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FROM THE EDITOR

LUCIE ELLIS
EXECUTIVE EDITOR
IN VIVO

Looking back at 2020 is an interesting endeavor: a global pandemic rocked the world, ground-breaking research and development efforts came to fruition for the biopharmaceutical and medtech sectors at record-breaking speeds, virtual became reality and political events encroached on health care systems.

Looking ahead into 2021 is tricky. No one could have predicted the events of the past 12 months, and the year to come will certainly throw surprises at the life sciences sector. Still, our team of journalists and analysts have come together for Outlook 2021, to provide insight and scrutiny on various trends and topics critical to pharma and medtech decision-makers.

Outlook 2021 also includes the annual Scrip 100, Medtech 100 and Generics Bulletin Top 50 league tables – evaluating the performance of the pharma and medtech sectors throughout fiscal year 2019. Find out which companies hold the top spots this year and how the tables might turn in the near future.

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David Wallace

DESIGNERS
Carla Antill
Kosh Naran
Nancy Pham
Paul Wilkinson

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Customer Services: Tel +44 (0) 20 7017 5540 or (US) Toll Free: 1 800 997 3892

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Biopharma Outlook: Turning Uncertainty Into Opportunity

A singular focus on defeating COVID-19 will likely dominate the biopharma agenda at the beginning of 2021 and will determine how quickly the industry, and world, can bounce back to something like normalcy. New digital capabilities and learnings will continue to emerge as the pandemic ebbs, and strong industry balance sheets will keep the deal volume moving, according to experts and executives.

BEN COMER
EXECUTIVE EDITOR, US

The year 2020 was chaotic, to put it charitably. It was a year that makes gazing into a happier future – past the COVID-19 related suffering and hardship, past continuing racial injustice, past the political and environmental onslaught – something of a welcome respite. Our problems are far from solved, making optimism sometimes difficult to muster and a happier future challenging, at times, to picture. And yet, there are strong reasons to believe that hard work, collaboration and perseverance will help to ameliorate our present situation; witness the grit displayed by essential workers, the unprecedented cooperation and speed of research happening in the scientific community, and the tireless activism of Black Lives Matter. We have been down in 2020, but we are far from out.

In fact, a closer look reveals a myriad of positive responses to our current crisis, and new developments that will shape the global health care ecosystem for years to come. In the realm of health care's plodding digital transformation, necessity became the mother of transition. The biopharmaceutical innovation engine – and the fundraising that fuels it – did not sputter, despite a flagging economy. Corporate culture, diversity and inclusion gained a renewed focus and vigor, and turned into a strategic imperative. And the race to find a safe and effective vaccine for COVID-19 brought academics, drug developers, regulators and other stakeholders together, shaving years from the standard vaccine development timeline.

Many challenges remain. At a macro level, shifting global trade policy and the 2020 US election bring new uncertainties. With the arrival of winter, COVID-19 case numbers and deaths are ticking up, brightening the spotlight on vaccine and therapeutics developers, and dimming the hope for a speedy economic recovery. Even so, 2021 will be a year of striking opportunity for the biopharmaceutical industry. New gene and cell therapies will stimulate deal activity and become available to patients, along with new pricing models; early stage cancer detection diagnostics could upend cancer care; and new treatments for rare diseases will address staggering unmet needs. And of course, the whole world is waiting for a COVID-19 vaccine, the handling of which could make or break biopharma's reputation.

"It's striking how functional the financing markets have been." – Michael Gaito

COVID-19 PREVALENCE

It is hard to understand how the decision to wear a mask turned into a political statement, and much has been said and written about the public's responsibility – or irresponsibility – in slowing the spread of the SARS-CoV-2 virus. "Everybody knows that pestilences have a way of recurring in the world: yet somehow we find it hard to believe in ones that crash down on our heads from a blue sky," wrote Albert Camus in *The Plague*, his 1947 novel about the social dilemmas inherent to combatting an infectious and deadly disease. Vaccine manufacturers and distributors will face challenges beyond the supply and logistics of access and delivery, including the need to overcome "vaccine hesitancy" among skeptical consumers.

Next year will be a "tale of two cities," meaning that what happens during the first half of 2021 will determine how different the second half of the year will be, said Arda Ural, Americas industry markets leader, health sciences and wellness, at Ernst & Young. "The number one area of uncertainty for next year will be the prevalence of COVID-19." The longer that high prevalence rates last, the more negative impacts will radiate outward across individuals and the economy. "Twenty-five million Americans are receiving government assistance, and 10 million have lost their jobs," said Ural. If the virus lingers, more people will lose insurance coverage, more will go undiagnosed, and more will lose affordable access to medications. "There will be some downstream impact on the life sciences industry, depending on loss of insurance," he said.

Strategic planning will be critical for managing COVID-19 vaccines, therapeutics and other products as well. "It's about how can organizations forecast the surge and decline at a rapid pace heading into the future," said Karen Young, US health industries leader at PwC. Industry CEOs will need modeling and forecasting tools akin to a flight simulator to successfully run their businesses, said Young. A "CEO simulator" can bring agility and nimbleness to business decisions, incorporating surveillance systems to predict business portfolio performance and diversification, and supply and demand.

The US FDA issued more than 300 Emergency Use Authorizations (EUAs) for diagnostics, therapeutics, personal protective equipment and other medical devices between February and September of 2020, noted Young, compared with a total of 24 EUAs between 2010 and 2019. "The scale in what has occurred during this eight-month period definitely will show a stickiness in how trials will be run," said Young, adding that 11,000 trials are listed as using connected digital products or remote data collection. "Transparency has become front and center, and that collaboration will start to evolve into something that hopefully will improve the trust factor in our industry. Gaining trust among recipients of a COVID-19 vaccine will require a transparent, five-pronged approach between manufacturers, regulators and policymakers, including trial methodology, standard of accountability, data, side effects and regimen," said Ural. "Then it becomes a change management and educational effort."

FINANCIAL HEALTH IS STRONG

Although many sectors have been hard hit by COVID-19, strong liquidity and balance sheets in the biopharma industry have provided a degree of stability in very unstable times. That strength reflects the life sciences' "innovation for change" focus, which is part of the new economy, said Adam Lohr, a partner and senior analyst for the life sciences industry at RSM, a professional services firm. "As a country, the US is moving away from energy and industrials, and moving toward very highly technical products, whether it's financial services, technology or life sciences … that is the direction that the economy is moving, and the returns are significantly better there."

Interest rates are likely to stay near zero for years to come, which stimulates investment. "People are looking out on the long run, and investment in life sciences allows people to get an above average return over an extended period of time, without being susceptible to short term volatility," said Lohr. "It's striking how functional the financing markets have been," said Michael Gaito, global head, healthcare investment banking, at JP Morgan, during a Demy Colton virtual salon on 29 September 2020. The first half of 2019 saw an all-time high in global fundraising, and the first half of 2020 was even higher than 2019, said Gaito. At JP Morgan, 2020 fundraising had outpaced the full year of 2019 by the end of the third quarter, including $18bn from IPOs, and $50bn in follow-ons, he said.

Ural said his colleagues working in EY's venture capital group are seeing "significant oversubscription in IPOs, even with preclinical assets, which is unheard of … Liquidity is driving a lot of that valuation, so it's a great time to be a biotech innovator." Innovation is also driving deal activity; the FDA had approved 42 New Molecular Entities by early November, compared with 48 NMEs during the full year of 2019. That level of innovation means that "biotech or midsize pharms who are innovating will be acquired as a bolt-on," said Ural. "That trend will continue,

because big pharma requires that innovation to replenish its aging portfolio." Gaito at JP Morgan also noted high premiums in mergers and acquisitions, and predicted "robust M&A activity into 2021."

DIVERSITY AND INCLUSION AS A STRATEGIC IMPERATIVE

Following the death of Breonna Taylor from a police gunshot in March 2020, and the death of George Floyd under the knee of a police officer in May, the Pharmaceutical Research and Manufacturers of America (PhRMA), like many organizations around the country, spoke up. 'Systemic Racism Is As Real As Any Disease. Our Industry Is Not Immune,' said the headline of a PhRMA print ad launched in July. 'Diversity is essential to a robust innovation ecosystem that can create new medicines for those who need them,' the ad continued. Last January, the Biotechnology Innovation Organization launched its first annual Measuring Diversity in the Biotech Industry: Building an Inclusive Workforce report. The report, based on survey data from 98 companies, illustrated the need for stronger gender parity and racial and ethnic representation in the biotech workforce.

In an interview with *In Vivo*, Percival Barretto-Ko, president of Astellas Pharma US, said, "COVID truly unraveled a lot of deep-rooted issues around not just racial inequality, but racial injustice and health care inequities in society." Ethnic and racial minority groups have been disproportionately impacted by COVID, due to overrepresentation among essential workers, discrimination in housing and health care access, inequities in education and other factors. Barretto-Ko said Astellas makes an effort to understand the issues patients face every day, "not just out of pocket costs, but also access to medicines." He cited prostate cancer as a "good example of health care inequities that exist particularly among African-American men, all the way from diagnosis to treatment." Astellas co-markets the prostate cancer treatment Xtandi (enzalutamide) with Pfizer. "The way that we approach this disparity is to do an audit ourselves of what exactly we as an organization are doing to address those inequities."

Astellas established a diversity and inclusion (D&I) council "several years back," composed of over 30 leaders across the global Astellas organization. "Over the last year, we've really focused on understanding metrics, and really looking at our HR systems to understand the number of promotions, the rate of promotions, the rate of recruitment, and terminations as well, both voluntary and involuntary. As a science and data driven-organization, it's important for us to know the status," Barretto-Ko said. Astellas developed a three-year people strategy based on three pillars for talent: attract, retain and develop. Under each of those workstreams, "we have strategic imperatives and tactics from establishing deep relationships with historically black colleges and with professional organizations to track talent, to talent review and mentorship and sponsorship of people of color and diverse populations within Astellas," he said.

There is hope that a shift toward increasingly virtual or decentralized trials will increase racial diversity in clinical trial enrollment, a critical issue for research. Diversity among clinical researchers is important too – just as police forces work better when they reflect the communities they serve, diverse trial investigators can help build trust and participation rates among people in underserved communities, said Bristol Myers Squibb chair and CEO Giovanni Caforio, during PwC's 180 Health Forum. BMS's foundation pledged $100m over the next five years to train and develop 250 racially and ethnically diverse clinical investigators.

D&I initiatives are being built into the fabric of the employers, said Lohr at RSM. "More women are coming up through the STEM programs in our academic institutions, and we'll probably see that in hiring over the next couple of years," he noted. "There are funds that invest only in companies that have a diverse board of directors, because they out-perform their non-diverse peers," he said. Investment groups committed to company diversity as a prerequisite for funding include Plum Alley and Astia, and financial institutions such as Goldman Sachs and Softbank are providing funding vehicles specifically for female-led companies and entrepreneurs of color.

US ELECTIONS

Despite a change of administration in the Executive Branch, the 117th Congress will remain divided when it convenes for the first time in January 2021, with Democrats maintaining control of the House of Representatives, and Republicans likely holding the Senate. A divided Congress provides a check on the ambitions of a single party, which is preferable for most businesses.

Health care reform and health care affordability – including drug pricing – will likely take a back seat to COVID-19 deliberations in the short term, particularly the negotiation and passage of a COVID-19 stimulus package. Biopharma companies must pay close attention to the leadership selections at key regulatory agencies, such as the Department of Health and Human Services and the FDA, to better understand and adapt to any new policy direction for the new year. Trade and tax policies are likely to change with the new administration, and the industry should also be listening closely for policies dealing with manufacturing overseas. Consultants speaking with *In Vivo* recommend a "China plus one" supply chain strategy to help mitigate plant outages or problems with imports. Onshoring of manufacturing is not expected to become mandatory, or to happen in the short term – it would take years and many millions of dollars to bring API manufacturing back to the US after 30 years overseas, but the specter of "Buy American" may linger through the new year. Hopefully, COVID-19 will not.

ASHLEY YEO
EXECUTIVE EDITOR, EUROPE

Into 2021 Medtechs Prioritize Third-Wave Coronavirus Readiness

Coronavirus has definitively changed health care delivery and the perceptions of health technologies and digital ecosystems. Industry will need to adjust to the aftermath of COVID-19, take opportunities and learn lessons from 2020 or 2021 could be every inch as challenging.

Before the first wave of the pandemic had tailed off and the second wave fears were not yet borne out, MassMutual Ventures' Ryan Collins expressed a regret: he wished that that his Asia-focused venture capital firm had done more deals going into 2020, before the coronavirus first slowed business, and then changed the way it had to be done.

Collins, a partner at the Singapore-based branch of MMV, was addressing an *In Vivo*-hosted panel at the APACMed annual conference, one of the many 2020 meetings that became a hybrid of screen-based and face-to-face events. Remote meetings were seized upon for their ability to offer medtech companies what has turned out to be a workable option for a semblance of business as usual.

Throughout the pandemic, MMV's investment focus did not waver from telemedicine and digitally enabled general health care administration systems. Its investment in remote patient monitoring and digital therapeutics company Biofourmis typified its value approach. Collins' comments were a reminder of the need for firm business strategies, pipelines and constant forward planning even during unprecedented health care emergencies.

The spread of SARS-CoV-2 infection pushed medtech stakeholders off course; once they readjusted, it was clear that pandemic management must sit alongside routine business activity for the foreseeable future.

In 2020, medtech's commercial fortunes differed, depending on where businesses sat in the chain of the provision of emergency care. Some were able to repurpose production lines, and some, like Medtronic, Cardinal Health and ResMed, were already seeing the impact of the pandemic on annual revenues in 2019-2020.

The effects of the pandemic will extend deep into 2021. As such, 2020 has provided useful experience of the virtual networking platforms that were a lifeline for businesses during the first wave and will continue to be critical.

These communication tools, eagerly seized upon by medtech industry stakeholders, have their limitations, however, with users often needing multiple and longer sessions to reach comfort levels with clients, due partly to the inability to read body language or facial reactions through a screen. "While we're all still getting used to using Zoom, it's difficult to get a read on people and many of the social cues you use to judge if someone is comfortable with a set of questions," said Optum Ventures principle Ashish Patel during one investor panel – held virtually – in 2020.

MEDTECHS TAKE A DEEP LOOK AT THEMSELVES

COVID-19 has compelled medtech manufacturers, and regulators and governments too, to take a good look at what they do, and how they can do it better. There is nothing like a crisis to focus the mind.

More open regulatory pathways have given medtechs the scope to innovate more rapidly. Stryker CEO Kevin Lobo cited the case of an emergency use, collapsible COVID-19 bed in Australia that went from concept to product in less than two weeks. For Lobo, it showed

how governments can be supportive in the innovation cycle.

What lessons will be carried over into business in the new normal when the pandemic is safely in the past? One is that COVID-19 will not be the last time public health care emergency resources will need to rolled out. COVID-19 has put national testing, screening and monitoring strategies to the test. They have been found wanting.

Even Germany, with a solid lab testing infrastructure and a good record of infection control in the first wave, has had second wave problems. Ever-higher demand for testing prompted the authorities in early fall 2020 to roll out, alongside its one million plus per day PCR test capacity, a structured rapid antigen testing system, with test quality overseen by the Paul-Ehrlich and Robert Koch institutes.

The UK's infrastructure was less able to cope with the sudden demands of COVID-19; its new 29-hub system not geared up for public health emergencies on such a scale. Local lab test suppliers were often wrong-footed by central decisions. But there was never a problem on the industry supply side; the issues were in swab processing, said the IVD industry.

Some companies' plans were upset totally. Smiths Group said the urgency of COVID-19 challenge, in terms of market demand, employee safety, supply chain and cash management, led it to postpone the separation of its medical business in 2020.

Myriad Genetics found itself in the wrong area of diagnostics, and revenues tumbled. The biggest Australian medtech group, Cochlear, saw implant volumes fall by 60% in April. But by June/July, it said its implant revenues were back to 85% of 2019 levels.

And digital health companies that had not already implemented their technology or did not have existing structural relationships with providers pre-COVID found that those providers did not have the bandwidth to take on brand new projects with unknown entities at the height of the pandemic.

In late 2020, major medtechs began to reveal their initial experiences of coping with COVID. Johnson & Johnson said it had found new ways to collaborate as a global company – much more so than in the past few years. COVID-19 united staff around a common cause, it said, observing that joint project working was happening both inside and outside the group. Stryker, too, had seen the trends, and commented that previously decentralized divisions and regions had begun working together very well.

Medtech leaders were, more than ever, listening intensely to the needs of the health care systems that were setting the agenda during the pandemic. The big groups admitted they did not have all the answers, and were often taking their cues from clinicians and staff on the frontline. They were in "heavy servant leadership mode," as Johnson & Johnson's Ashley McEvoy put it.

LONG-AWAITED FULL-BLOWN ADOPTION OF TELEHEALTH

Telehealth rapidly became the best tool for remote GP consultations, rising to 60% adoption at the height of the first wave. HealthXCapital partner Seemant Jauhari told *In Vivo* that virtual patient consultations were hovering at around 5-10% adoption, pre-COVID. When the first lockdowns eased, usage rates fell back, but they will stay at some 15-25% in the future, he predicted.

The floodgates were opened for telehealth in the US in March, when state and federal regulators sought to reduce barriers to its use. This allowed for new programs and the expansion of existing networks, the private care provider and academic health care research institute Cleveland Clinic, said. These fundamental shifts in policy at both US government and provider level will carry over into 2021, said the clinic, listing the integration of telehealth among its top 10 health care innovations for 2021.

Another of its health care-changing innovations for 2021 will be bluetooth-enabled pacemaker devices, used in conjunction with a mobile app to remedy issues of disconnection between patients and their cardiac treatment. Cleveland Clinic's top 10 predictions, compiled each fall, are pointers that serve to show how far medtech and pharma innovation is changing as the patient voice becomes louder.

COVID-19 crystalized minds around the digital revolution that was already well underway in 2019 – but paradoxically still some way off.

The pandemic provided the push that no one wanted, yet everyone needed. Philips head of connected care Roy Jakobs noted that providers who had had been stalling over new technology adoption and system transformation suddenly became more decisive. Their change in behavior opened up new ways of diagnosing, monitoring and treating.

Similarly, the value of teleproctoring, where surgeons teach others on a new technology, has been seen in full. At Stryker, Lobo said that up to 80% of physician training could be done remotely. It is hard see that trend not being maintained post-COVID-19.

Big medtechs can be expected to be an even bigger partner in provider workflows and efficiencies in 2021 and beyond. COVID-19 has crystalized minds around the need to complete the digital revolution that was already well underway in 2019 – but paradoxically was still some way off.

The growing acceptance of health care apps and validation by clinicians of artificial intelligence have done much hasten the creation of the digital health care ecosystems to provide value and improved outcomes. The opportunities from COVID-19 must be identified and exploited, said ZS principle Brian Chapman in a September 2020 blog that urged medtechs to take advantage of these strangest of times to review their expectations. The pandemic should be used by companies to make the changes they have been wanting to do for a long time.

They could for instance reflect on: increasing digital communication methods among specialized field teams who have been focused exclusively on in-person interactions; the default of turning to price mechanisms as the end of the quarter approaches; seriously considering how to make innovation pay over the longer term; and what truly drives value for customers.

It was time for medtechs to rethink, reinvent and reset, said Chapman. Medtechs should not squander this rare opportunity to be truly creative, he argued.

LONG-TERM VALUE PARTNERSHIPS AND OTHER INNOVATIONS FOR 2021

With the technology and AI capabilities now available, Johnson & Johnson said COVID-19 had made it feel more comfortable about co-creating value for customers. There are greater opportunities to do collaborations and becoming a "solutions partner beyond the implant."

This will be a major theme for many global medtechs going forward: just how far do they want to wander away from their traditional technology core and become solutions companies that jointly affect outcomes and makes hospital systems more efficient?

Siemens Healthineers' long-term value partnerships were already worth over €1bn ($1.19bn) in 2019-2020, CEO Bernd Montag said in November. One of the last of the top medtechs to file 2019-2020 annual revenues for inclusion in our Top 100 ranking, Siemens Healthineers announced flat sales – in a year that included more than six months of COVID-19-impaired business. For 2020-2021, the group has forecast a 5-8% sales uplift.

Stryker is weighing up its potential involvement in value partnerships. While its "sweet spot" – the acute care intervention space – is clear, the group is considering how far to move down the continuum of care route, and whether this should be by internal means, acquisition or partnering with other companies or hospital systems. The dilemma for global medtechs is whether to be deeply involved, or simply to play to strengths.

"COVID-19 has given a huge kick to value-based contracting as a guaranteed revenue stream." – Chris McCann

For Royal Philips, the continued uptick in the number of long-term strategy partnership agreements being signed was the best pointer for future business robustness. CEO Frans van Houten said working with customers gives medtechs deeper insights into their needs and about how to innovate in the way care is provided. And this must happen alongside COVID-19 control measures.

Although COVID-19 increased economic uncertainty in the short term, its spread has accelerated the trend towards value-based care in the long term, insisted Elekta. The Swedish group is set to become the largest standalone radiotherapy equipment company in 2021 once Siemens has completed its acquisition of Varian Medical Systems.

Speakers on a Future of Innovation in HealthTech panel at the London Tech Week, in September 2020, agreed with Elekta on this point. Value-based health care in the US has been seen in a new light during the pandemic. Fee for service-driven hospitals lost revenue streams almost overnight when non-COVID-19 patients were told not to present for procedures.

COVID-19 has "given a huge kick to value-based contracting, and it's a guaranteed revenue stream that will drive remote health even further post-COVID," said Chris McCann, CEO of Current Health.

Philips Ventures partner Lara Koole echoed that. The transition to value-based care and all its elements could be seen as a health care innovation in itself, she said. "Making the outcomes measurable is the most difficult part," she noted, pointing an opportunity for innovators. "The question is how to track a patient over time and create a reimbursement model around that."

Other hot innovation areas where VCs are willing to invest include the general field of "personal medicine," including diverse issues such as understanding individuals' personal circumstances and the microbiome.

Rob Stephen, a partner at global law firm CMS, said that the way in which gut bacteria could influence, say, a cancer treatment, was a whole new field of science just a decade ago. Today it fits squarely under "very disruptive technology," and a lot of companies are working in this area. "It is one to watch" in 2021, said Stephen.

So are the developing fields of 3D printing; behavioral health technologies; digital mental health; remote care delivered at home; the whole panoply unmet needs, including women's health and maternal health; and generally the areas that are currently under-resourced.

Optum Ventures' Ashish Patel suggested that the under-resourced fields include "middleware" – the "pipelines" and infrastructures of health care systems that enhance efficiencies. This is an ostensibly unexciting area for investors, but one where there are real opportunities for innovation that guarantees the seamless patient journeys that all providers seek.

CHALLENGES – SYSTEMIC AND NEW – FOR MEDTECHS IN 2021

During the pandemic, medtechs have risen to the innovation challenge and seen how it is possible to be flexible in the way that they innovate.

The linear, step-wise, approach has been changed, given the need for speed, and the process of innovation has become more about doing more things in parallel in, say, gathering physician input, and doing product iterations and prototyping. Manufacturers are factoring in that innovation is not focused only on the technology itself, but also on methods of use and the materials used to enhance patient outcomes.

Other medtech industry and market access challenges for 2021 include:

1) **The landscape for the medtech industry that the US Democratic administration under newly-elected President Joe Biden will create and oversee. The device tax has gone – Democrats were as keen as Republicans to end that part of the 2010 Affordable Health Care Act, but what of the fate of the ACA overall before and after Biden's inauguration on 20 January 2021?**
2) **Adjusting to the EU Medical Device Regulation in 2021 and the In Vitro Diagnostic Regulation (IVDR) in 2022, compliance with which will cost over 5% of companies' annual revenues, according an August 2020 survey by Climedo.**
3) **Partnering with governments to address persistently high barriers to market entry, in terms of: approval requirements, and time taken by regulators in dealing with complex technologies in certain markets; and difficulties in securing reimbursement for proven, outcomes-improving technologies that meet clinical and economic value criteria;**

4) **Overcoming surgeon preference for familiar tools, given that many customers of medtechs continue to prefer tried-and-tested solutions. This has been highlighted by Dräger, among others;**
5) **The sluggish global economy, which grew by 2.8% in 2019, its lowest rate since 2008-2009, according to the International Monetary Fund's World Economic Outlook, issued in mid-October 2020. 2020 is currently set for a global contraction of 4.4% (with Germany shrinking by 6%, the US by 4.3%, the UK by 9.8% and the Euro area by 8.3%). Only China will post growth, of 1.9% and will increase that to 8.2% in 2021;**
6) **The rise of non-communicable diseases by a predicted 80% by 2040 in the over 65s. Global life expectancy in high-income countries has risen as a factor of better control of infections and cardiovascular diseases, and this leads to more cancer cases and more people living with cancer as a chronic condition. The World Health Organization estimates that there were about 18 million new cancer cases globally in 2018;**
7) **In digital technologies, the pressure on medtechs to hire software engineers. There is a shortage of talent, and medtech is competing with the tech sector for staff whose input can shape all aspects of a device innovation, the service delivered, maintenance schedules, post-case analysis and methods of engaging with patients;**
8) **Factoring in the post-COVID-19 effects on certain fields of medtech where products have been subject to high demand in 2020. For example, the likely lower demand for, and oversupply of, COVID-19 equipment in 2021, given that the global increase in demand for respiratory care products during 2020 was largely met;**
9) **The faltering return to elective and planned care routines in the second and subsequent waves of COVID-19, following the postponement of non-emergency care in the first wave. Surgeries resumed quite rapidly in the US, Germany, Japan and northern Europe, but the return was much slower in the UK, Italy and Spain; and**
10) **Brexit, which will have an unquantifiable impact on medtechs accessing the UK market, and navigating a new national regulatory system as of 1 January 2021. In spite of COVID-19 and the persistent failure of the EU and UK to agree a free trade deal, "there will be no transition period extension," the UK Office for Life Sciences insisted during a 4 November webinar.**

TWO BLOCKBUSTERS AND FIVE BILLION DOLLAR+ M&A DEALS

Major medtech M&A deals in the first ten months of 2020 were fewer than in recent years, and one planned high level deal, Thermo Fisher Scientific's $11.5bn bid for Qiagen, was rejected, in August.

Two double-digit billion dollar deals did take place: Siemens Healthineers' $16.4bn purchase of radiotherapy group Varian Medical Systems, in August, which is set for completion in the first half of 2021; and Teladoc Health's $18.5bn merger agreement with Livongo Health.

Teladoc Health expects to become a global leader in "consumer-centered virtual care," ranging from preventive care to complex cases. The merger was scheduled to bring 2020 pro forma revenues of approximately $1.3bn. Teladoc Health also spent $600m on InTouch Health, a telehealth provider for hospitals and health systems.

Elsewhere, Illumina brought liquid biopsy cancer detection tests group Grail back under its roof, for $8bn, having spun out the company in 2016. The next-generation sequencing group is undergoing an interesting evolution, having received a US Emergency Use Authorization (EUA) for the sequencing-based test, COVIDSeq, which went from concept to EUA in just 60 days. It now sees an opportunity for genomics-based surveillance to provide early warning systems in the transmission and virulence of pathogens and to track epidemiology.

Also in diagnostics, Invitae bought cancer molecular diagnostic tests developer Archer Dx for $1.4bn; and fast-growing Exact Sciences, which doubled its sales in 2019, boosted by key acquisitions, and rose to number 70 in the Top 100. In October 2020, it bought multi-cancer testing company Thrive Earlier Detection Corp for $2.15bn and UK cancer DNA methylation and mutation analysis company Base Genomics.

Shortly before Stryker got the green light in November to proceed with its purchase of Wright Medical – a full year after making its $4bn bid – Smith & Nephew dipped a toe into the orthopedic extremities segment with the $240m purchase of Integra Lifesciences' shoulder replacement, implants, fixation devices and hand, wrist, elbow, foot and ankle surgery accessories business. In a relatively active M&A year for the UK group, it also bought ear infection device manufacturer Tusker Medical, and patient management software company MiJourney, to allow health care providers to plan orthopedic cases in ambulatory surgery centers and other outpatient settings.

Aside from the Wright Medical deal progress, Stryker was unusually absent from M&A activity in 2020, as was another regular M&A player, Boston Scientific.

But Medtronic was once again very visible, paying $228m for France's Medicrea, a company in AI-driven surgical planning, personalized spinal implants and robotic assisted surgery. It also bought spinal cord therapy company Stimgenics, as well as smaller players in: vascular access (Avenu Medical); insulin pen delivery (Companion Medical); and surgical AI and digital training (Digital Surgery).

Incoming CEO Geoff Martha struck an upbeat tone when announcing Q1 2020-2021 revenues that showed a 13% fall in a rare 14-week quarter. The group was undergoing a faster than expected recovery from the depths of the pandemic in April, he said.

LOOKING BEYOND COVID-19

Pandemics have happened in the past 20 years – SARS coronavirus in 2003 affecting 26 countries; Middle East respiratory syndrome coronavirus (MERS-CoV), reported in 27 countries since 2012; and the Ebola Virus Disease in 2014-2016 in West Africa – but not on the global scale of COVID-19, and not impacting the west.

ZS' Chapman said that the enormity of the reset forced by COVID-19 is giving medtechs a unique moment to reinvent. And looking beyond the crisis, Stryker's Lobo said the medtech industry stands on the cusp of bringing into use digital, robotics and other technologies that will change health care delivery profoundly. "There has never been a more exciting time to be in medical devices than now," he said.

SCRIP 100

SPONSORED BY: ICON

Pharma's Digital Transformation: How To Best Incorporate Wearables Amid An Evolving Landscape

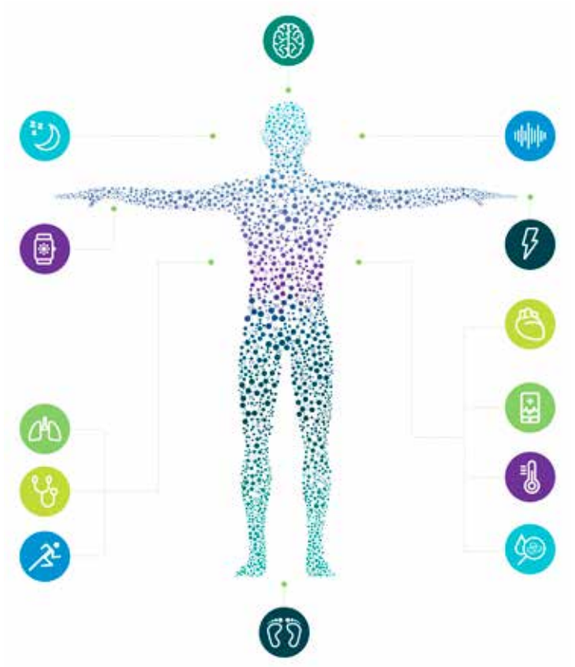
The COVID-19 pandemic has accelerated pharma's digital transformation and spurred a restructuring of the clinical trials landscape. While some clinical trials had harnessed decentralized trials and digital health technologies – such as wearables, sensors and apps – before the emergence of the pandemic, disruptions have forced sponsors, clinicians and regulators to embrace digital's full potential to keep clinical trials moving forward.

Since the onset of the pandemic, social distancing measures and restricted travel have decreased patient mobility and investigator and site availability – disrupting clinical trials and drug programs. Approximately 1,000 organizations have reported trial disruption, consistent with a reported nearly 80% decrease per site in new patients entering trials in April 2020 compared with April 2019. Further, of all active trials in ClinicalTrials.gov, 13% reported increases in trial duration in March through May 2020, compared with 9% over the same period in 2019.[1]

As clinical trials proceed, sponsors will need to determine the best way to quickly move forward with delayed trials. Further, pharmaceutical and biotech companies will have to plan for the next wave of challenges, such as deciding how to address those trials for which data may already be compromised.

The challenges that the coronavirus poses to clinical trials may persevere until vaccines or more effective treatments become widely available. As such, global trials may continue to see disruptions amid regional virus resurgences, as some countries recover and others remain on lockdown. So, how can clinical trials be reimagined to better prepare for future disruption?

Over the coming months, and possibly years, sponsors will need to consider agile trial designs that integrate virtual elements and wearables. To maximize the value of incorporating wearables into a clinical trial, they will need to understand how to implement an end-to-end approach. At ICON, our framework maps the transition from device selection to digital endpoint validation, leading to a better understanding of the operational excellence needed for managing data and mitigating risk.



KEEPING TRIALS ON TRACK WITH WEARABLES AND VIRTUAL TRIALS

The spread of COVID-19 challenged traditional clinical trial models, requiring a shift to more patient-centered, decentralized clinical trial designs. Sponsors had to rewrite protocols to allow for remote patient monitoring and in-home delivery, in addition to other digital capabilities, such as telemedicine, to keep clinical research viable. Among major pharma companies, 60% are already using telemedicine for trial visits in response to the COVID-19 crisis.[2] In fact, investigators reported 57% of patient interactions and 79% of interactions between sponsors and contract research organizations (CROs) are taking place remotely, according to a recent report in *Nature Reviews Drug Discovery.*[1]

During this time when patients may be unable to visit sites for assessments, due to compromised immune systems or travel restrictions, digital health technologies can provide remote patient monitoring to collect vital data. Wearables and sensors can gather data on patients' biometrics and functionality, including gait, heart rate variability, sleep, glucose monitoring and sweat analysis, effectively capturing how a treatment or disease affects them every day.

In addition, sponsors can apply digital health technologies to preventive monitoring. Wearables can detect changes in heart rate, sleep patterns and other variables, potentially detecting whether an individual may be infected with the COVID-19 virus. By providing an early warning, wearables could help prevent or halt transmission.

As patients are able to access the options of home care and remote monitoring, visits to sites and clinics will be reduced, further accelerating the adoption of the virtual trial model. At the same time, virtual trials will free up hospitals and clinics so they can better allocate resources to improve management of patients infected with COVID-19 or who have other essential medical issues.

A FRAMEWORK FOR IMPLEMENTING WEARABLES

The integration of wearables into trial design starts with choosing the necessary digital endpoints. Digital endpoints harness the data from sensors and other digital health technologies that are collected during an individual's everyday life, allowing for the capture of existing measures in a new way. Using digital endpoints places the patient at the center of a clinical trial, as endpoints need to be clinically significant and meaningful to individuals.

To maximize the value of wearables in a clinical trial, sponsors will need to understand how to implement an end-to-end approach. Combining the experience of a dedicated digital health technology team and patient-centered scientists can help sponsors create a framework to map the process from device selection to digital endpoint validation. Adopting a framework, such as the one outlined below, can set trials up for success – especially during times of crisis when managing data and mitigating risk are of the utmost importance.

Step 1: Adopt a patient-centered approach

Using a patient-centered framework that has evolved from proven clinical outcome assessment (COA) principles and techniques can help build the evidence required for submission to regulatory bodies. Previously, the industry focused on the selection of devices for use in clinical trials, and not the endpoints. Today, however, sponsors must shift their attention to endpoints, particularly those that are meaningful to patients. In some instances, endpoints may be focused on assessing improvement in everyday functioning, while in others, it will be about measuring stability or deterioration in a condition – how quickly, and by how much. Once sponsors understand which outcomes are meaningful to patients, they then can begin to identify and select the optimal measures to assess these endpoints.

Step 2: Select the device, along with evidentiary requirements

After identifying relevant, patient-centered endpoints, sponsors can next consider device selection, which includes device identification, patient acceptance testing, and technical usability and feasibility testing.

Sponsors will need to select the evidentiary requirements necessary to support device selection, including any gaps that need addressing. Collecting evidence could include using existing literature, developing a validation plan or using an industry-led endpoint qualification. COA instruments may be applied to help fill gaps and evidentiary needs. Further, sponsors will have to consider how to collect and interpret data from the device and establish meaningful change thresholds for each novel digital endpoint.

Step 3: Adhere to operational excellence in digital endpoints

Operations are essential to ensure robust, accurate and compliant data collection. Overlooking operational excellence can jeopardize endpoints. Here, sponsors need to consider the end-to-end process holistically and implement risk contingencies, including data management and compliance. For example, sponsors will need to decide how to manage missing data, whether random (e.g., patient takes device off in the shower) or not (e.g., patient takes device off because it is itchy), to ensure the data collected throughout the study remain usable.

Moreover, sponsors should provide plans to capture and address non-compliance with regards to when, where and how often a device is worn and the loss or malfunction of a device. As such, patients will need device training, as well as an understanding of how data will be shared. Sponsors should set up patient support, including direct outreach, reminder apps and dedicated help desks, to keep patients compliant and engaged. Lastly, site and study staff should be device trained, and equipped and prepared with firewalls, ample storage and technology support.

THE POST-PANDEMIC CLINICAL TRIAL LANDSCAPE

Drug and device developers will need to embrace innovation and plan for a future with evolving regulations, new digital technologies and transformed clinical trial designs. We will witness the industry pushing the boundaries on digital, data and analytics strategies, as sponsors continue to deploy remote assessment of vitals and use digital endpoints, increasing virtualization of trials.

Sponsors will need to consider the digital patient journey, as the demand for virtual trials continues to rise. Equally important, as future crises emerge, including possibly the next pandemic, succeeding clinical trials will have to build in more flexibility for virtual and digital elements to mitigate risk and to prepare for uncertainty.

However, implementation brings new challenges, including patient acceptance, device suitability, data management complexity, and privacy and security issues. Having a strategic partner with wearables and COA expertise can help to mitigate risk and lead to the successful use of digital endpoints.

www.iconplc.com/wearables

REFERENCES

1. Xue, J, et al. (2020). Clinical trial recovery from COVID-19 disruption. Nature Reviews Drug Discovery 19, 662-663. doi: https://doi.org/10.1038/d41573-020-00150-9
2. Agrawal, G, Ahlawat, H, and Dewhurst, M. Winning against COVID-19: The implications for biopharma. (2020). McKinsey Insights. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/winning-against-covid-19-the-implications-for-biopharma

Pfizer Holds Number One Spot And Takeda Breaks The Top 10

Takeda's acquisition of Shire fueled the company into a top 10 pharma company in the latest Scrip 100 rankings, as other mega-mergers are set to shape the leaderboard in the future.

JESSICA MERRILL
SENIOR EDITOR, US

Takeda Pharmaceuticals grew into a top 10 pharmaceutical company for the first time in 2019 in a sign of how drug developers often rely on M&A to fuel game-changing growth. The company ranked as the number nine pharmaceutical player in the world in the Scrip 100 rankings, based on 2019 pharmaceutical revenues of $30.19bn, moving up substantially in the rankings from number 16 in 2018 and number 18 in 2017.

It was the acquisition of the rare disease specialist Shire that powered Takeda into the top 10. The change represents strong growth for the Japanese pharma, which generated $18.43bn in pharmaceutical revenues in 2018 but completed the $61bn acquisition of Shire in January 2019. The acquisition greatly expanded Takeda's portfolio and pipeline, with a focus on oncology, rare disease, gastroenterology and neuroscience.

Mega-mergers are the surest way to scale, and the Takeda/Shire merger was followed by other deals that will change the Scrip 100 rankings even more in the future. The most recent Scrip 100 rankings are based on drug manufacturers' 2019 pharmaceutical revenues, so they do not reflect deals and acquisitions that have closed more recently. However, the mega-mergers of Bristol Myers Squibb/Celgene and AbbVie/Allergan will have a substantial impact on the rankings in 2021 and showcase how important M&A is in driving industry growth.

BMS completed the acquisition of Celgene in November 2019 and so Celgene is included in the current rankings based on nine months of revenues, while the BMS revenues include about one month of Celgene sales. AbbVie completed the merger of Allergan in May 2020, so the companies are included independently for the full year in the latest Scrip 100.

The rankings also reflect the playing field in the times before COVID-19, which emerged as a global threat in Spring 2020 and continues to impact the pharmaceutical industry in several ways – from lockdowns affecting prescribing practices and clinical trials to creating a spotlight as biopharma steps up to develop treatments and vaccines. COVID-19 has been a bigger hit to some drug makers than others, based on their portfolio of drugs and how they are administered, but generally industry has shown resilience during the pandemic. The increased spotlight on pharma could also be a bigger benefit if the industry is able to showcase its R&D engines as a public health benefit.

A LONG ROAD TO GETTING SMALLER

Another big change ahead for the industry will be Pfizer's drop in the Scrip 100 rankings. While the firm has been a longtime leader and is at the top of this year's board, Pfizer is following through on a long-considered move to slim down. The company's spinout of its Upjohn established products business to merge with Mylan into a new company called Viatris closed in mid-November 2020. For Pfizer, it means shaving off a significant portion of its business and trying to become a more focused, innovative firm – the culmination of years of back and forth as it considered splitting up its bulk. Viatris hopes to realize $1bn in cost synergies through the merger, but it is not expected to be a near-term growth story. Some analysts do not expect Viatris to generate top-line growth until 2023.

Meanwhile, Pfizer's trimmer biopharma business is expected to post 2020 revenues of $40.8bn-$42.4bn compared to the full 2020 business forecast of $48.8bn-$49.5bn, so the company is poised to fall in our rankings. Thus the 2019 rankings are likely the end of Pfizer's reign as the number one pharmaceutical company in the world, with pharma revenues of $49.65bn.

But Pfizer is also expected to get a substantial and unexpected boost from being the frontrunner in the race to bring a COVID-19 vaccine to market. The vaccine – which it and partner BioNTech are developing without government support – is not likely to have a big impact financially in 2020, although could be a near-term blockbuster in 2021.

Roche supplanted Novartis as the number two pharma company, with 2019 pharmaceutical revenues of $48.82bn, powered by strong sales of newer products like Ocrevus (ocrelizumab) and Hemlibra (emicizumab). Biosimilar competition to some of Roche's biggest selling products like Avastin (bevacizumab), Herceptin (trastuzumab) and Rituxan (rituximab) is taking a toll in 2020, however. During Roche's third quarter financial update, the company acknowledged the hit to revenues in 2020 will be more than originally anticipated, about CHF5bn ($5.5bn).

> *COVID-19 has been a bigger hit to some drug makers than others, based on their portfolio of drugs and how they are administered, but generally industry has shown resilience during the pandemic.*

AstraZeneca is another company that experienced substantial growth, increasing to number 11 in the top pharmaceutical company rankings, fueled by 12% product sales growth in 2019, led by strong sales of its oncology brands including Tagrisso (osimertinib). AstraZeneca jumped three spots in the ranking, having placed number 14 last time.

Meanwhile Amgen, Gilead, Lilly and Teva all dropped in the rankings due to slower growth. Teva fell the most substantially to number 16 in the Scrip 100 from number 12 the previous year, as the company's revenues declined 8% to $16.89bn, largely due to generic competition to Copaxone (glatiramer). Teva has been working on a massive turnaround strategy since 2017, but is yet to return to top-line growth. The company had been hoping 2020 could be the year but it has continued to be challenging for Teva due to impacts from COVID-19 and ongoing legal pressure around opioid liability.

Gilead has been on a slow decline, ranking at number 13 this year, down from 11 in 2018 and nine in 2017, as its hepatitis C and HIV antiviral franchises have matured. Growth was lackluster in 2019 despite the promise of new leadership from CEO Daniel O'Day. In 2020, Gilead saw at least a short-term boost from Veklury (remdesivir). As one of the first treatments to market for COVID-19, Veklury has generated a lot of attention, despite being approved with limited data. It generated $873m in sales in the third quarter, proving it will be a blockbuster seller for Gilead, though it might be short-lived now that further antibody treatments have reached the market and vaccines appear poised for success.

Gilead also has spent the year bulking up its oncology pipeline with acquisitions like Forty-Seven for $4.9bn and Immunomedics for $21bn, which gave the company a near-term growth driver Trodelvy (sacituzumab govitecan), an antibody drug conjugate.

Amgen fell to number 12 from number nine as revenues in 2019 decreased, driven by ongoing biosimilar competition to some of its core older brands, though the company appears on track to generate stronger growth in 2020.

The top 20 players remained fairly stable in 2019, but even without the COVID-19 pandemic upending the industry, more changes are on the way. The M&A dust is starting to settle from the most recent set of mega-mergers and companies are looking to convince investors of their long-term strategies, as well as snapping up bolt-on acquisitions to keep them on track.

