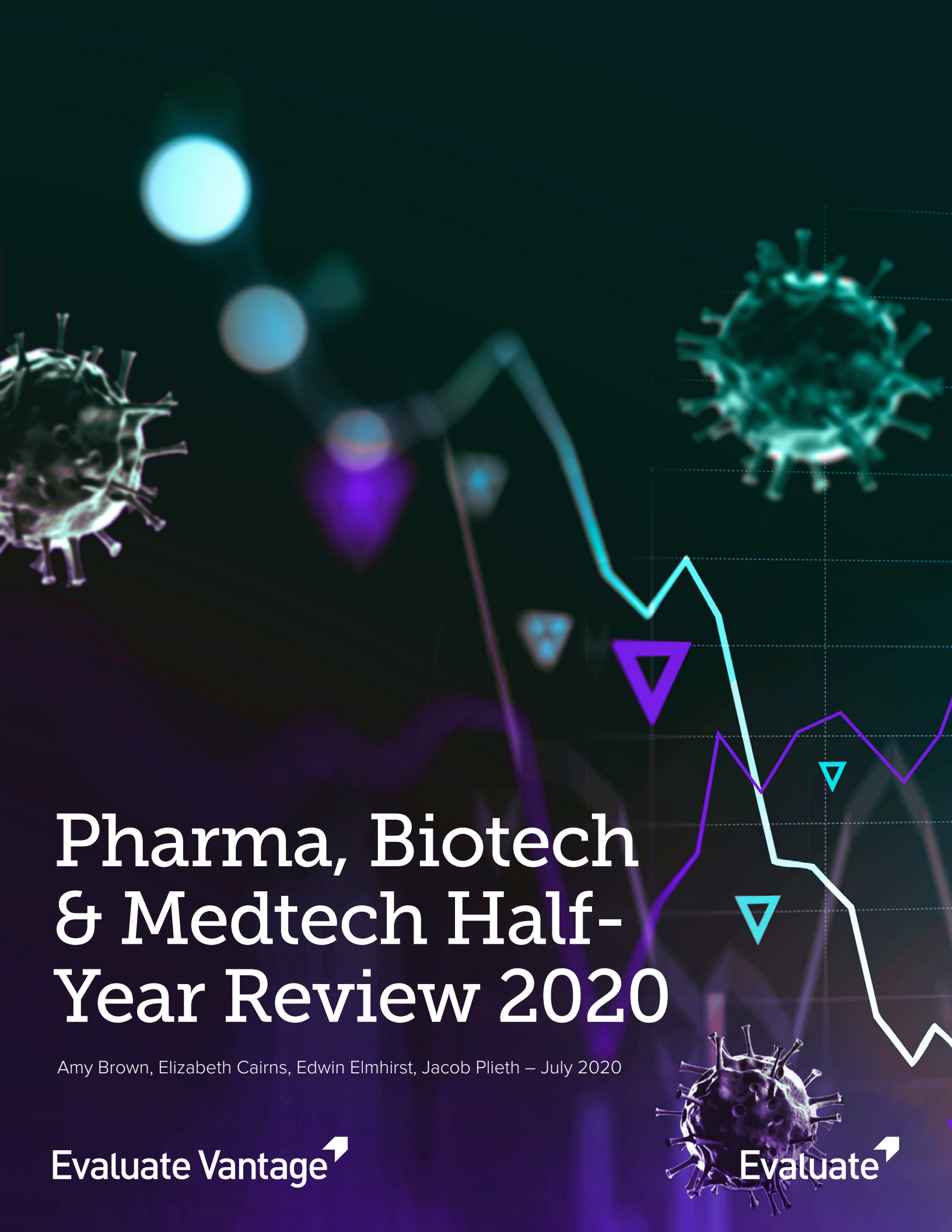

Pharma, Biotech & Medtech Half-Year Review 2020

Amy Brown, Elizabeth Cairns, Edwin Elmhirst, Jacob Plieth – July 2020

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Evaluate Vantage Pharma, Biotech and Medtech Half-Year Review 2020

The coronavirus pandemic has been the driving force shaping the biopharma and medtech sectors over the first half of 2020. And, while much of the fallout has been predictable, certain events and trends have surprised.

The speed of the recovery, for one, at least on the financial markets. Stock markets crashed as the scale of the Covid-19 outbreak became clear, but the selloff lasted a mere month. By the end of March investors had apparently come to terms with the situation, and by the half-year point most global indices were well on their way to a full recovery, led by healthcare stocks.

Incredibly, by April the Nasdaq Biotechnology Index was already setting new highs, as investors rushed to back the sector that promised to deliver vaccines and treatments for Covid-19. Gilead has already won emergency approvals for its antiviral remdesivir, and many more projects are in development. This report summarises biopharma's efforts so far, pinpointing the most advanced vaccines and therapeutic approaches that will hopefully follow remdesivir to market.

Covid-19 diagnostics, too, have been rushed to market, with industry leaders such as Abbott and Roche being rewarded for their efforts. Tests for the virus will be instrumental in developing vaccines and therapies, binding the fates of drug and diagnostics developers together.

This data-driven report also highlights how the pandemic has affected the business of biopharma and device makers. Surging stock markets have kept the IPO window wide open in the US, for example, with biotechs and device makers alike raising decent sums.

Another major surprise is how the venture sector has seemingly shrugged off the pandemic. Start-ups in the drug development world were handed a huge $9.7bn in the first half of the year, putting 2020 on track to set records, according to EvaluatePharma. In the medtech arena too venture cash has been surprisingly plentiful as investors move to ensure that portfolios are protected against the rough times that might be on the way should the pandemic cause a recession.

The biggest dent in activity has been seen in M&A, where restrictions on global travel deterred executives from taking on larger transactions. Smaller deals are happening, but the biggest takeover the pharma world mustered was Gilead's $4.9bn move on Forty Seven. In medtech the effect was even more pronounced, with only two megamergers being signed and device companies across the board having unprecedented difficulty in closing deals.

The pandemic is far from over, but the business world is adapting. With the second-quarter reporting season getting under way at time of writing, it is clear that many multinational companies' worst-case scenarios are not unfolding. Device makers in particular reported faster and more profound second-quarter recoveries than expected, as lockdowns were lifted and elective procedures were able to go ahead.

Biopharma and medtech companies came through the first half of 2020 in relatively good shape, all things considered. But with Covid-19 far from under control in the US, and frequent outbreaks occurring even in well-suppressed regions in Europe, the rest of the year will be a long way from normal.

Report authors | **Amy Brown, Elizabeth Cairns, Edwin Elmhirst, Jacob Plieth** – July 2020

Unless stated, all data are sourced to Evaluate and were compiled in July 2020.

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Covid-19: Biopharma's response

Before considering Covid-19's knock-on effect on business development and general investor sentiment, investors will be aware of one much more obvious way in which the coronavirus pandemic has shaped biopharma: the industry is working on ways to treat or prevent the virus, and the markets have rewarded companies working on such approaches.

The first half of 2020 has marked out the battleground into three broad groupings: vaccines as a primary means of defence; antivirals and other approaches designed to reduce the effects of the virus; and antibodies whose ultimate aim is to cure a patient of an infection.

Within each area early leaders have emerged, at least in investors' eyes. Moderna and Biontech/Pfizer are seen leading the charge of anti-Covid-19 vaccines, though it is Novavax that has secured the most US government funding. In treatment it is Gilead that has won with an antiviral, while antibody development leaders include Lilly and Regeneron.

The US government's willingness to put money behind work against Covid-19, showering several vaccine developers with cash in an effort called Project Warp Speed, should not be underestimated. Technically this is a partnership between the US Department of Health and Human Services, the FDA, the NIH, Barda and the Department of Defense, but it basically allocates taxpayer dollars.

The US said in May that 14 "promising" vaccine candidates had been chosen for this project from over 100 in development at the time. These undisclosed 14 are being narrowed down to "about seven", it revealed, representing the most promising candidates from a range of technology options.

So far four vaccine makers' names have been revealed on account of them qualifying for cash awards, which in two cases have exceeded $1bn. There is also one non-vaccine beneficiary of Project Warp Speed: Regeneron, whose two-antibody "cocktail" treatment is now in a phase III study.

The biggest beneficiary so far has been the biotech Novavax, whose status as the best-performing stock of 2020 was confirmed when it was singled out for a $1.6bn award in early July. This trumped the $1.2bn handed out to Astrazeneca/Oxford University two months earlier.

Warp Speed bonanza – summary of disclosed awards

Source: EvaluatePharma®, July 2020

Date	Company	Project	Detail	($m)
30 Mar	Johnson & Johnson	Ad26.COV2-S	Adenovirus type 26 vaccine; ph1 starting 22 Jul, ph3 27 Jul 2020	465
16 Apr	Moderna	mRNA-1273	mRNA vaccine in ph1; ph3 starting 27 Jul 2020	483
21 May	Astrazeneca	AZD1222	Chimp adenovirus vaccine in ph1; ph3 starting 14 Aug 2020	1,200
7 Jul	Novavax	NVX-CoV2373	Nanoparticle vaccine; ph1 data late Jul; ph3 starting 15 Oct 2020	1,600
7 Jul	Regeneron	REGN10933 + REGN10987	MAb "cocktail" in ph1 & ph3; NB, not a vaccine	450

Novavax had earlier managed to secure $388m from the Coalition for Epidemic Preparedness Innovations (Cepi), the largest award that body has paid out to date. The Cepi and Warp Speed funding alike are for development of Novavax's nanoparticle vaccine NVX-CoV2373 and its accompanying adjuvant.

The $1.6bn will be used to fund a 30,000-subject phase III trial starting in the autumn, build out manufacturing and supply the US government with 100 million doses by "as early as late 2020". The funding was a big gamble: Novavax has never successfully brought a vaccine to market, and unlike others in the Covid-19 vaccine race it has not published any human data on its candidate.

Results from the Cepi-funded phase I/II trial in 130 subject in Australia are imminent, and Novavax has promised immunogenicity data, including antibody as well as T-cell responses, alongside safety results.

It is not immediately clear whether the Novavax funding is tranched or contingent on certain milestones, but it seems possible that the 100 million doses will be delivered before the pivotal trial reads out. Before Novavax the biggest beneficiary of Warp Speed's largesse was Astrazeneca, whose $1.2bn award was more than double that secured by Moderna.

It is worth asking why such large sums of taxpayer cash are being thrown at large, well-financed and sometimes highly profitable enterprises, and Astra at least has hinted at a quid pro quo. The UK group has said that its Covid-19 vaccine will be "widely accessible around the world in an equitable manner".

But neither it nor Moderna has tackled directly the thorny issue of how any vaccine would be priced, or whether and how soon it would have to be profitable. A separate controversy was that Moderna, a company with $1.7bn in the bank, had secured up to $483m from Project Warp Speed, and was then still able to tap investors for a further $1.3bn.

One view might be that Warp Speed funding will give the US government part-ownership of a resulting vaccine, but the precedent set by Car-T therapy is that this is fanciful thinking.

The hunt for a vaccine

Five vaccines have generated clinical data so far, and the market seems to have declared the early skirmish a victory for Pfizer/Biontech's BNT162. This is deemed to have jumped ahead of Astrazeneca and Moderna, while firmly in the must-try-harder camp are the laggards Cansino and Inovio.

As data have emerged, the key early indicators of success have slowly become evident. For instance, vaccine data are pretty meaningless without disclosure of their ability to elicit neutralising antibodies – at least up to a target level, with the general rule that the higher the better. Neutralising antibodies are those that are capable not only of binding to virus but also interfering with its ability to infect a cell.

Equally important is a vaccine's ability to elicit a CD8+ T-cell response, as it has been hypothesised that to prevent severe Covid-19 infection and generate a long-lasting effect it might be necessary for a vaccine to stimulate cellular as well as humoural (antibody-based) immunity.

It is not yet clear what levels of neutralising antibodies or indeed CD8+ T cells might give protection from the virus, but nevertheless these are becoming important benchmarks in ranking rival vaccine approaches.

Safety is also key, given that a Covid-19 vaccine would be expected to be given to a broad patient population, and that some of the most vulnerable patients might also be the least able to tolerate toxicity. Investors should look for an absence of inflammatory symptoms, for instance.

Biontech/Pfizer's BNT162b1 is one of four separate approaches that the companies' BNT162 project comprises, and the b1 iteration is nanoparticle-formulated and nucleoside-modified.

The first clinical data, relating to a US study in a scientific paper preprint, concerned 36 subjects given single BNT162b1 doses of 10µg, 30µg or 100µg. These showed neutralising antibody levels of between 0.9x and nearly twice those seen in a panel of sera from recovered subjects, within 21 days.

On the safety side, fatigue and headache were more common with BNT162b1 than control (an additional nine subjects got placebo), but there were two severe adverse events: grade 3 pyrexia and sleep disturbance.

Results of a separate German study of BNT162b1 were later published in another scientific preprint, and as well as detailing a strong neutralising antibody effect they showed the vaccine's stimulation of CD8+ T cells. The trial enrolled 60 subjects across four 1-50µg dose levels. 36 of these were tested for a cellular response, the companies said, and 29 mounted what it called a functional CD8+ T-cell response "comparable to memory responses observed against CMV, EBV and influenza virus".

The first BNT162b1 study reported said nothing about cellular responses, while Moderna's mRNA-1273 had shown rather modest effects on CD8+ T cells, according to the latest findings, published in the NEJM.

