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Go or no go? Ionis, Sanofi, Regeneron and Roche await big regulatory decisions

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October looks to be a big month for label expansions, with Dupixent and Hemlibra both poised to move into big new patient populations. Meanwhile Ionis is awaiting a make-or-break FDA verdict.

Drug developers big and small are awaiting crucial decisions from the US FDA on October. And updates on companies' efforts to expand into new markets look just as likely to move share prices as first-time approvals.

Sanofi and Regeneron are in both camps – their atopic dermatitis drug Dupixent is awaiting approval to move into asthma, while the partners' anti-PD1 antibody cemiplimab should get a green light for its first US market launch. Among the smaller players, Acacia Pharma and Paratek should all learn in October whether their commercial ambitions will be fulfilled.

Notable October first-time approval decisions			
Product	**Company**	**PDUFA date**	**Product NPV ($bn)**
Bryhali	Bausch Health	Oct 5	0.11
Barhemsys (Baremsis)	Acacia Pharma	Oct 5	N/A
Tegsedi	Ionis Pharmaceuticals	Oct 6	1.67
Tegsedi	Akcea Therapeutics	Oct 6	1.61
Omadacycline (IV)	Paratek	Early October	0.11
Omadacycline (Oral)	Paratek	Early October	0.51
Seysara	Almirall/Allergan	October (Evaluate estimate)	N/A*
Cemiplimab	Regeneron	Oct 28	1.23
Cemiplimab	Sanofi	Oct 28	1.79
TX-001HR	TherapeuticsMD	Oct 28	0.57
**Consensus from Almirall analysts not yet available; Source: EvaluatePharma.*			

Bausch Health, formerly known as Valeant, is waiting for news on one of its new topical psoriasis treatments, Bryhali. A formulation of halobetasol, it is forecast to sell $66m by 2024, according to *EvaluatePharma*, making it the company's eighth most important sales growth driver. While the approval itself is not hugely pivotal to Bausch, it does represent a test of management's turnaround strategy for the company's shrinking dermatology unit. A demonstrable ability to get new products to market will also help shake off the shadows of the Valeant days.

Acacia Pharma has much riding on timely approval of Barhemsys. The antiemetic, targeted at a post-operative market, is the small British drug developer's most advanced project; investors who backed the company's IPO on Euronext earlier this year are expecting a yes. The fact that the regulator decided not to convene an advisory committee to discuss the product could be taken as a promising sign. Barhemsys is an intravenous formulation of the dopamine antagonist amisulpride, so the active ingredient is well known to the regulator.

Antisense worries

The path might not be so straightforward for others. Questions around the approvability of Ionis's Tegsedi were raised when the FDA knocked back Waylivra, another project from the company's antisense platform, in August. Like Waylivra, Tegsedi has been associated with thrombocytopaenia, a safety signal that the regulator will not take lightly.

So investors in the RNA researcher and its spin-off Akcea will be nervously awaiting the verdict – a second setback will be a huge blow. Tegsedi has been filed to treat polyneuropathy in patients with hereditary transthyretin amyloidosis, and encouragingly has already received a green light in Europe. The FDA, however, has already delayed its decision by three months, and the lack of an advisory committee hearing means that it is hard to glean any insight into the agency's eventual decision.

Meanwhile, the backing of an advisory committee in August for Paratek's novel tetracycline antibiotic bodes well for a green light. Paratek is hoping to receive approval for both intravenous and oral forms of omadacycline, for two uses: acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. However, a more decisive vote in favour of the former leaves some doubts about the breadth of the label.

Paratek is essentially a one product company – consensus for omadacycline sales in 2024 total $417m, according to *EvaluatePharma* – so the company has much riding on the outcome.

When Almirall agreed to pay Allergan $550m for five dermatology products in August, Seysara stood out as the biggest commercial hope. The Spanish group predicted peak sales of $150-200m for the oral, narrow-spectrum tetracycline antibiotic, which is up for approval to treat acne. Its unique selling point is better safety and tolerability than, but comparable efficacy to, the widely-used doxycyclines. The transaction has yet to conclude and presumably is not contingent on a green light for Seysara, though the fact that the product's PDUFA date falls in the crucial closing period will be making both companies nervous. Paratek will also be awaiting this decision with interest – it originally licensed Seysara to Allergan and is entitled to royalties on sales.

Sanofi and Regeneron are waiting to hear whether cemiplimab will become the fifth anti-PD(L)-1 checkpoint inhibitor to reach the US market, an accolade of questionable commercial potential. The sellside is currently pencilling in sales of $245m in 2024, according to consensus from *EvaluatePharma*; the partners argue that having an in-house checkpoint inhibitor to combine with other mechanisms is important for the future. This initial approval is required first, however; cemiplimab has been filed in advanced cutaneous squamous cell carcinoma, for which there are no approved treatments. The regulator's decision is unlikely to prove controversial, though questions about the product's longer-term potential could linger.