COMPANY	COUNTRY	PHARMA SALES ($M)	SCRIP 100 RANKING
Pfizer	US	49,652	1
Roche	Switzerland	48,826	2
Novartis	Switzerland	47,445	3
Johnson & Johnson	US	42,198	4
Merck & Co.	US	41,751	5
Sanofi	France	35,195	6
AbbVie	US	33,266	7
GlaxoSmithKline	United Kingdom	31,550	8
Takeda	Japan	30,194	9
Bristol-Myers Squibb	US	26,145	10
AstraZeneca	United Kingdom	24,384	11
Amgen	US	23,362	12
Gilead Sciences	US	22,449	13
Eli Lilly	US	22,320	14
Bayer	Germany	20,108	15
Novo Nordisk	Denmark	18,296	16
Teva	Israel	16,887	17
Boehringer Ingelheim	Germany	15,885	18
Biogen	US	14,378	19
Celgene*	US	12,941	20
Astellas	Japan	11,934	21
Allergan	Ireland	11,804	22
Mylan	Netherlands	11,501	23
Daiichi Sankyo	Japan	9,007	24
Bausch Health	Canada	8,601	25
CSL	Australia	8,539	26
Otsuka Pharmaceutical	Japan	8,479	27
Fresenius SE & Co. KGaA	Germany	7,746	28
Merck KGaA	Germany	7,516	29
Eisai	Japan	6,382	30
UCB	Belgium	5,500	31
Servier	France	5,166	32
Alexion Pharmaceuticals	US	4,991	33
Regeneron Pharmaceuticals	US	4,834	34
Grifols, S.A.	Spain	4,822	35
Sun Pharmaceutical	India	4,664	36
Abbott Laboratories	US	4,486	37
Sumitomo Dainippon Pharma	Japan	4,429	38
Menarini	Italy	4,246	39
Vertex Pharmaceuticals	US	4,163	40
Mitsubishi Tanabe Pharma	Japan	3,484	41
Sino Biopharmaceutical	Hong Kong	3,428	42
Shanghai Pharmaceutical Group Co., Ltd.	China	3,401	43
Jiangsu Hengrui Medicine Co. Ltd.	China	3,319	44
Mallinckrodt	Ireland	3,163	45
Shanghai Fosun Pharmaceutical Group	China	3,131	46
Asahi Kasei Pharma	Japan	3,099	47
Aurobindo	India	3,082	48
STADA	Germany	2,920	49
Endo International	Ireland	2,914	50
Kyowa Hakko Kirin	Japan	2,897	51
CSPC Pharmaceutical Group Ltd.	Hong Kong	2,725	52
Baxter International	US	2,690	53
Ipsen	France	2,574	54
Lundbeck	Denmark	2,554	55
Sichuan Kelun Pharmaceutical	China	2,521	56
Dr Reddy's	India	2,462	57
Cipla	India	2,409	58
Chiesi	Italy	2,231	59
Hikma Pharmaceuticals	United Kingdom	2,203	60
Jazz Pharmaceuticals	Ireland	2,162	61
Lupin	India	2,151	62
Vifor Pharma	Switzerland	2,071	63
Santen	Japan	2,060	64
Shandong Buchang Pharmaceuticals Co., Ltd.	China	2,018	65
Meiji Holdings	Japan	1,874	66
Ono	Japan	1,851	67
Nichi-Iko	Japan	1,801	68
Incyte	US	1,775	69
Zydus Cadila	India	1,773	70
Sawai	Japan	1,729	71
Joincare Pharmaceutical Group Industry Co., Ltd.	China	1,702	72
BioMarin Pharmaceutical	US	1,686	73
Harbin Pharmaceutical Group Co., Ltd.	China	1,685	74
KRKA	Slovenia	1,672	75
Swedish Orphan Biovitrum AB	Sweden	1,645	76
Amneal Pharmaceuticals	US	1,626	77
Leo Pharma	Denmark	1,620	78
DaShenLin Pharmaceutical Group Co., Ltd.	China	1,594	79
Gruenenthal	Germany	1,561	80
Shionogi	Japan	1,460	81
United Therapeutics	US	1,449	82
Recordati	Italy	1,433	83
Glenmark Pharmaceuticals	India	1,420	84
Teijin Pharma	Japan	1,412	85
Gedeon Richter	Hungary	1,372	86
Hisamitsu	Japan	1,336	87
Livzon Pharmaceutical Group	China	1,334	88
CR Double-Crane Pharmaceuticals Co., Ltd	China	1,330	89
Horizon Therapeutics plc	Ireland	1,300	90
Hansoh Pharmaceutical	China	1,270	91
Jubilant Life Sciences	India	1,222	92
GC Pharma	South Korea	1,176	93
AlfaSigma	Italy	1,175	94
KPC Pharmaceutical Inc.	China	1,158	95
Kwang-Dong Pharmaceutical	South Korea	1,063	96
Pierre Fabre	France	1,057	97
Torrent Pharmaceuticals	India	1,048	98
Orion Corporation	Finland	1,022	99
Towa	Japan	1,013	100

*Celgene figures represent 9 month period of 2019, prior to acquisition by Bristol Myers Squibb

The Scrip 100 ranking is based on Informa Pharma Intelligence's analysis of fiscal year 2019 prescription pharmaceutical sales data for the top 100 biopharmaceutical companies. For more information contact Lucie.Ellis@informa.com.

SCRIP 100

Outlook 2021

The Scrip 100 universe gathers FY 2019 financial performance data and compares the activities of the Top 100 biopharma businesses.

Who gets in?

Top 100 companies based on pharmaceutical sales only for fiscal year 2019

Combined pharma sales of Top 100 **$834.4bn**

Combined pharma sales of Top 20 **$577.2bn**

TOP SPOT FOR 2021 **Pfizer**

Pharma Sales: **$49.7bn**

Number of people employed by Top 20 **1.7m**

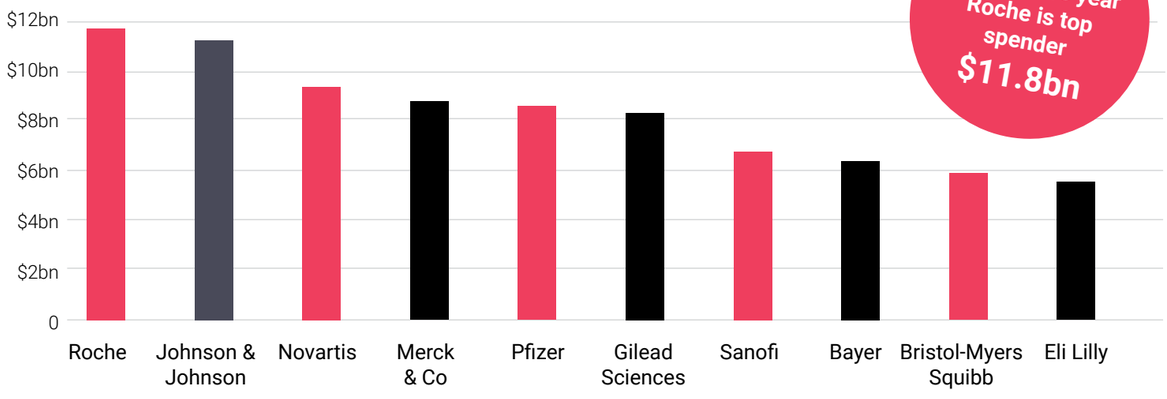
R&D Spend*

Top 20 **$123.0bn**

Top 100 **$165.3bn**

*Some companies do not report R&D expenditure; R&D spend not limited to Pharma only in all cases

For second consecutive year Roche is top spender **$11.8bn**



In Vivo
Informa Pharma Intelligence

Takeda moved into the Top 10 for the first time with pharma sales of **$30.2bn**

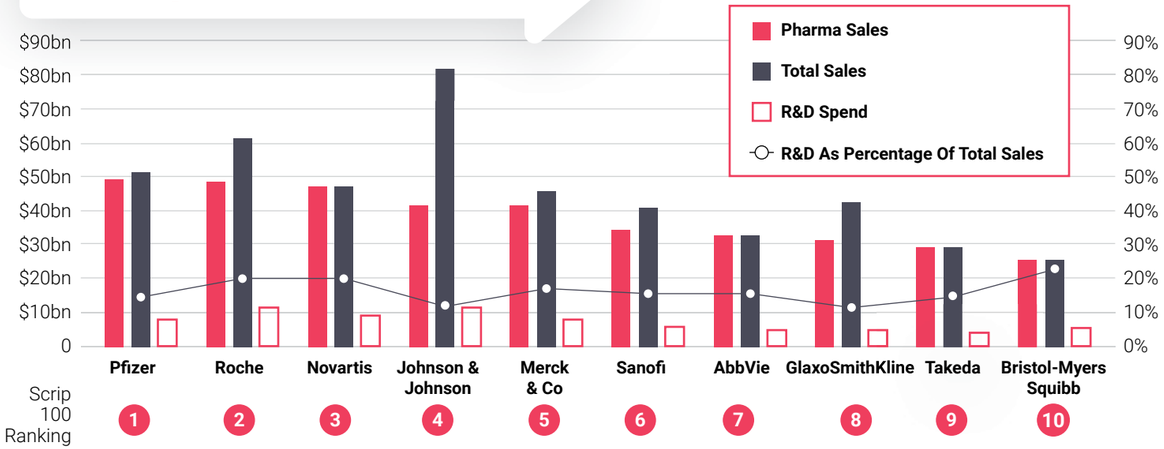
Teva has fallen from number 12 to number 16. The company's revenues declined 8% to **$16.89bn**

Bristol-Myers Squibb completed acquisition of Celgene in **November 2019**

Top 100 By Location

Top 20 By Location

The Top 10: A Closer Look



Company Overview

ICON plc is a global provider of outsourced drug and device development and commercialisation services to pharmaceutical, biotechnology, medical device, and government and public health organisations. The company specialises in the strategic development, management and analysis of programs that support clinical development from compound selection to Phase I-IV clinical studies. With headquarters in Dublin, Ireland, ICON currently operates from 94 locations in 40 countries and has approximately 15,250 employees.

Full Service Portfolio: Early Phase to Commercialisation

Early Phase Services
- PK/PD Modelling
- Pharmacodynamic Models & Simulation
- Data Visualisation & Analysis
- Clinical Research Unit
- NONMEM® Software
- PDx-POP®

Drug Development Services
- Preclinical/Non-Clinical Development
- Chemistry, Manufacturing & Controls (CMC)
- Clinical Development
- Pharmacokinetics
- Due Diligence & Asset Valuation

Commercialisation & Outcomes
- Real World Intelligence
  - Real World Evidence Strategy & Analytics
  - PUBSHUB™
  - Real World & Late Phase Research
  - Research Services
  - Site Management Associates
  - Direct to Patient Contact Solutions
  - Strategic Regulatory Services
- Value, Access and Outcomes
  - Health, Economics & Outcomes Research
  - Pricing, Marketing Access & Reimbursement
  - Medical communications
  - Market Research & Analytics
  - Creative Design & Digital Solutions
- Language Services
  - Clinical & Medical Translation
  - Linguistic Validation
  - iTrans Translation Management System

Clinical Research Services
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- Clinical Operations
- Feasibility & Study Start-Up
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  - Patient Recruitment & Retention Services
  - Accellacare
  - FIRECREST
- Biometrics
  - Data Management
  - Biostatistics
  - Medical Writing & Publishing
  - Adaptive Trials & ADDPLAN®
- Scientific Operations
  - Medical Affairs
  - Endpoint Adjudication/Data Monitoring Committees
  - Pharmacovigilance
  - Regulatory Affairs
  - Medical Imaging
  - Interactive Response Technology & Clinical Supplies Management
- Investigator Payments and Grant Budgets

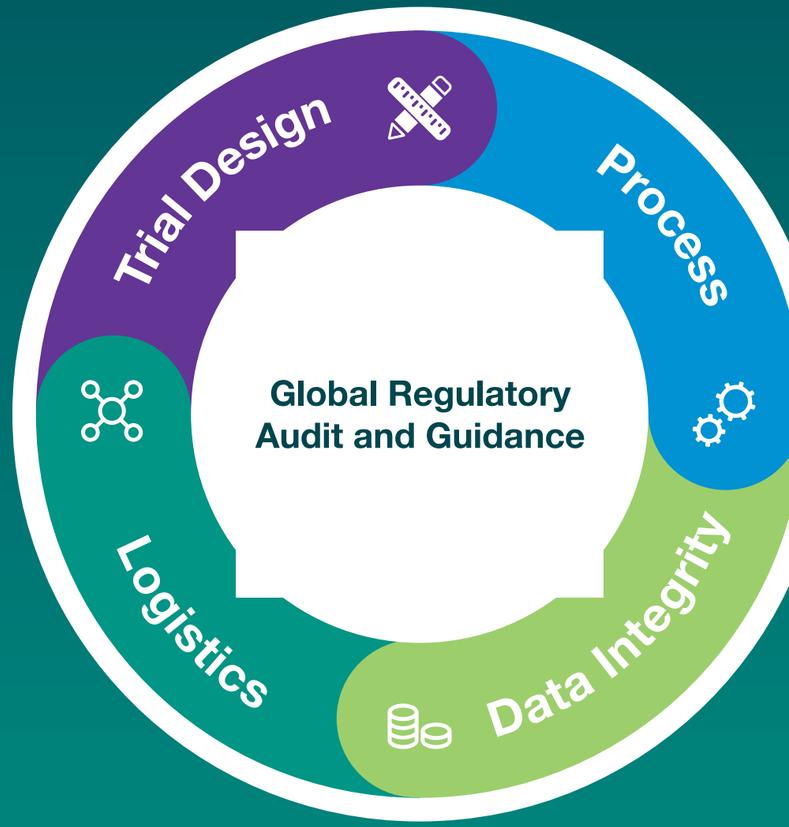
Laboratory Services
- Bioanalytical Laboratories
- Global Central laboratories
- Specialty Laboratories
- Integrated Clinical Research & Laboratory Services

Functional Services
- DOCS

ICONplc.com

Agile Study Management

Keeping your trial on track during COVID-19 and beyond



An integrated solution

ICON has adapted to the current conditions to protect the welfare of patients, safeguard our employees and ensure the continuity of research programmes.

Study teams are working with customers to develop study-specific plans to minimise the risk of delays.

We have a range of services that will help you to keep your trial on track;

- Strategic regulatory advice
- Decentralised trials including In-home clinical services
- Remote and Centralised clinical monitoring with remote SDV
- Direct to patient support
- Pre-recorded investigator meetings and remote training
- eDocument distribution and management for sites

ICONplc.com/covid-19

COLLABORATION

SPONSORED BY: Rentschler Biopharma

It Takes A Village To Raise Novel Medicines

Rentschler Biopharma SE's Strategy For A Network Of Win-Win Collaborations

Strategic collaborations are a key component of Rentschler Biopharma's overall strategy, says CEO Dr. Frank Mathias. Joining forces with external partners allows the company to "always offer our clients the best available and best-fit solution possible."

Rentschler Biopharma uses external partnerships to expand its offerings and provide a "world-class service portfolio" across the biopharmaceutical value chain. Its external partnerships also drive innovation within the company itself.

"We seek strategic alliances with other organizations that have proven best-in-class capabilities," explained Rentschler Biopharma's CEO, Frank Mathias, in an interview with *In Vivo*. "Their offerings are integrated seamlessly into our business processes, ensuring all parts of the project are aligned."

As a result of working with top-level partners, Mathias said, "Our clients not only benefit from outstanding services, their time to clinic and to market also is reduced significantly."

Rentschler Biopharma has an ongoing alliance with Leukocare AG for formulation development. Leukocare's technology combines bioinformatics and an algorithm- and database-driven approach for drug product stabilization. "This tactic helps to explore a broader design space as compared to conventional approaches and strongly increases the probability of success while avoiding high-throughput-screening," Mathias explained.

Leukocare and Rentschler Biopharma have combined their resources to improve the stability and quality of biologics: potentially including high concentration formulations, viral vectors, vaccines, and dry formulation products. Leukocare also applies its technology and expertise to stabilize and protect proteins in biofunctionalized devices.

Recently, Rentschler Biopharma teamed up with another partner, Vetter, around aseptic fill and finish, and drug product manufacturing. The collaboration's goal is to create long-term value through aligning manufacturing approaches, enabling CDMO clients to bring products to patients more efficiently. "The alliance will leverage Rentschler Biopharma's extensive experience in drug substance manufacturing, including bioprocess development and API production, and Vetter's strong expertise in aseptic fill and finish and secondary packaging," said Mathias.

Rentschler Biopharma and Vetter have identified opportunities where "early and active exchange of know-how and best practice" will benefit CDMO clients and patients, Mathias noted. These opportunities are being further validated in pilot client projects with joint teams from both companies.

BUILDING THROUGH ALLIANCES NOT ACQUISITIONS

"Rentschler Biopharma has always run a different race. Companies offering complementary services are not seen as competition, but rather as an opportunity to evolve through collaboration," Mathias said when describing Rentschler Biopharma's recent partnerships. "Our collaborations leverage technological leadership and long-standing experience, for best-in-class project delivery for our clients. Our partners continue to conduct their own business interactions and further develop knowledge and offerings, which creates value for all stakeholders."

Mathias noted Vetter and Rentschler Biopharma make for a clever collaboration, with the companies being well-established on their own and well-matched together. The strategic collaboration aims to reduce complexity for clients, with the joint goal of bringing promising new therapies to patients with serious and rare diseases faster than before. The companies initiated their collaboration in July 2020 with an unconventional elbow bump, in substitute for a handshake due to COVID-19, between Mr. Vetter and Mr. Rentschler.

Vetter is a key provider of quality services in aseptic fill and finish and secondary packaging. While Rentschler Biopharma is a leading CDMO in the production of complex biopharmaceuticals. "Very quickly we discovered synergies between our organizations and services," Mathias said.

Rentschler Biopharma's external partnerships are driven by the need of its clients to have "access to world-class solutions from one source," said Mathias. The company continues to seek other collaborations to increase its offerings. "We are looking at the modification and bioconjugation of antibodies, as well as cell and gene therapy."

With new alliances, Mathias said geography comes in second after the skills and qualities of the right partner. "The regions we are looking at are Europe, the US and Japan," he said, noting that in Japan, Rentschler Biopharma is building strategic partnerships, supported by Summit Pharmaceuticals International Corp. "But, when it comes to potential partnerships, it is the partner that matters and geography doesn't play a relevant role in this decision," Mathias noted.

TRUST IS EVERYTHING

Rentschler Biopharma also considers its relationships with CDMO clients as partnerships. "Within client partnerships, a defining factor is trust. Our clients trust us to find the best-fit solutions from bioprocess development through commercial manufacturing, and to deliver on our promise," Mathias said. "We have earned this trust because of our commitment, experience and expertise."

Focusing on the client company's point of view, Rentschler Biopharma creates a framework to best leverage its technologies to solve complex development and manufacturing issues. "This holds true for every client, every project, and every molecule," Mathias stressed.

An example of this is Rentschler Biopharma's partnership with BioNTech. They will use an innovative business model that is well suited for novel, urgently needed technologies and allows maximum flexibility to address BioNTech's development and manufacturing requirements. This includes responsibility for key aspects of cGMP (current good manufacturing practice) drug substance manufacturing of BNT162b2, BioNTech's mRNA-based vaccine against SARS-CoV-2 being developed with Pfizer. This vaccine candidate is being tested in a global Phase III clinical trial and has been submitted to the European Medicines Agency for a rolling review.

Rentschler Biopharma determined that the best way to address BioNTech's COVID-19 vaccine drug substance manufacturing need was to establish a dedicated mRNA production suite for the company at its Laupheim facility. This approach ensures capacity, staff and equipment are ready when needed without interruption of other ongoing projects. It is also an approach that is quickly and easily scalable to meet future demands.

Reflecting Rentschler Biopharma's strategy of maximizing its partnerships for greater efficiency, in addition to large-scale production services for the COVID-19 vaccine, the agreement also provides for small-batch manufacturing of BioNTech's other RNA programs for use in clinical trials.

WHAT DOES 2021 HOLD?

Mathias noted the company had "exciting" developments in store. "We are expanding into new modalities as we speak and will extend our expertise and specialize in mRNA technologies as well as enter cGMP production of cell and gene therapies." Furthermore, Rentschler Biopharma will continue to modernize and digitalize its sites.

Mathias highlighted how the COVID-19 pandemic has underlined the importance of a digital landscape, which allows people to stay connected. It is "essential to have updated information to make good decisions," he said. The novel coronavirus pandemic spurred Rentschler Biopharma to "strengthen our digital setup with dedicated training on how to quickly shift to digital meetings and move to paperless documentation."

Rentschler Biopharma's Digital Agenda and its initiatives will complement and enhance its existing services with digital capabilities, "which become increasingly important in our fast-paced and interconnected partner networks," Mathias noted. "We know the success of this vision depends 20% on technology and 80% on the people driving it – our focus has and will always be on investing in our people, as our employees are central to our success."

Predicting what 2021 will look like is tricky, as the world continues to grapple with COVID-19. As a cGMP service provider manufacturing highly complex biopharmaceuticals, Rentschler Biopharma is an important partner for the reliable supply of therapeutic drugs. Mathias emphasized that this is "especially important" in 2020. "We are meeting our responsibilities by supporting COVID-19 therapeutic developers, both for vaccines and symptomatic treatment," he noted. "We are doing everything in our power to support our clients in this extraordinary situation. Collaboration at all levels is key to overcoming the pandemic."

THE THREE RS

COVID-19 has led Rentschler Biopharma to evaluate its business through three lenses: resilience, reformation and reimagination.

Resilience: The CDMO has set up an initiative to strengthen resilience to disruptions in global supply chains and to focus on establishing alternative sources for raw materials as well as to balance global and local vendors.

Reformation: Rentschler Biopharma has analyzed its core business processes to make them more efficient and sustainable. It has reflected on its way of working and identified the potential for talent acquisition and retention. "Having the right people at the right place within the organization is very important," Mathias said.

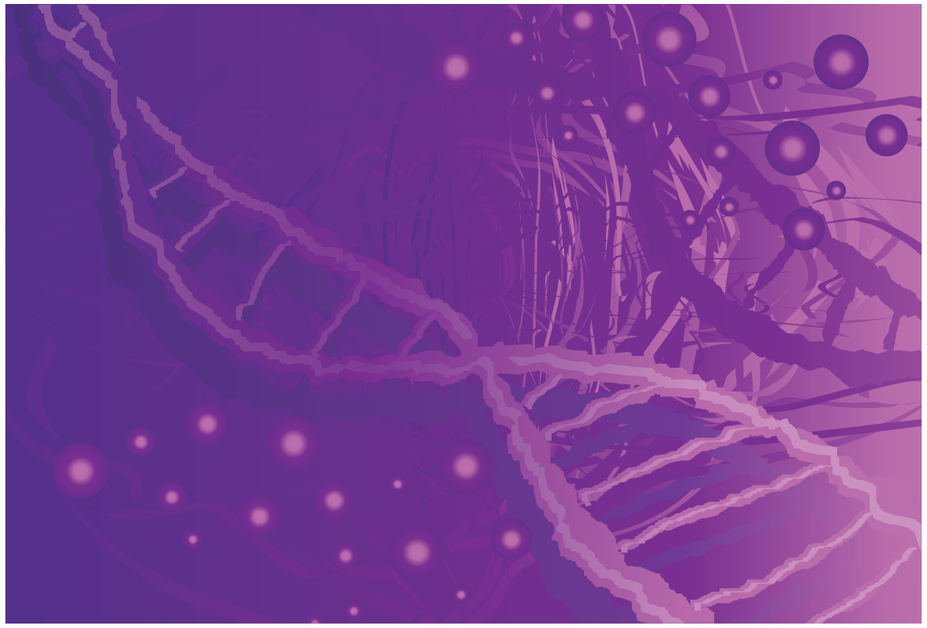
Reimagination: The company is reimagining the way it works internally as well as with clients. "With this, I allude to 'Rentschler New Work,' which is part of our strategy 2025 and central to our agile and learning organization. To drive this vision, we have established interactive leadership trainings, offered via our global Rentschler Academy, to address topics as diverse as the new economy, digital skills, business model generation, modern sales and employer branding."

Mathias concluded: "We strive to consistently assess and reinvent ourselves – more so in the time of crises, for the benefit of our clients and their patients."

MANDY JACKSON
MANAGING EDITOR, US

Pulling Back The Curtain On Biopharma Partnering In Cell And Gene Therapies

Janssen, Biogen And Astellas Execs Discuss Portfolio Priorities



Cell and gene therapies often originate at small biopharmaceutical firms, but big pharma and large biotech companies continue to increase their investments in these new modalities when they see external innovations that fit within their research and development strategies. Therapeutic area priorities and unmet needs drive these business development decisions, according to executives from Janssen, Biogen Inc. and Astellas Pharma Inc.

Sanjaya Singh, vice president and global head at Janssen BioTherapeutics and Janssen Research & Development LLC (subsidiaries of Johnson & Johnson), Biogen senior vice present of biotherapeutics and medicinal sciences Anabella Villalobos and Astellas senior vice president and head of portfolio strategy Claudia Mitchell spoke about their companies' portfolio strategies as part of the Alliance for Regenerative Medicine's Cell and Gene Meeting on the Mesa, held virtually during October 2020.

Villalobos said Biogen's approach to cell and gene therapy was guided by the marketed products and areas where the company wants to grow within its neuroscience therapeutic areas of interest – multiple sclerosis, neuromuscular diseases, neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, and ophthalmology.

"It's not how big the question is but how critical the question is." – Sanjaya Singh

Villalobos said Biogen's research unit heads and development unit heads lay out strategies and a roadmap within each disease area then identify drug targets of interest. "My department thinks with them about how

Exhibit 1. Cell And Gene Therapy Candidates In Development For J&J, Biogen And Astellas

DRUG NAME	LEAD COMPANY	PARTNER	DISEASE GROUP	DEVELOPMENT PHASE	MOLECULE
ACT Myoblast Therapy	Astellas	Terumo Corporation	Cardiovascular	Approved in other than US/EU	Cellular
DCP-001	DCPrime	J&J	Oncology	Development Outside US	Cellular
P-PSMA-101	Poseida Therapeutics	J&J	Oncology	I	Cellular
AAV-CNGA3	J&J	MeiraGTx	Ophthalmology	I/II	Viral Gene Therapy
AAV-CNGB3	J&J	MeiraGTx	Ophthalmology	I/II	Viral Gene Therapy
AAV-RPGR	J&J	MeiraGTx	Ophthalmology	I/II	Viral Gene Therapy
ASP7317	Astellas	CHA Bio & Diostech	Ophthalmology	I/II	Cellular
ASP7517	Astellas		Oncology	I/II	Cellular
BPX-601	Bellicum Pharma	Astellas	Oncology	I/II	Cellular
BPX-601	Bellicum Pharma	Astellas	Oncology	I/II	Cellular
P-BCMA-101	Poseida Therapeutics	J&J	Oncology	I/II	Cellular
ASP7317	Astellas	CHA Bio & Diostech	Ophthalmology	II	Cellular
DCP-001	DCPrime	J&J	Oncology	II	Cellular
JNJ-64041757	J&J	Aduro Biotech	Oncology	II	Cellular
BIIB112	Biogen		Ophthalmology	II/III	Viral Gene Therapy
CNTO 2476	J&J		Ophthalmology	IIb	Cellular
BIIB111	Biogen		Ophthalmology	III	Viral Gene Therapy
JNJ-4528	J&J	Legend Biotech	Oncology	III	Cellular
ASP7317	Astellas	CHA Bio & Diostech	Ophthalmology	Investigator Initiated	Cellular
Allogeneic T-Cell Therapy (ADAP/Universal)	Adaptimmune	Astellas	Oncology	Preclinical	Cellular
BPX-601	Bellicum Pharma	Astellas	Oncology	Preclinical	Cellular
CRISPR Program (Scribe/Biogen)	Biogen	Scribe Therapeutics	Neurology	Preclinical	Cellular
Gamma-Delta T Cell Antibody Program (Lava/Janssen)	Lava Therapeutics	J&J	Oncology	Preclinical	Cellular
iPSC Platform	Bayer	Astellas	Cardiovascular	Preclinical	Cellular
iPSC-Derived Cell-Based Cancer Immunotherapy Program (Fate/Janssen)	Fate Therapeutics	J&J	Oncology	Preclinical	Cellular
NSR-ABCA4	Biogen		Ophthalmology	Preclinical	Viral Gene Therapy
NSR-BEST1	Biogen		Ophthalmology	Preclinical	Viral Gene Therapy
P-BCMA-ALLO1	Poseida Therapeutics	J&J	Oncology	Preclinical	Cellular
ST-501	Biogen	Sangamo Therapeutics	Neurology	Preclinical	Viral Gene Therapy
ST-502	Biogen	Sangamo Therapeutics	Neurology	Preclinical	Viral Gene Therapy
XYP-117	Xyphos Biosciences	Astellas	Oncology	Preclinical	Cellular

Excluding drug candidates that have been labeled as "suspended" in development. Data correct as of October 2020.

to target it – with a small molecule or gene therapy," she said.

Singh said Janssen takes a similar therapeutic area-based approach; J&J's prescription drug development is focused on cardiovascular and metabolism, immunology, infectious diseases and vaccines, neuroscience, oncology and pulmonary hypertension.

"In Janssen, the therapeutic area [heads] have the responsibility for the portfolio," Singh said, explaining that they oversee assets all the way from very early R&D programs through to commercial products. With cell and gene therapies, he said Janssen's therapeutic area groups identify unmet patient needs and determine what expertise the company brings to the table and what it needs to access from external sources.

Mitchell said Astellas shifted its portfolio strategy a few years ago, focusing on unmet medical needs regardless of the therapeutic area. Once unmet needs are identified, the company looks at what therapeutic modalities are best to address the problem. "We didn't want to be constrained by therapeutic areas," she said.

HOW OFTEN DO YOU REASSESS THE PORTFOLIO?

Singh said Janssen's therapeutic area groups constantly reassess their portfolios to determine which programs are working and which treatment goals are not being met with current therapeutic candidates. "If there is an opportunity that is being left [behind] that can be better addressed by cell therapies, it becomes part of our portfolio planning," he said.

When assessing an unmet need for patients, "it's not how big the question is but how critical the question is," Singh noted. He pointed to Janssen's strategy for treating multiple myeloma with therapies targeting B-cell maturation antigen (BCMA).

The company's most advanced BCMA program is the chimeric antigen receptor T-cell (CAR-T) therapy JNJ-4528, which was licensed from Legend Biotech Inc. and is being studied in a potentially registrational study. However, Janssen also has a bispecific antibody targeting BCMA and CD3, which is designed to recruit patients' T-cells to kill myeloma cells. The two assets are being studied in various settings to determine the best lines of therapy and patient populations for each treatment.

"In oncology, one drug won't give you everything," Singh said, noting that supplementary therapies may be required to fill a specific unmet need.

Villalobos said Biogen's research units and development units also continuously reassess the programs in their portfolios. "We look at the overall strategy once a year, but that doesn't mean we wouldn't make course corrections," she commented. The company also assesses the competition as it lays out the roadmap within each of its disease areas.

HOW DO YOU VALUE EARLY-STAGE INNOVATIONS?

Mitchell said it was difficult to put a value on very early-stage cell and gene therapies and technologies that Astellas could bring into its portfolio. "It's an art more than a science," she said. Rather than try to formulate a complex valuation of something that is too early to quantify, Mitchell's team aims to find science that is compelling and has a reasonable likelihood of success – and then become the champions for that asset or platform.

Villalobos said the assessment of early-stage innovation must be about whether it fills an unmet need and not just about qualitative and quantitative measures of value. She noted that Biogen's spinal muscular atrophy drug Spinraza (nusinersen) did not serve a big patient population, but it was able to treat children who did not have any therapeutic options when the company made the decision to partner with Ionis Pharmaceuticals Inc. on the antisense drug's development.

Biogen thinks about internal versus external investment in terms of how they might complement each other. The company acquired Nightstar Therapeutics last year as a way to build out its ophthalmology therapeutic area. At the time Biogen was just starting to get into gene therapy, Villalobos noted.

DO INNOVATIONS NEED A CHAMPION?

Asked whether new technologies need a champion within their companies to make sure they are considered for a licensing deal, the executives said it helped.

Innovative cell and gene therapies will get a reasonably good look if they might fit within Janssen's R&D priorities, "but champions still make a difference," Singh said.

Villalobos said small companies should focus on generating robust and solid science and noted that "you may not have a perfect asset to go with that disease, but if people see you have a really good molecule" your technology will be considered.

However, she added, "Champions are critical. But the champion also needs to be objective – drive the science and be passionate about it but know when it's time to stand down."

Mitchell said young companies should present their product or technology to Astellas "and find a champion as soon as possible."

MELANIE SENIOR
HEALTHCARE &
SCIENCE WRITER

Pandemic Spotlights Tensions Between Profit And Philanthropy

The COVID-19 pandemic has triggered extraordinary levels of collaboration. But competition remains, and many newly created coalitions have yet to be stress tested.

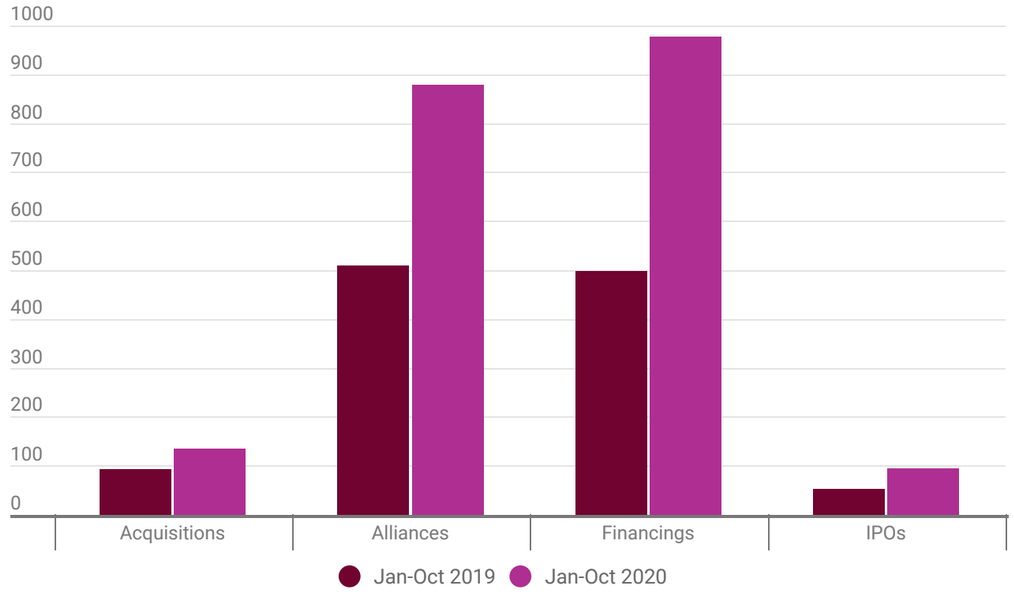
The quest for vaccines and therapeutics against COVID-19 has driven together institutions, companies, countries and scientific communities. Rivals have become partners and R&D timelines have shrunk: just 10 months following the publication of the viral gene-sequence for SARS-CoV-2, 11 vaccine candidates had started Phase III trials. By November 2020, highly promising efficacy results had emerged from a few of those candidates – including one from partners Pfizer and BioNTech, which gained approval in the UK in December 2020.

Data-sharing has expanded, between and among companies and academic institutions, and efforts have grown to integrate disparate data sources, including new kinds of real-world data. Regulators have bent over backwards to usher through early treatments and support flexible trial designs. Dozens of wealthy nations have pooled resources – and R&D risk – into COVAX, a vaccine procurement exercise designed to secure equitable access to a successful vaccine for nations, rich and poor. Pharmaceutical firms are working together, with some – like AstraZeneca and Johnson & Johnson – promising to put profit aside and provide an eventual vaccine "at-cost" during the pandemic.

With effective COVID-19 vaccines still emerging, these newly created coalitions have yet to be fully stress tested.

Competition and commercial instincts remain, even if they sit more awkwardly than normal alongside the need to save lives. Drug makers are racing each other, as well as the virus itself, to find and produce vaccines and therapies. As data emerges from one vaccine or therapy contender, analysts adjust their sales forecasts for another. Pumped-up biopharma valuations are driving frenzied deal-making: in the year to October 27, alliances, acquisitions, financings and IPOs have significantly topped the same period in 2019, according to data from Biomedtracker (*see Exhibit 1*).

Exhibit 1. What Crisis? Deal-Making Surges



Source: Biomedtracker

Several countries – most prominently, the US and China – are still engaged in "vaccine nationalism," notwithstanding growing momentum behind COVAX, and solidarity among key European Union countries (*see Sidebar 1*). Four of the 10 most advanced vaccine candidates are Chinese; three others each include a US-, Japan- and UK-headquartered big pharma. "There's a nationalistic, bunkered [approach] on the one hand, but unprecedented collaboration on the other," summarized Michelle McMurry-Heath, president and CEO of the US Biotechnology Innovation Organisation, speaking at the BIA's Life Sciences Leadership Summit in June 2020.

Competition is not a bad thing: the fight for funding, for markets and for recognition created most of the scientific foundations underpinning this rapid, remarkable response. But as COVID-19 continues to rage across the world – causing over 1.2 million deaths and an $11tr hit to global output for 2020-2021 alone – finding the right balance between collaboration and competition will be crucial. It will matter not only for tackling this global disease, but also in ensuring some positive legacies from this crisis.

SHAKY START

This collective response to COVID-19 did not fall into place all at once. It emerged as it became evident that even the world's richest nations were woefully underprepared for a pandemic. Despite warnings from experts and notwithstanding previous, more localized outbreaks such as MERS in 2012 and SARS in 2002, few governments had the required resources and expertise to hand. The US Centers for Disease Control had lost its pandemic preparedness team in 2018. Most major multi-national pharmaceutical firms had shut down anti-infectives R&D due to unattractive market dynamics.

Organizations set up to deal with major public health crises lacked funding and support. As the virus hit the US, the World Health Organisation found itself in President's Trump's firing line for having allegedly covered up the early days of the virus' spread in and around China. WHO remains a political battleground: the US,

SIDEBAR 1: COVAX

COVAX is the vaccine arm of the Access to COVID-19 Tools Accelerator launched in April 2020, with backing from GAVI, CEPI, WHO, The Gates Foundation, Wellcome and the World Bank, among others. This collective vaccine purchasing agreement includes 184 country-signatories, of which 79 are higher income nations. The US is notably absent from COVAX, though China signed up in October.

All signatory countries are promised doses of whichever of the nine supported vaccine candidates in clinical development eventually succeed. Each nation will receive supplies for between 10-50% of their populations, depending on their contribution. The vaccine candidates span several modalities (mRNA, DNA, adenoviral-based, sub-unit proteins) to hedge risk.

COLLABORATION

WHO's largest funder, left the organization in July, though President-elect Joe Biden says he will maintain membership.

CEPI, set up in 2017 to avoid a repeat of the disastrously dis-jointed response to the Ebola outbreak in Western Africa in 2014/2015, was also stretched too thin. Reliant on government and philanthropic money, CEPI is charged with funding research into (known) priority pathogens and supporting technologies that can enable a rapid response to a putative (now real) 'disease X.' But CEPI was still growing, and "not quite ready to deal with something of this scale," according to Thomas Evans, chief scientific officer at UK-based Vaccitech, who previously ran Aeras, a non-profit organization set up to develop tuberculosis vaccines (now part of the International AIDS Vaccine Initiative.)

INDUSTRY UNDER THE SPOTLIGHT

Despite these limitations, CEPI moved fast to jump-start financing for several vaccine programs in the first couple of months of the outbreak. After that, it was the multinational pharma firms which transcended borders, and politics. Many stepped up, without any guarantee of profit.

It was clear early on that almost all the capabilities required to deal with the pandemic – drug and vaccine research, development, scale-up and manufacturing, plus diagnostics and protective equipment – resided within industry. "We knew we couldn't make headway … unless industry really played ball, in a way that they haven't always," said Trevor Mundel, president, global health at the Bill & Melinda Gates Foundation, which has played a pivotal role in driving partnerships to help ensure global, equitable solution to this global crisis. The 500-strong global COVID-19 treatment and vaccine pipeline also includes an astonishing array of universities and research institutes, many in multi-way partnerships. But industry is critical for later-stage development and manufacturing in particular. Pfizer has also set up distribution for its vaccine in the US. The scale of the crisis means that even they have had to engage in unusual tie-ups (*see Sidebar 2*).

This crisis has gifted the pharmaceutical industry a unique opportunity to re-set its reputation. Putting near-term financial profit aside to 'save the world' may ultimately reap rewards – in policy and investment – that extend well beyond this pandemic. Already, several companies are enjoying government-funded, accelerated testing and potential validation of their platform technologies. The entire industry stands to benefit from the multi-lateral efforts to improve clinical trial coordination, regulatory flexibility, and data-sharing.

BIGGER, FASTER, BETTER CO-ORDINATED TRIALS

In March, it became clear that running dozens of smaller, regional trials of potential COVID-19 therapies was not going to suffice against a virus spreading rapidly across the globe. Two far larger studies of readily available, re-purposed drugs got underway – one in the UK, and the other global.

The UK's University of Oxford began the world's largest randomized clinical trial (RCT) for COVID-19 treatments, RECOVERY, involving all of the country's major hospitals. The study, which has now recruited over 16,000 patients, began with six treatment arms, and the option to add others as evidence of promising treatments emerged (aspirin is the most recent addition).

RECOVERY delivered its first policy-changing results within three months: hydroxychloroquine, an anti-malarial drug, does not help; the steroid dexamethasone does. Key to the trial's speed and success were the NHS-linked hospital network, plus simple inclusion criteria, minimal red-tape and easy-to-use web-based data entry forms to streamline recruitment.

WHO's SOLIDARITY trial recruited 12,000 patients across 30 countries. Six months later, it, too, concluded that hydroxychloroquine did not impact 28-day mortality, the need to ventilate, or length of hospital stay. And neither, it found, did anti-viral duo lopinavir/ritonavir, interferon beta-1a, or Gilead's remdesivir (though Gilead's own trials showed sufficient benefit, in terms of reduced hospital stay, to gain emergency use and then full authorization).

UK clinicians hope that RECOVERY may provide a template for studying other treatments for life-threatening, wide-spread conditions. And SOLIDARITY "shows that large, international trials are possible … and may "quickly and reliably answer critical public health questions … even during a pandemic," said WHO in a statement.

As more candidate therapies and vaccines entered development across the world, including novel and patented ones, there was an urgent need to prioritize them, wherever they came from. Trial protocols required harmonization and streamlining, relevant biomarkers needed to be agreed and approved, and clinical trial network capacity inventoried.

This drove the creation, in April, of Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), a private-public partnership led by the US National Institutes of Health. It combines 20 biopharma firms, BARDA, CDC and, critically, the US and European regulators. Working groups are focused on preclinical as well as clinical and trial capacity needs. "I have never worked so fast with regulatory agencies as we are now," said Paul Stoffels, CSO at Johnson & Johnson, speaking at BIO-Europe Digital in October. He added that the company's own vaccine candidate took just 10 days from Phase II data to starting Phase III trials. The regulators review data as it emerges, working out of hours to accelerate development.

Such resource-mobilization cannot happen for every product, in normal times. But the experience "trains us on how to work together" in future urgent situations, said Stoffels. It "brings us all to the next step, faster."

The academic research community is following a similar philosophy. Cross border collaboration – always there – has now become "faster and more urgent," said Justin Stebbing, professor of cancer medicine and oncology at Imperial College London. And it is happening among a wider range of disciplines. Stebbing is first author, with over 50 other authors from 30 institutions across Europe, Asia and North America, on a new paper setting out how baricitinib, a rheumatoid arthritis treatment sold by Eli Lilly as Olumiant, may help patients with severe COVID-19.

Baricitinib, an oral Janus kinase (JAK1/2) inhibitor, was first identified as a promising candidate using AI technology developed by UK-based BenevolentAI. It was predicted to have both anti-viral and anti-inflammatory activity, plus helpful pharmacokinetic properties setting it apart from others in the class. The paper, published in *Science Advances*, provides both laboratory *in vitro* and clinical evidence supporting this original computer-powered hypothesis. It draws on RNA-sequencing, organoid work, super-resolution microscopy, molecular biology, bioinformatics and clinical studies across countries, assembling geriatricians, rheumatologists, oncologists, virologists, pneumologists and more. "Walls are coming down," said Stebbing, who has co-authored over 20 COVID-19-related papers this year. Baricitinib went from computer to Phase III clinical trials in months; Lilly's own global RCT began in June. The compound is also being studied in other investigator-led trials.

The pandemic is also pulling down walls between different health data sources – many of which remain fragmented, incompatible and inaccessible (*see Sidebar 3*).

BUILDING TENSION

In a joint communique issued by the Gates Foundation on 30 September, 16 pharma CEOs re-iterated their commitment to speedy R&D of COVID-19 solutions and to ensuring affordability for lower- and middle-income countries. They also advocated for equitable distribution of future solutions and maintaining public confidence.

There are already cracks in the show of solidarity, though. Signatory Gilead was first into the pricing spotlight when its anti-viral remdesivir (Veklury) won full FDA approval in October 2020. After giving away the first 1.5 million doses, the company began to charge $2,340 per 5-day course of the drug, shown to reduce hospital stay length. The upshot: $873m in the third quarter – a "very good return on investment," according to CEO Daniel O'Day, speaking on an earnings call. Pfizer has not pledged to shun profits, either. And its CEO sold millions of dollars' worth of shares on the day the company's positive vaccine data was released – not a good look for an industry seeking to clear up its image.

ROI is allowed, even if it looks a little ugly in today's context. Gilead deserves credit for its speedy development: having failed in RSV, HCV and Ebola, remdesivir was dusted off and approved in months. But some question Gilead's defence of its own (positive) trial results in the face of SOLIDARITY's negative data, and its plans for line-extensions. If SOLIDARITY had read out before Gilead's own studies, "remdesivir would have been toast," said one senior clinician working on COVID-19 therapies.

As the pandemic and the treatment pipeline evolve, two things are becoming clear. The first is that we are in it for the long-haul. The second is that there will be no single magic-bullet therapy or vaccine. There will more likely be several, progressively better, medical solutions. The frontrunner vaccine candidates look unlikely to reach beyond rich nations, given pricing, and requirements for deep-freeze storage.

A long-term, evolving market need with room for multiple solutions should work in industry's favor – even as market forces displace earlier, less effective therapies, or vaccines that are trickier to distribute or administer. But these dynamics also create further tension between philanthropy and profit. Manufacturers pledging to provide solutions "at cost" "for the duration of the pandemic" will have to define and defend both those terms. Few companies have been willing to commit to a WHO-defined pandemic timeline, according to Mundel; some talk about the end of 2021.

Pharma's costs are notoriously opaque, complicated by the cost of failed R&D projects. Manufacturing is typically only about 10%. Lilly CEO Dave Ricks is limiting his company to only a "modest" financial return on the emergency-use-authorized bamlanivimab, but even that risks sounding slippery in an industry accustomed to 70-80% margins. "We need transparent, open negotiations [on pricing], which taxpayers and everyone else can see," argued David Mitchell, founder of Patients for Affordable Drugs.

Transparency is still lacking. Most contracts between industry and governments remain opaque. The leading vaccine contenders only published trial protocols under pressure to do so.

COVID-19 will not eliminate these long-standing tensions in industry's relationship with society. But its spotlight may help reduce them. This pandemic has drawn out new ways of working and of collaborating that will not be forgotten. Whether or not an effective vaccine emerges, "something very impressive is being achieved," said Gates' Mundel.

