

In Vivo

Outlook 2022



Optimize your portfolio and licensing strategy with end-to-end intelligence for the global drug development pipeline

Pharmaprojects and Biomedtracker give you all the intelligence and analysis you need with the granular detail you want to make better strategic decisions about your pipeline and portfolio.

Do you need to know:

- 1 **What are the optimal in- and out-licensing opportunities for my business?**
- 2 **Who are my competitors and what are they doing in the market?**
- 3 **How many assets in the pipeline are likely to be approved and why?**
- 4 **What is the future market potential for drugs in the pipeline?**

THE SOLUTION

Together, Pharmaprojects and Biomedtracker form the leading end-to-end intelligence solution designed to help you understand the global drug development pipeline, competitive landscape and the so-what of your competitors' drugs and trial milestones.

IN VIVO EXECUTIVE EDITOR

Lucie Ellis-Taitt

IN VIVO MEDTECH EDITOR

Ashley Yeo

EDITORS-IN-CHIEF

Ian Haydock
Eleanor Malone
Ryan Nelson
Denise Peterson

HEAD OF EDITORIAL OPS

Karen Coleman

CHIEF CONTENT OFFICER

Gail Parziale

CUSTOM CONTENT MANAGING EDITOR

Maire Gerrard

CUSTOMER CONTENT WRITER

Lori Ellis

CONTRIBUTORS

Brian Bossetta
Shannon Brown
Daniel Chancellor
Bowman Cox
Anju Ghangurde
Derrick Gingery
Nielsen Hobbs
Mandy Jackson
Jessica Merrill
Reed Miller
Andrew Odame-Kwakye
Barnaby Pickering
Jo Shorthouse
David Wallace
Marion Webb

DESIGNERS

Kosh Naran
Nancy Pham
Carla Antill

All stock images in this publication

courtesy of www.alamy.com unless otherwise stated.

Customer Services:

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

Email: subscriptions@informa.com

To subscribe, visit:

<https://in vivo.pharmaintelligence.informa.com/>

To advertise, contact:

christopher.keeling@informa.com

In Vivo is published by Informa UK Limited.

©Informa UK Ltd 2019. All rights reserved.

ISSN 2160-9861



LUCIE ELLIS-TAITT,
EXECUTIVE EDITOR

COVID-19 framed much of the discussion around the pharma and medtech industries in 2021: vaccines were developed and deployed at record speeds and at-home COVID diagnostic tests became a staple in people's day-to-day lives. And while the world grappled with lockdowns and restrictions to battle the pandemic, the life sciences sector thrived.

Biopharma raised record sums of venture capital financing in 2021, companies still managed successful IPOs and M&A action was continuous throughout the year – even if so-called megamergers were absent.

Certain companies and technologies became household names all around the globe because of their efforts to

prevent and treat COVID-19, which opened the whole industry up to a new audience of connected, active, health-conscious patients.

Making predictions for the year ahead is always tricky, even more so with the Omicron variant raising new challenges for suppressing the spread of coronavirus and revealing the knowledge gaps we still have when it comes to understanding SARS-CoV-2. But the overall impression from biopharma and medtech insiders is a guardedly optimistic one. More deals and more financing opportunities are expected by the biotech crowd, as investors compete for the best assets in a cash-rich environment. And while European regulatory changes will present hurdles for medtech firms in 2022, there is room for growth – particularly in connected care and digital innovation. Elective care may well face another difficult year as COVID causes delays in hospitals. However, health care systems are not expected to close themselves off to non-urgent procedures to the same degree as was seen at the start of the pandemic.

We are not out of the woods yet with COVID-19 and “learning to live with the virus” is becoming more of a reality. Still, biopharma and medtech leaders have much to be positive about as we enter a new year.

Outlook 2022 includes exclusive interviews, features and industry league tables for Scrip 100, Medtech 100 and Generics Bulletin's top 50.

OUTLOOK	4
SCRIP 100	16
MEDTECH 100	28
BUSINESS	36
DIGITAL	44
GENERICS & BIOSIMILARS	50
LEADERSHIP	62
MANUFACTURING	72
MEDTECH	82
POLICY & REGULATION	88
R&D	100
WORLD VIEW	106

THANK YOU TO
OUR SPONSORS



Pharma Outlook 2022: What Next After A Year Of Innovation And Growth?

The biopharma industry broke records again in 2021 with the amount of money raised for drug development. After a year of rapid growth, what will 2022 bring for market dynamics and R&D catalysts in biopharma?



BY LUCIE ELLIS-TAITT, EXECUTIVE EDITOR, EUROPE

The biopharmaceutical sector did not relax in 2021. Biotech raised record sums in private financing rounds and emerging companies went public with huge IPOs, while larger pharma players announced several billion-dollar M&A deals – even if the atmosphere for mega-mergers remained quiet.

The biopharmaceutical industry set a record in venture capital (VC) financing raised in a single year, with one quarter left to go in 2021. Drug developers raised \$28bn in VC funding through to the third quarter versus \$27.4bn for all four quarters of 2020, according to the Pitchbook-NVCA Venture Monitor, from Pitchbook and the National Venture Capital Association.

Even with the amount of venture capital raised declining from quarter to quarter from \$11.8bn in Q1 to \$9.3bn in Q2 and \$6.9bn in Q3, the 2021 total will far exceed 2020. With 1,042 VC deals last year and 871 deals this year (up until the end of Q3), fewer private biopharma companies are raising money, but they are bringing in larger sums with average deal sizes of \$32.1m in 2021 versus \$26.3m in 2020.

Even with huge amounts of cash being raised in 2021, market spectators expect this trend to continue well into the new year. Björn Odlander, founder and managing partner of Healthcap, told *In Vivo* he expected VC funding momentum to continue in 2022 for both earlier and later rounds of private financing. However, Odlander warned

that given financing rounds have increased, “it is important to make sure that the capital is deployed in a disciplined way ... Tranched financings are therefore becoming the norm, gating financings to achievements and certain milestones.”

Even in the later months of 2021, biotech companies continued to raise significant sums in VC cash – including a \$143m series B round that CinCor Pharma, Inc. announced on 12 October and a \$100m series A round that newly launched Rectify Pharmaceuticals, Inc. revealed on 14 October.

Cincinnati-based CinCor previously raised a \$50m series A round in May 2019 to fund early clinical development of CIN-107 – a selective, oral, small molecule adenosine synthase inhibitor licensed from Roche Holding AG – in treatment-resistant hypertension and primary aldosteronism. The new funding will support ongoing Phase II clinical trials in resistant hypertension and in hypertensive patients with primary aldosteronism. The company also plans to initiate a Phase II trial in uncontrolled hypertension and a study of CIN-107’s impact on blood pressure and kidney function in patients with chronic kidney disease (CKD).

Atlas Venture, Omega Funds, Forbion and Longwood Fund co-led Rectify’s series A round, which will fund the company through human proof-of-concept studies for its initial positive functional modulator (PFM) programs. PFMs

are designed to restore the function of ABC transporters, which are a 48-member family of membrane-bound proteins with etiological loss-of-function mutations in multiple organ systems, including the lungs, liver, gastrointestinal tract, eyes and central nervous system.

Naveed Siddiqi, senior partner at Novo Ventures, told *In Vivo* that investor interest in earlier financing rounds would remain strong in 2022. “VCs have raised record amounts of cash in recent years, and they have to deploy capital ... We have seen a strong trend of investors gravitating to earlier stage companies with crossover investors also playing selectively in A rounds. As such, we envisage that early stage private financings will remain relatively unaffected by the softening in US public markets as capital supply remains high,” he said. Still, Siddiqi warned that investors could become more cautious around the type of stories they choose to back in 2022. “In certain therapeutic areas and modalities, we may see earlier round valuations adjust to more accurately reflect development risks and investor appetite, but the sector will remain attractive for all stakeholders – especially so in Europe where the sector is very well positioned.”

Stephan Christgau, from EIR Ventures, was less convinced of change for early stage companies in the new year. He told *In Vivo*, “Although more money has been allocated to venture funds, it is predominantly to existing funds that have become larger. This means an increased focus on larger rounds, which requires companies to have a certain maturity of strategy and management. For the early stage companies, i.e. university spin outs looking for the first seed round, there probably still exists a ‘valley of death,’ the difficult transition from promising research to an actual company and development program, with relatively few professional investors that go in that early. This is particularly the case in Europe and that situation is probably not likely to change significantly in the coming year.”

IPO Market

Private financing aside, biotechs have continued to make the leap onto the public markets, where they have been able to secure significant funds. The scope of biotech companies going public has been interesting in 2021, from artificial intelligence-based drug developers and gene therapy companies to biotechs with new models for growth. July alone saw 13 IPOs that brought in \$100m or more and together accounted for \$3.2bn (about 69%) of the total public financing that month (see Exhibit 1).

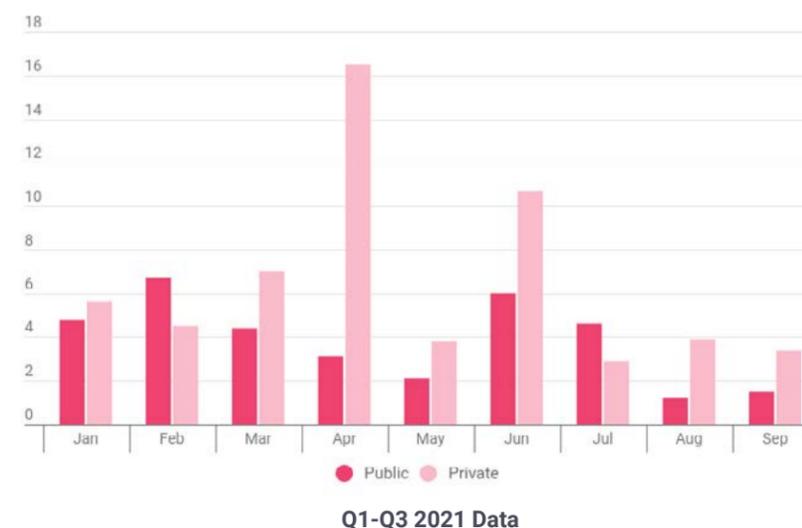
Seth Harrison, founder and managing partner of Apple Tree Partners (ATP), noted the rise in opportunity within biotech. “Within our current fund, to date ATP has created 15 new life sciences companies in the US and UK, most of which are early stage,” he said. “The opportunities are compelling and we expect the momentum to continue and likely intensify, driven by the pace of scientific breakthroughs, leaps forward in operational and regulatory efficiencies accelerated by COVID-19 and growing investor interest, as evidenced by the wave of IPOs.”

Two artificial intelligence drug developers went public in 2021: Exscientia and Recursion Pharmaceuticals. In October 2021, Exscientia, a University of Dundee spin-out founded in 2012, concluded its upsized initial public offering on NASDAQ that raised gross proceeds of \$350.4m, up from the original forecast of \$304.7m. Over 15.9 million American Depositary Shares were sold at \$22.00 each.

The Oxford-headquartered company, which has offices in Miami and Osaka as well as Dundee, also sold nearly 7.3 million shares at \$22 in a concurrent private placement to Softbank and the Bill & Melinda Gates Foundation, raising another \$160m. The fresh injection of over half a billion dollars comes on top of the \$525m brought in through a series D financing in April and \$100m from a series C in March. It is a considerable pile of cash amassed for a company that has never successfully completed a clinical trial but has evolved into a developer as well as a discoverer of drugs. Exscientia is currently advancing more than 25 projects, including the first three AI-designed candidates to enter the clinic, one developed internally and two molecules from Sumitomo Dainippon Pharma Co., Ltd.

In April, Recursion Pharmaceuticals raised a whopping \$436.4m net from a listing to advance its 48 R&D programs, led by REC-4881, a Phase II-ready MEK1/MEK2 inhibitor for familial adenomatous polyposis which has just been granted orphan drug designation by the US Food and Drug Administration. Recursion, an artificial intelligence- and machine-learning-enabled drug discovery and development company, raised \$432.9m in venture capital before deciding to go public, including a \$239m series D round in September 2020 supported by Bayer AG’s Leaps by Bayer initiative.

Exhibit 1: Public Versus Private Biopharma Financing (\$bn)



Source: Source: Biomedtracker; In Vivo

Hakan Goker, managing director of M Ventures, told *In Vivo* that with good numbers of new company creations and more advanced ones heading to public markets in 2021, the new year holds a lot of promise. “Extrapolating from our internal deal flow, number of new investments and portfolio company developments, we expect 2022 to follow in the same positive path. We in fact expect to see even higher numbers of earlier stage financings in the biotech sector as the IPO and M&A pull continues to mature existing companies,” Goker said.

He added, “We are confident 2022 will be another healthy year where we will see and finance cutting-edge science and enabling technologies towards products and the market.”

Looking at “cutting-edge science,” 2021 saw a number of cell and gene therapy companies go public, including Sana Biotechnology, which secured the largest IPO of 2021. Sana Biotechnology, a preclinical stage company, eventually launched at more than four times its initial target set in mid-January 2021. The company earmarked about \$380m to support the development of its cell engineering technology, split between its in vivo and ex vivo platforms. All of its candidates on both platforms are expected to move through preclinical development and at least three assets of each kind through clinical proof-of-concept. Sana will invest \$80m in manufacturing for those candidates and put about \$40m into R&D aimed at broadening both of its platforms. INDs are slated for 2022 and 2023, according to the company’s SEC filing.

2021’S LARGEST IPOs

Sana Biotechnology Inc.	1	\$587.5m
Recursion Pharmaceuticals Inc.	2	\$501.8m
Evotec SE	3	\$435m
Lyell Immunopharma Inc.	4	\$425m
Centessa Pharmaceuticals plc	5	\$379.5m
Instil Bio Inc.	6	\$368m
Adagio Therapeutics Inc.	7	\$355.8m

M&A Activity In 2021

The biggest buyout in 2021 saw Merck & Co (known as MSD outside of the US) complete its \$11.5bn acquisition of Acceleron Pharma, giving the company access to sotatercept, a pulmonary arterial hypertension (PAH) candidate currently in Phase III which has been touted as a blockbuster..

The primary completion date for the pivotal Phase III STELLAR trial of sotatercept in PAH is December 2022, but two additional planned Phase III studies to support label expansions for the drug have not been initiated. Merck said when it announced the deal to acquire Acceleron that it anticipates launching sotatercept in the US in 2024 or 2025.

A busy acquirer in 2021, Sanofi announced the acquisition of Translate Bio in August, valued at around \$3.2bn. Sanofi had already been collaborating with the Cambridge, MA-based mRNA vaccines company since 2018. The French big pharma expects to bring a minimum of six non-COVID mRNA candidates into clinical development by 2025.

“We are confident 2022 will be another healthy year.”

Hakan Gokar, M Ventures

The acquisition gives Sanofi full control of the mRNA-based COVID-19 vaccine jointly developed with Translate, which is in Phase I/II. The company also brings in an mRNA-based seasonal influenza vaccine in Phase I and a candidate in cystic fibrosis, MRT5005, with discovery work ongoing in other rare conditions and liver diseases. Sanofi believes Translate’s expertise could complement another of its recent acquisitions, Tidal Therapeutics, which has an mRNA platform in immunology and inflammatory diseases.

Sanofi is not the only company with an mRNA flu vaccine in development. The most advanced product candidate is Novavax’s NanoFlu, a quadrivalent seasonal flu vaccine – currently in Phase III studies. Moderna, Pfizer/BioNTech and GlaxoSmithKline also all have mRNA flu vaccines in development, with Moderna the closest follower after Novavax, with mRNA-1010 in Phase I/II trials.

Amgen was another active buyer in 2021, announcing the acquisitions of Five Prime Therapeutics in March and TeneoBio in July – deals potentially valued at up to \$1.9bn and \$2.5bn, respectively.

Amgen’s purchase of Five Prime was motivated by its Phase III-ready, first-in-class FGFR2b-targeting antibody bemarituzumab in the treatment of HER-negative gastric cancer. FGFR2b is thought to be overexpressed in about 30% of HER2-negative gastric cancers. The acquisition gave Amgen a much-needed addition to its late-stage R&D pipeline and the company touted the potential for bemarituzumab to offer growth opportunities beyond gastric cancer in breast, lung and ovarian cancers.

“This acquisition represented a compelling opportunity that strengthens our innovative oncology portfolio, adding a complementary molecule to our own internal gastric cancer programs within our [bispecific T-cell engager (BiTE)] portfolio,” Amgen chief financial officer Peter Griffith said at the time of the acquisition announcement. “Importantly, this deal advances our strategic imperative to grow our business internationally and in Asia-Pacific in particular, where gastric cancer is highly prevalent and where we previously stated we expect to generate roughly 25% of our revenue growth over the next 10 years,” Griffith said.

In July, Amgen entered into an agreement to acquire the private US venture Teneobio, Inc. for \$900m in cash upfront,

Exhibit 2: Top 10 M&A Deals By Value (January To October 2021)

	Buyer	Seller	Deal Value	Motivation For Deal
1	Merck & Co	Acceleron Pharma	\$11.5bn	Reblozyl, an erythroid maturation agent approved to treat anemia; drug discovery and development platform focused on the transforming growth factor (TGF)-beta superfamily of proteins
2	Jazz Pharmaceuticals	GW Pharmaceuticals	\$7.2bn	Approved therapy Epidiolex
3	Sanofi	Translate Bio	\$3.2bn	Phase II drug MRT5005, an inhaled mRNA for cystic fibrosis; Phase I asset MRT5500, mRNA vaccine for COVID-19
4	Horizon Therapeutics	Viela Bio	\$3.05bn	Approved treatment Uplizna, a B-cell depleting humanized mAb for rare neuromyelitis optica spectrum disorder; Phase II assets VIB4920 and VIB7734; and Phase I drug VIB1116
5	Amgen	TeneoBio	\$2.5bn	TNB-585, a bispecific T-cell engager for metastatic castrate-resistant prostate cancer
6	Pfizer	Trillium	\$2.26bn	Two lead assets – TTI-622 and TTI-621 – target signal-regulatory protein α (SIRPα-CD47), considered a key immune checkpoint in hematological malignancy
7	Bayer	Vividion Therapeutics	\$2bn	Pipeline of precision therapeutics targeting traditionally undruggable targets in oncology and immunology
8	Amgen	Five Prime Therapeutics	\$1.9bn	Phase III asset bemarituzumab, an anti-FGFR2b antibody
9	Sanofi	Kadmon	\$1.9bn	US-approved oral transplant treatment for chronic graft-versus-host disease
10	Merck & Co.	Pandion Therapeutics	\$1.85bn	Phase I drug PT101; TALON technology

Source: Biomedtracker; In Vivo

plus future contingent milestone payments worth up to an additional \$1.6bn, in a bid to build out multiple technologies in the antibody space.

The deal brings to the biotech giant Teneobio’s lead internal asset TNB-585, a Phase I stage bispecific anti-PSMA/CD3 T cell-engager for the treatment of metastatic castrate-resistant prostate cancer, plus others in a new class of heavy-chain antibodies and proprietary bispecific/multispecific platforms with potential in a range of disorders. These “complement our existing capabilities and could potentially give us a more diverse set of building blocks that can be developed into new multispecific therapeutics,” Amgen R&D head David Reese said at the time of the deal. In addition, Teneobio’s CD3 engager technology “will allow us to broaden our capabilities in generating bispecifics ... and with our own technology, enable customization of the T-cell engaging domain of the molecules depending on the disease and target,” Reese said.

The year saw a number of other \$1bn-plus acquisitions (see Exhibit 2). In February alone, Jazz Pharmaceuticals announced the purchase of UK company GW Pharmaceuticals for \$7.2bn, Horizon Therapeutics struck a deal to buy Viela Bio for \$3.05bn and Merck & Co announced the acquisition of Pandion Therapeutics for \$1.8bn.

Amanda Micklus, managing consultant at Pharma Intelligence, told *In Vivo*: “Even though megamergers were

absent again in 2021, the pharma industry still saw very healthy and promising numbers in dealmaking.” She does not expect to see any super mergers in 2022 either. “Megamergers, the likes we have not seen in a couple years now, might not return for a while, as bolt-on biotech acquisitions are largely in favor, and that will continue into 2022.”

Therapy Areas To Watch

While the super-fast development, approval and rollout of novel COVID-19 vaccines stole the show in 2021, the pharmaceutical sector still produced a high number of novel approvals throughout the year, on a par with 2020 and higher than 2019.

As of 7 October 2021, the US Center for Drug Evaluation and Research had approved 41 new molecular entities (NME), compared with 42 approvals between January and October in 2020, and 33 for the same timeframe in 2019. The total number of NME approvals by CDER for all of 2019 was 48, but this figure reached 53 in 2020. Both years saw a high number of approvals between November and the end of December.

The pharma sector is expected to continue this trend with a high number of novel products reaching the market again in 2022, as well as late-stage pipeline readouts that will ignite investors and competitors.

Looking ahead to the new year, the *In Vivo* team has highlighted four exciting development areas to watch, which

Exhibit 3: TIGIT Development Pipeline

Drug Name	Lead Company/ Partner	Most Advanced Indication	Development Phase
AB308	Arcus Biosciences	Hematologic Cancer	I
AGEN1327	Agenus	Solid Tumors	Preclinical
AGEN1777	Bristol Myers Squibb/ Agenus	Cancer	I
AK127	Akeso	Solid Tumors	Development Outside US
AZD2936	AstraZeneca	NSCLC	I/II
BGB-A1217	BeiGene	NSCLC	III
BMS-986207	Bristol Myers Squibb	Solid Tumors	I/II
COM902	Compugen/ AstraZeneca	Solid Tumors	I
Domvanlimab	Arcus Biosciences/ Gilead Sciences	NSCLC	III
DSP502	KAHR Medical	Cancer	Preclinical
DW2008	Dong Wha Pharmaceutical	COVID-19 Treatment	Development Outside US
EOS-448	iTeos Therapeutics/ GlaxoSmithKline	Solid Tumors	I/II
Etigilimab	Mereo BioPharma	Solid Tumors	I/II
HLX-301	Shanghai Henlius Biotech/ Hengenix Biotech	Cancer	Development Outside US
HLX53	Shanghai Henlius Biotech/ Hengenix Biotech	Solid Tumors	Preclinical
IBI321	Innovent Biologics/ Eli Lilly	Solid Tumors	Development Outside US
IBI939	Innovent Biologics	Solid Tumors	Development Outside US
JS 006	Shanghai Junshi Biosciences	Solid Tumors	Preclinical
LP010	Lepu Biopharma	Solid Tumors	Development Outside US
M6223	Merck KGaA	Solid Tumors	I
MK-7684	Merck & Co	NSCLC	III
PH-804-ACT	Phio Pharmaceuticals/ Glycostem	Cancer	Preclinical
PH-804-TME	Phio Pharmaceuticals	Solid Tumors	Preclinical
SEA-TGT	Seagen Inc	Cancer	I
SL-9258	Shattuck Labs	Cancer	Preclinical
STW264	Stainwei Biotech	Solid Tumors	Preclinical
TGFb Trap/TIGIT Program (Compass)	Compass Therapeutics	Cancer	Preclinical
TIGIT/PD-L1 Inhibitor Program	Dr. Reddy's Laboratories	Cancer	Preclinical
Tiragolumab	Roche	NSCLC	III
YBL-012	Y-Biologics	Cancer	Preclinical
YH-29143	Yuhan Corporation	Cancer	Preclinical

Source: Biomedtracker, November 2021

are all expected to reveal highly anticipated late-stage data and regulatory approval decisions next year.

TIGIT Inhibitors

Immune checkpoint inhibitors blocking CTLA-4 or PD-1/PD-L1 can provide durable antitumor benefits to certain patients who respond to them; however, the percentage of responders is low, estimated at around 15% to 25%. It is hoped that agents targeting other checkpoint molecules in immunotherapy combinations can fill that gap to provide therapeutic coverage. T-cell immunoglobulin and ITIM domain (TIGIT) inhibitors are a promising new avenue in immuno-oncology therapy that could fill this gap. TIGIT interacts with CD155 expressed on antigen-presenting cells or tumor cells to down-regulate T-cell and natural killer (NK) cell functions.

In early 2021, Roche's tiragolumab, which is designed to bind to TIGIT, was granted breakthrough therapy status by the FDA, in combination with Tecentriq (atezolizumab) for the first-line treatment of people with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression with no EGFR or ALK genomic tumor aberrations. Tiragolumab was the first anti-TIGIT therapy to be granted breakthrough therapy designation. It leads a pack of anti-TIGIT monoclonal antibodies in development from Bristol Myers Squibb, Merck & Co, Beigene, Mereo BioPharma, Potenza Therapeutics, Arcus Biosciences and Seagen Inc.

Roche has Phase III trials ongoing for tiragolumab in NSCLC, small cell lung cancer and esophageal cancer, as well as a Phase II trial in head and neck cancer and earlier stage clinical studies in cervical cancer and solid tumors.

Topline data is expected in 2022 from the Phase III SKYSCRAPER-01 trial of tiragolumab in combination with Tecentriq in NSCLC. Cowen Equity Research analysts said in a 4 October note that Roche's primary area of interest for tiragolumab is solid tumors, while its prospects in blood cancers are considered icing on the cake. The analysts are predicting tiragolumab sales of CHF250M (\$274m) in 2023 and CHF750M in 2025.

The pipeline for TIGIT inhibitors has expanded quickly with 13 unique product candidates in clinical development, as well as several in the preclinical stage or in development outside of the US (see Exhibit 3).

RSV Vaccines

Sanofi is expected to lead the respiratory syncytial virus (RSV) market from 2023 and is gearing up to submit data for its monoclonal antibody treatment, nirsevimab, with the



European Medicines Agency in Q1 2022 and with the FDA the following quarter.

Analysts expect nirsevimab, which is partnered with AstraZeneca, to become the standard of care for RSV once it reaches the market.

RSV is the most common cause of hospitalization of infants worldwide, as well as a major cause of hospitalization and mortality in immuno-compromised patients and the elderly. The development pipeline is bulging with RSV vaccines for adults, with many results expected in 2022.

Pfizer sprang a surprise in this age category too, when in July 2021 it announced 100% observed efficacy against mild-to-moderate symptomatic infection in people 60 years or older in a small challenge study. It followed this up by initiating the pivotal Phase III RENOIR study in this age group in early September, helping it to steal ahead of its main competitors.

RENOIR is due to read out in Q1 2022, with results expected to be accelerated by a surge in global RSV cases triggered by post-lockdown lifting of social distancing measures.

SVB Leerink predicts the overall RSV market will exceed \$7bn by 2030, with consensus estimates forecasting nirsevimab revenues of €514m by 2025.

Existing consensus estimates for Pfizer's RSV vaccine across adult and maternal uses are \$655m for 2025, most of which is expected from use in adult populations.

Given the high level of competition, and flood of results expected in 2022, there is still much to play for in terms of RSV market share. Two other notable contenders in the field are Moderna, which is using its mRNA platform for its candidate currently in Phase I studies, and J&J, which has a vaccine in Phase III, plus its oral antiviral rilematovir in Phase I (see Exhibit 4).

