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Breakthrough Bounceback Looks Unlikely At US FDA's CDER, But CBER Is Riding Wave Of RMATs

by Bridget Silverman

Only two breakthrough-designated novel agents remain on the US FDA drugs center's 2023 user fee calendar, while CBER stacks up on vaccines and gene therapies under both BTD and RMAT programs.

The US FDA's marquee expedited review program, the breakthrough therapy designation, is likely to see less of an impact on novel approvals in 2023 than in past years, a Pink Sheet analysis indicates.

The Center for Drug Evaluation and Research has approved nine breakthrough-designated novel agents so far this year, or 21% of CDER's 43 new molecular entity and novel biologic approvals in 2023. If that BTD percentage were to hold for the full year, 2023 would have the lowest share of BTD approvals since 2015.

Only two new molecular entities with BTDs are known to have user fee goal dates in the rest of 2023, according to the Pink Sheet US FDA Performance Tracker's Breakthrough Therapy Designations chart: *Bristol Myers Squibb Company*'s next-generation tyrosine kinase inhibitor repotrectinib for ROS1-positive non-small cell lung cancer and *SpringWorks Therapeutics Inc.*'s gamma secretase inhibitor nirogacestat for desmoid tumors.

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Coincidentally, repotrectinib and nirogacestat share a PDUFA goal date – 27 November 2023.

The two BTD drugs account for just 13% of the 15 novel agents are known to be under review at

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CDER with user fee goal dates in the remainder of the year.

Of course, FDA is not limited to acting on the PDUFA goal, and the agency's expedited approach to high-priority applications often results in shorter reviews. The first two months of 2024 host user fee goals for two BTD novel agents, *Eli Lilly and Company*'s Alzheimer's therapy donanemab and *AstraZeneca PLC*'s danicopan for paroxysmal nocturnal hemoglobinuria with extravascular hemolysis (PNH-EVH), that could see early action.

Ripple effects of the COVID-19 pandemic delayed FDA inspections for two novel PD-1 inhibitor candidates with BTDs that were developed in China, leaving reviews of *Coherus BioSciences, Inc.*'s toripalimab and *Akeso Inc.*'s penpulimab running past their 2022 user fee goal dates, both for nasopharyngeal carcinoma indications.

Coherus is now expecting FDA action by year-end after announcing the completion of clinical study site inspections in China on 25 September. The company noted that one site received an FDA Form 483 with one "readily addressable" observation.

CBER Tells A Different Story

While CDER has already exceeded 2022's novel approval total of 37, the heady highs of a few years ago are unlikely given the agency's recent and energetic history of complete response letters. The Center for Biologics Evaluation and Research, on the other hand, is poised for an exceptional year.

CBER's 11 novel biologic approvals to date already make 2023 the best year since 2017, and the center has five more BLAs with Q4 2023 user fee goals.

CBER's purview includes both BTD products and those with the newer, biologics-focused Regenerative Medicine Advanced Therapy (RMAT) designation. Novel biologics with either (or both) of the expedited review designations accounted for six of the 11 approvals so far this year – 55%, or more than double the percentage of CDER approvals with BTDs.

The five pending 2023 BLAs include two gene therapies with RMATs for sickle cell disease – *Vertex Pharmaceuticals Incorporated*/*CRISPR Therapeutics AG*'s exagamglogene autotemcel, with a 8 December goal date following a 31 October advisory committee review, and *bluebird bio*'s lovotibeglogene autotemcel with a 20 December goal – and *Valneva USA Inc.*'s BTD-holding chikungunya vaccine, which now has a November goal date after a three-month extension.

RMATs Ahead

Spring of 2024 brings likely user fee goals for two products that can claim both BTD and RMAT designations: *Abeona Therapeutics*'s gene-corrected skin graft EB-101 for recessive dystrophic epidermolysis bullosa and Pfizer's hemophilia B gene therapy fidanacogene elaparvovec.