Like BNT162b1 mRNA-1273 is an mRNA vaccine, and an *NEJM* paper in July detailed data in 45 volunteers. The results showed all 45 subjects generating neutralising antibodies after receiving two doses of mRNA-1273. But the trade-off between efficacy and tolerability could limit mRNA-1273's use to those who need it least: healthy people might accept side-effects like fever and chills, but these could be an issue in older and sicker patients – the populations that need protection from coronavirus the most.

Cross-trial comparison of Covid-19 vaccine data

Source: Company statements, scientific paper preprints, NEJM & Lancet. RBD=receptor-binding domain, July 2020

Project (company)	Doses	Study	Neutralising antibodies at relevant levels	T cells	Toxicity
BNT162b1 (Biontech/Pfizer)	10-30µg prime & boost, 100µg single	NCT04368728	Seen in 36/36 volunteers	No data	Grade 3 AEs in 2/36 (vs none for placebo); no serious AEs
	1-50µg prime & boost, 100µg single	NCT04380701	Seen in 48/48 volunteers	RBD-specific CD8+ responses in 29/36; mean 1.04% of cells	"Occasional" grade 3 reactogenicity; no serious AEs
AZD1222 (Astrazeneca)	5n10 viral particles, single or prime & boost	NCT04324606	Seen in 32/35 volunteers, rising to 35/35 after boost	Unspecified T-cell responses in 43/43; mean ~0.1% of cells	No serious or grade 3 AEs (vs 1 serious in control)
mRNA-1273 (Moderna)	25-250µg prime & boost	NCT04283461	Seen in 45/45 volunteers	Very modest; S-specific CD8+ responses seen in 2 outliers, at 0.1-0.2% of cells	No serious or grade 3 AEs
Ad5-nCoV (Cansino)	1n11 or 5n10 viral particles, single	NCT04341389	Seen in 210/382 volunteers	Unspecified T-cell responses in 342/382; mean ~0.01% of cells	Grade 3 AEs in 10/382 (vs none for placebo); no serious AEs
INO-4800 (Inovio)	1mg or 2mg, double doses	NCT04336410	No data, just "overall immune responses" in 34/36 volunteers	No data	No serious AEs

Astrazeneca's AZD1222 had been played up in the UK media as a vaccine that has shown stimulation of killer T cells, but in the event, when its first clinical data were published in the *Lancet*, they came up somewhat short of the mark.

The Lancet detailed data on part of the 1,077-strong phase I population that Astra wants to enrol. The key findings related to 35 for whom neutralising antibody levels were available: 91% showed detectable neutralising antibody responses after a single AZD1222 dose, and this became 100% after a booster, the authors wrote.

T-cell response data, meanwhile, were available for 43 subjects, and a response was induced in all, "peaking by day 14, and maintained two months after injection", Astra said in a statement. However, the Lancet paper said nothing about whether these were CD4+ (helper) or CD8+ (killer) T-cell responses.

There is no doubt that AZD1222, a chimp adenovirus vector-based project in development at the UK's University of Oxford, is still a potentially viable Covid-19 vaccine project. But it has been overshadowed by the stellar Biontech/Pfizer results and by unrealistic expectations.

True, with so few patients studied so far it is hard to say which project has the best chance of succeeding, though the markets are at present leaning towards BNT162b1. The adverse event profile of mRNA-1273 should give investors reason for pause, and it is clear now why Moderna dropped the highest dose, 250µg, given cases of severe fever and chills seen in this cohort.

Moderna is pushing on and plans to enrol the first of 30,000 patients into a placebo-controlled phase III trial. Four other vaccines are also set to begin pivotal studies this year, each in 30,000 subjects: Johnson & Johnson's Ad26.COV2-S, Astrazeneca's AZD1222, Novavax's NVX-CoV2373, and one of the projects in which Sanofi is involved.

A further twist is that Moderna has lost a patent dispute against Arbutus, meaning that it might not have rights to the lipid nanoparticle technology it uses in its mRNA vaccines. Arbutus has licensed this tech to Biontech for use in BNT162.

Selected vaccines in development for Covid-19

Source: WHO list, EvaluatePharma® and company statements, July 2020

Company/org	Vaccine	Type	Detail
Moderna/NIAID	mRNA-1273	mRNA vaccine	45/45 volunteers producing strong neutralising antibody levels
Cansino Biologics	Ad5-nCoV	Adenovirus type 5 vaccine	50-75% of 108 volunteers generating neutralising antibodies
Inovio	INO-4800	DNA vaccine	Immune responses claimed, but no data on neutralising antibodies
Biontech/Pfizer	BNT162b1	mRNA (modRNA) vaccine	36/36 volunteers producing strong neutralising antibody levels
Biontech/Pfizer	BNT162a1, BNT162b2 & BNT162c2	mRNA (uRNA, modRNA & saRNA) vaccines	Phase 1 data due Jul 2020
Astrazeneca/ Uni of Oxford	AZD1222	Chimp adenovirus vaccine	35/35 neutralising antibody responses after boosted dose
Novavax	NVX-CoV2373	Nanoparticle vaccine	Phase 1 data due Jul 2020
Dynavax/Clover/ GSK	SCB-2019	Trimerised fusion protein	Phase 1 data possible Aug 2020
Curevac	CVnCoV	mRNA vaccine	Phase 1 started Jun 2020
Zydus Cadila	ZyCoV-D	DNA vaccine	Phase 1 started Jul 2020
GSK/Medicago (Mitsubishi Tanabe)	?	Coronavirus-like particles	Phase 1 started Jul 2020
Johnson & Johnson	Ad26.COV2-S	Adenovirus type 26 vaccine	Phase 1 starting 22 Jul 2020; phase 3 Sep 2020
IMV	DPX-COVID-19	Peptide vaccine	Phase 1 starting “summer” 2020
Arcturus	LUNAR-COV19	mRNA vaccine	Phase 1 starting “as soon as possible”
Translate Bio/Sanofi	?	mRNA vaccine	Phase 1 starting Q4 2020
GSK/Sanofi	?	S-protein antigen, adjuvanted	Phase 1 starting H2 2020

The situation is much worse for Inovio, a biotech famous for jumping on pandemic bandwagons – from bird flu to swine flu to Ebola, Zika, Mers and finally Covid-19 – without yet bringing a single vaccine to market. The company has claimed “overall immune responses”, but has said nothing even about neutralising antibodies.

For its part, the Chinese group Cansino has generated what is by far the largest of any vaccine to read out so far: its trial of Ad5-nCoV has been conducted in 382 volunteers, but published data have disappointed.

Novavax bulls, meanwhile, will have to wait until early August to find out whether the US government was right to give the company $1.6bn, and whether the group’s $8bn valuation is justified. Novavax’s clinical trial tests two NVX-CoV2373 doses, 5µg and 25µg, the latter with or without an adjuvant, in 131 volunteers.

There is still much to play for, especially given the scope for accelerated development, and a view that countries might not exit fully from lockdown until a Covid-19 vaccine is available. That said, the early winners and losers have now emerged.

Treating the symptoms

In the Covid-19 treatment arena Gilead's remdesivir remains the hottest near-term hope. The antiviral has already been approved by the US FDA under emergency use measures, notwithstanding its suboptimal profile and largely unproven efficacy, as evidenced by the numerous perverse clinical datasets it has generated.

A major development occurred on June 19 when Gilead priced the drug – at $2,340 for a five-day course. Gilead investors were thus kept on side, though the US watchdog Icer deemed that the price chosen was only cost effective if remdesivir had a survival benefit – which it has so far failed to show.

Little wonder that Gilead moved quickly to claim that remdesivir does indeed show a mortality benefit, on July 10 presenting an analysis comparing the antiviral's outcomes data versus what it called a real-world cohort of Covid-19 patients receiving standard of care.

Still, a threat is emerging in the shape of dexamethasone, a cheaply available steroid that has managed to demonstrate a survival benefit, according to an NEJM paper on part of the prospective, 15,000-patient, multi-agent Recovery trial run at the UK's Oxford University.

Summary of dexamethasone cohort in Recovery trial (NCT04381936)

Source: NEJM, July 2020

	Dexamethasone	"Usual care"	Suggestive of benefit?
N	2,104	4,321	
28-day mortality overall	22.9%	25.7%	Yes, p<0.001
Subgroup analyses			
28-day mortality (mechanical ventilation)	29.3%	41.4%	Yes
28-day mortality (oxygen w/o ventilation)	23.3%	26.2%	Yes
28-day mortality (no respiratory support)	17.8%	14.0%	No

For its part remdesivir has, so far, demonstrated only a marginal benefit. Findings from Gilead's latest study, in moderately ill patients, suggest that the antiviral has some activity, but that overall it is not a game changer. Clearly no in-depth analysis is possible until the data are published in a peer-reviewed publication.

Cross-trial comparisons of remdesivir's four datasets

Source: EvaluatePharma®, July 2020

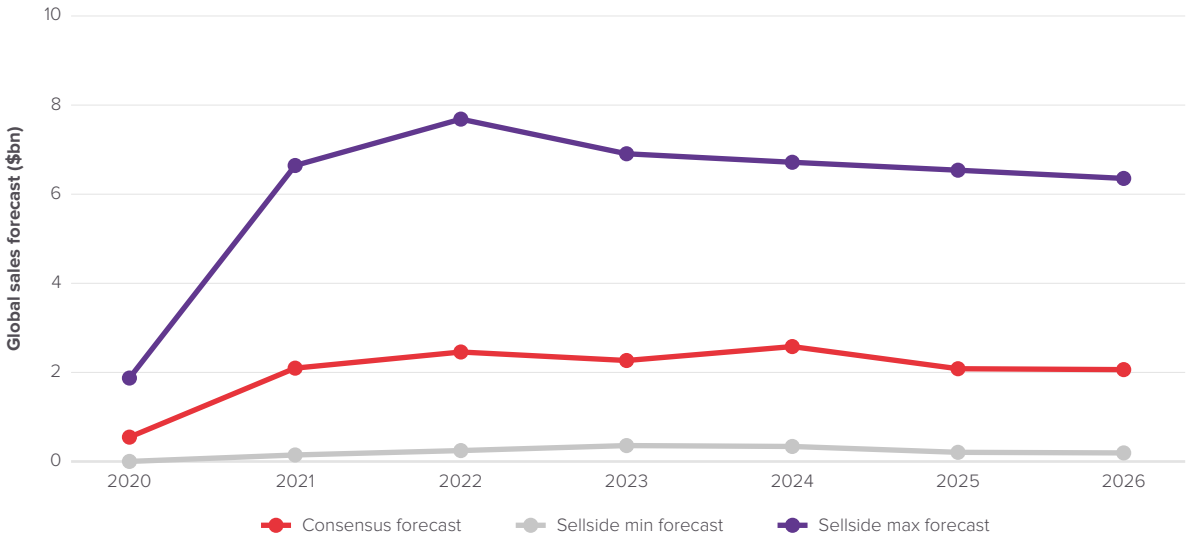
Company/org	Gilead moderate trial	Gilead severe trial	China trial	NIAID trial
Trial ID	NCT04292730	NCT04292899	NCT04257656	NCT04280705
Enrolment	584 (target 1,600)	397 (target 6,000)	Halted at 237 (target 453)*	1,063
Covid-19 severity	Hospitalised, not on ventilation, ≤4 days since PCR confirmation of disease	Hospitalised, severe, ≤4 days since PCR confirmation of disease**	Hospitalised, confirmed lung involvement, ≤12 days since illness onset	Hospitalised, ≤72 hours (some exceptions) since PCR confirmation of disease
Design	Open-label, 5-day or 10-day course, vs SoC	Open-label, uncontrolled, 2-cohort (5-day/10-day)	Quadruple-blinded, placebo-controlled	Double-blinded, placebo-controlled
Primary endpoint	Odds ratio for improvement at day 11***	Odds ratio for improvement at day 14^	Time to clinical improvement at day 28	Time to recovery^^
Result	31% improvement for 10-day (not stat sig); 65% improvement for 5-day (p=0.017)	54-65% had ≥2-point improvement	21 days vs 23 days (HR=1.23, not stat sig)	11 days vs 15 days (p<0.001)
Mortality result	1% for 10-day, 0% for 5-day, 2% for SoC	8-11%	14% vs 13% (not stat sig)	8% vs 12% (not stat sig)

*Terminated early because, China's Covid-19 epidemic having been brought under control, no further eligible patients could be enrolled; **cohort of mechanically ventilated subjects was added in Apr; ***changed from hospital discharge at day 14; ^changed from normalisation of fever and oxygen saturation at day 14; ^^changed from disease severity improvement at day 15.

Criticism notwithstanding, sellside analysts now have a price on which to model future sales; the graphic below, from *EvaluatePharma*, shows that current consensus comprises some very different numbers. Partly this will reflect differing opinions on demand, as well as price; these forecasts also predate the dexamethasone finding.

Remdesivir sellside forecasts

Source: EvaluatePharma®, July 2020



“Cytokine storm”?

A separate theory that has been gaining traction is that, apart from the deleterious effects of the Covid-19 virus itself, infected people are also harmed by a surge in cytokines, in particular IL-6.

The theory, akin to the “cytokine storm” experienced by some cancer patients given Car-T therapy, is controversial. One expert, for instance, has told *Evaluate Vantage* that a more subtle response is at play, featuring several cytokines, and argues that IL-6 levels in Covid-19 patients are multiple orders of magnitude lower than what is seen with Car-T therapy.

