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US FDA's Use Of CRLs Hit A High Note In 2022: One-Third Of Novel Agent Decisions Were Not Approvals

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Pink Sheet infographic details the 20 complete response letters the US FDA issued for novel agents last year.

The number of US FDA complete response letters known to have been issued for novel agents in 2022 inched up from 2021 – from 18 to 20, according to the Pink Sheet FDA Performance Tracker's Complete Response Letters chart – but the drop off in novel approvals in 2022 gave the CRL its biggest workout in years: 31% of the agency's decisions on novel agents resulted in a CRL.

With 2021's high novel approval count of 60 agents across both FDA's drug and biologics centers, CRLs only made up 23% of last year's novel agent actions, but that proportion continued a steady upward trend over the past few years. The leap to 31% in 2022, however, is the biggest single year jump.

The COVID-19 pandemic contributed to the growth in non-approval actions from CRLs to deferring decisions past user fee goal dates; while the worldwide impact has lessened, COVID-19 restrictions remain a major factor complicating the evaluation of candidates from the growing Chinese biotech industry. But many of those same products also raised concerns independent of the pandemic.

In particular, the FDA has emphasized the need for efficacy data from trials conducted in clinical contexts that are applicable to US patients. *Eli Lilly and Company*, for example, chose to discontinue development of the PD-1 inhibitor sintilimab, from its Chinese partner *Innovent Biologics, Inc.*, after the FDA's CRL called for multiregional trials. (Also see "*Foreign Data: Sintilimab's Development Shows What Not To Do When Pursuing US Approval*" - Pink Sheet, 16 Feb, 2022.)

Almost half of the 2022 CRLs called for a new clinical trial, an expensive and time-consuming step for sponsors.

The FDA has also been working to head off negative decisions before reaching the end of a review cycle. At least 10 applications were withdrawn or received a refuse to file (RTF) letter in 2022. (Also see "*With 37 Novel Approvals in 2022, US FDA CDER's Five-Year Hot Streak Comes To An End; Gene Therapies Carry CBER To 8 Novel Approvals*" - Pink Sheet, 2 Jan, 2023.)

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