Exhibit 4: RSV Development Pipeline

Company	Candidate	Program	Phase	Catalyst	Timing	Approval (Forecast)
Sanofi/AstraZeneca	Nirsevimab	Infant mAb	III	Regulatory filing	Q1 2022 EU H2 2022 US*	2022
Merck	MK-1654	Infant mAb	IIb/III	Phase IIb Results	2022*	2025
Pfizer	RSVpreF	Maternal	III	Interim analysis	Mid-2022	2023
GSK	RSVPreF3	Maternal	III	Topline results	H2 2022	2023
Moderna	MRNA-1365	Maternal	I	Initial results	N/A	null
Pfizer	RSVpreF	Adult	III	Topline results	Q1 2022	2022
GSK	RSVPreF3	Adult	III	Topline results	H2 2022	2023
J&J	Ad26.RSV.preF	Adult	III	Topline results	H2 2022*	2023
Bavarian Nordic	MVA-BN RSV	Adult	II	Phase III initiation	TBA	2024
Moderna	MRNA-1345	Adult	I	Phase IIb/III initiation	YE 2021	2025

Sources: SVB Leerink, company announcements, *SVB Leerink forecasts, October 2021

Alzheimer’s Therapies

Treatment for Alzheimer’s disease had seen little change for decades until 2021, when Biogen and Eisai won a first approval for a so-called disease modifying drug. Aduhelm (aducanumab) was granted accelerated approval by the FDA in June despite a lack of any robust evidence that it helps to slow the progress of the disease, as well as concerns about safety. Adding further bad news to its troubled launch, the companies announced on 17 November that the Committee for Medicinal Products for Human Use (CHMP) had given a “negative trend vote” following an oral explanation on the drug filing from the partners at the November meeting of the committee.

The US approval was also strongly opposed by many Alzheimer’s physicians and Aduhelm has suffered from a far lower uptake in the US than originally hoped for, earning just \$300,000 in Q3, far below the analyst consensus forecast of \$12m-\$17m for the period.

Still, Aduhelm’s success with the FDA has ignited interest into Alzheimer’s disease research again, opening doors for other developers attempting to bring novel treatments to this ever-expanding market. The US National Institute on Aging estimates people over the age of 65 will make up 16% of the world’s population by 2050 — up from 8% in 2010. According to a 2021 report from the Alzheimer’s Association International Conference (AAIC), the number of people with dementia will nearly triple to more than 152 million by 2050. AAIC also notes

that each year an estimated 10 in every 100,000 individuals develop dementia with early onset (prior to age 65). This corresponds to 350,000 new cases of early onset dementia per year, globally.

Considering large catalyst events in 2022, market spectators are closely watching Eli Lilly, which has begun a rolling biologic licensing application (BLA) in the US for donanemab; an investigational antibody that targets a modified form of beta amyloid called N3pG. Lilly announced in October 2021 that it will run a Phase III head-to-head trial testing donanemab against Aduhelm to see which antibody does a better job of clearing amyloid from the brain. The head-to-head (TRAILBLAZER-ALZ 4) is expected to report primary endpoint data during the second half of 2022.

Lilly hopes to complete the rolling BLA filing over the next few months and perhaps obtain accelerated approval of donanemab before the end of 2022. The company is building on ambitions stated earlier in 2021 to follow the approval pathway established by Biogen and the FDA and use it to take a leadership spot in Alzheimer’s disease. “We’re committed to facing the challenges of effectively communicating donanemab’s clinical data and value proposition and to ensuring that the diagnostic and patient management ecosystems are adequately well prepared,” said Lilly’s chief scientific officer Daniel Skovronsky during a Q3 2021 investor call. “Given the current environment, we think it’s reasonable

to have modest expectations for the scale of patient impact for anti-amyloid therapies available under accelerated approval prior to the readout of their definitive Phase III data.”

A number of companies are also expecting late-stage clinical trial data readouts in 2022 (see Exhibit 5), adding momentum to the development space following Aduhelm’s surprise regulatory success in the US.

Gene Therapy Landscape

Looking at the cell, gene and RNA development pipeline as a whole, the majority of therapies are in trials for rare diseases outside of oncology. Amyotrophic lateral sclerosis is in the top five non-oncology rare diseases for all three categories of therapy, according to Pharma Intelligence’s Q3 2021 Data Report on the Gene, Cell & RNA Landscape, in partnership with the American Society of Gene & Cell Therapy.

For non-oncology rare diseases, 323 gene therapies were in preclinical development in Q3 2021, while 127 gene therapies were in Phase I through to pre-registration. The majority of gene therapies in development for non-oncology rare diseases are for neurological or blood disorders.

Looking at the whole pipeline, there were 1,890 gene therapies (including genetically modified cell therapies such as

CAR-T cell therapies) in development as of October 2021, from preclinical through to pre-registration.

This active pipeline highlights that there is much more to come for cell and gene therapies. As of October 2021, there were only 19 approved gene therapies globally – 11 of which were yet to be approved in the US.

More investor money is being poured into cell and gene therapies, a trend expected to continue in 2022. In the first three quarters of 2021, 58 cell and gene companies raised seed or series A rounds. In Q2 2021 and three biotechs raised more than \$200m each in start-up financing.

The Fundamentals

The mood is optimistic for 2022, considering available cash and advances in science. COVID-19 shut down most of the world in 2020 and continues to present challenges, but the biopharma sector has seen some of its highest highs in 2021. Vaccine success has boosted public interest in drug development and pipeline successes have spurred investor interest in biotech, particularly in the US and Europe.

Maina Bhaman, partner at Capital Funds, summarized the situation, telling *In Vivo* that “the fundamentals remain strong for biopharma: continuing demand for new medicines and outstanding returns.”

Exhibit 5: Alzheimer’s Disease Data Readouts Expected In 2022

Company	Drug	Expected Date	Catalyst - Top Line Results	Target
Athira Pharma, Inc.	ATH-1017	1/1/2022	Phase II ACT-AD	Brain-derived neurotrophic factor
Eisai Co., Ltd.	Lecanemab	9/1/2022	Phase III Clarity AD	Amyloid Beta/Amyloid Plaques
AgeneBio, Inc.	AGB101	11/1/2022	Phase IIb/III HOPE4MCI	SV2A synaptic vesicle protein
Axsome Therapeutics, Inc.	AXS-05	7/1/2022	Phase III ACCORD	Dopamine Reuptake
Eli Lilly and Company	Donanemab	7/1/2022	Phase III TRAILBLAZER-ALZ 4	Amyloid Beta/Amyloid Plaques
Anavex Life Sciences Corp.	ANAVEX 2-73	7/1/2022	Phase IIb/III - Early AD (004)	Muscarinic acetylcholine receptor
Roche Holding AG	Gantenerumab	7/1/2022	Phase III GRADUATE - 1	Amyloid Beta/Amyloid Plaques
Roche Holding AG	Gantenerumab	7/1/2022	Phase III GRADUATE 2	Amyloid Beta/Amyloid Plaques
BioVie, Inc.	NE3107	10/1/2022	Phase III Mild to Moderate Alzheimer’s	Tumor Necrosis Factor-alpha
Athira Pharma, Inc.	ATH-1017	9/1/2022	Phase II/III LIFT-AD -	Brain-derived neurotrophic factor

Source: Biomedtracker

The Post-COVID Mantra For Medtechs: Prioritize, Optimize And Modernize



Industry Leaders Back At The Wheel Are Driving Health Care Transformation

Medtech’s resilience and flexibility have been clear to see during the COVID-19 pandemic. In this forward-looking view for 2022, CEOs from some of the Top 50 global medtechs share their perspectives on the present and the future, from company and health care system standpoints.



BY ASHLEY YEO,
EXECUTIVE
EDITOR, EUROPE

Smith & Nephew best summed up the mood among medtechs with a message that would apply to companies serving COVID-affected health care markets, no matter what branch of industry they work in. Wrapping up the company’s 2020 financial accounts, CEO Roland Diggelmann said: “Our first priority for 2021 is to return to top-line growth and recapture the momentum we were building prior to COVID-19.” For him, improving the financial performance through operating leverage was paramount.

And with good reason. With a non-COVID care portfolio of orthopedic recon, sports medicine and ENT businesses, Smith & Nephew was ill-suited to meeting the pandemic’s emergency health care needs. The low point came fairly quickly, in the second quarter of 2020, when the company’s sales dipped by 30%.

However, throughout the ongoing difficulties, the company kept a focus on developing and launching new products so that it could regain momentum as soon as the markets recovered.

Expanding on this theme during AdvaMed’s 2021 MedTech Conference, Diggelmann said that early on in COVID, he ringfenced investment in R&D. Post-pandemic, the demand would still be there, he stressed, a prediction the entire industry counted on.

As the pandemic tails out in 2022, health care service delivery transformation will once again become the central focus. Progress towards this goal has in fact been expedited. One of the COVID

“dividends” was the changed thinking among health care decision makers, who realized the advantages of expediting the commissioning of faster and more efficient workplace methods and systems.

The pandemic sped up the adoption of digital tools by seven years, said Medtronic president and CEO Geoff Martha. Digital, data and artificial intelligence will help industry and providers reach more patients and make health care both more predictive and personal, he believes.

The Patient As Consumer

Speaking at the APACMed 2021 meeting in October, Martha said because of capacity constraints, the world was witnessing the consumerism of health care, from both a patient and provider standpoint. People are feeling more empowered, and their expectations are changing.

Minimally invasive approaches to care, which are potentially speedier, safer and mean less patient time spent in the hospital, need to be prioritized in the coming years, he said.

Care models are shifting to focus on the patient as the consumer. Medtechs are now reimagining when, where and how health care is delivered, and this is happening with the aid of novel partnerships that have sprung up as a function of COVID, Martha noted. Such arrangements will be particularly needed in emerging nations, where there is a lack of both health care infrastructure and awareness of therapies among health care professionals.

China And The Global View

Partly as a result of this situation, the emerging markets will see higher average medtech growth rates, reaching some 7%, in the coming years, according to Haemonetics CEO Chris Simon. Established markets, by contrast, will be restricted to 4% to 6% growth.

Europe and the US will continue to account for two-thirds of the global market, but for Simon, the key geographical question for medtechs to consider is how they can compete in emerging markets.

Nothing yet – not even China – can trump the US market, said Teleflex Medical CEO Liam Kelly. He said Brazil and Latin America represented significant long-term market opportunities, and highlighted that Japan had a better reimbursement system than China.

But China’s volume-based procurement had become an important global issue, Kelly claimed during the Medtech Conference in an interview with AdvaMed’s Abby Pratt. He pointed to the pricing chaos unleashed by China’s November 2020 drug-eluting coronary stents tender, issued under the new national centralized tender program that started with biopharmaceuticals. “Jaw-dropping” was how the Boston Healthcare consultancy described the outcome: the tender winner offered a price of around \$100 – just 7% of the \$1,850 average prices that had been set under previous provincial tenders.

Nevertheless, China is poised to overtake Japan to become the second-largest country market, behind the US. China presented worries, but with a rising middle class it could also represent a “tremendous opportunity,” said Kelly.

Chronic Disease Challenge Needs Digital Solutions

Chronic disease kills 41 million people a year, representing some 75% of all deaths globally, and many are preventable or treatable if caught early. Chronic disease took a backseat during the pandemic, yet associated costs are skyrocketing, Martha observed.

Chronic disease patients need better education and optionality, said Rice Powell, CEO and chair of the management board of Fresenius Medical Care. That must sit in the center of what industry does, he said, stressing that industry must become digitally fast and use apps and iPads to access health records. “We can’t expect people to live in today’s world, surrounded by consumer technology, while we keep them 20 years in the past,” he said. It is incumbent on industry to continue to push into digitization and meet the needs of patients, just as the modern world meets their needs in the consumer side of their lives.

Kidney disease technology company Fresenius Medical Care is focused on chronic care and building an ecosystem around patients that adds value to their lives. “It takes a team to do that,” said Powell, a team that includes regulators, payers and governments.

Earlier in 2021, Edwards Lifesciences CEO Mike Mussallem expressed a similar sentiment. The pandemic brought “a great

reminder that it takes a village – industry, providers’ care, the support of regulators and the input of payers – to actually get treated,” he told the MedTech Forum in April.

The pandemic has made health care into a talking point at the kitchen table. Another of its legacies is that certain trends – like the acceleration of telehealth, digital care and remote connectivity, and virtual proctoring which can guide surgeons through complex cases while at remote global locations – will not go away. But nothing can replace person-to-person interaction. Mussallem said Edwards would remain a “high touch” company in that regard.

Transformation Of Care

Smith & Nephew wants to be a full player in this transformation of care and the shift to digital and better-connected health care – including in the operating room. Continued spending on major programs, like the company’s new ARIA digital care management platform, meant cutting back on

other discretionary spending during COVID, said Diggelmann. The digital rollout is global, he asserted. In the area of robotics and robotic-assisted surgery tools, Smith & Nephew’s new CORI platform is to be launched in Europe and India, which are two important markets for surgical robotics.

Medtronic’s Hugo robot was used in late 2021 at the Apollo Hospitals chain, in India, where the company also opened its 10th global surgical robot training center. The global medtech leader is digitizing the OR by using artificial intelligence to triage stroke patients. It has partnered with Viz.ai, a leader in AI-driven intelligent care coordination, to synchronize stroke care. Viz.ai’s flagship product, the FDA-cleared Viz LVO, uses advanced deep learning to communicate time-sensitive information about stroke patients directly to specialists. In 2020, Viz LVO was granted the first New Technology Add-on Payment (NTAP) for AI software by the US Centers for Medicare & Medicaid Services.

AI is becoming pervasive, while robotics, sensors and virtual reality are improving exponentially, and health data will drive the development of innovative devices. Taken together, they represent the biggest opportunity to propel the digital transformation of health care. But health data is sensitive, and privacy and security must be protected, said Martha. It is a balance, and while a complicated issue, “it is essential we enable use of data for patient benefit,” said Martha.

For Powell, the key to the future is that patients “trust us and our data.” Industry must demonstrate that it is a good partner, and use data wisely, he said.

Johnson & Johnson’s Ashley McEvoy, executive vice president and worldwide chair of medical devices, stressed on several occasions in 2020-21 how much of a gamechanger digital is. Her expectation is that digital will help reduce variation, keep people out of hospital and improve outcomes. And it will improve the way companies work, how supply chains are organized and how product development takes place.

“Value chains are global by design and by default.”

Roland Diggelmann,
Smith & Nephew

Another COVID benefit was the widespread realization over the past 18-24 months that health care is an investment, and not an expense. McEvoy was heartened that more of society has now seen clearly that the medtech industry works with customers, payers and regulators to achieve more consistent outcomes at reduced cost.

Decentralization Of Care

The coming years will see an acceleration in the shift to decentralized care. In response, Smith & Nephew has been providing Positive Connections ASC solutions programs to US ambulatory surgery centers (ASCs) to aid patient identification and patient connections.

Medicare pays less for procedures performed in ASCs than at hospitals, says the US Ambulatory Surgery Center Association (ASCA). Patient co-pays are also significantly lower in an ASC. US health care would save \$2.5bn a year if just 50% of eligible surgical procedures were performed by ASCs, the association claims.

Decentralized care is also seen as providing solutions to capacity and manpower issues, bearing in mind the nurse staffing shortage problems in the US and internationally that do not look likely to improve in the short term.

The Top Issues For Global Medtechs

Finding ways to work in China, which is becoming more protective on access to locally generated data and accessing the market with medtech innovations, is, in Kelly’s eyes, one of the top four challenges for medtechs operating a global strategy in 2022. Moreover, China is a market where it is difficult for medtechs to read the pace of change, he observed. But market access skills can be very differentiating for companies there.

Another top challenge is the continuing shift to value-based care. Rice notes that the health care universe has realized that fee-for-service is no longer the direction industry wants to take. Rather, it should be more about getting paid for outcomes via bundled reimbursement, risk sharing and reducing costs in the health care system.

The COVID-19 pandemic is Kelly’s third major challenge. And the fourth is supply chain resilience, given that many large companies have faced rising freight costs, raw materials inflation and shortages of electronic parts and other products.

Additionally, there is always the potential for individual incidents – like the 2021 Suez Canal blockage and closure of China’s Ningbo-Zhoushan port after a worker was infected with COVID-19 – to disrupt the global supply chain. Companies must respond by forecasting, planning, setting up dual supplies and making strategic shifts to not be reliant on single sources.

Building a global supply chain is one way of addressing this issue. Value chains are “global by design and by default,” as the resulting system provides quality, capacity and cost efficiencies. Nearshoring is not the exclusive answer, Diggelmann believes.

The US-China tariff wars and COVID, among other things, have resulted in a hit to international cooperation and trade in recent years, but the Smith & Nephew CEO is clear: “We

operate in a global world of transnational agreements that leverage the best of all the regions to make [trade] happen.”

A long burning issue has been the EU Medical Device Regulation, which came into effect in May 2021. The MDR will be a major challenge for companies in 2022, but the consensus among the industry’s majors is that while most are making good progress on working with the MDR, the burden is high for smaller companies, and there is a fear that some may exit the medical device market entirely.

Haemonetics’ Simon sees the EU as a regulatory story, not just because of the MDR, but also regarding the revived debate on the use of the plasticizer DEHP (Di(2-ethylhexyl) phthalate) in devices (the Court of Justice declared in October 2021 that the European Commission was justified in granting permission for recyclers to use plastics containing DEHP) and other environmental regulatory changes coming to the fore.

“It’s a dynamic and shifting landscape,” Simon said.

Optimizing In The Market

Medtechs must maximize their resources and focus their strategy. Medtronic did just that when it set out to create a new operating model that was implemented in early 2021. The new plan prioritized accelerated decision-making, improved commercial execution and more effective leveraging of scale.

Smith & Nephew has moved to optimize its manufacturing network with digital technologies and lean manufacturing, adding more warehouse automation and a new orthopedics facility in Malaysia for 2022. That follows progress the company had already made on commercial optimization. Buying out a number of third-party sellers brought the company closer to individual sales representatives and customers in certain markets, as well as removing a layer of cost.

Partnerships Are The Answer

In the challenging health care delivery market, Martha has called on governments to adopt an investment mindset in health, accelerate pro-innovation regulations, and design legal frameworks for data-sharing and protection. For this, a partnership approach is needed between industry and government.

Diggelmann concurs. He believes industry can be more than just a commercial supplier, and also become a key provider of medical education and training. It can supply patient-centered innovative solutions and logistics support where needed. These are the priority macro messages that industry will continue to lobby governments on as health care modernizes and transforms.

The leading companies assert that the fundamentals of the industry remain very sound, and that medtech will continue to benefit from the global megatrends of a demographic shift and a population that is aging and requiring more health care. The other good cards that medtech holds are increasing access to health care in emerging markets and the continued flow of innovation that provides better clinical outcomes to more people around the world. Regardless of COVID-19.



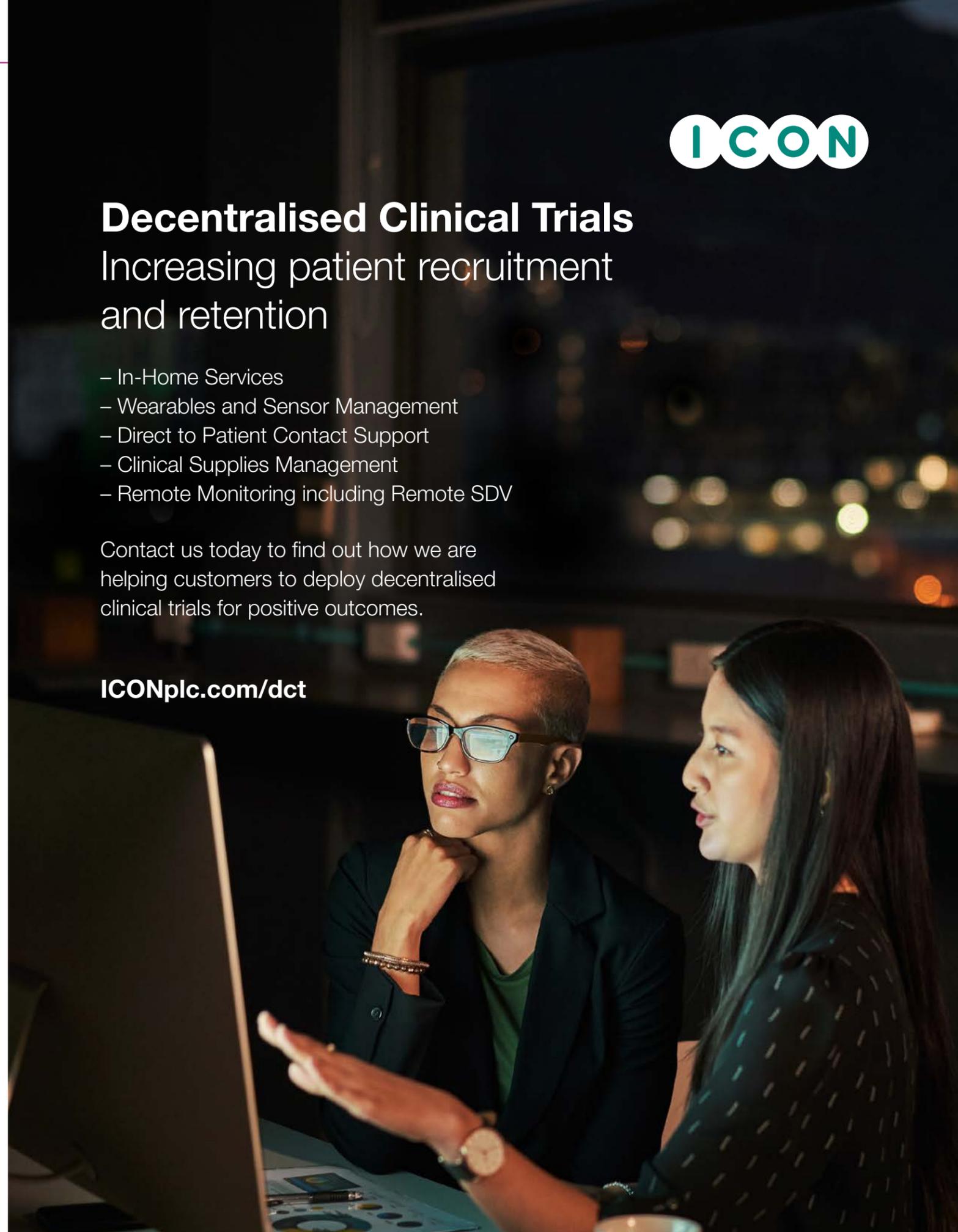
Decentralised Clinical Trials

Increasing patient recruitment and retention

- In-Home Services
- Wearables and Sensor Management
- Direct to Patient Contact Support
- Clinical Supplies Management
- Remote Monitoring including Remote SDV

Contact us today to find out how we are helping customers to deploy decentralised clinical trials for positive outcomes.

[ICONplc.com/dct](https://www.iconplc.com/dct)



SPONSORED BY:



Understanding The Rationale And Potential Barriers To Diversity And Inclusion In Clinical Trials

AUTHOR: **NUALA MURPHY**, PRESIDENT, GLOBAL SPECIALTY SOLUTIONS, ICON PLC.



Growing consciousness of health inequity and other social injustices has also likely propelled diversity to become a priority in clinical research. Consideration during drug development has always been given to the populations for which a drug is intended, but the difference now is that if it is not done adequately, there may be regulatory ramifications – if not immediately, then potentially down the road. It is expected therefore that diversity and inclusion will continue to be a focus of the clinical research community for the foreseeable future.

Examining how the field of clinical research approaches diversity and inclusion gives us a baseline understanding upon which we can build as we continue to make necessary changes for improvement into the future.

To take this first step we need to understand why this is so important and explore the potential barriers to accessing underrepresented subgroups.

Underrepresentation Of Disease-appropriate Subgroups In Clinical Trials

Despite the potential complexities of incorporating diversity in clinical studies, it is important to do so because distinct populations have been known to respond differently to treatments. For example, patients with different racial and ethnic demographics have been found to respond differently, age does impact organ development and function, and weight can have an influence on drug distribution in the body.

Predilection to specific diseases

One example showing the exclusion of disease-appropriate subgroups can be seen in oncology. Some racial minorities can have equal or higher cancer rates compared to the population as a whole. For example, in 2020, the American Association for Cancer Research reported that African Americans have 1.5 times the incidence and twice the death rates from prostate cancer compared to any other race or ethnicity. While prostate cancer is a dramatic example and other cancers have different incidence rates, it is clear that cancer treatment is particularly relevant to racial minorities. However, in that same year, only an estimated one percent of registered cancer clinical trials were directed toward racial and ethnic minority populations, and only a third reported race and ethnicity in trial results.¹

Why Now?

The importance of diversity and inclusion in clinical research is nothing new, however the coronavirus pandemic heightened the awareness of the issues that may arise when communities impacted by the disease or virus are underrepresented in clinical trials. As researchers raced to develop vaccines, industry discourse emphasized the importance of involving the people who needed them the most.

Another factor stoking more recent interest in diversity and inclusion is the FDA's issuance of new guidance in November 2020. The FDA publication offers recommendations for making clinical trials more inclusive of multiple populations and specifically for ensuring that the people participating in trials represent the populations most likely to use the investigational product once approved. The guidance considers demographic characteristics of study populations (e.g., sex, race, ethnicity, age, location of residency) as well as non-demographic characteristics of populations (e.g., patients with organ dysfunction, comorbid conditions, disabilities, those at the extremes of the weight range, and populations with diseases or conditions with low prevalence).

Gender-based differences

It is scientific fact that women process drugs differently than men, which can affect treatment outcomes and the incidence of adverse events. Gender-based differences have been found in drug absorption, distribution, metabolism, and elimination.²

There have been documented instances which have shown how problematic this can be, if not addressed correctly. It is estimated that only half of clinical trials perform gender-based analysis and only 35 percent conduct proper subgroup analyses. This can result in misleading conclusions, reduced external validity, distrust of the trial process, and consequences for women's health.

For instance, the results of a digoxin trial were published in 1997, demonstrating positive outcomes. However, a few years later, in 2002, Rathore *et al.* repeated the same study with the addition of an analysis based on gender. The results were identical for men, but showed that digoxin significantly increased mortality among women, and the drug-associated reduction of hospitalizations for heart failure was less.³

Barriers To Accessing Disease-appropriate Underrepresented Populations

Social determinants of health

A number of barriers can make it difficult for marginalized populations to take part in clinical trials. One useful schema for looking at these barriers is data on the Social Determinants of Health (SDOH) – the environmental conditions that impact people's health and quality of life. These can be broken into the five domains: economic stability, education access and

quality, healthcare access and quality, neighborhood and built environment, and social and community context. SDOH are often out of individuals' control, and can include features such as language, neighborhoods, racism, and discrimination.

SDOH can play out in a number of ways that influence patient recruitment and retention and the practicality of participation. Access to health care can have an impact on access to trials, whether that means access to transportation, to the appropriate technology, or even to information about available trials. Another major consideration is the economic impact of clinical trial participation, as it may mean missing work or requiring childcare. By considering these determinants, trial sponsors can better navigate the barriers that might stand between certain groups of people and participation.