Be that as it may, two anti-IL-6 antibodies are already available under special Covid-19 measures. Roche’s rheumatoid arthritis drug Actemra in China and Biocon’s psoriasis treatment Alzumab in India. Other MAbs against the IL-6 pathway have been rushed into the clinic, including Sanofi/Regeneron’s Kevzara and Eusa Pharma’s Sylvant.

However, Kevzara has had a phase II/III study’s moderately severe hospitalised patient cohort scrapped after an interim analysis showed no benefit, and later failed to show an improvement versus standard of care alone in the trial’s remaining population, Covid-19 patients on ventilators.

Selected antibodies blocking IL-6

Source: EvaluatePharma®, July 2020

Project	Company	Clinical work in Covid-19 infection
Actemra (tocilizumab)	Roche	Phase 3 Roche study, and ~50 others run by academia; approved for emergency use in China
Alzumab (itolizumab)	Biocon/Equillium	Approved for emergency use in India
Kevzara (sarilumab)	Sanofi	2 company-sponsored studies and 13 others run by academia
Clazakizumab	CSL	Investigator-initiated trials only
Sylvant (siltuximab)	Eusa Pharma	Investigator-initiated trials only
Levilimab (BCD-089)	Biocad	Company-sponsored study
Sirukumab	Johnson & Johnson	Company-sponsored study
Olokizumab	UCB/R-Pharm	Company-sponsored study
TZLS-501	Tiziana	Clinical trial planned

The antibody approach

As potentially the most effective way of treating a person infected with Covid-19, antibodies designed specifically to target the virus's structure are a key area of focus for several companies. Perhaps because of the relatively long timelines and high risk involved, several have wasted no time to start clinical trials.

Regeneron's two-MAb cocktail, for instance, is entering a phase III prevention trial in 2,000 asymptomatics. This is the Warp Speed-funded project, which is also in phase I studies in hospitalised and ambulatory subjects. The study in asymptomatics is important because of its potential to make a real difference to healthcare workers and people with close exposure to a Covid-19 patient.

Also prominent are two separate Lilly assets, one partnered with Abcellera and the other with Junshi. The former, coded LY-CoV555, is in phase II in 400 mild to moderate Covid-19 patients, comparing it against placebo in a double-blind fashion, with change in day-11 Covid-19 viral load as primary endpoint.

The separate Lilly/Junshi project, JS016, which binds a different epitope on the virus's spike protein, has completed enrolment into a healthy volunteer trial. The spike protein-targeting approach is similar to that of several of Lilly's competitors. The protein is present on the virus surface, and the virus uses it to dock with the Ace2 receptor on target cells, allowing it to be internalised and infect.

The next project into the clinic with this mechanism could come from Vir's partnership with Glaxosmithkline, which has so far identified two lead MAbs. Also keenly awaited is a project under way at Astrazeneca; the hope is that these antibodies can prevent the virus docking, or hit another part of it that leads to antibody-mediated destruction. The last two are noteworthy because they are based in part on plasma derived from patients who have recovered from Covid-19 infection.

Though many projects have the same target in common, there is additional variability in antibody structure. For instance, while most are based on IgG, a tie-up between Atreca, Beigene and IGM Biosciences is looking at those derived from IgM and IgA, which, the companies argue, have more binding domains and hence greater binding power than IgG.

A separate tie-up Vir has with Xencor looks to develop MAbs with an engineered Fc domain to give an extended half-life, and similar thinking lies behind the so-called Darpins in development by Molecular Partners.

There are also bispecific approaches and fusion proteins, for instance SI-F019, in development by Systimmune, a private US group focusing on MAbs, bispecifics and antibody-dug conjugates. This combines two proteins each mimicking Ace2, aiming to take up the relevant binding sites on Covid-19 and prevent its interaction with the endogenous Ace2 receptor.

While many companies are making claims about the superiority of their respective approaches, these are of course all based on animal or in vitro data. No comparison will be possible until the first clinical trials read out – and this will not happen for some time yet.

Selected antibodies and related biologicals in development for Covid-19

Source: EvaluatePharma®, July 2020

Companies	Lead, if identified	Mechanistic approach	Clinical development?
Lilly/Abcellera	LY-CoV555/ LY3819253	IgG1 MAb vs spike protein	Ph2 study in mild to moderates
			Ph1 study in hospitalised subjects
Regeneron	REGN10933 + REGN10987	Two-Ab cocktail	Ph3 prevention trial in asymptomatics
			Ph1 trial in hospitalised subjects
			Ph1 trial in ambulatory subjects
Lilly/Junshi	JS016	Fully human MAb vs spike protein	Ph1 in volunteers
Celltrion	CT-P59	MAb vs spike protein receptor binding domain	Ph1 in volunteers
Sab Biotherapeutics	SAB-185	Polyclonal	Ph1 in volunteers
Glaxosmithkline/Vir	VIR-7831 & VIR-7832	MAbs vs spike protein	Clinical trial in Jul-Sep 2020
Astrazeneca	–	MAbs, incl based on recovered patients	Clinical trial in Jul-Sep 2020
Sorrento	STI-1499	Fully human MAb vs spike protein	Clinical trial due Q3 2020
Brill Bio	–	Fully human MAb	Clinical trial due Q3 2020
Yumab	–	MAbs, incl based on recovered patients	Clinical trial due H2 2020
Molecular Partners	–	Darpin proteins	Clinical trial due H2 2020
Systimmune	SI-F019	Bivalent Ace2 fusion protein vs spike protein	IND filing due 2020
Xencor/Vir	–	Fc-engineered MAbs	–
Atreca/Beigene/IGM	–	IgM & IgA MAbs vs novel epitopes	–
Amgen/Adaptive	–	MAbs based on recovered patients	–
Ossianix	–	Single-domain VNAR MAbs vs spike protein	–
Sorrento	STI-4398	Ace2-Fc protein vs spike protein	–
Sorrento/Mabpharm	STI-4920	Bispecific vs 2 domains on spike protein	–
Fusion Antibodies	–	Fully human MAb vs engineered Ace2 protein	–
Fusion Antibodies	–	Fully human MAb vs spike protein	–
Virna	–	Neutralising Abs vs spike protein	–

Note: Excludes anti-IL6, anti-GM-CSF and other MAbs not directly targeting Covid-19.

Diagnostics

In the medtech sphere, too, Covid-19 had dramatic effects on companies' fortunes at the half year point. Most obvious beneficiaries were the testing groups, many of whom rushed to develop Covid-19 molecular assays and, later, antibody tests to identify those who may have developed some form of immunity to the virus.

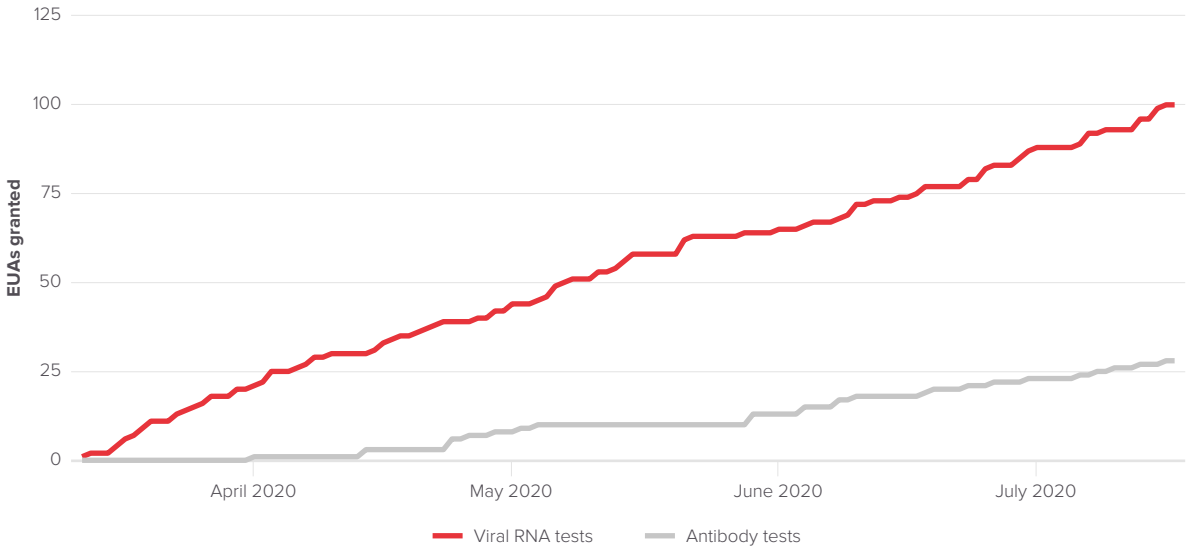
Roche, the world's largest diagnostics company by test sales, was one of the first off the mark developing a viral RNA test by mid-March. It was soon joined by other big groups such as Abbott, Thermo Fisher Scientific, LabCorp and Hologic. By July 21 over 100 molecular tests for the new coronavirus developed by commercial medtech companies had received individual authorisation from the FDA.

Despite the wide range of viral RNA tests available and the large production capacity – many companies have stated that they can perform hundreds of thousands of these tests per day – the demand has outstripped supply. With this in mind in mid-July the FDA allowed the pooling of samples, a technique by which nasal swab samples from up to four people are being mixed together before testing.

This technique allows for rapid diagnosis of large numbers of people, but is imprecise. The only test so far authorised for use in this manner is Quest Diagnostics' Sars-CoV-2 rRT-PCR assay, but it is possible that others may follow.

EUAs granted to Covid-19 tests

Source: FDA, July 2020



EUA = emergency use authorisation. Commercial tests only; cumulative figures.

The second type of testing to take off was assays to detect the presence of antibodies in people who have recovered from Covid-19, possibly while being asymptomatic. If a definitive link can be made between the presence of antibodies in the blood and immunity to reinfection, these assays will be crucial to efforts to develop and allocate vaccines, and to safely get people back to work.

Accuracy, however, will be key. The FDA has been reassessing the sensitivity and specificity of all the antibody tests for which it has issued emergency authorisation, but this has been a slow process; only 12 of the nearly 30 authorised antibody tests have been checked by the agency. It is perhaps a good sign that only one of the 12, that from Chembio, was found to be markedly less accurate than initially thought, leading to its EUA being revoked.

Surprisingly, some of the most interesting data on the accuracy of these tests has come not from the US regulator but from a UK health agency. Public Health England conducted a head-to-head study of four antibody tests from four of the largest and best-known diagnostics developers and determined that Siemens Healthineers' was the best. The Healthineers test was the only one to meet the performance target set by the UK regulator, the MHRA, of 98% sensitivity and specificity; those from Abbott, Roche and Diasorin met the specificity criterion only.

UK accuracy findings for four Covid-19 antibody tests Source: Public Health England & Evaluate Vantage calculations, July 2020

Company	Assay	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%)	NPV (%)
Abbott	Architect Sars-CoV-2 IgG	92.7 [90.2, 94.8]	99.9 [99.4, 100]	98.0	99.6
Diasorin	Liaison Sars-CoV-2 S1/S2 IgG	95.0 [92.8, 96.7]	98.6 [97.6, 99.2]	78.1	99.7
Roche	Elecsys anti-Sars-CoV-2	97.2 [95.4, 98.4]	99.8 [99.3, 100]	96.1	99.6
Siemens Healthineers	Atellica COV2T	98.1 [96.6, 99.1]	99.9 [99.4, 100]	98.1	99.9

PPV & NPV = positive & negative predictive values. PPV and NPV calculated at 5% prevalence.

Crucially, none of the assays was able to match the accuracy data the companies had submitted to the FDA, underscoring the importance of the US regulator pursuing its own independent evaluations.

Biopharma shares shake off the pandemic

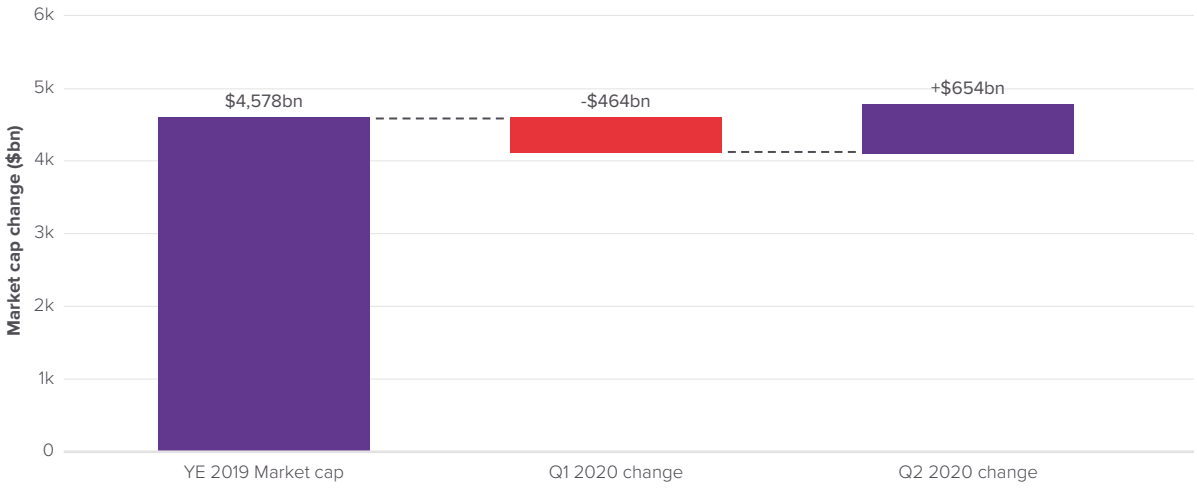
The pandemic was a fleeting affair as far as the stock market was concerned. Biopharma's key role in fighting Covid-19 did not prevent across-the-board declines in March – with a few notable exceptions – and then the second quarter witnessed an unmistakable return to health.