SIDEBAR 2: RIVALS JOIN FORCES TO EXPAND THERAPY PRODUCTION

Rivals are collaborating to manufacture and distribute COVID-19 therapies. Pfizer in August 2020 agreed to help manufacture supplies of Gilead Sciences' remdesivir, even though the big pharma has its own anti-viral research efforts, plus a leading vaccine. Amgen is providing Eli Lilly & Co. with additional manufacturing capacity for Lilly's antibody-based therapies, one of which received FDA Emergency Use Authorisation for mild-to-moderate COVID-19 in mid-November. Roche has similarly agreed to help Regeneron with its potential antibody-duo.

The tie-ups are not charitable. Roche, effectively a development partner, will handle ex-US regulatory and distribution of any potential therapy. And the two-by-two arrangements were a next-best scenario, after initial discussions broke down among a much larger group of developers and manufacturers, according to someone close to the talks.

SIDEBAR 3: UNLOCKING DATA SOURCES

The International COVID-19 Data Research Alliance and Data Analysis Workbench aims to assemble and unlock Covid-19 relevant clinical trial, biomedical and health research data for researchers across the globe, in a bid to accelerate treatment R&D. Some companies agreed to provide summary trial data to the Data Alliance, which is being run by Health Data Research UK.

The value of new kinds of "real-world" data in managing health has also become even clearer. Smartphone-collected data has been crucial in tracking population movements and enabling contact tracing. In the UK, digital health company Huma partnered with the NHS to trial a Covid-19 remote monitoring solution that advises self-isolating patients on appropriate care.

Such data may also help predict infection: in a study published in *Nature Medicine* in May, a crowd-sourced app collecting reported symptom data determined that loss of smell and taste were strongly predictive of COVID-19 infection.

COLLABORATION

Spotlighting Major Deals

14 SEP — Merck & Co./ Seattle Genetics

Merck announced a pair of significant deals with Seattle Genetics – agreeing to develop and commercialize LIV-1-targeting ladiratuzumab vedotin for breast cancer and other solid tumors and licensing commercial rights to Tukysa for HER-2-positive cancers in Asia, the Middle East and Latin America. Seattle Genetics got $725m up front plus a $1bn equity investment from Merck under the two deals, with earnout potential of $2.75bn.

13 SEP — Gilead/ Immunomedics

In the largest biopharma M&A deal of the year, Gilead agreed to pay $21bn to acquire Immunomedics and its first approved solid tumor therapy – the Trop2-targeting antibody-drug conjugate (ADC) Trodelvy (sacituzumab govitecan) for third-line metastatic triple-negative breast cancer (TNBC). Negotiated for about six months, the deal valued Immunomedics at 108% premium of $88 per share, and is Gilead's 10th major cancer deal of 2020.

19 AUG — Lilly/ Innovent

Lilly paid $200m up front with earnout potential up to $825m obtain worldwide rights, except for China, to Tyvyt (sintilimab), the PD-1 checkpoint inhibitor it co-developed with Innovent.

17 AUG — BMS/ Dragonfly Therapeutics

BMS paid undisclosed upfront cash with potential for milestones and royalties to license Dragonfly's IL-12 cytokine program, with an eye on developing therapies that will boost the effectiveness of its IO drugs such as Opdivo.

10 AUG — Ligand/ Pfenex Inc.

Ligand agreed to pay about $438m to acquire Pfenex in a transaction that will bring it protein-expression platform technology and multiple revenue-producing partnerships.

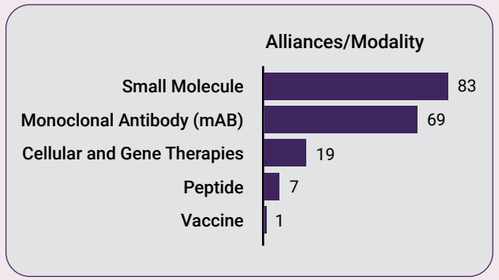
27 JUL — AstraZeneca/ Daiichi Sankyo

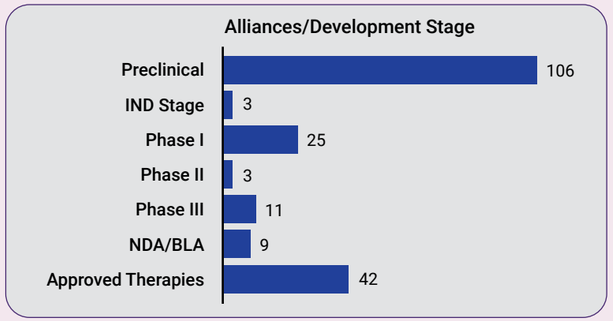
AstraZeneca paid $1bn up front with potential total value of $6bn to acquire a Phase I antibody-drug conjugate therapy for lung and breast cancer indications, following a 2019 deal between the two firms for another ADC.

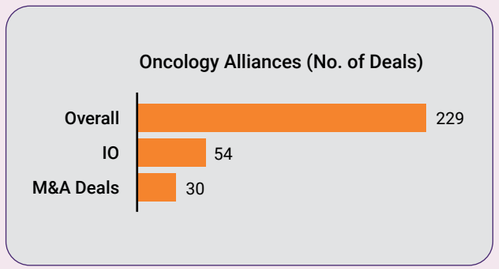
CANCER DEALS

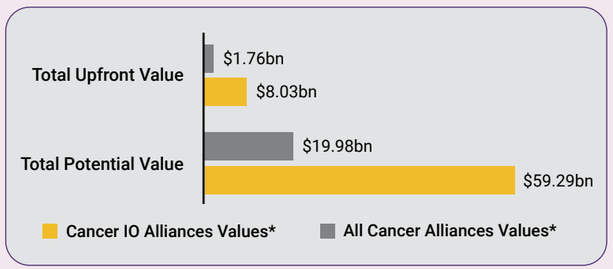
That Grabbed Headlines In 2020

2020 Cancer Deal Trends









All data correct as of 14 Sept 2020
* Not all deals reported this

24 cancer deals with upfront value of **≥$100m**

Highest-Value Cancer Deals

COMPANY/COMPANY	DEAL DESCRIPTION	UPFRONT VALUE	TOTAL POTENTIAL VALUE
Gilead/Immunomedics	Acquisition, 13 September	$21bn	$21bn
Gilead/Forty Seven	Acquisition, 2 March	$4.9bn	$4.9bn
Merck & Co./Seattle Genetics	Development/commercial, 14 September	$1.6bn	$4.2bn
AstraZeneca/Daiichi Sankyo	Development/commercial, 27 July	$1bn	$6bn
MorphoSys/Inctye	Development/commercial, license, 13 January	$900m	$2bn
Roche/Blueprint	Development/commercial, 14 July	$775m	$1.7bn
AbbVie/Genmab	Development/commercial, 10 June	$750m	$3.15bn
Menarini/Stemline	Acquisition, 4 June	$677m	$677m
Bristol Myers Squibb/Dragonfly	License, 17 August	$475m (incl. near-term payments)	N/A
Ligand/Pfenex	Acquisition, 10 August	$438m	$516m
Cellular Biomedicine/Consortium of management, investors	Public-to-private acquisition, 12 August	N/A ($19.75 per share)	N/A
Gilead/Arcus	Partnership, option to license, 27 May	$375m	$5bn
Gilead/Tizona	Partial acquisition, option to buy, 21 July	$300m	$1.55bn
Gilead/Pionyr	Partial acquisition, option to buy, 23 June	$275m	$2.9bn
Immatics/Arya	Private-to-public acquisition, 18 March	$247.8m	$247.8m
Pfizer/CStone Pharmaceuticals	Partnership & license, 29 September	$200m	$479.4m
AbbVie/I-Mab	License, 4 September	$200m	$1.94bn
Eli Lilly/Innovent	License expansion, 19 August	$200m	$1.025bn
Merck & Co./Seattle Genetics	License, 14 September	$125m	$275m
Gilead/Tango	Partnership expansion, 17 August	$145m	$6.4bn
Gilead/Jounce	License, 1 September	$120m	$805m
Kyowa Kirin/MEI Pharma	Development/commercial, license, 14 April	$100m	$682.5m
GlaxoSmithKline/IDEAYA	Partnership, option to license, 16 June	$100m	$3.03bn
Janssen/Fate Therapeutics	Partnership, option to license, 3 April	$100m	$3.9bn

14 JUL — Roche/ Blueprint Medicines

Roche paid $675m up front and made a $100m equity investment in Blueprint in exchange for global development and commercial rights to a potential precision medicine RET inhibitor filed for approval in the US and EU for lung and thyroid cancer.

10 JUN — AbbVie/ Genmab

AbbVie paid the Danish biotech $750m up front with potential for milestones up to $3.15bn to jointly develop and commercialize three bispecific antibody candidates.

27 MAY — Gilead/ Arcus Biosciences

Gilead enhanced its IO pipeline in a 10-year R&D collaboration giving it option rights to multiple candidates including an anti-PD-1, an anti-TIGIT and a dual adenosine receptor antagonist candidate.

3 APR — J&J/ Fate Therapeutics

J&J paid Fate $50m and made a $50m equity investment in the US biotech to collaborate on the development of off-the-shelf stem cell therapies in the CAR-T and NK classes.

2 MAR — Gilead/ Forty Seven

Gilead paid about $4.9bn to acquire Forty Seven and its first-in-class anti-CD47 candidate magrolimab, one of five significant IO-driven deals Gilead made during the year.

13 JAN — Incyte/ MorphoSys

For upfront consideration of $900m including a $150m equity investment, Incyte partnered with MorphoSys to develop and commercialize anti-CD19 candidate tafasitamab for lymphoma and leukemia indications.

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Challenges, Innovation And Value Creation In Generics And Biosimilars

The COVID-19 pandemic has highlighted the importance of a smoothly functioning supply chain in ensuring patients have timely access to much-needed medicines. In the fast-moving market for generics and biosimilars, delivering high-quality products at acceptable cost is even more imperative, with or without COVID-19. Here, Fran DeGrazio, Chief Scientific Officer of West Pharmaceutical Services, talks to *In Vivo* about current trends and challenges in the sector.

***In Vivo:* How did West plan for the potential impacts of COVID-19?**

DeGrazio: We really defined our priorities: first, the health and the safety of our teams, and then ensuring continued support for our customers and communities. Continued support is about maintaining uninterrupted supply of high-quality containment and delivery devices to customers and ultimately, the patient. We also focused on investing. We really accelerated our investment as soon as we saw what was going on with the pandemic.

We were already supporting growth of our base business, but we knew more production capacity would be needed to support COVID-19 vaccines and therapeutics. So, we had to move very quickly. One example is, about a month ago, we installed new manufacturing equipment at one of our high-value product sites to prepare for future demand, especially in respect of our FluroTec® and NovaPure® product lines. That capacity is already operational, and additional equipment is being installed at several other sites.

The other thing, of course, is making sure we continue to communicate and be transparent with our customers, so everybody understands any potential impacts of the pandemic on our business.

How has West navigated maintaining supplies as countries opened and closed borders periodically in response to the pandemic?

We are very fortunate to have manufacturing capabilities throughout the world. We can use that global network to really help ensure supply. The ability to deliver quality product consistently and in a timely manner has never been more important than now. We're constantly monitoring our supply chain to make sure we can minimize any disruption. Our sites and facilities are open, and we comply with all restrictions based on country, state, regional or local guidance.

There's always a lot of planning for unexpected delays. All of this is monitored daily by our supply-chain organization. Another key piece is our ability to access dependable transportation. That goes for the raw materials we receive, and our ability to transport finished goods to our customers. We have experienced some delays in air and sea shipments. There have also been some delays in certain areas of the US that are starting to see an increase in COVID-19.

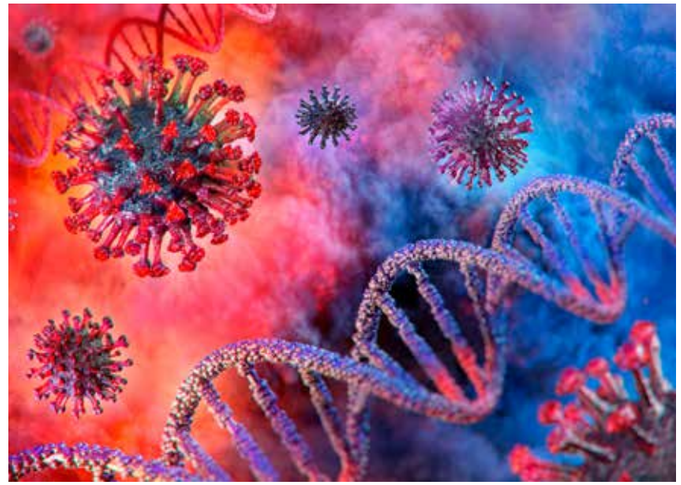
Again, we've really been able to manage that through good communication with our suppliers and our customers. Another benefit is that we have long-term agreements in place with our suppliers. We have risk-mitigation plans, and we've increased our safety stock of raw materials. We created a task force to ensure that we're prioritizing COVID-related needs and matching those needs as we look at our global capacity.

Leaving aside COVID, what other trends, developments and updates are you seeing in your sector?

Although COVID is on everybody's mind, the reality is that there are many other drugs in development that are vital to patients. One trend we're seeing is continuing diversity in the drug pipeline: for instance, increased growth in biologics, and not just simple monoclonal antibodies, but also the addition of many cell and gene therapies. When you look at these trends, they really connect quite well with some of our product lines, like our NovaPure® stoppers and plungers, Daikyo Crystal Zenith® ready-to-fill syringes and RU vials and the SmartDose® on-body delivery system.

What role do you see generics and biosimilars playing in the future?

We're seeing continued growth from both generics and biosimilars. The compound annual growth rate right now is estimated at seven to eight percent, with a market value that should be close to $5 billion by 2024. This is really driven by some key markets: the US, of course, and China. And the demographics are also changing, i.e., there is an aging population across the board: the US, China, and certainly in Europe as well.



For all the growth in generics and biosimilars, though, the quality standards don't change. We are very much challenged by the need to keep costs manageable, while maintaining good quality and patient safety priorities.

And the regulations can vary in each region. In the US, for example, we have a 505 (b) (2) submission which allows generics companies to leverage data they perhaps didn't generate *per se* to accelerate development. But that kind of avenue is specific to the Food and Drug Administration. There may be similar regulations in other countries. But how documentation gets assembled and how it is submitted is somewhat different for every country or every region.

There are also a lot of updates of commonly used standards. For instance, the United States Pharmacopeia has just updated USP Sections 381 and 382. Those are directly applicable to elastomeric components. USP 381 relates more to chemistry and the physicochemical characteristics of the elastomer.

USP 382 generally states that you can't expect your suppliers, for instance, to provide data on how a component functions, because what's critical is the interplay between all the components as a system. That's just one example of how we're seeing more and more complexity, even from the standards viewpoint. Ultimately, the standards now recognize that you can't evaluate function as a singular component. You need to know what system the pharma company is going to use.

In this environment, what kind of innovations are you seeing from generics organizations?

Instead of just considering price, companies are now looking at the total cost of ownership. Many companies are moving away from a simple vial format and towards, for example, putting a product in a prefilled syringe, or a prefilled syringe with an additional delivery device, like an auto-injector. It's just easier to use a syringe system versus a disposable syringe and a vial, as it removes the step of having to first withdraw the drug from the vial with the syringe before making the injection. It's also about potential differentiation in the market.

You have mentioned some changes in the regulatory environment. What is their impact on product development?

Both from a generics standpoint and across the board, there are a lot of changes in regulation globally. One change that has caused perhaps the most complexity is where customers want to develop drug-device combination products.

A prefilled syringe system, for instance, is a combination product. On-body delivery systems are combination products. A syringe with an auto-injector is a combination product. There is a lot of activity in that space. Certainly, it's innovation, but it's driven by people looking for more at-home self-administration of drug products.

Combining the drug or biologic with the delivery device eases self-administration. Also, due to COVID, people are much more hesitant about going to a doctor or clinic. So, the industry is exploring how it can accelerate at-home treatment. This whole trend is not just easier on the patient, in the long run, it will provide a cost savings as well.

These products are a little more challenging from a regulatory standpoint. There has been a whole set of guidelines, certainly from the FDA, because when you combine a drug and a device, you need to meet the regulatory requirements for both pathways.

In Europe, companies are being challenged by the update to medical devices regulations. The update was supposed to take effect earlier this year, but it has now been pushed back to 2021, due to COVID. Pharma companies are really trying to understand what this regulatory change means for them in executing drug-device combinations.

What role does technology play in how West conducts its business?

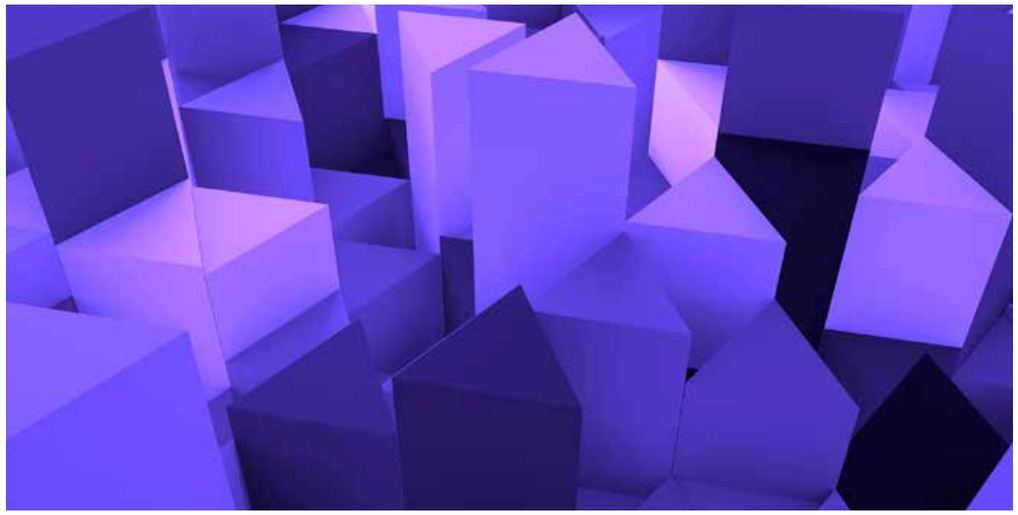
Probably the biggest area of focus is - how do we stay connected to our customers? In the past, we have participated in many in-person events, including conferences and trade shows. Of course, today, everything has gone virtual. So, we've really worked hard to create a kind of West virtual world [**https://www.westpharma.com/360/**], offering a more immersive and fully interactive experience for our customers.

In addition, we're actively involved in hosting even more webinars and training programs virtually. Fortunately, several years ago we developed our West Knowledge Center, which is accessible online through our website. It's really a repository of publications and other literature focused on the science in the injectables space. We offer a lot of technical information, regulatory information and, for our customers, certain product information they may need.

Any final thoughts?

Although the COVID situation is a challenge, it has really accelerated some out-of-the-box thinking, showing people different ways of doing things that can be very effective.

BY DAVID WALLACE
EXECUTIVE EDITOR, EUROPE



A Year Of Surprises Shakes Up Off-Patent Industry

After an eventful year for the off-patent industry, the world's leading generics and biosimilars players have switched places in Generics Bulletin's newly compiled global sales ranking.

After a year that has seen major changes for some of the biggest players in the global off-patent industry, it is perhaps no surprise that annual rankings of the world's top 50 generics and biosimilars companies reflect this upheaval.

This year, annual rankings produced by *In Vivo*'s sister publication Generics Bulletin paint a picture that looks quite different to predictions made by industry onlookers just 12 months ago, particularly when it comes to the top of the table.

Last year, Mylan topped the list, followed by Sandoz and Teva. At the time, Generics Bulletin predicted that Sandoz would slip down the table in future due to its deal to divest a large chunk of its business – in the form of its US solid-dose and dermatology units – to India's Aurobindo.

However, while that deal had been expected to close by the end of 2019, it eventually fell apart altogether. As a result, Sandoz has not only maintained its position in the top three but has vaulted to the top of sales rankings, with its $9.37bn total for the combined generics, biosimilars, active pharmaceutical ingredients and OTC category narrowly exceeding that of Mylan, despite the Novartis unit seeing a 1% drop in turnover in 2019.

MYLAN PREPARES FOR VIATRIS MERGER

While Mylan's total company sales in 2019 grew by 1% to $11.5bn, the latest ranking excludes from the key category around $1.8bn of Mylan's turnover from respiratory and allergy brands such as EpiPen (epinephrine), Perforomist (formoterol) and Tobi (tobramycin).

Mylan was also a firm with very different expectations hanging over it midway through last year, with investors keenly anticipating the firm's long-trailed management announcement of restructuring plans expected to revitalize the company. But eventually the firm revealed significantly more far-reaching change, in the form of a merger with Pfizer's Upjohn off-patent unit to become Viatris.

Although the close of this merger was pushed back to late 2020, and had no effect on Mylan's 2019 figures, the successful completion of the deal in November promises to leave the company in a very different position 2021's industry rankings.

Sandoz and Mylan's leading positions this year come at the expense of Teva, which remains in third place after seeing its group sales drop by 8% to $16.89bn with its generics, biosimilars, APIs and OTC figure making up $9.33bn.

Teva president and CEO Kåre Schultz had been clear that the firm expected 2019 to represent "the bottom of the trough" for the company's sales and earnings, as it emerges from a years-long period of upheaval in the form of a restructuring program that has seen it shed thousands of staff, shutter more than 20 manufacturing sites and prune its product portfolio, especially in the US. The firm is also focusing on brands such as Ajovy (fremanezumab) and Austedo (deutetrabenazine) as major growth drivers, especially as Copaxone (glatiramer) sales continue to atrophy in the face of global generic competition.

Working down our top 10 list, we see Pfizer no longer listed under the banner of Pfizer Essential Health – after the company reorganized its reporting structure in 2019, eliminating this grouping – but instead ranked according to its combined sterile injectables and biosimilars business, much of which was inherited from the legacy Hospira unit. The figure of just under $6bn includes a significant portion of biosimilars sales that are likely to top $1bn in 2020 after reaching $911m in 2019.

As major firms like Sandoz, Mylan and Teva do not typically split out sales of OTC products separately from their generics offerings, the ranking includes OTC products alongside prescription generics and biosimilars.

This means that Perrigo's extensive range of consumer health care products – many of which are approved through the generic abbreviated new drug application pathway in the US – puts it squarely in the top 10 when combined with the Prescription Pharma unit that it is considering selling or spinning off. The firm is taking its time to secure adequate value for the Prescription unit but says the recent sale of its UK-based Rosemont Pharmaceuticals liquid generics business proves that attractive multiples are still out there in the generics space.

Sun Pharma's business enjoyed double-digit growth in 2019, although the Indian company has been weighed down recently by a costly settlement connected to the US price-fixing investigations relating to its Taro subsidiary. And Fresenius Kabi ranked in seventh position this year thanks to its large intravenous portfolio, even as it recently conceded that its biosimilars business had been slower off the mark than it had expected.

Aurobindo, meanwhile, has climbed up the rankings from 10th to eighth position despite the collapse of its deal with Sandoz that would have likely propelled it even higher.

Rounding out the top 10 are China's Shanghai Fosun – that saw 15% growth to more than $3bn for its pharmaceuticals unit – and Germany's Stada, which saw a group increase of 12% to $2.92bn in the wake of an acquisition spree in 2019. The firm's generics, biosimilars, APIs and OTC figure of $2.75bn excludes its branded products Apo-Go (apomorphine) and value-added bortezomib that together accounted for $171m in 2019.

MID-TABLE ALSO SEES MOVEMENT

However, significant movements were not limited to the industry's largest handful of players, with a group of major Indian companies also jostling for position just outside the top 10.

Dr Reddy's climbed above rivals Lupin, Intas – including its Accord business – as well as UK-based Hikma, from 15th place last year to 12th this year, thanks in part to Dr Reddy's substantial active pharmaceutical ingredients business now being included in our key category.

While our top 50 ranking compiles sales data for 2019 or the closest available reported year, many Indian companies report on the basis of financial years that ended 31 March 2020, meaning that some of these firms may have seen some effect from coronavirus-related stocking towards the very end of this period.

Meanwhile, the disaggregation of Hikma's reported sales total is based on an estimated 90%-10% turnover split for generics and brands communicated to Generics Bulletin by the company.

Japanese firms Sawai and Nichi-Iko also featured highly in our rankings – again based on financial years ending in March 2020 – while Slovenia's Krka rounded out the top 20 with double-digit growth in 2019 after several years of reliable increases.

Slightly further down the table is Amneal, which has seen mixed fortunes since its merger with Impax and which reported its 2019 results after Chirag Patel and Chintu Patel returned as co-CEOs of the firm they co-founded midway through last year.

Other significant movements include Sanofi's generics business falling from 16th position to 24th, in the firm's first full year of reported sales following the divestment of its Zentiva generics business in Europe.

Meanwhile Korea's Celltrion scraped into the top 30 – with growth of more than half in 2019 thanks to its expanding portfolio of biosimilars, marketed worldwide through various partnerships as well as its own burgeoning front-end operations – and Japan's Towa also moved up the list slightly, from 30th to 28th position, with its recent purchase of the Pensa Investments generics business from Spain's Esteve promising to potentially propel it even further up the ranking next year.

Lower down the table, Aché and Hypera both registered sales of just under $850m in 2019. And a little behind these two Brazilian firms, troubled Mallinckrodt and Akorn featured, despite both experiencing difficulties and grappling with bankruptcy proceedings.

Meanwhile, Biocon rose up the rankings from 43rd position last year to 40th position this year, as its successful biosimilars business closed in on a sales target of $1bn by the end of its financial year ending in March 2022.

The ranking puts Biocon close to fellow Indian firms Ipca and Alembic, as well as Wockhardt which earlier this year closed a deal worth around $260m to divest a chunk of its branded generics business in India and certain international territories to Dr Reddy's. Meanwhile, Strides was smaller in 2019 following earlier divestments.

Rounding off our top 50 are a pair of new entrants this year. US biosimilars specialist Coherus BioSciences reported 2019 turnover of $356m from almost a full first year of sales from its Udenyca (pegfilgrastim-cbqv) rival to Neulasta that launched in January 2019. And Bangladesh's Beximco enjoyed 29% growth to around $278m, having made headlines recently with the launch of the world's first generic version of remdesivir.

With major deals still in the works, biosimilars continuing to grow in significance and the COVID-19 pandemic promising to reshape the industry landscape at the same time as it exerts short-term pressures on supply and demand, the global off-patent industry continues to operate in a shifting environment that makes predicting the future a difficult task. As the industry continues to work its way through the turbulence of 2020, it is possible that next year's ranking will once again look very different.

Generics Bulletin Compiles Top 50 Rankings For The Off-Patent Sector

COMPANY	GENERICS / BIOSIMILARS / APIS / OTC ($M)	PRESCRIPTION BRANDS ($M)	OTHER ($M)	TOTAL TURNOVER ($M)	CHANGE %	NOTES
Sandoz	9,731	-	-	9731	-1	Total includes $534m from sales of anti-infectives to third parties
Mylan	9,566	1,805	130	11,501	+1	Prescription Brands is Respiratory and Allergy therapeutic category
Teva	9,326	3,389	4,172	16,887	-8	
Pfizer Injectables & Biosims	5,946	-	-	5,946	-1	
Perrigo	4,837	-	-	4,837	+2	Comprises $967m from Prescription Pharma, $2,488m from Consumer Self-Care Americas and $1,382m from Consumer Healthcare International
Sun Pharma	4,539	-	19	4,558	+13	Financial year ended 31 March 2020; converted from Indian rupees
Fresenius Kabi	3,292	-	4,457	7,749	+4	Generics / Biosimilars / OTC / APIs figure is Intravenous Drugs unit; converted from euros
Aurobindo	3,257	-	-	3,257	+18	Financial year ended 31 March 2020; converted from Indian rupees
Shanghai Fosun	3,066	-	962	4,028	+15	Converted from Chinese yuan
Stada	2,750	171	-	2,921	+12	Converted from euros; branded products includes Apo-Go sales of €74.5m and value-added bortezomib sales of €78.5m
Cipla	2,360	-	56	2,416	+5	Financial year ended 31 March 2020; converted from Indian rupees
Dr Reddy's	2,311	151	-	2,462	+13	Financial year ended 31 March 2020; converted from Indian rupees
Lupin	2,135	-	33	2,168	+5	Financial year ended 31 March 2020; converted from Indian rupees
Intas	2,108	-	-	2,108	+14	Financial year ended 31 March 2020
Hikma	1,973	219	11	2,203	+6	Figures based on approximate 90:10 revenue split for generics and brands
Zydus Cadila	1,692	-	318	2,010	+8	Other sales are Consumer Wellness & Animal Health segments; Financial year ended 31 March 2020; converted from Indian rupees
Sawai	1,679	-	-	1,679	-1	Financial year ended 31 March 2020; converted from Japanese yen
Nichi-Iko	1,655	65	29	1,749	+14	Financial year ended 31 March 2020; converted from Japanese yen
Servier Generics	1,549	-	-	1,549	+8	Financial year ended 30 September 2019; converted from euros
Krka	1,546	-	122	1,668	+12	Converted from euros
Glenmark	1,471	-	29	1,500	+8	Financial year ended 31 March 2020; converted from Indian rupees
Aspen	1,373	888	-	2,261	+1	Generics/Biosimilars/OTC/APIs comprises $1037m from Regional Brands and $336m from APIs and FDFs; financial year ended 30 June 2019; converted from South African rand
Amneal	1,309	318	-	1,626	-2	
Sanofi Generics	1,204	-	-	1,204	-28	Converted from euros
Alkem	1,177	-	-	1,177	+13	Financial year ended 31 March 2020; converted from Indian rupees
Gedeon Richter	1,172	230	382	1,748	+12	Prescription Brands is Vraylar (cariprazine), Reagila (cariprazine) and Esmya (ulipristal acetate); converted from euros
Torrent Pharma	1,052	-	67	1,119	+3	Financial year ended 31 March 2020; converted from Indian rupees
Towa	1,016	-	-	1,016	+5	Financial year ended 31 March 2020; converted from Japanese yen
Endo	985	1,929	-	2,914	-1	Generics plus injectable ertapanem authorized generic
Celltrion	928	-	-	928	+54	Converted from South Korean won
Ache	848	-	-	848	+5	Converted from Brazilian reals
Hypera	834	-	-	834	-12	Converted from Brazilian reals
Jubilant	806	-	485	1,291	0	Generics/Biosimilars/APIs/OTC figure is Pharmaceuticals segment; Financial year ended 31 March 2020; Converted from Indian rupees
Sopharma	777	-	-	777	+9	Converted from Bulgarian lev
Mallinckrodt	739	2,424	-	3,163	-2	
Akorn	682	-	-	682	-2	
Ipca Labs	665	-	-	665	+23	Financial year ended 31 March 2020; converted from Indian rupees
Lannett	655	-	-	655	-4	Financial year ended 30 June 2019
Alembic Pharma	649	-	1	650	+17	Financial year ended 31 March 2020; converted from Indian rupees
Biocon	646	-	275	921	+15	Financial year ended 31 March 2020; converted from Indian rupees
Orion	605	455	117	1,177	+8	Converted from euros
Wockhardt	586	-	-	586	+6	Financial year ended 31 March 2020; converted from Indian rupees
Kalbe Farma	585	-	947	1,532	+7	Converted from Indonesian rupiah
Advanz Pharma	508	-	-	508	-5	
Bausch Health Generics	459	-	-	459	+11	
Adcock Ingram	408	-	4	412	+11	Financial year ended 30 June 2019; converted from South African rand
Strides Pharma Science	390	-	-	390	+26	Financial year ended 31 March 2020; converted from Indian rupees
Coherus Biosciences	356	-	-	356	-	
Natco Pharma	285	-	-	285	-9	Financial year ended 31 March 2020; converted from Indian rupees
Beximco	278	-	-	278	+29	Financial Year Ended 30 June 2019; converted from Bangladeshi taka

The top 50 ranking compiles sales data for 2019 – or the closest available reported year – for those firms for which generics and/or biosimilars is a major part of their business. This excludes companies predominantly focused on active pharmaceutical ingredients, some of which report sales totals that would otherwise be sufficient to be featured in the list.

It also means that firms such as Biogen – which markets biosimilars, but not as its primary focus – are not are not included, even though these figures would again be enough to otherwise put them in contention. Also excluded are companies that do not split out generics, biosimilars, APIs and OTC sales from larger units housing mature, often off-patent brands. For this reason, Abbott and its Established Pharmaceuticals unit encompassing branded generics operations in emerging markets is not in the list. We also do not include companies that do not disclose detailed sales information.

Sandoz Sees Revolution In US Biosimilars Market

Five years on from the first US biosimilar approval, the country's biosimilars market is starting to fulfil its potential, in part driven by a recent oncology "revolution" according to Sandoz' Sheila Frame.

BY DAVID WALLACE
EXECUTIVE EDITOR, EUROPE

In an exclusive interview, Shelia Frame, Sandoz US vice president for marketing, market access and patient services shared her thoughts on the journey taken by the US biosimilars market over the past five years, as well as the key developments on the horizon for US biosimilars.

Asked whether the US market was delivering on its potential, five years after the approval of Sandoz' Zarxio (filgrastim-sndz) , Frame said "I think in many ways it is. It's probably a lot slower than what we thought it was going to be when we first launched five years ago, but if you step back and look at the actual facts in the filgrastim market specifically, the latest IQVIA data from the second quarter of 2020 showed us at just a little over 50% market share."

Meanwhile, one of the earlier rivals to Amgen's Neupogen, Teva's Granix (tbo-filgrastim) – not approved under the Biologics Price Competition and Innovation Act pathway – was "probably sitting at around 28%-29% market share," Frame added, "so you have around 80% penetration. And then you have Pfizer in there as well."

"I think you have to ask whether 86% penetration in the marketplace at five years is something that you might expect. And in fact it is pretty consistent with what the experience has been in other countries, particularly in Europe which is roughly 10 years ahead of [the US]."

"So in that case you could say this is pretty good penetration," Frame commented, even though "it took a while."

However, not all biosimilars in the US had enjoyed similar success, she acknowledged. "I think the contrast in the US that has given a lot of companies pause is really in the case of infliximab, where I don't think they've even hit 10% penetration on biosimilars yet with three in the marketplace."

Nevertheless, recent indicators were more hopeful, Frame suggested. "This year, when you look at what I think is almost a revolution in oncology, with what's been happening with rituximab and bevacizumab, you're seeing really the fastest uptake we've ever seen."

"So it looks like oncology is definitely setting the pace and is being much more open to biosimilars," she observed, adding that "I think rheumatology is the big unknown right now."

INTERCHANGEABILITY AN 'UNNECESSARY HURDLE'

Asked about the main factors influencing this differing uptake in various treatment areas, Frame said there were a couple of key issues. "I think the first one is confidence among prescribers," she said. "So we have seen some misinformation out there, some suspicion on the part of prescribers as to whether they really buy into the concept of biosimilarity."

"If I was going to prioritize the marketplace, I think oncology is going to lead the way in the short and longer term." – Sheila Frame

"I also think the US has put in place a higher hurdle than other countries with the whole notion of interchangeability," Frame suggested. "I think that remains an unnecessary hurdle, at least based on what the experience has been around the world with that."

"A lot of it comes back to education – do the physicians really understand biosimilarity? – so we have done a lot as an industry I think to try and educate on what that is," Frame said. "And so has the FDA, they have certainly supported that."

The US biosimilar market also suffered from incentive mechanisms that did not always work well together, she suggested. "I think we have got incentives that are sometimes playing against each other, the financial incentives in the system. Rebates on the payer side certainly seems to have been one of the barriers in immunology … And then you've got some incentives around pass-through type situations on oncology that have actually helped biosimilars quite a bit."

"You've got some pros, some cons," she summarized.

"As an industry we've been pushing very much to adopt some of the incentives that have worked in the European systems, for example shared savings models where the system can actually reinvest the savings in better patient care," Frame noted. "We've advocated for an average sales price plus a higher percentage in the [Medicare] Part B space for physicians, to actually incentivize them financially to use a biosimilar and more quickly adopt it; and I think we probably would advocate something similar in the Part D space as we look to pharmacy benefits when the immunology space opens up."

Asked whether the biosimilars industry in general was currently behaving more like a generics model or a specialty model, Frame said "I think right now it's kind of its own dynamic. I think what you're seeing now is this blend of big pharma – obviously with Pfizer and Amgen deeply embedded in the marketplace they're playing like big pharma – and then you've got Mylan, Teva, Celltrion and others, Coherus, and ourselves, more with generic experience."

"With the people who have been in generics a long time, they say this feels like the small-molecule generic evolution of 15 years ago. But it's really going to be its own thing in the sense that we're trying to take the best of the generics industry and mix it with the best of the branded industry to come up with a model that provides broader access to more patients at an affordable cost."

COVID-19 CREATES OPPORTUNITIES BUT SHRINKS MARKET

Frame also observed that the COVID-19 pandemic had brought with it both tailwinds and headwinds for US biosimilars.

On access, she said that due to pandemic-related financial constraints "I definitely think that there's an opportunity to accelerate it … and maybe more of a sense of urgency to take a serious look at what the incentives could be, and how they could be set up in order to accelerate the uptake."

But "at the same time, COVID has created a situation where at least in oncology it would seem that patients are staying away from physicians' offices and I think that certainly new patient diagnosis is really down," she pointed out.

"So I think that's the piece that we just don't know yet. If people are staying away from treatment and diagnosis, then that shrinks your market at the same time."

STILL OPPORTUNITIES TO ACHIEVE GREATER SAVINGS

Turning to the savings potential of biosimilars – with biosimilar filgrastim alone having generated savings of more than $1bn – Frame pointed to opportunities to increase the savings from biosimilars even further in the US.

"I think it comes back to the system," she said. "I think in the context of the system in the US, [biosimilars] have been incredibly successful." But "I think it all comes down to the way that the system is currently set up."

The US system "favors the incumbent," she noted, "so the biggest market share if you're in a rebate system makes it very hard – if you don't have that forced conversion that you've seen in more socialized medicines systems – if you don't have that forced conversion quickly, then it's not economically feasible for someone to favor your biosimilar over the originator."

Pointing to possible legislative solutions, she said, "We'll have to see whether or not some of the discussions – I think there are five bills at the moment that include a biosimilar provision, whether it's shared savings or additional incentives – whether or not they can accelerate through Congress in order to open that up."

"At the same time," she said, "I think it's really important to look to the future. We have a number of biologics coming off-patent in the next five to 10 years, and I think that's where we're going to see the US market really open up."

Asked whether US intellectual-property protections for biologic brands were still a big part of the problem for biosimilars – with the industry in the past having pointed to "patent thickets" that were unfairly shielding major biologics from competition – Frame noted that the US system for IP was quite different to the rest of the world. "At Sandoz we've continued to be the major pioneer – we went all the way to the Supreme Court and won – and so we've started to chip away at what you might perceive as a barrier."

"But certainly, to try and open up the system more quickly we're continuing to challenge on the etanercept patent situation," Frame noted, referring to ongoing litigation over Enbrel. "And if we are not able to overcome that, then etanercept will have been in the marketplace for 30 years. Now there's not a patent system in the world that ever contemplated that kind of monopoly domination."

HUMIRA RIVALS HIT IN 2023

Looking ahead to key developments on the horizon for US biosimilars, Frame gave a positive overview. "We've got some data that would say that 1.2 million US patients could gain access to biologics by 2025, just because of the availability of the biologics that are going to biosimilars that will be available by then," she suggested. "And in particular, in the US at least, the patients that tend to benefit are lower-income, women and the elderly, so you're going to be able to provide access and benefits to people that otherwise would not have them. There's a huge opportunity just with the biosimilars that have been approved already."

And Frame highlighted the next wave for biosimilars. "You think about immuno-oncology as the big wave that will come off-patent in the 2026-2030 timeframe, then by then biosimilars will be much like what the generics market is. I think we'll see a significant portion of the marketplace being treated with biosimilars as they come into the marketplace, so I think that's pretty exciting."

And in the nearer-term, Frame said "I think the insulin market in the next two to three years might be very interesting to see what happens. [There is] a lot of legislative focus on that, a lot of patient need in insulin, so we'll see how that evolves."

"If I was going to prioritize the marketplace, I think that oncology is going to lead the way in the short and longer term, just because of the way in which those patents are coming off; I think immunology has started, with infliximab, and we'll see if etanercept actually wins, getting through the legal barriers – and then adalimumab (Humira) will be a huge boost in 2023 as there are nine or 10 all coming to the market at around the same time, so that will be very interesting; and then I think insulins in the shorter term; and ophthalmics in the longer term."

She concluded, " Then we'll see what happens as innovation continues. We certainly have a very broad portfolio in biosimilar development looking out towards 2030."

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COVID Brings CDMO Value, Strategic Partnerships Into Focus

The COVID-19 pandemic has brought into sharp focus the importance of an agile, reliable and efficient supply chain for pharmaceutical active ingredients and finished products. COVID-related supply-chain disruption has ranged from reduced patient access to clinical trials, to national lockdowns and border closures, raw-material shortages, or diversion of pharmaceutical funding and resources in health care systems.

In Vivo asked Stephan Haitz, president, CDMO sales and marketing for Cambrex, how the US-based provider of drug substance, drug product and analytical services for small-molecule therapeutics has leveraged its capabilities, particularly in breadth of service and speed to market, to ensure much-needed medicines reach patients in this volatile environment.

In Vivo: **In what ways have you seen COVID-19 disrupt the supply chain for small-molecule drug substances and products?**

Haitz: We do select our suppliers very carefully. What was really unprecedented for us was the closure of borders to people. And because people couldn't move across borders, there has also been a knock-on effect on goods. It actually left many of our suppliers helpless.

It put us in an extraordinary situation. It helped a lot that we had safety stocks and could reach out to various suppliers. But it was hard work for our supply chain, and also for our suppliers, to get us back on track. I think we are there now; we really feel comfortable with the current situation. However, it has been quite a shocking experience for the whole world that borders were closed.

How long do you expect this disruption to last?

Haitz: We have all found ways now to mitigate that. I do not expect us to have more issues with border closures in the supply chain. What we are now monitoring very carefully is a secondary effect: because of widespread COVID-19 infection, particularly in the US, there are workforce shortages, because staff are all quarantined.

We mitigate that through very clear, close and weekly communications with our suppliers, to make sure we know what their situation is and how operational they are. The border problems are now behind us and, until we have vaccinations, it is about monitoring the workforce situation at our suppliers.

Cambrex offers a broad range of services for small-molecule therapeutics, from R&D to commercial production, taking in active ingredients and finished products as well as associated analytical solutions. How has this breadth of offering helped Cambrex to mitigate the particular supply-chain challenges presented by COVID-19?

Haitz: There are three main factors here. We have multiple sites. We have a lot of resources and resource power available. And we also have a good number of experts helping us.

With the multiple sites, we have been able to move product within our network. To give an example, we have a site in Sweden. If we saw we were going to have a delay or something in Sweden, we would fill that slot in Sweden with another product that we produce in Charles City [US]. So, we really can make good use of our manufacturing network.

We do a lot of work around qualification of new suppliers. That is normal: when you take on new suppliers, you need to qualify them. You need a lot of analytical resources, which we have. But also, we have our own people in all the major markets: Japan, India, China. Despite the borders being closed, we have still been able to audit and qualify new suppliers, because we have local teams and local capacity. From that perspective, our broad reach has helped us to mitigate any supply-chain impact of COVID-19.

How does Cambrex's depth of experience in custom development and manufacturing of small-molecule therapeutics give it the flexibility to respond promptly to shifts in market demand under pandemic conditions?

Haitz: There was a race, and there is still a race, in the pharmaceutical industry to help societies dealing with COVID. The focus, as we know, is clearly on vaccination. But we should not forget the need to treat those who are already ill. So, there is a lot of demand for treatment, and our customers have really been struggling when it comes to speed and quality.

We need to employ new technologies, such as continuous flow [manufacturing], which has the benefit of not having to upscale. You don't need to go from 10 kilograms to as much as two tonnes: you just multiply it. We have to apply new technologies. We have to be very flexible, with a lot of skilled people.

What we have at Cambrex is a lot of strong scientific expertise, which enables us to partner with our customers. And what I've seen so far from our customers is that we've all learned to work together. There is a lot of trust. And I think the whole pharmaceutical industry is up to the challenge.

If you look at things now, the UK recently approved the first vaccine for COVID-19 [Pfizer/BioNTech's BNT162b2]. We are really meeting the challenge in the pharmaceutical industry.

You have already talked a little about multiple sites. Is there anything more you want to say about how Cambrex has leveraged its size and global presence in addressing these COVID-related challenges?

Haitz: Yes, it is about having multiple sites and a global presence. But it is also very important that we have our own audit teams for suppliers in the local countries. We are not using third-party vendors to audit; we have our own people. That means, for example, if there is a supplier in China, we give our Chinese team a call, and they can travel within a day and be on the site. That is where global and local resources come together. We are a global company at Cambrex, but we also have a strong focus on the local markets.

To what extent has COVID-19 simply aggravated existing pressures on supply chains, and how is Cambrex dealing with these?

Haitz: One broader trend I would like to highlight is that the industry was very much driven previously in the way the automotive industry was: we were a supplier, we had to be cheap, and we had to deliver just in time. I think that has changed now, along with the perceptions of our customers.

Our customers have realized now how much value reliable suppliers can create. I think also the element of trust in timing, and always choosing the cheapest products, most of our customers are reconsidering that approach. That's one change we are seeing.

The other is really that we're in partnership. I hear that much more when I speak to customers: that they want us to deliver expertise, and not only materials. With our scientific expertise here at Cambrex, we are very well positioned to harvest that trend, so we can support our customers even more.

So, you're talking about positioning yourself more as a strategic partner to your customers?

Haitz: Yes. In my view, that is where the trend is heading. You have to create value for your customers, and I think our customers now are more perceptive about value. A supplier creates value in multiple ways: not just the usual materials, but also the support we have available in development and ensuring high quality. As a broad company with an end-to-end offering, I think we are very well positioned to be that strategic partner for the pharmaceutical industry.