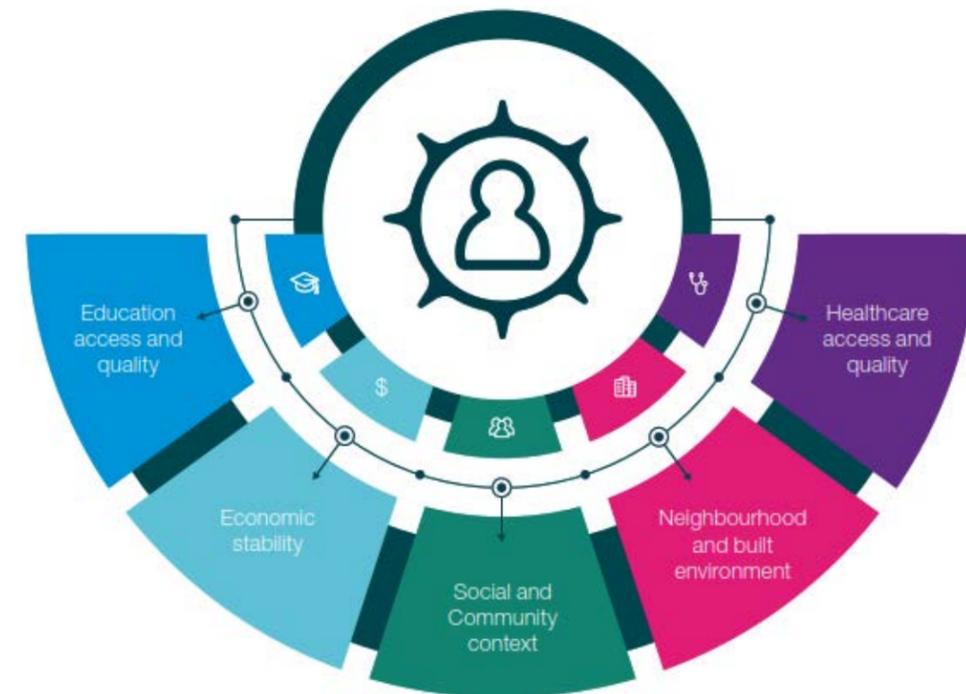
Building trust in the community

Related to social and community context, attitudes toward, and trust in, researchers have been identified as significant challenges in motivating underrepresented populations to participate in trials. If the group conducting clinical trials does not work to cultivate community relationships and treat participants with respect, feelings of exploitation and distrust can emerge. Indeed, a history of exploitation can play into some populations' views of clinical trials.

There have been instances in the past in which the medical field has been criticized for taking advantage of disenfranchised groups by conducting research without properly informing participants or gaining consent. Perhaps most famously, the USPHS Syphilis Study at Tuskegee Institute

conducted a government medical experiment in the Tuskegee, Alabama, area that allowed hundreds of African American men with syphilis to go untreated so that scientists could study the effects of the disease.

A history of what may seem to some as inappropriate exclusion in research may have varying levels of influence over patient populations, depending on individuals and their culture. It may also lead to the researcher's conscious or unconscious bias, believing that certain minority patients will not participate due to anecdotal knowledge or that they are likely to early from the study. As a result, it is important for those conducting clinical trials to be aware of the historical context when they are building relationships with the relevant communities.



Social determinants can influence the practicality of clinical trial participation.



Building community relationships with a foundation of trust is a long-term process. When diverse participation goals are an afterthought, patient recruitment can be less successful. Establishing relationships with local influencers early and partnering with advocacy groups will support inclusion of diverse subgroups.

Identifying And Choosing The Right Sites For Diverse Subgroups

When identifying and choosing a trial site, its location and accessibility are crucial to recruiting and enrolling a diverse population. There can be a tendency to rely on established sites. However, these may not necessarily be accessible to diverse populations due to various factors such as location, lack of reliable transportation links, or patient mobility issues, which could ultimately limit their involvement.

A perception that FOHCs - which are primary care providers for those who have limited access to healthcare - lack experience and resources has made some researchers hesitant to involve them in clinical trials. Without their involvement, many qualified racial and ethnic minorities may continue to be excluded from clinical trials.

Particular subgroups also are challenged to access sites. One analysis published by the Alzheimer's Association found that the location of clinical trial sites conducting memory studies does not align cohesively with areas where adults over the age of 60 reside, putting excessive pressure on those sites that do align with the population and leaving many high-population zones without a trial site within 50 miles.⁴

Health Economics Aspect

One consideration that has previously impacted trial participants relates to insurance. For example, in the U.S., private insurers are required to provide reimbursement for participation in clinical trials. However, this previously was not the case for Medicaid, the federal- and state-run insurance program for people with low incomes.

However, in December of 2020, the U.S. Congress passed the Clinical Treatment Act, which requires Medicaid to cover routine care costs for patients with life-threatening conditions

who are enrolled in clinical trials.⁵ The act is expected to reduce health care disparities and level the playing field for millions of Medicaid recipients.

The NHS in the UK has recently set up an independent organization, Race and Health Observatory (NHSRHO), to identify and tackle health challenges facing people in Black, Asian and minority communities and examine health inequalities.

Conclusion

There are a multitude of compelling reasons for biopharmaceutical companies to embark on a journey to practice greater diversity and inclusion in clinical development as well as in their broader business strategies, including:

- The ability of sponsors and investigators to more accurately test the safety and efficacy of novel medical products in diverse populations where these medical products will be used
- An increased pool of individuals to be considered in clinical research
- The opportunity to address health disparities and to aim at equity
- Enhanced new perspectives and innovation by including diverse personnel

But above all giving access to the participants who can benefit most from the treatments makes sense if, as an industry, we are to be truly patient centric and improve patient lives.

References

1. <https://www.asco.org/sites/new-www.asco.org/files/content-files/>
2. <https://www.bmj.com/content/371/bmj.m3808>
3. <https://www.nejm.org/doi/full/10.1056/NEJMoa021266>
4. <https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.044244>
5. <https://www.congress.gov/bill/116th-congress/house-bill/133/text>

This article is an extract from the Whitepaper: Paving the way for diversity and inclusion in clinical trials: establishing a platform for improvement. Download [Whitepaper](#)



Comprehensive pharma news and analysis that goes beyond the headlines

Easily understand the impact of global pharma news on your business with Scrip. Discover Scrip's direct access to industry decision makers, reliable competitive intelligence, and best-in-class proprietary data.

Go behind the headlines with Scrip's worldwide team of industry experts. Access up-to-the-minute insights and analysis of the events and topics in pharma that affect you most:

- Licensing opportunities
- Clinical trials updates
- Product lifecycle value chain info
- Partnership deals
- R&D activity
- Company developments
- Updates and analysis for multiple therapeutic areas.

Register for your free, no obligation, 7-day trial at pharmaintelligence.informa.com/scríp

Novartis Slips Into Pfizer's Number One Pharma Slot Amid Leaderboard Shakeup

Pfizer has dropped to number seven in our top pharma rankings after a long reign. AbbVie has risen to number three, growing through merger expansion.



BY JESSICA MERRILL, SENIOR EDITOR, US

Pfizer gave up its reign as the number one pharma company in the world based on pharmaceutical revenues in 2020, handing the title to Novartis for the first time since 2016 in the Scrip 100 rankings. Novartis's pharmaceutical revenues grew in 2020 while Pfizer strategically pared down its business by spinning out its established products business, a move that dramatically reshaped the company.

Pfizer dropped to number seven in the Scrip 100 rankings after leading almost every year for at least a decade. The one exception was the 2016 Scrip 100, when Novartis wrestled the title from Pfizer by a narrow margin.

Novartis stepped into Pfizer's number one spot with pharmaceutical revenues of \$48.66bn in 2020, growth of 3% over 2019, despite commercial disruptions caused by COVID-19.

Pfizer, meanwhile, reported substantially lower revenues of \$41.9bn, excluding Upjohn, which was spun off with Mylan in 2019 into a new company named Viatris. Pfizer's 2020 pharma revenues were 16% lower than in 2019 when it included Upjohn.

In a sign of just how drastically Pfizer's organization has been scaled back over the years, the company's pharmaceutical revenues in the Scrip 100 in 2012 were \$58.52bn, when the company solidly ranked number one in the industry after completing the acquisition of Wyeth in 2009. Now, Pfizer's pharmaceutical revenues have shrunk 28% off that peak. The separation of Pfizer's established products business was part of a decade-long transformation at the big pharma to make it nimble, lean and more focused on innovative R&D.

Novartis was able to step over Roche on its way to the top. Roche was the second leading pharmaceutical company last year, but biosimilar competition stunted its growth in 2020.

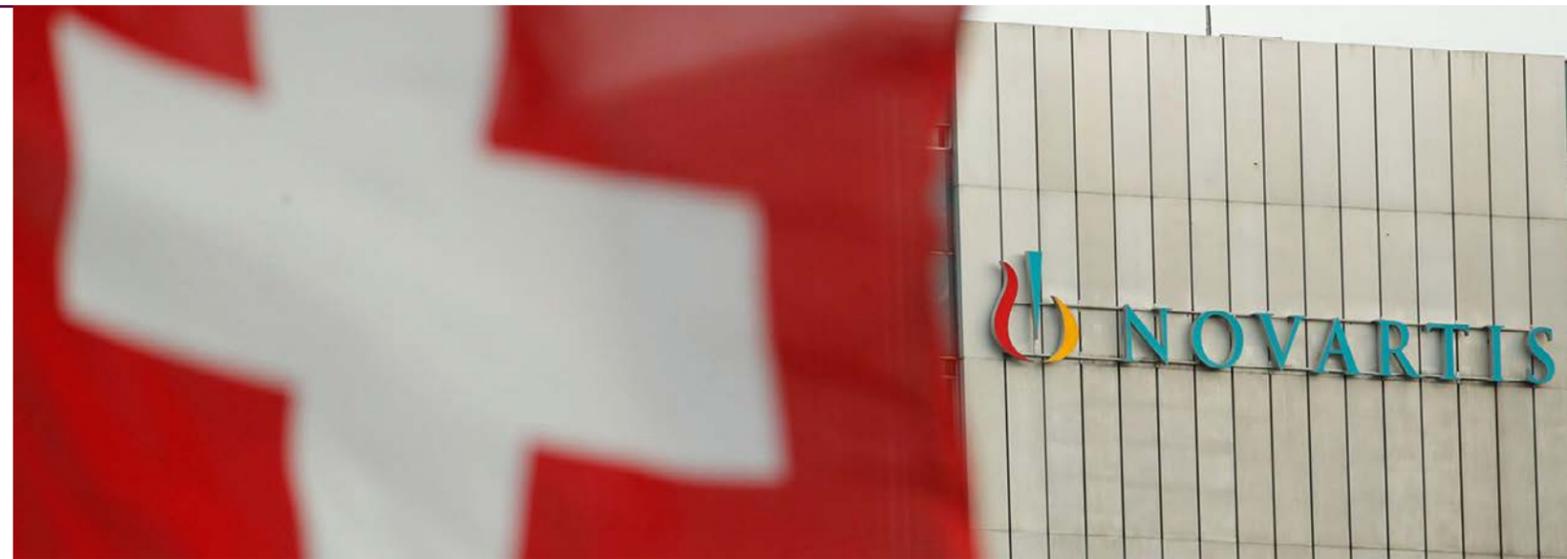
Pfizer will be solidly poised to reclaim its number one position next year, however, driven by the commercial success of its COVID-19 vaccine, Comirnaty, developed in partnership with BioNTech. The company has forecast 2021 revenues will reach an astounding \$78bn-\$80bn in 2021 driven by the vaccine, which it expects will generate \$33.5bn. Excluding the vaccine, the revenue guidance would be \$44.5bn-\$46.5bn, a forecast that could nonetheless position the company to move up in the rankings.

Strong revenues from Pfizer's vaccine reflect an unprecedented global vaccination effort to combat COVID-19, so the growth is expected to be one-time in nature, though the vaccine could continue to contribute to Pfizer's top line for the foreseeable future.

The small biotech Moderna – which previously had no sales and, as such, has not been included in the Scrip 100 before – is also poised to make a big debut in the rankings next year, powered by the strength of its mRNA-based COVID-19 vaccine. Moderna has said it could generate \$20bn in revenues this year, which would position the company within range of a top 20 ranking.

Novartis Outpaces Roche

For now, Novartis has taken the lead on the strength of blockbuster brands like Cosentyx (secukinumab) for psoriasis and other immune indications, Entresto (sacubitril/valsartan) for heart failure, Gilenya (fingolimod) for multiple sclerosis and Tassigna (nilotinib) for leukemia.



Novartis was able to step over Roche on its way to the top spot. Roche was the second leading pharmaceutical company by pharma sales in the Scrip 100 in the previous year, but biosimilar competition to three key brands stunted its growth in 2020. Roche's top line declined 3% in 2020 to \$47.49bn, paving the way for Novartis to claim the top spot with relatively modest growth. Roche's headwinds have continued in 2021, though its pharmaceutical revenues appear to be stabilizing as it absorbs the loss of exclusivity for Avastin (bevacizumab), Herceptin (trastuzumab) and Rituxan (rituximab).

AbbVie And BMS Are Big Movers Driven By M&A

Meanwhile, in another notable change to the Scrip 100, AbbVie jumped up in the rankings to become the number three pharmaceutical company in the world based on pharma revenues of \$45.8bn. It was a substantial move for AbbVie, which ranked seventh in the Scrip 100 a year ago. AbbVie's pharma revenues grew 38% in 2020, powered by M&A. The company completed the \$63bn acquisition of Allergan in May 2020, gaining a substantial new business franchises, including a blockbuster-sized aesthetics business made up of Botox and Juvederm.

The mega-merger was a key element of AbbVie's strategy to diversify the company away from Humira (adalimumab), a Goliath-sized drug that is already facing biosimilar competition in Europe and is poised to face biosimilar competition in the US in 2023. Humira generated \$16.11bn in the US in 2020 so there is a lot at stake for AbbVie as the biosimilar entry date looms closer.

The company is leaning on newer growth drivers like Skyrizi (risankizumab) and Rinvoq (upadacitinib) – as well as continued growth of the Allergan portfolio – to help patch some of the gap.

Bristol Myers Squibb was another big mover in the Scrip 100, similarly driven by M&A. BMS moved from number 10 in the rankings to number six, powered by the acquisition of Celgene in 2019. BMS's pharmaceutical revenues catapulted 63% in 2020 to \$42.52bn. The \$74bn acquisition of Celgene allowed it to leapfrog ahead of Sanofi, Pfizer, GlaxoSmithKline and Takeda Pharmaceutical Co. Ltd. in the rankings.

The addition of Celgene's blockbuster blood cancer drugs Revlimid (lenalidomide) and Pomalyst (pomalidomide) – which together generated more than \$15bn in revenues in 2020 – strengthened BMS's top line.

Last year, Takeda was the big mover in the Scrip 100, growing into a top 10 pharmaceutical company for the first time through the \$61bn acquisition of Shire in 2019. Takeda ranked number nine in the Scrip 100 last year but moved down to number 10 this year.

While there was substantial change in the top 10 pharmaceutical rankings in the Scrip 100 this year, there was little change among the companies that rank 11-20. AstraZeneca, Amgen, Gilead, Eli Lilly & Company, Bayer, Novo Nordisk, Teva Pharmaceutical Co. Ltd, Boehringer Ingelheim and Biogen all held their positions, while Astellas Pharma moved into the top 20 to take the spot formerly claimed by Celgene.

TOP 10 COMPANIES BY PHARMA SALES

Novartis	1	\$48,659
Roche	2	\$47,492
AbbVie	3	\$45,805
Johnson & Johnson	4	\$45,572
Merck & Co	5	\$43,021
Bristol Myers Squibb	6	\$42,518
Pfizer	7	\$41,908
Sanofi	8	\$36,132
GlaxoSmithKline	9	\$30,866
Takeda	10	\$29,961

All sales in \$M.

Scrip 100 Ranking	Company	Country	Pharma Sales (\$m)
1	Novartis	Switzerland	48,659
2	Roche	Switzerland	47,492
3	AbbVie	United States	45,804
4	Johnson & Johnson	United States	45,572
5	Merck & Co	United States	43,021
6	Bristol Myers Squibb	United States	42,518
7	Pfizer	United States	41,908
8	Sanofi	France	36,132
9	GlaxoSmithKline	United Kingdom	30,866
10	Takeda	Japan	29,961
11	AstraZeneca	United Kingdom	26,617
12	Amgen	United States	25,424
13	Gilead Sciences	United States	24,689
14	Eli Lilly	United States	24,540
15	Bayer	Germany	19,687
16	Novo Nordisk	Denmark	19,445
17	Teva	Israel	16,659
18	Boehringer Ingelheim	Germany	16,458
19	Biogen	United States	13,445
20	Astellas	Japan	11,707
21	CSL	Australia	9,151
22	Daiichi Sankyo	Japan	9,018
23	Otsuka Pharmaceutical	Japan	8,949
24	Mylan	Netherlands	8,232
25	Bausch Health	Canada	8,027
26	Fresenius SE & Co. KGaA	Germany	7,965
27	Merck KGaA	Germany	7,580
28	Vertex Pharmaceuticals	United States	6,206
29	Alexion Pharmaceuticals	United States	6,069
30	Eisai	Japan	6,052
31	UCB	Belgium	5,768
32	Regeneron Pharmaceuticals	United States	5,568
33	Servier	France	5,366
34	Grifols, S.A.	Spain	4,844
35	Sumitomo Dainippon Pharma	Japan	4,834
36	Sun Pharmaceutical	India	4,522
37	Abbott Laboratories	United States	4,303
38	Jiangsu Hengrui Medicine Co. Ltd.	China	4,022
39	Asahi Kasei Pharma	Japan	3,822
40	Mitsubishi Tanabe Pharma	Japan	3,540
41	Shanghai Pharmaceutical Group Co., Ltd.	China	3,443
42	STADA	Germany	3,437
43	Sino Biopharmaceutical	Hong Kong	3,429
44	CSPC Pharmaceutical Group Ltd.	Hong Kong	3,158
45	Shanghai Fosun Pharmaceutical Group	China	3,153
46	Aurobindo	India	3,118
47	Kyowa Hakko Kirin	Japan	2,983
48	Endo International	Ireland	2,903
49	Baxter International	United States	2,863
50	Ipsen	France	2,719
51	Lundbeck	Denmark	2,707

52	Cipla	India	2,563
53	Dr Reddy's	India	2,561
54	Chiesi	Italy	2,545
55	Sichuan Kelun Pharmaceutical	China	2,387
56	Jazz Pharmaceuticals	Ireland	2,364
57	Hikma Pharmaceuticals	United Kingdom	2,341
58	Shandong Buchang Pharmaceuticals Co., Ltd.	China	2,321
59	Mallinckrodt	Ireland	2,213
60	Horizon Therapeutics plc	Ireland	2,200
61	Santen	Japan	2,199
62	Seattle Genetics Inc.	United States	2,176
63	DaShenLin Pharmaceutical Group Co., Ltd.	China	2,115
64	Incyte	United States	2,069
65	Lupin	India	2,047
66	Zydus Cadila (Cadila Healthcare)	India	2,044
67	Ono	Japan	2,010
68	Amneal Pharmaceuticals	United States	1,993
69	Joincare Pharmaceutical Group Industry Co., Ltd.	China	1,961
70	BioMarin Pharmaceutical	United States	1,860
71	Vifor Pharma	Switzerland	1,819
72	Meiji Holdings	Japan	1,814
73	Nichi-Iko	Japan	1,763
74	Sawai	Japan	1,754
75	KRKA	Slovenia	1,752
76	Swedish Orphan Biovitrum AB	Sweden	1,664
77	Recordati	Italy	1,598
78	Celltrion	South Korea	1,570
79	Harbin Pharmaceutical Group Co., Ltd.	China	1,564
80	Leo Pharma	Denmark	1,552
81	Genmab AS	Denmark	1,549
82	Livzon Pharmaceutical Group	China	1,525
83	Gedeon Richter	Hungary	1,487
84	United Therapeutics	United States	1,483
85	Glenmark Pharmaceuticals	India	1,477
86	Towa	Japan	1,451
87	Teijin Pharma	Japan	1,393
88	GC Pharma	South Korea	1,277
89	Shijiazhuang Yiling Pharmaceutical Co.,Ltd	China	1,273
90	Hansoh Pharmaceutical	China	1,260
91	CR Double-Crane Pharmaceuticals Co., Ltd	China	1,233
92	Pierre Fabre	France	1,123
93	KPC Pharmaceutical Inc.	China	1,119
94	Chong Kun Dang	South Korea	1,106
95	Torrent Pharmaceuticals	India	1,080
96	Hisamitsu	Japan	1,073
97	Zhejiang Medicine Co., Ltd.	China	1,062
98	Kwang-Dong Pharmaceutical	South Korea	1,056
99	Orion Corporation	Finland	1,049
100	Neurocrine Biosciences, Inc.	United States	1,046

The Scrip 100 ranking is based on Informa Pharma Intelligence's analysis of fiscal year 2020 prescription pharmaceutical sales data for the top 100 biopharmaceutical companies. For more information contact: Lucie.Ellis@informa.com.

Outlook 2022

The Scrip 100 universe gathers FY 2020 financial performance data and compares the activities of the top 100 biopharma businesses, ranked by pharma sales

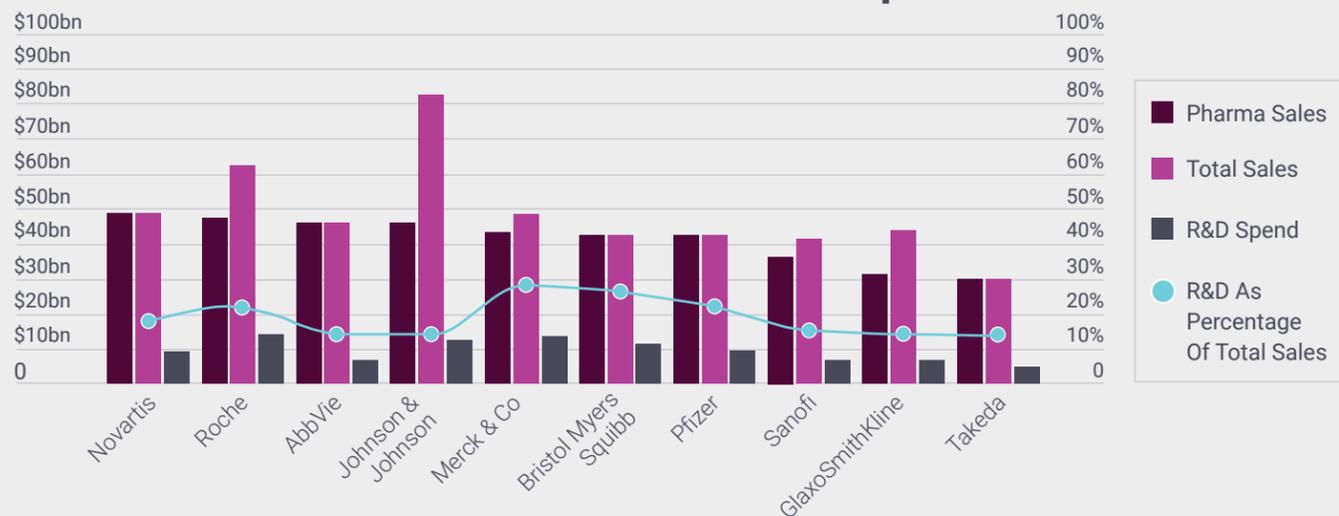
Who gets in?

Top 100 companies based on pharmaceutical sales only for fiscal year 2020



- \$610.6bn** Combined pharma sales of Top 20
- \$852.3bn** Combined pharma sales of Top 100
- 2,949,646** Number of people employed by Top 20
- Top Spot This Year**
Novartis
Pharma sales **\$48.66bn**

A Closer Look At The Top 10

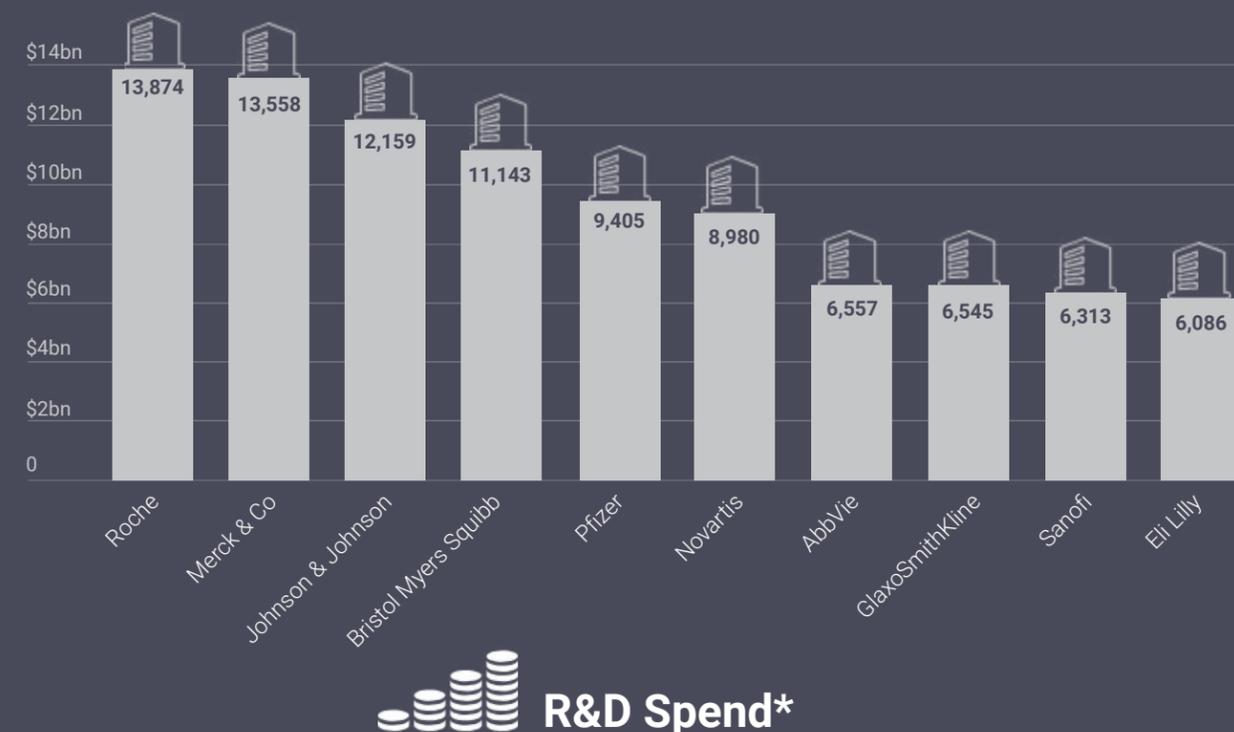


Based on **FY 2020** pharma sales, **Pfizer** dropped to number seven in the **Scrip 100** rankings after leading almost every year for at least a decade

Pfizer has forecast 2021 revenues will reach **\$78bn-\$80bn** driven by COVID-19 vaccine sales, which it expects will generate around **\$33.5bn**

Novartis has taken the lead in the Scrip 100 rankings on the strength of blockbuster brands like **Cosentyx, Entresto, Gilenya** and **Tasigna**

Top 10 Companies By R&D Spend



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

Top 100 By Location



Top 20 By Location

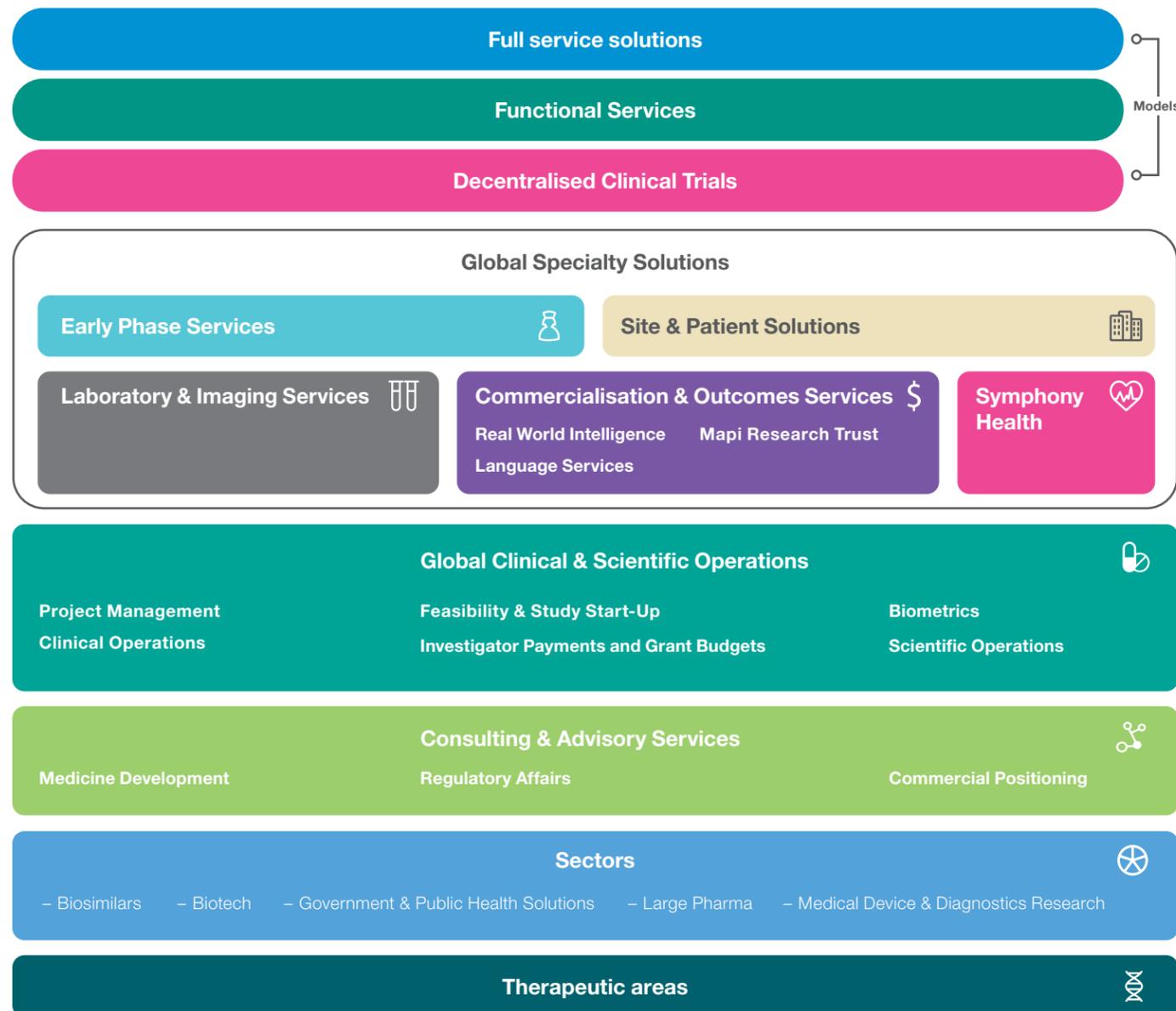




Company overview

ICON is a world-leading clinical research organisation. From molecule to medicine, we advance clinical research providing outsourced development and commercialisation services to pharmaceutical, biotechnology, medical device and government and public health organisations. We develop new innovations, drive emerging therapies forward and improve patient lives. With headquarters in Dublin, Ireland, ICON operates from 137 offices in 46 countries and has approximately 38,000 employees as of 1 November 2021.