The revival mirrored broader stock market recoveries and *Evaluate Vantage's* quarterly look at the sector's share prices shows that drug developers of all sizes posted strong gains over the second quarter. In fact, at the half-year stage our universe of global stocks had grown in value over the end of 2019, which is remarkable considering that much of the world is still afflicted by the coronavirus outbreak.

This analysis concerns all listed drug makers covered by *EvaluatePharma*, from across the world – a cohort of 579 companies. Micro-caps, those with a market value of less than $250m at the start of the year, have been excluded, as have subsectors like medtech or diagnostics; only developers of therapeutics are included.

The shifting valuation of global drug makers

Source: EvaluatePharma®, July 2020

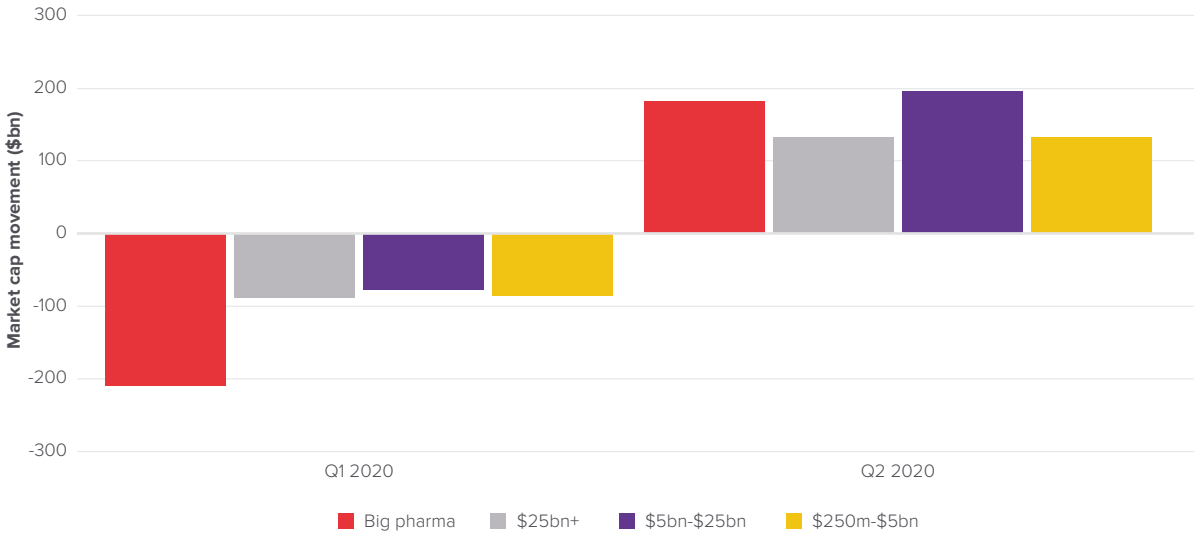


As can be seen above, the combined market cap of this group is already greater than at the start of the year. This is real growth: those companies that have arrived via IPO so far in 2020 have not been added, to allow a like-for-like comparison over the year.

The charts below, meanwhile, show that all cohorts other than big pharma more than recovered value lost in the first quarter. Among the big caps Merck & Co and Pfizer are feeling the heat, down 15% and 17% respectively at the half-year stage, largely on concerns about replacing existing franchises.

Absolute market cap gains and losses, by size bracket

Source: EvaluatePharma®, July 2020



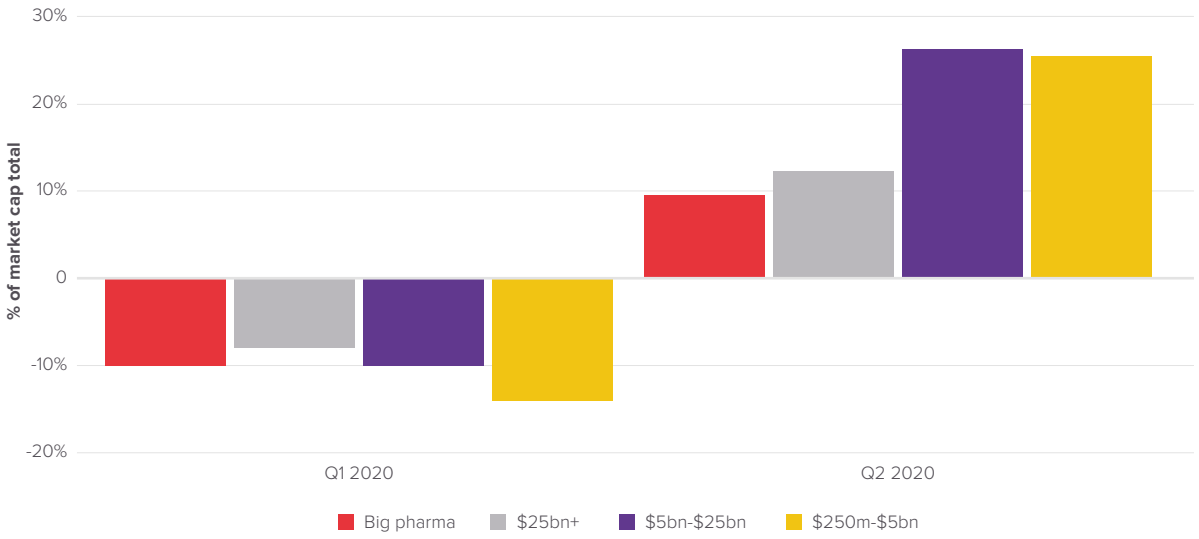
Another mid-cap second-quarter winner was Moderna, which added $14bn in market cap in the second quarter, as its share price more than doubled. The RNA researcher has been one of the biggest beneficiaries of shareholder interest in Covid-19 research.

Regeneron is another huge pandemic play: its valuation grew by $16bn over the second quarter, and with a market cap of $66bn in early July the group is sitting at record highs.

Among those that are doing well for non-pandemic reasons Vertex stands out. The group's shares have surged 33% this year, giving it a market cap of $75bn, as investors continue to reward it for complete domination of cystic fibrosis.

Percentage market cap gains and losses, by size bracket

Source: EvaluatePharma®, July 2020



Companies involved in finding Covid-19 treatments still stand out among the winners at the half year stage, in the table below. But there are always losers in a biotech market, and despite the recent rally around half of the stocks in our universe were under water at the half year.

And of course, there are always car crashes to be found in this high-risk sector. Amarin for example has seen more than half its value erode on a surprise patent loss, while Intercept has seemingly fallen foul of regulators, which are for now refusing to approve its Nash project.

Biggest share price gainers of H1 2020

Source: EvaluatePharma®, July 2020

Company	Share price gain	Market cap gain ($bn)	Market cap at June 2020 ($bn)
Big pharma			
Eli Lilly	25%	30.84	157.03
Abbvie	11%	42.09	173.03
Astrazeneca	6%	7.99	138.81
Drug makers +$25bn			
Chugai	72%	37.70	89.86
Regeneron Pharmaceuticals	66%	28.49	69.02
Lonza	42%	11.98	38.38
Mid-caps			
Moderna	228%	17.32	23.84
Biontech	100%	7.47	15.14
Samsung Biologics	79%	17.71	41.91

Continues over the page...

Company	Share price gain	Market cap gain ($bn)	Market cap at June 2020 ($bn)
Small caps			
Inovio Pharmaceuticals	717%	3.93	4.26
Mesoblast	708%	0.47	1.22
Cytodyn	468%	2.61	3.00
Arising from the micro caps...			
Novavax	1994%	4.73	4.83
Adaptimmune	734%	1.41	1.54
Arcturus Therapeutics	330%	0.79	0.96

Biggest share price fallers of H1 2020

Source: EvaluatePharma®, July 2020

Company	Share price loss	Market cap loss ($bn)	Market cap at June 2020 ($bn)
Big pharma			
Pfizer	-17%	35.18	181.64
Merck & Co	-15%	36.37	195.19
Bristol Myers Squibb	-8%	-17.43	133.05
Drug makers +$25bn			
Shiseido	-12%	-3.40	25.38
Fresenius	-12%	-9.07	21.61
Takeda	-11%	-6.83	56.31
Mid-caps			
Amarin	-67%	-5.03	2.67
Bausch Health	-39%	-4.06	6.49
Arrowhead	-32%	-1.67	4.40
Small caps			
Genfit	-71%	-0.55	0.21
Nextcure	-62%	-0.69	0.59
Intercept	-61%	-2.48	1.58

A more detailed analysis of this data can be found here:

Covid-19 hits Europe drug stocks hardest

Biopharma shares shake off the pandemic

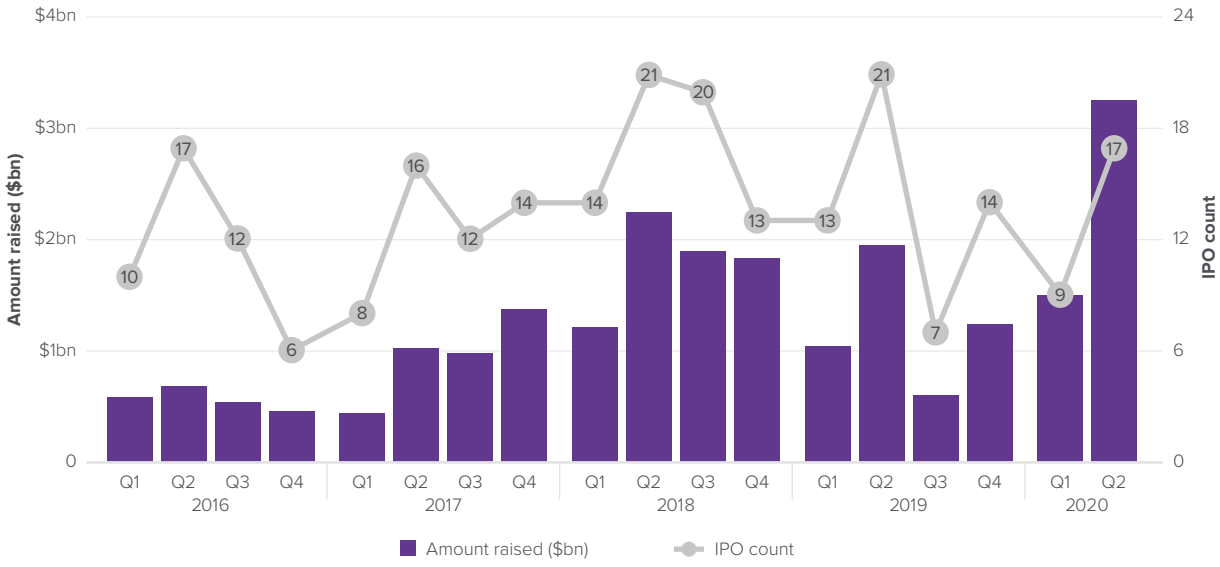
What pandemic? Biotech floats break records

Given the depths of the panic that sent stock markets crashing in late February, the strength and speed of the recovery has been remarkable. And there are few places where this is more evident than biotech IPOs, the statistics around which show few signs of a global pandemic.

Of course it could be argued that the arrival of Covid-19 spurred much of the demand seen recently for young drug developers; investors have been reminded of the sector's worth, while chasing potential beneficiaries of the outbreak. Biotech was already on a run before the pandemic hit, however, so this is far from the only explanation for the record sums raised in the second quarter.

Biotech IPOs by quarter on Western exchanges

Source: EvaluatePharma®, July 2020



This view of the sector concerns only those companies developing human therapeutics – excluding medtech, diagnostics and digital health – so it provides a snapshot of the riskiest end of healthcare. Flotations on all Western exchanges are tracked.

The pandemic did cause IPOs to pause for most of March, so to a certain extent the huge second quarter can be explained by companies that were to have gone out that month being pushed back.

This result is also down to the huge amount of capital being made available to these firms. The average amount raised by an IPO in the first half came in at $193m, another record. It should be noted that Royalty Pharma's $2.2bn flotation is not included in the tally.

Tracking demand for IPOs

Source: EvaluatePharma®, July 2020

It is abundantly clear that there is huge demand for these flotations. The chart above shows that on average companies received more than they had originally set out to raise in the second quarter, with investors' largesse apparently at levels not seen for at least five years.

The premium or discount is calculated from the midpoint of the initial share price range proposed, and the float price at IPO.

The second quarter's largest IPO, of the China-US cell therapy researcher Legend Biotech, illustrates this enthusiasm. It amassed a $487m haul, after first setting out to raise up to $100m.

In fact no company had to offer a real discount to get away, with the worst result being a price within the initially proposed range.

Biggest biotech IPOs by amount raised in H1 2020

Source: EvaluatePharma®, July 2020

Company	Primary focus	Amount raised ($m)	Premium/ (discount); float price to initial range	Share price change since float to end June
Legend Biotech	Cell therapy for oncology and other diseases	487	21%	85%
Forma Therapeutics	Small molecules for rare haematological diseases and cancers	319	18%	132%
Avidity Biosciences	Oligonucleotide-based therapies for genetic diseases	298	20%	57%
Vaxcyte	Vaccines for infectious diseases	287	7%	87%
Revolution Medicines	Targeted oncology; Ras and mTor signalling	273	13%	86%

Note: Analysis looks at Western exchanges only, but all five largest occurred on Nasdaq.