Are there any other significant market trends in small-molecule therapeutics you want to talk about, where Cambrex's particular capabilities give it advantages as an outsourced provider?

Haitz: What we provide, and what the COVID situation has highlighted, is that you need to have capacity. And you need to have spare capacity to react quickly. We have just invested 50 million dollars in expanding our capacity in Charles City. We are investing in capability expansion, like biopharmaceutical analytics at our Durham [US] facility. So, we do our bit to have the best expertise and capacity available.

We are also following trends, such as continuous flow, in the development of high-quality products. And then at Cambrex we can also help by covering the whole of development, from APIs to final products, along with release testing. So, for those partners who want it, we basically offer an end-to-end solution.

One other thing I would like to mention is that I think the public perception of our industry has changed. That's something that is really pleasant to see. Because we produce so many vital drugs. Yet we've also been criticized a lot in the last 10 or 20 years.

I think all the hard work by the hundreds of thousands of people in the industry is now being recognized by the general public. It's really good to see that we're getting more appreciation, which I believe we deserve, as value creators through pharmaceuticals. Faced with the COVID-19 pandemic, industry has risen to the challenge and delivered.

LUCIE ELLIS,
EXECUTIVE EDITOR, EUROPE

Building The Talent Pipeline Starts With Access For All

Diversity in all forms is critical to innovation in health care, says AstraZeneca's chief medical officer, Ann Taylor. She talks about the company's work in education, and why tackling issues around diversity and inclusion must be driven by the C-suite alongside community initiatives.

Ann Taylor, chief medical officer at AstraZeneca, has always been fascinated by the idea of using chemistry to answer biological problems. Her inquisitiveness about human health and the way things work in the body led her to medical school. She studied internal medicine, "because that covers all the organs of the body," before moving on to endocrinology.

Taylor, who joined the company in 2018, recalled in an interview with *In Vivo* that she was lucky to be based in Boston, "where I had exposure to some fantastic research and started to see the potential in putting research into clinical care." She moved on to become a clinical investigator. "I worked at Massachusetts General Hospital with NIH-supported grants in human physiology for many years." She began working with students, participating in mentoring and work experience programs. "We had a summer program for minority students, high school and college, to encourage them into medicine and then I also helped to support the house staff and residents in thinking about clinical research careers."

After having children, Taylor shifted to a career in the biopharmaceutical industry. "I started at Pfizer in early clinical development as a clinical lead. That was really an eye-opener," she said. "Doctors are taught to give orders. They are the ones that run the show and they tell people what to do. That does not work at all in industry, where we are collaborative, and everybody brings something to the table."

This collaborative approach has shaped how Taylor thinks about the broader pharma industry. After Pfizer, she joined Novartis. "I worked [at Novartis] for 10 years, leading the group in metabolism and then leading what was called the program office, in the project management portfolio, as well as the knowledge center and a couple of other educational functions." In these roles, Taylor focused a lot "on principles of good teamwork." She wanted to build teams that could get the best out of each other by working together. "This time was very influential to me."

DIVERSITY IN INDUSTRY

"Diversity of opinion and perspectives around the table makes a huge difference in the creativity, the novelty and the innovation that the team is able to bring," Taylor said. "If everyone is looking at a problem the same way, you get the same thing. You need people who come to the table and say 'Hey, I've got a different perspective – you forgot about me' or 'You didn't include this.'"

Taylor added that it is just as important for companies to think about where that pipeline of diverse team players comes from. "We realized that we needed to be active, going out there and reaching younger students of diverse backgrounds who might not have thought that they could be at the table. We want to help them realize it is not an unachievable goal to do science."

"I'm very proud to see that all the companies I've worked at and the ones that I interact with in multiple venues have significant interest in diversity and inclusion," Taylor noted. She highlighted two key issues for the pharma industry today:

1. unconscious bias; and
2. new ways to build a talent pipeline.

This is why STEM education is so important to Taylor. "We need to make the connections early."

Looking at AstraZeneca as an example, Taylor said there was great representation of women at high levels. However, she noted that data on racial diversity were lacking. "It is a challenge because of global laws. There is inconsistency, and in some places you cannot collect this information and privacy rules restrict us, so our data are not as great there." Taylor added that AstraZeneca has less diversity in age. "We have more older people and fewer younger people. Some of that reflects the experiences required, but we could do better there, and listen more."

AstraZeneca could also do more to address "neurodiversity, disabilities and other kinds of diversity." Again, gathering data in these areas is tricky. Taylor believes "this discussion will move forward when we have more data and metrics."

As CMO, Taylor easily drew comparisons in the office or lab to the diversity challenges in running clinical trials. "I also lead a large enterprise initiative to increase the diversity of participants in clinical trials. So, we have the same problem. I think what we're going to end up doing is finding some global way to talk about diversity that will work for both trials and employees."

C-SUITE RESPONSIBILITY

When it comes to addressing the issues related to diversity and inclusion in the biopharma sector, Taylor said change needs to be driven from the top.

ANN TAYLOR

"Certainly, from the bottom we're going to try to empower young students to demand access," Taylor said. She again drew a parallel with recruitment for clinical trials. Here the company is "trying to change the language around recruiting subjects for trials to not be 'We want to try to talk you into this' but instead focus on 'You deserve to be in the trial and you should ask for a trial and find a doctor who will put you in a trial if you need one.'"

Taylor expects to see a similar change of language in the corporate world, including in the pharmaceutical industry. More people will be able to say, 'I deserve a job in this field, I've done everything I need to do,' she believes.

"From the top down, though, you have to set goals; you have to expect people to be more open," she said. It is about "helping people to realize that a different way of looking at a problem shouldn't make them uncomfortable but should inspire them to think differently."

WORKING WITH THE NEXT GENERATION

Taylor highlighted that the concept of mentoring is important to understand when working in STEM educational programs. "Mentoring is not just about giving somebody advice, there are other aspects to it. One of these is modeling behavior of what it could look like to be in that job."

Another part of the equation is sponsoring. "You actually have to help your mentees; you have to suggest them for different opportunities and show them that they can do it. That was really impactful in my career and, as much as I grew up relatively privileged and had family members who encouraged me, I realized that many women and many under-served students don't have that."

Taylor recalled a bit of advice that her father gave to her, which she "rejected adamantly when I was young and brash." He told her to take advantage of connections. "I fought with my father about that, saying 'I am not going to take advantage of your connections – I'm going to do this on my own.'"

Over the years, though, Taylor realized how much these connections mattered, "alongside putting yourself in positions where you get to meet people." Even as an introvert, Taylor said it was critical for her career to have built up a strong network. "You can call people with a casual question; you can get advice on a lot of different things by having a larger network. I have found that over the years my network has been extremely helpful to my career and my productivity."

AstraZeneca has several informal and formal programs for mentoring and education. Taylor highlighted some of the key "community initiatives." For example, employees are given two days of paid leave per year for volunteering purposes. Taylor said many employees used this time to volunteer in the community in STEM-related areas. "Within AstraZeneca, we continually receive requests to engage in educational activities from our passionate employees that want to be STEM ambassadors in their communities," she said. "We take all of this as positive feedback that we are making a difference."

"We also have a couple of bigger programs. One is called the USA Science & Engineering Festival." For 2020, AstraZeneca had two virtual booths for the digital festival. These included a 'Girls In STEM booth,' which is part of a bigger national program. "It had thousands of students watching online this year."

The Girls In STEM program should have been in person, but Taylor cited it as one example of how mentoring and educational schemes could be adapted to meet the needs of students, despite challenges presented by the ongoing COVID-19 global pandemic. Originally the program would have reached around 600 students. Instead, the sessions were able to move online. "Each event was able to be recorded and watched in your own time. My understanding is that there have been thousands of students that have been able to participate. That's pretty exciting and actually shows the potential of new ways of doing things online." In Taylor's session, she ran a project about extracting DNA from strawberries. "You can actually do this with things that you have in your home, nothing fancy, and you come up with these great strands that almost look like dental floss – the DNA from a strawberry. So, it's pretty visual."

THREE KEY SKILLS

In giving advice to the next generation, Taylor cited three critical elements for future biopharma leaders: subject matter expertise, vision and teamwork.

"I had expertise in the neuroendocrinology of polycystic ovary syndrome before I started expanding into other fields. The reason for that expertise, in pharmaceuticals at least, is that you need to deeply understand the scientific process and be able to think like a scientist in terms of developing a hypothesis, and then designing an experiment to test the hypothesis, and then evaluating its results and figuring out what to do next. You need to understand that it's an experiment. You don't design it to get a good answer; you design it to answer the question."

Along with this, the next generation of leaders need strong visions and beliefs. "People need to understand what you're trying to accomplish and buy into that, and then you get a lot of support to go forward."

Finally, they must be able to work in a team. "You can still do that as an introvert," Taylor said, "as long as you are able to watch, observe and speak up at the right time when you need to provide your input."

JESSICA MERRILL
SENIOR EDITOR, US

Rebuilding Reputations: COVID-19 Presents A Big Responsibility And Opportunity

The global COVID-19 crisis has presented a chance for industry to improve its reputation by highlighting the value of its R&D engines. Pharma executives and observers outline why they are optimistic about a chance to regain public trust.

The pharmaceutical industry has found itself in a place few could have imagined at the start of 2020 – fulfilling the role of scientist hero, trying to end a global pandemic. The industry now hopes that if it is indeed successful at helping to end the global health crisis caused by COVID-19 through the development of treatments and vaccines, it will offset some of the bad press that has built over decades.

The rare chance for pharma to reset its reputation in the eyes of the public with the whole world watching has been on the minds of industry leaders as they navigate the unexpected and precarious path COVID-19 has taken.

Novartis AG CEO Vas Narasimhan called it a "remarkable, perhaps once-in-a generation opportunity" back in April during the company's first quarter earnings call. In interviews, many industry leaders and outside observers said they were cautiously optimistic that the industry's response to COVID-19 could create an inflection point in its interactions with the public. And they said industry's effort was motivated mostly by a genuine desire to end the pandemic – not commercial opportunity.

"Most of us got into this field because we were excited about the opportunity to make an impact on human health, and there are lots of other professions we could have chosen," Roche Holding AG CEO Bill Anderson said. "When something like this comes along, I have to say, I think people put away the calculators and think about 'Hey, what does our company want to be known for?'"

Industry's reputation problem has been earned over decades. In the 1980s, the fraud and corruption of the generic drug scandal cast a pall over the industry and while pharma came up with antiretroviral therapies for HIV/AIDS, it came under fire for how those drugs were priced. The blockbuster era of the 1990s that introduced drugs like Bristol Myers Squibb Company's Plavix, Merck & Co., Inc.'s Zocor and Pfizer Inc.'s Lipitor and Viagra had a massive impact on primary care, but the decade also came to be known for me-too drugs, pharma greed and marketing might that long impacted public perception of the industry. The 21st Century so far has been marked by major scientific advancement, but the high cost of drugs – and particularly a longstanding pattern of double-digit price increases – has left a lasting impression.

Changing the public dialogue around pharmaceuticals from prices and copays to science and innovation has been a top priority for the industry for several years now. But a safe and efficacious vaccine for COVID-19 could do what no Pharmaceutical Research and Manufacturers of America (PhRMA) Go Boldly advertising campaign could ever do on such a large scale – renew faith in maintaining a well-funded industry that can deliver valuable medicines in a crisis.

Some early studies have shown the public perception of the industry has improved, like the FutureBrand Index 2020 survey and study conducted in April and May – which showed health care companies gaining on perception and goodwill.

"I think trust is the foundation stone of the enterprise," Amgen, Inc. senior VP-global development Elliott Levy said. "For the biopharmaceutical industry, it is absolutely critical for the public to be able to trust in the quality, the safety and the efficacy of our medicines, and I think it is also critically important for them to believe that the sector as a whole offers benefit to the society. That is what ultimately justifies our patents, our pricing freedom, our competitive model. It is ultimately the belief that society benefits from all of that."

But winning over the court of public opinion for the long-term will not be easy and any positive uptick for the industry will have to be considered as one step on a longer recovery route. It will mean establishing trust with the public, sidestepping politics, being absolutely transparent about the safety and efficacy of new products, and not appearing greedy or cavalier when it comes to selling them. In other words, it will require not messing this chance up.

Some outside industry observers think it may already be too little too late. Peter Bach, the director of Memorial Sloan Kettering's Center for Health Policy and Outcomes and a frequent industry antagonist, said the public's concerns were too deeply seated to turn around because of COVID-19. "There are a couple of things that I think will prevent this from being a transformational moment for the industry," he said. "This horrendous reputation has been hard-earned by the industry for years and years, and it cuts across a bunch of dimensions."

A GOOD REP HAS ITS BENEFITS

There has never been a chance quite like COVID-19 for the industry to show off the power of its long-term investments over decades – in science, human capital, manufacturing and supply chain expertise. Industry hopes now to remind the public why those investments are valuable and that they may need to be deployed again in the future.

"It's the culmination of years and years of investment by so many across our industry," said Sanofi's Adam Gluck, who leads the company's external communications, including public affairs, patient advocacy and government affairs. "It speaks to the importance of maintaining, to continue to invest in science because you don't know what is going to come next, you don't know when it is going to come next."

PhRMA believes that reminder could even be helpful on Capitol Hill, where the debate over high drug prices in the US is being waged and various policy proposals are under consideration that would be negative for the industry. "I hope that through this process people have an appreciation for the fact that it isn't a given that companies can come forward and do this kind of work, but it really is dependent on the system that we have in place in the US today and it is a fragile system," PhRMA chief operating officer Lori Reilly said.

"The fact that we have a policy dynamic in place in the US that allows companies to go at risk, to take the kinds of necessary risks in the case of the global pandemic or multitude of other conditions, depends upon the ability to have a public policy environment that incentivizes innovation and entrepreneurship and risk taking," she said.

The industry is arguing that now is not the time to distract drug makers from the acute challenge at hand – ending the global pandemic. Industry would especially like to diminish political support for some of the harsher drug pricing policies that have been floated – like President Trump's "most-favored-nation" order, which would limit the amount Medicare pays for Part B and Part D drugs based on global benchmarks.

Trump has not entirely gotten industry's message, releasing four executive orders on drug pricing in July 2020 and a regulation almost on the eve of the November election. Pfizer CEO Albert Bourla spoke out against the exec orders during the company's second quarter earnings call in July, arguing, "They pose enormous distraction at a time where the industry needs to be completely focused on developing a potential COVID-19 vaccine or treatment."

House Democrats also convened a drug pricing hearing in September 2020 and called in several drug company CEOs to testify, but the hearing did not make big headlines, and several Republican members used pharma's COVID-19 response as an opportunity to show appreciation for the industry.

Some pharma outsiders think an improved reputation could help manufacturers beat back policy changes in Washington, DC, even if it is not necessarily a significant long-term boost. "An enhanced brand and reputation will have broader public relations benefit, and at a minimum reduce some of the distractions from management of having to battle back against political shots by politicians," PwC pharmaceutical and life science advisory leader Greg Rotz said. "When you are an easy target you have to spend more time defending yourself."

LOOKING BEYOND POLICY

Outside of policy momentum, there are other benefits a good reputation could deliver to pharma, like recruiting top talent and clinical trial awareness that could benefit trial recruitment and diversity.

Roche's Anderson said he was hopeful that widespread exposure to clinical trials and drug development would be positive for clinical trial participation among the public, including minority populations – where the industry recognizes it has even more work to do to rebuild trust. "Clinical trials and recruitment, all of that kind of thing, now that has gone mainstream. It's on the front page of USA Today, so it's possibly a unique opportunity to highlight to people the important role that clinical trials play," he said.

A better reputation could also help recruit more talent to the industry. As PwC's Rotz said, "Highly specialized talent in data analytics have multiple choices on what they can do in their careers and it is more attractive to work for an industry that is held in high regard," he said.

CAUTION AHEAD

It appears increasingly likely the industry will be able to bring to market novel treatments and vaccines for COVID-19 beyond the initial rounds of treatments like Gilead Sciences, Inc.'s Veklury (remdesivir). In November, both Eli Lilly & Co. and Regeneron Pharmaceuticals, Inc. were granted emergency use authorizations (EUAs) for antibodies to treat COVID-19. Regeneron's antibody cocktail has had a particularly high profile after it was given to President Trump when he was diagnosed with COVID-19.

On the vaccines front, Pfizer, Moderna, Inc., AstraZeneca PLC and Johnson & Johnson are all progressing quickly. It is an exciting time but one with perils too – for example, if the efficacy disappoints or the safety becomes an issue.

"I think it offers a tremendous opportunity, and with every opportunity comes a risk because the public has a certain view of what a fantastic outcome would be whether it's a vaccine or a treatment," cautioned Steven Pearson, president of the Institute for Clinical and Economic Review (ICER), a non-profit drug pricing watchdog.

As has been the case with Gilead's antiviral Veklury, early promise has not necessarily delivered the long-term efficacy data some were hoping for, though the drug is already on track to become a fast blockbuster. Veklury was first approved under an EUA in May based on limited data that it could shorten hospitalizations. However, a large-scale open-label study by the World Health Organization of repurposed drugs for COVID-19 found remdesivir did not improve survival, raising more questions about its value.

There are no guarantees the new products being developed for COVID-19 will be safe and efficacious across the board, and there are plenty of other risks for the industry ahead – including negative perceptions that could materialize longer-term around the cost of vaccines or treatments, product safety or politics.

LEADERSHIP

ALEX SHIMMINGS,
EXECUTIVE EDITOR, EUROPE

Sanofi's Berger On Creating A Sleek R&D Engine Fit For Purpose In The 2020s

A change in direction for the French firm means a new approach to R&D. Sanofi's global head of development and chief medical officer Dietmar Berger talked to *In Vivo* about what was needed to get the company's R&D machine back on track.

If you want to make a statement of intent, dropping R&D in an entire therapeutic area for which your company is renowned is guaranteed to work, even when the writing had been on the wall for some time.

Sanofi's decision in 2019 to exit diabetes research was the starkest manifestation of the major changes its new CEO Paul Hudson was bringing to the floundering French major. Hudson has no intention of being hidebound by historic R&D successes, such as the long-acting insulin Lantus, and following some lackluster performances of newer cardiovascular products like Praluent (alirocumab), he has turbocharged the company's move towards specialized fields of immunology and oncology spearheaded by the anti-inflammation biologic Dupixent (dupilumab). In doing so, Hudson is not so much turning a supertanker as trying to helm a speedier, more agile sort of craft.

The confirmation of Sanofi's diabetes exit came as Hudson outlined his new growth strategy to investors in December 2019, just three months after taking over from former CEO Olivier Brandicourt.

Alongside Hudson as global head of development and chief medical officer is Dietmar Berger who, following a sojourn in biotech at Atara Biotherapeutics, returned to big pharma in May 2019, just a few months ahead of Hudson's arrival. At Sanofi, the former Roche/Genentech executive is once again working with global head of R&D John Reed, who also came to the French group via Roche. Together they are playing their part in turning around Sanofi's fortunes and navigating the knock-on impact this is having on how the company's R&D operation functions.

Berger spoke to *In Vivo* about the changes he has seen even in the year or so since his arrival at Sanofi, "in my view, to the right direction." The most fundamental shift for the French major is the pivot from primary to specialist care.

The decision to switch directions lay with the realization of where the greatest patient needs lie, Berger said. "Yes, there's need in primary care as well but primary care patients are very well served at this point, and when you think about the needs in oncology and immunology,

DIETMAR BERGER

in neuroscience, in hematology, that's where I believe really large unmet medical needs are, that's also where I believe the large scientific advancements are."

These areas are where the newly focused Sanofi R&D machine is directed. The company has earmarked for special attention six pipeline products that span them, and they are also where Sanofi is aiming the cutting-edge drug discovery prowess of its novel platform technologies. Chief among these are the nanobody multi-specific antibody technology gained via its 2018 acquisition of Ablynx, and the Synthorin synthetic biology platform from the Synthorx buy the following year. These are soon to be augmented by Principia Biopharma, which Sanofi bought in August 2020 to further strengthen its autoimmune capabilities, and Kiadis, for which Sanofi has made a bid for its allogeneic or 'off the shelf' NK cell technology platform for immuno-oncology.

But what does the change in focus mean for how R&D is done at Sanofi? Mainly, Berger said, the company is having to up its pace. "You're developing in a different way." Out are the lumbering 20,000-plus patient cardiovascular trials in favor of the smaller, shorter and altogether nippier studies found in cancer R&D – it is a "different type of machinery," he said. "You define your new target, you work with much, much smaller studies, you work with decision making that's much faster, so you also need a different organization."

Cardiovascular development aiming to demonstrate small differences over the long term requires "large studies that you kick off and then you just move them forward. Whereas, when you think about oncology or hematology, you work in a very rapidly advancing field of science. You have to be able to react in a nimble and agile way to new information that's coming out at an ASCO or an ACR [clinical] meeting," he said.

"You're also usually in rather competitive environments," Berger continued. "You look at a new biology being described, and then within six months to a year, there are numerous agents that are trying to address that biology. So now, suddenly, you need to be very fast."

He cited as an example the rapid progress of the investigational brain-penetrating BTK inhibitor SAR442168 for multiple sclerosis – one of the company's 'six' – which was "unprecedented at Sanofi." The Principia buyout will give Sanofi full control of this asset. The Phase II study for '168 was done using a different design "that's about a year faster than what you usually see. Then between the Phase II readout and the start of the Phase III, we just had four and a half months," Berger noted.

"You can see how that requires different decision making, requires a different set-up for your operations group, requires different integration between operations and science, requires a different integration with manufacturing. So, there's all kinds of steps that you need to take in order to reshape the company."

In cancer, where the company recently made its return to the field with its anti-CD38 antibody, Sarclisa (isatuximab), he said the firm was learning how to negotiate the more complex development pathways required. The product, Sanofi's first novel anticancer to be developed entirely in-house in 10 years following Jevtana (cabazitaxel), was approved in March 2020 for use in relapsed/refractory multiple myeloma.

Multiple myeloma is a hugely crowded market dominated by Johnson & Johnson's $3bn anti-CD38 drug, Darzalex (daratumumab), and with a new class of BCMA-targeting drugs in the offing being quick-footed in developing the product for use at earlier stages of the disease is a necessity. The aim is to move step-wise until the early, smoldering stages of the disease are reached where the hope is to cure patients, "an entirely new paradigm shift," Berger said. "And you learn as you go, you try and take your decisions quickly, and you work not only internally, you work with external partners, and you change your approach based on what you see in the environment, [which] with myeloma is very dynamic," he said. "It's a very different feel compared to a program that is run for a long time."

CLOSER INTEGRATION

The skills being mastered in the process are helping in another dynamic environment: the fight against COVID-19. In the quest to develop a successful vaccine, Sanofi is using both its established baculovirus vaccine platform and, with partner Translate Bio, a novel mRNA vaccine approach, "which it is good to gain experience with." A similarly quick move to test its interleukin-6 inhibitor Kevzara (sarilumab) for severe inflammation seen in very sick COVID-19 patients did not succeed, however.

Such flexibility, Berger said, required much closer integration between research and development. In developing Sarclisa for multiple myeloma, for instance, it was necessary to distinguish between the antibodies produced by the diseased plasma cells and the antibody product being used to treat it. "You need an assay in research that can help you do that. Now you take the samples from your clinical trial and give them to the research group and say, 'Hey, can you do the assay for me?' And that type of integration is necessary in those disease areas."

The situation is similar in its immunology pipeline. "We're trying to understand type 2 inflammatory disease and we are working on what we call precision immunology, so that we can understand the immunologic patterns in individual patients, and then try and think about how can we utilize that knowledge then influence how we treat disease in that patient."

Sanofi's $10bn-plus mega-blockbuster ambitions for the IL-4/IL-13 blocking pipeline-in-a-product Dupixent are well documented. First approved in the US In 2017 for atopic dermatitis, the product has since gained expanded indications in asthma and chronic sinusitis with nasal polyps. Recent Phase III data show its potential in eosinophilic esophagitis and a decision has also now been made to pursue chronic obstructive pulmonary disease (COPD) too.

But this is not the end of Sanofi's plans for the product. "We then have two additional waves of indications in type 2 inflammatory disease that we're looking at," Berger said. "And if you look at each of those, again, we can have an approach that is actually very fast from decision making to study implementation, with similar timelines as you've seen for the BTK program."

While Berger would not specify the precise indications, the company has earmarked prurigo nodularis, chronic spontaneous urticaria and bullous pemphigoid as prioritized type 2 indications for Dupixent.

"That's a different way of developing because we're coming from an understanding of what is type 2 inflammatory disease, we're coming from disease biology, and from assumptions regarding what drives other types of type 2 inflammatory disease, and then we say, 'Does IL-4 or IL-13 play a role in those patients? Do we have any biology signals in that regard? Then let's go quickly into a development program' because we feel that patients can benefit."

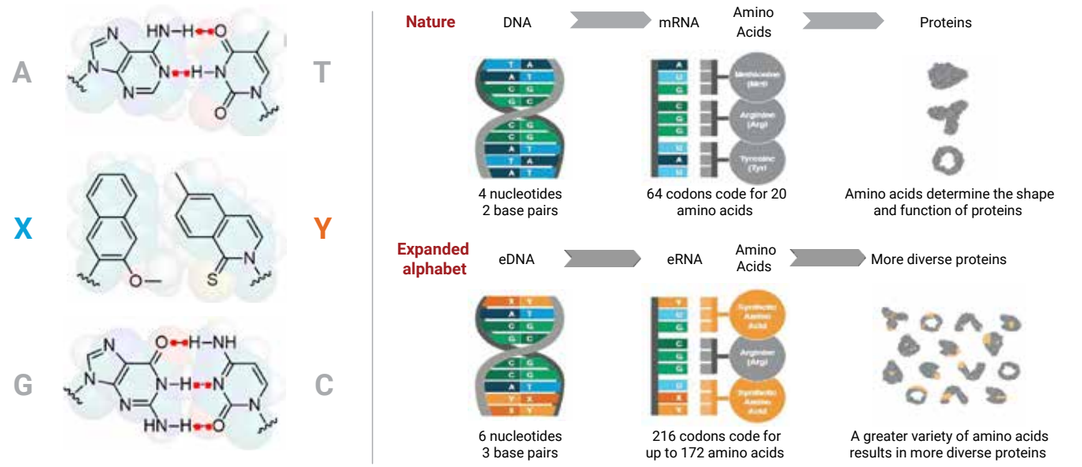
NOVEL TECHNOLOGIES

Fundamental to Sanofi's change of direction are its novel technologies obtained on the acquisition trail.

The purchase late last year of US biotech Synthorx was made to obtain its Synthorin synthetic biology platform that will now underpin Sanofi's immuno-oncology development goals. In addition to its PD-1/L1 inhibitor, Libtayo (cemiplimab) developed with Regeneron, Sanofi in the longer term is looking to its lead Synthorin product, THOR-707, to play a part in treating multiple solid tumor types both as a single agent and in combination with immune checkpoint inhibitors. To this end, it has just inked a deal with Merck & Co. to develop it in combination with Keytruda (pembrolizumab) in various cancers.

The Synthorin synthetic biology platform expands the genetic alphabet through the creation of a new DNA base pair to add to the A-T and G-C couplings found in nature. The new base pair, dubbed 'X' and 'Y', means that the number of amino acids that can be coded for shoots up from the usual 20 to 172, giving a wealth of new options

Synthorin Platform: Expanding The Genetic Alphabet To Generate More Diverse Protein Drugs



Source: Sanofi

that allow for a high degree of fine tuning of the shape and thereby the pharmacological properties of biologics (*see diagram*).

THOR-707 is a version of interleukin-2, a cytokine long approved for use in cancers. IL-2 has a variety of pharmacological effects borne out of the different ways it engages with its three receptor subtypes (α, β and γ), some of which are good for treating cancer and some of which are not.

On the plus side, IL-2 can induce the proliferation of tumor-fighting CD8 T effector and natural killer cells. Less helpfully, it can also promote the proliferation of suppressive CD_4 regulatory T-cells (or Tregs) and activate type 2 innate lymphoid cells and eosinophils which leads to eosinophilia, the driver of vascular leak syndrome. These unwanted effects are caused by IL-2 engaging with the alpha chain of the receptor, something that has led to a number of companies looking at 'not-alpha' IL-2 products, including Alkermes with ALKS-4320 and Roche with RG-7461, both in Phase II.

Sanofi's approach to the problem is to use the Synthorin technology to produce an IL-2 that has a new amino acid residue conjugated to a PEG molecule that blocks any engagement of the alpha chain of the IL-2 receptor without affecting its interaction with the other receptor subtypes.

"In immuno-oncology, one of the most impactful developments more recently was checkpoint inhibitors. What we don't have in the armamentarium at this point in time is something to further stimulate T-cells to prevent T-cell exhaustion, to stimulate T-cell proliferation, and then you can unleash those T-cells with a checkpoint inhibitor. To get to that T-cell response, that is where non-alpha IL-2 would be helpful," Berger said.

A second IL-2 variant, this time a "more-alpha" THOR-809, is also in development that has been fine tuned for reduced beta affinity for use in autoimmune disease. This selectively expands CD_{4+} regulatory T-cells, with no expansion of CD8+ T and NK cells, and is in preclinical development. Both products also benefit from an increased half-life and reduced immunogenicity risk thanks to their pegylation which cloaks the new amino acid from immune surveillance.

Berger said using synthetic biology to influence a protein's effects was "very elegant science" that could be used in tandem with Sanofi's nanobody platform, which it gained via the 2018 acquisition of Ablynx. "You can combine the two from a chemical perspective – you can use click chemistry and bring them together. So now you could literally merge some of the nanobody platform with some of the synthetic biology platform and we're also actively looking into those types of development," he said.

"So, we've not only acquired a very promising non-alpha IL-2, there's a portfolio behind that which I think is intriguing, largely for immunology, but potentially also for oncology. And then [we have] this platform technology which fits nicely into some of our other research activities."

But Sanofi's R&D ambitions do not all involve a break with tradition. Unlike diabetes, one heritage area that Sanofi remains wedded to is rare diseases, "a real commitment for Sanofi," particularly with its novel approaches in hemophilia and in gene therapy.

"Gene therapy is a very logical and important area for us to be in," Berger said. Initially, its focus is monogenic diseases in hematology, rare disease and potentially neurosciences. "That's why it's interesting for us, we are present in those areas, we understand the biology, we understand the patient and physician community. And that's where gene therapy can play a key role for us."

In another orphan area, lysosomal storage diseases, Berger said it was Sanofi's understanding of rare disease biology that could allow it to use the product to treat more common diseases. Another of its key pipeline assets, the glycosylceramide synthase inhibitor, venglustat, is being investigated in Parkinson's or polycystic kidney disease, he noted. It is this kind of marriage between Sanofi's past strengths and novel technologies that the company hopes will underpin its R&D transformation, and position the French firm for the future.

ANJU GHANGURDE,
DEPUTY EDITOR, APAC

Pharma CEO Pay Trends In India: What Lies Ahead?

In Vivo discusses dimensions around pharma CEO pay in India and whether it should be part of cost management efforts amid the pandemic.

C-suite remuneration across half a dozen leading pharma companies in India inched upward in 2019-2020, with CEOs and managing directors of local firms continuing to draw larger pay-outs overall versus their counterparts in foreign listed entities.

But with the coronavirus pandemic clouding broader business outlook, pharma, like other industries, is keeping a tight grip on costs. *In Vivo* discussed the touchy issue of whether CEO pay thresholds need to form a key part of pharma's cost management efforts in India, though unlike many other sectors most drug makers have had a reasonable run, at least so far, amid the upheaval.

Data on some of the frontline listed companies compiled by *In Vivo* (*see Exhibit 1*) show that Cadila Healthcare's MD Sharvil Patel, who is the son of chair Pankaj Patel, led the earnings chart by a significant margin over his peers, taking home INR250m ($3.4m) in 2019-2020 – though his salary remained unchanged from the previous year. Significantly, Cadila executive director Ganesh Nayak, a long-serving company official, received remuneration of INR278.9m for the financial year ended 31 March, 2020.

GlaxoSmithKline Pharmaceuticals India's outgoing MD, Annaswamy Vaidheesh, drew the highest salary among the foreign firms on the list but the executive's emoluments included retirement benefits and a "share value plan" paid in May 2020. Vaidheesh retired in March 2020, with Sridhar Venkatesh taking over as MD from 1 April.

Cipla Limited's global CEO Umang Vohra is the only executive on the list who reported a decline in salary in 2019-2020 versus the previous year. And Sun Pharmaceutical Industries Ltd. founder and MD Dilip Shanghvi took home the least compared with other local CEOs.

The higher earnings of MDs/CEOs at leading Indian firms compared with the bosses of foreign companies come with a caveat – some local firms, in which the founding group is also the largest shareholder, are led by members of the founding family and a comparison of their remuneration with peers at foreign entities may not entirely be like-to-like. That is not to take away from the fact that scions at the helm of most family-controlled Indian firms are seasoned and qualified for the top job.

There are some other considerations for the data. Large multinationals like Merck & Co Inc., Eli Lilly and Company, Johnson & Johnson and Roche Holding AG whose operating firms are unlisted in India are not covered. Besides, top-level executive changes at some foreign firms – for instance Novartis's new MD took charge on 15 June 2019 – have meant that some of the remuneration figures are not for a full 12-month period, and some CEOs may receive stock options directly from the parent firm which is not typically reflected in the local annual report.

FREEZE CEO PAY HIKES?

While CEO pay in India has been generally buoyant in 2019-2020, industry pundits appear divided on whether remuneration for top leadership needs to stay static at least in the upcoming year in the unpredictable operating environment caused by COVID-19.

Prabir Jha, ex-global HR head of companies including Dr. Reddy's Laboratories Ltd. and Cipla, said that CEO compensation in the pharma industry has mirrored the need to upgrade the quality of talent, given a historical "lower talent quality" for leadership roles. The need to attract and keep such niche talent in a "hyper transforming" industry will demand the rewards philosophy to mirror it. Companies, he noted, were open to hiring from beyond the industry and to paying even for the 'individual' brand.

"Rising private equity interest in smaller pharma firms has also made options available to leadership talent like never before. I do not think executive compensation is likely to see any major dip in the near term, when the market actually presents some generational shifts," said Jha, founder and CEO of Prabir Jha People Advisory.

Some experts, though, said that much will depend on how well the pharma sector fares during the pandemic; it has a critical role and is seen as an "essential sector" to the economy, particularly to ensure the health and well-being of the country. And to that extent pharma is different from the hospitality or the travel industry where pay cuts have become necessary due to the revenue hit.

"If pharma CEOs are asked to deliver a greater amount of innovation to drive their business, then hikes in compensation are justified, particularly if CEOs can demonstrate continued growth and sustainability during difficult times," Dr. Davinder Gill, ex-CEO of Hilleman Laboratories, an equal joint-venture partnership between Merck & Co. Inc. and the Wellcome Trust, told *In Vivo*.

Similarly, Dr. Ajit Dangi, president and CEO of Danssen Consulting, maintained that unless a firm is doing

LEADERSHIP

Exhibit 1. C-Suite Salary Packages, FY 2019-2020

COMPANY	CEO/MD	SALARY FOR 2019-2020 (INRM)	INCREASE % (APPROX.)	RATIO OF CEO REMUNERATION TO MEDIAN EMPLOYEE REMUNERATION
GSK India	A Vaidheesh[1]	127.4m	7	105.8
Abbott	Ambati Venu[2]	71.5m	10	90.9
Pfizer India	S Sridhar	41m	13	43.4
Sanofi India	Rajaram Narayanan[3]	38.4m (for year ended Dec 2019)	8	65
Novartis India	Sanjay Murdeshwar[4]	7.2m	NA	(see note[5])
Cadila Healthcare	Sharvil Patel	250m	Nil	577.4
Aurobindo Pharma	N Govindarajan	168.87m	15	341
Dr Reddy's	GV Prasad[6]	143.76m	16	283
Cipla	Umang Vohra	135.7m	-10	378
Lupin	Nilesh Gupta (MD) Vinita Gupta (CEO)	59.68m 128.28m	NA[7] NA[7]	130 280
Sun Pharma	Dilip Shanghvi	32.6m	NA[8]	64.65

"extremely badly," there is no reason for CEOs of pharma companies in India to be open to pay cuts, as they strive to deliver their key result areas (KRAs) in extremely challenging times during the pandemic. "India is a highly taxed country and the take home pay of most Indian CEOs is significantly lower than the CEOs of the 100 FTSE companies. What one could consider, however, is voluntarily freezing CEO pay till we are out of the woods," said Dangi, a former president and executive director of Johnson & Johnson in India.

Others argued that extraordinary times require extraordinary leadership and extraordinary leaders do not need to be told to consider "lesser/more moderate" rewards and compensation when there are large-scale layoffs or hardship in general within the organization. "While pharma still hasn't seen much of layoffs, it doesn't seem insulated from the possibility. CEOs will always be open to pay cuts given a bad year for the organization," Salil Kallianpur, a former executive vice-president at GlaxoSmithKline plc in India, who now runs a digital health consultancy, explained.

In India, pharma appears less impacted, with organizations leveraging portfolios well (over-the-counter, chronic brands), while others launched very "timely" products – such as remdesivir, favipiravir and hydroxychloroquine – and have more or less managed the balance sheet better than CEOs in "less fortunate" industries, Kallianpur said.

Data from the market research organization AIOCD AWACS indicated a bounce-back in September 2020 of the Indian pharmaceutical market, which registered a growth of 4.5% (on a moving annual total basis growth was at 3.5%). Some therapeutic segments such as cardiology and diabetes reported robust growth over August, the data show.

'EVERYONE IS TAKING A HAIRCUT'

Others were, however, less definitive on the need for C-suite pay hikes, noting that these are "unparalleled times requiring unparalleled solutions" and if business performance is impacted going forward then this should reflect in the compensation of the CEO and senior management.

"Most businesses are less likely to go back to previous growth levels in 2021, so at the minimum there should be no salary increases and if staff are being laid off then the principles of fairness and equity dictate that CEOs lead the way with a visible salary cut," the ex-chief of a foreign firm told *In Vivo*. The executive, who sits on the board of various firms in India, also noted how some of the sectors that have been hit hard have shown the way, with India's Tata group, among others, reported to be effecting a 20% salary cut at the senior management level.

He does not anticipate major pay cuts in pharma but equally suggests "very limited" or no pay increases. "Everyone is taking a haircut and the pharma industry cannot sit on the perch with the excuse they will lose talent. In many companies while the directors took their sitting fees, they gave up their commissions fully or 50%," the expert added.

A recent report by the UK-headquartered CIPD on FTSE 100 index CEO pay in 2019 and during the pandemic indicated that 50 firms paid less to their CEOs in 2019 than in 2018, with the number of companies with CEO pay of over £10m down from eight to six. As of 3 July, 2020, 36 firms had cut CEO pay due to the impact of COVID-19, with measures ranging from temporary deferral to the reduction of salaries, as well as the cancellation of bonuses, said the report by the professional body for HR and people development. The companies that made pay cuts were predominantly in some of the hardest hit sectors such as retail, hospitality, construction and manufacturing, as well as banks and other financial services.

FLOOR AND CEILING FOR SALARIES

Meanwhile, the India data also show that the ratio of remuneration of CEOs to the median remuneration of employees in the firms reviewed is rather sharp.

HR strategist Jha explained that these sharp ratios are a trend across industries and geographies and there is an "emotive and popular angle" to the debate. He believes it is up to each company to decide where the "economic value add" really gets most differentiating. "A top-quality CEO or management team should help the company deliver significantly superior results, enabling it to also improve median compensation significantly, irrespective of the inter se ratio," he said.

Companies need to make their offering attractive enough to get the right CEO but at the junior and middle levels, they have relatively more latitude. Compensation practices today reflect just this reality of demand and supply, he added.

Danssen's Dangi, however, believes that the high ratio is certainly not a very healthy sign, noting that India is a middle income country and "we don't have to follow global trends" particularly like in the US, where the market caps of some companies have crossed the GDP level of some low- and middle-income countries. Apple for instance touched $2tn in market capitalization in August 2020.

Kallianpur explained that while CEOs must certainly receive remuneration according to the role, responsibility and status of the positions they hold, commanding a differential of 300-600 times is "ridiculous."

"One may rationalize that CEO salaries are influenced by global levels while salaries in lower ranks are influenced more by local conditions, but reports show that some British and American CEOs earn 331 times that of median salaries in their organizations. Indian companies certainly don't seem very different," Kallianpur observed.

The CIPD report said that the median FTSE 100 CEO reward package is 119 times the median UK full-time worker salary of £30,353 and 145 times the median salary of all UK workers (£24,897).

Hilleman's Gill suggested that despite the large gap between the "top and the bottom" level salaries, it is important for organizations to establish a "floor and a ceiling" based on their respective business. "This way, the organization can ensure no employee will fall below the floor – which should be a healthy compensation enough to support the employee and their family, irrespective of job designation – and that no CEO, no matter how well they might have performed, will cross a ceiling that is consistent with company values and market dynamics."

Nevertheless, most experts see little reason for top executive pay to be set in a more democratic fashion, for instance with the company's workforce given the opportunity to feed into the process, via an employee representative on the remuneration committee (RemCo), as suggested by CIPD.

Gill noted that the pandemic has thrust into focus the importance of issues such employee welfare, societal good and environmental sustainability and therefore, it will be necessary for RemCos to factor in these metrics in determining CEO compensation as opposed to largely basing it on company bottom line. That said, the process "cannot be democratic," he asserts.

"At the general employee level, awareness of the complexity of running a business and the challenges associated with it, does not necessarily exist. And therefore, inclusion of an employee representative could jeopardize the process by given it a 'popularity-based' versus a merit-based approach," he said.

Jha neither supports nor sees a need of a workforce union representation on the RemCos of boards. He explains that growing HR maturity of pharma firms has meant more "real-time benchmarking" of compensation, though the final call is both a function of a firm's chosen rewards philosophy, which is very scattered in Indian pharma, and its ability to attract and retain the talent it needs.

"The affordability of talent is a two-way street and both companies and individuals do what is best for them. Let the market determine it for both the individual employee and the company, though I think many companies need help to think differently in this space," Jha said.

Others underscore that the role of the board and specifically those of the independent directors on it is to represent society at large – they are meant to be the voices that "balance" an organization's ambition with social need, its focus on customers, culture, diversity and the environment. "Organizational culture, fairness and wider workforce reward policies should come under their ambit as well," ex-GSK executive Kallianpur said.

A senior industry executive noted that in general remuneration committees in India have been performing their role as per law, but whether you get a "pragmatic 360-degree view" even from other parts of the organization would differ across organizations. Factoring in broad-based feedback is perhaps more important in the Indian context, which rarely sees the kind of shareholder activism as in the US, where hedge fund representatives flag up prickly issues including CEO pay. "The level of fiduciary governance and expectations in the West are of a different order and we are lagging. The environments are quite different," the executive added.

While a dramatic change in the trajectory of C-suite pay in India in the short-term may not be on the cards, leadership with compassion, perhaps forgoing some benefits temporarily, could set the bar higher and perhaps also help safeguard some jobs at the lower rungs if things take a turn for the worse.

EDITORIAL NOTES:

[1] Annaswamy Vaidheesh retired as managing director of GSK India from 31 March 2020; the outgoing MD's remuneration includes retirement benefits and a "share value plan" paid in May 2020. Sridhar Venkatesh took over as MD effective 1 April 2020.

[2] Ambati Venu was managing director of Abbott India up to 29 February 2020. Anil Joseph was appointed as Managing Director effective 1 July 2020.

[3] Sanofi India does not have a scheme for grant of stock options. However, the managing director and whole time directors and some senior executives of the company are granted stock options/performance shares of the ultimate holding company, Sanofi SA. The amounts accrued in the financial statements for the year ended 31 December 2019 for stock options/performance shares granted to Rajaram Narayanan was INR9.6m.

[4] Mr. Sanjay Murdeshwar took over as vice-chair and managing director of Novartis India with effect from 15 June 2019; Value of perquisites u/s 17(2) Income-tax Act, 1961 excludes charge in relation to restricted shares and tradeable options to the extent not vested.

[5] Novartis's annual report indicates that information required pursuant to Section 197 of the Companies Act, 2013 read with Rule 5 of the Companies (Appointment and Remuneration of Managerial Personnel) Rules, 2014 in respect of employees of the Company, will be provided upon request. In terms of Section 136 of the Act, the Report and Accounts are being sent to the members and others entitled, excluding the information on employees' particulars, which is available for inspection by the members.

[6] GV Prasad is co-chair and MD of Dr Reddy's; Erez Israeli, previously COO, was appointed CEO effective 1 August 2019, with a remuneration of INR195.32m for FY2020; Prasad's remuneration includes commission, salary and perquisites. Commission for FY2020 will be paid in FY2021.

[7] Vinita Gupta and Nilesh Deshbandhu Gupta opted out of receiving any remuneration for the one-year period from 8 August 2018 to 7 August 2019, hence amounts for the current year and previous year are not comparable. Vinita Gupta is an employee of Lupin Management Inc, USA, a wholly owned arm of Lupin.

[8] The increase in remuneration of Dilip Shanghvi for FY2020 and FY2019 are not comparable as the salary drawn by him in FY2019 was INR1 (excluding notional perquisite amount of INR262,800).

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SARAH KARLIN-SMITH
SENIOR WRITER, US

Drug Discount Programs Create More Cloud In Quest For Transparency

Drug discount programs such as GoodRx have become popular in the US, and routinely criticize soaring list prices. Yet behind them are pharmacy benefits managers and even drug companies themselves. So, are they helping to drive down costs, or just another player in an opaque system facilitating higher US drug prices?

Since 2011, GoodRx has operated a web- and mobile app-based business that lets consumers search for the best cash-based deals on prescription drugs. Enter a drug name and zip code, and voila, you get a list of nearby pharmacies and the discount that GoodRx coupons can get you on the product at various locations, including via mail-order.