TherapeuticsMD won approval for Annovera, a novel birth control product, in August, and will be hoping to repeat the trick with TX-001HR. This is intended as a treatment for moderate-to-severe vasomotor symptoms of menopause, including hot flushes and night sweats; it comprises bio-identical hormones, estradiol and progesterone, in a single pill. The sellside has attached some eye-watering numbers to the project – consensus sits at $803m by 2024, according to *EvaluatePharma*, a remarkable number considering the product is essentially available generically. TherapeuticsMD's biggest challenge could well prove to be the market, rather than the regulator.

October should also hold some pretty big news on the label expansion front.

Roche's Hemlibra has already stormed a niche of the haemophilia A market – patients with inhibitors. And Roche will hope to do the same in the broader non-inhibitor population, with an FDA decision due here by October 4.

Approval looks likely after impressive data from the Haven 3 trial, but the main battle might be getting well-controlled patients to switch, particularly after several patient deaths, which Roche has maintained were not related to therapy. Barclays analysts estimate that around 30% of non-inhibitor patients are not well controlled, while 40% are "semi-controlled" – and Roche will likely target these groups initially. The company will need to make a mark in non-inhibitor patients if Hemlibra is to hit the $3.9bn 2024 sales forecast by sellside consensus.

Supplementary approvals and other notable regulatory decisions for October			
Product	**Company**	**Event Type**	**Date**
Hemlibra	Roche	Label extension to haemophilia patients without inhibitors.	Oct 4
Gardasil 9	Merck & Co	Label extension to older women and men.	Oct 6
Dupixent	Regeneron/Sanofi	sBLA in persistent asthma.	Oct 20
Bivigam	ADMA Biologics	Decision to allow the company to relaunch its IVIG product.	Oct 25
Xyrem	Jazz Pharmaceuticals	sNDA in excessive daytime sleepiness in paediatric narcolepsy patients.	Oct 27
Keytruda	Merck & Co	sBLA in first-line, metastatic squamous NSCLC.	Oct 30
Ilaris	Novartis	Decision on canakinumab in cardiovascular risk reduction.	October
Invokana	Johnson & Johnson	Decision on inclusion of cardiovascular outcome data.	October
Saxenda	Novo Nordisk	Decision on inclusion of cardiovascular data.	October
Tymlos	Radius Health	Decision on the addition of data from the ActiveExtend study	October
Xarelto	Bayer/Johnson & Johnson	Decision on inclusion of Compass data and two new indications.	October
Source: EvaluatePharma.			

Sanofi and Regeneron will be hoping for good news on Dupixent in the form of a second approval in persistent asthma. The anti-IL4 antibody is already on the market as a treatment for atopic dermatitis, which is forecast to be a $4bn indication by 2024; adding asthma could bring in another $1.3bn in sales that year, analysts believe. Anything other than approval will come as a huge surprise, although the devil could be in the details of the label. Other antibodies, namely the anti-IL5 class, are restricted to patients with high eosinophils, but the Dupixent partners are hoping to tap into a much broader patient population. The phase III trials designed to support this claim were not as clearly positive as hoped, so the approval could yet be tinged with disappointment.

Approval for Novartis's canakinumab to reduce the risk of cardiovascular events is another big supplementary decision looming, although the Swiss giant has been pretty tight-lipped about the project. The drug, which is currently on the market as a gout treatment, demonstrated intriguing efficacy in a subgroup of patients in the Cantos trial, appearing to show a lowering of risk of heart attack in patients with high levels of a marker called hsCRP. Novartis has said it expected an adcom on the drug's use in the cardiovascular space but none has been announced, and any update on the way forward in what could be a lucrative new space for the drug is eagerly awaited.

Merck is hoping to add yet another string to Keytruda's bow with approval in squamous non-small cell lung cancer – following a widely-applauded presentation at this year's Asco, it seems likely that physicians are already using the checkpoint inhibitor to treat this very poorly served lung cancer niche. The company has sought approval on the back of the Keynote-407 study, regardless of PD-L1 expression, and anything other than a green light will be a huge surprise.

Meanwhile, Johnson & Johnson and Bayer hope to expand the label for their blood thinner Xarelto based on the Compass trial data. Adding cardiovascular event reduction in chronic coronary and peripheral artery disease patients, and acute limb ischaemia prevention in patients with PAD, could be some consolation for the companies after recent failures of Xarelto in other label-expansion studies.