Congress of the United States
Washington, DC 20515

March 26, 2023

Peter Marks, M.D.
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Marks,

We write to you today to inquire about the Center for Biologics Evaluation and Research's (CBER) recent efforts to address the growing number of biologics license applications for cell and gene therapies and to raise concerns about the increase of clinical holds the Food and Drug Administration (FDA) has recently issued delaying a proposed clinical investigation or suspending an ongoing investigation for such products.

According to recent reporting, FDA saw a 43 percent increase in the number of requests to conduct clinical trials using experimental drugs between 2014-2021 and a 66% increase in clinical holds during that same time period.[1] Annually, holds averaged 664 between 2017 and 2021, which is up from 557 average annual holds from each of the five previous years. For CBER, specifically, related holds, "is likely due to more new clinical trials for cell and gene therapies," according to an agency spokesperson interview by the *Wall Street Journal*. Further estimates show that 90% of all clinical holds at the Agency are now being generated by CBER; This is double the historical average over the past 12 years, and 40% of all clinical holds at FDA are on studies of cell and gene therapies.[2]

To be clear, we recognize that clinical holds are an important regulatory tool, but they should be used judiciously and appropriately. CBER should not, for example, use clinical holds as a means for FDA to gain additional time to review a clinical protocol. Unless patients are exposed to immediate and serious risks, FDA's regulations require it to discuss deficiencies with researchers and sponsors and attempt to satisfactorily resolve the matter. Specifically, FDA's own regulations (21 C.F.R. 312.42(c)) provide that "FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order." We are therefore concerned, after hearing from researchers and patients, that CBER seems to be applying holds on some cell and gene therapies for issues that could possibly be resolved through discussions with sponsors without an issuance of a clinical hold.

[1] https://www.wsj.com/articles/fda-increasingly-halting-human-trials-as-companies-pursue-risky-cutting-edge-drugs-11673322324
[2] https://endpts.com/hold-the-phone-biopharma-fda-imposed-clinical-holds-are-on-the-rise/

Further, CBER also appears to be increasingly relying on written response only (WRO) communications.[3] As you have noted[4], some issues with investigational new drug (IND) submissions could be resolved through simple interactive meetings. WRO may lead to unnecessary delays when CBER's expectations are not made clear to the sponsor or are subject to interpretation in the written response—a problem that could be mitigated through in-person or virtual meetings with the sponsor.

Congress has enacted provisions that allow cell and gene therapies that treat serious diseases to receive a Breakthrough Therapy designation, when there is preliminary clinical evidence suggesting that the product may demonstrate substantial improvement over existing therapies.[5] That designation allows sponsors of these therapies access to meetings with the FDA review team throughout the development of the drug, access to timely communication with the review team, and access to FDA senior managers for collaborative, cross-disciplinary reviews (among other things). In 2016, Congress also added section 506(g) to the FD&C Act[6] to foster the development of certain regenerative medicine therapies by creating a "Regenerative Medicine Advanced Therapy" (RMAT) designation for certain products that treat serious disease, where preliminary clinical data suggest that the product may address an unmet medical need. RMAT designation provides access to the same types of interactions with the FDA review team as Breakthrough Therapy designation.

In your own guidance document entitled "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" issued in 2019, CBER outlines a list of criteria the Center may consider when determining whether a product qualifies for the RMAT designation.[7] These include the rigor of data collection, the consistency and persuasiveness of the outcomes, the number of patients, the number of sites, and the severity, rarity, or prevalence of the condition. The document also outlines a set of important procedural standards product sponsors should expect when pursuing the RMAT designation, including an answer on the fate of this RMAT designation within 60 days of a request for designation and additional access to reviewers within the Office of Tissues and Advanced Therapies (OTAT) through the Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) program.

Each of these are important steps toward addressing the higher volume of cell and gene therapy applications being filed at CBER and ensure these novel therapies reach patients as soon as possible. Excitingly, we now have 27 approved cell and gene therapies on the market.[8] We hope CBER continues building off past accomplishments in the cell and gene therapy space to advance the number of approvals even higher. Furthermore, we encourage the FDA to use its regulatory discretion where necessary to make these innovative products available to patients in need, particularly those with ultra-rare or fatal diseases or for whom there are limited or no treatment options.