The aim is typically to help uninsured patients or those in high-deductible health plans access drugs at more affordable prices than paying the pharmacy's cash price. And in some cases, these businesses say a consumer might even be able to get a lower price than their insurance copay.

The use of GoodRx and similar services are growing. The National Community Pharmacists Association told *In Vivo* they had seen around a 15% uptake in these types of coupon services between 2019 and 2020.

On 28 August, the nearly decade-old business filed an S-1 form with the US Securities and Exchange Commission in preparation to take the company public, indicating that GoodRx's business had experienced a compound annual growth rate of 57% since 2016, reaching $388m in 2019 up from $250m in 2018. Ninety-four percent of that revenue, or $364m, came from prescription transactions fees in 2019 that the company receives from PBMs.

GoodRx regularly puts out reports on list price increases and the most expensive drugs in the US, which they feed to media outlets, generating a significant amount of criticism directed toward the drug industry. "Drug prices have increased faster than any other commodity ... Since 2014, prescription drug costs have risen by 33%, far outpacing goods, and services like food, utilities and public transportation," one recent report reads.

The recent S-1 form constructs a narrative of a company that works to protect Americans from these prices. "We can reduce the cost of virtually every generic and brand prescription by more than 70% off the list price, resulting in a price that's often less than a typical insurance copay," co-founders and co-CEOs Doug Hirsch and Trevor Bezdek wrote in a letter in the S-1 form.

GoodRx claims to shed transparency on a cloudy business and help people get a better deal. To an extent they do help some consumers – but they also profit off the cloudiness of the system and the high list prices as well.

That is because GoodRx relies largely on pharmacy benefits managers (PBMs) to offer discounted prices. Academics have documented that much of the growth in list drug prices faced by consumers is "due to increased payments to intermediaries in the market (PBMs and distributors)," wrote Emery P Weinstein of Columbia University and Kevin Schulman of Sandford in a September paper for the American Heart Journal, which updated their past research on the role of PBMs. More than two-thirds, 67.4%, of net revenues from 13 drug manufacturers, or $141.4bn,went to intermediaries in 2019, they found. In 2011, the same 13 manufacturers only made payments to intermediaries that totaled 29.2% of net revenue.

List price increases and payments to intermediaries are growing disproportionately to manufacturer net income, Weinstein and Schulman found.

The prescription transaction fees the company collected last year represented about 15% of the total consumers using GoodRx's program spent on drugs in 2019, Adam Fein, CEO of Drug Channel Institute wrote. Fein, who consults for drug companies, assumes that PBMs are earning more than what they pay GoodRx.

"It really is the sort of PBM style model, they're just playing that arbitrage in a different way," said Sean Dickson, when considering the approach of GoodRx and similar services, such as RxSaver, Optum Perks and Inside Rx. Dickson is director of health policy at West Health, a group of three-nonprofit organizations funded by former telecommunications executives turned philanthropists Gary and Mary West with the goal of lowering US health care costs.

For years GoodRx's private status has made it difficult to fully penetrate their business model, leaving it shrouded in the same secrecy that surrounds much of the drug supply chain. But interviews with drug pricing experts and the newly filed S-1 form helped illustrate the extent to which the company is reliant on the current drug pricing system they criticize.

GoodRx works with PBMs to tap into their already existing negotiated agreements on drug prices with pharmacies and manufacturers that bring prices down below the cash price a pharmacy would otherwise charge a consumer without insurance – often known as the usual and customary rate. It has created a marketplace where PBMs can compete for business from consumers by looking at the GoodRx data which directs them to the PBM and pharmacy combinations offering the lowest price for a drug.

PBMs charge a transaction fee to the pharmacy each time one of the GoodRx coupons is used and GoodRx shares in that fee. The majority of GoodRx's contracts with PBMs provide that GoodRx makes a percentage of the fee PBMs charge the pharmacy. The GoodRx website indicates they make money from advertisements on their website and "referral fees," but the average consumer is unlikely to understand how this is tied to PBMs and other supply chain intermediaries pocketing some of the money baked into a drug's price.

"They are able to leverage some of the purchasing power that the PBMs have. Because the large players represent such large numbers of people and patients than they might be able to get access to lower priced drugs than one would get if they just walked up to any brick and mortar pharmacy," explained Jing Lou, an assistant professor of medicine at the University of Pittsburgh's Center for Pharmaceutical Policy and Prescribing.

Pharmacies usual and customary price is typically set higher than the average wholesale price, to give them negotiating leverage with PBMs. Pharmacies usually cannot just lower the usual and customary price for cash paying patients because it would violate their agreement with PBMs, explained Jesse Dresser, a partner at Frier Levitt who focuses on pharmacy practices, insurance billing and PBM regulation. This creates an opening for services like GoodRx. "My understanding is they use PBM data to really drive a lot of the engine of GoodRx because pharmacies submit these absurdly high usual and customary prices to PBMs, which gives GoodRx the ability to come in much like PBMs do and say, 'We're saving you all this money,' when in actuality almost nobody pays those retail prices that are on the GoodRx website," said Antonio Ciaccia, the chief strategy officer of 3 Axis Advisors, a consultancy firm specializing in the drug supply chain. He formerly headed up government affairs for the Ohio Pharmacists Association.

GoodRx's S-1 form acknowledges that their "ability to generate revenue are directly affected by the pricing structure in place amongst" industry participants and that any changes in medication pricing and pricing structures could adversely impact their business. In particular, the company notes that the less money PBMs make, the less GoodRx makes as well.

"Changes in the fee and pricing structures among industry participants, whether due to regulatory requirements, competitive pressures or otherwise, that reduce or adversely impact fees generated by PBMs would have an adverse effect on our ability to generate revenue and business," the form adds.

While GoodRx says that most of its utilization is for generic medications, it does offer discounts on brand drugs as well. For brand drugs, it is unclear if GoodRx also shares in the rebates PBMs receive from drugmakers. On the patient end, it is also not clear what portion of the manufacturer rebate would go to the patient, and what is kept by the PBM and GoodRx for the service.

Most outsiders assume the generic business is dominant because GoodRx does not have enough guaranteed volume to get the higher rebates PBMs might get on brands for their bigger clients. So consumers with insurance are likely better off going through insurance for brands, and consumers without insurance may still find the brands unaffordable even with GoodRx's PBM discounts.

To offer another way for consumers to access brand medications – which account for about 20% of the consumer searches on their platform per the company's S-1 filling – GoodRx has teamed up with drug manufacturers to advertise and integrate the company's copay coupons on their website. GoodRx receives money from the brand companies for directing consumers to these coupons, typically on a fixed-fee basis, they say. This revenue has more than quadrupled in the first half of 2020 compared to the same period in 2018.

These brand manufacturers coupons have long been criticized as a tool that allow list prices to remain high and also allow brand companies to direct patients to higher cost options when lower cost products may be sufficient.

A PRIVATE-SECTOR PATCH TO A PUBLIC-SECTOR PROBLEM

Most drug pricing experts agree that it is hard to completely criticize GoodRx and similar services. The businesses are putting medicines in reach of a particularly needy population of Americans. But the way they go about it is at best a patch on a broken system. "They advertise and they make more transparent that prices are really high. More people are out there going 'these prices are very high,' that's a good thing," said Mark Miller, executive vice president of health care at Arnold Ventures, who leads the philanthropy's work to lower the cost and improve the value of health care. And "in a very spot, one-off way they help some consumers," he added.

They "create some downward pressure on prices, let's call it list price in this instance. But keep in mind if they were successful at that, they'd be out of business. So, there's a little bit of an awkwardness in their model if you think about it," Miller said.

And "to the extent that we as a society engage in these marginal fixes that allow the manufacturer to have high launch prices and maintain high list prices, then we're perpetuting the system," Miller said, adding that this was not a direct criticism of these businesses. "It's criticism of the fact that Congress, the administration, we as a society, have not taken on the drug problem directly."

GoodRx exists, Miller argues, because of the market failure and the distortion between the list price a drug company places on its product and the net prices achieved by PBMs and other payers in the system. "They are kind of playing the edges of things ... You have this difference between list and net prices, which means that at any point of time even if you have insurance and show up at the counter, your copayment can be higher than what the ultimate net price of the drug is and so at the moment your ability to acquire the drug can be somewhat compromised."

"The growth of these programs show that we've had insurance designs that make life-saving medications inaccessible to people," said West Health's Dickson, but he added that services like GoodRx were "not necessarily consumer friendly," and "they're not certainly a systems level solution to our drug spending problem."

FRANCESCA BRUCE
SENIOR REPORTER, EUROPE

The COVID-19 Economic Crisis – Fallout And Opportunities

In the wake of the COVID-19 pandemic and the ensuing economic fallout, pharmaceutical companies could face a range of measures designed to cut government spending on medicines. From relaxing intellectual property rights to delaying reimbursement, *In Vivo* examines what might be in store for industry.

The global economic crisis triggered by the COVID-19 pandemic will undoubtedly put pressure on public spending and health care budgets.

The situation for many brings to mind the 2008 debt crisis and the slew of resulting European government austerity measures affecting biopharma, including price cuts, increased reference pricing, reimbursement controls, introduction of rebates and increased tendering. Whether European governments will respond with the same "blunt instruments" aimed at cutting drug budgets remains to be seen. The pharmaceutical industry's key role in developing COVID-19 products and in turn helping drive economic recovery may mean that cost-saving measures will be neither as immediate nor as harsh as they might have been otherwise.

Industry experts pointed both to interest in safeguarding R&D budgets, at least for now, and to what many see as pharma's improved reputation as factors influencing policymakers. At the same time, the pandemic may accelerate more fundamental changes in the health care delivery system that could eventually provide new opportunities for companies to show the value of their products.

Stephen Majors, director of public affairs at the Alliance for Regenerative Medicine, said the two economic crises are difficult to compare but in the pandemic "it has become increasingly clear that the rapid response of the biotechnology industry to create effective vaccines represents the best prospect for returning to economic growth."

The industry has demonstrated its value in bringing innovation by creating potential new vaccines and by repurposing older products, according to Alan Crowther, general manager of global pricing and access at the consultancy firm Eversana. "I don't think the public think this is a one-time event, they see this as an ongoing risk and recognize the value of the industry more, and that's an absolute positive for the industry," Crowther said.

Companies had enjoyed a "status as a key political interlocutor" during the crisis, said Yannis Natsis, policy manager for universal access and affordable medicines at the European Public Health Alliance. As such, he believes that governments will initially step back from very hostile or harsh measures while they face uncertainty due to the pandemic.

Natsis, who also sits on the European Medicines Agency's management board as a representative of patient organizations, said: "I think as long as the COVID-19 crisis persists, governments will think twice before challenging the industry."

Nonetheless, Natsis believes that a little further ahead, attention will shift to drug pricing as pressure on health care spending increases and as companies introduce more expensive drugs to the market. The debate about excessive pricing that had paused during the pandemic would reignite, he said, predicting that "the next insanely priced oncological product in the market" will move public opinion and turn decision makers against industry.

Michael Schröter, a founding partner at Swiss-based asset management firm Viopas, predicts that there will be an eventual impact on pricing and further restrictive measures. Health care budgets have been allowed to rise to deal with the crisis, but the extra demand on systems will hit those budgets very hard, he believes. "The only way for health care systems to deal with that kind of disconnect is to further squeeze the budgets and they will pass that on to their suppliers in the health care industry."

IMPACT AND MEASURES

Natsis anticipates initiatives that will keep prices lower and limit expenditure, including rebates and claw backs. "To some extent this will feel like déjà vu," he said. Several markets, including Spain, Italy, Greece and Portugal mandated several rounds of price cuts following the debt crisis of 2008.

However, this time around Natsis thinks there could be more flexibility for member states to choose cost-saving measures. With the last crisis, he pointed out, cuts in some markets such as Greece were heavily influenced by the Troika of the European Commission, The European Central Bank and the International Monetary Fund.

Crowther urged a long-term outlook when evaluating spending curbs. "Populist" measures such as weakened intellectual property rights and "blunt tools" like referencing pricing could do more harm than good by introducing long-term impacts to a short-term budget strain and eventually damaging innovation, risking employment and reducing the ability to respond to future pandemics.

More action was likely in those countries which suffered the biggest hit to GDP, Crowther noted. More significant measures in the reimbursement process are more likely in countries where budget impact is a bigger consideration, for example Spain, than in markets which conduct cost-effectiveness analysis, like the UK. These markets are likely to continue to approve product reimbursement under existing criteria.

Mechanisms that could be deployed include accelerated uptake of biosimilars and an increase in therapeutic class referencing, Crowther believes. He also expects that payers will delay reimbursement of some new therapies in an attempt to minimize budget impact. For example, products belonging to therapeutic groups where existing competitors are coming off patent may potentially be affected.

Companies could respond to these delays with more aggressive pricing policies to try and speed up price negotiations. "That's a difficult decision because you are affecting the price over the full life cycle of the product once you do that," Crowther noted.

Companies may face a trade-off between compensating for the lower price by trying to increase volume of sales and take share from competitors – assuming they have the evidence to support such a strategy. Alternatively, they could accept slower launch plans until economies recover fully, but recognize slower revenue growth over time as a result, if they want to maintain what they see as an appropriate price over the product life cycle.

Outcomes deals were also a possibility and could help payers defer costs further down the line to meet budget demands and help them see the value of the product, said Crowther.

ARM's Majors suggested that "innovative payment models will be attractive to governments and payers during a time of economic strain." ARM members were willing to "put reimbursement at risk" through such payment models based on whether their products meet pre-defined milestones in patients, he said.

Such agreements have helped bring high-cost medicines to patients in certain markets for some time but are now starting to emerge in others where they have not traditionally been used. The German insurer GWQ, for example, in 2019 announced an outcomes based deal it struck with Novartis over its CAR-T therapy Kymriah (tisagenlecleucel). Earlier in 2020 the insurer announced a pay-for-performance deal for Avexis/Novartis' gene therapy Zolgensma (onasemnogene abeparvovec), which it said would protect it from "financial risk if the therapy fails. It also signed a similar agreement with bluebird bio for its gene therapy Zynteglo (betibeglogene autotemcel).

Meanwhile, markets that use health economic analyses to make reimbursement decisions may revise their thresholds for what is acceptable. For example, cost per quality-adjusted-life-year thresholds in the UK could be revisited. Decision makers might also restrict patient populations, said Schröter.

Trends set in motion before the current pandemic could also be accelerated.

By way of example, Natsis predicts that there will likely be a revitalization of the cross-country collaborations that have been forged over the past five years to tackle high prices and access to medicines, including BeNeLuxA and the Valletta Group. Before the pandemic, governments in Europe started to realize they could leverage their combined strength in different ways to "address power and information asymmetries in the pharmaceutical system." For example, collaborations have been engaged in joint pricing and reimbursement negotiations, health technology assessments and information sharing. However, the dynamic has shifted as countries respond to the pandemic, but that pressure could be renewed again, said Natsis.

Jaume Vidal, senior policy advisor at the NGO Health Action International, believes that governments now have an opportunity to introduce policies that maximize public spending as opposed simply to cutting costs, which risks disproportionately affect more vulnerable populations. Transparency in pricing was one area for action where momentum had already been building in Europe, Vidal said.

Research and development costs should be transparent in pricing, and industry must acknowledge the public contributions to the development of many of its products, the HAI advisor asserted. "It is unacceptable that pharma is getting subsidies to develop medicines and there are no accessibility clauses. We need to ensure public return on public investment," he said.

Vidal is calling on industry to bring some new ideas to the table and for the European Commission to remind vaccine developers of the public money they receive when they agree to procurement deals.

Already European countries have been calling for more transparency. The Valletta Group, which comprises Ireland, Portugal, Spain, Italy, Malta, Cyprus, Greece, Slovenia, Croatia, and Romania, is pushing for initiatives on more transparency in pricing. Italy has introduced new legislation increasing transparency requirements for companies during the pricing process, and insurers in Germany want reform that will see companies set out public contributions to R&D during pricing talks.

Another important tool for governments, said Vidal, was the World Trade Organization Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities, such as compulsory licensing to drive competition from generics and biosoimilars.

Vidal believes that measures to "restrain the abuse of intellectual property rights" are coming to the fore. He pointed to a recent victory in the Dutch courts for an insurer that accused AstraZeneca of evergreening an old patent for the company's old antipsychotic, Seroquel (quetiapine).

COST OFFSET AND OPPORTUNITIES

According to Viopas' Schröter, the crisis will further drive health care systems to adapt and adopt a more holistic approach to budgets which can often be very siloed within a system. Indeed, Schröter thinks that the crisis offers an opportunity to "catalyze a new and sustainable way of running a health care system that brings innovation to the market while allowing payers to safeguard their budgets."

For example, companies that show how their product can help payers reduce overall costs in the system perhaps by displacing a more expensive therapy or by reducing hospital admission will be better off, he said. Roche's hemophilia A treatment Hemlibra (emicizumab), for example, is reaching or exceeding sales forecasts because it reduces bleeds by 98% and helped cut overall costs of treatment by 50% in the US.

Meanwhile, companies with products that add costs to the system will be hit hardest, seeing reimbursement denied, or access substantially limited.

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COVID-19 Transforms IVD Industry From Concept To Market

The emergence of COVID-19 forced rapid change within the In Vitro Diagnostics (IVD) industry. Approximately three months passed between the first notification of SARS CoV-2 in Wuhan in December 2019 and the WHO classification of COVID-19 as a pandemic in mid-March 2020.

With the rapid transmission of the virus, the need for tools to quickly diagnose infection became critical, and with that an industry that has long struggled to be perceived as more than a commodity, became a household name and front and center of leadership discussions at the highest level in government.

Very quickly, IVD manufacturers were pressured to help facilitate ramp up of testing capacity across the globe and help build out existing and new channels for testing. The circumstances of the pandemic forced companies to reallocate investments in R&D, production processes, and supply chain management, while having to critically assess traditional commercial models. Ultimately, companies were pressured to innovate their entire operational model from concept to market. This disruption will impact the industry well beyond 2020 and drive permanent change in how companies orchestrate across business processes to thrive.

R&D DISRUPTION DURING COVID-19

The pandemic provided stimulus for innovation across multiple functional pillars, initially with pressure to drive swift R&D, followed by the ability to rapidly increase manufacturing speed and scale.

COVID-19 Test Development And Production

Transparent communication with health organizations and sharing of information such as the genomic sequence of the SARS CoV-2 virus were critical in the industry's ability to respond globally. Still, industry remains under pressure to adequately support the global healthcare infrastructure in the management of the pandemic.

Within weeks, IVD manufacturers needed to refocus their R&D expertise and resources to develop high-quality COVID-19 tests. What often takes two to three years, had to be achieved within one to two months, putting IVD manufacturers, OEMs, and laboratories to the test.

FDA responded quickly by providing guidance on Emergency Use Authorization approval for SARS CoV-2 tests and by mid-March the first commercially produced test received EUA approval in the U.S.[1] Since then, more than 250 tests have been cleared for temporary commercialization in the U.S. under EUA.[2] More and more companies will seek to transition to full 510k clearance in 2021, but many will not make this changeover once EUA is lifted. This will require collaboration with a competent CRO that has experience in collecting data pre and post commercialization to minimize costs and facilitate a timely and smooth transition.

Despite clearance, volume remains an issue. The IVD industry typically does not operate with excess manufacturing capacity. To ramp up test volume, investments in new manufacturing and production facilities need to be made, but those take planning and time. OEM partners quickly saw requests for equipment and machinery to help with the aggressive assembly and production of needed supplies. Development cycles were pressured to produce materials and equipment in less than half the normal cycle time.

Now, more than six months later, companies have benefited from government funds made available to increase COVID-19 testing capacity. In total, more than 20 diagnostic companies have received U.S. BARDA funding to scale up manufacturing; total BARDA funding to diagnostic companies has exceeded $60 million.[3] Still, as of September 2020, 30% of laboratories interviewed in a recent IQVIA survey reported COVID-19 testing capacity falling below testing needs.[4]

Learnings from delivering in line with such aggressive development and commercialization timelines will last beyond 2020 and include the effective utilization of CROs that can facilitate orchestration across critical functional pillars and ensure that the standards stipulated to obtain BARDA funding are met.

The Need For Data Integration

Data integration, connectivity, and analytics will also need to remain at the forefront of innovation in 2021.

Today, transmission of data remains problematic. The integration of data into various types of electronic systems and into a patient's electronic health record remain elusive goals. The COVID-19 pandemic highlighted the ongoing challenges in coordinating patients' results across multiple channels and testing entities.

Identifying solutions to the ongoing interoperability of data and electronic medical records will see much attention and investment in 2021. In light of reduced facility access, remote instrument performance monitoring and maintenance tools, as part of software and middleware solutions will also gain additional relevance in 2021 and beyond.

With some of the financing and investments laboratories have received as part of the COVID-19 pandemic, some larger CAPEX projects are being considered and are expected to get attention in 2021, including some of the more challenging projects around data integration. In a recent study, 72% of laboratories referenced an increase in their 2021 budget as a result of COVID-19.[4]

IVD manufacturers who can bring meaningful change through partnerships or internal competencies in the area of data integration will see demand for such offerings increase in 2021.

MANAGING SUPPLY CHAINS

Shortages of testing supplies were and continue to be widespread. Industry was unprepared to address the rapid change in laboratory demands for test kits and supplies. Laboratories were ill prepared with in part outdated testing equipment. Demand for raw materials needed for instrumentation more than doubled shortly following the onset of the pandemic. Laboratories, OEMs, and large IVD manufacturers increased staff to manually assemble products because of delays in receiving automated equipment. According to a recent IQVIA survey, laboratories invested on average nearly 11% more in instrumentation since the start of the pandemic and increased staff by approximately 8% to address bottlenecks.[4]

An overdependence on select suppliers and their geography during times of aggressive demand, led to supply shortages and sample backlogs. Laboratories specifically called out shortages of viral transport media, swabs, reagents, and tubes; shortages that still remain in part today.[4]

Going forward, IVD manufacturers will look to de-risk supply management, minimize overdependence and carefully reevaluate the geography of the supply chain with the goal to spread out bottlenecks and address potentially challenging cross-border logistics. In parallel, laboratories will diversify their instrumentation to become less reliant on a single test provider and platform. Implementing and preparing for these changes in industry and at the customer level will be key in 2021.

THE ERA OF A NEW COMMERCIAL MODEL

The wide-ranging disruptions stemming from the COVID-19 pandemic are also expected to permanently change broader interaction and go-to-market models. IVD manufacturers needed to be flexible and creative in supporting their customers, the laboratories, in setting up testing capabilities efficiently and rapidly in an environment where face-to-face interactions were challenged.

With an investment focus on equipment and aggressive test and instrument production, IVD manufacturers have begun to recognize the need to change the traditional commercial model. Funds traditionally used for conferences and roadshows are now being used for webinars and virtual events. Sales reps are increasingly interacting with their customers remotely because of limited access to facilities. In the U.S. alone, remote rep interactions have increased by close to 400% compared to pre-COVID levels.[5] While rates may settle, establishing a successful remote engagement system will be essential and a consistent component of a successful commercial model in the future.

Less established companies who have been aiding in the development of COVID-19 tests are needed to address unmet needs. However, many lack the resources to invest in sales teams. Transitioning, even temporarily, toward a highly skilled and trained contract sales force would provide manageable opportunities. Given the uncertain environment, this model is expected to be adopted more frequently in 2021 and beyond, to provide flexibility and responsiveness to quickly changing market conditions, while managing capital and staying in control.

CONCLUSION

Orchestrating seamlessly across functional pillars will be critical in 2021. As uncertainty remains, such orchestration will be required to ensure rapid commercialization of quality tests and data management solutions, while remaining flexible and implementing a cost-effective, innovative commercial model. Laboratories will seek to invest based on funds that were received during the pandemic. IVD manufactures need to be able to respond quickly with commercial development and execution. To achieve this entails taking a business process view of the full IVD product life cycle, from concept to market, and bringing together the technology, products, services, consulting, data, and technology-enabled managed services necessary to combine each link in the value chain. In practice, these changes will require IVD companies to use the collective resources and industry experience they possess and that of their trusted partners. Companies that make this transformation will be best positioned to emerge from these times of change in a position of strength.

REFERENCES

1. FDA, "Policy for Coronavirus Disease 2019 Tests During the Public Health Emergency (Revised). Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff", May 2020.
2. FDA 2020, accessed 25 October 2020, ‹https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.
3. U.S. Government 2020, U.S. Department of Health & Human Services, accessed 25 October 2020, ‹https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx?filter=diagnostic›
4. IQVIA, "IVD COVID-19 Global Laboratory Pulse Survey", Wave 2, September 2020.
5. IQIVA, "BrandImpact". Baseline: weekly average of the 8 weeks ending 3/6/20 of stable detail, patient visit and treatment volumes.

The Calm Before The Storm – But Some Medtechs Already Reflect The Ravages Of COVID-19

ASHLEY YEO
EXECUTIVE EDITOR, EUROPE

2019 saw fewer revenues-boosting major acquisitions by top-tier medtechs. Companies that reported after the calendar year-end were the first to see the consequences of the pandemic on their annual figures.

Our sales ranking of the top 100 publicly traded medtech manufacturers is COVID-19-affected for a relatively sizeable proportion of companies – those whose reporting periods closed during 2020. The effect of the pandemic on their sales was often significant and gave a foretaste of what the rest of the industry will experience when filing calendar year 2020 accounts.

The first implications of the pandemic became apparent for health care provider systems in countries beyond China at the end January 2020, the global implications were clear by late February, and a pandemic was declared in mid-March. Before the start of the second quarter, medtechs were in pandemic response mode, and, depending on their product mix, were either rushed off their feet or concerned about business sustainability.

MEDTRONIC FIRST AGAIN, BUT IN ANOTHER SENSE

Medtronic's April 2020 year-end meant that a full month of post-lockdown, coronavirus-affected business was reflected in its annual revenues. This group reported a 5.4% drop in annual sales (and a fourth quarter fall of 26%), bringing it below the $30bn threshold it had broken through temporarily in its fiscal 2019. Spine sales for the year dropped by 5.7% and cardiac and vascular sales were down by 9%. Extracorporeal life support products, ventilators, pulse oximetry, capnography, advanced parameter monitoring products and diabetes supplies and consumables were in high demand, however.

Managing through the coronavirus was a challenge new CEO Geoff Martha would not have chosen, as he took on the board chair role in December. He had quite an act to follow: Omar Ishrak, the group's first non-American CEO, left with a nine-year record of growing emerging markets, innovating and overseeing creative business models.

But the group did not provide financial guidance in Q4 2020, and neither for Q1 of its fiscal 2021.

Among the leading 20 medtech companies, only Cardinal Health, Becton Dickinson and Siemens Healthineers report later than Medtronic. The Japanese firms in the global top 30, reporting on 31 March 2020, also saw the initial effects of COVID-19 on their year-end sales.

Other Top 100 companies already reporting a coronavirus-related effect on annual sales, include: ResMed, Elekta, Smiths Medical, Cochlear, Cantel Medical, Myriad Genetics, Abiomed, AngioDynamics, Accuray and Sectra.

Respiratory and sleep apnea group ResMed's product mix helped ensure its sales to June 2020 rose by over 13%. But the group pointed to another key factor that has been welcomed by the global devices industry: the repeal on 1 January 2020 of the 2.3% excise tax on US device sales. In force since 2013, the tax was an element of the 2010 US Affordable Care Act that was designed to support the cost of insurance expansion.

On the diagnostics side of the industry, Myriad Genetics said it began to see a business impact from COVID-19 from the end of March. In early April, predominantly elective tests volumes (such as for hereditary cancer, potential drug interactions and rheumatoid arthritis) declined by 70-75%, and prenatal tests by 20-25%.

In common with industry counterparts, the group stopped in-office visits, restructured to ensure lab operation continuity, implemented cost-saving initiatives and initiated furloughs. It also obtained a debt covenant waiver until March 2021 from creditors. Towards the end of its fourth quarter, it began to see a significant recovery, with test volumes averaging 75% of pre-pandemic levels

CARDINAL HEALTH'S PPE BUSINESS LIMITS NEGATIVE IMPACT

Cardinal Health estimated that the COVID-19 pandemic had a net negative operating earnings impact of $100m across its pharma and medtech segments in fiscal 2020.

Reporting on the year ended 30 June 2020, the Dublin, Ohio group's medical products segment saw lower sales volumes overall, apart from in PPE products, such as masks, gowns and gloves. Cardinal manufactures and distributes PPE. The COVID-19 negative impacts will likely continue in fiscal 2021, the group said.

The adverse effects of the pandemic were partially offset by growth from Cardinal Health at-Home Solutions, which distributes medical products to patients' homes in the US. This limited the group's drop in annual sales to 1%. Cardinal's range of products (syringes, incontinence, nutritional delivery, wound care, cardiovascular/endovascular, fluid suction, urology and OR supplies) puts it in competition with, among others Owens & Minor, Medline and Becton Dickinson (BD).

BD's reporting year ends on 30 September, and it normally files annual results after the Top 100 is compiled. For 2019-2020, new CEO Tom Polen announced on 5 November 2020 that fourth quarter revenues were up 4.4%, driven by a 97% rise in diagnostic system sales due to COVID-19 testing demand. Annual sales of $17.12bn were reported for the 2020 fiscal year.

Announcing its 2019 results, the word coronavirus not yet uttered, the group issued guidance for a 4-4.5% revenue increase in 2020. But as seen with Medtronic, once the crisis began, companies declined to issue guidance. As it transpired, BD's sales were 1% down in FY 2020. Its 2019 reported sales were 5.2% up at $17.29bn, in a year when it made no significant purchases, and when its divisional sales rises were more in keeping with traditional medtech market averages – BD Medical segment increasing by 5.2% to $9.1bn; and BD Interventional up 5.2% at $3.9bn. Between fiscal 2015 and 2019, BD's M&A – including CR Bard in 2017 and CareFusion in 2015 – helped the group to expand by 68%.

SIEMENS' VARIAN PURCHASE OFFERS RESPITE

Siemens Healthineers' news in August 2020 that it would complete the €16.4bn purchase of precision oncology systems company Varian Medical Systems in H2 2021 provided a distraction from the pandemic. But its Q3 2019-2020 results delivered at the same time showed that diagnostic division sales were down by 15.9%, while imaging and advanced therapy revenues were down by 3.3% and 1.8%, respectively.

Resilience (along with "uncertainty") has become the word of a choice among medtechs whose adjustments and efforts are helping to bring them through coronavirus. CEO Bernd Montag employed the term accurately on 2 November when reporting on a Q4 recovery, and annual sales for the 2019-2020 year that were down by just 0.4% on a reported basis. The strengthening of the Euro currency by 5% against the US dollar in 2019 worked against Siemens Healthineers in terms of its dollar-ranked sales and ranking position in our latest Top 100.

AND IN BC (BEFORE CORONAVIRUS) TIMES

While coronavirus was not a factor for the global second-leading medtech group, Johnson & Johnson, its medical devices sales in 2019 dipped by 3.8%, only slightly less than industry leader Medtronic's decline. Negative currency impacts accounted for 2.1% of its sales fall. Its sales were split fairly evenly among the US ($12.4bn) and OUS ($13.6bn) divisions.

The divestitures of LifeScan and Advanced Sterilization Products (ASP) had negative growth impacts of 3.8% and 1.6%, respectively. But there was growth in wound closure, hips, knees (in the OUS region), trauma and vision products. The standout was interventional products, with approaching $3bn of sales, driven by atrial fibrillation procedure growth and catheter sales.

Royal Philips completed three acquisitions, including that of the Healthcare Information Systems business of Carestream Health. Its gross revenue of €19.5bn (including license fees and royalties) was 8% up on 2018 in local currency. Connected care had a "challenging year," with sales of €4.7bn. Diagnosis & treatment, at €8.5bn, saw improved revenues based on strong innovation flow in the delivery of precision diagnosis and targeted therapy. The group also teamed up with US insurance company Humana, to improve care for at-risk, high-cost populations.

GE Healthcare and Abbott Laboratories were level pegging in 2019, at just under $20bn sales, but whereas GE had flat growth, Abbott continued to expand, as in the previous two years, due to general volume growth and the 2017 acquisitions of St. Jude Medical and

diagnostics group Alere, in particular. Diabetes care, structural heart, electrophysiology and heart failure sales drove much of Abbott's 2019 medical device segment growth of 10.5%. Its diagnostic sales increased by 5.9%, excluding the impact of foreign exchange.

MIXED FORTUNES IN ORTHOPEDICS

J&J's DePuy Synthes is the leading orthopedics organization worldwide, but the only one of the big four arthroplasty companies to record a sales fall in 2019, its 0.5% reverse resulting from a negative currency impact of 1.7% which erased operational growth of 1.2%. It had growth in hips, in knees (outside the US) and in trauma but underwent base business declines in spine.

Stryker's reported sale rose by 9.4%, with spine sales showing 31% growth, to top $1bn, and the neurotechnology/spine division posting an increase of 19.2%, as reported. The larger orthopedic and medsurg divisions posted increases of 5.2% and 8.8% for the year, as reported. The group completed $802m-worth (plus $294m contingent on future milestones being reached) of acquisitions. POC companies Mobius Imaging and Cardan Robotics were bought for $360m plus $130m in milestones. They will join the spine business. In March, rotator cuff tears specialist OrthoSpace Ltd was acquired for $110m plus $110m milestones.

The November offer for extremities and biologics specialist Wright Medical Group NV did not trouble the annual sales compilers in 2019, as it was only approved by UK and US merger authorities in November 2020. Wright was a top 10 orthopedic manufacturer in the $53bn global orthopedics market in 2019. Its sales in 2019 were made in upper extremities ($448m), lower extremities ($340.5m), biologics ($113.5m) and sports medicine ($19m). The US market for surgical products used by extremities-focused surgeons is valued at some $3.56bn, said Wright.

DJO Global, the eighth-largest orthopedic company in 2018, was acquired by Colfax for $3.15bn in February 2019, and became the fabrication technology company's medical technology segment. Purchasing the injury prevention-to-rehabilitation group was part of Colfax's strategic plan to build a platform in high-margin orthopedics. Colfax's net sales for 2019 from its new orthopedic segment were $1.1bn. Colfax said it had grown that business by over 4% since acquiring it.

Zimmer-Biomet's sluggish annual growth continued, with the group scoring a meagre 0.6% increase in overall sales (including dental, bone cement and office based technologies) in 2019 after posting just 1.6% growth in 2018. The group is number 1 in both hips and knees globally. In February 2020, the group was forecasting up to 3.5% growth in 2020, but cautioned that this did not factor in any impact from outbreaks of coronavirus and its potentially "near-term and long-term effects."

In a year where organic growth was largely more important than M&A-assisted growth for the leading medtech companies, sales performances of the individual groups should in theory have provided more meaningful comparisons.

EU REGULATIONS AHEAD

B. Braun, a top 20 global company and Germany's second-largest medtech group, increased its sales by 8.2% in 2019. Its orthopedic instruments division, Aesculap, expanded its sales by 7.9%, driven by growth in China (especially in interventional therapies), the US (sterile goods management) and Russia. The scheduled implementation of the EU Medical Device Regulation in May 2021 put a strain on sales, even if the "evolution" to the MDR, as the European Commission has described it, was delayed by a full year to spring 2021 as a result of COVID-19.

There were no such immediate problems for fellow European group Roche, the global leading diagnostics organization in an industry segment where compliance with the EU's "revolutionary" Vitro Diagnostics Regulation is not enforced until May 2022. The Swiss group reported sales of CHF12.9bn, an increase of 3% at constant exchange rates, the growth coming mainly from centralized and POC solutions (accounting for 60% of sales) and immunodiagnostics especially. But a modest 0.6% reported sales increase and a strengthening of the Swiss franc meant its dollar-ranked 2019 sales went backwards compared with 2018. Its molecular diagnostics sales were up 6%, due to increased demand in blood screening, while diabetes care sales increased by only 1%.

A YEAR OF DIFFICULT PERFORMANCE COMPARISONS

In a year where organic growth was largely more important than M&A-assisted growth for the leading medtech companies, sales performances of the individual groups should in theory have provided more meaningful comparisons.

But against the backdrop of COVID-19, and factoring in the different reporting schedules of many companies, analyzing their 2019 performances was, if anything, more difficult. The rankings for 2020 will be colored by the entire industry's struggles with the effects of the coronavirus, even if those with certain product offerings stand to gain from the pandemic.

COMPANY	TOTAL SALES ($M; 2019)	RANKING	NOTES
Medtronic	28,913	1	Year ended 24 April 2020 (FY2020)
Johnson & Johnson	25,963	2	
Philips Healthcare	21,297	3	Excludes IP and licensing income
Abbott Laboratories	19,953	4	
GE Healthcare	19,942	5	
Becton Dickinson	17,290	6	Year ended 30 September 2019 (fiscal year 2020 sales: $17.12bn)
Siemens Healthineers	16,197	7	Year ended 30 September 2020
Cardinal Health	15,544	8	Medical sales; year ended June 2020
Stryker	14,844	9	
Roche Diagnostics	13,035	10	
Boston Scientific	10,735	11	
B Braun	8,369	12	
Zimmer Biomet	7,982	13	
Baxter International	7,850	14	
Alcon Laboratories	7,362	15	
Danaher	6,662	16	Diagnostics only following divestment of dental
3M	6,641	17	
Olympus	5,889	18	Year ended 31 March 2020
Terumo	5,771	19	Year ended 31 March 2020
Grifols	5,711	20	
Smith & Nephew	5,138	21	
Fujifilm	4,626	22	Health care; year ended 31 March 2020
Intuitive Surgical	4,479	23	
Edwards Lifesciences	4,348	24	
Fresenius Medical Care	4,037	25	
Dentsply Sirona	4,029	26	
Canon Medical Systems	4,024	27	
Thermo Fisher	3,718	28	
ResMed	2,957	29	Year ended 30 June 2020
Shimadzu	2,812	30	Year ended 31 March 2020
Getinge Group	2,810	31	
Sysmex	2,771	32	Year ended 31 March 2020
Hologic Inc	2,771	33	
Coloplast	2,690	34	Year ended 30 September 2019
Teleflex Medical	2,595	35	
bioMérieux	2,443	36	
Align Technology	2,407	37	
Dräger	1,951	38	
ConvaTec	1,827	39	
Varian Medical Systems	1,784	40	Radiotherapy (proton and oncology)
HU Group (Miraca)	1,732	41	Year ended 31 March 2020
Bausch Health	1,717	42	
Nihon Kohden	1,698	43	
Carl Zeiss Meditec	1,635	44	Year ended 30 September 2019
Straumann	1,607	45	
Elekta	1,545	46	Radiotherapy; year ended 30 April 2020
Qiagen	1,526	47	
Integra LifeSciences	1,518	48	
DexCom	1,476	49	
Bio-Rad Labs	1,412	50	
Shinva Medical Instrument	1,269	51	
ICU Medical	1,266	52	
Integer	1,258	53	
Fukuda Denshi	1,224	54	Year ended 31 March 2020
Smiths Medical	1,172	55	Year ended 31 July 2020
NuVasive	1,168	56	
AGFA Healthcare	1,141	57	
LivaNova	1,084	58	
Colfax (DJO Global)	1,080	59	
Omron	1,032	60	Year ended 31 March 2020
Cantel Medical	1,016	61	Year ended 31 July 2020
Merit Medical Systems	995	62	
Haemonetics	988	63	Year ended 31 March 2020
CONMED	955	64	
Cochlear	940	65	Year ended 30 June 2020
Masimo Corp	938	66	
Invacare Corp	928	67	
Wright Medical Group	921	68	
Guerbet	915	69	
Exact Sciences	876	70	
Abiomed	841	71	Year ended 31 March 2020
Konica Minolta	806	72	Year ended 31 March 2020
MicroPort Scientific	793	73	
Diasorin	791	74	
Globus Medical	785	75	
Cooper Companies Inc	681	76	Year ended 31 October 2019
Jiangsu Yuyue Medical Equipment	671	77	
Myriad Genetics	639	78	Year ended 30 June 2020 – includes pharma and clinical services
Varex Imaging	597	79	
Quidel	535	80	
Hamamatsu Photonics	532	81	Year ended 30 September 2019
LePu Medical Technology	524	82	Medical devices only in 2019
Natus Medical	495	83	
Heraeus Group	476	84	Medical components; estimated
Orthofix Medical	460	85	
Ypsomed	396	86	
Accuray	383	87	Year ended 30 June 2020
Hogy Medical	342	88	Year ended 31 March 2020
Luminex	335	89	
RTI Surgical	303	90	
CryoLife	276	91	
AngioDynamics	264	92	Year ended 31 May 2020
Stratec Biomedical Systems	248	93	
Cardiovascular Systems	237	94	
Horiba Ltd	232	95	
AtriCure	231	96	
Meridian Bioscience	201	97	Year ended 30 September 2019
Cutera Inc	182	98	Non-surgical aesthetic procedures
Orasure Technologies	155	99	
Sectra	151	100	Year ended 30 April 2020

BEN COMER
EXECUTIVE EDITOR, US

Early Cancer Detection: Will New Screening Technology Disrupt Cancer Care?

The emergence of multi-cancer blood tests for early detection is captivating investors and driving multi-billion-dollar acquisitions. Companies such as GRAIL, Thrive Earlier Detection and Guardant are predicting revolutionary change in the way cancer is diagnosed and treated. The biggest hurdle, however, may be coaxing health care systems and health insurers to join the revolution.

Early cancer detection diagnostics, along with the success of anti-smoking campaigns, are the two biggest reasons for declining mortality rates in cancer over the last several decades, even as immunotherapies, precision oncology treatments and other innovations targeting late stage cancers are improving outcomes – to an extent. To truly bend the mortality curve in oncology, early cancer detection is needed beyond the five cancer types for which routine screening products and national guidelines already exist: breast cancer, cervical cancer, prostate cancer, colon cancer and lung cancer in high-risk individuals, according to a growing number of clinicians and cancer researchers, and early detection diagnostics product developers.

In late October 2020, *In Vivo* and *Medtech Insight* convened a virtual panel to better understand the potential impact of early, multi-cancer detection diagnostics, as well as the significant challenges to broad adoption and commercialization. Panelists included Sam Asgarian, chief medical officer, Thrive Earlier Detection; Helmy Eltoukhy, CEO, Guardant Health; Harris Kaplan, managing partner, Red Team Associates and CEO of Healogix; and Azra Raza, Chan Soon-Shiong professor of medicine and director of the MDS Center at Columbia University in New York City. Raza, an oncologist and researcher who has treated cancer patients for over 20 years, lost her husband, Dr. Harvey Preisler, director of the Rush Cancer Institute in Chicago, to lymphoma in 2002. He was 61 years old.

Raza, author of *The First Cell: And The Human Costs Of Pursuing Cancer's Last*, published in October 2019, is an outspoken advocate for early cancer detection. "Early detection can be curative for a lot of patients," said Raza. Currently in the US, "we are spending something like $27bn in screening measures, and we detect 9 million positive cases," said Raza. "But of those 9 million, only 200,000 are real cancers, and 8.8 million are false positives. We need sophisticated molecular and genetic markers for screening healthy individuals, to find illness before it has become a bona fide clinical disease, and to prevent it. We are still using the old techniques of slash, poison and burn [to treat cancer] and that has got to stop."

High false positive rates in single cancer detection may contribute to adoption and reimbursement barriers for emerging multi-cancer early detection diagnostics, a situation similar to the way that adverse immune responses to early cell therapies in the 1990s created a higher burden of proof for the next generation of cell and gene therapies. Single cancer screening tests save lives, but they "focus on sensitivity, and give up on specificity, which leads to a lot of false positives," Josh Ofman, chief medical officer and external affairs at GRAIL, an early cancer detection diagnostics company, told *In Vivo*. "The efficiency to find cancer today is pretty poor. You're spending most of your money on false positives; it can cost on average up to around $90,000 to $100,000 to diagnose a case of cancer today."

EARLY MULTI-CANCER DETECTION

Early studies point toward wider detection and lower false positive rates with multi-cancer screening technology, or 'liquid biopsy,' which requires only a blood draw, instead of the standard tissue biopsy for making a cancer diagnosis. And the market for molecular diagnostics in cancer is expected to grow substantially in the next five years, according to Meddevicetracker (*see Exhibit 1*).

Thrive Earlier Detection, which launched just over a year ago with $110m in series A financing, is developing the CancerSEEK liquid biopsy, a technology licensed in from Bert Vogelstein's lab at Johns Hopkins University. In October, Thrive was acquired for $2.15bn by Exact Sciences Corp., a cancer screening and diagnostics company marketing the Cologuard screening test for colon cancer, as well as Oncotype tumor profiling tests that help guide treatment decisions for cancer patients.

In its interventional DETECT-A study, published in April 2020, Thrive screened 10,000 healthy women aged 65 to 75 for multiple cancers, and detected 26 previously unknown tumors among the participants, or twice the number found with conventional screening. The two key outcomes of the study, said Asgarian, were to "detect cancer early enough so that the treatment is curative, and to find of it we can do it in a safe way." Notably, cancer types with no currently approved screening test, such as ovarian cancer, were detected in the study. There were 101 false positives. The study was a success, and Thrive now plans to "work very closely with the FDA" to design a pivotal registration trial across multiple cancers.

