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Gene And Cell Therapy Clinical Holds Decline While Those For Drugs Hit 12-Year High

by Brenda Sandburg

FDA's Center for Biologics Evaluation and Research saw IND clinical holds for gene and cell therapies dropped to 70 in calendar year 2022, a 52% decline from 2018. Center for Drug Evaluation and Research's total clinical holds in fiscal year 2022 were 380, the highest number in the past 12 years.

Despite recent scrutiny of US Food and Drug Administration clinical holds on investigational cell and gene therapies, the number of holds has declined in the last three years to 70 in calendar year 2022. That is half the number of clinical holds implemented in 2018, the highest number in the past decade.

FDA's Center for Biologics Evaluation and Research had a total of 115 investigational new drug (IND) clinical holds in calendar year 2022, including 45 for non-cell and gene therapy. For 2023 to date as of last month, the total was 65, 40 for gene and cell therapy and 25 for non-cell and gene therapy.

The issue of clinical holds caught the attention of members of Congress. In March, the House Energy and Commerce Committee's Health Subcommittee chair Brett Guthrie, R-Ky., and ranking member Anna Eshoo, D-Calif., sent a letter to CBER director Peter Marks expressing concern about a reported increase in clinical holds. They said CBER seems to be applying holds on some cell and gene therapies for issues that could possibly be resolved through discussions with sponsors without the issuance of a clinical hold. (Also see "*US FDA Gene Therapy Review Reorg Draws Congressional Interest*" - Pink Sheet, 11 Apr, 2023.)

However, based on data obtained from CBER through a Freedom of Information Act request, the number of cell and gene therapy clinical holds decreased 52.3% percent from a high of 147 in calendar year 2018 to 70 in 2022. The number of non-cell and gene therapy holds reached a high

of 95 in 2020, declining to 45 in 2022. (*See chart at end of story.*)

On the drug side, the number of clinical holds over the past 12 years reached a record high last year. The Center for Drug Evaluation and Research had 380 total clinical holds in fiscal year 2022, of which 259 were full clinical holds and 121 were partial clinical holds. That is a 62.4% increase from 2018 when total holds were 234 and a 91.9% increase from the low of 198 total holds in 2012.

FDA regulations specify that an IND goes into effect 30 calendar days after FDA receives the IND unless the agency imposes a clinical hold. If all the trials covered by an IND are delayed or suspended, CDER will impose a full clinical hold. If only some trials covered by an IND (such as a specific protocol or part of a protocol) are not allowed to proceed, CDER will impose a partial clinical hold. (Also see "*US FDA Tweaks IND Clinical Hold Policy As Number Of Holds Rises* " - Pink Sheet, 1 Mar, 2018.)

Shift In FDA's Approach

Marc Scheineson, a partner at Alston & Bird and former FDA associate commissioner for legislative affairs, said that on the 29th day after receipt of an IND the agency may begin rounds of questions which result in the sponsor providing the equivalent of a mini new drug application just to get the right to do more tests.

"That's caused a huge bottleneck," he said. "And after three or four or five rounds of questions some trials never go off clinical hold."

Scheineson noted that in the past the agency would wait to raise efficacy questions until Phase III, and an IND would be rubber stamped if the sponsor had toxicology data and proved through animal studies that the drug was safe to use.

There is skepticism that the agency asks questions and delays greenlighting research to buy more time since the statutory deadline to respond to an IND is so short, he said. "These questions always hit at the end of the ninth inning."

CBER's Marks commented during the Prevision Policy/Friends of Cancer Research Biopharma Congress that there are multiple causes for the high number of clinical holds in the cell and gene therapy space. He cited the increase in clinical trials, the inexperience of sponsors in the space, and INDs that are missing key pieces of information. (Also see "*US FDA Cell/Gene Therapy Office 'Aggressively Recruiting' Amid Reorg, Senior Staff Departures*" - Pink Sheet, 27 Feb, 2023.)

He has said that the workload at CBER is also a factor in the number of clinical holds. (Also see "*US FDA Open To Cell Therapy 'Assessment Aid' That Could Speed Development Of Next-Gen Cancer Drugs*" - Pink Sheet, 13 Mar, 2023.)

