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05 Jul 2021 | **Analysis**

US FDA's Novel Approval Count Hits 32 In First Half Of 2021, With More Than 40 Goal Dates Ahead

by Bridget Silverman

CDER approved a record 27 novel agents between January and June, while a wave of cell therapy and vaccine applications could carry the biologics center to new heights. Merck could close year with four novel approvals.

The strength of the regulatory system set up by the Prescription Drug User Fee Act (PDUFA) and its reauthorizations has been highlighted by the US FDA's strong and consistent performance on review metrics during the disruptions of a historic disease outbreak.

The FDA's Center for Drug Evaluation and Research cleared 27 new molecular entity and novel biologic approvals in the first six months of 2021 – the largest first-half novel agent tally in a decade. The previous high-water mark for first half approvals, 25, was set in the similarly pandemic-influenced year 2020. (*See sidebar for infographic.*)

The Center for Biologics Evaluation and Research approved five new biologics, matching the center's 2020 full-year novel therapeutic biologic approval total before the end of June 2021. With user fee goal dates for six more CBER BLAs in the second half of the year, the biologics center could match its recent record for full year approvals: the 11 novel CBER therapeutic biologic approvals in 2017.

CDER's user fee calendar for July to December 2021 features 36 novel agents. That number all but guarantees another remarkable annual tally for the full year. (Also see "*Lineup Of US FDA's Potential Novel Approvals In H2 2021*" - Pink Sheet, 5 Jul, 2021.)

2021 Approvals By The Numbers

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The agency has been issuing complete response letters and missing user fee goals more often during the pandemic than in the years immediately before, but the numbers are still low. During 2019 and first half 2021, CDER approved three-quarters of the pending novel agents. In 2018, 87% of CDER decisions on novel agents were approvals.

05 Jul 2021
Looking ahead and looking back, our infographic describes the approval trends at the midpoint in this extraordinary year.

Read the full article here

If the agency were continue approving 75% of applications during the second half of 2021, CDER would approve another 27 novel agents for a full-year tally in the neighborhood of 54 novel agents.

However, historically the second half of the year sees more approvals than the first. And 2021 could see a small one-time approval bolus of applications with missed user fee goals, now that the FDA is able to schedule manufacturing inspections previously precluded by COVID-19 travel restrictions

Keep An Eye On Merck

Only a few companies are in position to expect multiple novel agent approvals in 2021. *Merck & Co., Inc.*started out front, receiving the first novel approval of the year on 19 January for Verquvo (vericiguat), a soluble guanylate cyclase (sGC) stimulator for symptomatic chronic heart failure patients with an ejection fraction less than 45%. Merck is likely to stay in a leading role, given the company's three novel agents with second half 2021 user fee goals.

Merck's novel applications come from across the company's divisions. The vaccines business is awaiting FDA action on the breakthrough therapy-designated 15-valent pneumococcal vaccine V114 by its 18 July user fee goal. In oncology, Merck's hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor belzutifan for treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC) has a 15 September user fee date. And as the year comes to an end, Merck will be looking for an FDA decision on gefapixant, a selective P2X3 receptor antagonist with 21 December goal for treatment of refractory chronic cough (RCC) or unexplained chronic cough (UCC) in adults.

Johnson & Johnson's *Janssen Pharmaceuticals Inc.* business was the only sponsor to receive multiple approvals in the first half, thanks to one approval each in the two most active therapy areas, oncology and nervous system therapeutics. The sphingosine 1-phosphate receptor modulator Ponvory (ponesimod) was approved for relapsing forms of multiple sclerosis on 18 March. The bispecific EGF receptor- and MET receptor-directed antibody Rybrevant (amivantamab-vmjw) received accelerated approval on 21 May for a breakthrough-designated

indication for platinum-experienced non-small cell lung cancer (NSCLC) patients with EGFR exon 20 insertion mutations.

Janssen's next novel approval opportunity will come from CBER. The B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy ciltacabtagene autoleucel (cilta-cel), which holds a breakthrough therapy designation, has a 29 November goal date for relapsed and refractory multiple myeloma.

If approved, cilta-cel would be the third novel CAR-T therapy approved in 2021 and the sixth overall. CBER approved two *Bristol Myers Squibb Company* CAR-T products in the first half: the BCMA-targeting Abecma (idecabtagene vicleucel), approved 26 March for multi-refractory multiple myeloma, and the CD19-directed Breyanzi (lisocabtagene maraleucel) for third-line or later large B-cell lymphoma on 5 February. Both Abecma and Breyanzi hold breakthrough therapy designations (BTDs); Breyanzi also carries a regenerative medicine advanced therapy (RMAT) designation.

Pfizer Inc. has one product under review at CBER – the tick-borne encephalitis vaccine TicoVac, with a likely user fee goal in August – and two upcoming user fee dates at CDER. The oral Janus kinase 1 (JAK1) inhibitor abrocitinib has a late July user fee goal for moderate to severe atopic dermatitis after receiving a three-month extension. Pfizer partnered with *Opko Health* on somatrogon, a glycosylated long-acting human growth hormone, which has a likely October user fee date for pediatric growth hormone deficiency.

Two novel agents from *Takeda Pharmaceutical Co. Ltd.*, both with BTDs, are in line for autumn FDA decisions. Takeda is seeking accelerated approval for the kinase inhibitor mobocertinib for platinum-experienced NSCLC patients with EGFR Exon 20 insertion mutations with a 26 October goal date. The oral antiviral maribavir is under review for refractory post-transplant cytomegalovirus (CMV) infections in solid organ transplant or hematopoietic cell transplant (HCT) recipients, with a November goal.

Manufacturing Inspections: The Rate-Limiting Step?

The pandemic forced the FDA to develop alternative tools to assess manufacturing facilities while travel was precluded, including remote review of records and remote site visits, keeping the backlog of applications with missed inspections to a manageable level – and reducing (but not eliminating) concerns that a bolus of overdue inspections in addition to the FDA's normal workload could result in future bottlenecks or delays. (Also see "*Drug Manufacturers Beg US FDA To Inspect Facilities, But Still Find Difficulties*" - Pink Sheet, 1 Mar, 2021.)

During the pandemic, the agency is known to have missed the user fee goals for just six novels agents that were missing a pre-approval inspection but did not pose other issues necessitating a complete response letter. Three of the COVID-19-delayed entities have already been approved.

Acting FDA commissioner Janet Woodcock told a recent Senate appropriations hearing that the agency expects to have its facility inspection program "running fully" this summer in the US. Foreign inspections could take longer to return due to local conditions. In India, for example, a spike in COVID-19 infections caused the agency to suspend the restart of in-person facility inspections. (Also see "*Domestic In-Person Inspection Work Could Be Back To Normal This Summer, Woodcock Says*" - Pink Sheet, 17 Jun, 2021.)