Exhibit 1. Combined Market Forecast For Molecular Diagnostics Products ($m)

COUNTRY/ REGION	2019	2020	2021	2022	2023	2024	CAGR (%) (2019–24)
US	245	251	259	268	279	292	3.6
5 Euro*	119	125	133	143	156	173	7.7
Japan	34	36	38	41	44	49	7.2
RoW	295	328	479	537	593	646	16.9
Total	**694**	**741**	**909**	**989**	**1,073**	**1,159**	**10.8**

*5 Euro = five major European markets of France, Germany, Italy, Spain and the UK
Source: Meddevicetracker, 'Molecular Diagnostics' September 2020

PRIMARY CARE COORDINATION

GRAIL is also developing a liquid biopsy test for multiple cancers, called the Galleri test, capable of detecting over 50 cancer types at early stages. Originally spun out of Illumina, a genomic sequencing company, in 2016, GRAIL attracted high profile investors including Jeff Bezos and Bill Gates, as well as pharma companies including Johnson & Johnson, Bristol-Myers Squibb and Merck & Co. In September 2020, Illumina announced that it would acquire the company back for $8bn. Of the 50 cancers the Galleri test can detect, 45 have no recommended screening, Ofman notes, adding that "70% to 79% of all cancer deaths in the US occur in cancers that don't have a recommended screening test at all." The FDA granted a breakthrough device designation to the Galleri test in May 2019, but the company plans to launch the product as a lab-developed test in 2021. Potential FDA clearance for the test is still "a couple of years out," said Ofman.

Studies conducted by GRAIL, including the STRIVE prospective study of 100,000 women receiving mammograms, the SUMMIT study of 25,000 men and women ages 50 to 77 with a high risk of lung cancer, and most recently, the investigational PATHFINDER study enrolling 6,200 patients and evaluating the impact of the Galleri test in clinical practice, aim to demonstrate the utility of multi-cancer early detection. The PATHFINDER study is important in that it addresses a needed shift to primary care for early detection, and treatment guidance, something GRAIL and Thrive see as the future.

Since the multi-cancer tests also predict a tissue of origin, such as ovarian or head and neck, for example, physicians can evaluate those signals in specific locations or regions, or refer the patient to the appropriate specialist to the do the work-up. "Right now, we practice sick care, secondary and tertiary care beyond the reach of primary care providers," said Asgarian. With a simple blood draw, a primary care doctor can "work with the patients and population that he or she knows so well. They are diagnosing diabetes, allergies, all these other diseases and illnesses, and now they will have the tool and can do the same thing but apply it to cancer. Not to treat it, but to coordinate the care and allow a specialist to see it at an earlier stage where the treatment can be curative."

"Technology is moving against reimbursement headwinds." – Harris Kaplan

Guardant Health was founded in 2012 and taken public in 2018. The company's Guardant360 liquid biopsy test has been validated by more than 150 peer-reviewed publications, and more than 150,000 tests have been used to date. However, the Guardant360 test is used for genomic profiling in advanced cancer patients, to guide drug therapy decision-making. For example, it serves as a companion diagnostic for AstraZeneca's non-small cell lung cancer drug Tagrisso (osimertinib). Guardant360 is "able to detect very low concentrations of cell-free DNA and reconstruct the genomics of the tumor in those patients. Then we can match the mutations in the genome with the best possible therapies," said Eltoukhy, Guardant's CEO. Guardant is currently testing its LUNAR-2 assay in the 10,000-volunteer ECLIPSE trial for the early detection of colorectal cancer. "When we started the company eight years ago, there was $90m total of NIH funding for early detection, out of tens of billions of dollars. Now you see the funding rounds, with Thrive, with other companies, with Guardant. It has been gratifying to see that investors really do appreciate the impact that early detection can have on this space."

REIMBURSEMENT CHALLENGES

Despite the dazzle of early study results for multi-cancer screening, real challenges exist in driving adoption and product reimbursement. Part of the reason that Guardant is going after early detection of colorectal cancer in its ECLIPSE study, is because the pathway to commercialization has already been forged by companies like Exact Sciences and Cologuard. "The technology is moving against reimbursement headwinds," said Kaplan at Red

Exhibit 2. Molecular Testing Services/LDT Market ($m)

COMPANY	2017	2019	CAGR (%) (2017–19)
Exact Sciences*	266.0	815.1	75.1
Myriad Genetics	679.4	789.4	7.8
Genomic Health	340.5	403.5	8.9
Foundation Medicine	91.7	343.0	93.4
Guardant Health	42.1	180.5	107.1
NeoGenomics	68.2	115.6	30.2
Agendia	15.0	26.0	31.7
Biodesix	20.0	19.1	-2.3
MDxHealth	27.7	8.1	-46.1
MetaMark	4.0	2.1	-27.4
Total (excluding Others)	1,554.6	2,702.3	31.8

Source: Meddevicetracker, 'Molecular Diagnostics' September 2020

Team Associates. "When it comes to screening, I think payers are very sensitive to paying twice." For example, if a patient gets a positive result from an Exact Sciences Cologuard test, which costs $600, the next step is a colonoscopy to confirm the result. Even so, revenues for Exact Sciences's cancer screening tests tripled between 2017 and 2019, according to Meddevicetracker. And more than 335,000 Cologuard tests were covered by Medicare in 2018, with payments of over $170m (*see Exhibit 2*).

Many companies are now working to develop early detection diagnostic technologies. But the extent to which new screening technology will be adopted by the health care system, and how quickly, remains an open question. There is a pathway in colorectal cancer screening, paved by Exact Sciences, which "laid out the way to get into clinician workflows, into screening guidelines, and most importantly, to get reimbursement, because we're piggybacking on colonoscopy where multiple studies have shown the med-health benefit ... that helps things move much more quickly," said Eltoukhy.

"I would say that 80% of the challenge is actually getting a technology that works into the health care system, changing the standard of care, changing clinician workflows, getting reimbursement, getting into [screening] guidelines ... all of those things are frankly much harder and a much bigger expense" than technology development, said Eltoukhy. "We're starting with a single cancer, but then we're going to multi-cancer quickly, with liquid biopsy for the metastatic setting starting with lung cancer and then expanding horizontally from there to over a hundred cancer types. We believe the same thing can happen in early detection, but you really have to pick your beachhead."

Companies such as GRAIL and Thrive may need more data, in the form of long-term, multi-year studies, to demonstrate overall survival, in order to get over reimbursement hurdles and accelerate adoption of early detection for multiple cancers. There is also the issue of positive early cancer results in healthy, asymptomatic patients. Raza acknowledged that widespread multi-cancer screening would be very hard to apply to the entire population right away. There is also the danger associated with a positive test screening. "If today I go and get my blood tested for circulating tumor cells and they come and tell me Dr. Raza, we are finding adenocarcinoma cells hanging around in your blood, the next thing I'll do for myself is run to get a PET scan, and see which gland in my body is producing cancer," said Raza. "Let's say the PET scan comes back negative. Now what do I do? How many times do I repeat this blood circulating tumor cell test on myself? And should I schedule another PET scan in six months? It's going to expose me to a lot of radiation. And all these months I'm going to be very anxious."

Ultimately, however, detecting a cancer early means there's more chance to manipulate it to the patient's advantage, Raza believes. Earlier cancer detection may also lead to better treatment options, if screening tools are used for clinical trial recruitment to investigate new therapies. "We think this is going to be really helpful for drug developers who are trying to test the value and effectiveness of their products in earlier stage cancers," said Ofman. "The problem we have right now is that we don't detect very many early-stage cancers, so it's really hard for [biopharmaceutical companies] to study their drugs" in those cohorts.

SCREENING GUIDELINES

Thrive and GRAIL would both like to see their multi-cancer screening tools added to cancer screening guidelines that already exist. "Once a year, if you're over the age of 50, which means you're at an elevated risk of cancer, add a multi-cancer early detection blood test, so we can look for all those other cancers," said Ofman. "We'll find some additional breast cancer, colon cancer, others ... but the majority of the value will be finding cancers that we're not currently screening for."

According to Raza, the US health care system does not have a choice about moving to early cancer detection, and away from the current focus on extending life in advanced stages of cancer. She uses the acronym "CRUSH" to describe the problem: Complexity of cancer addressed by Reductionist approaches, creating Ultra hype about minor advances (in mouse models), paired with Simplistic clinical trials, and High fiscal cost. "It's unconscionable that 42% of people who are diagnosed with cancer lose every penny of their life savings in two-plus years," she said. "It's obscene, and we shouldn't be doing it."

AMANDA MAXWELL
MANAGING EDITOR, EUROPE

One-Stop Shop: Is Timely Compliance With The EU's MDR And IVDR Still Possible?

Change, change and more change on the regulatory front is what medtech companies can expect for the first half of 2021 in these unprecedented times.

During the first eight months of 2020, politics and pandemic panic heavily influenced the regulatory momentum of the medtech sector. Companies flexible enough and with sufficient resources to adapt to the changing demands and landscape are most likely to weather these storms. But we are constantly warned that not all will. Many have felt battered by constant change and are unprepared. That is especially the case among small- and mid-sized enterprises, which make up 90-95% of medtech companies.

So where are we now? And how can industry best prepare for 26 May 2021, the date of full application of the EU Medical Device Regulation (MDR)?

Firstly, it is worth remembering that up until late April 2020, the medtech sector was expecting the MDR to fully apply by 26 May 2020. If that had happened, many in the sector would have experienced problems, some companies even failing to be compliant in time because of the lack of guidance and notified body capacity, and due to the ongoing absence of fundamental elements of the infrastructure, such as the Eudamed medical device database and standards.

The one-year delay to the full application date of the MDR to 26 May 2021 means the problems foreseen have been averted – for now. But the big question is whether these problems will be solved by the one-year delay, or whether they will they resurface again when the deadline hits.

MDR DELAY

A delay in the full application of the MDR was something industry had long lobbied for. The European industry association, MedTech Europe, was convinced that the sector was not sufficiently ready in the early part of 2020. And it was not alone; even representatives of EU competent authorities and the US Food and Drug Administration had been adding their voice to the plea for extra time. All feared that products essential for health care would have to be pulled from the market on 26 May 2020.

But the European Commission was not convinced by this argument; it continued to make plans based around its original 2020 timetable, confident its program of designating notified bodies and posting MDR guidance documentation would be sufficient for successful – even if not fully complete – implementation to take place on time.

It was not until COVID-19 struck and overwhelmed the devices sector that the priorities and ways of working of medtech stakeholders – authorities, noti-

fied bodies and manufacturers, as well as the commission itself – had to shift. At this point, the commission conceded to the need for a one-year delay to the MDR, making the new deadline 26 May 2021. But the postponement is not the solution many had wished it would be. This is for many reasons, including:

- The one-year delay applies only to the MDR and not the IVDR. This means that there will be just one year between full application of the MDR on 26 May 2021 and the IVDR on 26 May 2022, putting pressure on those players who have staff working on both, including at authority and even commission level.
- The grace period, which allows many MDR products, and some IVDR products, to remain on the EU market until 26 May 2024 (where compliant with the current medical device directives), has not been extended, meaning the grace period will be three years, instead of four, for products under the MDR and remain two for those under the IVDR. So, auditing under the new regulations will need to be concentrated into less time.
- The Eudamed medical device database, a critical factor in transparency and traceability, is not likely to be fully ready until 26 May 2022.
- Because COVID-19 has resulted in social distancing and travel restrictions, physical audits of notified bodies by designating authorities and physical audits of manufacturers by notified bodies are generally not taking place. This is placing obstacles in the way of notified bodies auditing products against the new MDR and IVDR – and this is likely to remain the status quo for the near- to mid-term too, creating a potential paralysis in certification against the MDR which is only nine months away.
- Dealing with COVID-19 products is going to continue to be a major feature of notified body work over the near future.

In other words, it was COVID-19 and its challenges that brought about the MDR's one-year delay. But the problems around trying to address the coronavirus crisis are also the most likely obstacle to the successful full implementation of the MDR in 2021.

THE IVDR

Although medical devices and IVDs are being regulated under the same broad framework, the sectors have their own EU regulation because of the differences in the nature of the products.

So, while many of the problems that are besetting the medical device industry, which needs to comply with the MDR, are also impacting the IVD industry, the IVD industry has its own challenges in ensuring it is compliant by the IVDR full application deadline of 26 May 2022. The scale of these challenges is particularly great and there is growing concern among experts in the industry that the IVD industry is slow to understand the urgency with which it needs to begin compliance activities.

The Eudamed medical device database, a critical factor, is not likely to be fully ready until 26 May 2022.

These are the some of the issues the IVD industry is facing:

- There has been no delay to the full date of application to the IVDR; it will now follow merely a year after the 26 May 2021 full application date of the MDR.
- Some 85-90% of IVDs do not need the involvement currently of a notified body under the EU IVD Directive. But under the IVDR, about 85-90% will, meaning a steep learning curve for manufacturers and notified bodies alike and considerably more work.
- Given that 85-90% of IVDs will need to involve a notified body for the first time, these products will not be eligible to benefit from the grace period, which is two years for products under the IVDR where it applies.
- IVDs will be subject to performance evaluation for the first time, the IVDR equivalent of clinical evaluation under the MDR.

As there has been a one-year delay to the date of full application of the MDR, the IVD industry is still hopeful that it will benefit from the same kind of delay. It is also lobbying for a greater number of IVDs to be able to benefit from the grace period.

It is encouraged by the recent concession granted by the European Commission to class I upclassified medical devices under the MDR, which were latterly included in the list of products have been able to benefit from this grace period in addition to other products already listed in the original regulation.

Expect strong lobbying to continue in 2021, in a bid to seek a "stay of execution" for these products.

COVID-19 has had an enormous impact on many manufacturers' ability to transition to the IVDR according to their original plans and timelines. Some companies who were as ready as they could have been at this stage in terms of IVDR compliance have had plans their heavily impacted. This might have been, for example, because audits cannot go ahead with their notified body or because they were expecting their notified body to be designated under the IVDR this year and the timeframes are no longer clear.

Many IVD manufacturers now have clinical studies on pause too, because of COVID-19, and some estimates suggest it could be nine months before they can restart them. This obviously delays when they can file for conformity assessment.

MedTech Europe is also frustrated that the EU chose not to opt for the possibility of pan-European derogations from the need for full conformity assessment procedures for IVDs intended to help in the COVID-19 pandemic as well as for medical devices, within the amending regulation. This means that manufacturers must seek national derogations in every member state where their product is to be marketed and this could cause them to prioritize the bigger markets.

NOTIFIED BODY DEVELOPMENTS

As of mid-August 2020, there were 20 notified body designations in total, 16 under the MDR and four under the IVDR. These include two designations for BSI UK – under the MDR and the IVDR. BSI is due to lose its designation status on 31 December 2020 at the end of the EU/UK Brexit withdrawal period, which means just 18 of the current designations will remain valid from the beginning of 2021.

The hope is that there will be more designations in the meantime. But notified bodies cannot even begin testing under the MDR and IVDR before they are designated, so each day of delay could further threaten their ability to finalize the conformity assessment of MDR products before the 2021 deadline. There are, of course, many other factors that are compromising the likelihood of timely compliance (for example the appointment of expert panels in the case of higher risk products).

The figure of 20 notified bodies under the MDR and IVDR compares with over 80 designations under the Medical Devices Directive at its height (there are 54 now), and 22 under the IVD Directive.

The European Commission had originally promised 20 designations under the MDR and IVDR by the end of 2019. But it has defended its record by stating that the larger notified bodies were among the first designated and therefore there has not been the kind of capacity issue shortfall at notified bodies that such a number would suggest.

It is also noteworthy that there are already six notified bodies based in Germany that have been designated against the MDR and three in the Netherlands. But no other country has more than one designation.

The start of 2021 is a critical time for the medtech sector. Is this a time when as many obstacles as possible are going to be removed so that the sector can focus whole-heartedly on compliance, rather than on the politics and uncertainties?

EUDAMED MEDICAL DEVICE DATABASE DELAYED

The new version of the European medical device database, Eudamed 3, is being designed to support the implementation of the MDR and IVDR and has six main modules: actor registration; unique device identification (UDI)/device certificate registration; notified body certificates; clinical investigations; market surveillance; and vigilance.

It is a cornerstone of the new MDR and IVDR, providing critical transparency and traceability. Its six main modules are interlinked and will provide an unprecedented oversight of which products are on the EU market where, how they are performing and how safe they are.

While Eudamed 3 was intended for launch at the same time as the full application of the MDR, the database has been beset by the type of delay that was predicted by many experts who cite historic problems with the vast majority of EU databases developed by the European Commission..

The database is now due to go live in its entirety in May 2022. The notice to trigger the go-live will be published in 2022, after a positive independent audit to assess that Eudamed has achieved full functionality and meets the functional specifications.

After much debate over whether individual modules of the database could go live before the database goes live in its entirety, the commission has agreed that from 1 December 2020, medtech manufacturers should be able to register – voluntarily – in the actor registration module.

BREXIT, SWIXIT AND TURKEY

It is already clear that the medtech sector has some very big technical and political challenges ahead and is swimming in uncertainty and in urgent need of greater clarity.

But the political situations between the UK and the EU and between Switzerland and the EU, as well as Turkey and the EU, have made implementation of the MDR and IVDR even more complex.

There have been clues about how the UK will move forward after Brexit. UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), said in 2020 that the UK will continue to use and recognize the CE marking for medical devices and IVDs until 30 June 2023. Certificates issued by notified bodies based in the European Economic Area will, therefore, continue to be recognized in the UK until that date.

This puts an end to the previous UK position, and to concerns that if the UK still leaves the EU at the end of 2020 with no deal that EU notified bodies and their certificates would no longer be recognized in the UK.

Ironically, this would have included the only remaining UK notified body, BSI UK.

This will be a welcome reprieve for BSI, although it had already set up a Dutch notified body to which most BSI UK medtech and IVD certificates have been transferred. BSI Netherlands is designated against the medical device directives and the MDR and IVDR. BSI UK had been among the first of the EU notified bodies to be designated under the MDR and the IVDR.

Switzerland, meanwhile, is still trying to work out the basis for its future relationship with the EU, and indeed the UK. As of late-2020 it had one notified body, SQS – Schweizerische Vereinigung für Qualitäts- und Managementsysteme, designated under the MDD (although none under the IVD Directive), and no new Swiss notified bodies are expected to be designated under the new EU regulations until the Swiss-EU mutual recognition agreement is finalized.

And, because of a similar political issues, no Turkish organization can apply to be a notified body under the MDR or IVDR until the Turkish customs agreement has been signed. This is a potentially big hit to notified body numbers, as Turkey has five notified bodies under the MDD and one under the IVDD.

The start of 2021 is a critical time for the medtech sector. Is this a time when as many obstacles as possible are going to be removed so that the sector can focus whole-heartedly on compliance, rather than on the politics and uncertainties? Or are we now at a stage where deadlines are going to need to be continually put back while COVID-19 wreaks havoc on the industry?

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Intelligently Automating Safety And Regulatory Processes

How Artificial Intelligence is streamlining pharmacovigilance and regulatory workflows

UPDESH DOSANJH
Practice Leader,
Technology Solutions

CHAM WILLIAMS
Associate Director,
Business Systems

Pharmacovigilance (PV) and Regulatory leaders may have different goals, but they face many common obstacles. One of the biggest is the enormous number of manual steps involved in their workflows. More than half of the activities completed by both departments involves the manual collection and extraction of data from one format and/or database into another.

In addition, almost half of the source information received – by PV for example – requires translation to English before it can be submitted to regulators and partners; many submitted documents will require additional translations from English back to another language to complete the process.

The results of these manual efforts are frustratingly inconsistent. Data shows that on average, PV and regulatory teams spend 40 percent of their time on data entry and another five percent in training and retraining[1] because data extraction rules are constantly changing. Despite the time and training:

- 80 percent of PV source documents are found to be extracted incorrectly even after manual quality control.

- 50 percent of cases have significant data consistency errors between extracted fields, i.e. the same data entered differently in the same case.[2]

The lack of automation of these steps and the high rate of error, means a vast amount of time is spent on tasks that don't help meet core objectives – bringing products to market quickly and maintaining them in market. Instead, highly skilled PV and regulatory professionals are spending their days doing manual data entry tasks that fail to leverage their skills, training and expertise.

And the work is piling up. According to statistics compiled by Dell EMC, health data grew by 878 percent between 2016 and 2019. In safety/PV, the number of adverse events (AEs) alone is growing by about 20 percent per year. With this increasing volume, manual models of data creation, translation and management are no longer sustainable. To adapt, PV and regulatory professionals need to embark on a digital transformation process to streamline these steps and make better use of their resources and expertise.

Recent advances in artificial intelligence technologies are making that transformation possible.

AI TO THE RESCUE

A new range of AI solutions is bringing smart automation to many of these activities, making it possible to complete even complex evaluation, translation, and extraction steps with minimal to no human intervention. The evolution of these tools will change how safety and regulatory teams work, cutting costs and shrinking processing time, while delivering higher data quality.

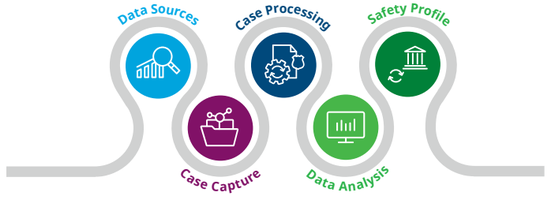
It may sound like an exaggerated value proposition. However, comparison data proves that using AI-driven automation tools for regulatory and PV consistently delivers higher quality results with fewer errors in less time than it takes humans to complete these tasks.

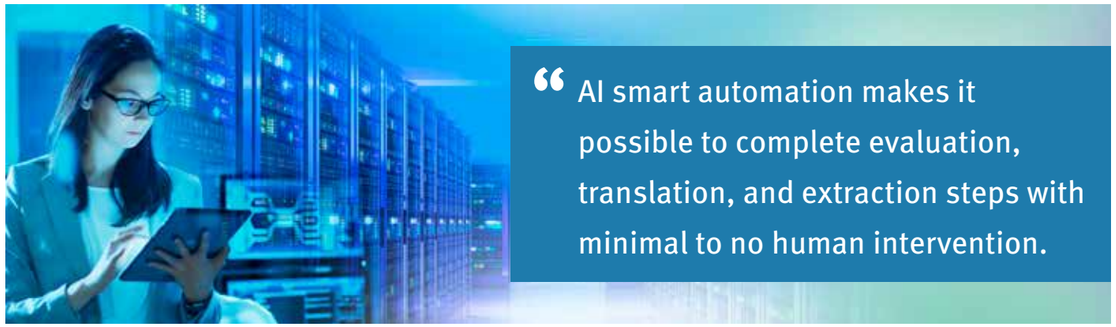
THE JOURNEY IS COMPLEX

Even when they have the time and resources to complete the work, the rate of human error is higher than that seen with AI tools. But these obstacles can be overcome.

By combining translation management and natural language processing (NLP) technology, new solutions can automate multi-sourced data extraction, translate documents, normalize formatting, and port data into relevant databases for further processing. These NLP solutions are specifically built for regulatory and PV workflows by life sciences industry experts who understand the complex and evolving nature of the regulatory environment. By working with industry experts, developers bring context to the technology design and algorithm training, ensuring consistent relevant interpretation for every local regulatory environment.

These technologies can extract the most common attributes relevant to PV and regulatory tasks, including as-reported events, event dates, patient details, reporter details and product/therapy





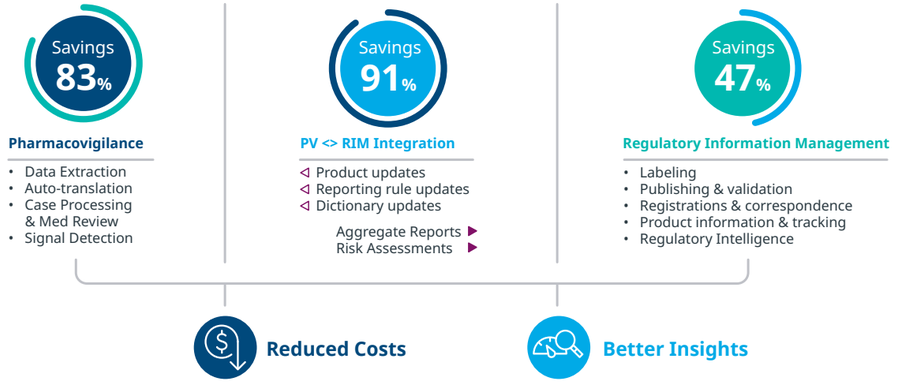
details. And the impact is significant.

Our data shows automation of PV and regulatory steps using AI-driven technology yields cost savings of up to 91 percent for case processing and system management; 83 percent for case intake steps; and roughly 50 percent on aggregate reporting, data analytics, signal detection and risk management.

HOW IT WORKS

In a typical PV workflow, data comes from a variety of sources in structured and unstructured formats. These range from case reports and clinical data to social media posts, academic literature, webinars and patient calls. PV professionals could dedicate hundreds of hours a month reviewing this information to identify potential adverse events, monitor data integrity, translate documents, and put them into the necessary formats – and still not cover it all. That can cause life sciences companies to miss critical regulatory deadlines, and delay identification of safety events.

BENEFITS ACROSS PV AND REGULATORY



AUTOMATED LANGUAGE TRANSLATION BENEFITS

The benefits include the ability to analyze and translate documents into multiple languages, which is key to the successful automation of regulatory and PV tasks.

When done manually, language translation steps can take days to complete. And because they require professionals with PV and regulatory expertise as well as full fluency in the languages being translated, the costs are significant.

Life sciences companies can spend up to 50 percent[3] of their PV and regulatory budgets on translation steps, and most of these documents still require substantial revisions due to translation errors. Some companies have tried to use commercial translation tools like Google Translate to mitigate the burden, but these tools aren't designed to handle complex regulatory language and can only deliver rough translations.

However, translation tools that are built specifically for the life sciences industry can handle even the most sophisticated translations. IQVIA's Linguamatics NLP system features Google's neural machine translation (NMT), which uses artificial neural networks to predict how sequences of words should be translated.

The technology can learn in-country speech patterns, along with rules, acronyms and abbreviations for any language and regulatory body, including Japanese Med-device entities, Chinese Pre-Ordering Rules, Korean Pharma Tokenizer, and Spanish Localization rules. The translations are supported by human review to ensure every translation aligns with the latest regulatory language.

In 2019, IQVIA's solution translated 45 million words, and it can now handle translations in 25+ languages across multiple file formats. The innovation achieved with this technology means regulatory and PV teams have almost instant access to translated

> The benefits of AI for regulatory and PV tasks are clear. These tools reduce manual labor, while bringing unprecedented speed and accuracy to complex regulatory tasks.

documents that average a BLEU score of over 85.[4] In contrast, when life sciences companies rely on outsourced vendors to translate documents manually, the same quantity of work requires days to complete and best case delivers a BLEU score of 80. The cost of automated translation is also lower and more predictable because rates are based on number of documents translated, rather than time and complexity of the work.

50 YEARS OF DOCUMENTS

Using this technology, clients can translate hundreds of pages in minutes, while maintaining formatting in the same rendering as the original file. The impact is significant.

For example, IQVIA recently worked with a global pharmaceutical company that wanted to automate extraction of adverse event submissions from source documents to meet EU EudraVigilance mandates.

The company deployed IQVIA's Translation and NLP solutions, developing queries around specific business rules for English, French and German, and incorporating relevant specialist vocabularies, (including MedDRA, EDQM Standard Terms database). As a result, the company was able to index data for various uses in risk assessment which would have been impossible manually.

In another example, a tier 1 pharma company partnered with IQVIA to address a legacy data analysis issue related to a regulated medicinal product. The company had 1300 relevant documents in five languages (English, French, Spanish, German, Italian) spanning 50 years. To meet ISO Identification of Medicinal Products (IDMP) standards, they had to extract key data attributes from 30 different fields, and map them to internal schema.

Using a combination of IQVIA's Translation and NLP solutions, IQVIA's team was able to build and run automated queries in all five languages to extract data elements that were then mapped to the client's exact output schema.

The result showed that 94 percent[5] of the fields in the samples assessed corresponded to accurate extraction, enabling the client to reduce manual review time to a few days per expert.

AUTOMATION AND LABELING

AI-driven innovations are also benefitting labeling tasks, which are essential for maintaining products in the marketplace.

Labeling processes must comply with continually evolving rules for 150 regulatory bodies. Product labels can undergo frequent changes due to factors ranging from safety and efficacy concerns to graphics changes, and must be adapted to the unique requirements of every market.

Keeping track of these changes requires constant monitoring and creates many opportunities for human error that negatively impact or delay labeling approvals. Noncompliance could lead to lost market authorization and potentially jeopardize patient safety.

The use of AI in these tasks can drive down costs, freeing time and resources that can be invested in activities that drive strategic value.

As with translation steps, AI-driven automation brings speed and precision to the labeling process, reducing time and risk in the workflow. Current iterations of automation technology can process massive amounts of information, expediting regulatory processes, while freeing regulatory professionals to spend more time on activities that drive market advantage.

In the future, more advanced intelligence will make this speed even greater while adding a higher degree of accuracy. Labelers will be able to compare any number of countries' labels simultaneously, react to global regulatory insights proactively, and make adjustments before noncompliance becomes a possibility. This, in turn, will ensure resilience against the unpredictability of the regulatory compliance landscape.

Intelligence in labeling may also bring added safeguards for patients. These tools can process information in almost real-time, which means pharmaceutical companies may soon be able to relay label updates directly to patients taking those drugs. It will help them address potential adverse events more rapidly, and create greater transparency between developers, physicians and patients.

CONCLUSION

The benefits of AI for regulatory and PV tasks are clear. These tools reduce manual labor, while bringing unprecedented speed and accuracy to complex regulatory tasks. The tools have been trained using millions of regulatory documents, and have been proven repeatedly to deliver higher quality results in a fraction of the time. By adding AI and ML to these workflows, pharma companies can optimize their signal surveillance process in a simplified manner to monitor risks across multiple data sources.

The transition to automated systems will require time, planning, and partnerships with industry experts, but the sooner companies begin this transformation, the sooner they will slash time and risk from these tasks, and create a safer environment for all of the patients they serve.

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REFERENCES
References 1-5, Internal IQVIA data 2019-2020

SARAH KARLIN-SMITH
SENIOR WRITER, US

KATE RAWSON
SENIOR EDITOR, US

Time For Independent US FDA? COVID Political Pressure Reignites Debate

The political spotlight on the FDA during the coronavirus pandemic has renewed a long-standing debate as to whether it should be made an independent, Cabinet-level federal agency and freed from direct HHS oversight.

The argument for an independent US Food and Drug Administration (FDA) has taken on renewed interest following President Trump's political pressure on the agency to rapidly clear COVID-19 products, most notably a vaccine. But while the idea of a more independent agency enjoys broad stakeholder support, it is far from universal, and practical considerations suggest that the FDA will always face a fair degree of oversight by elected officials.

Still, it remains the hope of many – especially former commissioners who have sat in the political hotseat – that the FDA could obtain a greater degree of operational independence. In a January 2019 commentary in Health Affairs, seven former FDA heads – Robert Califf, Margaret Hamburg, Jane Henney, David Kessler, Mark McClellan, Andrew von Eschenbach and Frank Young – argued that the FDA should be moved out of the Department of Health and Human Services (HHS) and reconfigured as a separate federal agency.

"FDA policies and actions are not driven by partisan politics: the scientific foundation for its decision making is guided by legislation that almost invariably has strong bipartisan support," the former commissioners wrote. "We believe that our recommendations fit squarely within that bipartisan tradition of keeping the agency as up-to-date and effective as possible." The commentary was accompanied by a white paper from the Aspen Institute and followed a 2016 panel discussion with six of the commissioners where they first presented that consensus view.

The commissioner at the time the exes made their proposal was Scott Gottlieb, who left the post a few months later and added his name to the effort. But with his tradename compassionate realpolitik, Gottlieb also noted that independence was unlikely to be achieved.

"The momentum is away from these independent agencies and [the Office of Management and Budget] is trying to exert more control over the rulemaking processes for all agencies, including these so-called independent agencies," Gottlieb said during an interview in May 2019. "And I don't think Congress is likely to want to give up control and allow FDA to become an independent agency either."

"I'm willing to support it," he added. "I love the debate. But I just don't see it happening, unfortunately."

Since then, the stakes of the debate seem to have only grown, with public confidence in a coronavirus vaccine showing continued drops throughout the pandemic, doubtless influenced by the repeated questions about whether the FDA has made science-based decisions in clearing some COVID-19 products for emergency use.

EX-CHIEF COUNSELS MORE SKEPTICAL THAN EX-COMMISSIONERS

Sounding a note of caution as good advisors always should, a panel of five former chief counsels and the current chief deputy in the Office of Chief Counsel, Elizabeth Dickinson, expressed less enthusiasm for the idea of an independent FDA during the Food and Drug Law Institute's annual conference in October 2020.

The FDLI panel did not come to any clear consensus on the question, with some former chief counsels arguing that the FDA's status as a science-based agency already renders it largely independent and pointing to the benefits of being able to coordinate with sister agencies within the common framework of HHS.

During the discussion, conducted online like all sessions of the conference in 2020, others argued that an independent FDA would allow it to manage its workload more efficiently and be more accountable to Congress.

Sidley Austin LLP's Rebecca Wood, who served under Gottlieb, gave a balanced view of the issue. "FDA already functions in many respects as an independent agency. There is an incredibly strong culture. There is an incredibly strong sense of mission among the career professionals. And it's a science-driven, data-driven agency."

That said, "there are a lot of good arguments for why the agency should be independent in terms of managing its own workloads, in terms of being better suited and better fitted for its purpose from Congress," Wood observed. "Historically, there have been some counter-arguments – that it's helpful to have structural oversight and to have checks and balances."

King & Spalding LLP's Sheldon Bradshaw, who served under commissioners Lester Crawford and Andrew von Eschenbach, agreed. A move "may just cut out a layer of HHS that perhaps isn't necessary," Bradshaw said. He was careful to explain his definition of an independent FDA as an agency that is separate and apart from HHS but still reports to the White House and is not completely removed from the executive branch. If independent is interpreted to mean "there's no control over what the agency is doing by the White House and OMB, then I think that would be a bad idea," Bradshaw said.

"I don't like the idea of an independent agency that just decides on its own, irrespective of the administration, what it is going to do. But there might be some utility in breaking it away from HHS and giving it more independence in that regard," Bradshaw said.

Wood suggested that FDA independence could come in different forms: "Are people satisfied with the current system, or could it be improved going forward? It's going, at the very least, to inject new interest into that debate, and the related question: should the agency have independent litigating authority? There are all sorts of different ways that you might become an independent agency. Should it also decide its own case law, or continue to work with the Department of Justice in bringing its cases?"

Gerald Masoudi, who succeeded Bradshaw under von Eschenbach and now is with Covington & Burling LLP, suggested some benefits to the current reporting structure. "If you look at the other functions within HHS with which FDA interacts on a regular basis," such as the Centers for Disease Control and Prevention, the National Institutes of Health and the Office of the Surgeon General, "having those function together under common expert leadership on health care issues is very important."

Covington & Burling's Peter Barton Hutt, who served under Richard Nixon appointees Charles Edwards and Alexander Schmidt, called the need for FDA independence a "false issue." The FDA, he said, has always been under political pressure – usually from Congress – and making the agency a direct report to the Oval Office would not change that reality. "There has never been a time when political pressure wasn't brought on FDA. Most of the time it's from Congress – not from the President or the White House – and you can't insulate even an independent agency from Congress," Hutt said.

> *"There has never been a time when political pressure wasn't brought on FDA." – Peter Barton Hutt*

PANDEMIC HIGHLIGHTS THE PROBLEM

While the discussion on independence among the former commissioners began well before COVID-19, questions about the FDA's scientific independence have resurfaced during the pandemic. "There's going to be a renewed interest with the political firestorm that we're seeing in the current environment asking, now that people see how important independent, science-driven decision making is on these sorts of questions with medical countermeasures," Wood said during the FDLI meeting.

The former FDA commissioners, other than Young, who died in November 2019, were joined by Gottlieb in a September 2020 op-ed in the Washington Post to warn against White House interference and again call for an independent, science-based process. "Scientists should make decisions based on data, unfettered by political pressure or the intrusions of ideology or vested interests. Political intrusion only prolongs the pandemic and erodes our public health institutions."

According to a staff analysis from the House Select Subcommittee on the Coronavirus Crisis, the administration has interfered in the coronavirus response 47 times between February and September 2020. The report was unveiled before an October 2 hearing with HHS Secretary Alex Azar.

Examples include pressuring the FDA to review the botanical extract oleandrin as a COVID treatment, issuing an emergency use authorization (EUA) for plasma over the objections of scientists, pushing hydroxychloroquine as an unproven treatment and the accusation of the "deep state" at the FDA slowing a vaccine until after the election.

IF NOT THE FDA, THEN WHO?

The threats to the FDA's independence have troubled not just US stakeholders, but foreign regulators as well, since the agency has long been seen as the global "gold standard" because of its relatively large resources and its patient-level review of data in applications.

But now, for the first time, the World Health Organization will require manufacturers to share the data they have submitted to other regulators and have the manufacturers agree that WHO can share sponsors data with other global regulators for COVID-19 vaccines.

This should help ensure transparency and global trust in vaccines, said Emer Cooke, WHO's director of regulation of medicines and other health technologies at the 2020 US National Academies of Science Engineering and Medicine meeting on regulatory reliance and the current pandemic.

"I think that's something that's really going to make a difference. I think we have as a global community, we have to stand up and be counted. We can't hide behind the confidentiality, the trade secret information. We have to be competent in the products that we're getting, in the assessments that are being done, if we're going to ask other people to rely on them. We can't ask them to rely on a black box," Cooke said.

Cooke said that there has been unprecedented cooperation in COVID-19 vaccine development and that she is confident "we'll all step up to the mark and be able to ensure that we have independent science, safe and effective products. Because if we don't we all suffer, if we do we all gain."

The panelists at the meeting agreed that COVID-19 had created one of the strongest cases for international regulatory cooperation, even as they worried about how to do that with a politicized FDA.

Brexit: The View For Pharma In 2021 And Beyond

With the end of the Brexit transition period fast approaching, life sciences companies need to be ready for some major changes to drug regulations as well as the impact of new border and customs controls on the flow of medicines between Great Britain, Northern Ireland and the EU. *In Vivo* looks at what is at stake, and what still needs to be done, as the UK prepares to leave the EU single market and customs union at the beginning of 2021.

BY IAN SCHOFIELD
EXECUTIVE EDITOR, EUROPE

Whatever the outcome of the protracted and often painful negotiations on the future UK-EU trade and security relationship, the life sciences companies in the UK will be entering a very different regulatory landscape in January.

On the positive side, the UK will have its own, fully standalone medicines and medical devices regulator in the form of a strengthened Medicines and Healthcare products Regulatory Agency (MHRA) with new drug licensing procedures and what it calls a "powerful new vision" for fostering innovation in the post-Brexit era.

In other respects, though, January will usher in a host of rules and regulations that companies will need to be prepared for. Uncertainties will linger over batch testing and release as well as the impact of the complex new relationship between Great Britain and Northern Ireland on regulation and trade. More visibly, widespread delays to medicines deliveries are expected at the Channel ports as a result of the new customs and border controls that will begin to be enforced starting in January as a result of the UK's leaving the EU's single market and customs union. The UK government has taken steps to secure freight space for medicines on alternative ferry routes away from the Channel, but there are still fears of major disruption to supply chains.

In November the Department of Health and Social Care wrote to medicines suppliers urging them to "act now" to "mitigate the risk of delay and disruption at the short straits." It pointed out that the while border controls would not be fully implemented until mid-2021, the biggest potential cause of problems was "traders not being ready for controls implemented by EU member states on 1 January 2021."

All this, of course, will coincide with the disruption caused by the continuing COVID-19 crisis and the winter peak in National Health Service (NHS) hospital admissions.

Matters will be far worse if the UK and the EU fail to reach an agreement and the two sides have to impose tariffs and other strictures under World Trade Organization rules. The UK government's Office for Budget Responsibility has forecast that UK GDP will shrink by 11.3% this year as a result of the coronavirus pandemic, and that without a deal, GDP would be a further 2% lower in 2021 and 1.5% lower in 2025.

WHAT INDUSTRY WANTS

No one needs to be reminded of the political and organizational chaos that has characterized the preparations, first for Brexit and then the end of the Brexit transition period on 31 December.

In October Steve Bates, CEO of the UK BioIndustry Association, took exception to suggestions that companies had failed to properly prepare for the end of the transition period. Bates argued that the government lacked consistency and had changed its position on several occasions. "The challenge we face as businesses is that there is an ask of the sector to be ready to go, but you can only be ready if there is clarity on the detail," he declared.

In a similar vein, Richard Torbett, head of the Association of the British Pharmaceutical Industry, said it was "absolutely clear that it's in nobody's interest – and certainly not patients – to face the future with uncertainty around how medicines will be regulated, tested and moved throughout Europe and the UK."

Ideally the life sciences sector would like to see a comprehensive free trade deal agreed with the EU, together with some degree of regulatory alignment. Failing that, it wants at the very least a mutual recognition agreement on good manufacturing practice.

At the time of publication, the outcome of the negotiations was still unknown, although there were suggestions that the bulk of the work had been done and that some last-minute high-level political compromises on issues such as the level playing field and fisheries might be enough to get a deal of some sort over the finishing line.

> *"There is an ask of the sector to be ready to go, but you can only be ready if there is clarity on the detail." – Steve Bates*

A NEW-LOOK MHRA

Regardless of the nature of the future UK-EU relationship, much of the regulatory landscape that will be awaiting pharma firms next year is already clear. The UK regulator, the MHRA, will have a new role in assessing medicines, and has been quietly building up its structures and developing new procedures so it can hit the ground running on 1 January.

In September, the MHRA's interim chief executive, June Raine, revealed what she called a "powerful new vision" for the agency in terms of fostering innovation, developing new lifecycle-driven regulatory approaches, and being more responsive to patient safety.

The MHRA, Raine said, would have a "global voice" and a "new leadership role," helped by the "amazing opportunities" offered by digital technology, analytics, artificial intelligence, novel clinical trial designs and strengthened horizon scanning.

NEW LICENSING PROCEDURES

These claims will be put to the test when the MHRA gets the power to assess new drug applications that are currently under the purview of the European Medicines Agency, mainly new active substances, biological products (including most vaccines) and advanced therapy medicines.

The key new development is the Innovative Licensing and Access Pathway (ILAP), described by the agency as a "radical and ambitious" route for novel medicines that meet specific criteria, such as treating life threatening conditions or rare diseases. Companies using this pathway will benefit from the 'innovation passport' – a designation intended to open the way to a 'target development profile' (TDP) similar to the target product profile many companies are already familiar with.

The TDP will lay out a roadmap for the development of a new drug, spelling out details such as key regulatory and development features, any scientific advice, potential pitfalls and so on. The pathway will be accompanied by a set of measures to support product development, including adaptive inspections, enhanced patient engagement, manufacturing support, novel clinical trial design support, continuous risk-benefit assessments, and integrated real-world evidence.

The MHRA has developed a new national portal for regulatory submissions that it says will be ready by 1 January, 2021. It is important to note here that the MHRA's marketing authorizations (MAs) for novel products will be valid only for Great Britain – EU medicines regulations will continue to apply in Northern Ireland under the Northern Ireland Protocol to the Brexit Withdrawal Agreement.

The MHRA plans to mirror some EU regulatory practices, including accelerated assessment and conditional approvals, as well as making greater use of rolling reviews.

The 150-day accelerated review mechanism for Great Britain will be open for both new and existing active substances, and will cover orphan drugs,

medicines submitted for conditional and full approval, and those for approval under exceptional circumstances.

The conditional approval scheme will have the same eligibility criteria as the EU system, aimed at products for unmet medical needs such as serious and life-threatening diseases without any satisfactory treatment methods, or where the product offers a major therapeutic advantage.

The existing rolling review process, currently reserved for emergency circumstances, will be extended to cover novel substances including biologicals/biosimilars.

CONVERTING CAPS TO GB MAS

New procedures have been introduced to deal with EU centrally authorized products (CAPs) whose marketing authorizations were issued either before or after the end of the transition period on 31 December.

Existing centralized MAs will automatically be converted ('grandfathered') to GB MAs free of charge, although the MA holder will need to provide a data submission package at some point within 12 months of 1 January 2021. The information required will include a single eCTD "initiating sequence" for the converted MA and a summary of all historical regulatory activity from the grant date of the original centralized MA.

Companies have been told to take action now on converted MAs. In early November the MHRA wrote to company heads of regulatory affairs explaining that they should review all their existing EU centralized approvals and notify it of the products' marketing status and any products or presentations that are no longer approved or marketed. The MHRA also informed marketing authorization holders (MAHs) that they could opt out of the conversion process for all or some of their CAPs by notifying the MHRA in writing by 21 January 2021. "If an MAH chooses to opt out, after 21 January 2021 their product(s) will no longer be licensed in Great Britain."

Once a converted MA has been issued, it must be transferred to a GB-based MAH by 1 January 2023. The MAH will then have another year in which to make sure that all the products it releases to the market is in compliant packaging. The renewal date of converted CAPs will be based on the date of the original EU MA, as will any periods of data protection or market exclusivity.

THE RELIANCE ROUTE

For companies seeking EU approval that do not also wish to apply directly to the MHRA, the UK has said that it will continue to recognize EU centralized approvals for two years from 1 January 2021. Under the so-called 'reliance route,' companies will still have to file an approval application with the MHRA, including all the data originally provided to the EMA. Keith McDonald, deputy director of the MHRA's licensing division, said in October that the agency would recognize EU decisions "subject to a risk-based review in the context of UK clinical practice and any GB-specific considerations." If the application was submitted as soon as the CHMP opinion was available, he said, the GB MA approval "would be made at the time of the EC decision."

There will be some instances where new drugs were filed for EU approval but were still awaiting either a CHMP opinion or a European Commission MA decision as of 31 December. The UK will treat these as 'in-flight assessments,' and the company will need to apply to the MHRA for a GB MA application in parallel with the EU application. In such cases the UK agency will take account of any evaluations that the EMA has conducted before 1 January 2021, and will aim to complete its own assessment no later than the issuance of the EC decision.

Alternatively, the applicant can wait for the CHMP positive opinion and then apply for a GB MA using new reliance route. The application will be determined after the European Commission has taken its decision on approval.

For variations to converted CAPs, the company must submit a 'minimal initiating sequence' and related documentation. The procedure followed will depend on the type of variation sought and the point the variation procedure has reached as of 1 January 2021.