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More (just) RMAT-designated gene therapies are on the dock. *Rocket Pharmaceuticals Inc.*'s marnetegragene autotemcel for leukocyte adhesion deficiency-I (LAD-I) has a 31 March 2024 goal date; *Orchard Therapeutics Limited* atidarsagene autotemcel has an 18 March goal for early-onset metachromatic leukodystrophy. Vertex/CRISPR's exagamglogene autotemcel has a second indication with an RMAT but standard review (as opposed to the priority review for the sickle cell indication) for transfusion-dependent beta thalassemia on 30 March.

The goal date for *Iovance Biotherapeutics, Inc.*'s RMAT tumor-infiltrating lymphocyte (TIL) cell therapy for metastatic melanoma has been extended from 25 November 2023 to 24 February 2024.

CDER's 2024 Outlook

The breakthrough novel agents with CDER goal dates in 2024 span a wide range of indications. *Day One Biopharmaceuticals, LLC*'s kinase inhibitor tovorafenib holds down the cancer front, seeking an indication in pediatric low-grade glioma. Two drugs for paroxysmal nocturnal hemoglobinuria patients, AstraZeneca's danicopan and *Novartis AG*'s iptacopan, are up for FDA action.

The high-profile indication of non-alcoholic steatohepatitis (NASH) recently saw one BTD candidate, *Intercept Pharmaceuticals, Inc.*'s obeticholic acid, discontinued after a complete response letter. *Madrigal Pharmaceuticals, Inc.* is hoping for a different outcome by the 14 March 2024 goal date for its BTD NASH candidate, the thyroid hormone receptor-β selective agonist resmetirom.

X4 Pharmaceuticals is targeting a rare primary immunodeficiency, WHIM syndrome, with its chemokine receptor CXCR4 antagonist mavorixafor; if the FDA grants X4's priority review request, the user fee would likely fall in early May.

Sun Pharmaceutical Industries Ltd.'s deuruxolitinib is the third of three breakthrough-designated alopecia areata therapies to head to the FDA. Sun acquired deuruxolitinib developer *Concert Pharmaceuticals, Inc.* earlier this year, hoping to take on the two approved alopecia areata therapies – *Pfizer Inc.*'s Litfulo (ritlecitinib), recently approved 23 June 2023, and Lilly's Olumiant (baricitinib), approved 13 June 2022. All three of the alopecia BTD drugs target different combinations of Janus kinases; deuruxolitinib is a JAK1 and JAK2 inhibitor.

Merck & Co., Inc.'s activin receptor type IIA-Fc fusion protein sotatercept holds the distinction of the only BTD for pulmonary arterial hypertension (PAH). The BLA has a 26 March priority review goal date.

Breakthroughs Beyond Novel Agents

Most of the pending applications with BTD or RMAT designations are for novel agents, but a few

new indications and new formulations are also on deck.

US WorldMeds, LLC's oral eflornithine passed out of an advisory committee 4 October 2023 with a 14-6 vote that efficacy had been demonstrated for pediatric high-risk neuroblastoma based on an externally controlled trial with animal data as confirmatory evidence. (Also see "*US WorldMeds' Neuroblastoma Drug: External Controls, Confirmatory Evidence, And A Concern About Precedent*" - Pink Sheet, 12 Oct, 2023.)

The candidate is being evaluated under the FDA's Real-Time Oncology Review pilot program, although the drug cannot be one of the super-fast RTOR approvals; the NDA was submitted 22 November 2022.

Earlier in the year, *AbbVie Inc.* discontinued a topical cream formulation of the ornithine decarboxylase inhibitor approved as Vaniqa for unwanted facial hair.

Takeda Pharmaceutical Co. Ltd.'s TAK-721, an oral viscous formulation of the steroid budesonide for eosinophilic esophagitis formerly known as Eohilia, is back at the FDA more than a year after the company discontinued development in the wake of a complete response letter. The resubmitted NDA seeks a revised indication for short-term treatment. A February goal date is likely.

Mirum Pharmaceuticals, Inc. is seeking a second BTD indication for the ileal bile acid transporter inhibitor Livmarli (maralixibat). The company recently announced an extension of the user fee date for its sNDA for progressive familial intrahepatic cholestasis (PFIC) to 13 March.

And Servier's Tibsovo (ivosidenib) has a likely December 2023 goal date for a new indication for IDH1-mutated relapsed or refractory myelodysplastic syndromes.