Evaluate Vantage

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Regulatory developments over the Christmas period

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The FDA and Biogen come in for fierce Congressional criticism, and a handful of new cancer drugs are approved in Japan.

Regulators in the US and Japan have granted a spate of end-of-year green lights, allowing companies including TG Therapeutics, Astrazeneca, Regeneron and Roche to start the new year with new products for multiple sclerosis and various cancers.

The big news came late on Thursday, though, with the publication of a Congressional report on the assessment, approval and pricing of Biogen's Aduhelm. Both the company and the FDA were sharply castigated for a number of irregularities, including unusual levels of co-operation between the two parties.

December 29:

A US Congressional report, the culmination of an 18-month investigation into the approval of Aduhelm, found fault with the FDA's regulatory approach to **Biogen**'s Alzheimer's drug.

The report said the FDA's interactions with Biogen were "atypical and failed to follow the agency's protocol", with some of the meetings between the agency and Biogen not being properly documented. It also found that the FDA and Biogen had "inappropriately collaborated" on a briefing document for Aduhelm's November 2020 adcom, glossing over disagreements within the FDA about the drug's benefits.

Ardelyx said the FDA had allowed it to appeal against a complete response letter issued last year for Xphozah for the control of serum phosphorus in adults with chronic kidney disease on dialysis, an indication that last month got a positive adcom vote. The previous day the agency refused to U-turn on **Minerva**'s schizophrenia project roluperidone, which got a refuse-to-file letter in October.

December 28:

The setbacks of **TG Therapeutics**' ublituximab were briefly forgotten when the drug got US approval for multiple sclerosis after a three-month delay. It will be trademarked Briumvi, and will compete against other anti-CD20 MAbs, including **Roche**'s behemoth Ocrevus; the key selling point will be administration via one-hour infusion – shorter than Ocrevus's 2-4 hours.

There was a flurry of Japan approvals too, with **Astrazeneca**'s Imfinzi plus Imjudo approved in front-line liver, biliary tract and non-small cell lung cancers. The combo added these three uses to its US label recently, while

in the EU the biliary tract indication is approved and the other two have received positive CHMP opinions.

Five days earlier the Japan regulator had approved **Regeneron**'s Libtayo for the first time. The drug's first indication is second-line cervical cancer, the same use that had been withdrawn in the US, likely as a result of insufficient data on Libtayo's effect in patients who were not PD-L1-positive.

December 27:

Springworks filed its gamma secretase inhibitor nirogacestat in the US for the niche use of treating desmoid tumours, based on the Defi study, whose results had impressed at Esmo. An FDA decision is due in 2023, but multiple myeloma remains key to unlocking nirogacestat's full potential.

Acer and its partner **Relief Therapeutics** managed to secure US approval for ACER-001, their urea cycle disorder therapy, at the second time of asking. The drug is branded Olpruva, and will be available to treat deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinic acid synthetase.

Acer's share price dropped by a third, however. The approval unlocks a $42.5m term loan Acer secured in March, and while this ought to give Acer a cash runway to the second half of 2023, debt funding is always risky. 2028 forecasts for Olpruva sit at $109m, according to *Evaluate Pharma*'s sellside consensus.

December 24:

Wegovy, **Novo Nordisk**'s form of semaglutide for obesity, gained a label extension in the US, with the FDA approving the GLP-1 receptor agonist for use in patients aged 12-18 with BMI at the 95th percentile or greater. The approval was based on the phase 3a Step-Teens study, in which Wegovy allowed a 16.1% decrease in BMI, versus a 0.6% increase with placebo.

December 23:

Ipsen's palovarotene got a US complete response letter for fibrodysplasia ossificans progressiva. This marked the latest in a litany of setbacks for a project Ipsen had bought for $1bn through Clementia; along the way palovarotene had gone on clinical hold, failed its phase 3 trial, and seen off Ipsen's chief executive, David Meek.

Intercept resubmitted obeticholic acid for US approval in Nash, a year after pulling an EU filing, and two and a half years after receiving a complete response letter citing concerns that activity based on a surrogate histopathologic endpoint might not outweigh potential risks. An FDA decision is due in mid-2023.

The filing came shortly after **Madrigal**'s resmetirom scored in a pivotal Nash study, but Madrigal itself is now mired in a minor controversy. Though the study in question, Maestro-Nash, aced its primary endpoints, once the dust settled sharp-eyed observers noticed that somewhere along the line the company had changed its definition of one of these, Nash resolution.

What had previously been defined as a reduction in Nash activity score was this year changed to a reduction in NAFLD activity score. What the FDA makes of the appropriateness of such an endpoint will only become evident once resmetirom goes before the regulator in the second half of 2023.

December 22:

Roche's anti-CD20 bispecific Lunsumio got US approval for follicular lymphoma, adding to the EU green light it received in June. A separate Roche project with this mechanism, glofitamab, is awaiting US approval for the more aggressive diffuse large B-cell lymphoma, as is Abbvie/Genmab's competitor epcoritamab.