Full service portfolio: Early Phase to Commercialisation



ICONplc.com



Clear focus. Better outcomes.

With more than 38,000 employees ICON is the world's largest CRO with a singular focus on clinical research and commercialisation. We are completely committed to achieving customers' clinical development programs. Regardless of size, we work your way to deliver better outcomes.

ICONplc.com



Medtechs Drive To Keep The Status Quo In A Year Like No Other



The performances of the leading medtechs in the first year of the COVID-19 pandemic were impossible to compare and certainly unrepresentative of normal business cycles and competitive activity. Elective care was largely put on hold and emergency needs boosted exceptional demand for certain product types. More than anything else, 2020 tested management skills and planning.



BY **ASHLEY YEO**,
EXECUTIVE
EDITOR, EUROPE

Demand for certain types of medtech, industrial operations, supply chains and distribution systems were all impacted to some extent by COVID-19 in 2020. So were product development milestones, clinical trials, regulatory clearances and approval timings.

During the pandemic, leading orthopedic and some cardiology suppliers saw sharply negative outcomes, while the opposite was the case for companies whose devices and diagnostic tests answered the needs of emergency COVID care.

IVD companies' portfolios not targeted at the pandemic's needs experienced lower revenues in 2020, as Medtech Insight's Top 100 companies by sales for fiscal 2020 illustrates. Others saw almost stratospheric growth, but at the same time, they were careful to stress the temporary nature of such developments.

To their great credit, medtechs rapidly set out plans to control the spread of COVID-19 infection in Europe, the US and globally after the World Health Organization declared a pandemic in March 2020.

For companies targeting the European market, the pandemic even supplanted preparations for compliance with the EU Medical Device Regulation as the biggest concern among medtechs globally. The MDR was postponed by a year just weeks before its scheduled May 2020 effective date. COVID-19 had made it impossible for the majority of companies to achieve sufficient compliance with the regulation's stringent new standards. The ongoing absence of the necessary MDR infrastructures had been a mounting concern for industry long before the pandemic hit.

Financial Performances In Fiscal 2020

Respiratory device maker ResMed was among those to find itself on the front line of COVID-19 control based on its portfolio of ventilators, masks and consumables for chronic lung disease patients. In its financial year ended June 2020, which included one full fiscal quarter of revenues under the pandemic, its sales rose by over 13%. In the financial year to June 2021, they were up by a further 8.1%, to \$3.2bn.

But as the company indicated in its latest annual report, there is a flip side to certain products being in huge demand at the time of an extreme health care emergency. In 2020-21, it observed only minor incremental demand for its ventilators and masks, and said it did not expect COVID-19-generated demand for certain products to continue in the fiscal year to 30 June 2022.

On the contrary, its diagnostic pathways for its sleep apnea treatments, used in physician practices and sleep clinics, and software-as-a-service business, were negatively impacted. Like its industry counterparts, in late 2020 and into 2021 ResMed began progressively returning to normal patterns of work at its global offices.

Medtronic was the first company to report a full year of COVID-impacted sales when its fiscal year ended in April 2021. But unlike in 2019-20, when its sales fell back below the \$30bn threshold, this year the medtech industry's global number one company by revenue scored a 4.2% rise.

Its rebound in 2020-21 was primarily related to the recovery of procedure volumes, a slightly longer financial year (adding at least \$360m), and favorable currency impacts from its non-US markets, when foreign sales were translated into US dollars. Medtronic recorded declines in two subdivisions, coronary/peripheral vascular and surgical innovation, but all four of its main divisions (cardiovascular, medical-surgical, neuroscience and diabetes) grew by between 2% and 6%. Medical-surgical grew by 5% due partly to demand for ventilators, airway and other COVID-related products.

Elsewhere among the top 10 medtechs, the COVID effect on sales was clear.

Abbott Laboratories (+13.2%), Roche (+12.8%), Cardinal Health (+7.4%), Siemens Healthineers (+26.9%), BD (+18.3%) and Royal Philips (+2.7%) all had portfolios that were pandemic-attuned to a greater or lesser extent.

On the contrary, Stryker (-3.3%) and Johnson & Johnson (-11.6%) lost ground in the first year of COVID, as did GE Healthcare (-9.7%), but for structural reasons. The average growth rate of the top 10 in 2020, in US dollars, was 6.1%. Most of them reported on 31 December 2020, but Cardinal's fiscal year ended in June 2021, and BD and Siemens Healthineers, which added Varian Medical Systems for part of the year, both reported their annual earnings for the year ended 30 September 2021.

Siemens Healthineers had a powerful fiscal 2021, but CEO Bernd Montag was at pains to stress the one-off effect seen in its rapid antigen tests business, which added €1.1bn to sales. Siemens Healthineers' overall diagnostic/IVD sales rose by an unprecedented 38.1% in what Montag called "an extraordinary year." Varian added €1.3bn to sales, and the other divisions (imaging +8%, and advanced therapy systems +5.4%) also contributed to record company revenues of €18bn (\$20.56bn) in fiscal 2021.

BD became the sixth company with sales in excess of \$20bn in the year ended September 2021. It grew by 18% on a reported basis, compared with a fiscal 2020 figure of \$17.12bn that was down marginally on the 2019 total of \$17.3bn. Its fiscal year 2021 revenues were boosted by COVID diagnostics sales of \$1.96bn. Its integrated diagnostics solutions sales rose by 44.1%, and by 7.4% excluding COVID diagnostics. BD expects COVID-only revenues of \$200m in 2022, and for its overall sales to dip to \$19.3-19.5bn.

Given its product exposure and the market conditions in 2020, only one of Johnson & Johnson's medtech franchises saw a sales increase. Its interventional solutions sales of \$3bn were 1.6% up on 2019, with atrial fibrillation procedures growth driving the electrophysiology (EP) business. Vision and surgery sales declined by 15% and 13.4%, respectively, under the negative impact of COVID-19. Hips, knees, trauma and spine/sports medicine were all down, too, but product leadership and new launches in this franchise restricted the overall decline to 12%.

In hindsight, COVID-19 will be seen as an accelerator in health care, worldwide chair of medical devices at Johnson & Johnson, Ashley McEvoy, said at APACMed, one of the many industry meetings that went virtual in 2020. The pandemic enforced a new way of looking at health care management and hospital system use, and prioritized science and the value of technology and data, she said.

The same elective care experiences played out at Stryker, albeit boosted by the addition of Wright Medical's extremities portfolio. Trauma and extremities sales combined increased by 5% to \$1.7bn, but those of hips and knees – and spine with sales of just over \$1bn – all dropped.

The addition of Alere, St Jude and Auris Health, principally, have seen Abbott Laboratories gallop up the medtech sales rankings in recent years, but in 2020, its rise was COVID-19 led. The group's worldwide diagnostics business expanded by 40.6% in 2020, boosted by strong demand for its BinaxNOW, Panbio and ID NOW rapid testing platforms used in COVID control.

Abbott's rapid diagnostics sales went from \$2bn in 2019 to \$4.3bn in 2020, and molecular testing from \$440m to \$1.44bn. The familiar story was that core lab and POC test sales declined. Lower procedure volumes in cardiovascular and neuromodulation saw device segment sales (excluding foreign exchange impact) decrease by 3.8%. Pricing pressures on drug-eluting stents was also a factor. But as at Medtronic, Abbott's diabetes sales increased, in Abbott's case, in the double digits.

Pureplay diabetes technology company Dexcom put in another strong performance in 2020, with sales up by \$451m (+31%), driven by disposable sensor volumes and the global expansion of its customer base. Pricing pressures held back growth. Reusable hardware accounted for 19% of its sales, down from 22% of the total in 2019. The continuous glucose

Medtronic was the first company to report a full year of COVID-impacted sales.

monitoring company has grown by 87% in the past two years, from sales of \$1.0bn in 2018 to \$1.9bn in 2020.

However, Roche's diabetes care sales decreased by 5%. The Swiss group also experienced lower demand for routine testing, but still secured 12.2% overall growth in 2020. The global leading IVDs player's major growth area was molecular diagnostics, up by 90%, led by the cobas SARS-CoV-2 PCR test. In all, Roche's sales of COVID tests in 2020 totalled CHF2.6bn (\$3bn), compared with Abbott's 2020 COVID-19 test sales of \$3.9bn.

Personal protective equipment (PPE) drove a 7.4% increase at Cardinal Health, as the company's medical segment experienced dramatically increased demand for these products, such that it needed to find additional sources of these goods. It also raised its selling prices to mitigate higher production costs. But it was hit by lower demand for surgical products resulting from reduced elective procedures.

The largest European medtech group, Royal Philips, managed to secure a 2.7% increase in reported sales, in spite of a major decline in its diagnosis & treatment businesses, due to the postponement of installations and elective procedures. Personal health sales also dropped, but connected care's monitoring, analytics, and sleep and respiratory care were in demand during COVID-19. Intact Vascular was the largest of its three M&A plays in 2020.

GE Healthcare pursued the opposite M&A path, selling its biopharma business to Danaher in March for \$21.1bn. The business logged biopharma 2020 sales of \$830m prior to the disposal; in 2019, its revenues were \$3.3bn. This is one reason why GE's 2020 sales were a comparatively low \$18bn. Healthcare equipment sales, at \$15.4bn, were up 5% on 2019. Pharmaceutical diagnostics (PDx) is the other element in GE's sales mix.

A second reason was a reduction in demand and delays in procurement of products and services that were not critical to pandemic response efforts, or where procedures were postponed. MRI, contrast agents and nuclear tracers were affected by these developments. Over the long term, the company predicts that the health care systems equipment market will continue to expand at low single-digits, which, in turn, should increase demand for PDx's contrast and tracer-enhanced biomarkers.

Health Care Market Expands, China Plans Big

Regardless of COVID-19 and the associated lockdown measures that led to a sharp recession in the global economy, the global health care market continued to expand in 2020. This was driven by the macro trends: the growing and aging population; and increasing chronic and lifestyle-related diseases. Demand for health care increased in emerging markets in particular.

China's national health strategy, Healthy China 2030, an action program designed to promote the health of China's 1.4 billion population, is expected to add to growth in demand. But just how far foreign medtechs will benefit is the subject of much reflexion, given the ambitions China has set out for local medtechs in its 14th five-year plan, published in 2021. China's

volume-based procurement (VBP) initiative is a particular concern for many overseas medtechs.

But in 2020, the Chinese market often provided support to medtechs' global revenues. Royal Philips said that across all its markets using local currencies, only Greater China showed growth in 2020. The rest of the markets all suffered full-year recessions, with Oxford Economics data reporting a global real GDP contraction of 3.9% in 2020.

Across all markets, using local currencies, Royal Philips found that only Greater China showed growth in 2020.

In 2020, the depreciation of the US dollar against the EU and Swiss currencies affected the US dollar-translated sales of the leading European and Japanese companies listed in the Medtech 100. Against the dollar, the Swiss franc strengthened by almost 6%, the euro by almost 5%, the Danish Kroner by 2.2% and the Yen by 2.1%.

COVID Effect On IVD Company Revenues

Roche and Abbott together saw sales of \$6.9bn in COVID-related IVD products, while both noted declines in their routine testing businesses. Similarly, top 20 IVDs company Thermo Fisher experienced particularly strong demand for products that supported the diagnosis of COVID-19, offset by lower sales of other products due precisely to pandemic-related impacts on customer activity.

Bio-Rad Laboratories reported the same story, with clinical diagnostic sales falling, but strong demand for products associated with COVID-19 testing and related research.

In the lower reaches of the Top 100, Meridian said that the pandemic had both positive and negative effects on its business. Its life science segment products were well positioned to respond to IVD manufacturers' needs for reagents for molecular, rapid antigen and serology tests. But its diagnostics segment reported decreased revenues in the second half of 2020, as health systems focused on SARS-CoV-2 testing over traditional infectious disease and blood-chemistry testing.

The COVID effect was at its most visible at Quidel, which, after two steady years of sales of just above half a billion, truly had the year like no other in recording sales up 211%, at \$1.66bn. Rapid immunoassays were the largest contributor to growth, and molecular diagnostics grew by \$201m. On the other hand, cardiometabolic immunoassay and specialized solutions sales dropped.

Italy's largest medtech player DiaSorin reported triple-digit growth at its molecular business (+313.4% at constant

exchange rates). This was largely driven by tests for COVID-19 diagnosis in the US, Canada and Europe. Its overall Euro-reported revenues were up by 25% at €881m.

Qiagen's net sales for 2020 increased 23%, as the company experienced very strong demand for product groups addressing the critical demand for COVID-19. It also observed an improving trend for non-COVID-19 products during the second half of 2020.

Horiba noted a decrease in the number of tests performed at hospitals, leading to sales declines for its diagnostic systems and test reagents. Elsewhere, the company focused on building up the micro-blood analysis system business acquired from Rohm Co. in 2018, and on expanding its business outside and in Japan.

Exact Sciences has grown rapidly from a relatively small base in recent years and made its presence felt in the Medtech Top 100. Its screening (Cologuard test) and precision oncology (Oncotype IQ) laboratory service revenues were impacted by COVID-19 in 2020, but in response, it began conducting COVID-19 testing and thereby gained additional revenues of \$235.8m. While Cologuard revenues were flat at \$815m, precision oncology revenues were up more than six-fold at \$440m, due to the consolidation of the revenues of Genomic Health, acquired in November 2019. Exact was active three times on the M&A front in 2020, and continued that momentum into 2021.

Elsewhere among the leading IVD groups, Danaher's sales rose by 11% 2019, following increased demand for molecular diagnostics, acute care instruments and consumables to support the response to COVID. Patient volumes remained down year-on-year, but improvements were visible from the second quarter. Core sales in the clinical lab business decreased year-on-year across all major product lines.

For Sysmex, the pandemic broke out in the fourth quarter of its fiscal 2019, and the company experienced a decline in sales in its mainstay hematology field. A 1% rise in reported currency sales to JPY305bn became a 3.2% rise in US dollars in its year ended 31 March 2021. At bioMérieux, molecular biology product growth carried a 21% rise in dollar-converted sales.

Diagnostics is the largest business segment at Hologic, accounting for \$2.07bn of the company's sales in 2019-2020. (Hologic's individual IVD and imaging segment sales were not provided in its initial annual financial report for 2020-21). In 2020, Hologic's IVD sales rose by 76% on the back of a \$966m increase in molecular diagnostics (excluding blood screening), attributable mainly to revenues of \$929m from its two COVID tests and instrument sales.

Away From Diagnostics

Cytiva's move from GE Healthcare to Danaher's life sciences segment and Siemens Healthineers' planned integration of cancer radiation therapy company Varian Medical Systems (a transaction valued at \$16.4bn and completed in spring 2021) were the top medtech M&A talking points of 2020 across the medtech industry.

Varian's 2020 product revenues decreased by 11% in 2020 due primarily to a decline in hardware product revenues from oncology systems following customers' capital constraints, site access challenges and delays to pre-installation activities resulting from COVID. Including service revenues, Varian made overall revenues of \$3.17bn in its last full year as a standalone company.

Top 20 company 3M completed the divestment of all its drug delivery business (except the transdermal business) to Altaris Capital Partners, in spring 2020, for \$617m. This included a non-cash element – a 17% interest (valued at \$60m) – in the new company Kindeva Drug Delivery. The divested business had annual sales of approximately \$380m. 3M also sold a small dermatology products business. Excluding food safety sales, the company still achieved a 13.5% rise in sales in 2020.

Further down the Top 100, companies were largely reporting a variation on the main theme. For instance, consolidated revenues at Natus decreased by \$80m, due to a decline in demand for its neuro, hearing and balance products, as a result of the pandemic. CryoLife's revenues were negatively impacted by delays or cancellations of certain surgical procedures, as well as patients' ongoing reluctance to undergo procedures once the adverse impacts on capacity and other restrictions had eased. And CooperSurgical's revenues in its year to October 2020 were disrupted by a significant reduction in physician office visits, and health care centers postponing or cancelling capital purchases. Sales of Paraguard IUD and other surgical products, such as uterine manipulators and closure products, decreased, as did IVF consumables.

Making Time For Strategic Thinking

The medtech industry was not exclusively COVID-fixated in 2020, as shown by strategic planning initiatives by companies at both ends of the Top 100. Medtronic implemented its "new operating model" late in the fiscal year. That should lead to accelerated decision-making, improved commercial execution, and more effective leveraging of scale.

Further down the leading 100, vascular access company AngioDynamics also made time to pursue strategic plans to transform itself from a company with a broad portfolio of largely undifferentiated products to one more focused on medical technology and innovative health care solutions.

It aims to shift its portfolio away from the mature, lower-growth markets, and will invest in technology that provides access to larger and faster growing markets. A two-tier business, split according to "Med Tech" (high-tech lines) and "Med Device" (the remainder of the portfolio), will be the result.

AngioDynamics was not without COVID-related business concerns of its own, but a 10% rise in its annual sales to May 2021 would have put added momentum behind its new focus on differentiated innovation. It was another reminder that, although the pandemic seemed all-consuming, medtechs ensured they kept efficient business management initiatives and strategic planning in sharp focus.

Medtech Top 100 In 2020					
Ranking 2020 (2019)	Company	Fiscal 2019 sales US\$ million	Fiscal 2020 sales US\$ million	2020 notes	Industry activity
1 (1)	Medtronic	28,913	30,117	Year ended 30 April 2021	Cardiovascular, medical surgery, neuroscience, diabetes
2 (2)	Johnson & Johnson	25,963	22,959		EP, neurovascular, orthopedics, surgery, vision
3 (4)	Abbott Laboratories	19,952	22,592		IVDs, rhythm management, EP, HF, cardiovascular, diabetes
4 (3)	Philips Healthcare	21,297	21,869	Excludes IP & licensing income	Diagnosis & treatment, connected care, personal care
5 (7)	Siemens Healthineers	16,197	20,556	Years ended 30 September 2020 & 2021; includes Varian since 15 April	Imaging, radiotherapy, IVDs, POC testing, advanced therapies
6 (6)	Becton Dickinson	17,117	20,248	Years ended 30 September 2020 & 2021	Medication delivery, syringes, needles, infusion therapy, delivery systems, diabetes care, IVDs, surgery, critical care, urology, peripheral intervention
7 (5)	GE Healthcare	19,942	18,009		Imaging, ultrasound, acute care systems, contrast and molecular imaging agents
8 (8)	Cardinal Health	15,544	16,687	Medical sales; year ended 30 June 2021	Sharps, incontinence, nutritional delivery, wound care, fluid suction, urology, OR supplies, electrode products
9 (10)	Roche Diagnostics	13,035	14,708		IVDs, tissue diagnostics, POC, patient self-testing, next-gen sequencing, lab automation, IT, decision support
10 (9)	Stryker	14,844	14,351		Orthopedics, med surg, neurotech, spine
11 (11)	Boston Scientific	10,735	9,913		Endoscopy, urology, CRM, EP, neuromod, cardio & peripheral vascular
12 (12)	B Braun	8,369	8,482		Infusion, nutrition & pain therapy, infusion pumps & systems, surgical, suture materials, hip & knee implants, dialysis equipment, ostomy, disinfection & wound care
13 (14)	Baxter International	7,850	8,120	Excludes pharma & clinical nutrition	Dialysis, IV solutions, infusion systems, parenteral nutrition therapies; inhaled anesthetics; generic injectables; surgical hemostat & sealant products
14 (16)	Danaher	6,662	7,403		IVDs/lab diagnostics, critical care, molecular & analytical pathology
15 (17)	3M	6,300	7,150	2019 restated to exclude food safety	Skin & wound care, infection prevention, dentistry, reimbursement software
16 (13)	Zimmer Biomet	7,982	7,025		Orthopedic recon, sports medicine, biologics, extremities & trauma products; spine, craniomaxillofacial & thoracic; dental implants
17 (20)	Grifols	5,711	6,100		Blood plasma-based products, devices, clinical lab reagents
18 (18)	Olympus	5,889	5,863	Year ended 31 March 2021	Endoscopy

Ranking 2020 (2019)	Company	Fiscal 2019 sales US\$ million	Fiscal 2020 sales US\$ million	2020 notes	Industry activity
19 (19)	Terumo	5,771	5,754	Year ended 31 March 2021	Interventional systems, neurovascular, cardiovascular, hospital systems, infusion pumps
20 (28)	Thermo Fisher	3,718	5,343	Specialty diagnostics	IVDs, reagents, culture media, instruments
21 (22)	Fujifilm	4,626	5,322	Healthcare; year ended 31 March 2021	X-ray, ultrasound, cell culture media, pharma, life sciences
22 (21)	Smith & Nephew	5,138	4,560		Advanced wound management, sports medicine, ENT, orthopedics
23 (24)	Edwards Lifesciences	4,348	4,386		TAVR, TMTT, structural heart, critical care
24 (23)	Intuitive Surgical	4,479	4,358		Robotic-assisted surgery products
25 (25)	Fresenius Medical Care	4,037	4,277	Healthcare products (excludes services)	Dialysis, disposable renal products
26 (27)	Canon Medical Systems	4,024	4,087		CT, MR, X-Ray, ultrasound, healthcare informatics
27 (-)	Zoll Medical	3,166	3,823	AK healthcare division	Pharma & diagnostic reagents, artificial kidneys, therapeutic apheresis, virus removal filters, AEDs, wearable defibrillators
28 (15)	Alcon Laboratories	4,174	3,710	Surgical sales only	Ophthalmic surgery, vision care
29 (26)	Dentsply Sirona	4,029	3,342		Dental equipment & consumables
30 (31)	Getinge Group	2,810	3,250	Acute therapies + life sciences + surgical workflows	Acute care, disinfection products
31 (33)	Hologic Inc	2,771	3,227	Year ended 25 September 2021 (excludes service income)	IVDs, breast, gyne, skeletal health, products for women
32 (29)	ResMed	2,957	3,197	Year ended 30 June 2021	Respiratory & sleep products, software as a service
33 (30)	Shimadzu	2,812	2,957	Year ended 31 March 2021	X-ray, fluorescence imaging
34 (36)	bioMérieux	2,443	2,954	Excludes industrial and other	IVDs
35 (32)	Sysmex	2,771	2,859	Year ended 31 March 2021	Hematology, urinalysis, immunochemistry reagents, robotics
36 (34)	Coloplast	2,690	2,841	Year ended 30 September 2020	Ostomy, urology, continence, wound care
37 (38)	Dräger	1,951	2,630		Critical & neonatal care, anesthesia, monitoring
38 (35)	Teleflex Medical	2,595	2,537		Vascular access, anesthesia, urology, respiratory products, OEM activity
39 (37)	Align Technology	2,407	2,472		Dental scanners, alignment technology
40 (41)	HU Group (Miraca)	1,732	2,090	Year ended 31 March 2021	IVDs (SRL, Fujirebio, Nihon Stery companies)
41 (49)	Dexcom	1,476	1,927		Diabetic care continuous glucose monitoring
42 (39)	ConvaTec	1,827	1,894		Wound, continence & critical care, ostomy, infusion products
43 (43)	Nihon Kohden	1,698	1,872		EEG, ECG, AEDs, pacemakers, monitors
44 (47)	Qiagen	1,526	1,870		IVD kits & instruments, bioinformatics