Biggest IPOs by market cap post-money, pre-float

Source: EvaluatePharma®, July 2020

Company	Primary focus	Market cap post-money/ pre-float ($bn)	Amount raised ($m)	Premium/ (discount); float price to initial range	Share price change since float to end June
Legend Biotech	Cell therapy for oncology and other diseases	3.17	487	21%	85%
ADC Therapeutics	Antibody-drug conjugates for oncology	1.31	268	12%	146%
Schrödinger	Physics-based computational drug discovery platform	1.11	202	13%	439%
Revolution Medicines	Targeted oncology; Ras and mTor signalling	1.03	274	13%	86%
Generation Bio	Non-viral gene therapy platform	0.92	230	12%	11%

Further support for biopharma can be found in a brief look at the secondary market, below; listed biopharma companies are apparently having no problem topping up their coffers. The chart shows a count of S3 or F3 registration forms, the documents firms must submit to the SEC before selling new shares.

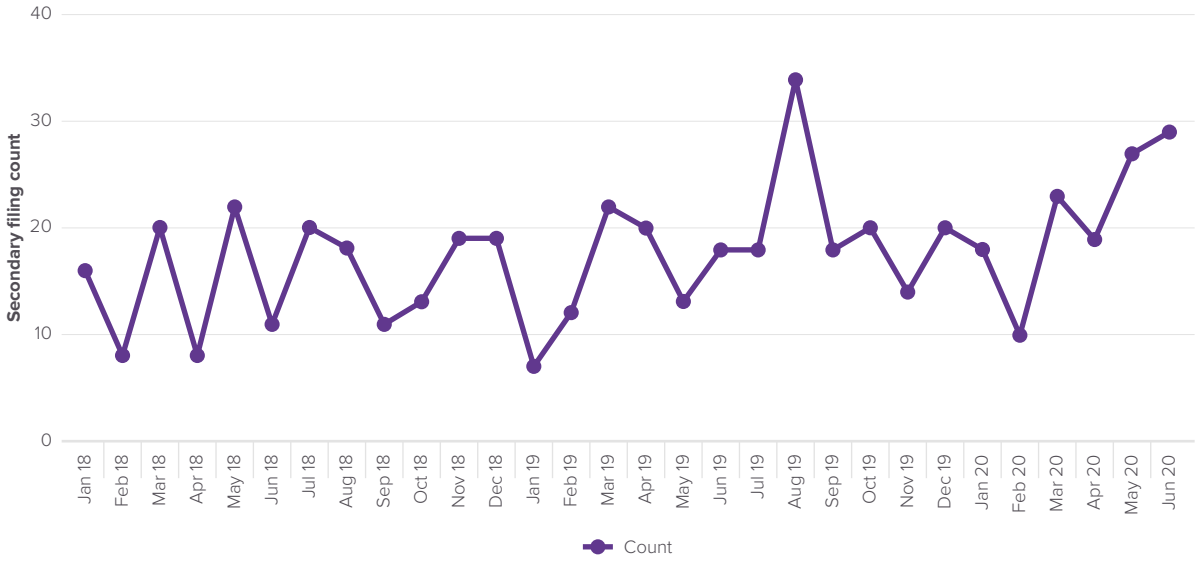
The pandemic is making the future unpredictable, and persuading companies to stock up while they can. Investors are also favouring companies with "fortress balance sheets", bankers at RBC Capital Markets wrote recently.

It is worth remembering that much of this strength is US-centric, however. Only one European IPO has happened this year, that of Belgium's Hyloris in June, though several continental firms took advantage of Nasdaq's strength and listed across the Atlantic.

Given the deep pools of capital that are readily available, it is easy to see why foreign issuers are attracted to the US markets.

Topping up the coffers – A count of biopharma secondary fundraisings

Source: sec.gov, EvaluatePharma®, July 2020



A more detailed analysis of this data can be found here:

Covid-19 stalls biotech flotations

What pandemic? Biotech floats break records

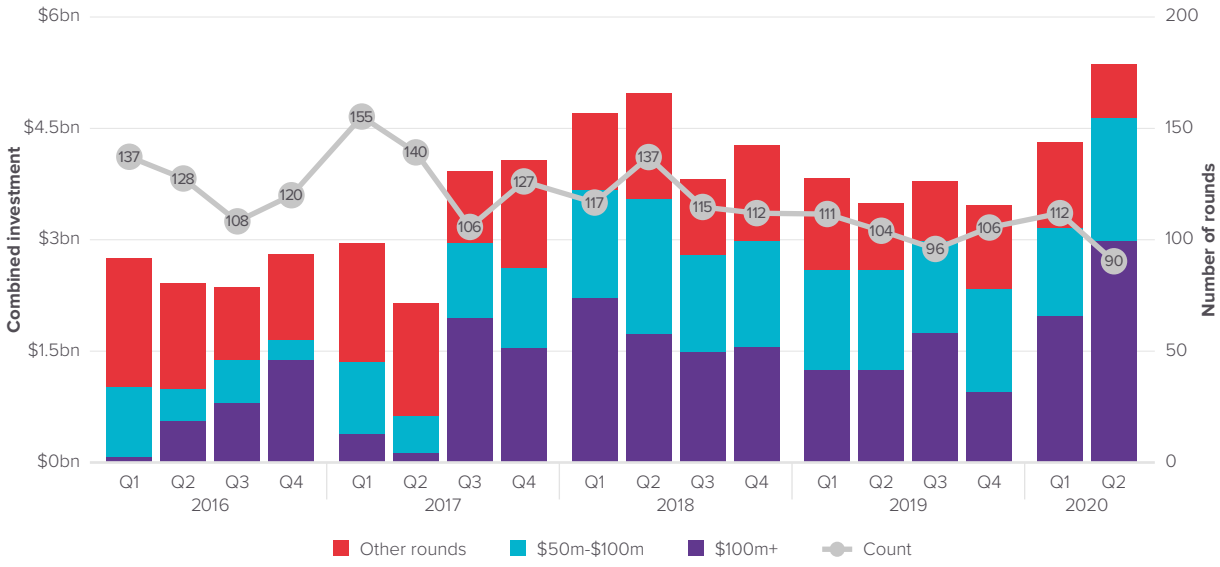
Venture investors: biotech's preppers?

Being locked down is no barrier for venture investors, apparently – private drug developers are awash with cash. Or at least some of them are: the second quarter saw a record $5.4bn raised by these start-ups, though the number of deals being done sits at 10-year lows.

Fewer but bigger is the investment model of choice at the moment, of course, while the huge pools of capital available only make this trend more obvious. A prime example of what investors are after right now is Sana Biotechnology: with a well-known executive team that had "done it before" and a focus on cell and genetic engineering, the company managed to amass $700m in its initial financing rounds.

Quarterly biopharma VC rounds

Source: EvaluatePharma®, July 2020



The pandemic is having the opposite effect in the venture world than in areas like M&A, which has seen the amount of money being deployed dip this year. Raise money while you can is one philosophy driving this boom – investors will be very keen to see that their portfolio companies are as strong as possible in case times do get tougher.

The last quarter saw a notable jump in the number of mega rounds, those of more than $100m. As a result, the average size of a financing at the half-year stage is around double that being raised only a few years ago.

Annual biopharma venture investments

Source: EvaluatePharma®, July 2020

Year	Investment ($bn)	Financing count	Avg per financing ($m)	No. of rounds ≥$50m	No. of rounds ≥$100m
H1 2020	9.73	202	49.15	71	29
2019	14.67	417	36.41	116	36
2018	17.89	481	39.06	130	38
2017	13.21	528	27.40	76	19
2016	10.44	493	22.51	52	15

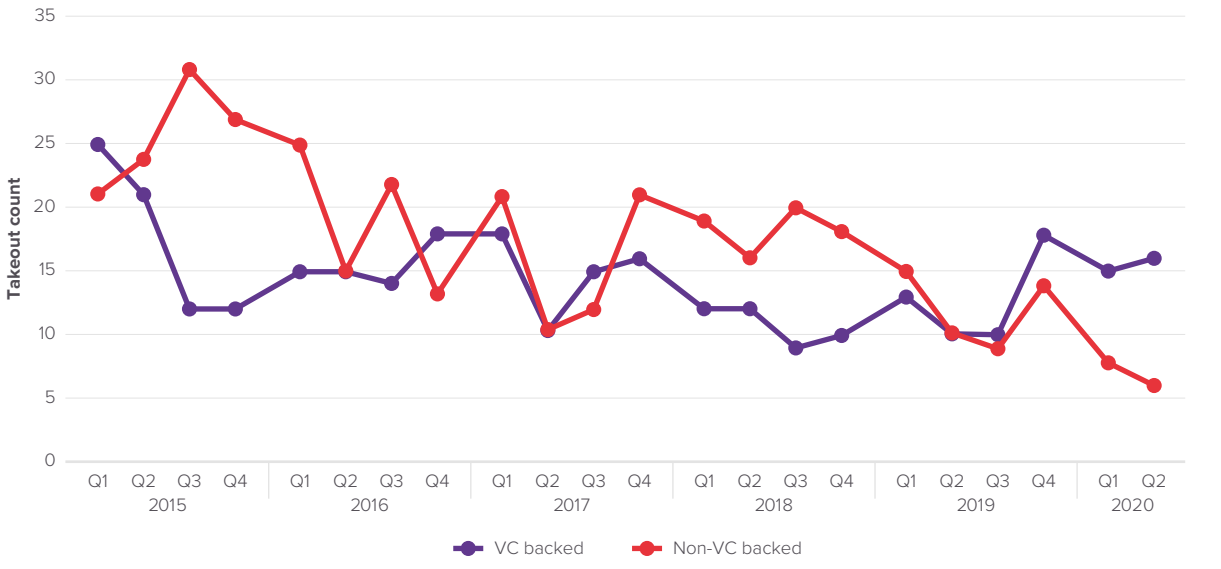
A healthy exit environment is helping drive these hums sums of money through the venture system. The surge in IPOs, detailed previously, shows that these start-ups can be quickly passed on to welcoming equity investors – albeit with a lot of support from existing shareholders, who are typically retaining substantial stakes at float.

More encouraging news on the exit front can be found in the M&A market. An analysis of company takeouts shows that venture-backed firms have proved steadily attractive to buyers over the past few years, with deal flow actually climbing in the last couple of quiet quarters.

Notably, two of the biggest transactions that have happened this year were over VC-backed companies – the takeout of Corvidia by Novo Nordisk and Gilead's move on Pionyr. Both involved contingent payments or options, suggesting that venture firms are being flexible with terms while valuations are so high, in order to keep the deal wheels turning.

Biopharma takeouts – VC-backed vs. other

Source: EvaluatePharma®, July 2020



Fundraisings by Sana and Lyell Immunopharma are still outliers, however. Both are considered "unicorns" – with valuations above $1bn – and given the early stage of these companies a move onto the public markets seems more likely than an acquisition.

They certainly dwarf rounds that would otherwise be topping the tables. However with $9.7bn raised so far this year, 2020 is on the way to breaking the annual record set in 2018 for this sector, a year in which venture investors ploughed $17.9bn into young drug developers.

Few expected this figure ever to be broken, but then 2020 has certainly not been a typical year.

Biggest biotech venture rounds of H1 2020

Source: EvaluatePharma®, July 2020

Company	Focus	Investment ($m)	Financing round
Sana Biotechnology (US)	Cell therapy	700*	Seed/Series A
Lyell Immunopharma (US)	Cell therapy	493	Series C
Everest Medicines (China)	Commercialising US approved novel medicines in Asia	310	Series C
Mabwell (China)	Antibody technology	279	Series A
Atea Pharmaceuticals (US)	Anti-virals	215	Series D

*Reportedly includes seed funding of around $220m.

A more detailed analysis of this data can be found here:

Biopharma venture investors shrug off Covid-19

Venture investors: biotech's preppers?

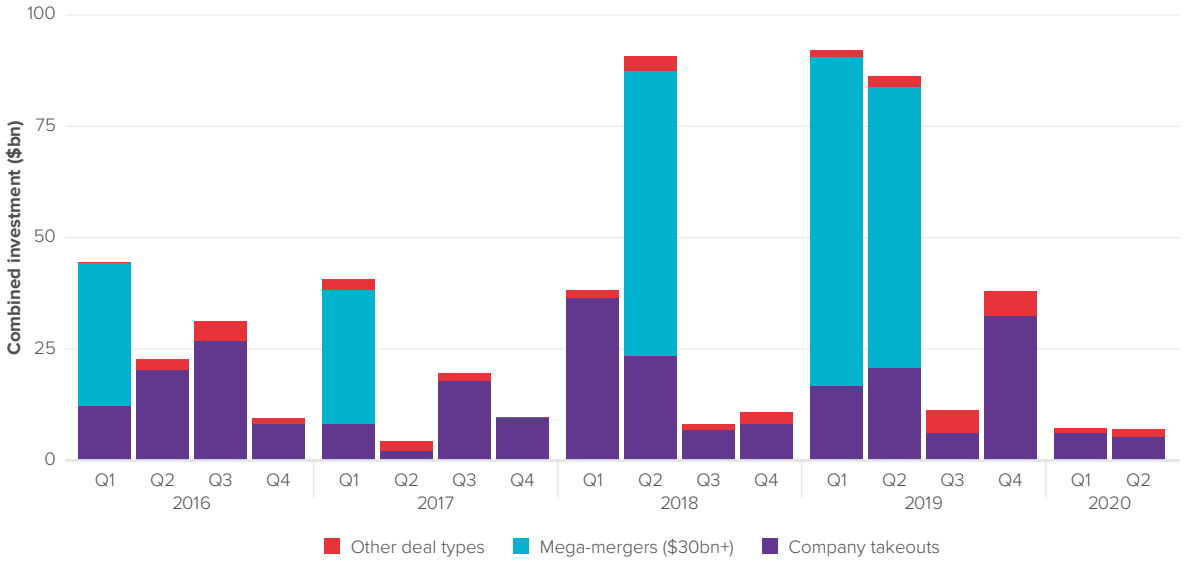
Biopharma takeovers show quantity, if not quality

With the coronavirus pandemic turning 2020 into a year unlike any other investors have piled into biopharma, helping the sector avoid the spreading doom and gloom. One area not helped by this surge of sentiment, however, is mergers and acquisitions.