The MHRA has published detailed guidance on submitting variations in general, which among other things addresses how variations submitted to the EMA before and after the end of the transition period will be dealt with by the MHRA, and the processing of variations to CAPs in Northern Ireland.

BATCH TESTING AND RELEASE

Companies also need to make sure they are prepared for changes in areas such as batch testing and release, pharmacovigilance, and processes for orphan drugs and medicines for children.

Batch testing and release have proved a real Brexit bugbear for the industry, which has been pressing for an MRA allowing the UK and the EU to recognize each other's testing and avoid duplication of effort. In the event of a no deal, or a "skinny" deal with no MRA, the UK has said it will continue to recognize batch testing done in EEA countries, but only for two years from 1 January 2021. After that the batch testing would have to be repeated in the UK, which would mean companies having to set up new testing labs – a process that industry sources say can take up to two years.

THE NORTHERN IRELAND QUESTION

Due to the unique situation of Northern Ireland in the Brexit scenario, special provisions are in place for batch testing and other aspects of drug regulation there, as well as for medicines moving between NI and GB.

According to new EMA guidance published on 26 November, based on the Northern Ireland Protocol, batch release by an importer/manufacturer established in NI will be recognised in the EU/EEA after 31 December 2020. Similarly, quality control testing for the purpose of release to the market conducted by testing sites in NI will be recognised in the EU/EEA.

Medicinal products shipped from GB to NI after 31 December 2020 will be considered imports to the EU and will be subject to the requirements concerning quality control testing and batch release. Where products are shipped from one part of the EU internal market to another (e.g. from France to the Republic of Ireland) via the "land bridge" (mainland Britain), they are not considered as placed on the UK market and will not have to undergo quality control and QP release upon arrival in Ireland.

It has also been agreed that medicines regulation specifically for NI will be phased in over 2021, rather than being implemented immediately on 1 January. The aim here is to give businesses more time to prepare for the new rules, particularly for batch testing, medicines import and the requirements of the EU Falsified Medicines Directive (i.e. the safety features on medicine packs).

The MHRA has also published separate guidance on moving goods between NI and GB.

ORPHAN DRUGS AND MEDICINES FOR CHILDREN

The rules on orphan drug designation are also changing next year. Companies seeking orphan status in Great Britain will need to apply for it at the same time as they file the product's marketing authorization application (MAA). There will be no pre-marketing authorization orphan designation for Great Britain.

Incentives for orphan drug development will be provided in the form of market exclusivity and full or partial refunds for marketing authorization fees, while waivers from scientific advice fees will also be available for UK-based small and medium-sized companies.

It is important to note that the orphan exclusivity will be dated from the time of first approval of the drug 'in GB or EU/EEA' – this is understood to be a way of encouraging companies to file their MAA with the MHRA at the same time as the EU application.

Companies developing medicines for children will need to file pediatric investigation plans (PIPs) with the MHRA. They should include any information relevant specifically to the UK, particularly with respect to any areas of unmet needs in the pediatric population that the drug is intended to cover. The submission format and terminology will be the same as in the EU, which means that the scientific content and assessment required will be kept in line with the EMA's guidance documents.

PHARMACOVIGILANCE

From January 2021, the Qualified Person for Pharmacovigilance (QPPV) must be based in UK or EU. For QPPVs based in EU, companies will have 12 months from 1 January 2021 to establish a UK based contact person and inform the MHRA accordingly.

The existing rolling review process, currently reserved for emergency circumstances, will be extended to cover novel substances including biologicals/biosimilars.

POLICY & REGULATION

Indian Telemedicine Prospects Boosted By Long-Awaited Guidelines

VIBHA RAVI
SUB-EDITOR, APAC

Guidelines outline permitted practices and patient safeguards for both physicians and technology platforms.

India is a promising country for the expansion of telemedicine, which has been available for almost two decades and has gained additional fuel with the growth of telecom networks and availability of mobile phones even in the country's most remote areas.

But it is also a classic case of regulations lagging growth and need for oversight. That is changing now with the Telemedicine Practice Guidelines, issued 25 March 2020. Accelerated by even greater interest in telemedicine during the COVID-19 pandemic, the guidelines encompass both medical practice and digital tools, and include provisions to specify which prescription drugs can be prescribed based on a telemedicine examination.

They also give powers of regulatory oversight to the Board of Governors or the Medical Council of India (MCI), both of which have now been replaced by the National Medical Commission.

India's doctor-to-population ratio of 1:1541, compared to the World Health Organization's standard of 1:1000, points to the huge potential of telemedicine, with its efficiencies and geographic reach, to expand access to a wide range of health care services. The guidelines' clarity on permitted practices and patient safeguards could help fulfill this potential.

Telemedicine made an official debut in India in 2000, when then-US president Bill Clinton commissioned the Apollo Hospital Group's first telemedicine unit in the village of Aragonda in Southern India to offer services of a tertiary care center in Chennai. Following this pilot project, the state-owned Indian Space Research Organization (ISRO) deployed the first nation-wide satellite-based telemedicine network in 2001 and with initiatives by ISRO and various government departments, telemedicine services began expanding. It truly grew wings of its own with new technology platforms and providers.

Telemedicine services have been governed by a scattered set of regulations including the Information Technology Act, 2000, the Drugs and Cosmetics Act, 1940, the Indian Medical Council Act, 1956 and the Clinical Establishments (Registration and Regulation) Act, 2010. The services came under the combined jurisdiction of Ministry of Health and Family Welfare (MoHFW) and the Department of Information Technology.

This situation meant services have often operated in a gray area. A 2018 judgement of High Court of Bombay led to panic among doctors as the court held that a patient died because, among other things, she was prescribed treatment over telephone without appropriate diagnosis and concluded such practice to be an act of criminal negligence. As a result, some State Medical Councils reportedly went to the extent of banning teleconsultation.

Though guidelines specifically addressing telemedicine were already under consideration, the COVID-19 crisis pushed the government to issue them just a day after a strict lockdown was imposed across the country. With patients at first unable and later unwilling to travel to hospitals for risk of exposure, telemedicine quickly became a channel of choice for health care rather than a fallback.

The guidelines, issued by the MoHFW under the Indian Medical Council (Professional Conduct, Etiquette, and Ethics) Regulations, permit a patient, caregiver or health care worker to consult a registered physician via telecommunications/digital tools while also permitting doctors to discuss cases or share knowledge. Medical practitioners registered under the Indian Medical Council Act can offer teleconsultation services via voice, audio, text and digital data exchange. They must complete a yet-to-be designed online course within three years of its creation.

The guidelines make teleconsultation optional for patients and orient it to primary or secondary care. For example, physicians cannot insist on a teleconsultation if a patient is willing to travel to a facility and/or requests an in-person consultation.

With nearly 70% of the Indian population residing in villages and nearly 60% hospitals and 80% of doctors in urban areas, the provision of a first consult for diagnosis and treatment in non-emergency situations as well as follow-up consults aids the cause of patients who live in areas far from a formal health setup. However, if a physical examination is critical for consultation, an in-person consult is essential before a teleconsultation. About 80% of health care services in India are primary or secondary care.

The service cannot be availed for emergency care if in-person service is available and even when it's the only way to provide timely care, it should be limited to first aid and life-saving measures following which an in-person interaction with a doctor at the earliest should be advised.

The guidelines also exclude surgical or invasive procedures and do not provide for consultations outside India. In the past, teleconsultation has been used to guide or supervise such procedures, especially in areas where the technology is new and experts few.

Physicians are to issue signed physical or e-prescriptions and can only prescribe certain medicines that are on predefined lists updated from time to time. List O includes over-the-counter medicines and those deemed necessary during public health emergencies, List A includes medicines with low abuse potential such as for hypertension and List B has additional drugs that can be prescribed to patients undergoing follow-up post an in-person consult for the same medical condition.

In a move to prevent drug misuse, medicines on a prohibited list, which includes narcotic and psychotropic substances, cannot be prescribed.

TECHNOLOGY IS A TOOL, NOT DECISION-MAKER

Physicians can draw upon information from platforms based on artificial intelligence/machine learning to aid in patient evaluation or management. But the guidelines direct that treatment decisions and counseling services must be made and delivered by the physician themselves.

Physicians also are required to maintain prescription records, phone logs, email records, chat/ text record, video interaction logs, patient records, reports, documents, images, diagnostics and other digital or non-digital data for specified periods of time.

The guidelines place the onus of adhering to current data protection and privacy laws on the physician, though some physicians might not be competent at or comfortable with this. The rules prohibit any action that willfully compromises patient care, privacy and confidentiality and they even cite transgressions via social media such as uploading explicit images of patients on social media platforms or adding a patient to a virtual support or educational group. Physicians also cannot solicit patients for telemedicine through any advertisements or inducements.

Digital consultation platforms like Practo, Lybrate, Mfine, Ask Apollo and Just Doc, which kept the practices of health care professionals going even when patients could not visit clinics, have also been brought under the purview of the Telemedicine Guidelines.

Technology platforms including websites and mobile apps which provide telemedicine services are now obligated to ensure that they conduct due diligence before allowing practitioners to use their platforms and must maintain various details about them.

Every technology platform also must have a mechanism to address queries or grievances from patients. The technology platform is to report non-compliance by registered physicians to the MCI, which can take appropriate action. And a platform found in violation of the guidelines can be blacklisted.

Building a robust and secure patient data management system will require an investment. Apps like SlashDr can provide physicians with means of maintaining electronic health records as well as provide consultations for a fee, however, individual practitioners might not be willing or able to bear the annual cost of INR25,000 ($335).

In October 2020, one of India's leading pharma companies, Dr. Reddy's Laboratories Ltd, was the subject of a ransomware attack. If such a presumably well-guarded system can be hacked, accessing data residing in much less sophisticated systems could be child's play.

Other vulnerabilities include access to telemedicine data by information technology staff, who might not be bound by a strong code of conduct as physicians are.

"The biggest areas [of concern] are data privacy and portability rules. Who owns the data? If third-party players are gateways to telemedicine, can they have access to de-identified information or is that a strict no-no? Can payment gateways be commissioned for fees? Are there specified gateways or they are left to individual choice?" asked Salil Kallianpur, former executive vice-president at GlaxoSmithKline plc in India, who now runs a digital health consultancy.

Mobile health care apps could also cause privacy concerns. Such apps could have tie-ups with third parties interested in creating ads based on a patient's needs, a practice which might not just be a breach of privacy but could also be unethical.

The Indian Judiciary has recognized citizen's rights over data protection, but there is no clear law to ensure this. A government committee proposed the Personal Data Protection Bill 2019 which would be the country's first law solely on data protection. However, it is still to see the light of day.

IS TELEMEDICINE HERE TO STAY?

Despite these constraints, telemedicine has been gaining momentum, coming into even sharper focus during the pandemic.

"Teleconsulting is a useful tool, especially for senior citizens and for those who have had surgical procedures recently. It's particularly handy now for other patients as well who need follow-ups – in fact, my colleagues tell me that they're likely to continue with this practice as it saves time, money and labor for patients," Vivek G Shetty, joint replacement surgeon and consultant orthopedic at P D Hinduja National Hospital, one of the most prominent hospitals in Mumbai, said.

Rakesh Ranjan, consulting neurosurgeon at Aditya Birla Memorial Hospital and Jupiter Hospital in Pune, agrees, saying it is easier done at hospitals where payments are handled smoothly and the patient-doctor interaction is recorded, adding "it doesn't work if payments can't be made by patients remotely."

However, with more Indian citizens getting used to online payment systems and having installed apps like PayTM and GPay on their mobile phones during the nationwide shutdown when ecommerce services were permitted for essential commodities, this does not seem to be a stumbling block any longer. India had 502.2 million smartphone users as of December 2019, according to a report by market research firm TechARC. According to Cisco, India will have over 907 million internet users by 2023, accounting for 64% of the population.

At the same time, some physicians' reluctance to issue receipts could be more of a stumbling block. "Though hospitals issue receipts, how many private practitioners give you a receipt? Teleconsultations will demand greater income transparency which might not be acceptable to everyone," said an industry expert.

Still, with no end in sight to the pandemic which has not just taken patients' lives but also that of several doctors, it is likely that most will adopt telemedicine in some form even if physical visits are not completely substituted. No wonder then Ernst & Young India projects that the Indian teleconsulting market will be worth $700m by 2025, with e-pharmacy sales at $4.5bn.

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LY NGUYEN-JATKOE, COMMERCIAL STRATEGY DIRECTOR, PHARMA INTELLIGENCE

CHRISTINA VASILIOU, PRINCIPAL CONSULTANT, INFORMA PHARMA CONSULTING

Pipeline-In-A-Pill: Still A Winning Strategy?

'Pipeline-in-a-pill' has increasingly entered the biopharma executive's vernacular, denoting an attractive asset that has considerable sales potential owing to the number of discrete patient populations it can target. While the phrase or concept may be in vogue, in reality it is one of the many guises or iterations of lifecycle management.

Life cycle management (LCM) is an expression that conjures up thoughts of price increases, "evergreening" and patent litigation – all of which carry negative connotations. But LCM is a fundamental part of every successful drug, with many separate strategies underpinning the growth profiles and longevity of the industry's top-selling drugs.

Pipeline-in-a-pill is one such strategy, clearly evident with the 10 indications of AbbVie's Humira (adalimumab), or 100-plus pages that constitute Merck & Co.'s Keytruda's (pembrolizumab) US prescribing information. Its popularity is leading to saturation and creating opportunities for more nimble companies that are taking alternative approaches. In this article, we would like to introduce "pipeline-in-a-platform" and "pipeline-in-a-portfolio" as contrarian LCM strategies *(see Exhibit 1)*, each with their own merits depending upon capital, expertise, appetite for risk and market conditions. Adopting the optimal tactic from the outset requires careful forward planning and clarity of thought around desired goals.

PIPELINE-IN-A-PILL DRIVES DEVELOPMENT AND ACQUISITION STRATEGY

The term pipeline-in-a-pill remains a nebulous one, designed for the investment community to describe developmental strategy more than anything else. Assigning a definition would be arbitrary, but the general concept is to illustrate the broad therapeutic and commercial potential of a single drug or target. The concept is increasingly in vogue, cropping up in more and more investor call transcripts and analyst notes, particularly within the past few years *(see Exhibit 2)*.

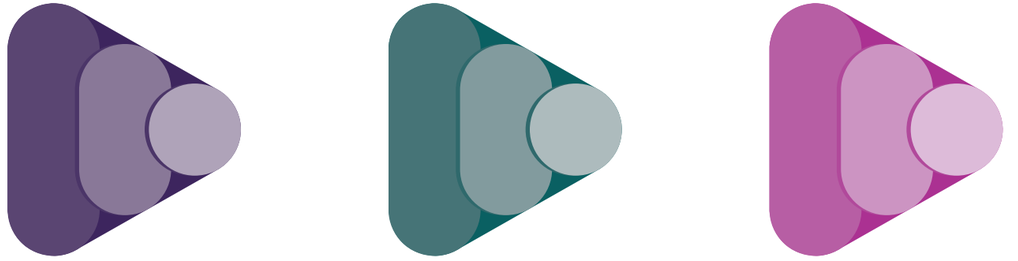
Five years ago, at the start of 2015, the average new molecular entity or biologic asset in Phase III development or beyond had 1.5 separate late-stage indications, with a total of 36 drugs having at least five different treatment settings. In 2020, while the typical indications per drug remains at 1.5, the corresponding number of 5+ indication drugs has expanded to 54, according to data from Biomedtracker. As the definition of pipeline-in-a-pill is extrapolated out to more extreme requirements, for example up to 10 separate indications, the expansion within the last five years has become more apparent, as Exhibit 3 shows. Many of the drugs in the 2015 dataset have received continued investment, while up-and-coming new entrants have joined the mix for 2020.

The attraction of a single pipeline asset that affords several developmental opportunities is undeniable. R&D spend can be allocated with high efficiency, creating discrete commercial opportunities without the additional discovery, preclinical and early clinical-stage development. Once on the market, promotional activities can have an amplifying effect across the entire product's therapeutic potential, to be harnessed by a single dedicated sales force. Many of the highest-selling drugs can be deemed as pipelines in a pill, from Humira and the anti-TNF class, to targeted oncology mega-blockbusters such as Roche's Avastin (bevacizumab) and AbbVie/Johnson & Johnson's Imbruvica (ibrutinib), not to mention the immuno-oncology universe which includes the PD-1 inhibitors Keytruda and Bristol Myers Squibb's Opdivo (nivolumab).

Pipeline-in-a-pill also permeates the lower reaches of the industry, with countless examples across a range of therapy areas. In particular, it is a prudent development strategy for clinical-stage drug discovery companies seeking to utilize cash reserves as efficiently as possible, while still retaining considerable upside. Efficacy and regulatory validation in a proof-of-concept indication creates a highly valuable asset, which can then be fully developed within the pipeline of a larger organization. Such drugs routinely form part of pharma's bolt-on acquisition strategy, with several of the largest transactions of 2020 justified by the long-term commercial potential of single assets. These include Gilead's acquisitions of Immunomedics ($21bn) and Forty Seven ($4.9bn), the $6.5bn deal agreed by Johnson & Johnson for Momenta, and more recently Bristol Myers Squibb's mavacamten-focused purchase of Myokardia for $13.1bn.

Focusing on such assets though does carry developmental risks for biotech, as failure in the primary indication can crater the overall value proposition, with the singular focus on a lead asset coming at the expense of overall pipeline diversity. Incyte's failure with its IDO inhibitor epacadostat for solid tumors is a cautionary example, with the setback and accompanying R&D spend continuing to cast a shadow over the company's current position. Furthermore, there are also notable commercial risks to concentrating resources around single assets, most notably through exposure to competition. Fast-followers in the same drug class can quickly saturate the market opportunity by showing a comparable clinical profile or leapfrogging timelines in untapped patient groups, while

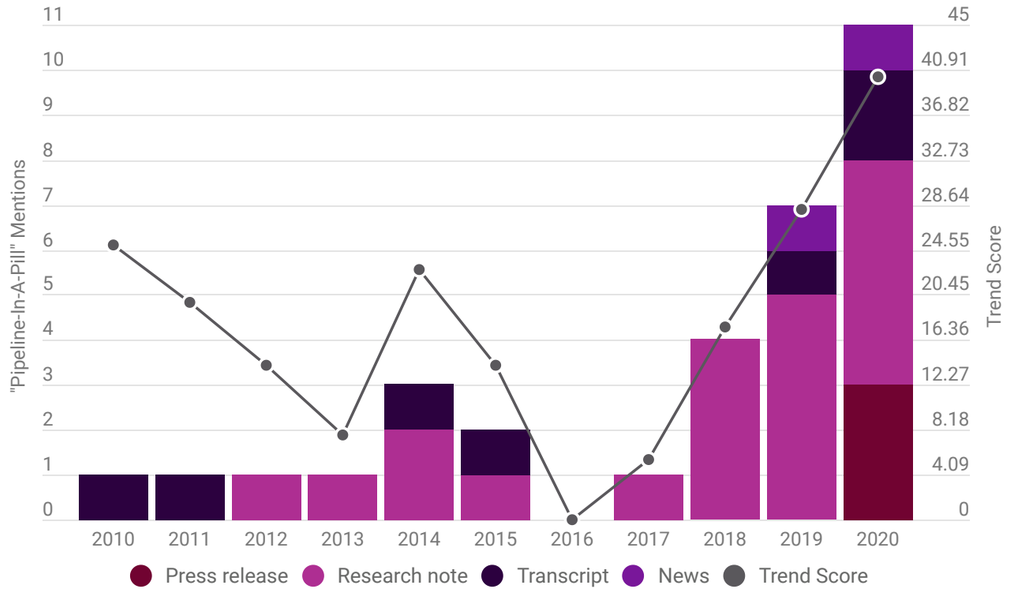
Exhibit 1. Strategic Considerations For Leading Developmental LCM Strategies



PIPELINE IN A PILL	PIPELINE IN A PORTFOLIO	PIPELINE IN A PLATFORM
✓ Maximum commercial potential	✓ Optimized clinical profiles	✓ Efficient engine for new candidates
✓ Reduced developmental costs	✓ Pricing and access flexibility	✓ Lower developmental risk
✓ Sales and marketing efficiencies	✓ Mitigation of competitive threats	✓ Attractive partnering opportunities
× Saturated number of opportunities	× Considerable R&D investment	× Limited by disease understanding
× Vulnerable to competitive threats	× Reduced commercial potential	× Susceptible to next-gen advances

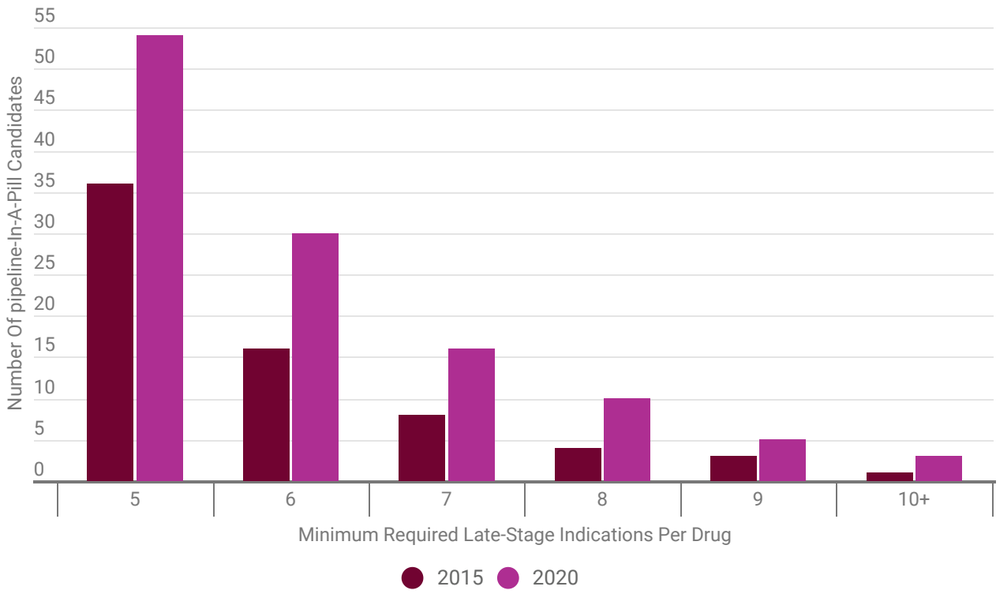
Source: Pharma Intelligence

Exhibit 2. 'Pipeline-In-A-Pill' Sentiment Analysis Within Public-Facing Industry Documents



Source: AlphaSense, September 2020

Exhibit 3. Growth In Pipeline-In-A-Pill Candidates With Varying Definitions



Source: Biomedtracker, September 2020

an unexpected patent ruling, such as that of Amarin's Vascepa (icosapent ethyl), can prove disastrous and leave long-term LCM plans in tatters.

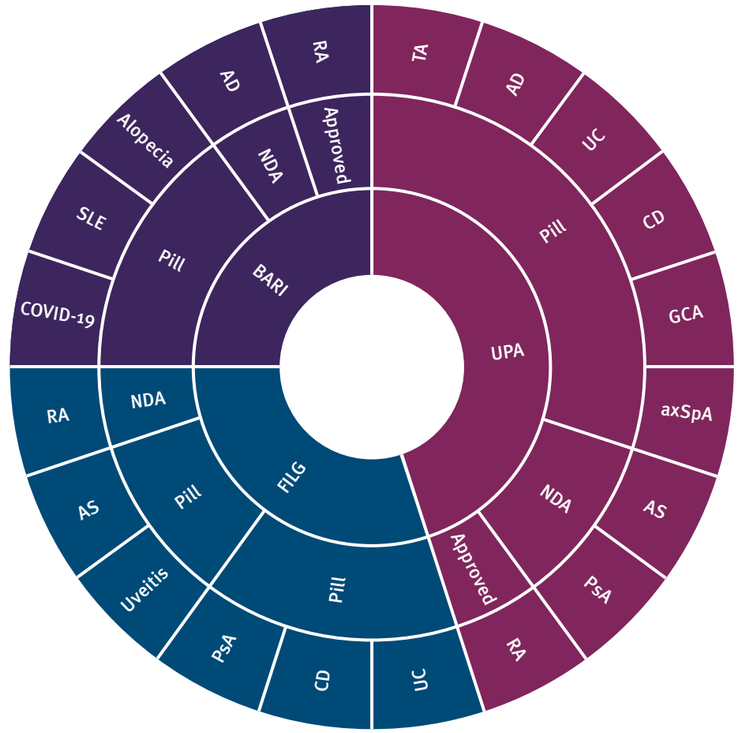
PORTFOLIO APPROACH IS THE NATURAL COUNTER STRATEGY

The oral JAK inhibitor market is hosting one of the most interesting dynamics today. Recent entrants such as Olumiant (baricinitib; Eli Lilly) and Rinvoq (upadacitinib; AbbVie) are aggressively expanding beyond an initial product opportunity within rheumatoid arthritis into other inflammatory conditions such as atopic dermatitis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis, to name a few, very much adopting the pipeline-in-a-pill playbook. Gilead intends to add further competition with filgotinib and its broad late-stage clinical development program *(see Exhibit 4)*. Pfizer, which was the first to create this market opportunity in 2012 through Xeljanz (tofacitinib), is attempting to minimize direct confrontation and is staking its future position in the market on a pipeline-in-a-portfolio approach. Rather than concentrating further resources in Xeljanz, which is unlikely to yield comparable return on investment with limited exclusivity remaining, the company is splitting its long-term LCM strategy between four separate pipeline assets with differentiated formulations and affinities against the JAK family of enzymes (JAK1-3, TYK2).

These candidates are abrocitinib, brepocitinib, ritlecitinib and PF-06826647, with their differentiated pharmacokinetics emphasized during Pfizer's virtual investor event over 14-15 September 2020. JAK pathways play an important role in facilitating inflammatory processes involving over 50 different cytokines, so subtle differences in how JAK enzymes are targeted can translate into notably different clinical profiles in different disease settings. Atopic dermatitis for example is mediated by IL-4, IL-13, and IL-31, while psoriasis is additionally driven by IL-23-associated inflammation. As summarized by Richard Blackburn, president of Pfizer's inflammation and immunology business, "Our approach is not one of developing a single molecule for multiple different indications. It's obviously unlikely that any medicine will represent a breakthrough option in six different diseases. Our approach is to purposefully match the right molecule to the disease where we believe it can make the most difference." A further candidate, the IRAK inhibitor PF-06650833, will attempt to cement Pfizer's existing leadership position within the JAK inhibitor class for rheumatoid arthritis via combination therapy.

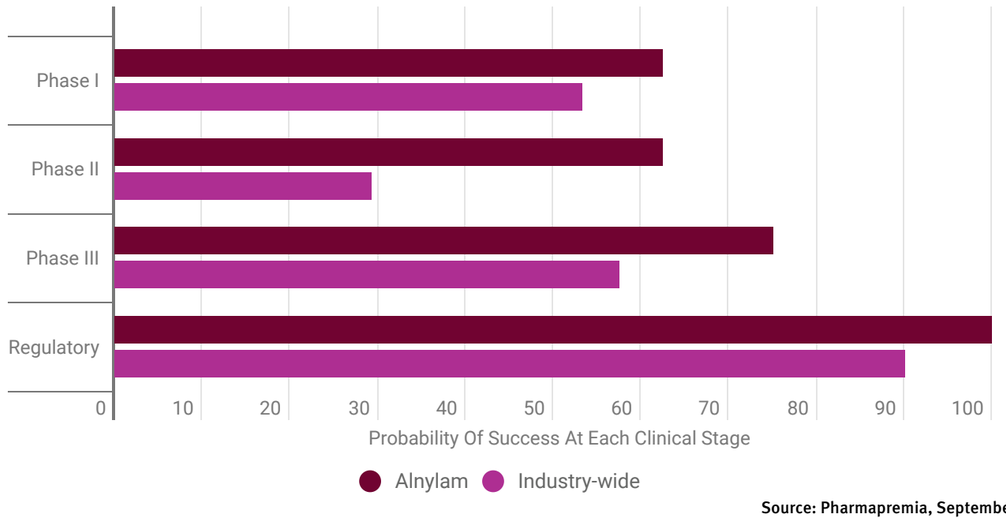
Realistically, pipeline-in-a-portfolio is only accessible to companies with deep R&D pockets and an existing commercial presence within a therapy area to springboard from. In such a way, it is a lower-risk, defensive strategy that is unlikely to generate commercial rewards on the scale of a best-in-class pipeline-in-a-pill. It is the natural counter strategy to the pre-eminent position of market leaders such as Humira and Keytruda, for which no one single drug is likely to effectively compete. Rather, it is advisable to segment and decide which opportunities to enter. Unlike a pipeline-in-a-pill, the target

Exhibit 4. Late-Stage Development Universe For Leading JAK Inhibitors



Source: Pharmaprojects, September 2020

Exhibit 5. Probability Of Success Benchmarks For Alnylam Versus Total Industry, 2010-Present



Source: Pharmapremia, September 2020

product profile can be adapted for each opportunity, optimizing variables such as pharmacokinetics, dosing, formulation and pricing strategy to create the most compelling competitor.

The portfolio approach, in which multiple assets are available across the spectrum of a disease, also benefits from sales and marketing synergies, and commercial longevity. Using the example of Biogen's position within multiple sclerosis built-up over time with a combination of in-house drug discovery and external partnerships – the company can offer a range of therapeutic options to address many different clinical needs. Biogen markets a portfolio of injectable treatment options for relapsing multiple sclerosis with different risk/benefit profiles, while Tecfidera (dimethyl fumarate) leads the oral market segment and Fampyra (fampridine) can be prescribed for related spasticity symptoms. When a competitive threat emerges, even a new standard-of-care such as Roche's Ocrevus (ocrelizumab), the diversity and balance within Biogen's portfolio have allowed overall revenues to remain resilient. With additional royalty revenues from Ocrevus, Biogen can defend its portfolio with a pipeline that includes next-generation BTK inhibitors and therapies with potential to induce remyelination and reversal of nerve damage.

DRUG PLATFORMS BYPASS THE TRADITIONAL COMPETITION

The alternative developmental LCM strategy that focuses on efficiencies of scale, without venturing into therapeutic area specialism, is the so-called 'pipeline-in-a-platform' approach. Particularly viable for biotech companies creating value at the discovery stage, it relies on considerable upfront execution and scientific expertise within a platform technology. Once a drug discovery platform is validated with a clinical proof-of-concept, then additional pipeline assets can be created from the template at scale, capitalizing on an increasing basic understanding of human disease. In particular, indications characterized by a known genetic or molecular component can be rapidly addressed via platforms. In 2020 this has been most evident in the rapid deployment of innovative vaccine technologies against the known sequence of SARS-CoV-2, but the same idea holds for a range of platforms, from gene therapies to RNA interference and antibody-drug conjugates (ADCs).

Alnylam is one such biotech platform company attempting to make the transition from platform player into long-term profitability as an independent commercial entity, following in the footsteps of Regeneron. Its RNA interference technology, long shunned by the industry after initially failing to meet its therapeutic promise, has now resulted in three approved therapies in Onpattro (patisiran), Givlaari (givosiran) and Oxlumo (lumasiran). Projects with large target populations such as inclisiran (dyslipidemia) and fitusiran (hemophilia) have been out-licensed to partners with broader commercial reach, while the company continues to advance its own pipeline against rare genetically validated diseases.

Lumasiran is the next likely approval in December 2020, while platform improvements will allow the company to address new targets outside of the liver, including central nervous system and ocular diseases. With a now-proven RNA interference backbone, such clinical work can be done with high likelihoods of success, meaning that the company can confidently progress 2-4 new IND-stage candidates through its pipeline each year. As demonstrated in Exhibit 5, Alnylam can reach industry-high levels for probability of success at each clinical stage, on the strength of its platform. Since the beginning of the last decade, Alnylam's likelihood of approval for an asset entering Phase I testing has been 29.3%, versus an industry-wide benchmark of just 8.1%.

Tapping into the trend for pharma companies to be modality-agnostic as to how they attack a particular drug target, platform companies are increasingly becoming the source of big pharma's most attractive, and valuable, pipeline assets. Novartis is one company taking the agnostic approach to the extreme, with internal or partner capabilities spanning all of the major advanced therapy types, including cell therapies, gene therapies, RNA interference and radiopharmaceuticals. Inclisiran, originally discovered by Alnylam, represents its first foray into RNA therapies, acquired at considerable cost from The Medicines Company for $9.7bn. One of the hottest targets in oncology, BCMA (B cell maturation antigen), is set to become a big pharma battleground for externally sourced drugs spanning cell therapies, bi-specific antibodies and ADCs.

On the topic of ADCs, recent months have seen a frenzy of deals as initial technological limitations have been overcome, resulting in improved antibody-to-drug ratios and therapeutic potency without systemic side effects. Gilead's $21bn purchase of Immunomedics brings the TROP2 ADC Trodelvy (sacituzumab govitecan), while Merck & Co. acquired developmental rights to ladiratuzumab vedotin, a LIV-1 ADC from Seattle Genetics for $1.6bn upfront.

Expect platform biotech companies to continue to enjoy favorable deal terms and reap the rewards of advances in the underlying technology, as they are also shouldering all of the developmental risk. Should the platform ultimately turn out to produce unviable treatments, the entire value proposition of a company is lost, and early pioneers also face existential threats if a newcomer tweaks and optimizes the technology enough to make prior versions redundant. Particularly in cell and gene therapy, with so many variables in the process, balancing refinement of the platform versus commitment to progressing clinical-stage assets is a daunting task.

This article is based on a series of presentations prepared by Ly Nguyen-Jatkoe, commercial strategy director, Pharma Intelligence and Christina Vasiliou, principal consultant, Informa Pharma Consulting in September and October 2020. If you have any questions about any of the themes discussed in this article, or would like to learn further about Pharma Intelligence's products and consulting offerings, please contact Ly or Christina.

R&D

New Treatment Modalities: Protein Degraders And Molecular Glues Gain Traction

JOHN DAVIS
SENIOR EDITOR, EUROPE

In 2020, investors poured millions of dollars into biotech companies searching for new therapeutics that interact with cellular processes involving the destruction and recycling of cellular proteins. These protein degradation-targeted therapies, and molecular glues, have been attracting the attention of big pharma too.

Walking in the woods in the UK would more than likely reveal ash trees marked with colored paint, flagged for felling because of the presence of the lethal 'ash dieback' fungus, *Hymenoscyphus fraxineus*. Having a system of identifying and sorting healthy from diseased trees seems to work well for managing timbered areas – the tagging is specific and tailored to the problem at hand.

The process is not dissimilar to what happens in human cells. Throughout the animal kingdom, a way of marking unneeded or damaged proteins for cellular recycling has also evolved, the ubiquitin-proteasome system, which was first discovered and extensively explored by researchers in the 1970s and 1980s.

Ubiquitin is a highly conserved 76-amino acid small protein found in mammalian cells, and in fact in all eukaryotic cells. When it is attached, or tagged, to a protein, that protein is marked for destruction by proteasomes, large molecular complexes which break peptide bonds. Proteasome inhibitors like bortezomib (Takeda Pharmaceuitcal's Velcade) are already used to treat various cancers, so understanding cellular recycling is already of importance in therapeutics. Cancer cells seem more sensitive than healthy cells to the effects of bortezomib on cell cycle regulation, and can lead to apoptosis and death.

But what is causing recent excitement is progress in developing new generations of candidate therapeutics that interact with the ubiquitin-proteasome system or with similar cell-cycle control processes. It is apparent they have the potential to target structural proteins, transcription factors and other molecules that do not have enzymatic activity, and were previously considered to be, 'undruggable.'

As knowledge of cellular processes accumulate, more possibilities for therapeutic intervention are emerging; these include the E3 ubiquitin ligase enzymes that add ubiquitin to proteins, and deubiquitinating enzymes (DUBs) that remove ubiquitin. Further, cellular molecules called molecular glues appear to "paint" the surface of proteins, allowing them to come closer to other proteins and to embolden protein-protein interactions.

The year 2020 has been a particularly busy one for new protein degradation therapeutics, with emerging biotechs beginning their journeys, big pharma companies taking an interest in collaborations, and candidate therapies collecting their first data in clinical studies.

One of the pioneers of this new "protein degrader" therapy modality is US biotech Arvinas Inc, which in November 2020 started a Phase II clinical trial with ARV-110, one of its PROTAC (proteolysis targeting chimera) drugs. PROTACs are small molecules with three regions – a protein ligand domain, which binds to the targeted protein; a ligase ligand area which recruits a specific E3 ubiquitin ligase; and a linker region, which lines up the target protein and the E3 ligase. The target protein is tagged with ubiquitin and later destroyed by proteasomes.

ARV-110 targets and destroys the androgen receptor and has potential in prostate cancer, and the New Haven, Conn-based biotech has a second PROTAC, ARV-471, in Phase I which targets the estrogen receptor and may have a role in breast cancer. Initial results for ARV-471 are expected soon. Arvinas also has research programs in neuroscience, including targeting the mutant HTT protein, but not wild-type HTT, in Huntington's disease, and programs against undruggable targets such as KRAS and Myc. Big pharma has taken an interest in what Arvinas is doing – it already has collaborations with Pfizer and Genentech in health care, and with Bayer in the crop science area.

Another US biotech, San Francisco, CA-based biotech Nurix Therapeutics, said in September 2020 it was about to enter Phase I clinical studies with lead candidate NX-2127 from its targeted protein degradation platform. Already in 2020, the company had been busy raising funding including a $120m venture financing in March and net proceeds of $218.1m from a NASDAQ IPO in July.

Nurix, founded in 2012, is developing both bifunctional "chimeric targeting molecules (CTMs)" and small molecules that interact with E3 ligases themselves. Modulators of specific ligases are expected to increase or decrease target protein levels. Its first drug candidates, in oncology and immunology, are expected to enter the clinic in the first half of 2021. Nurix's lead CTM candidate, NX-2127, targets Bruton's tyrosine kinase (BTK) and may be of use in the treatment of relapsed or refractory B-cell malignancies. Nurix has already attracted Sanofi and Gilead Sciences as collaborators.

Four-year-old US biotech Kymera Therapeutics also went public in 2020, raising $213.3m in gross proceeds from a NASDAQ IPO in August, to develop targeted protein degradation (TPD) technology and a portfolio of small-molecule heterobifunctional drugs. The funding followed a multi-program deal signed in early July with Sanofi to develop protein degraders targeting interleukin-1 receptor associated kinase 4 (IRAK4). The approach is expected to be of use in the treatment of immune-inflammatory disorders.

Kymera's lead compound, the IRAK4 degrader KT-474, is expected to enter initial clinical studies in the first half of 2021. IRAK4 is believed to play a key role in rheumatoid arthritis, atopic dermatitis and hidradenitis suppurativa, with the latter being the initial indication to be explored. The Cambridge, MA-based company has already attracted GlaxoSmithKline and Vertex as collaborators.

C4 Therapeutics Inc. raised $209.76m via an IPO in October 2020 to support its research into two types of protein degraders, with its lead candidate, CFT7455 for hematologic cancers, expected to enter Phase I/II studies in the first half of 2021. The company also closed a $150m series B round in June 2020.

BIG PHARMA INTEREST

Multinational pharmaceutical companies want to be involved in protein degradation. For Bristol Myers Squibb, it is a core research platform, and its cereblon E3 ligase modulator iberdomide (CC-220), was reported at a November 2020 rheumatology meeting to have therapeutic benefits in a Phase IIb study in patients with systemic lupus erythematosus. Cereblon is a protein that forms part of the E3 ubiquitin ligase complex, and iberdomide binding is believed to induce the degradation of two transcription factors, Aiolos and Ikaros. Iberdomide is also being evaluated in multiple myeloma and non-Hodgkin lymphoma.

Shanghai,China-based Kangpu Biopharmaceuticals is also developing a cereblon modulator, KPG-818, which has completed Phase I studies.

Big pharma Roche entered the protein degradation fray in May 2020, paying $135m upfront in a potentially multi-billion-dollar deal with Vividion Therapeutics Inc. to develop small molecules targeting E3 ligases in oncology and immunology. San Diego, CA-based Vividion, which was spun out of Scripps Research Institute in La Jolla, has developed technology to screen for molecules targeting E3 ligases.

Meanwhile Novartis AG is evaluating a number of candidate therapeutics based on molecular glue technology. Molecular glue compounds bring together proteins which do not usually interact, and can lead to one or other of the proteins being marked for destruction. They can also clog up proteins, for example keeping an active site closed. Novartis is working on TNO155, an inhibitor of the phosphatase SHP2, which appears to be involved in the development of cancer and is in early clinical studies in patients with KRAS G12C mutations.

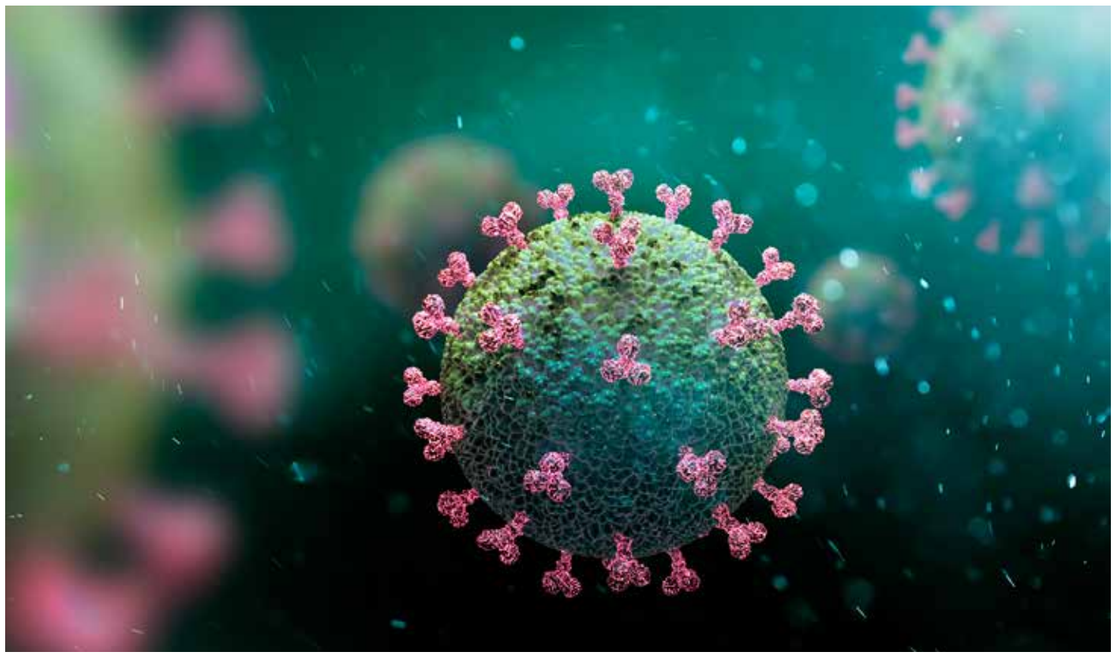
And Eli Lilly & Co. announced on 13 November 2020 it was linking up with New York-based Seed Therapeutics, a subsidiary of BeyondSpring, to collaborate on research into new small molecules with drug-like chemical properties that can act as molecule glues. Seed Therapeutics received a upfront payment of $10m to pursue its targeted protein degradation research.

VC DRIVEN R&D

Venture capital has also been a driving force for protein degradation R&D. Boston, MA and Basel, Switzerland-based Monte Rosa Therapeutics raised $32.5m in a series A funding round in May 2020 and a further $96m in a series B in September 2020. The company is focused on protein degradation for the treatment of cancer and other diseases.

Monte Rosa was set up in 2020 with support from the UK's Institute of Cancer Research and Cancer Research UK. Its lead compound, MRT-048, is due to enter clinical studies towards the end of 2021. The startup is building a library of small-molecule protein degraders that can destroy disease drivers, and its approach will hopefully expand their use beyond cancer into a broader group of diseases.

Boston, MA-based Cedilla Therapeutics, launched in 2018, raised a $57.6m series B in October 2020 to pursue its research into protein stability and degradation. US start-up, Dialectic Therapeutics Inc., based in Callas, TX, received $3m in seed funding in February 2020 to develop its preclinical candidate, DT2216, which selectively induces cancer cells to degrade the over expressed anti-apoptotic protein, B-cell lymphoma extra-large (BCL-XL). DT2216 is expected to enter the clinic in 2021. And Plexium Inc. was set up in October 2019 in San Diego, CA, with $28m in series A funding to use its technology platform to discover novel E3 ligase modulating small molecules.



DANIEL CHANCELLOR,
THOUGHT LEADERSHIP DIRECTOR, PHARMA INTELLIGENCE

DUNCAN EMERTON,
CUSTOM INTELLIGENCE DIRECTOR, INFORMA PHARMA CONSULTING

Pharma R&D's COVID-19 Scar

Months of pandemic-induced disruption to health care systems and freedom of movement undoubtedly carries a cost. For the biopharmaceutical industry, this can be mitigated by its essential role in providing therapeutic interventions and leading the fightback via prophylactic vaccines. This softens the blow somewhat, certainly compared to other industries that are fully exposed to COVID-19 headwinds.

The short-term hit to company financials as reported in the 2020 second quarter earnings season, with patient visits greatly reduced during April and May, will be compounded by a longer-term loss of R&D momentum as clinical trial sponsors have been forced to take defensive measures. While it is still too early within the lifetime of the pandemic to point toward any slowdown in regulatory filings and drug approvals, this article quantifies the disruption to clinical trials and the accompanying slowdown to pipeline progression.