Ranking 2020 (2019)	Company	Fiscal 2019 sales US\$ million	Fiscal 2020 sales US\$ million	2020 notes	Industry activity
45 (80)	Quidel	535	1,662		Rapid diagnostic testing solutions
46 (40)	Varian Medical Systems	1,784	1,588	Year ended 2 October 2020	Radiotherapy, proton & oncology
47 (42)	Bausch Health	1,717	1,566	Devices only	Intraocular lenses, ophthalmic surgical equipment, aesthetics devices
48 (60)	Omron	1,032	1,564	Year ended 31 March 2021	Blood pressure monitors & thermometers
49 (44)	Carl Zeiss Meditec	1,635	1,525	Year ended 30 September 2020	Ophthalmic technologies
50 (45)	Straumann	1,607	1,521		Dental implants, scanners, orthodontics
51 (46)	Elekta	1,545	1,500	Year ended 30 April 2021	Radiotherapy, surgery, brachytherapy
52 (70)	Exact Sciences	876	1,491		Cancer screening, IVDs
53 (-)	Teijin	1,443	1,394	Human chemistry division (includes pharma)	Orthopedics, home healthcare, pharma
54 (54)	Fukuda Denshi	1,224	1,376	Year ended 31 March 2021	Diagnostic & monitoring equipment, pacemakers, ventilators
55 (48)	Integra LifeSciences	1,518	1,372		Neurosurgery, instruments, orthopedics, tissue technologies
56 (51)	Shinva Medical Instrument	1,269	1,326		Sterilization equipment
57 (50)	Bio-Rad Labs	1,412	1,305	Clinical diagnostics only	IVDs
58 (52)	ICU Medical	1,266	1,271		Infusion therapies & systems, critical care
59 (55)	Smiths Medical	1,172	1,264		Infusion systems, vascular access, critical care
60 (66)	Masimo Corp	938	1,144	Year ended 2 January 2021	Pulse oximetry, monitoring
61 (59)	Colfax (DJO Global)	1,080	1,121		Orthopedics
62 (61)	Cantel Medical	1,016	1,069	Estimate for year end 31 July 2021; acquired by Steris in June 2021	Infection prevention, endoscopy, dental, dialysis services
63 (56)	NuVasive	1,168	1,051	Hardware + surgical support	Spinal solutions
64 (53)	Integer	1,200	1,038	Excludes non-medical sales	Cardio, vascular, CRM, neuromod, surgical, orthopedics
65 (65)	Cochlear	940	1,032	Year ended 30 June 2021	Hearing implants, acoustics
66 (72)	Konica Minolta	806	1,023	Healthcare, includes pharma services; year ended 31 March 2021	Digital radiography, precision medicine
67 (74)	DiaSorin	791	1,007		IVDs, instruments
68 (77)	Jiangsu Yuyue Medical Equipment	671	975		Respiratory, cardiovascular & endocrine system devices
69 (62)	Merit Medical Systems	995	964		Spine, oncology, endoscopy
70 (58)	LivaNova	1,084	934		Cardiovascular, neuromod
71 (63)	Haemonetics	988	870	Year ended 3 April 2021	Blood & plasma collection, surgical suite, hospital transfusion services
72 (64)	CONMED	955	862		Minimally invasive surgery

Ranking 2020 (2019)	Company	Fiscal 2019 sales US\$ million	Fiscal 2020 sales US\$ million	2020 notes	Industry activity
73 (67)	Invacare Corp	928	851		Non-acute DME (respiratory, wheelchairs)
74 (71)	Abiomed	841	848	Year ended 31 March 2021	Circulatory support, oxygenation
75 (69)	Guerbet	915	814		Contrast media
76 (57)	AGFA Healthcare	1,141	805	Year ended 30 April 2020	Radiology & healthcare IT
77 (75)	Globus Medical	785	789		Orthopedics, robotics
78 (73)	MicroPort Scientific	793	649		Cardiovascular, CRM, heart valves, orthopedics, neurovascular
79 (76)	Cooper Companies	681	588	Year ended 31 October 2020	CooperSurgical: fertility, diagnostics & contraception
80 (79)	Varex Imaging	597	585	Medical only; year ended 2 October 2020	X-ray imaging
81 (81)	Hamamatsu Photonics	532	499	Year ended 30 September 2020	Electron tubes
82 (82)	LePu Medical Technology	524	493		Lab consumables, cardiovascular, hemodialysis, surgical, IVDs, orthopedics
83 (86)	Ypsomed	396	461	Year ended 31 March 2021	Delivery systems & diabetes care
84 (-)	Steris	421	427	Healthcare; year ended 31 March 2021	Infection prevention, sterile processing
85 (89)	Luminex	335	417	Acquired by DiaSorin (completed 14 July 2021)	IVDs
86 (83)	Natus Medical	495	416		Neuro, newborn, hearing
87 (85)	Orthofix Medical	460	407		Biologics, spine & extremities
88 (87)	Accuray	383	396	Year ended 30 June 2021	Radiotherapy solutions
89 (88)	Hogy Medical	342	342	Year ended 31 March 2021	Surgical kits, instruments, sterilization
90 (78)	Myriad Genetics	639	300	New year end of 31 December 2020 – six months sales only in 2020	Genetic testing, precision medicine
91 (92)	AngioDynamics	264	291	Year ended 31 May 2021	Vascular access, minimally invasive devices
92 (93)	Stratec Group	248	286		IVDs, life sciences
93 (-)	iRhythm Technologies	215	265		Ambulatory ECG monitoring
94 (94)	Cardiovascular Systems	237	259	Year ended 30 June 2021	PAD/CAD devices
95 (97)	Meridian Bioscience	201	254	Year ended 30 September 2020	IVDs
96 (91)	CryoLife	276	253		Aortic disease tissues, devices
97 (-)	Guardant Health	180	236	Excludes service revenues	Precision oncology testing
98 (96)	AtriCure	231	207		Cardiac arrhythmia management
99 (95)	Horiba	232	197		IVDs, hematology analyzers for POC testing
100 (-)	SonoScape	188	174	Listed in Shenzhen	Ultrasound, endoscopes, blood analyzers

Source: Medtech Insight



Managing Lifecycles Amid Stifling Competition

Biopharma is entering a new period of intense competition from new sources, requiring a change in approach to portfolio strategy and lifecycle management.



BY DANIEL CHANCELLOR, DIRECTOR OF THOUGHT LEADERSHIP, EUROPE

As biopharma has pivoted towards biologics with higher barriers to competition, traditional drug lifecycles and patent cliffs have become a thing of the past. Older products can be enduringly lucrative, giving rise to concentrated investment in single pipeline-in-a-pill assets. In turn, this creates added incentives towards fast-follower approaches to R&D. Added to signs of biosimilar maturity, biopharma is entering a new period of intense competition from new sources, requiring a change in approach to portfolio strategy and lifecycle management.

In recent years, a subtle change in narrative has emerged concerning portfolio strategy. Drug

company executives are increasingly leading with probability of success metrics when gauging R&D performance and long-term pipeline potential. Pfizer is one such company toasting a four-fold improvement in its likelihood of approval, transitioning from laggard to leader over a five-year period as shown in *Exhibit 1*.

The simplest way to raise this is to pursue validated drug targets and mechanisms, often at the expense of first-in-class therapeutic opportunities, which alongside best-in-class was the old mantra and imperative for portfolio strategy. In a world where biotech advances are spawning a variety of new ways of creating drugs, there is much more room for clinical differentiation against known targets compared to small molecule drug design. As the definition of class stretches to include this range of drug design and delivery, first-in-class or best-in-class becomes a more nebulous concept. An emerging example of this is BCMA-targeting drugs, where cell therapies, antibody-drug conjugates and bispecific antibodies are all converging as new options to treat multiple myeloma.

The direct consequence of R&D strategies and pipelines being optimized for probability of success is the concentration of competition within certain therapy areas and drug targets. The classic example still playing out today can be seen in the PD-1/L1 inhibitor class. Even with the insurmountable lead that forerunners Keytruda (pembrolizumab) and Opdivo

Exhibit 1: Pfizer R&D Success Rates

Clinical Trial Success Rates (new molecular entities only)	Phase 1 (3-year avg.)	Phase 2 (5-year avg.)	Phase 3/Reg (5-year avg.)	End-to-End Success Rate
Pfizer (through 2020)	48%	52%	85%	21%
Industry ⁽¹⁾ (through 2019)	40%	29%	72%	8%
Pfizer (through 2015)	48%	15%	70%	5%

End-to-End Clinical Success Rate Through 2020 More Than 2.5x The 2019 Industry Benchmark

Source: Pfizer, Fourth Quarter 2020 Earning

(nivolumab) possess, dozens of newly designed antibodies are created each year, without any realistic hope for a return on investment. A similar picture occurs across many oncology and immunology targets as fast-follower approaches are employed. This is in spite of discovery science continuing to deliver therapeutic opportunities at a consistent pace. Each year, the biopharmaceutical industry R&D database Pharmaprojects adds around 100 novel targets that drugs are designed against, with 2020 showing a record 139 targets mentioned for the first time.

Fast-Follower Chinese Biotechs Are Enabling Disruptive R&D And Pricing Models

The ultimate fast-follower approach is emerging from China. Over the last decade, the domestic biopharmaceutical scene has transitioned away from off-patent molecules and instead focused on the creation of innovative drugs. As a collective, Chinese biopharma has sustained an incredible 30% compound annual growth rate in the number of new chemical or biological entities originated domestically over a 10-year period (see *Exhibit 2*). In a mirror image of the global trend, approximately 60% of these drugs are biological rather than chemical, with a strong emphasis against established drug targets within oncology and immunology.

is one of a growing number of examples of Western companies seeking to license innovative assets from the labs of Chinese companies. Both Novartis and Eli Lilly have acquired ex-China rights to PD-1 inhibitors, while Biogen sourced its BTK inhibitor from Beijing-based InnoCare. With the addition of Chinese R&D players into the traditional competitive mix, the number of sources of innovation and potential business development partners is much larger. The natural progression will surely eventually see such companies expand commercial ambitions beyond the domestic market and seek to develop and market in the west.

This will be achieved not only through fast-follower drugs with competitive clinical profiles, but also through pricing disruption. Heavy discounts required to secure access to the National Drug Reimbursement List (NRDL) in China are difficult to reconcile with free market pricing practices in the US, meaning that potential Chinese entrants will undoubtedly enter international markets at lower cost. In the meantime, the availability of Chinese assets for licensing affords a new business model for start-up companies seeking to lower drug prices. Much has been written about EQRx and its lofty goal of remaking medicine. A major tenet of its strategy thus far is to acquire late-stage assets with high probability of success from Chinese biotech companies. It is doubtful that one

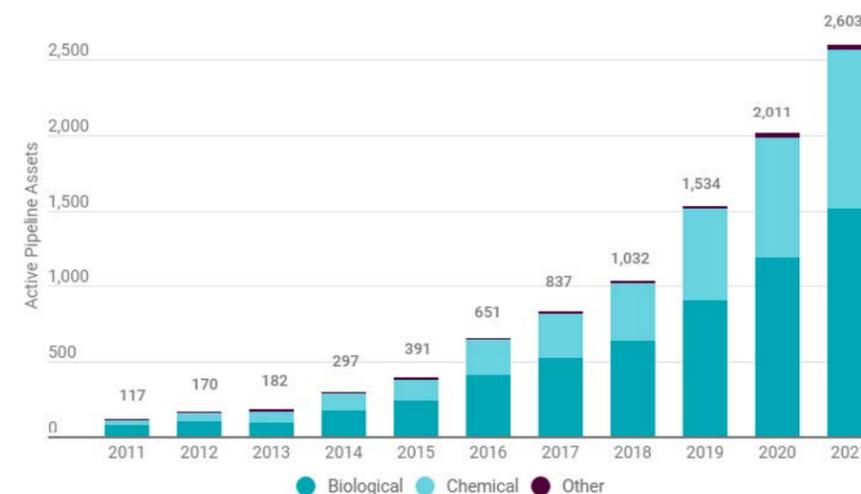
company alone can address the systemic challenges of healthcare expenditure, drug prices and patient access, although EQRx's mission appears to have also inspired incumbent companies. Eli Lilly is now talking openly about pricing its Chinese-sourced PD-1 inhibitor sintilimab at a significant discount.

Biosimilar Market Reaching Sustainability

In addition to the heightened competition from other innovative drugs during the patent-protected period of a drug's lifecycle, the first signs are emerging that the biosimilar market may finally be delivering meaningful savings following loss of exclusivity. This can be seen through the lens of Roche's recent results, during a period in which is facing new biosimilar competition in the US

for its three major oncology brands Avastin (bevacizumab), Herceptin (trastuzumab) and Rituxan/Mabthera (rituximab). Over two years, these brands have lost approximately 60% market share each, far higher than past examples would have suggested that Roche could expect. This has translated into a considerable revenue hole, exceeding \$10bn, that will take years of growth for new products to fill. As noted by Roche executives Severin Schwan and Bill Anderson, "The impact of

Exhibit 2: China-Originated R&D



Source: Pharmaprojects, October 2021

For emerging targets, the pace at which Chinese biotechs can now discover and develop a proprietary therapeutic is beginning to rival the timelines of first-in-class drugs from large multinational pharmaceutical companies. Again turning to the BCMA class as a case study, the Legend Biotech-originated CAR-T cilta-cel, now partnered with Johnson & Johnson, is poised for US approval in February 2022, just one year behind the first global availability of GSK's Blenrep. This

biosimilars was significant, somewhat higher than we originally expected [CHF5.7bn] ... We think this year, in 2021, the number will probably be closer roughly CHF4.6bn.”

This evidence for the performance of oncology biosimilars, plus an upcoming wave of 15 notable new biosimilar opportunities including Humira (adalimumab) in the US, have led analysts at Bernstein to project a \$19.3bn opportunity by 2027 (see Exhibit 3). The first interchangeable biosimilar in the insulin class will also help wider stakeholder acceptance.

In the short term, an attractive biosimilar ecosystem threatens biopharmaceutical revenues considering the industry-wide portfolio switch towards biologic therapies. Nevertheless, it is vital for the long-term health and sustainability of the wider market. Any initiative that provides budget savings on older drugs is helping the industry achieve its social contract whereby access to medicines increases over time. Companies with leading R&D capabilities are subsequently rewarded as spending power is returned for innovative drugs and underserved patients. Undoubtedly originator companies will still act within – and occasionally outside of – the spirit of regulations to defend against biosimilars, although their presence should be embraced. The alternative solution involves policy intervention and price negotiations that may harm innovators throughout the lifecycles of their drugs.

Lifecycle Management Strategies Must Adapt To New Threats

Pharma companies can expect to face stifling competition at every stage of the drug lifecycle. There are multiple new sources of competition, from risk-conscious innovators exploiting the increasing biological complexity of drugs to create low-cost fast followers, or a sustainable biosimilar market that can finally deliver cost savings on off-patent antibodies.

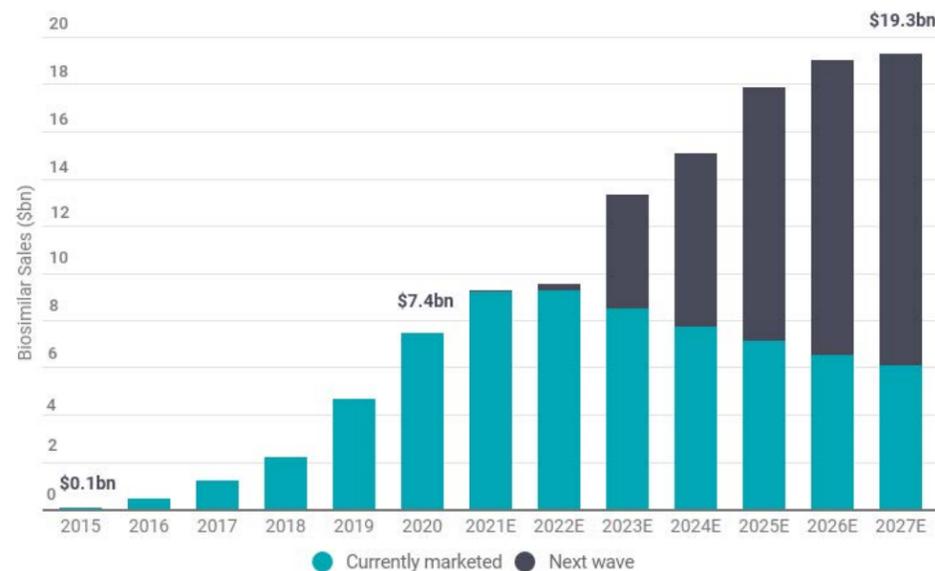
As a consequence, the pipeline-in-a-pill approach to lifecycle management, whereby the developer concentrates investment in a single asset to pursue as many indications as possible, will be unable to deliver comparable longevity.

Fast-followers will curb the lead that a first-in-class drug can achieve, while any return on investment deep into a drug lifecycle is diminished by market share losses once biosimilars arrive. Drugs such as Humira and Keytruda will not be able to

secure such dominant positions in the future. Rather, lifecycle management should be hedged across a range of assets at a portfolio or platform level to mitigate the risk of single competitors. In the decade ahead, successful companies will achieve this through diversification within their areas of focus, whether that is pharma companies and therapeutic area portfolio strategy, or biotech companies with novel drug platforms.

The ultimate way to get ahead of the competition lies in the strength of data supporting a drug. For this reason, the industry must embrace drugs with curative potential, not to mention the benefit that patients can derive from these. While certain technologies such as cell and gene therapies may be able to deliver functional cures, conventional drugs can be tested against more ambitious endpoints. Recent examples including hepatitis C antivirals through to COVID-19 vaccines show that drugs with curative data can achieve incredibly high sales early on in their lifecycles, saturating the opportunity for would-be competitors.

Exhibit 3: Worldwide Biosimilars Market Revenues



Source: Bernstein

This article is based on a series of presentations prepared by Daniel Chancellor, thought leadership director at Pharma Intelligence, in collaboration with colleagues Duncan Emerton, Ly Nguyen-Jatkoe and Timothy Pang in October 2021. 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: Daniel.Chancellor@informa.com.

Actionable and Expert In-Depth Intelligence Designed to Support Your Commercial Decisions and Long-term Business Strategy.

Rely on Datamonitor Healthcare for market assessments without the guesswork.

Access the Latest Market Research... analyzed and forecasted for you

Our seasoned analysts do the research, so you don't have to – layering in key takeaways so you can make decisions faster.

Discover Unmet Needs... and where the market is going

Interactive dashboards and models so you can see patient-based forecasts, sales-based forecasts, and epidemiology through the lens you need.

Build Your Strategy with Confidence... to get there

Make the right decisions for the long-term backed by expert data, analysis and insight, robust interactive tools and expertise on call.

SPAC Mergers Are Viable Funding Tools, But The Test Is Yet To Come

Performance Has Been Subpar For Most That Have Taken SPAC Route



BY MANDY JACKSON,
MANAGING EDITOR,
US

Dozens of health care-focused special purpose acquisition corporations have gone public during the past two years but many biopharma firms that have merged with SPACs have not performed well to date, raising the question of how long the SPAC boom will last.

Mergers with special purpose acquisition corporations (SPACs) have become lucrative financial transactions for biopharmaceutical firms because they can raise significant capital and become publicly traded companies in a single transaction, bypassing the traditional initial public offering path. However, the performance of drug developers that have taken the SPAC route to date has been largely negative, raising the question of how much longer these transactions will be viable financing options.

There also is the question of whether there are enough biopharma firms available to meet SPAC demands. Dozens of SPACs focused on health care and life science opportunities have gone public in the US since the start of 2020 and each one has a limited amount of time to complete a transaction – usually about two years. But with drug developer IPOs in the US occurring in record numbers and big pharma firms on the hunt for innovative companies, SPACs have a lot of competition for deals.

SPACs, otherwise known as blank check companies, launch IPOs to raise money that they hold in trust until they merge with another entity. The target company uses the SPAC’s cash to fund its ongoing operations and takes over the blank check firm’s stock market listing, going public without having to execute an IPO of its own. Companies often close private investment in public equity (PIPE) financings concurrent with the SPAC deal, increasing the cash consideration of these transactions.

Matt Toole, director of deals intelligence at financial data provider Refinitiv, said SPACs last became popular in 2007, at the height of the bull market in the 2000s. Increased mergers and acquisitions alongside a boom in IPO activity, and at a time when private equity and other investors are flush with cash – as has been seen in 2020 and 2021 – tended to boost SPAC activity, Toole explained.

“We also have seen many of the acquisitions taking place in some of the more niche or

experimental sectors – so biotech, but also sustainability,” he said. “For a SPAC who has industry expertise or has the know-how potentially to take on some of these names, you might see some more of that activity.”

SPAC Merger As An Alternative To An IPO

Experts who have taken SPACs public, who have advised companies considering a SPAC merger and who track SPAC activity agree that this path to the stock market offers an attractive financing alternative for relatively high-risk companies – for example, firms with novel technology that may be years away from generating revenue, like companies involved in drug development or sustainable energy. These companies, despite raising venture capital successfully in the past, may have a hard time enticing traditional IPO investors.

“We think SPACs are a very innovative and flexible instrument for private companies to go public,” Jonas Grossman, managing partner and president at the investment bank Chardan, told *In Vivo*.

Chardan has underwritten more than 90 SPACs, advised both SPACs and companies considering a merger, and sponsored multiple SPACs. Grossman was president and chair of Chardan Healthcare Acquisition 2 Corp. until the SPAC closed its merger with Renovacor Inc. in September 2021. The deal raised \$95.1m for Renovacor’s gene therapy development programs.

Vasilios Kofitsas, managing director in the investment banking group at Back Bay Life Science Advisors, said almost every financing discussion he has had with a private company board of directors during the past year and a half has included an evaluation of SPAC opportunities. The speed of a SPAC versus an IPO process is compelling, and the combination of cash held in trust by the SPAC plus a concurrent PIPE financing is attractive as well. “All of a sudden it’s not out of the question to have \$200m to \$300m in the bank coming out of the deal,” he said.

Grossman said there had been very little innovation in the typical IPO for decades, SPAC deals gave companies an alternative route to the stock market with potentially less downside. “It’s a risky proposition for private companies [to launch an IPO]; they spend a lot of money and they are at the vagaries of the market,” he said.

Valuations Are In Flux, But SPACs Still Are Active

Biotech company valuations have fluctuated wildly in 2021 with the Nasdaq Biotechnology Index up as much as 15% year-to-date at different points in February, August and September but down as much as 3% from the start of the year in February, March and May. The NBI was up 1.5% year-to-date as of 19 November.

Similarly, the average return for biopharma companies that launched IPOs in the US in 2021 has fallen from 11% for the 32 firms that went public in the first quarter to 1.1% for the 62 drug developers that priced IPOs through the second quarter. The average return turned negative for the 88 companies that went public through the end of the third quarter at -4%.

Nevertheless, SPACs continue to go public in the US, including health care-focused blank check companies. SPAC Track, an online database that founder Nick Gershenhorn began putting together in 2020 to track the SPAC market, reported that as of 19 November there were 662 active SPACs that had raised a total of \$183.1bn in their IPOs. That includes 85 active SPACs that have raised a total of \$20.9bn and have listed health care as at least one industry in which they are pursuing a deal.

Among the active health care SPACs, 69 are searching for a merger target and 16 have announced a definitive merger. Another 34 health care SPACs are in the pre-IPO stage.

SPAC Track’s Gershenhorn said that, ideally, a SPAC should merge with a company that did not really need the deal or the money but wanted to access the SPAC team’s specialized expertise.

“You really – especially in health care, which is so specialized – do want folks [in the SPAC] that know what they’re doing and have done several health care deals and can be effective partners to this target company that they’re merging with,” he said. “Because then you really know that you have someone in there that’s experienced and knowledgeable, that will be there, helping them grow and realize the business plan that they laid out in the investor materials.”

Depending on the quality of the SPAC sponsor there were plenty of merger targets available, Gershenhorn said. However, he added, “The issue is being able to identify them or come up

ARE YOU READY TO SPAC?

Vasilios Kofitsas of Back Bay Life Science Advisors said he runs through several key questions with biopharma clients considering a SPAC deal:

- Does the company have a good story to tell about its technology platform or drug candidates?
- Does the firm want to be a public company, which has a different structure and financial reporting requirements?
- Are the executives ready to lead a public company and be accountable to stock market investors?
- Will the company have a consistent flow of news coming over the next 12 to 18 months and through the next three years to keep investors interested?
- Can the company effectively deploy the large amount of capital it may raise in a SPAC deal in a reasonable amount of time?

“Going in at a high valuation is great,” he said. “Are you able to sustain it, is a whole different question.”

Exhibit 1: Few Firms Trading Higher After SPAC Merger

Only seven of 24 biopharma companies that completed a SPAC merger in 2020 or 2021 are trading above the SPAC's value at the time the transaction closed.

Company	SPAC	Date Merger Closed	Amount Raised (\$m)	Stock At Merger Close	Stock As Of 19 Nov.	% Change
180 Life Sciences Inc. (ATNF)	KBL Merger Corp. IV	9-Nov-20		\$3.09	\$4.05	31.1
4D pharma plc (LBPS)	Longevity Acquisition Corp.	22-Mar-21	39.8	\$12.06	\$7.26	-39.8
Celularity Inc. (CELU)	GX Acquisition Corp.	16-Jul-21	138	\$10.20	\$6.98	-31.6
Cerevel Therapeutics (CERE)	Arya Sciences Acquisition Corp. II	27-Oct-20	440	\$10.10	\$36.34	259.8
Clarus Therapeutics Holdings Inc. (CRXT)	Blue Water Acquisition Corp.	9-Sep-21	25.3	\$9.63	\$4.39	-54.4
Clene Inc. (CLNN)	Tottenham Acquisition I Limited	30-Dec-20	31.9	\$10.82	\$5.05	-53.3
eFFECTOR Therapeutics Inc. (EFTR)	Locust Walk Acquisition Corp.	25-Aug-21	65.9	\$16.98	\$8.04	-52.7
Ensysce Biosciences Inc. (ENSC)	Leisure Acquisition Corp.	30-Jun-21	7.8	\$14.49	\$1.59	-89
Gemini Therapeutics (GMTX)	FS Development Corp.	5-Feb-21	216	\$12.66	\$3.23	-74.5
Gingko Bioworks Inc. (DNA)	Soaring Eagle Acquisition Corp.	14-Sep-21	1,600	\$12.18	\$13.45	10.4
Immatics NV (IMTX)	Arya Sciences Acquisition Corp.	29-Jun-20	253	\$16.02	\$11.89	-25.8
Jasper Therapeutics Inc. (JSPR)	Amplitude Healthcare Acquisition Corp.	24-Sep-21	100	\$15.12	\$7.98	-47.2
NRx Pharmaceuticals Inc. (NRXP)	Big Rock Partners Acquisition Corp.	25-May-21	11	\$23.41	\$5.13	-78.1
Nuvation Bio Inc. (NUVB)	Panacea Acquisition Corp.	10-Feb-21	646	\$10.42	\$9.05	-13.1
POINT Biopharma Inc. (PNT)	Therapeutics Acquisition Corp.	30-Jun-21	286.7	\$10.27	\$8.82	-14.1
Procaps Group (PROC)	Union Acquisition Corp. II	29-Sep-21	160	\$9.86	\$9.81	-0.5
Renovacor Inc. (RCOR)	Chardan Healthcare Acquisition 2 Corp.	2-Sep-21	95.1	\$8.41	\$8.65	2.9
Reviva Pharmaceuticals Inc. (RVPH)	Tenzing Acquisition Corp.	14-Dec-20	9.4	\$8.75	\$3.39	-61.3
Roivant Sciences (ROIV)	Montes Archimides Acquisition Corp.	30-Sep-21	220	\$9.35	\$8.00	-15
SAB Biotherapeutics (SABS)	Big Cypress Acquisition Corp.	25-Oct-21	30	\$7.30	\$11.03	51.1
Science 37 Holdings Inc. (SNCE)	LifeSci Acquisition II Corp.	7-Oct-21	235	\$10.05	\$12.54	24.8
Surrozen Inc. (SRZN)	Consonance-HFW Acquisition Corp.	11-Aug-21	123.1	\$10.25	\$9.20	-10.2
Tango Therapeutics Inc. (TNGX)	BCTG Acquisition Corp.	10-Aug-21	342	\$9.99	\$11.97	19.8
Vincerx Pharma Inc. (VINC)	LifeSci Acquisition Corp.	23-Dec-20	62	\$19	\$12.56	-33.9
			Total: \$5.14bn			Average: -12.3

Source: Company press releases, SEC filings

with other innovative ways to make it work. Because if we were just looking at the US alone, for instance, of private companies, then I would say maybe there isn't enough to accommodate the demand ... But when you factor in the international opportunity, there's tons of great companies from tech to health care in Latin America, Asia, Europe, so there's a lot of opportunity there."

