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Drug rejections rise as Covid-19 bites

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Alkermes manages to shrug off yesterday's complete response letter, but US knockbacks in 2020 are creeping up.

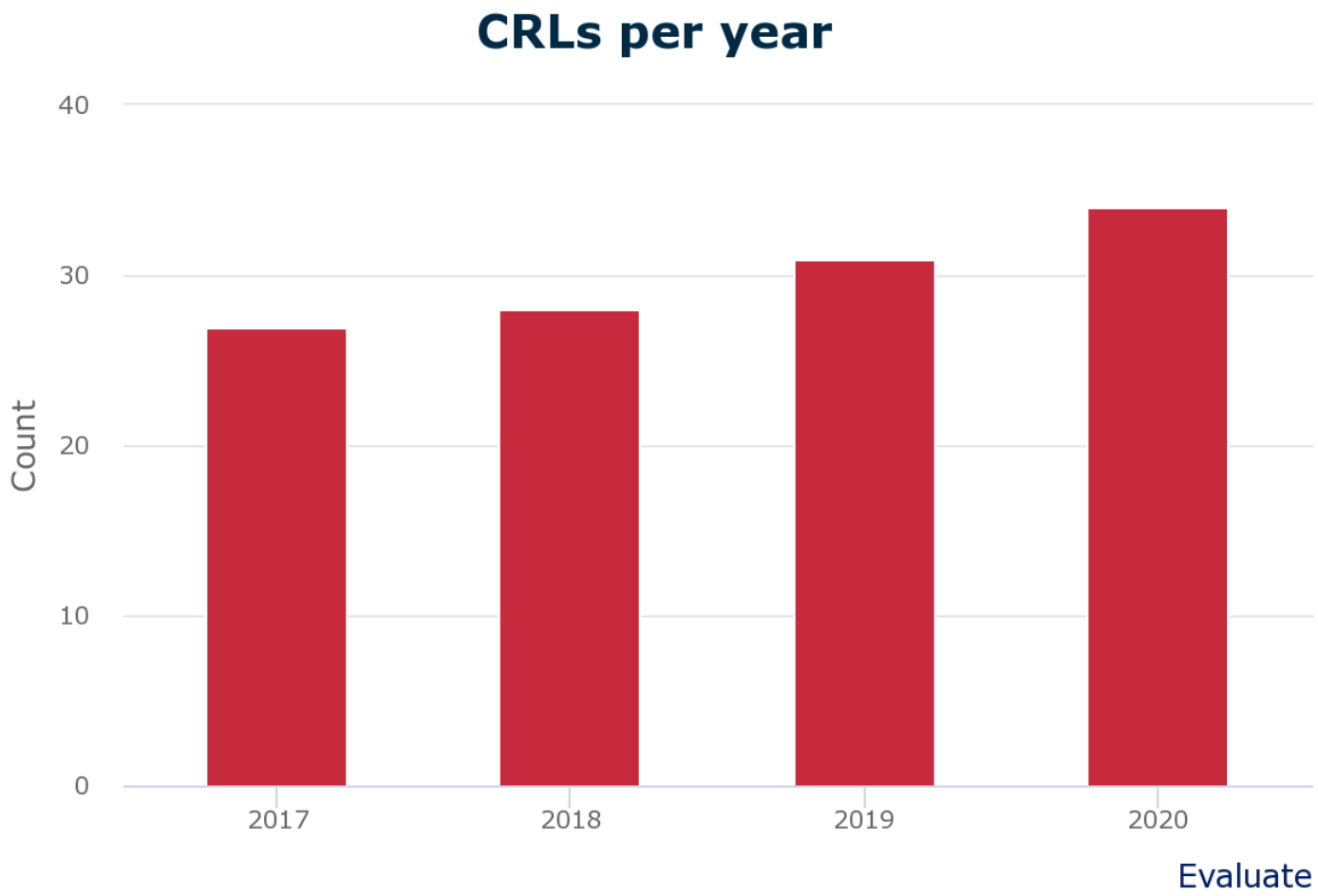
The coronavirus pandemic has had many negative consequences. One that is now beginning to bite for biopharma companies is that the US FDA cannot carry out as many inspections as in the past.

This has led to recent cases of delayed approval decisions and outright rejections. Alkermes yesterday became the latest to suffer this fate with a complete response letter for its antipsychotic ALKS 3831. Although the company seems to have convinced investors that this was just a minor blip, other groups might not be so lucky. And a look at the numbers shows that there have already been more CRLs in 2020 than in the past few years.

How many of these are down to Covid-19 is unclear. There has also been a perception that the agency is becoming stricter, partly spurred by the surprise August knockbacks for Galapagos's filgotinib and Biomarin's haemophilia A gene therapy valrox.

But in the past week there have been four CRLs related to chemistry, manufacturing and control issues, which might point to problems with inspections, plus a delay to a decision on Bristol Myers Squibb's liso-cel because Covid-19 travel restrictions left FDA staff unable to inspect a Texas manufacturing plant.

The latest rejections put the CRL count for this year, as of November 17, at 34 – already more than the 31 seen in 2019, as revealed in a previous analysis by *Evaluate Vantage* (*Has 2020 been a big year for regulatory knockbacks?, September 17, 2020*).



These analyses are based on publicly disclosed data and therefore probably understate the real figures.

The rise in CRLs could also be a function of more applications to the FDA; the latter have remained broadly in line over the past few years, according to the agency's annual report, but 2020 numbers are not yet available.

The previous analysis also found that, historically, CRLs tended to peak in August, with numbers dropping off in the last few months of the year.

That has not been the pattern in 2020: there were four CRLs in October, and there have already been four so far in November, supporting the idea that this autumn's Covid-19 surge might at least be partly to blame for the rising numbers.

The virus was certainly a major factor behind ALKS 3831's CRL. Covid-19 restrictions meant that, instead of an in-person inspection, the FDA carried out a remote records review, which raised issues with the tablet-coating process. Under the new procedures the agency then had two options: to extend the Pdufa date until an in-person inspection could happen, or issue a CRL asking for additional data.

Pre-Covid, in-person inspections would identify potential manufacturing problems that could be addressed before the Pdufa date; ultimately, the CRL "might not have happened had the pre-approval inspection been in person", Stifel analysts wrote.

According to Alkermes, the problems with tablet coating were resolved some time ago, and the group already has the data to address these – and it hopes to launch ALKS 3831 in the first quarter of 2021, as per its original plans. Its firefighting efforts yesterday paid off: after dipping in the morning Alkermes's stock closed up 3% yesterday.

However, as US Covid-19 cases continue to surge, things are only going to get worse, and Alkermes is unlikely to be the only company to face this kind of issue.

Novartis's Leqvio (inclisiran) is an example of a project that might be running out of time. The RNAi asset, gained through the $9.7bn acquisition of The Medicines Company, has a Pdufa date in December, but Novartis's chief executive, Vas Narasimham, said during the group's third-quarter earnings call on October 27 that an inspection of a facility in Italy had not been carried out.

Even with vaccines coming, it will be a while until FDA inspections get anywhere approaching normal. Until then, there might be a further rise in CRLs.

This story has been updated to take into account the number of filings with the FDA.