---

[3] Sue Sutter, *For Cell and Gene Therapies, Expedited Designation and Complex Questions Improve FDA Meeting Chances*, THE PINK SHEET (Jun. 2, 2022).
[4] https://www.raps.org/news-and-articles/news-articles/2023/2/top-fda-official-interested-in-project-orbis-for-c
[5] 21 U.S.C. § 356(a).
[6] 21 U.S.C. § 356(g)
[7] https://www.fda.gov/media/120267/download
[8] https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

We welcome the opportunity to continue working with the Center on achieving these goals and ensuring that FDA has the tools and resources necessary to expeditiously review these novel products. Toward that end, we request answers to the following questions:

1. For years 2021-2023, how many clinical holds has FDA placed on applications for cell and gene therapies? Please provide a breakdown of the number of holds placed on applications with RMAT designation, Breakthrough designation, and those seeking approval through the accelerated approval pathway.
    a. How many of these holds were lifted?
    b. After a response to clinical hold was received, how long did it take for FDA to lift clinical holds?
    c. How many holds were lifted after the 30-day period?
    d. How many holds were placed on original INDs vs ongoing INDs?

2. In order for us to better assess the timing of outreach to researchers and sponsors to resolve potential hold issues during the 30-day review period for a new IND, can you please describe:
    a. The process for FDA reviewers to raise concerns to supervisors;
    b. The timeline and process for reaching resolution with the sponsors during the 30-day IND review period;
    c. How often FDA reviewers reach out to researchers and sponsors during the 30-day IND review period to seek to resolve issues before issuing a clinical hold; and,

    In the event CBER is not currently tracking the instances described above, whether tracking of such occurrences would be useful.

3. In the most recently reauthorized user-fee agreement, PDUFA VII, FDA agreed to respond to a sponsor's complete response to a clinical hold within 30 days of receiving such response 90% of the time.[9] Are you currently meeting this goal? If not, why not?

4. How many applications does FDA receive on average for the RMAT designation and Breakthrough Therapy designation for cell and gene therapies within a full calendar year?
    a. What is the average amount of time it takes for CBER to issue a decision on the status of such applications?
    b. How many times has CBER taken longer than the required 60-day period to issue a decision on such applications?
        i. What is the cause of such delays?

5. Of those sponsors with IND applications for a cell or gene therapy product, how many were granted an OTAT or an INTERACT meeting? Of those sponsors whose products have received RMAT designation, how were granted an OTAT or an INTERACT meeting?
    a. How many times are clinical holds placed on applications that have used the resources available to the sponsors through OTAT or INTERACT meetings?

[9] https://www.fda.gov/media/151712/download

6. You recently stated you are transitioning OTAT to the Office of Therapeutics, or OTP, including the hiring of 125 new staffers to assist with review of cell and gene therapy products.[10] What specific problems within the review process are you attempting to address through the onboarding of these new employees? Were there, or are there still, gaps in knowledge or expertise, that need to be filled. If so, what are they?
    a. How will they specifically assist in the review process?
    b. Will the resources provided for by the recently reauthorized Prescription Drug User Fee Agreements, PDUFA VII, which directs FDA to increase the fee revenue and fees to support hiring and retaining employees ($9 million for FY23)[11] be used to hire and retain these 125 employees?
        i. Does CBER have a plan to ensure resources for reviewing cell and gene therapy applications are prioritized using these funds, including objectives for hiring and reviewing applications?
        ii. What are the specifics of such plans?

7. Please provide data on the percentage of WROs for each meeting type that received a WRO for all CGTs, including a separate breakdown for all CGTs and for the critical subset of RMAT-designated CGTs.

Thank you for your attention these important issues. We ask for your responses to our inquiries by no later than Friday, April 14, and responses can be directed to brian.fahey@mail.house.gov and celeste.woloshyn@mail.house.gov.

Sincerely,

Brett Guthrie
Member of Congress

Anna Eshoo
Member of Congress

[10] https://endpts.com/operation-warp-speed-for-rare-diseases-cber-leader-says-pilot-is-coming-soon/
[11] https://www.federalregister.gov/documents/2022/10/07/2022-21968/prescription-drug-user-fee-rates-for-fiscal-year-2023