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Marks addressed concerns regarding how CBER communicates about clinical holds at the American Society of Gene and Cell Therapy's annual meeting in May.

"I think we're going to be looking to see if we can find ways to try to find more mutually agreeable ways to deal with some of the issues because we do, in some of our other offices around our center, have some different procedures which have worked quite well that we can potentially export into or import into this area," Marks stated.

Research in cell and gene therapies has grown over the past decade. The Alliance for Regenerative Medicine noted in its Q1 2023 report that there are a total of 1,687 clinical trials in the sector. In 2014, the group reported a total of 699 preclinical and clinical stage trials. The Alliance also noted that the number of INDs at CBERs Office of Tissues and Advanced Therapies (OTAT) grew from less than 400 in 2014 to 666 in 2020. OTAT was reorganized to become the new Office of Therapeutic Products in March.

Bluebird Had Year-Long Hold

Information about clinical holds comes from sponsor disclosures. Investigational drugs that the FDA has put on clinical hold in the last two years include:

- *bluebird bio*'s lovotibeglogene autotemcel (lovo-cel), in development for sickle cell disease, was placed on partial clinical hold in December 2021 and the hold was lifted a year later. (Also see "*Busulfan-Induced Infertility May Deter Some Pediatric Patients From Bluebird, Other Gene Therapies*" - Scrip, 19 Dec, 2022.)

- *Sarepta Therapeutics, Inc.*'s gene therapy Elevidys (delandistrogene moxeparvovec-rokl) for Duchenne muscular dystrophy was put on clinical hold in June 2018 and the hold was removed two months later. The FDA granted the treatment accelerated approval in June 2023. (Also see "*Elevidys Clinical Development: Confidence In Surrogate Endpoint A Longstanding Concern For FDA Reviewers*" - Pink Sheet, 9 Aug, 2023.)

- *Inhibikase Therapeutics, Inc.*'s IkT-148009 for treatment of multiple system atrophy (MSA) and Parkinson's disease was put on clinical hold in November 2002. The clinical hold on the Parkinson's disease program was lifted in January and the hold on the MSA program was lifted in March. (Also see "*Inhibikase Back In Game As FDA Lifts Hold On Multiple System Atrophy Drug*" - Scrip, 8 Mar, 2023.)

- *Astellas Pharma, Inc.*'s AT845, an adeno-associated virus-based gene replacement therapy for adults with late-onset Pompe disease, was placed on clinical hold in June 2022 and the hold was lifted in January. (Also see "*Astellas CEO Yasukawa On Gene Therapy Challenges, Deal Strategies*" - Scrip, 23 Feb, 2023.)

- *Entrada Therapeutics, Inc.*'s ENTR-601-44 for Duchenne muscular dystrophy was placed on clinical hold in December. (Also see "*Duchenne Doldrums Continue As Entrada Hit With IND Clinical Hold*" - Scrip, 22 Dec, 2022.)

- *Gilead Sciences, Inc.*'s studies testing magrolimab in combination with *Bristol Myers Squibb Company*'s Vidaza (azacitidine) in myelodysplastic syndrome and acute myeloid leukemia were placed on partial hold in January 2022 and the hold was lifted in April 2022. (Also see "*Gilead's Magrolimab Mostly Back On Track As FDA Lifts AML, MDS Holds*" - Scrip, 12 Apr, 2022.)

In one case, a company struck back against a clinical hold with a lawsuit. *Regenxbio Inc.* sued the FDA in November 2019 requesting the US District Court for the District of Columbia to set aside the agency's partial clinical hold on its RGX-314 IND for treatment of wet age-related macular degeneration and the full clinical hold on the IND for diabetic retinopathy. Regenxbio claimed the agency did not offer a reasoned explanation for issuing a clinical hold without advance warning.

The FDA removed the clinical hold in January 2020. Regenxbio partnered with *AbbVie Inc.* in 2021 for development and commercialization of RGX-314, which is in Phase II clinical trials.

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Sue Sutter contributed to this article.