Moving CGTx Clinical Development Forward in 2023

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Clinical trials are foundational to developing innovative, life-saving treatments and cures for patients. For developers of cell and gene therapy (CGTx) products, the path to clinical success is fraught with vast and complex challenges. The CGTx field is becoming more crowded, with increased clinical trial volume and an influx of less-experienced sponsors contributing to an increase in clinical holds in the category. Such challenges intensify the pressure to succeed in a fiercely competitive environment.

This white paper is based on a webinar convened by Precision ADVANCE and Endpoints News featuring experts in the complexities of CGTx clinical development. Moderated by **Teresa Pokladowski**, Regional Vice President of Clinical Business Solutions, North America at Precision for Medicine, the webinar included the following experts

- **Dawn Buchanan**, Vice President, Clinical Operations, Affyimmune Therapeutics
- **Suma Krishnan**, President, Research and Development, Krystal Biotech, Inc.
- **Kinnari Patel**, President and Chief Operating Officer, Rocket Pharmaceuticals Inc.
- **Ramona Repaczki-Jones**, Executive Director, Treatment Center Operations, Iovance Biotherapeutics

Integration of CMC and Clinical Operations

CGTx innovators are “building the plane as we’re flying it,” quipped Buchanan, who noted that when devising a clinical strategy for a CGTx product, sponsoring companies should not rely solely on what others have done. The critical path toward regulatory filing traverses through chemistry, manufacturing, and controls (CMC). Many sponsors choose to engage CMC consultants, who should be onboarded early so the overall strategy is in place when initiating discussions with the FDA, and to avoid “whiplash” when the development program hits the proverbial accelerator.

The panelists spoke repeatedly of a “trifecta” of synergy between the FDA, manufacturing, and treatment centers. Manufacturers increasingly view treatment centers less as third-party vendors and more as partners. That is largely because both parties encounter challenges with scalability, logistics, and gaps in capabilities as products transition from clinical trials to commercialization; both parties also impact patient outcomes. Those factors underscore the need to recognize challenges early, scale up workflows and capabilities, and educate stakeholders to build a “circle of trust” across the trifecta.

Sponsors should evaluate prospective CMC vendors in terms of whether they have the requisite experience to initiate studies and/or manufacturing processes, as well as to coordinate assay and companion diagnostic development. Once a vendor is selected, the sponsor needs to devise a strong agreement with the vendor, paying close attention to legal aspects of the agreement as well as quality specifications; such attention to detail can ensure up-front alignment on the collaboration.

There is intense competition in the CMC vendor space, with many consultants experiencing high turnover. That underscores the importance of a strong relationship with a reliable vendor and shared incentives to succeed. At the same time, sponsors should not neglect the imperative to build in-house expertise. Internal control of CMC is critical not only for regulatory filing, but also for passing inspection and securing approval. The FDA means to be helpful but is overwhelmed with Investigational New Drug (IND) applications; a sponsor cannot expect the agency to understand the company's process or to be able to answer every question. Sponsors must therefore be prepared to "do the work" and present it to the agency.

Early Planning and Compressed Timelines

Sponsors must plan early for a CGTx product's eventual commercialization. It is vital to have plans in place for packaging, distribution, and cold chain control, and to complete shipping and validation studies well in advance.

While several CGTx developers have benefited from the Regenerative Medicine Advanced Therapy (RMAT) Designation, they have also learned important lessons from the designation process. A key imperative is to optimize operations, product quality, and final commercial product as early as possible. Whereas the "normal" progression from phase 1 to Biological License Application (BLA) takes from 12-15 years, that timeline may be consolidated to 5-6 years for a CGTx product, given the urgency of unmet medical need in this category. Therefore, the sponsor's internal team must know the data and product characteristics "as if [the patient] was their own child," according to Patel, who stressed the importance of expediting delivery to patients and making the experience "as positive as possible for the patient."

Clinical Trial Design Challenges

Although the randomized clinical trial (RCT) remains the gold standard of clinical research, the panelists agreed that it is not ethical to have a placebo arm in most CGTx trials. That is largely because patients with ultra-rare diseases can deteriorate rapidly. "Every month that they go without a treatment, you are basically depriving them of a quality of life that could have been improved," Krishnan noted, adding that the FDA is increasingly open to single-arm studies and use of surrogate endpoints in CGTx trials. However, the sponsor must be prepared to "stand behind" the benefit/risk data from any single-arm study.

