or all of a PPP loan. In fast-paced transactions, targets may not be able to apply and receive forgiveness prior to the transaction’s closing and thus, forgiveness as a closing condition is improbable. In such situations parties may opt to set-up an escrow account in an amount equal to the PPP loan forgiveness amount and, if negotiated, the out-of-pocket costs borne by the sellers related to the forgiveness application. Relatedly, among other things, sellers may also be required to indemnify acquirer(s) indemnitees from any losses arising from a target company’s obligation to repay any portion of the PPP loan that is outstanding as of the transaction’s closing, to the extent it is not forgiven. The combination of a separate and dedicated escrow account, along with a covenant to eliminate PPP loans and indemnification for related losses, can provide acquirers of life sciences companies (which are typically bigger and often do not meet the requirements for PPP loans) with some level of comfort with respect to the potential effects of PPP loans on their other operations.

---

[1] For an overview of the impact of COVID-19 on M&A see **client alert**