The second quarter continued the pattern of the first: acquisitions are happening in only slightly reduced numbers, *Evaluate Vantage* data show, but with no large deals the combined M&A value has haemorrhaged. It is worth asking whether Covid-19-induced apathy on the one hand and spiralling asset prices on the other have put some aspects of M&A on hold.

Combined M&A deal values

Source: EvaluatePharma®, July 2020



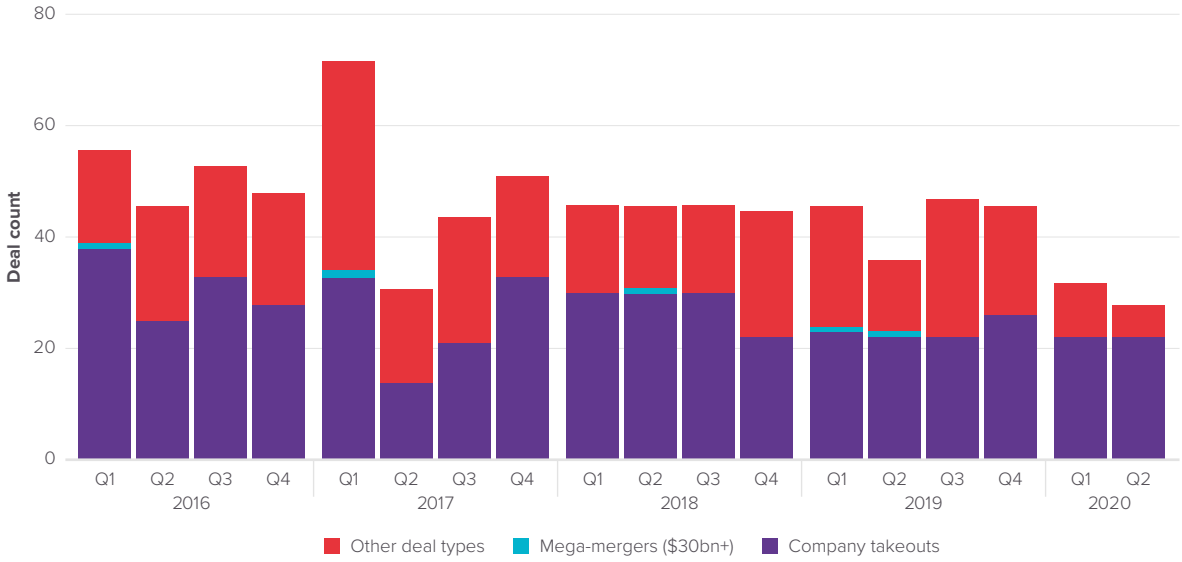
It is often said that surges in investor sentiment, and the resulting valuation increases, rarely coincide with upticks in big M&A activity. True, pharma pipelines are apparently forever in need of restocking, but acquirers need to be disciplined, and once a target's price exceeds what is reasonable a deal will not happen.

The overall quarterly deal value trends over the past few years lends some support to this theory. 2016, when the markets cooled off from the investor binge that peaked in 2015, was reasonably healthy for M&A, as was last year, during much of which the Nasdaq biotech index trod water.

The index today is at an all-time high, up 17% since January. And the last time quarterly acquisitions came in lower than the $7.1bn recorded in the period just ended was the second quarter of 2017; it might be coincidental, but three years ago the Nasdaq biotech index was standing up 19% year to date.

Quarterly M&A deal counts

Source: EvaluatePharma®, July 2020



These data include minority and majority stake purchases, reverse mergers, acquisitions of business units and options, and these are aggregated in “other deals”. And the numbers concern deals only between dedicated drug makers.

The biggest takeover of the year so far was Gilead’s $4.9bn buyout of Forty Seven, a deal which in many years would not be found at the top table.

The second quarter total of 22 takeovers is only slightly below the quarterly average of 27 since the start of 2016. The difference is the reduction in money being spent, an effect that might continue for some time yet.

Top 5 biopharma M&A deals of H1 2020

Source: EvaluatePharma®, July 2020

Buyer	Target	Deal type	Price ($bn)
Gilead	Forty Seven	Acquisition	4.9
Novo Nordisk	Corvidia	Acquisition	2.1*
Alexion	Portola	Acquisition	1.4
Eli Lilly	Dermira	Acquisition	1.1
Hypera Pharma	Takeda’s OTC & Rx portfolio in 7 S. American countries	Business unit	0.8

Note: *up-front amount was $725m.

A more detailed analysis of this data can be found here:

Biopharma acquisitions slow, but it’s not Covid-19’s fault yet

Biopharma takeovers show quantity, if not quality

Outlook

With coronavirus capturing investors' attention, and stock markets seemingly in good health, swathes of the biopharma sector are heading into the second half in a strong position. There are always clouds on the horizon, of course, the pandemic being the most ominous one right now.

For now, the worst projections of impact on the drug development process have not come to pass. Some clinical trials were suspended and delayed, but most work has got back on track. Businesses are coming to terms with remote working, and while this certainly adds complications the world is adapting.

Regulatory processes have, for now, also escaped lightly. Certain reviews have taken longer, but for now the volume of novel drug approvals makes for encouraging reading. The FDA gave a greenlight to 29 novel agents in the first half, in line with the run rate of the past couple of years.

Five biggest approvals in H1 2020, on 2026 sales

Source: EvaluatePharma®, July 2020

Product	Approved indication	Company	Annual WW sales ($bn) 2020e	Annual WW sales ($bn) 2026e	FDA Approval
Trodelvy	Advanced triple-negative breast cancer	Immunomedics	51	2.3	April
Nexletol	Very high cholesterol/ cardiovascular disease	Esperion/Daiichi Sankyo	58*	1.8*	February
Zeposia	Relapsing MS	Bristol-Myers Squibb	20	1.6	March
Palforzia	Peanut allergy	Aimmune	20	1.5	January
Tepezza	Thyroid eye disease	Horizon Therapeutics	183	1.4	January

Note: sales forecasts could include contribution from further indications. *Includes Japan partner sales.

The agency has warned about delays in the coming months, however, should it have to continue to shift resources. The potential implications of the worsening outbreaks in the US, and a widely expected upsurge of Covid-19 cases in the winter months across the Northern hemisphere, should not be ignored.

Should disruptions continue those with newly launched drugs could be particularly exposed. Sellside forecasts for recently launched products like Aimmune's peanut allergy therapy Palforzia and Horizon's eye disease treatment Tepezza already look ambitious.

With some very big decisions still to come in the second half of the year, the scope for delays and missed opportunity is real.

Five biggest pending decision in H2 2020, on 2026 sales

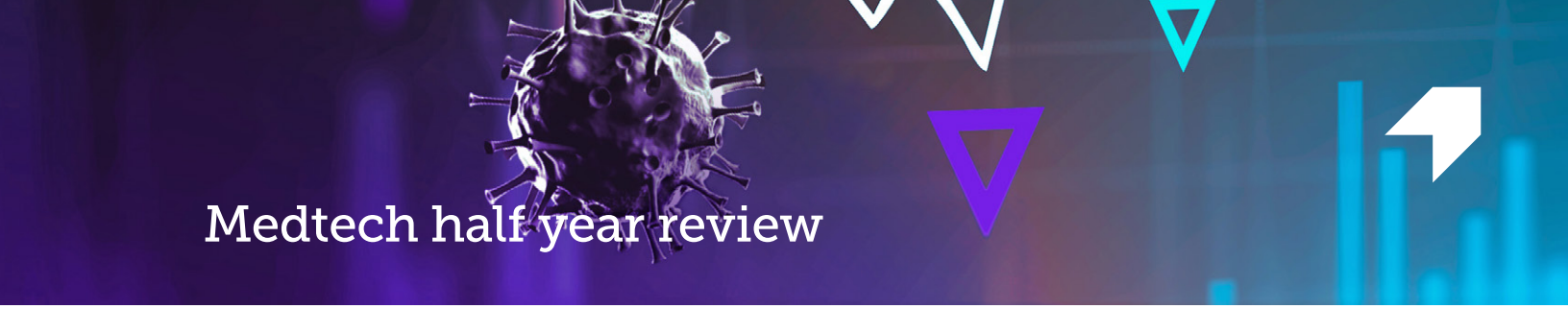
Source: EvaluatePharma®, July 2020

Product	Approved indication	Company	Annual WW sales ($bn) 2020e	Annual WW sales ($bn) 2026e	PDUFA date
Ofatumumab	Relapsing MS	Novartis	135	2.7	September
Inclisiran	Hyperlipidaemia	Novartis	170	2.0	Expected H2
Filgotinib	Rheumatoid arthritis	Gilead Sciences/Galapagos	28	2.0	July
Roxadustat	Anaemia caused by chronic kidney disease	Astrazeneca/Astellas/Fibrogen	130*	1.8*	December 20
Risdiplam	Spinal muscular atrophy	Roche	107	1.4	August 24

Note: sales forecasts could include contribution from further indications. *Includes Japan partner sales.

The other big event on the horizon for biopharma is the US Presidential election, which takes place on November 3. Heading into 2020, in pre-pandemic times, this was considered one of the biggest swing factors facing the sector this year.

The potential for policy change in the world's biggest drug market – either real or perceived – remains on biopharma's radar. But the fallout from Covid-19, and all the opportunities and disadvantages that this coronavirus is leaving in its wake, will be the dominant theme for the rest of the year. And probably well into 2021.



Medtech half year review

Covid-19 divides the biggest medtechs

No prizes for guessing the major factor impacting big-cap medtechs' share price performance across the first half of 2020. Ventilator manufacturers and testing specialists are up and orthopaedics and cardiology groups are down as the pandemic forces hospitals to reorder their priorities.

Intriguingly, though, the top riser had little to do with Covid-19. Blood glucose sensor developer Dexcom was up 85%, buoyed by collaborations and regulatory approvals. The group was hit by the wider stock market downturn in March as the scale of the Covid-19 crisis became apparent, but recovered easily by the end of the month, showing what can be accomplished even in hard times by a group with in-demand technology.

A look at share price indices covering this sector shows just how catastrophic the first half of 2020 has been. Over the course of last year, these metrics showed growth of around 30%; now they paint a picture of an industry struggling to find a path through the mire.

Stock index

Source: EvaluateMedTech®, July 2020

Stock index	% change in 2020
Thomson Reuters Europe Healthcare (EU)	1%
Dow Jones U.S. Medical Equipment Index	-1%
S&P Composite 1500 HealthCare Equipment & Supplies	-4%

Dig deeper and it becomes clear that the pandemic has split the big-cap cohort neatly into winners and losers along subsector lines. Ventilator companies Fisher & Paykel and Resmed were up, as were diagnostics groups, including Biomerieux, Bio-Rad, Sysmex and Hologic, all of which have Covid-19 tests approved in various territories.

Fisher & Paykel also benefited from its New Zealand base and listing; the country has done a superb job of first containing and then stamping out Covid-19, and the S&P NZX All Health Care index is up 17% so far this year.

Large cap ($10bn+) medtech companies: top risers and fallers in H1 2020

Source: EvaluateMedTech®, July 2020

Company	Share price 6-mth change	Market cap at Jun 30 ($bn)	Market cap 6-mth change ($bn)
Top 5 risers			
Dexcom ($)	85%	37.44	17.4
Fisher & Paykel Healthcare (NZ$)	60%	12.29	4.2
Biomérieux (€)	54%	15.73	5.4
Masimo ($)	44%	12.34	3.9
Abiomed ($)	42%	10.86	3.2
Top 5 fallers			
Hitachi (¥)	-26%	30.6	-10.8
Boston Scientific ($)	-22%	49.1	-13.9
Smith & Nephew ($)	-21%	16.7	-4.3
Zimmer Biomet ($)	-20%	24.6	-6.2
Medtronic ($)	-19%	123.0	-29.1

The fallers are just as easily delineated. All lost out because their products are used in the kinds of elective procedures that hospitals and other sites have had to shelve – mostly orthopaedic, cardiac and dental surgery.

Hitachi, whose medical business centres on imaging, saw big losses as patients in need of scans stayed away. Orthopaedics companies Smith and Nephew and Zimmer Biomet were hit hard, and Medtronic, active in both the cardiovascular and orthopaedics sectors, also suffered.

Even robotic surgery market leader Intuitive Surgical, a perennial stock market darling, was down 4% at the half year point.

Among the smaller device makers, too, the pandemic has made its effects felt – but in a different way. Many of the risers have either their headquarters or their listings in the Far East, whereas the fallers are almost all US-based. The recovery from the virus in many of the earliest-hit countries, and its disquieting resurgence in the US, are major factors in determining these companies' performance.