CGTx trials often hinge on centralizing testing and analytics, addressing manufacturing constraints, and validating assay potency as early as possible, while limiting product changes. It is also crucial to understand the disease from the perspective of both patient and treating physician, even before designing the IND protocol. Oftentimes, such understanding may arise from a robust natural history study, which may yield a clear contrast of the natural evolution of a rare disease with outcomes in treated patients.

One of the biggest challenges in rare diseases is that by the time a clinical program reaches the BLA stage, the knowledge gained during drug development may change the benefit/risk ratio, or may cause the sponsor to question its choice of primary and secondary endpoints. In such cases, the sponsor should allow the data to drive the decision of whether to change course, and should work with health authorities to ensure alignment at every step.

Playing off of Iovance's focus on tumor-infiltrating lymphocytes (TILs), Repaczki-Jones commented that "It takes a 'TIL-lage'" to align all the logistics in transitioning from clinical trials to a BLA submission. Everything depends on the trifecta's circle of trust, which can affect the environment the drug is to be delivered in.

Facilitating Patient Access

Patient access to CGTx products continues to be a major bottleneck for the industry. There are waiting lists for commercial CAR T-cell therapies, and demand for these products may double as more are approved, perhaps as soon as this year.

Adhering to best practices can enhance access by creating efficiencies in clinical trials and empowering scalability for CMC readiness, BLA submission, and commercialization. Such practices include:

- Building a team with direct patient experience
- Making logistical/operational adjustments in clinical trials to overcome patient burdens
- Adherence to Information Standard for Blood and Transplant (ISBT) 128 international guidelines for labeling cell therapy products

One of the most important best practices is to build an efficient patient access platform that integrates patient registration, drug product ordering, scheduling, chain of identity, and chain of custody. Instead of assembling multiple platforms, a single, user-friendly platform can ensure the treatment center and manufacturer remain in lockstep during development as well as post-launch, as both parties are active participants in chain-of-identity and chain-of-custody processes.

Essentially, patient access depends on adherence to the core values of generosity, curiosity, and trust. Manufacturers and treatment centers can practice generosity by sharing best practices through white papers, policy papers, guidance documents, and working with organizations such as the Alliance for Regenerative Medicine (ARM) and the American Society of Gene and Cell Therapy (ASGCT). Curiosity is largely a matter of being open about what one does not know, and asking for help in filling knowledge gaps. Fostering trust boils down to viewing patients holistically. "Patients are our north star," said Patel. It is vital to remember "how we treated them, what we learned, and how they've helped advance the knowledge of the disease…and the therapy they can help bring to the market."

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Racial and Ethnic Diversity in Clinical Research

Ensuring diversity can be challenging in rare disease trials. With patient populations as small as 100 and are large as 200,000, rare diseases themselves are not "fair," and may not comprise diverse populations. Certain rare diseases may be more prevalent in some sub-populations than in others. Moreover, it may not always be feasible for a CGTx trial to include every sub-population that the FDA stipulates.

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Such challenges underscore the "Every Patient Matters" imperative. CGTx developers need to augment their "book knowledge" of genetic mutations and disease severity by getting to know the patients that live with these diseases, whose knowledge may surpass the company's. Advocacy groups can be vital conduits to building patient relationships and to understanding disease manifestations, some of which may not be "fixed" by CGTx, but nevertheless impact quality of life.

Facilitating CGTx approvals

The FDA needs more resources to expedite therapies, and could benefit from more frequent interactions with industry, in that knowledge-sharing may enhance understanding of CGTx products' benefit/risk profiles. The so-called "flat platform" approach may thus streamline approval processes. Patel cited the example of Fanconi anemia, in which a company may obtain product approval based on its study of the *FANCA* gene. If that company takes the *FANCC, FANCD*, and/or *FANCG* genes to clinical studies, a flat platform may enable evaluation of CMC, vector, plasmid, analytics, and clinical data across these variants. The flat platform may thus decrease the complexities, time, and cost of clinical trials, and by extension, the level of investment.

Reasons for Excitement in 2023 and Beyond

The panelists expressed hope for more approved CGTx products offering life-saving treatment to patients lacking other options. Potentially disruptive technologies on the horizon include CRISPR-Cas9, redosable gene therapy, and the first topical gene therapy. The prospect of such therapies may motivate patients and treatment centers to pressure manufacturers "to come together and standardize some of the interactions with them," according to Repaczki-Jones. Pokladowski concluded the webinar by predicting that CGTx developers will "continue to move the needle and bring hope" to patients, regardless of the pace of approvals.

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2 Bethesda Metro Center
Suite 850
Bethesda, MD 20814

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