Spinouts, where large corporations divest divisions or subsidiaries that are underappreciated under the parent company, also have been a source of SPAC deals. "You need quality sponsors to be able to effectively carry that out," Gershenhorn noted.

Grossman said there likely were plenty of biotech opportunities to choose from for those with a focus on drug developers or device and diagnostic firms. He estimated that there were more than 100 and maybe as many as 200 later-stage biotech companies that could be a good fit for a SPAC deal, but agreed that a SPAC's search for a merger target may have to extend outside of the US.

Biotech SPAC Deals Still Need To Show Their Worth

In addition to finding interesting companies at compelling valuations to make a SPAC merger work, Grossman said the space also needed a longer track record of post-merger stock performance for biotech companies that had gone public through a SPAC merger. "They do need to come up with good data and start trading well, and then that'll be a driver of renewed interest," he said.

Only seven of the 24 biopharma companies that have completed SPAC mergers were trading above the SPAC's stock price when the deal closed as of 19 November, according to *In Vivo's* analysis, resulting in an average return of -12.3% (see *Exhibit 1*). Some companies that have gone public via SPAC have had setbacks contributing to their valuation declines.

For instance, Gemini Therapeutics Inc. announced a corporate restructuring on 5 October, and its stock was down 74.5% as of 19 November versus Gemini's stock price when it merged with a SPAC known as FS Development Corp. in February. The company shut down its R&D operations except for employees working on the late-stage development of GEM103, a complement regulator for the treatment of geographic atrophy in genetically defined age-related macular degeneration.

The volatility in biotech stock values is making some SPACs reevaluate their deals in the space. Valo Health LLC, which is using human-centric data and artificial intelligence to power its drug discovery and development platform, and Khosla Ventures Acquisition Co. (KVSA), a SPAC sponsored by affiliates of Khosla Ventures LLC, revealed on 15 November that they

had mutually agreed to terminate their merger, which had been announced back in June.

Valo and KVSA ended the deal, they said, "based on current market conditions, particularly in the biotechnology arena." KVSA plans to reinitiate its search for a merger target across a range of industries.

"There are some very prolific SPAC issuers that might have more of a track record that maybe they are able to get deals done where some of the other kind of one-offs, maybe they're not able to do so," Refinitiv's Toole said. "A lot of times you will see SPACs kind of changing strategy. They might say that they're after a certain type of acquisition but then it makes a totally different one in a different sector."

Valo, which would have brought in up to \$501.5m through the SPAC merger, is sticking with its plan to launch its first Phase II clinical trial this year and a second Phase II trial in the first half of 2022. The company has a strong balance sheet without the SPAC deal after closing a \$300m series B venture capital round in March.

Gelesis Sees Value Beyond Cash In Pending SPAC Deal

In another reassessment of a SPAC transaction, Capstar Special Purpose Acquisition Corp. announced on 10 November that the implied equity value of its merger target Gelesis Inc. had been reduced from \$900m to \$675m. The terms of the \$366m

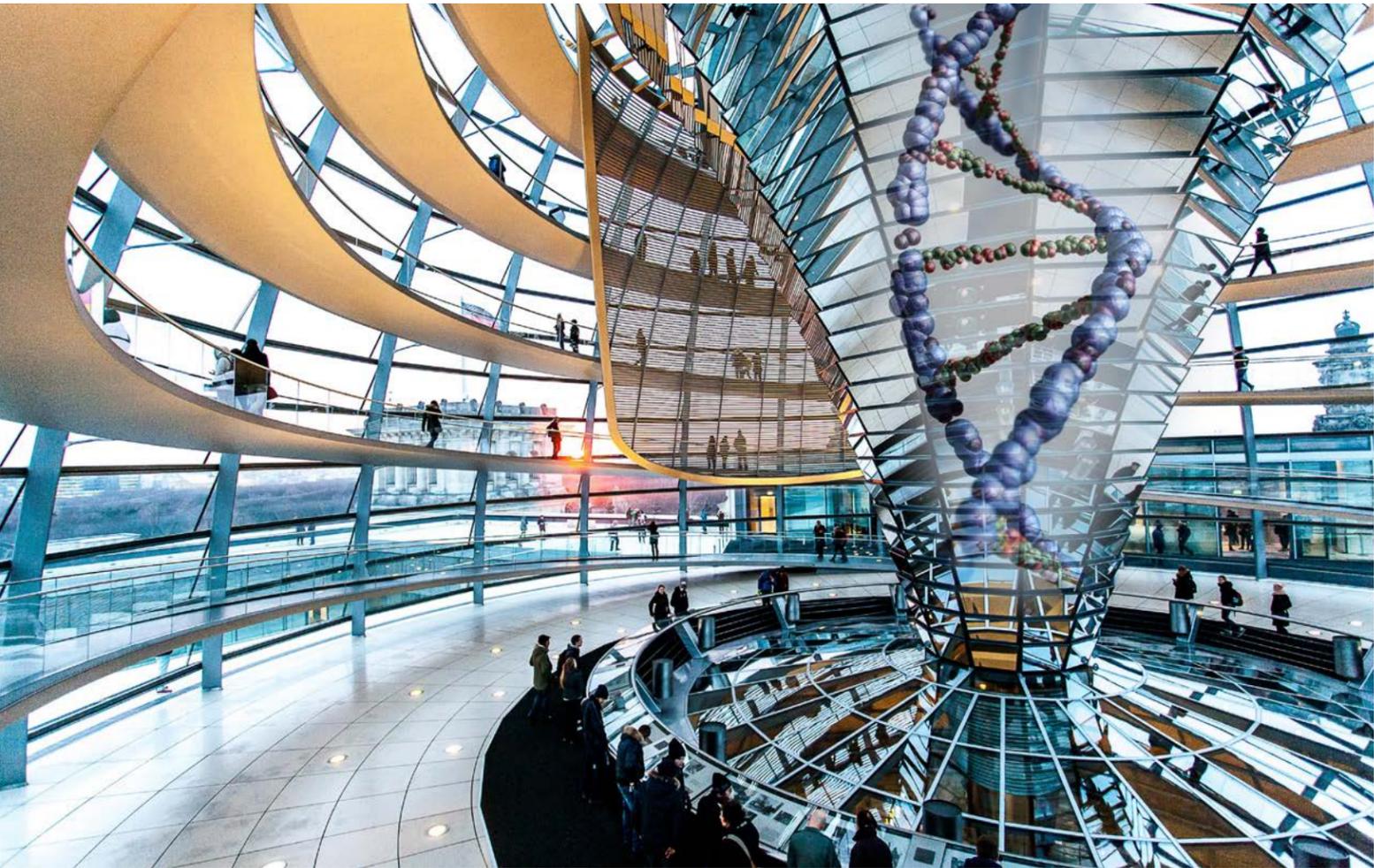
transaction have not changed; Gelesis still is expected to receive \$276m in cash held in trust by Capstar and \$90m from a concurrent PIPE financing. Gelesis will use the cash to fund the launch of its US FDA-cleared weight loss aid Plenity.

"In our assessment, the true value of a SPAC comes from working closely with a partner whose expertise aligns with the needs of the business," Gelesis CEO and founder Yishai Zohar told *In Vivo*. "We are a biotech company building a consumer brand with Plenity, which is a completely new approach to weight management. We are doing things very differently and we wanted a partner that could complement our areas of expertise. Going public via SPAC allowed us to benefit from the Capstar team's unique consumer brand-building expertise in an intimate way, which simply would not have been possible with an IPO or another fundraising vehicle."

Zohar said Gelesis will use the capital from its SPAC merger to fund the commercial launch of Plenity and expand manufacturing capacity to meet consumer demand. More than 60,000 customers tried Plenity in a beta product launch last year and Gelesis had been selling out of the weight loss aid as quickly as the company could manufacture it, he noted.

"When you factor in the international opportunity, there's tons of great companies from tech to health care in Latin America, Asia, Europe..."

Nick Gershenhorn, SPAC Track



BY JO SHORTHOUSE, CONTRIBUTOR, EUROPE

A New Generation Invents Pharma's Mirrored Future

Young businesses are getting set to disrupt every inch of the health care space with digital twin technology. *In Vivo* spoke to two startups on the brink of a data dawn.

Recent explosions in big data gathering and computational learning mean that advances in health care can now become reality.

One such transformative technology is digital twins, otherwise known as a reflection of the physical world in a digital format that can visualize and contextualize data.

A recent Accenture survey of 399 health care executives found that a quarter of respondents said their company had experimented with digital twins in 2021, while 66% expect their organization's investment in intelligent digital twins to increase over the next three years.

The application of digital twins could be revolutionary in areas such as personalized medicine, virtual organs, genomics, business processes, operational efficiency, supply chain management and clinical trials.

Drug and device developers have been working toward making clinical trials cheaper and faster for years. Finally, digital twin technology may be the key to unlocking this particularly rusty lock by predicting clinical outcomes from virtual patients.

In Vivo talked to two startups that have developed disruptive digital twin technology that could transform the patient experience forever.

Unlearn Puts Computation At The Heart Of Trials

Charles Fisher started Unlearn.AI with colleagues Aaron Smith and Jon Walsh four years ago. The biophysicist, mathematician and theoretical physicist had met conducting machine learning research at a virtual reality startup in San Francisco and were looking for a new project. The team investigated investment gaps in artificial intelligence and came across clinical trials as an underserved market.

Having secured its first round of venture funding with a developing business plan, the company began two years of working on machine learning technologies. Eventually the team developed a tool that could create patient-level simulations of clinical outcomes.

The company did not set out to “solve this problem of clinical trials,” its CEO Fisher told *In Vivo*. The scientists wanted to solve a challenge in machine learning, and after working through iterations of the product with pharmaceutical partners and advisors, they developed deep learning models that could generate clinical predictions, or digital twins. These digital twins describe what would have happened if a specific patient had received a placebo in a clinical trial. Unlike other approaches that leverage existing data, incorporating digital twins into clinical trials enables smaller, more efficient trials without introducing bias.

The foundational data used to train the disease progression models emanates from historical longitudinal clinical trials, observational data and electronic health record (EHR) data. These data are aggregated through partnerships with pharma and academia.

Unlearn is currently focused on Phase II and III studies in neuroscience and immunology because of the large unmet need in these therapeutic areas, and the well-known challenges that occur during these types of trials such as study run time and difficulties in recruitment.

Fisher explained that there is no higher probability of an incorrect result from trials using Unlearn's digital twin

technology, something that is mathematically proven and demonstrated empirically. The Type 1 error rate is unchanged, set to 5% probability of incorrectly rejecting the true null hypothesis.

Unlearn is partnering with leading pharmaceutical companies to accelerate late-stage clinical trials and is actively engaged with the FDA and EMA. Fisher is looking forward to expanding into other indications based on future partnerships.

Virtonomy's V-Patients Simulate Device Impact

Munich-based Virtonomy.io is the brainchild of Simon Sonntag and Wen-Yang Chu. Sonntag satiated his entrepreneurial desires in 2019 after a decade of academic research and industry experience of advising medical device manufacturers. During this time, he had become heavily involved in the regulatory approval process, especially digital methods such as computational modeling and simulation. He worked on the ISO (International Organization for Standardization) guidelines to help bring in digital elements to the approval process and saw the potential of digital twins and computer simulation, not just for product development but also for product approval.

In the last two years, despite the realities of fundraising during a pandemic, Virtonomy employs more than 10 people, has received seven-digit seed funding led by Dieter von Holtzbrinck Ventures, and has launched its first product, v-Patients.

This digital twin cloud-based technology, offered as Software as a Service (SaaS), enables medical device manufacturers – from product concept to post-market surveillance – to perform virtual testing by simulating the device in their target population based on real-world evidence data.

Data is gleaned from clinical partners and passes through secure networks. The verification and validation of all steps is essential, Sonntag, Virtonomy's CEO, told *In Vivo*, to ensure the credibility and accuracy of the results.

Unlearn CEO On Getting The Regulatory Approach Right

***In Vivo*: What does the pharmaceutical industry need to know about your technology?**



Charles Fisher: We want to enable pharma companies to run faster clinical trials, but we want those clinical trials to still produce reliable evidence. We can make clinical trials faster by making them smaller. We can reduce the number of patients in the clinical trial by 25%, which can speed up the time to market by a year, potentially, for some indications.

We use digital twins within the context of smaller randomized controlled trials in a way that enables us to get all the same statistical properties that you want out of a larger clinical trial, that also satisfies existing regulatory guidance.

Existing approaches like external control arms can increase efficiency and decrease the size of the trial, but they are not acceptable to regulators in many cases.

The approach that we've developed is unique. We can guarantee that it won't introduce bias and that you get valid results out of clinical trials in a mathematically guaranteed way. This gives us a different position when it comes to regulation, because we don't need to change today's regulations from the FDA and EMA, what we do is acceptable.

We're going through our own qualification procedures now with the EMA and hope to hear back from them within the next couple of months. We're doing our own work to make sure that we can demonstrate that these technologies are acceptable to regulators.

What feedback have you had from the pharmaceutical industry so far?

There's lots of interest in the concept of running a clinical trial one year faster. The extra year of revenue is enormous. If the drug works then patients can get that drug a year sooner. The value is clear. We're shrinking the number of patients who need to receive a placebo. We can't run trials in which zero patients receive placebo at Phase III because you need to have some randomization — that is the only technology that allows us to be sure that the results are because of the drug. However, we don't need an equal number in both arms of the clinical trial, so the patient has a much higher probability of getting the active treatment.

There is a lot of uncertainty about AI, how it can be used and what the regulators think about it. Our initial partnerships are with more progressive pharma companies that have initiatives to bring in new technologies.

Do you think the pharmaceutical industry is ready for this kind of disruptive tech?

I think pharma is totally ready for it. A lot of pharma companies say they would absolutely love to be our second customer. The regulators are extremely supportive. When we have confirmation from the regulatory direction everyone will adopt these approaches.

We can demonstrate that this is a fundamentally better way of running a clinical trial, a smaller, faster, less expensive clinical trial and we can guarantee that it produces the same level of evidence as larger studies. It is still early days, but we think that within a year or two we will see a wide variety of options in the disease areas we work in.

What opportunities do you see in the market for further digital twin development?

Clinical decision support. A digital twin is the output of a computational model that allows me to ask 'what if' questions about a person. Imagine if a physician could access a patient's digital plan, even remotely, and ask questions about their response to current treatment and envisage how that patient would react to a different medication. There are a lot of challenges to making that reality happen. There are technical challenges between where we are today and what models are required for that. We also need to think about who would pay for that technology.

Do you think this kind of technology can only come from a startup rather than a large pharma?

From my perspective, those companies [large pharma] should place more value on computation. They're starting to change a little bit, but it's slow moving. Company leaders are not computational scientists, they are physicians, biologists, chemists and finance leaders.

We are a computation-first organization. We started to solve problems in computation and AI. I think it's very different approaching this from a life sciences company with an overlay of AI, whereas Unlearn is AI at its core, and that's fundamentally different. Computation is going to disrupt a lot of the life sciences industry.

Virtonomy CEO On Trial Diversity In '20s

In Vivo: What does the medical device industry need to know about your technology?



Simon Sonntag: Virtonomy can shorten the time-to-market of medical devices by conducting data driven studies on virtual patients. v-Patients is based on an ever-expanding database to reflect anatomical variability, demographic diversity and pathological conditions.

These computer simulations on real clinical data have the potential to reduce the cost, and the time to market, by up to 50%. And above all, it also reduces the risk of failure. There are a lot of iteration loops that can be performed early on during the product development stage, so once you then enter the clinical trial domain you can be more confident in the safety and performance of your product. You can pressure test it in ways that you would never be able to if you used conventional approaches. You can elevate and extrapolate the tests to thousands, possibly even millions, of simulated scenarios to represent the variability of the whole patient population.

Diversity in clinical trials is still a major problem. Simulated studies can conduct trials on not only a larger scale but a more representative sample of patients.

What can be done to speed up adoption of digital twin technologies?

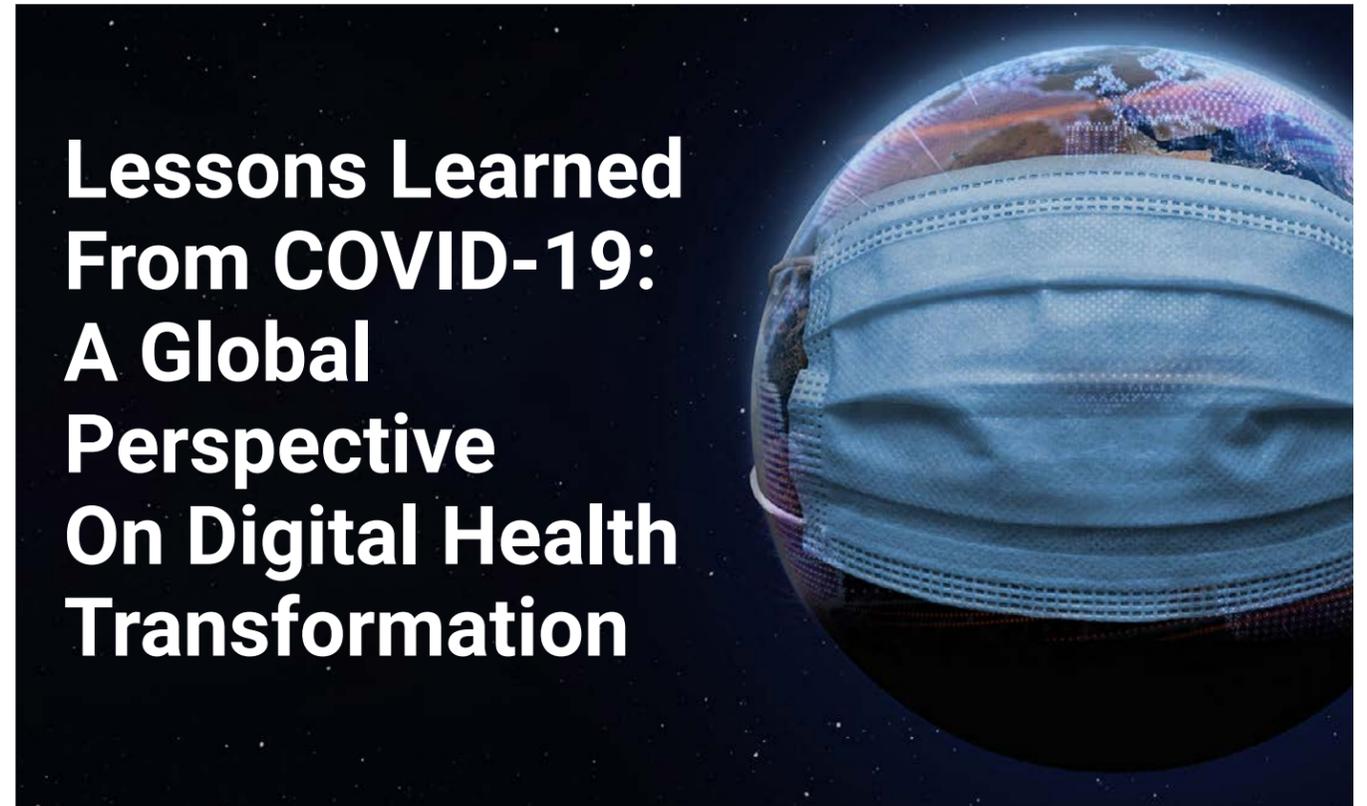
The regulators must understand the evidence because it is new to them. Regulatory uncertainty is still the major concern for the medical devices industry. A lot has happened within the last year, especially with the FDA. It has taken some big steps toward accepting digital evidence, but also on providing guidance documents such as the guidance on reporting of digital evidence, and it has been working with American Society of Mechanical Engineers (ASME) on verification and validation standards.

What opportunities do you see in the market for further digital twin development?

There is a market for treatment elevation and personalized medicine. Digital twins are used to represent the individual so, once a clinical decision is made, they could also be used to predict medical outcomes. It is like travelling into the future.

Is a startup better placed to drive this kind of innovation in the market rather than a large company?

Companies like Virtonomy have huge potential as it's a new market. We can be very innovative and fast moving, which is unlike large medtech or pharma companies. But, of course, smaller companies need financial power. Investors are increasingly seeing the potential within this field and supporting startups. If you can couple an innovative nature with the financial power of investors there is a clear advantage to smaller companies such as ours.



Lessons Learned From COVID-19: A Global Perspective On Digital Health Transformation

Health leaders from Sweden, Norway, Australia, Canada and Taiwan discuss the universal impact of digital solutions during the COVID-19 pandemic and lessons learned that will impact future care.



BY MARION WEBB, MANAGING EDITOR, US

While the experiences and strategies for combatting the COVID-19 pandemic may differ from one region to another, they have all seen the tremendous impact of digital technologies, according to a recent panel discussion of health care/tech leaders from around the world.

All the experts emphasized the importance of keeping patients and doctors connected and health care workers safe during the crisis, but they all believe that the digital transformation will provide many more opportunities to come.

The impact from the pandemic has been "exciting for innovators" but often "very stressful for clinicians," Ted Scott, chief innovation officer at Hamilton Health Sciences, told listeners during a 2021 AdvaMed MedTech Conference panel discussion focusing on lessons learned from COVID-19. Scott oversees research for a community of 15,000 staff, physicians and researchers serving southwestern Ontario, Canada.

He said that in the past, the publicly funded health system had been struggling to attract funding to create a digital business model for practitioners. But that all changed when the pandemic hit.

"It suddenly became possible to adopt many of the virtual care solutions that we previously have not been able to move forward ... virtual care visits and other things, which really added tremendous value to our patient experience, and, in many cases, has made our system much more efficient," Scott said.

His experience is in stark contrast to perspectives shared from panelists from Sweden and Norway. Their countries have similar populations and health care systems, but they were already highly digitized before the pandemic.

Sweden was already functioning as a "highly digitalized society" where citizens could access personal data on their own care, treatment and health status online, said Karina Tellinger McNeil, coordinator of Strategist e-health for Sweden's citizen-centered strategy that uses information and communication technologies to improve health care for all. She shared that the pandemic had led to an increase in the use of the "national health portal," which also provides information on pandemic-related issues, such as treatment options and vaccination sites. The portal has also seen a sharp rise in demand for online

consultations with physicians and for services. “The pandemic was a boost on our already existing digital national services, but it also increased demand for new solutions,” which put pressure on the system, McNeil explained.

In Norway, the pandemic promoted innovation and remote care solutions, said Trine Radmann, head of international affairs at Norway Health Tech, a technology cluster facilitating the growth of innovative health care solutions.

“Patients [in Norway] know more about their health than ever before,” Radmann said, adding that the pandemic had driven innovation that linked together different systems and had led to more connectivity and better communication.

Stefan Harrer, the chief innovation officer for Australia’s Digital Health Cooperative Research Centre, said his country’s adopted strategy of hard lockdowns since the start of the pandemic, even with moderate case numbers, had compelled the adoption of telehealth and virtual care to accommodate for routine services.

Even before the start of the pandemic, mental health disorders accounted for the highest disease burden in Australia, 46%, followed by neurological disorders with 37%. “Through these hard lockdowns, the general burdens that came with dealing with COVID have been really amplified,” Harrer said. As seen in the US, in Australia, the pandemic enticed companies to develop innovative solutions that found their way to the market thanks to the government’s easing of COVID-19-related regulatory restrictions, such as the creation of new reimbursement models.

Sean Wang, president of ITRI International Inc. in San Jose – a subsidiary of the Industrial Technology Research Institute in Taiwan – said Taiwan had learned valuable lessons from the SARS (severe acute respiratory syndrome) outbreak in 2003.

“There were only about 800 cases at that time, but people realized that masks and self-quarantine were key,” Wang told the audience. When the COVID-19 pandemic hit Taiwan, people immediately started to isolate and followed mask mandates, he said. He also attributes the use of contact-tracing with testing and isolation of confirmed cases for keeping COVID-19 at bay.

According to an editor’s note in *JAMA Internal Medicine* from 1 May 2020, as of late April 2020, Taiwan had about 330 confirmed cases of coronavirus disease and six deaths out of a population of 24 million people. That compared to 1 million confirmed cases of COVID-19 and 60,000 deaths in the US. As of late September 2021, COVID-19 cases were down to the “single-digits” in Taiwan, Wang said.

Changed Patient Experience

To alleviate the stress of frontline workers during the pandemic, ITRI and Taipei Medical University Hospital, Radica Health, Tranwo Technology Corp, Microsoft Taiwan and other industry groups and academic institutions jointly developed a contact-free

monitoring system that allows health care workers to remotely monitor patients’ vital signs such as heart rate, respiratory rate, body temperature and bed-exit events in real time.

The Contact-free Connected Health Care Platform collects patients’ vital signs, imaging and test results, analyzes it, and provides alerts if anything is abnormal. Wang said the remote sensing technology had reduced the need for nurses to physically enter a patient’s room from about 15 times a day to two, and thus, greatly reduced the risk of infection for nurses. And there are many other developments on-going, such as placing spirometers, devices that will expand the lung to help someone breathe, at patients’ homes.

“The trend is trying to move away from hospital use to personal use but still with digital and AI capability connected,” Wang said. “These are the major trends, because the health care system in Taiwan has been quite well developed and it’s a single-payer system and well taken care of.”

Telehealth consultations have increased dramatically since the start of the pandemic and the panelists believe that virtual visits

are here to stay, but not to the extent where it will replace office visits with doctors.

Before the pandemic, in Sweden, online consultations were offered mostly by start-ups, but have since extended to regions implementing virtual consultations themselves to meet the rising demand by patients, McNeil explained. “I think the public feels that the pandemic has made it easier to get in contact with your physician, but it’s been harder to get a physical meeting [to avoid risk of infection],” she said.

Both McNeil and Radmann touted the implementation and adoption of public electronic health records as self-empowering patients. By giving patients access to their own health data, they can better manage their own health and be an active part of the care team.

Sweden’s McNeil admitted that not all physicians liked the idea of making patients’ health records public, but said patients love getting access to the information they need to get a better understanding of their disease and treatment methods and being able to share that information with relatives.

Norway’s Radmann pointed to the convenience of having all health records in one place, which has been particularly beneficial during the pandemic, because “the different systems are communicating with each other to help the patient.”

Meanwhile in Canada, Scott said, the “patient experience has been near the bottom of the list of priorities” while the focus has been more on providers and institutions. But that also changed during the pandemic. In the past, orthopedic clinics filled up their waiting rooms with up to 50 or 100 patients at a time. Patients sat for hours until their name was being called, which was done mainly for the convenience of the doctor, he said.

