Evaluate Vantage

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Regulatory rejection flurry does not make a storm

Amy Brown

Fears of heightened scrutiny by the FDA will be calmed by a look at historic rates of complete response letters.

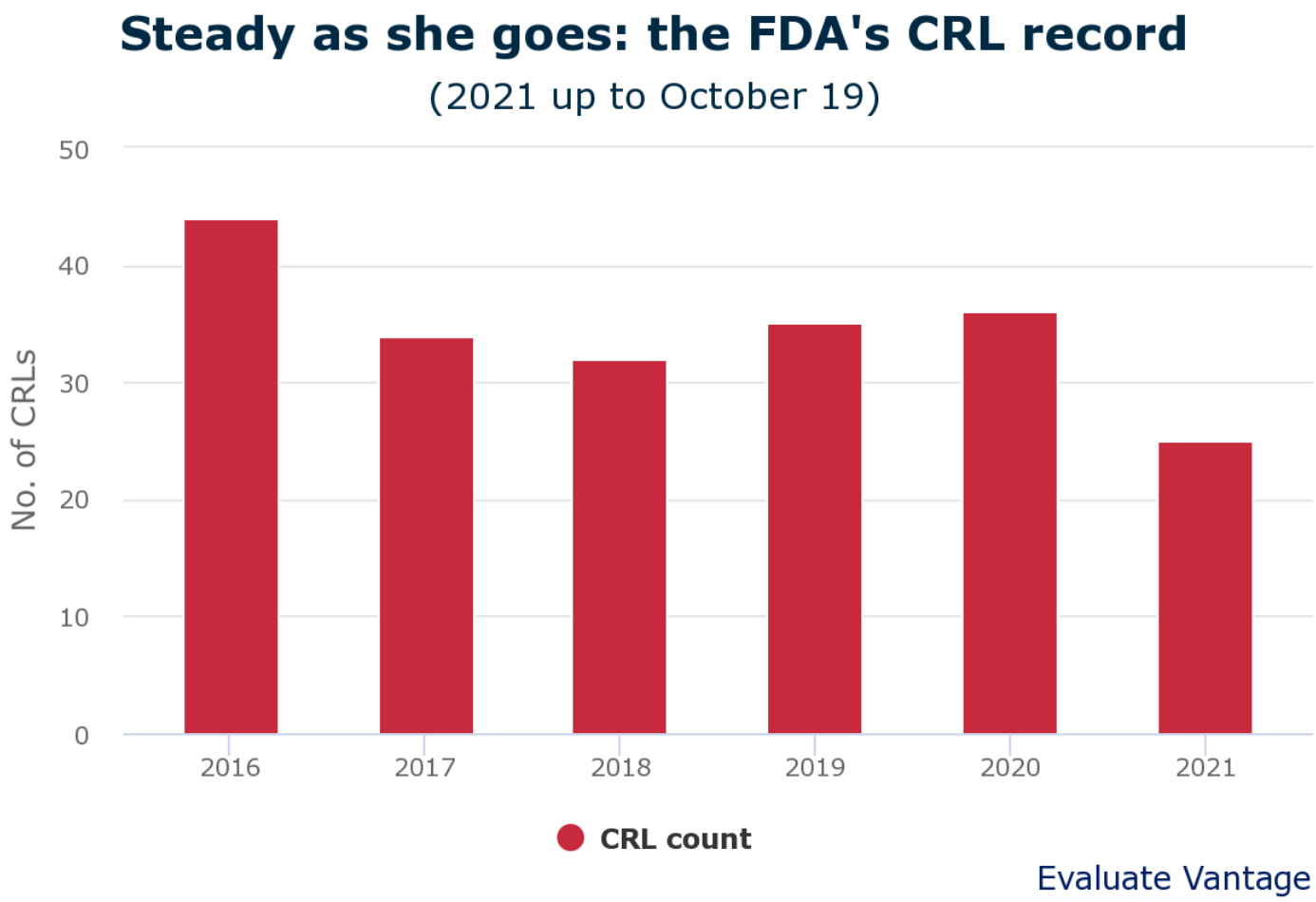
This week started with a bang for US regulatory action, with three complete response letters and two delays to an approval decision, a flurry that inevitably raised eyebrows. Whether the FDA is shifting away from what many believe is a permissive phase is a major preoccupation for biopharma.

However, the latest rejections take 2021's CRL tally to 25, according to *Evaluate Vantage's* calculations, meaning that this year is not shaping up to contain any more than previous years. This should provide some comfort to those in the business of getting drugs to market, though regulatory delay due to Covid-19 is still a live issue.

This was the reason cited by the FDA for missing bimekizumab's October 15 Pdufa date, according to the psoriasis MAb's developer, UCB. The FDA told the Belgian company that it was unable to conduct on-site inspections because of travel restrictions, certainly not the first time this has happened.

The agency has issued guidance for reviews being conducted during the pandemic, stating that action may be deferred if Covid-19 issues prevent on-site inspections, provided that "no deficiencies have been identified, and that the application otherwise satisfies the requirements for approval". Should these conditions not be met a CRL is given, so this will raise hopes for bimekizumab's eventual approval.

The pandemic will not always lie behind delays, of course, but because it is down to companies to disclose any reasons given investors cannot always fully determine what might lie behind a hold-up. This was certainly true with this week's other delay, for Avadel's narcolepsy project FT281. The company claimed that it was given no reason by the agency, and for now the lack of a formal CRL can possibly be read as a positive.



The issue of company disclosure raises the major caveat around the CRL count above: it is based on companies announcing publicly that they have received one. Private developers and some larger groups might not always disclose that they have been knocked back, or not at the time anyway, so the figures above could be an understatement.

This count was constructed from *Evaluate Vantage's* monthly FDA approval tracker, and *Evaluate Pharma's* Calendar of Events, which can help capture those CRLs revealed retrospectively.

There are limits to the conclusions that can be drawn from this, of course. A better idea of the agency's tolerance levels would probably require other inputs like the volume of drug applications each year and the rate at which CRLs were converted into approvals. But at the very least the chart rules out any notable uptick in CRLs.

All the while mixed messages continue to emerge from the FDA, keeping biopharma and its investors on their toes. Biogen's Aduhelm, for example, was approved despite very weak signals of efficacy, while the agency's rejection of Fibrogen's roxadustat on safety concerns came in spite of other major global regulators' willingness to grant the anaemia pill a green light.

October CRLs so far			
Project	**Company**	**Setting**	**Details**
Myring	Mayne Pharma	Generic contraceptive ring	Additional data on compatibility required
DaxibotulinumtoxinA	Revance	Glabellar lines (Botox follow-on)	Manufacturing deficiencies
Tyvaso DPI	United Therapeutics/ Mannkind	Pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease	Deficiencies at contract manufacturer
Narsoplimab	Omeros	Haematopoietic stem cell transplant-associated thrombotic microangiopathy	Additional clinical data needed
Source: Evaluate Pharma.			