Among the small cap risers, Korea's Seegene was one of the first diagnostics group off the mark with a coronavirus test, having ceased all non-Covid-19 development at the very start of the year and instead thrown all its efforts at developing a diagnostic for the disease. The resulting viral RNA assay test gained approval from the Korean Ministry of Food and Drug Safety in mid-February, and was authorised by the US FDA on April 22.

Other significant risers and fallers in H1 2020 (ranked on market cap)

Source: EvaluateMedTech®, July 2020

Company	Share price 6-mth change	Market cap at Jun 30 ($m)	Market cap 6-mth change ($m)
Top 5 risers			
Quidel ($)	198%	9,397	6,272
Livongo ($)	200%	7,355	4,987
Microport Scientific ($)	241%	6,989	5,081
Seegene (KRW)	268%	2,419	1,740
Meridian Bioscience ($)	156%	998	610
Top 5 fallers			
Novocure ($)	-30%	5,956	-2,384
Envista ($)	-29%	3,350	-1,349
Elekta (SKr)	-30%	3,187	-1,638
Intersect ENT ($)	-46%	441	-344
IBA Group (€)	-41%	250	-184

One positive for investors in these the mid-size and small-cap medical device companies is that the gains made by the risers are greater than the fallers' losses. But the number of mid and small cap companies which saw their value fall in the first half of the year outnumber those whose stock price rose; perhaps not surprising in an incredibly turbulent time.

A more detailed analysis of this data can be found here:

Covid-19 divides the biggest medtechs

Smaller device makers put in a muted performance

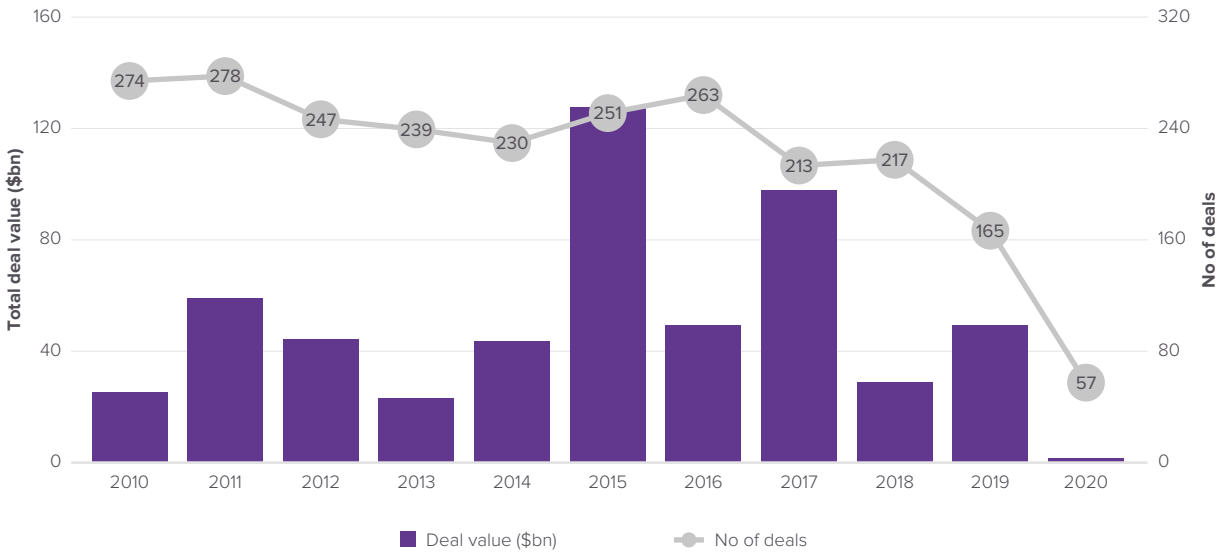
Medical device mergers on pause

Thanks to Thermo Fisher Scientific and Invitae, two groups brave enough to push ahead with multibillion-dollar acquisitions during a pandemic, the total value of medical device M&A announced in the first half of 2020 nudged over $16bn – though this is still a distressingly low figure. The real shock, however, is not the value of the deals announced, but of those that have been closed.

The medtech deals completed in the first half of 2020 have a total value of less than $2bn. This is despite mergers worth a total of more than $21bn remaining open. The Covid-19 pandemic seems to have made it harder to hammer out the legal or financial complications of closing deals than it did to conduct the negotiations in the first place.

Medtech M&As over the past decade – Number and value of deals closed

Source: EvaluateMedTech®, July 2020



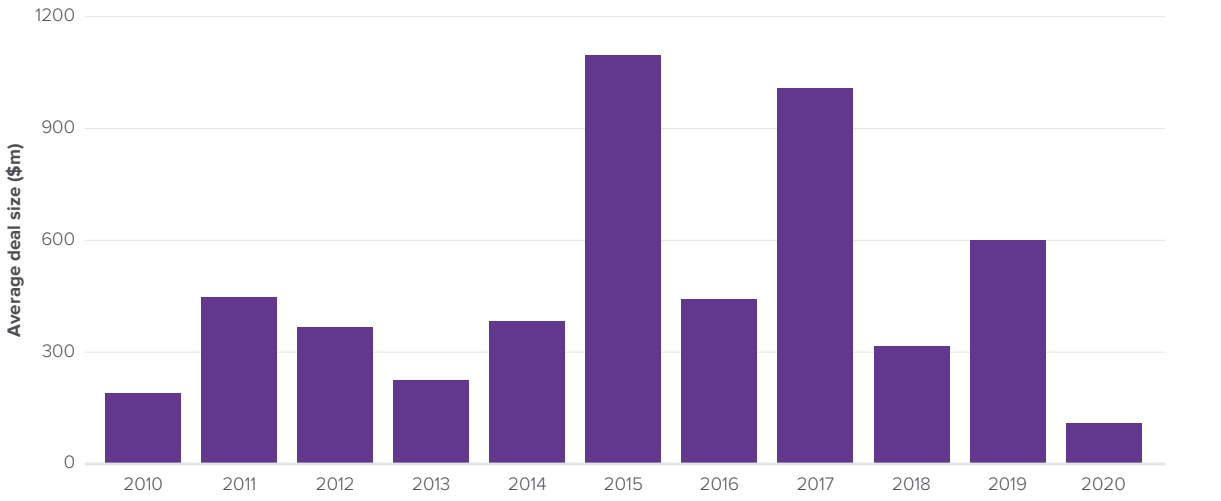
The average size of completed mergers is also lower than at any point in the past decade. The mean acquisition size was just $108m in the first six months of 2020; this figure has been erratic over the past 10 years, but shows an overall downturn since 2015.

It is also interesting that the two big acquisitions announced in the first half of 2020 were both diagnostics deals. The unveiling of the $12.5bn Thermo Fisher-Qiagen deal predates the WHO's designation of Covid-19 as a pandemic, and thus the deal has little to do with tests for the coronavirus itself – though Qiagen has subsequently developed and launched Covid-19 tests.

Neither was Invitae's $1.4bn takeout of Archer DX a Covid-19 play. This was to do with cancer testing, notably Archer's pan-cancer liquid biopsy Stratafide. Blood testing for cancer is increasing in popularity during the pandemic as blood can be drawn in doctors' offices or even at the patient's home, while tissue biopsies require hospital appointments. More liquid biopsy developers could come to be seen as acquisition targets if the state of emergency drags on.

Average deal size – Deals closed over the last decade

Source: EvaluateMedTech®, July 2020



As for what the second half of this year might hold, the trends in business development will depend on whether new waves of infections and deaths occur, and their magnitude if they do. If major lockdown measures are eased M&A activity ought to pick up, and orthopaedics companies might be a hotspot.

Companies such as Zimmer Biomet and Smith & Nephew, which have suffered as less urgent surgical procedures have been delayed, might wish to diversify their offering by picking up companies developing emergency trauma products, or even technologies outside their traditional specialities, such as telemedicine or patient monitoring devices.

As for the very largest deals, a resurgence will depend not only on the risk of a major second wave having passed but also on economic factors such as the availability of cheap credit. If the second half of 2020 sees the same number of medtech megadeals announced as the first – two – the industry might be regarded as having got off lightly.

Top 5 deals announced in H1 2020

Source: EvaluateMedTech®, July 2020

Announcement date	Acquirer	Target	Value ($m)	Focus
Mar 3	Thermo Fisher Scientific	Qiagen	12,500	In vitro diagnostics
Jun 22	Invitae	Archer DX	1,400	In vitro diagnostics
Jan 12	Teladoc Health	Intouch Health	600	Cardiology; obstetrics & gynaecology
Jan 13	Montagu Private Equity	OEM business of RTI Surgical	490	Orthopaedics; general & plastic surgery
Mar 3	Align Technology	Exocad	420	Dental; healthcare IT

Top 5 deals closed in H1 2020

Source: EvaluateMedTech®, July 2020

Completion date	Acquirer	Target	Value ($m)	Focus
Feb 12	Laborie Medical Technologies	Clinical Innovations	525	Gastroenterology; healthcare IT; in vitro diagnostics; obstetrics & gynaecology
Apr 2	Align Technology	Exocad	420	Dental; healthcare IT
Feb 18	Baxter International	Sepra Products business of Sanofi	350	General & plastic surgery
Feb 3	Anika Therapeutics	Arthrosurface	100	General & plastic surgery; orthopaedics
Jan 24	Anika Therapeutics	Parcus Medical	95	Orthopaedics

A more detailed analysis of this data can be found here:

Medical device M&A on pause

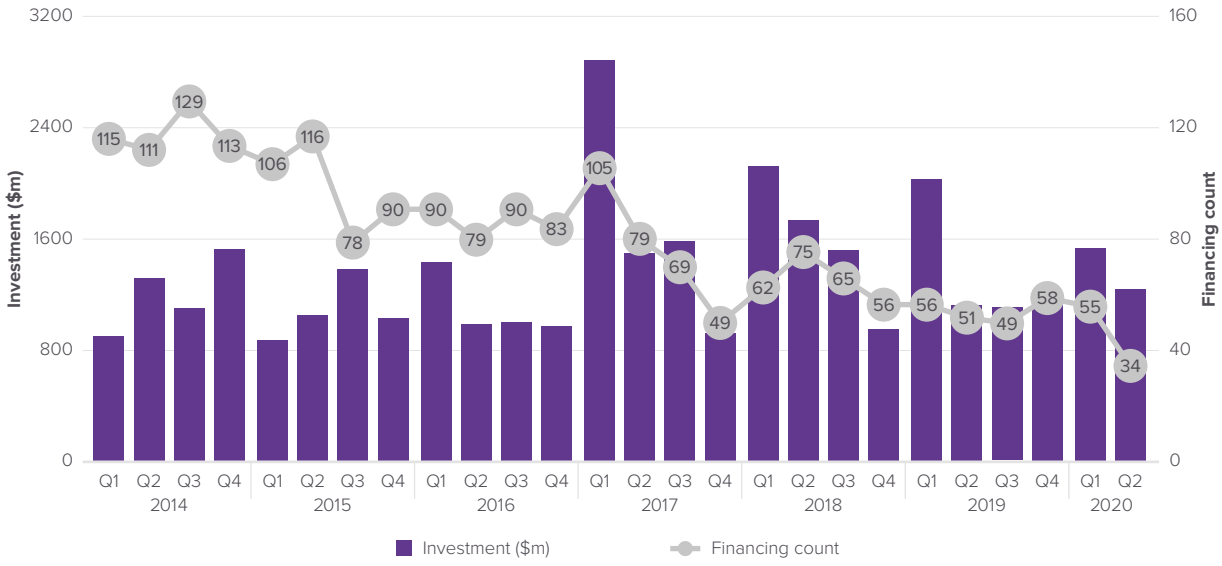
Medtech venture investors live up to their name

The first half of 2020 might be expected to have posed a uniquely difficult challenge for private medical device developers in need of cash. Not so, it appears. Venture investors were unable to meet start-ups' management in person but the money changed hands somehow: $1.2bn was invested in early-stage medtechs in the second quarter of this year, just when lockdown measures were at their harshest.

Overall the total venture investment raised by medtechs so far this year is very respectable. VCs also appear to be reacting to the riskier environment by banding together in bigger syndicates, and prioritising later rounds for relatively de-risked companies.

Medtech VC investment, 2014-2020

Source: EvaluateMedTech®, July 2020



A prime example of the trend towards big rounds for relatively established companies is Grail's $390m series D haul in May. The liquid biopsy developer has a track record of monster financings, notably its $1.2bn series B, raised over two tranches in 2017 and 2018. The most recent cash injection came partly from the Canada Pension Plan Investment Board – hardly a wild risk-taker – and Illumina, the sequencing giant from which Grail was spun out.

The second largest amount raised was the $165m funding of Karius, also a diagnostics company, and one that deploys the ever-appealing technology of artificial intelligence. Karius says it uses next-generation sequencing and AI to "map a patient's microbial landscape from a single blood draw", using the cell-free DNA shed by microbes to identify the pathogen causing the patient's disease.

VCs are investing money while they can – as the spike in total funding in the second quarter suggests. The economic impact of the pandemic means hard times are coming, and investors will want to load their portfolio companies up with cash to cushion them against an environment in which drumming up further money could be deeply challenging.

The same pattern is playing out a level above: VCs are themselves seizing what might be the last chance in a while to raise cash from their limited partners. For example, in mid-March the healthcare-focused venture firms LSP closed its largest ever European life sciences fund at $600m – notably more than the fund's $450m target.

The medtech venture funding landscape is looking good for now, despite the dearth of smaller deals. But harder times might well be coming.