With the demand for physical spacing during COVID, the clinic was no longer able to pack patients into waiting rooms and started texting individual patients to flow them in and out of the clinic. “It’s really a simple technical solution,” but it fundamentally changed the patient’s experience, Scott noted, adding that this is just one example of changes that ultimately benefit the patient experience.

Scott described the transition to a “new normal” as an “exciting time” with health systems reimagining new care pathways aiming to strip away duplicative efforts and leveraging telehealth and virtual care. The priority is now shifting to promoting patient engagement and connecting patients with providers, he believes.

New Normal

Scott offered another example where virtual care has improved access for patients.

In the past, he said, a heart failure clinic would see a patient every six weeks to optimize medications, but with virtual visits, patients’ medications can be dialed in in less than a week now. Similarly, rehabilitation services are also now being offered for patients to do exercises at home. “There’s a myriad number of ways in which we can improve. My hope is that we continue to discover new ways of enhancing the care and the outcomes,” but everyone agrees that finding the “sweet spot for virtual care versus face-to-face visits” remains challenging, he said.

Harrer said the pandemic has been a “turbo-charger” for telehealth and remote care in Australia and expects that trend to continue. He agreed with other panelists that virtual care however will not replace physical doctor visits.

“What should stay face-to-face and what should not, is really depending on the patient experience,” he said. “This is a very important interaction between carer and patient ... it should be really a supportive system, not a replacement.” Patients in urban Melbourne may want or need different experiences and health services than people in rural communities.

And he noted that it is critical that developers of new telehealth services work very closely with users to figure out what works and what doesn’t work.

“That feedback is utterly important to get telehealth right, because you can have the best service – if it’s not adopted, if it’s not trusted, if it doesn’t create any value, it will not be used,” he stressed. “We constantly look into this and adapt and develop and

innovate these services in an agile way and that is what we see going forward.”

In Taiwan, the digitalization of health care is well underway, and telehealth is a vital part of reaching rural communities, Wang said. But he echoed Harrer’s view that it cannot replace the human touch.

Taiwan’s government and the private sector are creating a roadmap that focuses on caring for the aging population and the shortage of health care workers. He said that Taiwan is also currently piloting a smart hospital with newer technologies aimed at improving care and prevention and creating efficiencies.

Aging at home is also a focus of the Australian digital health strategy, Harrer said, noting that the aging population Down Under is a highly addressable market. “It has been assigned a very substantial amount in the recent federal budget and has been identified as a key area for investment in research and development for the next three to five years and beyond,” he said. “There’s a real opportunity here, because we see a lot of excitement and a positive attitude towards these technology-driven telehealth solutions, especially in the aging care space ... but also by their families who are very tech-savvy.”

Similarly, McNeil said, in Sweden, the older generation is staying healthier compared to previous generations and they are tech savvy. She said that 73% of people ages 76 and older are online and 90% of people between 65 and 75 are active online, which means that Sweden will have to rethink aging care as well. She also feels that Sweden puts the patient at the

center and also understands that patients are a resource for the health care team, which is good economically and for the patient.

Scott hopes that patients will also be more actively involved in their health care in Canada. “Our folks have been very reactive and passive consumers of health care and our hope is to shift that dynamic to being much more proactive,” he said. He noted that the inability of patients to come to the hospital and doctor’s office has created a backlog for things like cancer screenings, and that could be something where patients can be more proactive.

“That’s just one example, but you can imagine across the continuum of care many different areas where patient engagement would drive value for their health outcomes and experience,” he said.

“Feedback is utterly important to get telehealth right.”

Stefan Harrer, Digital Health Cooperative Research Centre



Fueling The Growth Of Generics Post-COVID

Generics companies have played a pivotal role during the global pandemic, ensuring essential medicines are accessible for patients as the health care industry faces ongoing challenges. As vaccines roll out globally and we move from pandemic to endemic, West Pharmaceutical Services' David Maier, Vice President and General Manager, Generics discussed with In Vivo what this means for the generics and biosimilars market.



In Vivo: What will be the lasting impact of the COVID-19 pandemic on the generics and biosimilars market, and how is West adapting its operations to continue to serve this key part of the industry?

Maier: The generics and biosimilars markets were growing at steady rates even prior to COVID-19. The treatment of people who become very ill from COVID-19 has also increased the demand for generic injectable medicines.

From the onset of the pandemic, West has taken proactive measures to mitigate risk and provide our customers continuity of supply by expanding our manufacturing capability through an increased and accelerated total capital investment over \$500 million, which includes over 30 major facility modifications and over 400 incremental pieces of equipment, hiring over 1,000 new team members since the start of the pandemic and increasing production operations to run 24 hours a day, 7 days a week to meet this unprecedented global demand. The success of this approach requires partnership with our customers and suppliers, including a greater level of transparency regarding

production demands and filling schedules to ensure we are addressing the right need at the right time.

You note that supply chains have been challenged by significant disruption during the pandemic. What do you believe are the lessons learned with regards to risk planning and demand fluctuations?

Maier: What the industry has learned is the value of doing risk mitigation early and having greater flexibility while also maximizing your global networks. When the pandemic hit, industry had to quickly develop hundreds of millions of doses for some medicines, from manufacturing sites that were already operating without much spare capacity. In West's case, we found ways to use our existing assets more efficiently, while at the same time installing new equipment and developing contingency plans. This has allowed us to respond quickly to this unexpected demand, as well as future demand resulting from hospitalizations that occur from new waves of COVID-19 and other diseases.

We are also accelerating our move towards automation and more robust scalable manufacturing processes using a global operations strategy. We have done this by leveraging our 90+ years of manufacturing expertise and utilizing our perpetual 5-year sourcing plan. This includes second source qualifications, strong supplier relationships with master supply agreements and negotiated capacity commitments. Additionally, it includes maximizing the efficiency of our global manufacturing network and our ability to flex our operations, including shifting resources from one site to another to address gaps at different facilities.

What potential is there for future innovation in the generics and biosimilars space?

Maier: As more novel biologics reach the end of their patent lives, our generics and biosimilars makers are capitalizing on and investing in these molecules and technologies, resulting in more robust pipelines.

However, we hope that industry and healthcare systems do not repeat the mistakes made in some generics categories. Pricing and competitive pressures have been so fierce that it has forced several manufacturers out of the market in certain small-molecule generic therapeutic areas, resulting in too

many situations where there is only one sole provider of a critical generic drug.

Strategically, generics and biosimilar companies face a copy versus improved dilemma. If the original treatment is going off patent, the least risky option is usually to replicate it – this is the “copy” strategy. However, there has been a notable rise in the number of 505(b)(2) filings in the US, where the generic seeks to improve on the innovator drug. One example is treatments administered intravenously in hospital settings. There are now an increasing number of devices, including West's own Smart Dose® injector, that can move drug administration into a home care setting, which is better for patients and reimbursement costs and ultimately helps lower overall healthcare costs. This “improve” strategy is riskier for our customers and for West, but potentially more rewarding for patients, healthcare systems, and the companies that invest in an “improve” strategy.

The industry's reaction to the pandemic has highlighted accelerated speed to market. What opportunities do you see here and what are the key challenges of faster drug development from a delivery perspective?

Maier: Health care systems and governments have a financial incentive to increase the use of generic medicines as soon as possible. Faster regulatory review processes and accelerated approvals existed before the pandemic, but these appear to have slowed down somewhat for generics while regulators prioritize COVID-19 vaccines and therapies for public health reasons.

The COVID-19 vaccines themselves were a rapid, robust proof of concept for mRNA technology. The global life sciences community proved that it could develop, obtain approvals for, manufacture and distribute a new vaccine in a matter of months rather than years. First, this should give hope that mRNA technology could be effective for future health crises, but beyond that it proves the world can rally together and produce treatments quickly.

Going back to supply chains, this forces us to rethink how they work and create the ability to scale quickly, with flexibility to reprioritize when something unexpected occurs. In drug development, the manufacturing and supply process is rarely the bottleneck and usually does not take longer than the clinical trials. That said, now they might, given the urgency to respond to a pandemic and get product(s) to market quickly.

The role of digital technologies across industries has been increased in order to continue business operations. What is West doing in the digitization space to keep up with the demand?

Maier: Digital technology is something that West is heavily investing in. We are implementing more robust manufacturing execution systems and SAP S/4 HANA across our entire global network, as well as looking at better in-process controls, data feedback and automating record-keeping. Digital tools will replace manual process throughout the commercial and production value change. This digital technology is enabling

knowledge sharing across all value streams within our global manufacturing network, and by connecting our production equipment to the IoT platform, we are able to track site performance using real-time data to assist in quicker decision-making, preventative maintenance, equipment scheduling, and eliminating unnecessary manual efforts. Finally, by deploying increased automation capabilities, we've been able to increase the efficiency of manual processes, and in the future, we will be able to scale quickly and eliminate situations where the ability to onboard new employees is a limiting factor.

Beyond the impact of COVID-19, what are your predictions for the generics and biosimilars industry?

Maier: The good news is the outlook for the generics and biosimilars markets is a story of continued positive growth, even without the COVID pandemic demand. Nonetheless, there are also challenges. Some of these are not new, with the biggest one being margin compression and pricing pressures.

Biosimilar uptake has increased significantly in recent years across western markets and has resulted in savings of approximately \$10 billion in the US alone over the past 5 years generating savings for patients, payers and employers. Thus, while biosimilar approvals in the US slowed down during the COVID-19 pandemic, future growth in approvals is expected, as defined savings, clinical benefit and market acceptance of biosimilars increase.

Additionally, there is increased focus on improving quality standards across the industry. This can hit generics companies particularly hard where manufacturing facilities, the regulatory filing and original drug itself may all be decades old. Standards need to catch up, and we've observed a rise in the number of 483s and warning letters issued during inspections, especially for small molecule and generic drug manufacturers, as well as an increased use of aseptic lines for drug development. Our customers need to balance keeping prices competitive while improving their manufacturing operations, which is a challenge for them and their suppliers.

Do you have any final thoughts?

Maier: In summary, COVID-19 itself has been a global tragedy, but also an opportunity for the entire healthcare ecosystem to prove it can respond quickly to tragedy. The response to COVID-19 from the global scientific and medical community, the biopharmaceutical industry, regulatory authorities, and logistics carriers has been unprecedented in speed and scale. West is happy to have been able to work with many of the originators of some of the COVID-19 vaccines and treatments and we continue to seek out ways in which we can better meet customers' global needs.

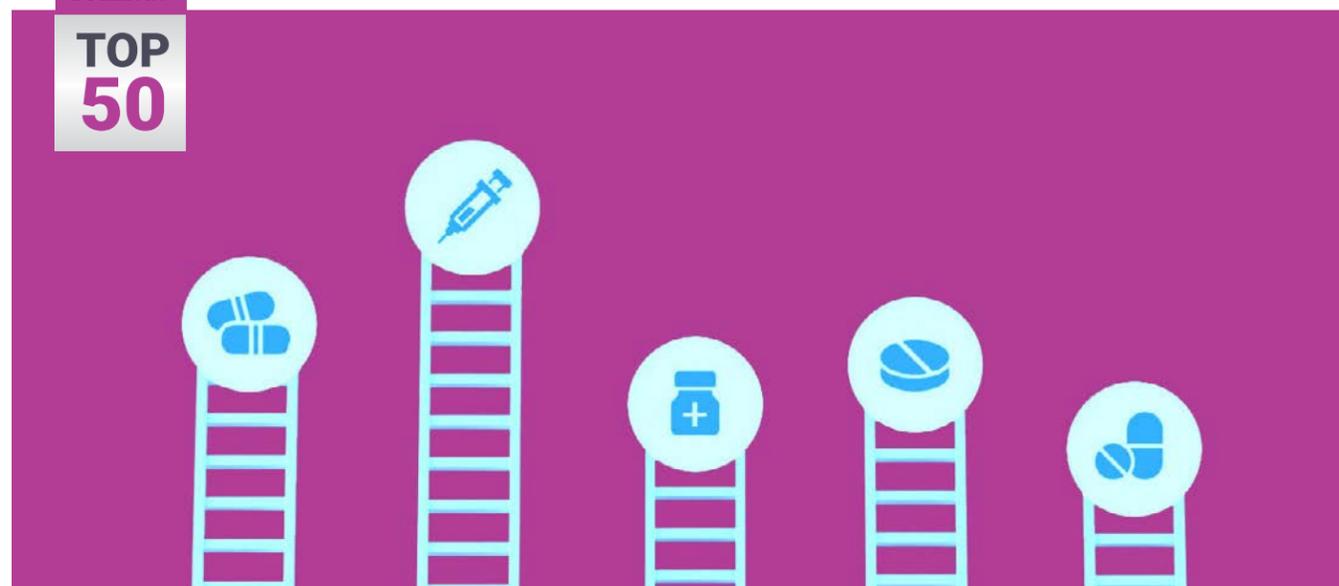
We recognize the importance of customers having partners from beginning to end as we navigate new challenges with biosimilars and increased regulatory and quality needs. Through our Integrated Solutions program, West is responsive to the unique needs of biologic, pharma and generic drug products as regulations continue to demand more in order to help deliver safety, quality and compliance.

Consolidation And COVID See Off-Patent Industry Rankings Rewritten

Viatrix Merger And Pandemic Disruption Shake Up Industry Leaders

GENERICIS BULLETIN

TOP 50



BY DAVID WALLACE, EXECUTIVE EDITOR, EUROPE

After an extraordinary year that saw demand patterns and the supply chain upended by the COVID-19 pandemic, as well as a major merger that has transformed one of the global off-patent industry's biggest players, *Generics Bulletin's* Top 50 has once again seen significant changes.

In the wake of what can only be described as an extraordinary year, *Generics Bulletin's* annual ranking of the world's top 50 generics and biosimilars companies has seen major disruption, as companies grapple with the impact of the COVID-19 pandemic on demand patterns and the supply chain at the same time as a major merger has reshaped one of the off-patent industry's biggest players.

Last year, Sandoz topped our table, followed by Mylan and then Teva.

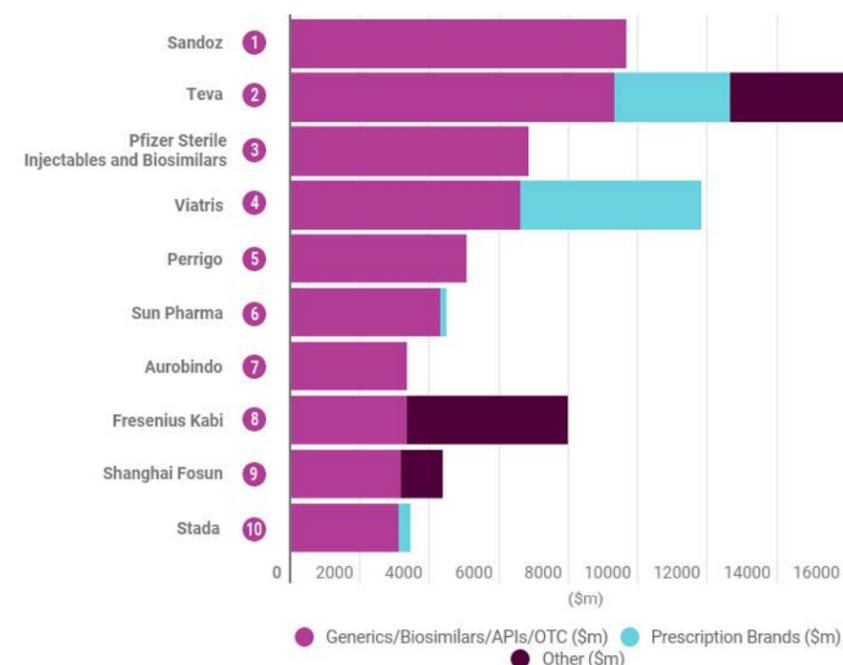
Sandoz retains its top spot this year – with CEO Richard Saynor insisting that the Novartis unit benefits from the clear focus of its “pure play” approach to the off-patent sector at the same time as parent company Novartis is planning a strategic review of the business. Sales slipped by 1% to \$9.65bn under constraints of the pandemic.

Nevertheless, Sandoz recently acknowledged that despite a “challenging” start to 2021, it was on track to stabilize in the back half of the year as it looked forward to a healthy slate of launches.

Following close behind Sandoz, Teva this year jumps to second position, with its \$9.32bn generics total for 2020 including just over \$4bn in North America as well as more than \$3.5bn in Europe. In North America, Teva has made headway with its Truxima (rituximab-abbs) biosimilar, as the company increasingly focuses on high-margin opportunities in biosimilars and complex generics following a pointed pruning of its portfolio.

The Israeli firm's total sales – including brand assets such as Copaxone (glatiramer acetate), Austedo (deutetrabenazine) and Ajovy (fremanezumab) and its Anda distribution business – slipped by just over 1% to \$16.66bn.

Exhibit 1: The Generics Industry's Top 10 By Product Sales



After Teva comes the major upset of our ranking this year, with Pfizer's biosimilars and sterile injectables business, much of which is rooted in former Hospira operations, overtaking Mylan – now part of Viatrix – to claim third place.

The reason for this is that Viatrix, formed by the merger of Mylan and former Pfizer mature brands unit Upjohn, reported financials for 2020 that reflected just 45 days of sales from the Upjohn business after the transaction closed on 16 November.

As such, the company reported just \$6.59bn in combined generics, complex generics and biosimilars sales for the year, of total sales that climbed by 4% to \$11.82bn. While Viatrix pointed *Generics Bulletin* towards an estimated pro-forma total of \$18.38bn for the combined business for 2020, it said it was not splitting this figure out by product category for competitive reasons.

This means that former Upjohn owner Pfizer has been able to leapfrog Viatrix into third place – albeit likely only for a short period, until Viatrix has a full year of sales under its belt – as Pfizer's booming biosimilars business grew to more than \$1.5bn and its sterile injectables segment delivered a further \$5.32bn in sales (see Exhibit 1).

Perrigo's Last Year In Top Five After Rx Divestment?

As major firms like Sandoz, Viatrix and Teva do not typically split out sales of OTC products separately from their generics offerings, our ranking includes include 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 has now been divested to Altaris in a \$1.5bn deal.

Given this divestment – with \$975m in 2020 sales coming from the Rx unit – it will be interesting to see where Perrigo places on next year's ranking.

The lower half of our Top 10 is led by the first of the major Indian off-patent players to feature in our rankings, Sun Pharmaceutical Industries, which enjoyed 3% growth in its financial year ended March 2021 – partly driven by global sales of its Ilumya (tildrakizumab) brand growing by more than half to \$143m – with the firm also contemplating moves into the biosimilars arena.

Another major Indian player, Aurobindo, follows in seventh position, continuing its climb up the rankings in rising by one place from last year – albeit with very little separating its

total from that of Fresenius Kabi's Intravenous Drugs unit, which ranks the German company in eighth place.

Rounding out the top 10, as in 2020, are China's Shanghai Fosun and Germany's Stada, with the disaggregation of Stada's reported sales total based on an estimated 90%-10% split between generics and brands.

GENERICIS BULLETIN'S TOP 50

Mid-Table Players Shift Position

The disruptive trend of the Top 10 continues into the middle of the pack, as the mixed fortunes of companies occupying positions 11 to 30 have seen some rise up the rankings at the same time as others have slipped down the table.

Starting off the mid-table, we find three major Indian players – Cipla, Dr Reddy’s and Intas – with sales growth in their financial years ended 31 March 2021 that enabled them to maintain their positions at the top of this second group.

However, Lupin – last year in 13th position – slipped slightly to 15th this year as its sales suffered a mild decline. At the same time, Hikma jumped up above Lupin into 14th place, after successfully weathering the headwinds of 2020, with the disaggregation of the UK-based firm’s reported sales total based on an estimated 90%-10% turnover split between generics and brands.

Other significant movements this year included Amneal jumping from 23rd to 19th position, as the “Amneal 2.0” strategy implemented by returning co-CEOs Chirag and Chintu Patel produced results, with almost \$300m in additional sales coming from the acquisition of AvKARE that closed in early 2020 and with the firm increasingly focusing on high-margin opportunities in complex generics and biosimilars.

Celltrion also vaulted up the rankings, from 30th place last year to 25th position this year, as its booming biosimilars business delivered growth of almost half in 2020.

On the other hand, Sanofi’s generics business continued to shrink following the divestment of its Zentiva unit in Europe in late 2018, with the pharma major’s generics sales declining by 13%. As a result, Sanofi Generics moved from 24th place last year to 29th position this year.

And rounding out the second table is Endo, which slipped by a single position after a difficult 2020 had a significant impact on the generics business that the firm is determined to stabilize this year.

Biosimilars Players Climb Rankings

Meanwhile, the growing importance of biosimilars to the global off-patent industry is highlighted in the third and final table, as following Celltrion’s leap from 30th to 25th position, smaller biosimilars players have also climbed the rankings.

Biocon – which boasts a significant biosimilars business in the form of its Biocon Biologics subsidiary, partnering with Viatris on multiple biosimilars including the Semglee (insulin glargine) rival to Lantus that this year won the first ever US interchangeability designation – climbed to 35th position this year, up from 40th in 2019 and 43rd in 2018.

Meanwhile, Coherus Biosciences – which was a new entrant in our Top 50 ranking in 48th position last year – rose to 43rd place this year, as its sales stemming entirely from its Udenyca pegfilgrastim biosimilar jumped by a third to \$476m. And it has ambitious growth plans for the future, aiming to capture at least a tenth of the US Humira (adalimumab) market when biosimilars launch in 2023 as well as branching out into novel treatments with partner Junshi Biosciences.

Bulgaria’s Sopharma rose to 31st position as its sales grew by 12% in 2020. Meanwhile, among a host of Indian players at the bottom end of the table that also included Jubilant, Alembic, Ipca and Strides, Wockhardt fell from 42nd place last year to 47th this year as it saw the effect of divesting its branded generics business in India and certain international territories to Dr Reddy’s Laboratories in mid-2020.

Natco Pharma this year slipped out of the Top 50 – joining a group just outside of our ranking that also included firms such as Nippon Chemiphar, Australia’s Mayne Pharma and ANI Pharmaceutical – with the Indian firm dislodged by Amphastar and Mexico’s Genomma.

However, some continuity was retained at the very bottom of our Top 50, with last year’s new entrant Beximco once again garnering the same 50th-place ranking that was previously achieved by the Bangladeshi firm.

With a variety of deals promising to reshape leading off-patent companies in 2021, biosimilars continuing to find their place alongside their small-molecule generic counterparts, and the effects of the COVID-19 pandemic far from over, the immediate future remains somewhat unpredictable for the global generics and biosimilars industry. As such, we can look forward to further changes in the rankings when *Generics Bulletin* compiles its Top 50 again next year.

A Note On Methodology

The *Generics Bulletin* Top 50 ranking compiles sales data for 2020 – or the closest available reported year – for those firms for which generics and/or biosimilars are 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 through its Samsung Bioepis joint venture – and Eli Lilly with its Basaglar follow-on insulin glargine brand – 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.

However, Servier’s generics business is included in our ranking, in line with other major originators that operate generics, biosimilars, APIs and OTC businesses that are clearly distinct from their branded interests. Servier’s Biogaran and Egis generics units respectively reported sales of €876m (\$999m) and €477m in Servier’s financial year ended 30 September 2020 – which would put both of them in contention for inclusion in the top 50 in their own right – while other Servier generics subsidiaries contributed a further €50m.

We also do not include companies that do not disclose detailed sales information, meaning that privately held players such as Apotex, Polpharma, Alvogen group and Zentiva are absent from our rankings.

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

Rank	Company	“Generics/ APIs/OTC (\$m)”	Prescription Brands (\$m)	Other (\$m)	Total turnover (\$m)	Change %	Notes
1	Sandoz	9646	n/a	n/a	9646	-1	Total includes \$474m from sales of anti-infectives to third parties
2	Teva	9315	3327	4017	16659	-1	
3	Pfizer Sterile Injectables & Biosimilars	6842	n/a	n/a	6842	15	
4	Viatris	6585	5235	n/a	11820	4	Results include only 45 days of sales from Upjohn business following merger on 16 November
5	Perrigo	5063	n/a	n/a	5063	5	Comprises \$975m from Prescription Pharma, \$2,693m from Consumer Self-Care Americas and \$1,395m from Consumer Self-Care International
6	Sun Pharma	4309	143	22	4474	3	Financial year ended 31 March 2021; INR: 0.0135 dollars
7	Aurobindo	3345	n/a	n/a	3345	7	Financial year ended 31 March 2021; INR: 0.0135 dollars
8	Fresenius Kabi	3330	n/a	4623	7953	1	Generics/Biosimilars/OTC/APIs figure is Intravenous Drugs unit; Euro: 1.14 US dollars
9	Shanghai Fosun	3151	n/a	1220	4371	6	Chinese yuan: 0.1449 dollars
10	Stada	3089	343	n/a	3432	18	Figures based on estimated 90:10 split for generics and brands; Euro: 1.14 US dollars
11	Cipla	2554	n/a	33	2587	12	Financial year ended 31 March 2021; INR: 0.0135 dollars
12	Dr Reddy's	2516	45	n/a	2561	9	Financial year ended 31 March 2021; INR: 0.0135 dollars
13	Intas	2237	n/a	n/a	2237	6	Financial year ended 31 March 2021
14	Hikma	2101	233	7	2341	6	Figures based on estimated 90:10 split for generics and brands
15	Lupin	2015	n/a	32	2047	-1	Financial year ended 31 March 2021; INR: 0.0135 dollars
16	Sawai	1754	n/a	n/a	1754	3	Financial year ended 31 March 2021; Yen: 0.00937 dollars
17	Zydus Cadila	1713	n/a	331	2044	5	Other = Consumer Wellness & Animal Health segments; Financial year ended 31 March 2021; INR: 0.0135 dollars
18	Nichi-Iko	1671	66	26	1763	-1	Financial year ended 31 March 2021; Yen: 0.00937 dollars
19	Amneal	1637	356	n/a	1993	23	
20	Krka	1624	n/a	120	1744	3	Euros: 1.14 US dollars
21	Servier Generics - including Biogaran, Egis & others	1599	n/a	n/a	1599	1	Financial year ended 30 September 2020; Euros: 1.14 US dollars
22	Aspen	1481	866	n/a	2347	9	Generics/Biosimilars/OTC/APIs comprises \$1025m from Regional Brands and \$456m from APIs and FDFs; financial year ended 30 June 2020; South African rand: 0.06072 dollars
23	Glenmark	1462	n/a	15	1477	3	Financial year ended 31 March 2021; INR: 0.0135 dollars
24	Towa	1451	n/a	n/a	1451	40	Financial year ended 31 March 2021; Yen: 0.00937 dollars
25	Celltrion	1379	n/a	n/a	1379	48	KRW: 0.000847 dollars
26	Alkem	1197	n/a	n/a	1197	6	Financial year ended 31 March 2021; INR: 0.0135 dollars

Rank	Company	"Generics/ APIs/OTC (\$m)"	Prescription Brands (\$m)	Other (\$m)	Total turnover (\$m)	Change %	Notes
27	Gedeon Richter	1158	294	389	1841	3	Prescription Brands is Vraylar/Reagila (cariprazine); Euros: 1.14 US dollars
28	Torrent Pharma	1081	n/a	n/a	1081	1	Financial year ended 31 March 2021; INR: 0.0135 dollars
29	Sanofi Generics	1062	n/a	n/a	1062	-13	Euros: 1.14 US dollars
30	Endo	849	2054	n/a	2903	0	Generics/Biosimilars/APIs/OTC figure is Generics (\$783.1m) plus injectable ertapenem authorized generic (\$65.6m)
31	Sopharma	839	n/a	n/a	839	12	Bulgarian lev: 0.583 dollars
32	Hypera	793	n/a	n/a	793	24	Brazilian real: 0.194 dollars
33	Jubilant Pharma	782	n/a	42	824	2	"Generics/Biosimilars/APIs/OTC figure is Pharmaceuticals segment; Financial year ended 31 March 2021; INR: 0.0135 dollars"
34	Alembic Pharma	728	n/a	1	729	17	"Financial year ended 31 March 2021; INR: 0.0135 dollars"
35	Biocon	693	n/a	301	994	14	"Financial year ended 31 March 2021; INR: 0.0135 dollars"
36	Mallinckrodt	690	2060	n/a	2749	-13	
37	Ipca Labs	687	n/a	53	740		"Financial year ended 31 March 2021; INR: 0.0135 dollars"
38	Ache	675	n/a	n/a	675	4	Brazilian real: 0.194 dollars
39	Kalbe Farma	611	n/a	1028	1639	2	"Indonesian rupiah; 0.00007092198 dollars"
40	Orion	568	479	182	1229	3	Euros: 1.14 US dollars
41	Lannett	546	n/a	n/a	546	-17	"Financial year ended 30 June 2020"
42	Advanz Pharma	526	n/a	n/a	526	3	
43	Coherus Biosciences	476	n/a	n/a	476	34	
44	Adcock Ingram	440	n/a	6	446	4	"Financial year ended 30 June 2020; South African rand: 0.06072 dollars"
45	Bausch Health Generics	415	n/a	n/a	415	-10	
46	Strides Pharma Science	379	n/a	n/a	379	26	"Financial year ended 31 March 2021; INR: 0.0135 dollars"
47	Wockhardt	356	n/a	17	373	-17	"Financial year ended 31 March 2021; "other" is vaccine business (£13m); INR: 0.0135 dollars"
48	Amphastar	350	n/a	n/a	350	9	
49	Genomma	338	n/a	312	650	9	Mexican peso: 0.0469 US dollars
50	Beximco	302	n/a	n/a	302	12	"Financial Year Ended June 30, 2020, BDT: 0.01178 dollars"

Source: Company Reports

The top 50 ranking compiles sales data for 2020 – or the closest reported year – for those firms for which generics and/or biosimilars is a major part of their business.