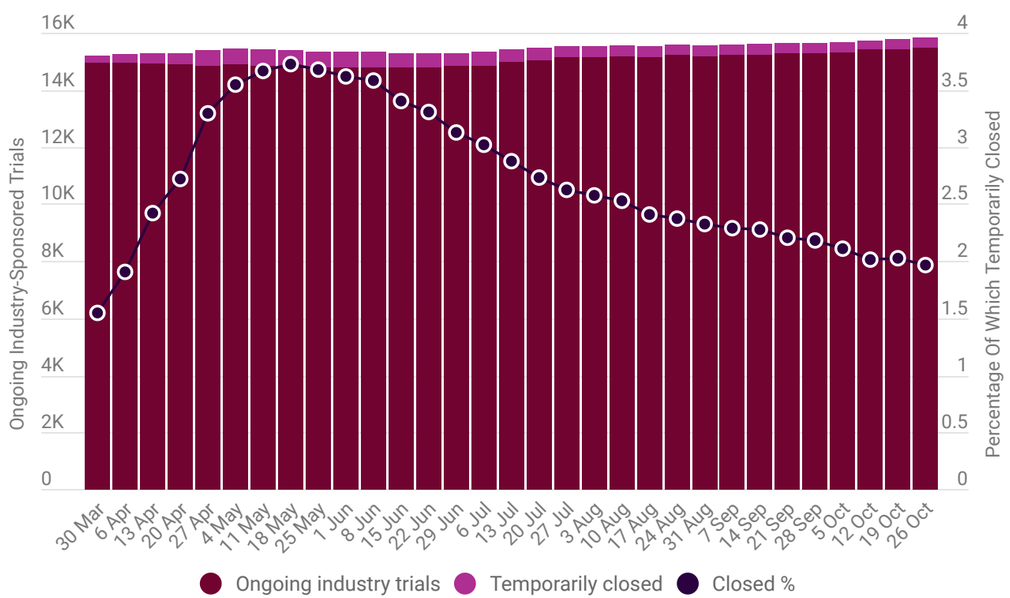
The pandemic has certainly wounded biopharma R&D, and with an acceleration back to normal levels unlikely in the immediate future, there will leave a noticeable COVID-shaped scar heading into 2021. It is certainly not all doom and gloom. Due to the incredible influx of capital into the sector in 2020 to fuel new innovations, the longer-term outlook is more positive. If this investment can be sustained, the scars caused by COVID-19 will fade over time, leaving the industry in rude health.

CLINICAL TRIAL ACTIVITY RECOVERING

Eli Lilly was among the first big pharma companies to publicly announce the disruption to and temporary closure of a portion of its clinical trials in late March 2020, as a wave of industry players disclosed their business continuity measures. While several of Lilly's peers shied away from comparably broad statements and blanket decisions concerning their trial portfolios, the reality was that the whole clinical trials ecosystem faced disruption. The considerable point-of-care burden at trial sites necessitated hospitals prioritizing resources towards the influx of COVID-19 patients, and many outpatients were also unable or unwilling to travel for scheduled follow-up visits.

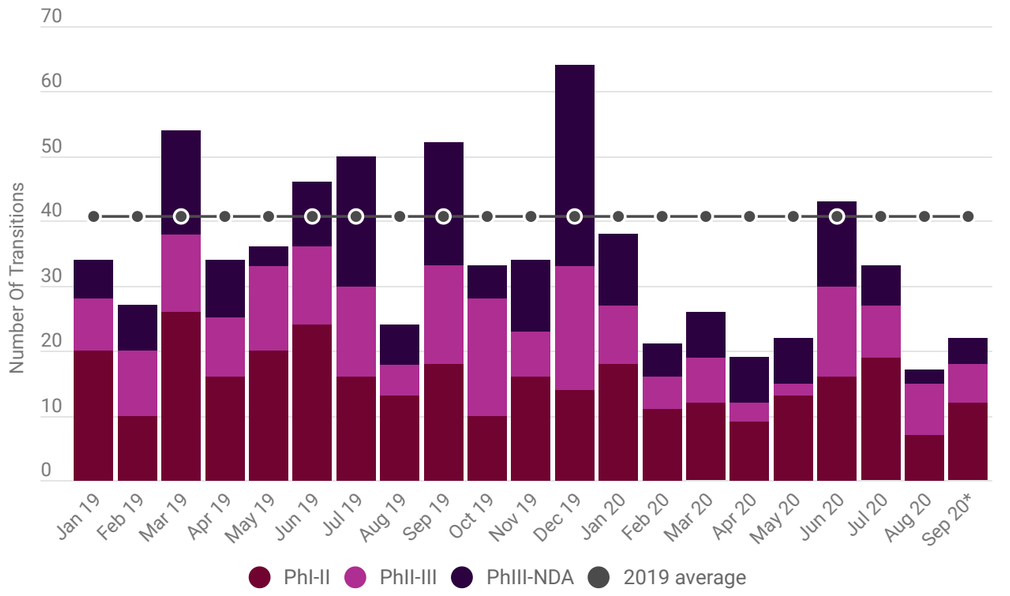
The net result was that large numbers of trials faced temporary closure to new patients, and fewer new trials were able to start during the initial pandemic months, with research into COVID-19 treatments the obvious exception. Digital solutions such as remote

Exhibit 1. Effect Of COVID-19 On Industry Trial Status



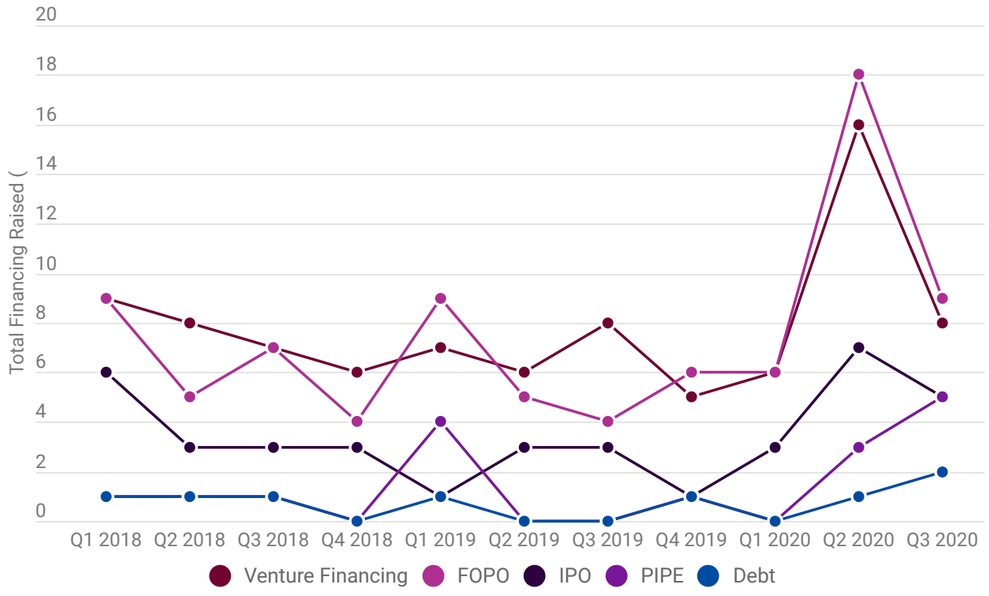
Source: Trialtrove, September 2020

Exhibit 2. Successful Phase Transitions, Pre- And Mid-Pandemic



Source: Pharmapremia, September 2020

Exhibit 3. Quarterly Biopharma Financing Trends



Source: Biomedtracker, September 2020

monitoring, telehealth and electronic informed consent have been employed at scale to enable continuity where possible, although slow uptake of these tools prior to the pandemic meant that pharma's collective experience of virtual trials was modest.

In total, Trialtrove analysts can identify approximately 1,000 separate clinical trials that have been directly affected by the pandemic, each with a publicly available reference pin-pointing the blame on COVID-19 and lockdown measures. In reality, the true scale is near-universal, as regulators issued guidances allowing sponsors to make trial-by-trial judgements on whether halting or continuing each study was in the best interests of patients.

An alternative way of measuring the pandemic's effect on clinical trial activity is to calculate the proportion of all ongoing studies that have temporarily closed recruitment. There are a variety of clinical, commercial and strategic reasons why this might be the case, and of course a global pandemic is certainly a compelling addition into the mix. At any given point in time, around 1% of the biopharma industry's currently ongoing trials are listed as temporarily closed across the various registries, although there is likely underreporting. As Exhibit 1 shows, this metric increased to nearly 4% in mid-May at the height of hospital pressures and lockdown measures in the West, when 554 of the industry's 14,843 ongoing trials were temporarily closed.

As the concentration of COVID-19 patients began to ease in the most common trial locations, and social distancing was loosened, clinical activity steadily returned with the re-opening of certain studies and initiation of new trials that were previously held back. As of 28 September 2020, the total number of ongoing industry trials reached a peak of 15,285, 333 of which remain closed, equivalent to a reduction of nearly 2%, beginning to approach the pre-coronavirus baseline.

PIPELINE MOMENTUM CONTINUES TO LAG

There has clearly been disruption to clinical trials, but patient enrolment and trial timelines tend to be quite elastic in nature. While a site may not be adding new patients for a period of a few months, logically demand will build up in the intervening period and missed progress can be caught up. However, it is more complicated to account for the missed diagnoses, referrals and general decline in health care-seeking behaviors witnessed through the pandemic. There has undoubtedly been a toll beyond simple clinical trial activity, extending into general pipeline momentum, as shown in Exhibit 2. Left unchecked, this will trickle down into downstream measures such as delayed pivotal events, regulatory filings and fewer approvals.

One clear measure of pipeline momentum is the flow of drugs sequentially through the various stages of clinical development. Of course, the later stages of clinical development are that much more expensive, and R&D spending can only sustain so many Phase III assets. Nevertheless, as the industry's collective pipeline continues to swell, the number of phase transitions should increase accordingly. To measure this, data were calculated by Pharmapremia, a probability of success benchmarking tool based on historical development programs in the US.

Through 2019, when a variety of different metrics pointed towards the biopharma industry being at its largest ever, there were an average of 40 successful phase transitions each month. Around half of these related to drugs completing Phase I trials and entering mid-stage development, and there was a fair degree of volatility, in part driven by the annual conference calendar of medical and investor meetings.

By contrast, 2020 saw over 30% fewer phase transitions, with notable underperformance during the start of the pandemic. As of November 20201, only one month of the year – June – had seen a performance reach the average benchmark set in 2019, while subsequent months failed to restore any lost R&D momentum. With the pandemic yet to be brought under control in any countries with therapeutic and behavioral interventions, it is highly unlikely that 2020 will outperform the previous year, resulting in considerable lost progress for the year as a whole. The longer the slowdown continues, the greater the scar will be in terms of subsequent missed catalysts, delayed regulatory filings and fewer drug launches.

LONG-TERM OPPORTUNITY WILL OUTWEIGH NEAR-TERM DETRIMENT

Another impressive year for new products reaching the market, 2020 saw 45 drugs cleared by the Centers for Drug/Biologics Evaluation and Research (CDER and CBER) as of the end of September – with more expected before the year's close. However, the huge focus that COVID-19 has demanded of the industry and its regulators has necessitated a reprioritization of resources.

Clinical trial disruption and stalling R&D momentum may take a year or more to have tangible effects, although there is undoubtedly an immediate and short-term hit too. For industry, there is lost productivity from the switch to homeworking and inability to run labs at full capacity, not to mention the strategic focus that the pandemic response has demanded of executives. R&D investment into COVID-19 has to a certain extent been subsidized by governments, but many companies are still incurring considerable financial risk, with no certainty of a return on investment.

On the regulatory side, there is a compensatory cost associated with actions such as the Coronavirus Treatment Acceleration Program, a reallocation of FDA scientific staff in order to progress new treatments into COVID-19 patients as soon as possible. On a practical level, this involves rapid pre-IND consultation and regular communication through the development process, with staff aiming to triage and acknowledge requests within 24 hours. The FDA itself has conceded, "With many staff members working on COVID-19 activities, it is possible that we will not be able to sustain our current performance level in meeting goal dates indefinitely."

It is nevertheless a period of huge opportunity, both immediate in terms of demonstrating the value of biopharmaceutical R&D through innovative treatments, and long-term as a result of the huge influx of capital into the sector. The year so far has seen buoyant biotech valuations as the sector is seen as an offensive investment, in contrast to its usual role as a defensive play during times of economic uncertainty. By the end of July, total fundraising activity in 2020 had already exceeded the totals of 2018 and 2019, as companies took advantage of available capital. In particular, the key pandemic months during Q2 saw an incredible $45bn raised, commonly achieved through venture financing and initial (IPO) or follow-on public offerings (FOPO). PIPEs, which have also seen elevated activities in recent months, refers to private investment in public equity.

This cash-rich environment allows biotech to progress and sustain greater levels of innovation, with the freedom of the knowledge that big pharma is always on the lookout for external partnerships or acquisition opportunities. In turn, this will create new clinical-stage assets and drug platforms, powering further pipeline progression to make any scarring left by the pandemic a distant memory. Now, more than ever, it is important for biotech investor confidence to remain strong and concentrated on the long-term value that the sector provides. Continued success with COVID-19 therapeutics and vaccines will be an important indicator and set solid foundations for the decade ahead.

This article is based on a series of presentations prepared by Daniel Chancellor, Thought Leadership Director, Pharma Intelligence and Duncan Emerton, Custom Intelligence Director, Informa Pharma Consulting in September and October 2020. If you have any questions about any of the themes discussed in this article, or would like to learn more about Pharma Intelligence's products and consulting offerings, please contact Daniel or Duncan.

VALUE OF DIGITAL

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Finding Common Ground: Bringing Together Perspectives On Connected Drug Delivery Devices

Health services around the world were already under pressure before the COVID pandemic, due to aging populations and the growth in chronic diseases. If more patients were able to self-administer treatments and manage their own conditions in the home setting, some of the pressure on health care systems would be eased. Digital transformation in health care plays a critical role in remote patient management, by enabling access to clinicians when a physical consultation is not possible or necessary, and by helping to ensure that prescribed therapies are administered using the correct dosage and frequency. Drug delivery devices with connectivity features to enable information transfer help to deliver these patient data to clinicians or even other health care players. Strides are being made in this area of device manufacturing. In fact, the global connected drug delivery device market (injectables and inhalation devices specifically) is projected to grow at over 25% CAGR to reach more than $700m in 2025.[1]

However, introducing such devices into the health care system is not straightforward. The potential of any device cannot be realized if regulations are not met, if designs are not user-friendly, or if hospitals and clinicians are slow to adopt. Moreover, there are multiple key stakeholders involved in the adoption of medical devices: patients, governments, payers, health care providers, and pharmaceutical companies. It is essential for these actors to work together to ensure effective implementation, especially as digitalization introduces a particular set of challenges. For instance, connected devices may be vulnerable to cybersecurity threats, so it is critical that electronic health records containing patient data are properly secured. This article explores the respective attitudes and approaches of health care stakeholders toward greater connectivity, and the value that digitalization will bring to their function.

UNDERSTANDING STAKEHOLDER PERSPECTIVES

The overarching goal of expanded connectivity is to increase patient adherence to treatments and therefore ultimately improve outcomes, but this cannot be achieved if the patient is not properly understood from the beginning. Human Factors research shows that digital capabilities are not currently uppermost in the patient's mind.[2] Instead, comfort and ease-of-use rank highest for injection devices such as auto-injectors. It is therefore critical that device designers prioritize these factors via thorough testing to ensure acceptance, avoiding the introduction of new challenges for both patients and clinicians. Tasks such as Bluetooth pairing and downloading and using apps can be confusing for some patient groups even though they may provide functional benefits. Pharmaceutical companies will also need to consider the impact of making treatment data available to patients, and this will need to be carefully managed. Though access to these data is empowering and can encourage greater adherence, regular data feeds may be overwhelming, or even distressing for some patients. Additionally, it is recommended that health care systems carry out programs for patients, caregivers and health care professionals to raise awareness of the benefits of drug delivery device digitalization, with the aim of encouraging adoption and use.

It is clear then that connected devices in their own right do not ensure patient adherence. However, with the help of embedded electronics and sensors, they can generate data on the time, volume and site of a self-administered medication, allowing clinicians to remotely track adherence where it would not otherwise be possible and in turn plan interventions to improve it. Clinicians' interest in connected devices is primarily from a patient benefit perspective, and further advances will enable more sophisticated monitoring capabilities than what is currently available. In the medium-term, devices are likely to go beyond dose reporting and reminders, and enable monitoring for side effects or evaluation of regimen changes. One such example is a closed-loop system that monitors a diabetic's blood glucose, and regulates insulin delivery accordingly to maintain target blood sugar levels. Records of these adjustments are then fed directly into a clinical database. A more distant possibility is remote dosage setting by clinicians, based on remotely monitored patient indicators, which would allow greater interactivity with the data generated.

Payers are increasingly seeing the valuable role that connectivity can play in reducing health care costs. For instance, in the US, the Centers for Medicare and Medicaid Services (CMS) – the single largest payer for seniors and chronically ill patients – has now widened health care provider access to payment for remote patient monitoring.[3] This followed a 2017 study of the organization's non-face-to-face Chronic Care Management program, which cited among the positive outcomes improved patient satisfaction and adherence to recommended therapies, improved clinician efficiency, and decreased hospitalizations and emergency department visits.[4] These benefits may be especially important for biological therapies, which are highly effective and help to prevent future escalation of co-morbidities, but can come with a considerable initial cost. From a payer point of view, connected devices are a

critical tool for helping to ensure that patients adhere to treatment regimens and therefore gain the maximum benefit from expensive medication, and they also help to prevent waste.

Pharmaceutical companies also welcome any means of reducing waste or misdosage, because inefficient use of a drug may ultimately affect its efficacy. From a commercial perspective, over time companies may lose competitive advantage if they do not offer digital capabilities, in light of the increase in self-administration and remote patient management, now given greater impetus by the pandemic. A number of pharmaceutical and medical device companies now offer a holistic patient service package alongside a drug, to support training, adoption and adherence monitoring of the therapy. Digital connectivity – especially through drug delivery mechanisms – would help to deliver such services more efficiently and economically, and produce data that build a more detailed picture of the complete patient treatment regimen. As governments and health insurers now require clear evidence on the efficacy as well as adoption and adherence of the drugs they procure, these data are invaluable in both demonstrating value for money and supporting economic outcomes in health care.

RESOLVING COMPLEXITIES

One obstacle to implementing digital devices and gaining all the benefits outlined above is clearing regulatory approval processes. Organizations such as the Food and Drug Administration (FDA)[5] in the US and the National Institute for Health and Care Excellence (NICE)[6] in the UK have established evidence-based standards for digital health technologies. However, this hard evidence is difficult to obtain without deploying connected drug delivery devices in the field. In a survey[7] of almost 200 pharmaceutical executives, just over half (59%) said that the primary challenge in developing smart drug delivery devices is winning regulatory clearance. Device electronic elements also make compliance more complex and introduce further regulatory requirements, such as compliance with WEEE (Waste Electrical and Electronic Equipment Regulation). Among other concerns cited by respondents are maintaining ease of use, utilizing appropriate technology, and managing costs. Developing new connected technologies comes with its own challenges, including ensuring accurate dose delivery and that the drug is compatible with device components, especially for combination injection products involving biologics. It is therefore crucial to invest in specialist knowledge and support as needed, to proactively resolve concerns, overcome technical issues and provide sufficient information to avoid a failed regulatory submission.

An important consideration in our more environmentally conscious world is the sustainability of digital devices and their electronic components. When implemented effectively, digital solutions can reduce a therapy's environmental impact. If patients are better able to manage their own conditions, this may reduce the frequency of consultations and interventions, and the associated consumption of energy, pharmaceutical products and equipment. One study found that overall, greenhouse gas (GHG) emissions were reduced by around 50% where a patient with poorly controlled asthma improved adherence using a smart inhaler.[8] However, limiting environmental impact can be a challenge when working with devices that are designed usually for single use. Creating entirely disposable connected devices would not be sustainable or financially viable, and embedded electronics within these devices use rare earth metals that are largely not recycled properly. These concerns are being addressed in some cases by taking a hybrid approach, where the product has two components: electronics are embedded in a re-usable, connected "shell" device, while the traditional auto-injector or pre-filled syringe sits within the shell and can be disposed of and replaced.

Lastly, greater digitalization in health care raises new challenges relating to data management. To ensure smooth implementation across different health care providers, data transfer protocols must be standardized so that devices are interoperable with standard clinical systems, and it is critical to put robust data protection measures into place from the outset. Industry stakeholders must decide which entities are responsible for data storage and clarify who owns the data collected. Each stakeholder will need to be a part of this dialogue, and collaborate to establish standards and procedures. Without this collective effort to address obstacles to implementation, it will take much longer for the health care industry to realize the full benefits of connected drug delivery devices.

REFERENCES

1. Owen Mumford Pharmaceutical Services, *Well Connected: An Update on the Connected Drug Delivery Device Market*, May 2020.
2. Owen Mumford Human Factors qualitative research conducted among a 120+ strong focus group.
3. Samsung Insights, *The New Rules for Remote Patient Monitoring Reimbursement*, September 2, 2020, https://insights.samsung.com/2020/09/02/the-new-rules-for-remote-patient-monitoring-reimbursement-2/
4. J. Schurrer, A. O'Malley, et al., *Evaluation of the Diffusion and Impact of the Chronic Care Management (CCM) Services: Final Report*, November 2, 2017, https://www.mathematica.org/our-publications-and-findings/publications/evaluation-of-the-diffusion-and-impact-of-the-chronic-care-management-ccm-services-final-report
5. See https://www.fda.gov/medical-devices/digital-health/guidances-digital-health-content for a list of guidance documents relating to digital health content.
6. See https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/evidence-standards-framework/user-guide.pdf for evidence standards framework for digital health technologies
7. Owen Mumford Pharmaceutical Services, in partnership with Pharma Intelligence, *INJECTABLE COMBINATION PRODUCTS: Industry Insights On The Challenges Of Meeting A Growing Global Need*, August 2020.
8. AstraZeneca, Sustainable Healthcare Coalition, *Digital Adherence Monitoring in Poorly Controlled Paediatric Asthma Care Pathway Case Study*, 2017, https://shcoalition.org/wp-content/uploads/2019/12/Digital-Adherence-Monitoring-in-Poorly-Controlled-Paediatric-Asthma-Final.pdf.

Locked And Bolted: How To Create A Data Fortress

Considering the increasing number of biopharmaceutical companies pursuing more virtual and digital tools, the need for world class digital protection is a pressing challenge. *In Vivo* talks to two cyber security experts about best practice when securing data assets.

JO SHORTHOUSE
SPECIALIST
WRITER, EUROPE

The way in which companies interact with their employees, customers and regulators is increasingly virtual. The COVID-19 pandemic has catalyzed satellite working practices with staff setting up offices at home, often for the first time.

While the global biopharmaceutical industry has also adhered to this new way of working, it has been embracing digital tools and creating an online working toolkit for the last decade. The value of the data the industry holds such as patient data, drug data, R&D data and commercial data is a huge draw to hackers.

"It is about people, process and technology." – David Atkinson

The novel coronavirus pandemic has illuminated areas ripe for innovation such as decentralized clinical trials and remote monitoring. Roles such as data scientist, machine learning engineer, blockchain developer and robotics engineer will all be central to the pharma industry as it continues to develop and invest in digital innovation.

This trend is not just for drug developers. In October the UK Health Minister, Matt Hancock, called for more technology and data usage in the National Health Service (NHS) when he revealed a £50m investment in artificial intelligence (AI) products.

As this trend toward digital continues, investment must be made to ensure data integrity. This has not always been the case, as Merck & Co. and Bayer can attest. In 2017 Merck was one of dozens of companies hit by a ransomware attack caused by the NotPetya strain of ransomware, causing the production of new drugs to be stopped which impacted company revenues. The following year, Bayer discovered its software had been compromised by malware called WINNTI. This allowed unauthorized users to access private systems, giving hackers time to look for internal vulnerabilities that could be potentially exploited.

It is not just companies that have been struck by cybercrime. In 2017 the WannaCry attacks hit health care networks globally, locking professionals out of patient records. More than 230,000 computers in 150 countries were affected which virtually shut down health care systems worldwide.

As health care continues to develop its innovative digital resources, two cyber security experts shared their four fundamentals with *In Vivo* to ensure data protection remains front of mind.

START YOUR STRATEGY

Complete an architectural review advises David Atkinson, CEO and founder of Senseon, a cyber security company that automates the process of threat detection, investigation and response.

Companies need to think about where and what its technology and process employees are doing in relation to cyber security. "There is no silver bullet. It is about people, process and technology to develop a cyber security strategy. Once you have a good sense of all those, look at innovative ways to deploy technology," he said.

"Once you have assessed your people, processes and technology, we would encourage [a company] to create a prioritized list of the cases to be solved, it may be training around phishing emails or enhancing visibility to the whole network, for example. You go from the strategic to the operational with cases," Atkinson explained.

Traditionally it takes about 28 to 36 months to deploy a strategy, and for a mid-sized pharma company it could cost anywhere between £500,000 to £2m in technological spend.

EMPOWER YOUR DEVELOPER

"We start with the core of the issue, and that is the developer writing the programs," said Matias Madou, co-founder of Secure Code Warrior. "We teach that developer and give them the tools to write secure code from the start."

Madou started the company because he saw that it was extremely easy to find problems with code if the original developer had not been educated in security at the start. "It is like asking a person to build a race bike, and once that bike is built you try to steal it because it's easy to do," he explained. He and his co-founder Pieter Danhieux created a gamified training platform in a framework and language that the developer is familiar with.

Start Left is Secure Code Warrior's mantra – advising the developer on security from when they are writing the code. "We teach the developers in a positive way, so they have less rework and feel better about the work. You still need checks and controls, but if you can do 80% of the code securely right from the start that's a huge step forward," he explained.

KNOW YOUR ENEMY

"SQL Injection is the number one attack used these days because it is so powerful it can empty an entire database, or modify data in a database, so this is becoming a high priority in health care," said Madou. A hacker "can do whatever they want with that data, they can cause brand damage, they can change the data, sell the data, keep you hostage, or perform identity theft."

Spear phishing emails are also a common tool used by hackers to make someone click on a link or open a document. Some of them have been almost indistinguishable from a true email, noted Senseon's Atkinson. A mis-configured working from home capability was also a very timely way for hackers to access data, he said.

This year has catalyzed ways for cyber criminals to lure people to click on false links. The COVID-19 pandemic meant there was often a rush to enable people to work from home when offices closed. "There are now people working at home who traditionally would have always been office-based or working in laboratories, therefore the propensity to have a misconfiguration in the set up by an IT team is quite high," Atkinson said.

"Hackers fundamentally exploit trusted relationships," he explained. They will always take the path of least resistance. If a local health center has a digital trust relationship with the hospital, realistically the health center is less likely to have real time monitoring, logging and reporting going on, so it makes sense for a cybercriminal to gain initial access there. Once in they can maneuver within the health network.

Ransomware should be top of mind for the health care industry now, said Atkinson, because there is an evolution of the tactics that ransomware groups are using. "These tactics are 'wormable' so it can hop from one computer to the next ad infinitum. In the last six months we have seen a move from these 'wormable' exploits to stealthier tactics. If they can exfiltrate data first, and then encrypt your environment the propensity for you to pay is so much higher," he explained. Ironically, when the hackers have the company's data, that business is facing a decision between paying a fine for breaching data protection rules or paying the ransom. The latter of those two choices is always priced to be the better of the two deals. "Cyber criminals are starting to use our own regulations against us," Atkinson said.

TAKE IT SERIOUSLY

Any good cyber security strategy starts in the boardroom. "You need to make sure it is a top down issue that is being taken seriously throughout the organization. I speak to about 15 different companies every month and it is instantly recognizable the ones who take cyber security seriously and those who do not. Bear in mind the penalty for not taking it seriously is 4% of global turnover," said Atkinson.

"This issue has to take a regular slot in board meetings. Look at this as security becoming an enabler to your business, do not look at this as a cost," he said. "People have got to trust the brand that they leave their data with. This is becoming more and more important, certainly today for the younger generation. It is not something any boardroom should pay lip service to. The harsh reality of the matter is that we are all susceptible, it is a question of when and not if."

The focus on security must be embraced by the entire organization, said Madou. "Security is not super sexy, and there are not many security people in this world. In an organization they are outnumbered. We need to embrace security within the development organization. All the developers should rally around, support and embrace security," he said.

In any business you do not want to be the slowest moving company in the herd, advises Madou. "Some companies are reacting, and some are ignorant to the threat. I have seen quite often that the weakest of the herd gets bitten and then everybody wakes up and starts to investigate their own cyber security." Madou compared this to installing a burglar alarm after someone had broken into your neighbour's house.

PLAY THE LONG GAME

"Leadership does not come from looking short-term," said Madou. What is built internally must be solid, it should be done right from the start so in the next five years there is no security breach. The database or website may be slightly slower in terms of features but there will not be a huge set back if something bad happens, and that is because of internal leadership.

Leadership externally is about being open and transparent. "Showing leadership is not about trying to hide your problems because ultimately, it's going to bite you back. Show what you are doing and how you are doing it. If things go south, it can happen, just be open and fix it," he advised.

"If a data breach does happen and you are found to be lacking you are going to erode trust," said Atkinson. "Some companies have come out relatively well from data breaches, and it had minimum effects, medium to long term, on the share price," he explained. Norsk Hydro, for example, a Scandinavian aluminium manufacturer was attacked in 2018. The damaging ransomware attack cost Norsk Hydro £45m, but it is a good example of handling an incident of the highest severity in a large business. In total, 22,000 computers were hit across 170 different sites in 40 different countries, the 35,000-strong workforce resorted to using pen and paper.

It had an excellent communication strategy, recalled Atkinson. This is something that must be considered in the boardroom.

A critical question for all health care leaders is 'How would you deal with a malicious data breach if it happened to your company?'

Atkinson said companies " should run drills of what you would do if it happened. Bear in mind that, if you are based in the UK you have 72 hours to report a data breach to the Information Commissioner's office. How are you going to strategically communicate what is happening to customers?" he asked.

"If you have not taken the relevant precautions beforehand, the brand and business, as custodians of data, will suffer," he warned. "It will always become obvious when you have had a data breach and have not taken precautions. Then you are going to be a lot worse off."

The Golden Winged Warbler And Supply Chain Immunity

Expert outlines how pharma can create resilient and secure supply chains and some benefits of localization.

ANJU GHANGURDE
DEPUTY EDITOR, APAC

Pharmaceutical companies should use digital technologies to immunize their supply chain networks against threats like the coronavirus pandemic while they are still brewing on the horizon, much as a certain species of bird native to a hurricane-prone region of the US somehow knows to take off long before the high winds arrive, a leading supply chain expert recently suggested.

Robert Handfield, executive director of the Supply Chain Resource Cooperative and professor of supply chain management at North Carolina State University, highlighted in a fall 2020 webinar the "exponential complexity" of global supply chains, with most organizations having "no idea" who their top 10 critical tier 2 suppliers are. Tier 2 firms are those that deal with a principal company's main direct suppliers.

Companies like Merck & Co., Inc. or Pfizer Inc. may have as many as 5,000 direct suppliers and each of these in turn may have up to 250 tier 2 suppliers of their own, resulting in more than a million different enterprises that are supporting an organization.

"What if there's a tornado, hurricane or a power outage? It only takes one incident because if you are producing a pharmaceutical good, you only need one supplier to fail you and if you don't have a backup, it can actually shut down production and lead to massive disruption in the supply chain," Handfield said in a keynote presentation at the virtual event. The webinar was organized by the Parenteral Drug Association India Chapter in collaboration with Rx-360, a non-profit industry consortium formed in 2009 in response to the economically motivated adulteration of heparin active pharmaceutical ingredient in China.

Handfield cited the instance of a congressional hearing in the US where 3M was questioned on the domestic percentage of face mask production. While that figure stood at around 35%, which he said "doesn't sound too bad," that was only end production – the assembly of the spun fabric, elastic bands and nose plates. The worrying aspect was that all of those materials were produced in China and essentially in one region, Wuhan, the original epicenter of the SARS-Cov-2 outbreak.

Similarly, in the pharma sector, a large number of active pharmaceutical ingredients (APIs) and API starting materials are produced in China and these are tier 2, 3 materials. Shortages in one of those areas could result in other spillover effects that would impact pharma companies.

The same holds true for India, where several APIs and critical materials are made. During the ongoing challenges amid COVID-19, organizations should be aware and look at alternative suppliers, perhaps in other parts of India and not all located in one area, Handfield advised.

LOCAL AND REGIONAL SUPPLY CHAINS

Handfield, who has consulted with more than 25 Fortune 500 companies across a variety of industries, noted how global supply chain networks started to break down as the pandemic spread. Fragmentation began as long lead times and export restrictions several nations imposed on personal protective equipment (PPE), drugs and critical materials exposed high risks in the chain.

"All of a sudden, countries were really looking after their own and not really willing to ship critical components – this occurred even for test kits," he said in the pre-recorded presentation.

One of the key critical components of COVID test kits is the nasal swab. But the single largest manufacturer of nasal swabs is in Italy, which had shut down its borders and was not permitting exports of the swabs to third parties. "With these physical networks shut down, it starts to raise questions – maybe we need to look more closely at building a domestic supply or a supply [chain] that's perhaps more expensive but closer to us," Handfield proposed.

Domestic supplies may have some benefits as well, since lean supply chains mean you do not carry too much inventory if you have a local supplier who is shipping on a regular schedule. "You don't have a lot of inventory on boats/planes, sitting in customs, which is a good thing because less inventory means you have greater working capital/free cash flow. So, there is a movement – a lot of people asking the question – should we be producing locally using domestic suppliers and a lot of discussion on that."

As organizations are starting to look at localization of certain critical industries, such as PPE, they are also thinking about building regional supply chains. India, Handfield said, has the potential to become a very strong player in terms of a regional hub that can serve much of Southeast Asia and other parts of the world as well.

Similarly, Mexico, Canada and the US may also emerge as another platform due to their proximity and trade agreements and the overall immediacy of organizations in these countries. "I think we will start to see the deglobalization of our supply chains and starting to move towards more of the localization of supply chains."

However, the scale and scope are going to be difficult to predict since strategic supply chain redesign is impacted by various forces including capability, costs and regulatory considerations.

SUPPLY CHAIN SENSING, IMMUNITY

The way forward is to develop more agile and resilient supply chains, and Handfield outlined a new model that envisages creating "immunity" in the chain.

In a fascinating parallel to drive home the point, he referred to the golden winged warbler, a bird known to live in the southeastern US that typically flies in a pattern "guided by some sixth sense, which involves intense collaboration between thousands of birds all in motion flying together."

"If we use this metaphor and think of how supply chains could become more efficient through the Internet of things, technology – if we had all the trucks on our roads moving together at 80 miles per hour, six inches apart or in an Interstate having self-guided vehicles working together" Handfield imagined, adding that this idea of a pattern/self-guided supply chain is one he is exploring in a new book.

Interestingly, experts on bird migration have noted how a large group of warblers in one part of the US suddenly flew away, leaving the region for Florida, just two days before a massive hurricane hit the region. The birds apparently sensed the impending storm through infrasonic sounds emitted by such weather systems while they are still far away.

"And the challenge here is can humans find a way to mimic these ways or other signals to better predict what might happen to our supply chains later this afternoon/next week/ next month? The more sensing we pick in our supply chains, the better we will be able to sense and avoid disruptions, and risk and technologies may one day be able to help us to do so," he explained.

The idea behind sensing bad weather is analogous to the human immune system recognizing invaders; there is also an acquired immune system. Handfield recommended creating similarly immune supply chains that are more agile in responding to threats.

CREATING KNOWLEDGE-DRIVEN SUPPLY CHAINS

Designing such supply chains will require thinking more broadly about emerging technologies, combined with the mapping of supply systems across all sub-tiers. Companies need to start mapping all the different components – chemicals, APIs, parts, delivery systems – to understand where they are produced and create a digital map of all the levels in the system.

"When we combine that with prescriptive technology and deep learning/machine learning technology that can recognize different events that are occurring in this big broad supply chain, then we can arrive to a point where we are creating knowledge-driven supply chains," Handfield observed.

These will allow machines to issue alerts about possible problems, although ultimately humans will still have to "interpret these signals, work with machines to understand what the indicators are," and then come up with a solution or way to respond to the different kinds of impending risks. "So, these are future improvements that might occur."

He pointed to a specific example along those lines pertaining to the 2017 landfall of Hurricane Maria in Puerto Rico, which was expected to significantly impact several suppliers and critical US FDA-regulated materials. By identifying single/sole-sourced, constrained raw materials mapped to the relevant sites before landfall, Resilinc Corp., a supply chain monitoring, mapping and resiliency solutions firm based in Milpitas, CA, was able to help the customer meet all patient needs by understanding where, for which parts and at which suppliers the disruptions were occurring.

Resilinc identified 30 parts from two suppliers prior to the storm's landfall that would have been disrupted, and the customer initiated dual sourcing to secure supplies ahead of time. The customer was able to secure $1.5m of IV bag inventory within four days of the hurricane and medications were available to 100% of its patients, Handfield showed.

"That's the ultimate goal … We don't want to shut down supply chains; we want to create more resilient and immune supply chains that can react and finally turn in solutions to a threat or disruptions on the horizon."

DATA LEVERAGING TOOLS

Creating such solutions will, however, also require significant investments in digital systems.

Handfield explained that, while many organizations have historical data looking at "what has happened in the past, keeping track of transactions and things, payments and work flows," as firms start looking more at real-time supply chains they can see not only where they are spending money and who they are contracting with, but also understand the risks in the system. "Eventually we want to get to a point where we can use predictive technologies/analytics that allow us to do analysis on what may happen in the future and create these innovative data leveraging tools that can help drive deep insights into business strategy problems," he added.

LUCIE ELLIS,
EXECUTIVE EDITOR, EUROPE

Femtech Presents Enticing Market Opportunity

A rush in the 2010s of high-tech and digital companies focused on women's health and wellbeing are maturing, adding weight to the more traditional women's health market that has struggled to get attention from investors in the past.

The femtech market is expected to see annual revenues of more than $1bn by 2024, growing at a compound annual growth rate of 12.9% according to recent data from consultancy group Frost & Sullivan. But femtech, when including more traditional women's health therapeutics companies alongside tech solutions, has the potential to be a $50bn market by 2025.

In a 2020 Demy Colton virtual salon, industry experts discussed the "rapid growth" of women's health, a traditionally "underserved" market.

WHAT IS FEMTECH?

Women's health is a familiar term in the biopharma industry. But as a therapeutic area it has seen limited investment and stifled innovation compared with other research areas like oncology and diseases affecting the central nervous system. However, a wave of high-tech and digital solutions focused women's health companies have come to the fore in recent years, adding weight to the market and expanding its reach.

Ida Tin, CEO of female health app, Clue, is credited with coining the term femtech. Clue, which launched in 2013, is used to track a woman's period. It is described as "an easy-to-use solution that helps you make sense of your periods, cycle patterns, fertility and menstrual health." Tin reportedly started using femtech as a way of grouping together technologies and digital products that were forming around the same time as Clue, all of which had an emphasis on women's health and research. The term, similar to medtech or fintech, made it easier to talk to the media and investors about these companies and their developments.

Femtech start-ups initially focused on issues such as pregnancy, periods and menopause – but the sector has grown to include products and services tackling specific diseases affecting women.

Per Frost & Sullivan's description, the femtech market covers devices, diagnostics, products, software, services or any combination that meets women's health needs. Under this definition, Frost & Sullivan has identified around 140 core companies globally, excluding more traditional women's health drug developers.

Taking out therapeutics, the femtech market is estimated to see annual revenues of $1bn by 2024 and be valued at around $10bn by 2025. Including pharma companies developing products for diseases affecting only women, market estimates are around $50bn by 2025.

Christina Jenkins, host of the virtual salon discussion on 30 September 2020, and venture partner for Portfolia's FemTech and Active Aging and Longevity Funds, said that generally speaking femtech products and services must be unique to women but importantly should include diseases that disproportionately impact women. "Cardiovascular disease kills more women that breast cancer does, women are three times more likely to be diagnosed with an autoimmune disease, they are twice as likely to be diagnosed with Alzheimer's disease or depression," she noted.

MARKET GROWTH

Jenkin's noted that a combination of factors was fueling growth in femtech, such as a general dissatisfaction with health care. "What we pay for what we get in outcomes is not adequate – particularly in the US," she said. Meanwhile, there has been an increase in the adoption of technological solutions globally, and greater understanding is evolving around the biological differences between men and women. There has been a realization more recently around "how little data and evidence we have about women specifically," Jenkins said. "As we aspire to achieve personalized medicine, we are leaving out half of the global population."

Menopause and general wellness are among the largest areas in femtech for market growth opportunities. Areas like menstrual care have the most widely adopted solutions to date. "The takeaway is that there is room for everyone to grow, this is an underserved market and we are bringing it mainstream," Jenkins said.

Jenkins highlighted that over the last five years, venture capital groups had invested around $1bn in femtech, with much of that cash coming from the US, followed by China and then Europe. Putting that into perspective, VCs invested around $7bn in digital health in general over the same timeframe.

WOMEN INVESTING IN WOMEN

As well as greater understanding of female biology and access to new technologies, something else is spurring growth in femtech. Jenkins noted a rise in the number of female investors in venture capital companies, who were "more likely to recognize and act upon opportunities in women's health."

Speakers in the virtual salon told stories of how they needed female investors when getting their femtech companies off the ground. Surbhi Sarna, founder and CEO of nVision Medical, which has developed a catheter-based device for early detection of ovarian cancer, was seeking seed funding in 2011 but initially found the process challenging. "The product I was describing sounded like science fiction," she explained. Sarna received between 30 to 50 'nos' from potential investors before getting a 'yes' from a female investor, who agreed to fund the start-up despite not having the backing of her "all male partnership," Sarna recalled. Two other female investors joined also in the seed funding.

Similarly, Kate Ryder, founder and CEO of Maven, a leading women's and family digital health company in the US, was seeking VC investment around 2014. Ryder said she got feedback early on from two male investors that they would not invest in the seed round, because the company would not be able to raise a series A. They told Ryder, 'No one invests in women's health.' Ryder, who had worked in the VC space, was able to raise a friends and family round to get Maven started. She launched the company while living in London, UK, which she said was a benefit because the stigma around women's health was not as prevalent in Europe as it was in the US. "When you talk to European investors there is not giggling around women's health conditions as much as there is in Silicon Valley. There is not the sheer discomfort on people's faces when you talk about post-partum care," for example. Maven's first product focused on helping new mothers return to work.

Still, Ryder said raising the series A round for Maven was a challenge. She went through around 40 meetings with potential funders before meeting a pregnant investor, who was able to help her male VC partners understand the needs in women's health and the opportunity at Maven.

Examples Showing Variety Of Femtech Companies In 2020

COMPANY	FOUNDED	LOCATION	TECHNOLOGY	FUNDING TO DATE
Ava	2014	Switzerland	Multi-sensor bracelet allowing women to predict fertile days	€42m
Natural Cycles	2013	Sweden	Only contraceptive app to have regulatory approval in Europe	€34m
Juno Bio	2018	UK	Machine learning and bioinformatics to analyse and predict vaginal microbiomes' impact on female fertility	Unknown
Elvie	2013	UK	Connected breast feeding pump and pelvic floor trainer	€45m
Maven Clinic	2014	US	Virtual clinic for women and family health	€74m
nVision Medical	2009	US	Developing devices to enable clinicians to assess the health of previously inaccessible parts of the female reproductive tract	€14m
Univfy	2009	US	Univfy AI Platform makes fertility cost and success more predictable	€13.6m

Sources: In Vivo & Sifted.eu

CEO of Mycovia Pharmaceuticals Patrick Jordan, representing the more traditional women's health company during the discussion, said it was important for companies in femtech and pharma to be able to demonstrate the value of their innovations. "Data becomes very important to surface these issues and show the value of what we are producing," he said.

Jordan noted that recurrent vulvovaginal candidiasis (RVVC), the condition Mycovia is developing a treatment for, has a $14bn economic consequence for lost productivity. "And that is just scratching the surface when looking at other women's health concerns that may have been silenced or don't have a good venue for dialog," he said.

COVID-19 FURTHER ACCELERATES FEMTECH

Asked about the potential impact of COVID-19 on the femtech sector, especially when considering shifting priorities of investors and large cap health care companies, the virtual salon panelists were optimistic.

Mylene Yao, co-founder and CEO of Univfy, said there would be disruption for some time across all of health care caused by the SARS-CoV-2 virus – both good and bad. But she highlighted the greater adoption of telehealth as a positive result of the pandemic for the femtech sector. She said women, especially mothers, were benefiting from more flexible access to health care through virtual and telehealth technologies.

Jenkins noted that among her contacts, investors were not slowing down during the pandemic and have continued their deal-making activities. "We have seen some great investment opportunities," she said.

Sarna noted that clinical trial enrolment had been a challenge over the last six months because of COVID-19, but she expects patient willingness and interest in clinical trials to "bounce back" soon.

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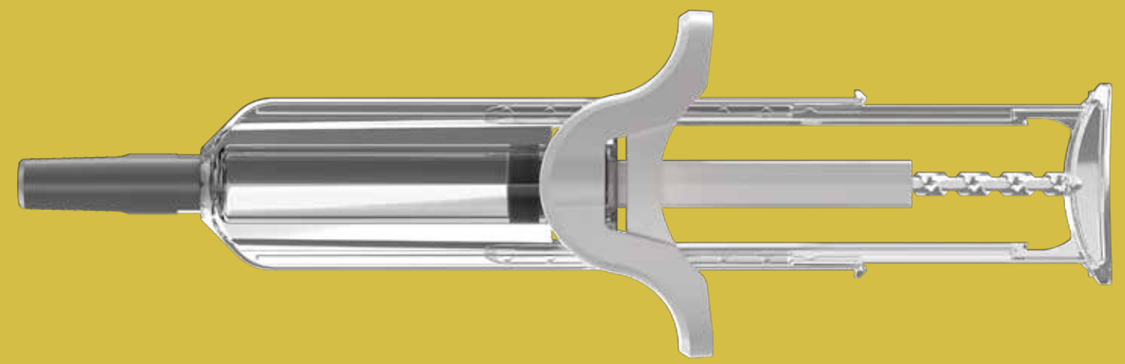

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