Top 10 VC rounds of H1 2020

Source: EvaluateMedTech®, July 2020

Date	Round	Company	Investment ($m)	Focus
May 6	Series D	Grail	390.0	In vitro diagnostics
Feb 24	Series B	Karius	165.0	In vitro diagnostics
Mar 6	Series F	Insightec	150.0	Diagnostic Imaging
Jan 2	Undisclosed	Oxford Nanopore Technologies	144.5	In vitro diagnostics
Feb 4	Series E	Outset Medical	125.0	Nephrology
Apr 16	Series D	Reflexion Medical	100.0	Radiology
Feb 4	Series C	Hinge Health	90.0	Digital health
Jan 6	Series G	Sonendo	85.0	Dental
Jan 8	Undisclosed	Zap Surgical Systems	81.0	Radiology
Feb 6	Undisclosed	Genapsys	75.0	In vitro diagnostics

A more detailed analysis of this data can be found here:

Medtech venture investors live up to their name

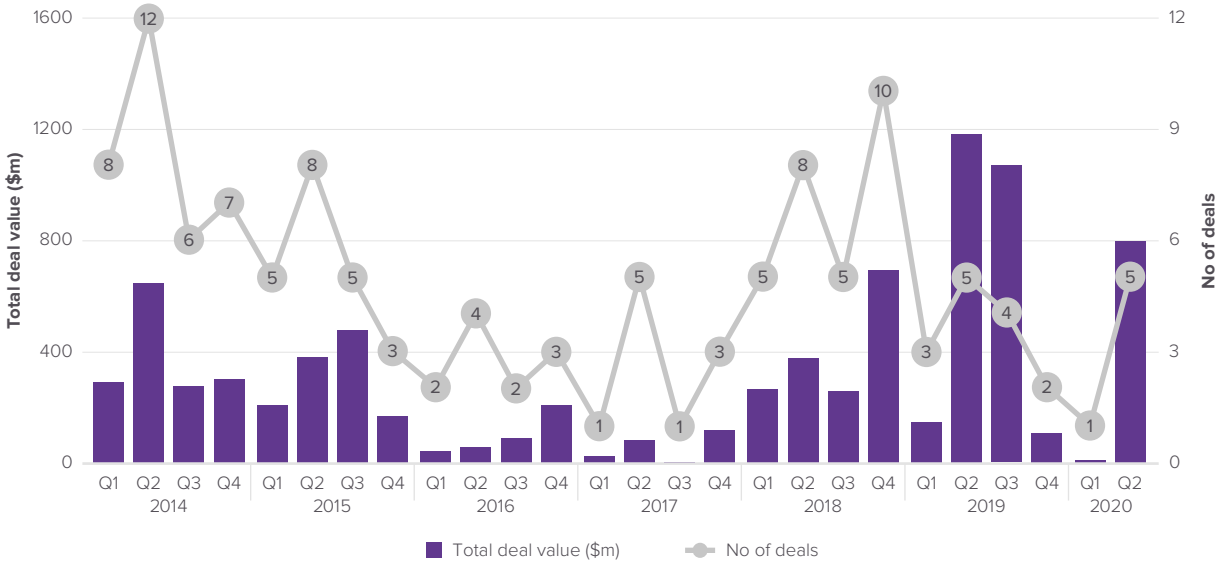
A baptism of fire for listing medtechs

This year is not looking as strong as 2019 when it comes to medtech IPOs, but the showing in the first half has been within the range of the last few years. The second quarter in particular was strong, with five floats raising a total of $800m, perhaps because companies feared that the opportunity to get these deals done could soon be snatched away.

Floating is one thing, holding your valuation another and amid turbulent markets shares in most of the newly-listed companies had drifted lower by the mid-year point.

Medtech IPOs, 2014-2020

Source: EvaluateMedTech®, July 2020



A look at exactly when 2020's listings occurred shows the effects of the pandemic. The liquid biopsy developer Anpac Bio-Medical Science went public in January, when Covid-19 was just beginning to ping on investors' collective radar. After that, no action for three full months as the equity markets plummeted. It is possible that some of these groups postponed IPOs originally scheduled for the first quarter, again contributing to the following period's impressive total.

But when the Nasdaq began to recover, private groups saw their chance. None of the floats in the last two months of the first half went out at a discount, and medtech's reputation as a safe and steady sector in times of turmoil might well have contributed to shareholders' desire for a piece of these companies.

As is often the case, particular technologies are cash magnets. 2020 has been the year of the liquid biopsy: as well as Grail's huge VC funding round, Anpac, Burning Rock Biotech (formerly known as Guangzhou Burning Rock Dx) and Genetron are all focused on cancer blood tests.

Medtech IPOs of H1 2020

Source: EvaluateMedTech®, company websites, July 2020

Date	Company	Focus	Amount raised ($m)	Discount/ premium	Share price change to June 30
Jan 30	Anpac Bio-Medical Science	In vitro diagnostics	16	-8%	-57%
May 1	Lyra Therapeutics	Ear, nose and throat	64	7%	-29%
May 22	Inari Medical	Cardiology	156	9%	154%
Jun 12	Burning Rock Biotech	In vitro diagnostics	223	14%	64%
Jun 19	Genetron Holdings	In vitro diagnostics	256	28%	-25%
Jun 20	Progenity	In vitro diagnostics	100	0%	-40%

All listings on the Nasdaq.

These three companies have another thing in common: despite their Nasdaq listings, all are based in China. The choice of the US as a destination reflects the continued strength of the American market for IPOs, which have been strong across all sectors this year.

One trend from 2019 that has continued into this year is that for huge deals. The five second quarter IPOs raised an average of $160m, a figure higher than in any period since *Evaluate Vantage* started tracking listings, with the exceptions of the middle two periods of 2019.

This is likely motivated by the same considerations driving VCs to participate in ever-larger rounds: the need to get the company to the next big inflection point, and to raise money while the going is good. How long the going might remain good is another question.

A more detailed analysis of this data can be found here:

A baptism of fire for listing medtechs

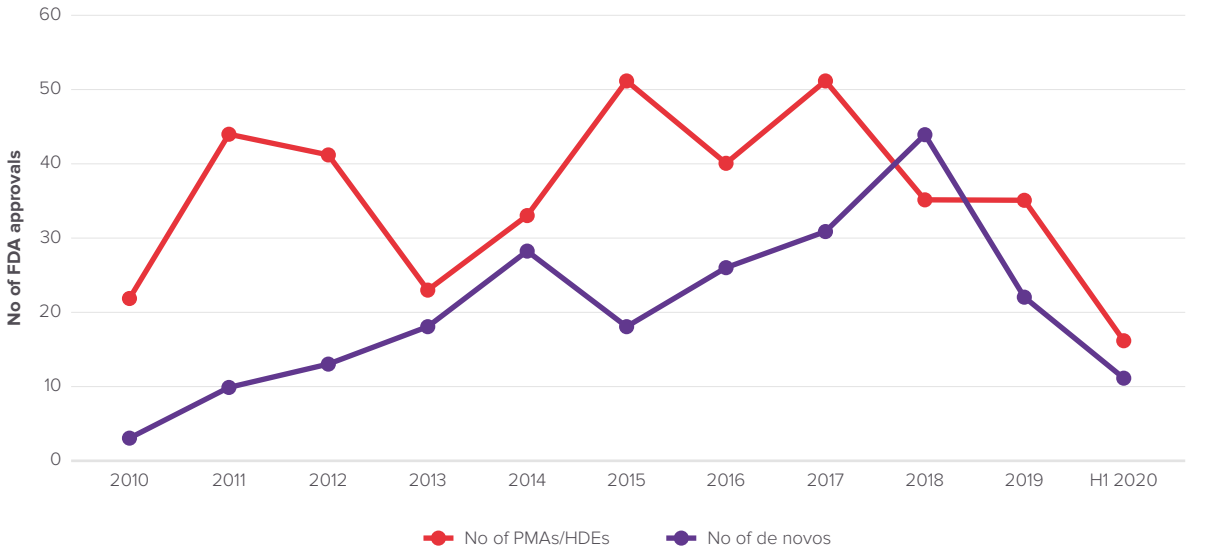
FDA keeps the new devices coming

As the FDA grapples with a once-in-a-generation crisis and tries to speed drugs, vaccines, devices and diagnostics to market, the less pressing business of evaluating and approving non-Covid-19-related medical technologies has taken a back seat. Even so, the number of devices approved by the agency has not dipped as much as might have been feared.

In the first half of 2020 the FDA approved 16 high-risk and 11 low-risk novel medical devices, putting it only slightly behind its performance last year. As importantly, the speed at which these products made it through the regulatory process has barely slowed. Still, last year saw a slowdown in the second half, so medtechs must hope that the FDA is able to keep up the pace in the coming months.

Medtech approvals over the past decade

Source: EvaluateMedTech®, July 2020



In vitro diagnostics make up the majority of products granted premarket approval by the FDA – the type of approval used for products intended to be used in supporting or sustaining human life or preventing impairment of health. Many of these high-risk diagnostics are for viral infections, including hepatitis B and C, HIV and human papillomavirus.

Absent from this analysis is any diagnostic for Covid-19 infection or test for immune response. The FDA has not granted approval or clearance for any such test – instead these are afforded regulatory oversight in the shape of emergency use authorisation, a less rigorous stopgap measure for a time of crisis.

Average review times of first-time PMAs by therapy area (months)

Source: FDA, July 2020

EvaluateMedTech classification	H1 2020	H1 2020
Cardiology	4	21.0
In vitro diagnostics	9	10.8
Neurology	1	9.6
Ophthalmics	1	5.9
Urology	1	30.0
Total	**16**	**-**
Average		**14.2**

Perhaps because of its determination to keep new technologies flowing, the agency has taken a fairly lenient stance on at least some of these approvals. The FDA granted a PMA for the ReActiv8 neurostimulator, developed by Mainstay Medical, despite the device having failed its pivotal trial. The agency awarded the approval after deliberating for less than 10 months.

Another potential worry, in terms of both sufficiently stringent oversight of new devices and maintaining a decent number of approvals by year-end, is the postponement of FDA advisory committee meetings. Adcoms scheduled to assess PMAs for Transmedics' ex-vivo heart perfusion and monitoring system and Refocus Group's VisAbility Micro Insert, an eye implant intended to improve near vision in presbyopic patients, have been postponed without new dates being announced.

Average review times of de novo 510(k)s by therapy area (months)

Source: FDA, July 2020

EvaluateMedTech classification	H1 2020	H1 2020
Cardiology	1	5.9
Diagnostic imaging	1	5.4
Endoscopy	1	9.3
Healthcare IT	1	2.0
In vitro diagnostics	3	10.5
Nephrology	1	18.7
Ophthalmics	1	11.6
Orthopaedics	1	16.6
Urology	1	10.8
Total	**11**	**-**
Average		**10.2**

The rate of de novo clearances – those granted to low-risk devices that are so innovative that no previously approved device can stand as a predicate – is tracking at exactly the same pace as last year. The first six months of 2020 saw 11 de novos granted in an average of 10.2 months, compared with 22 across all of 2019, in the same average time.

It is reassuring that the FDA is still attending to its routine work even as it is under political pressure to rush Covid-19 diagnostics and therapeutic devices on to the US market. Ventilators, for example, are also eligible for emergency use authorisation. Provided it can continue to do so during the second half of the year, this is one area in which 2020 could come to be regarded as almost normal.

A more detailed analysis of this data can be found here:

FDA keeps the new devices coming

Outlook

While Covid-19 has had a catastrophic impact on many medtechs in the early months of 2020, there are glimmers of hope. Johnson & Johnson and Abbott, for example, saw sharp drops in sales of their non-diagnostic medical devices in the second quarter of 2020 compared with Q2 2019 as elective procedures were deferred, with sales of surgical, orthopaedic and cardiovascular technologies being hit badly. But in both cases the fall was not as bad as had been feared, with signs of an earlier-than-expected recovery in May and June, raising hopes that other companies which had previously forecast big hits to their business will also be able to report good news.

Over the longer term, when cases of the coronavirus finally begin to diminish, a new normal will likely be established. Patients will still be wary of hospitals, and volumes of elective procedures might take some time return to levels seen in prior years.

Demand for diagnostics for active Covid-19 infections should fall if vaccines become available, but these assays will become a routine part of triage when a patient presents with breathing difficulties or other Covid-19 symptoms. There will always be a need for antibody tests, too, as they become necessary for establishing whether a vaccine has elicited an immune response.

Currently, though, the US is already in the grip of a second wave of infections. If a second wave of deaths manifests, or if infection rates rise once more in Europe and Asia, the divide between the medtech industry's haves and have-nots can only widen.

Many of the badly affected groups have been keen to stress that the second quarter was always going to be the toughest period of 2020, and made it clear that they expect sales to increase in the second half. But economies are struggling, and with health insurance linked to employment in countries such as the US, device makers' 2020 sales seem likely to remain below prior years.

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Evaluate Headquarters
Evaluate Ltd.
11-29 Fashion Street
London E1 6PX
United Kingdom
T +44 (0)20 7377 0800

Evaluate Americas
EvaluatePharma USA Inc.
60 State Street, Suite 1910
Boston, MA 02109
USA
T +1 617 573 9450

Evaluate Asia Pacific
Evaluate Japan KK
Holland Hills Mori Tower 2F
5-11-2 Toranomon, Minato-ku
Tokyo 105-0001, Japan
T +81 (0)80 1164 4754

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