Evaluate Vantage

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Drug rejections hold steady in 2020

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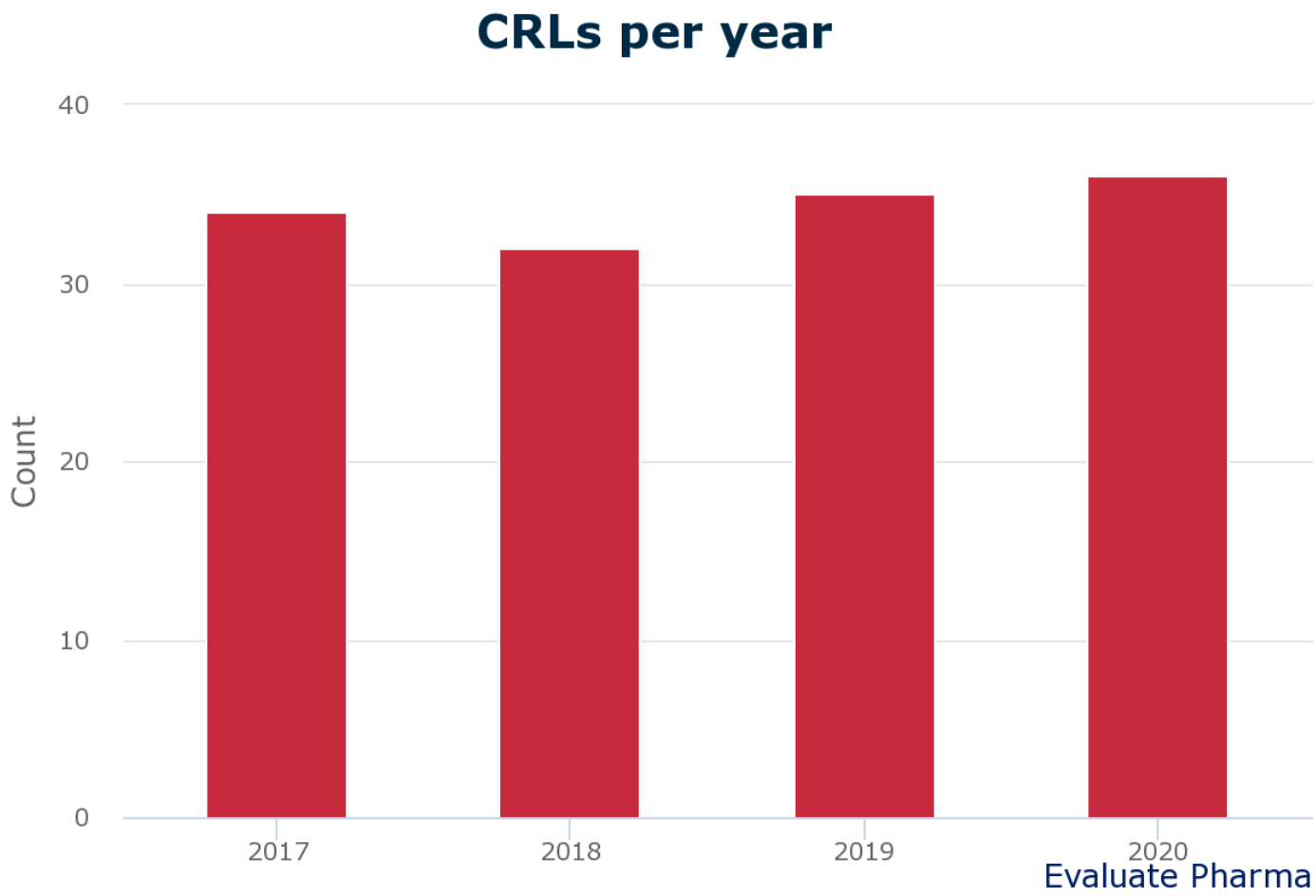
Concerns about a rise in complete response letters in 2020 come to naught, but this might not reassure drug developers.

Fears are growing that the US regulator is becoming strict, and several examples of the agency playing hardball have been seen in 2021. However, an *Evaluate Vantage* analysis of complete response letters finds little evidence of an uptick in last year's numbers.

It is possible that the situation has evolved more recently, and some analysts have warned investors about an increasingly harsh regulatory environment. But even the number of CRLs that the US FDA has issued so far this year – five, including yesterday's rejection for Acadia's Nuplazid in dementia-related psychosis – does not raise eyebrows.

This analysis uses *Evaluate Pharma's Calendar of Events*, which draws from all publicly available press releases, SEC filings and annual reports; the FDA does not release a count of CRLs so this analysis relies on company disclosure, meaning that the real numbers could be higher.



This CRL record should be read against a backdrop of a slight increase in filings: the FDA's most recent Pdufa reports show a total of 174 NDAs and BLAs in calendar year 2020*, compared with 156 in 2019 and 159 in 2018.

Even if CRLs are not on the rise, there are other reasons to believe that the agency might be clamping down after years of apparent leniency, such as the surprise adcom for Fibrogen/Astrazeneca's roxadustat, and another scheduled this month to discuss the status of accelerated approvals for six PD-(L)1 drugs.

Meanwhile, Abbvie has been hit by a three-month extension to the review time for its Jak inhibitor Rinvoq in psoriatic arthritis and, on Friday, atopic dermatitis, just as the safety profile of the Jaks is coming under closer scrutiny.

With approval decisions in atopic dermatitis due soon on two other Jaks, Pfizer's abrocitinib and Lilly's Olumiant, the agency's stance here should become clear shortly.

The perceived change in the regulator contributed to Leerink's Geoffrey Porges recently downgrading six biopharma companies to market perform; specifically, he highlighted "more challenging drug reviews at the FDA" as well as greater scrutiny of M&A by the Federal Trade Commission as factors leading to a tougher environment for biopharma.

Perhaps this is no bad thing. The FDA should not approve drugs without clear evidence of their efficacy and safety, and is arguably just doing its job by setting a high bar here.

Acadia falls again

But Acadia is clearly aggrieved at what it believes were shifting goalposts. The Nuplazid CRL itself was not a surprise after the agency said last month that it had identified deficiencies in its filing; the surprise was that the FDA found fault with Acadia's phase 3 trial, Harmony – apparently changing its mind about this trial's design. This could be a worrying development for other biopharma groups.

According to Acadia, the regulator had previously agreed that Harmony would analyse a broad dementia-related psychosis population – in which the trial met its primary endpoint – but has now said that there was a lack of statistical significance in some subgroups of dementia, and insufficient numbers of patients with less common dementia subtypes.

The FDA also described Acadia's phase 2 019 study, used to support the filing, as not adequate or well controlled. On the plus side, the agency did not raise any safety concerns.

Stifel analysts say the company will have to run one or even two more trials here, so it might be time to write off this potential money spinner: dementia-related psychosis is thought to be 10 times bigger than Parkinson's disease psychosis, for which Nuplazid is already approved.

Acadia fell 17% yesterday after already slumping 45% in March. Nerves will be jangling at other groups with questionable datasets and big approval decisions coming up. Biogen springs to mind.

**Note: FDA's financial year runs September to September, so 2020 Pdufa report covers Q1-Q3 calendar 2020, and 2021 Pdufa report covers Q4 calendar 2020.*