Unrivalled news and analysis of global generics, biosimilars and value-added medicines

Understand the impact of industry trends on your business and stay ahead of your competition with expert coverage from Generics Bulletin. Access powerful, comprehensive intelligence on generics, biosimilars, and value-added medicines you can't find anywhere else.

Turn to Generics Bulletin for continually updated coverage of:

- The latest industry news
- Exclusive executive interviews
- Expert policy analysis
- Insights into regulatory matters
- Legal and legislative updates
- Global company and commercial developments.

Register for your free, no-obligation, 7-day trial at pharmaintelligence.informa.com/generics-bulletin



US Biosimilars Enjoy A Year Of Firsts In 2021

Two Interchangeable Biosimilars And First Ophthalmic Biosimilar Approved

While US biosimilar approvals have been thin on the ground in 2021 – with products delayed due to the FDA’s inability to conduct certain facility inspections during the COVID-19 pandemic – the market has nevertheless seen several firsts this year, including two interchangeability designations and the first ophthalmic biosimilar approval.



BY DAVID WALLACE, EXECUTIVE EDITOR, EUROPE

With biosimilars gaining traction in the US in recent years thanks to multi-source competition on certain key products as well as healthy uptake in treatment areas such as oncology, 2021 saw the US biosimilars market take further steps forward with a number of firsts.

These included the first US FDA designations of biosimilar interchangeability, the launch of the first interchangeable biosimilar, and the first biosimilar to be approved by the FDA for ophthalmic indications.

However, at the same time several biosimilar developers saw their efforts to reach the market frustrated by delays to FDA approvals caused by the agency’s inability to conduct certain necessary facility inspections due to pandemic-related travel constraints.

Semglee Insulin Glargine Is First Interchangeable Biosimilar

The first US biosimilar approval of the year came in July, with the FDA’s formal designation of Viatrix’ Semglee (insulin glargine-yfgn) biosimilar as interchangeable with Sanofi’s Lantus blockbuster.

To meet this additional standard to biosimilarity, a product must not only be deemed biosimilar to its reference brand but must also demonstrate that it will “produce the same clinical result as the reference product in any given patient.”

Moreover, “for a biological product that is

administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product” must not be “greater than the risk of using the reference product without such alternation or switch.”

While industry views are still to some extent mixed on the desirability and necessity of interchangeability as a separate standard to biosimilarity in the US, the designation brings valuable prizes for successful applicants in the form of pharmacy-level substitution as well as a year of interchangeable biosimilar exclusivity for the first interchangeable biosimilar version of each product, dating from commercial launch of the interchangeable biosimilar.

In Viatrix’ case, the launch of the interchangeable insulin glargine biosimilar – which followed some months after approval, in November 2021 – offers the opportunity to build on the relatively low market share captured so far by the non-interchangeable version of Semglee, which is due to be rapidly phased out.

The company has also taken the step of launching the interchangeable biosimilar in both branded and unbranded versions, with the unbranded version offered at a wholesale acquisition cost of \$147.98 for a pack of five 3ml pens and \$98.65 per 10ml vial, representing a 65% discount to the list price of Lantus.

Meanwhile, the branded version of interchangeable Semglee comes in at a price that is a lot closer to the reference brand, with a WAC of \$404.04 per pack of five 3ml pens and \$269.38 per 10ml vial.

Humira Gets First Interchangeable Biosimilar Approval

Semglee was not the only biosimilar to be formally designated as interchangeable by the FDA in 2021. Several months later, in mid-October, the agency announced that Boehringer Ingelheim was to be the second recipient of an interchangeability designation, for its Cyltezo (adalimumab-adbm) rival to Humira.

The biosimilar – which was initially approved by the FDA in August 2017 – is scheduled to be among a chasing pack of Humira biosimilars that are expected to hit the US market in 2023, after Amgen launches its Amjevita (adalimumab-atto) version at the beginning of the year, under a series of settlement deals between biosimilar sponsors and originator AbbVie.

Boehringer Ingelheim has an expected launch date of 1 July 2023, putting it just after Samsung Bioepis on 30 June.

It remains to be seen how interchangeability will affect the biosimilars market more broadly and the biosimilar Humira market specifically. However, with so many adalimumab competitors expected to launch in the US from 2023 – the FDA has so far approved six Humira biosimilars, with more waiting in the wings – interchangeability and Boehringer Ingelheim’s year of interchangeable exclusivity could prove to be a significant differentiator.

Samsung Bioepis Bags First Ophthalmic Biosimilar

Another first for US biosimilars came in September 2021, when Samsung Bioepis – the joint venture between Samsung Biologics and Biogen – announced that it had received the FDA’s first approval for a biosimilar with ophthalmic indications, its Byooviz (ranibizumab-nuna) rival to Lucentis.

While biosimilar versions of Avastin (bevacizumab) are already available in the US – and, like the reference brand, are used off-label to treat eye disease – this has led to criticism from some quarters given the relative lack of supporting data in ophthalmic indications.

It was expected that Lucentis would face biosimilar competition in the US by the end of 2021. But as it received its Byooviz approval, Samsung Bioepis overturned these expectations by revealing that it would not launch the biosimilar before June 2022, following an undisclosed settlement with originator Genentech. “Pursuant to a global license agreement entered into with Genentech,” the company indicated, “Samsung Bioepis and Biogen will have freedom to market [Byooviz] in the US as of June 2022.

It remains to be seen how interchangeability will affect the biosimilars market more broadly and the biosimilar Humira market specifically.

Inspection Limitations Lead To Delays

Despite so many firsts for US biosimilars in 2021, some developers may see it as a year of missed opportunities to approve a greater number of biosimilars. International inspection constraints related to the COVID-19 pandemic prevented the FDA from conducting certain necessary inspections, pushing back the approval of multiple biosimilar candidates.

The first signs of this were seen at the very end of 2020, when Viatrix and Biocon revealed that their bevacizumab candidate had been indefinitely delayed as the agency was unable to conduct a facility inspection.

Then, in September 2021, Alvotech revealed that its AVT02 adalimumab candidate – potentially the first US biosimilar version of the 100mg/ml higher-concentration presentation of Humira – had been similarly delayed. Alvotech had also been seeking interchangeability for its adalimumab biosimilar.

Notably, the FDA’s inability to approve these two biosimilars contrasts with the approach of the European Medicines Agency, which has seen fit to endorse both of these products this year. Viatrix and Biocon gained a nod for their bevacizumab biosimilar in February while Alvotech’s filing for a higher-strength Humira biosimilar with partner Stada was granted a positive opinion recommending

a marketing authorization by the EMA’s Committee for Medicinal Products for Human Use in September.

More recently, Fresenius Kabi acknowledged that its proposed pegfilgrastim biosimilar had suffered from the same uncertainty over the US agency’s ability to conduct a necessary inspection, with the product pushed back to a likely FDA approval in 2022, from an originally expected date of 2020.

Responding to queries over these biosimilar delays, the FDA said it was “actively working on an approach for addressing outstanding inspections.”

“FDA is currently employing other tools to evaluate facilities, as appropriate,” the regulator indicated, “such as requesting records and other information under section 704(a)(4) of the FD&C Act or reviewing trusted foreign regulator inspection records under existing mutual recognition agreements. These tools have, in many cases, successfully allowed us to take actions on applications in lieu of an FDA inspection.”

“FDA continues to monitor the public health situation as well as public health advisory travel restrictions,” the agency concluded. “Once safe travel can resume, inspections will be scheduled based on a number of factors including the public health impact.”

China’s Bio-Thera Solutions had been looking to achieve yet another first in 2021, pursuing a landmark first FDA approval for a biosimilar developed by a Chinese manufacturer, in the form of its BAT1706 bevacizumab candidate. A goal date of 27 November 2021 for the firm’s application was disclosed earlier in the year, but as the date passed no approval was immediately announced.



WEST PHARMACEUTICAL SERVICES, INC.

COMMITTED TO COLLABORATION, QUALITY, SERVICE AND INNOVATION

West is a leading global manufacturer in the design and production of technologically advanced, high quality, integrated containment and delivery systems for injectable medicines. We are a trusted partner to the world's top pharmaceutical and biotechnology companies—working by their side to improve patient health.

WEST OFFERS PROPRIETARY PACKAGING, CONTAINMENT AND DRUG DELIVERY PRODUCTS

- **Stoppers and seals for injectable packaging systems:** to help ensure drug compatibility and stability, while also supporting operational efficiency
- **Syringe and cartridge components:** including custom solutions for the specific needs of injectable drug applications
- **Self-injection systems:** innovative, patient-centric technologies that are easy to use and can be combined with connected health technologies that have the potential to increase adherence
- **Containment and delivery systems:** including Daikyo Crystal Zenith®—a high performance polymer alternative to glass that can meet the challenges of sensitive biologics

CONTRACT MANUFACTURING - PHARMACEUTICAL, BIOTECH AND DIAGNOSTIC

West contract manufacturing harnesses a powerful combination of innovation, technology, infrastructure and expertise to serve the pharmaceutical, medical and consumer industries. Along with more than 50 years of experience, we bring customers quality, safety and reliability in injection molding, contract assembly and finished packaging from our eight locations throughout North America and Europe.

- NYSE: WST
- >10,000 GLOBAL EMPLOYEES
- FOUNDED IN 1923
- 2020 SALES: \$2.15 BILLION
- OVER 40 BILLION COMPONENTS & DEVICES MANUFACTURED EACH YEAR
- 112 MILLION UNITS*



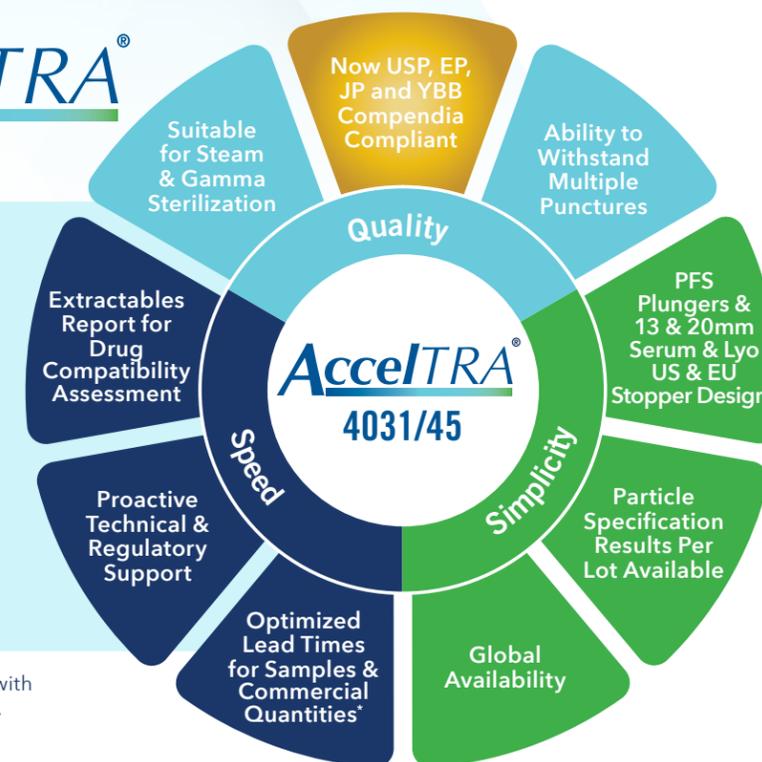
Are you a generic drug manufacturer wanting to standardize on a high-performing elastomer formula to reduce your inventory costs and operate more efficiently?

DO YOU NEED TO MOVE YOUR PRODUCT TO MARKET QUICKLY?



✓ CHOOSE **AccelTRA**®

- ✓ 6-week commercial lead times*
- ✓ Robust extractables package to help identify extractables of concern
- ✓ Multi-puncture performance
- ✓ Low particulate levels



*Commercial quantities available for customers in 6 weeks with provision of 90-day notification and drug product forecast.

RELY ON WEST'S MORE THAN 95-YEAR INDUSTRY-LEADING TECHNOLOGICAL EXPERTISE AND QUALITY - CHOOSE **AccelTRA**® COMPONENTS.

FOR MORE INFORMATION, CONTACT US TODAY AT WESTPHARMA.COM/ACCELTRA
NORTH AMERICA 1-800-345-9800 OPTION 8 | SOUTH AMERICA +55 11 4055 6061
EUROPE +49 (0) 2403-7960 | ASIA PACIFIC +65 6862 3400 | INDIA +91 40 4940111

End-To-End Partnerships Are Leading The Way In Drug Development

Manufacturing and supply chains have been a key topic of interest in the pharmaceutical industry during the course of the COVID-19 pandemic. Equally, the speed at which new treatments have come to the market for patients during this time has placed great expectation on the potential for future development.



In Vivo spoke with Dr. Stephan Haitz, President, CDMO Sales and Marketing at Cambrex, about the role that outsourced providers can play in creating efficiency in the drug development process, the importance of leading sponsors through disruption, and what the future holds for small molecule therapeutics and the US-based CDMO's capabilities.

In Vivo: The contract manufacturing industry is growing rapidly. What key trends in outsourcing small molecule drug development has Cambrex observed in the last two years?

Haitz: I think foremost it is the closer relationship needed between our customers and us. Despite COVID-19 putting distance between us, I think we all saw that we need to work closer together in a virtual world. There is a strong trend towards having many more interactions on technical and commercial levels, and using modern technologies like RealWear to give our customers the ability to actually be at the reactor in the manufacturing plant, or in the lab where their drugs are produced.

We are also seeing the consolidation of manufacturing service lines. Companies like Cambrex have a wide range of

capabilities and nowadays our customers prefer to work with one supplier who can offer most, if not at all, of what they need in the development cycle of their products.

What are the main benefits of working with an end-to-end drug development partner?

Haitz: I think for most it's the ease of working. A good example is quality audits. Instead of a pharmaceutical company needing to have ten different suppliers and audits for one development project, with a company like Cambrex, customers can really reduce those efforts based on one quality system.

There is also a project management benefit. Rather than having information packages passed on from one supplier to another everything is in our system, so our team have a holistic view on development. This also allows us to plan capacity accordingly, so we know where the project is at any given time and nothing comes as a surprise.

Finally, with end-to-end capability providers there is access to support. Every project needs additional assistance, we just don't always know exactly when. However, if you work with a company like Cambrex that support is always available, whether it is from our network of 12 sites or general analytical and technical expertise.

During the pandemic the importance of supply chain resiliency was highlighted. Is Cambrex prepared for future disruption?

Haitz: During the pandemic we all learned a lot, but did what we had to do to keep things moving. At Cambrex, we had done everything we could to prepare ourselves for disruption and learned that transparency between multiple sources is key. We know when our suppliers produce, when they ship, and we have the ability to track these shipments.

The most difficult part at the moment is transportation capacity, but this issue is not isolated to our industry. Again, transparency is important here, but it is also better to receive supplies earlier where possible, even though there are additional costs to this. These include capital and storage costs, but it's better for the overall project to put financial resource here and be prepared. Prior to COVID-19 we were used to

everything arriving just on time, sometimes to the minute, but this does not work anymore.

How is Cambrex expanding to grow its capabilities and further support small molecule drug developers?

Haitz: As I mentioned before, we have a holistic view on development because we can provide early-stage services as well as commercial manufacturing, so all our investments are driven by supporting that chain. As an example, we recently announced a \$30 million investment into our High Point, NC facility which produces Phase II and Phase III material. We also invested \$50 million in our Charles City, IA site to support our commercial manufacturing capacity.

These are large expenditures, but we are also doing more targeted investments, such as upgrading our Tallinn site for GMP, and in Longmont and Durham we have invested in our analytical services. We are not only adding capacity, but also capabilities across the continuum of development through to clinical phases. These decisions are based on close interaction with our clients, so we understand what they will need tomorrow as well as today. This enables us to be prepared for their requirements in the near future.

The regulatory landscape with regards to chemistry, manufacturing and controls (CMC) can be challenging to navigate, especially during the pandemic when in-person interaction was limited. What should sponsors be thinking about when approaching these requirements?

Haitz: We have had experience with virtual inspections, which was quite a change in what both the regulatory agencies and suppliers were used to. However, I think it will be a continuing trend moving forwards that a lot of audits and inspections will be virtual or partly virtual.

We are also having discussions with experts on our side regarding what the agencies will be asking two years from now. As we are developing and expanding our capabilities we have to have that in mind, so having that deep in-house regulatory knowledge is important.

Lastly, there are benefits to our end-to-end setup. We have all the data available, meaning it is easier for our sponsors to respond to questions from the agencies because they do not need to go to multiple sources. Instead, they can just talk to our project management team who have all the information in our systems.

What are your predictions for the future of small molecule manufacturing and how is Cambrex leading the way for innovation?

Haitz: The need for medication and new treatments is unbroken by COVID-19. We need to support our customers in developing new medications, and this is also driving innovation. For instance, we asked ourselves: can we do something faster than we are now? As a result, we have built continuous flow capabilities that are helping to develop drugs at increased pace. Another question is: can we do our chemistry with the right quality and purity? This is something we are looking into as well.



Another trend which will be important for all of us is sustainability. This is something which is only possible with sponsor buy-in and means that when we are taking on programs, we want to make them less environmentally burdensome. We have to look at things like electricity efficiency and consider how our wastewater treatments work. It will force us, on top of the quality of our products, to think about the environment much more, which will trigger new technologies.

Is there anything else you would like to add?

Haitz: I think it's important to recognize the performance of the pharmaceutical industry in providing a vaccine 13 months after the initial outbreak of COVID-19. This will have two implications. First of all, I think that society and communities have realized the value pharmaceuticals bring to daily life. However, this great achievement now comes with heightened expectation.

There are so many other unmet medical needs that the pharmaceutical community must tackle. These include orphan drugs, where there are indications that may have 10,000-20,000 people waiting for treatment. While these expectations are based on how excellently the industry helped us through COVID-19, we now have to do the same for other diseases and conditions. This comes back to what I hope for the future: for us to provide more solutions for as many illnesses as possible. Seeing patients that are able to access new treatments makes everyone going to work proud, and motivated to continue their efforts.

How Can Pfizer Leverage External Innovation After BioNTech Jackpot?

Uwe Schoenbeck, CSO of external science and innovation at Pfizer, knows the company set itself a high bar during the COVID-19 pandemic after rapidly bringing a breakthrough vaccine to market. While the circumstances for the development of Comirnaty were truly unique, Pfizer does not expect to rest on its laurels when it comes to innovative R&D.



BY LUCIE ELLIS-TAITT, EXECUTIVE EDITOR, EUROPE

The past two years have been transformational for Pfizer, thanks to its partnership with German biotech firm BioNTech. Uwe Schoenbeck, senior vice president and chief scientific officer, external science and innovation at Pfizer, spoke to *In Vivo* about how external innovation and internal agility are now key to the company's future success.

Heading into the New Year, Pfizer – now a household name the world over thanks to the success of its COVID-19 vaccine in partnership with BioNTech – is focused on “staying on the cutting edge of science.” The company is “identifying strong partners in the academic world and in the biotech world, that are able to help us and work with us on making the changes we need for patients in the gene therapy, mRNA and in degrader spaces,” Schoenbeck noted.

To maintain the momentum it has created through the COVID-19 pandemic, Pfizer will draw on its wide portfolio of novel modalities and its ability to select the best partners in revolutionary R&D, the executive said.

But in a recent talk at the October HLTH conference, Pfizer CEO Albert Bourla admitted that Pfizer had some way to go to convince market spectators that its mRNA COVID vaccine with BioNTech was not a one-off success story, in terms of bringing a novel modality to market and seeing success quickly. An issue that has plagued the first movers in gene therapy is that while the treatments work, the financial gains have not matched expectations.

Even if there remains skepticism about the sustainability and success of Pfizer's novel

pipeline, which includes gene therapies, mRNA drugs and novel protein degrader therapeutics, Bourla said Pfizer had been able to prove during the pandemic that a big pharma company could move with the speed of a biotech. “The biggest thing is the culture inside the company ... we have shown to the entire company that nothing is impossible,” he said. Now branded Comirnaty (a mashup of community, immunity, mRNA and COVID), Pfizer first teamed up with BioNTech to develop the COVID-19 vaccine BNT162b2 in March 2020. By November 2020, Phase III trials were complete and before the end of that year, Pfizer and BioNTech became the first companies anywhere in the world to get approval for a COVID-19 vaccination (see Exhibit 1). On 2 December, the Medicines & Healthcare Products Regulatory Agency (MHRA) in the UK granted a temporary authorization for emergency use for Comirnaty against COVID-19.

Pfizer sees its COVID-19 vaccine as a “lightspeed” project. The speed and agility shown in the development of Comirnaty are approaches Pfizer wants to replicate elsewhere. “Everyone [at Pfizer] now, in addition to vaccines, they want to have their lightspeed moment, on colon cancer, rare diseases, internal medicine, or neuroinflammation, and they are all bringing projects that they want to run with the same speed and the same ambition,” Bourla said during the HLTH presentation.

Pfizer's R&D is focused on five key therapeutic areas: vaccines, oncology, rare disease, internal medicine and inflammation and immunology.

Seeking Innovation

Innovation must have meaningful application, said Schoenbeck. “Innovation is novel approaches that have the potential for true breakthroughs for patients,” he defined. When assessing projects to bring into the fold, Schoenbeck asks, “Is it just interesting biology or an interesting technology, or does it really have all it takes to translate into a breakthrough therapy down the road?”

“That's the kind of innovation that we're really trying to focus in on, the kind we are trying to enable through partnerships, and then try to really leverage to bring to fruition,” he said. As an example, he highlighted mRNA as one modality for the Pfizer pipeline that fits the bill for true innovation, but he added, “We also have really game-changing activities in the gene therapy space and other areas as well.”

For external innovation to work, classical business development teams, corporate venture capital functions and the centers for therapeutic innovation (CTI) group, as well wet bench-based functions, must all work together under one umbrella, Schoenbeck emphasized. “Transparency is the key,” he said. “In this kind of role, you need to internally integrate a lot of different functions. But you also have to externally manage the interactions.” Working with external partners, “we have to make sure that internally, everything is lining up properly, to give the project the best chance.”

He added: “The bottom line really is that you're going to have to be very transparent in your communication. You have to be very frank in the expectations. And you have to be very open minded, to really be able to address all the different approaches that are out there that you want to work in.”

Appetite For Risk

After the success of the COVID-19 vaccine, the bar has been raised for what Pfizer will produce next.

Schoenbeck noted that COVID-19 was a very unique situation, and he praised the work of many pharma companies, biotech and government agencies that were able to work together in new ways. “It was a demonstration of what can be done in the health care sector,” he said. “We have around 280 different components in our vaccine, we have close to 90 different providers and more than 19 different countries to work with. The supply chain must be established to make sure everything is working. We have seen what can be done and what can be accelerated. This won't work for every program, obviously, but hopefully we can bring some of this innovation from the product development efforts into other projects.”

“We are hopeful that we will carry over some of these lessons as we go into the next level, not just on mRNA vaccines and in areas like flu and other infectious disease vaccines, but also other developments,” including gene therapies and more established modalities. Schoenbeck does not want to see companies cutting corners, but he also does not want developers to get dragged back to the slower, historic approach “when we have seen what can be optimized.”

Pfizer is continuing to invest in and expand its leadership in the mRNA space, both in vaccines and in RNA therapeutic

Exhibit 1: Comirnaty Development Timeline – Partnership To First Emergency Use Approval In 9 Months

Date	Event
17 March 2020	Pfizer and BioNTech agree to a letter of intent regarding the co-development and distribution (excluding China) of a potential mRNA-based vaccine aimed at preventing COVID-19 infection
5 May 2020	First participants receive vaccine doses in the US as part of global COVID-19 mRNA vaccine development program
13 July 2020	Pfizer and BioNTech get FDA Fast Track Designation for two investigational mRNA-based vaccine candidates against SARS-CoV-2
28 July 2020	The pair choose a lead mRNA vaccine candidate against COVID-19 and commence a pivotal Phase II/III global study
6 October 2020	Rolling submission initiated with European Medicines Agency for SARS-CoV-2 vaccine candidate BNT162b2
18 November 2020	Pfizer and BioNTech conclude Phase III study of BNT162b2, meeting all primary efficacy endpoints
2 December 2020	BNT162b2 is the first COVID-19 vaccine to receive emergency use approval, with the UK's MHRA granting a temporary authorization
11 December 2020	The vaccine secures emergency use authorization in the US; followed by approval in Europe in late December
23 August 2021	Comirnaty becomes the first COVID-19 vaccine to be granted FDA approval; more than 1.2 billion Pfizer-BioNTech vaccine doses have been delivered to more than 120 countries or territories around the world since December 2020

Source: Drugs.com; Press Releases; Scrip

approaches. The company is also investing heavily into its gene therapy portfolio. “We have seen innovative shifts in the overall portfolio of Pfizer. Now we're really looking for truly differentiated novel approaches,” Schoenbeck said.

What does this mean for the big pharma's appetite for risk? True novelty means success is harder to predict.

“If you do truly differentiated mechanisms, they have a little bit more of an inherent risk than if you're trying to give me-toos and me-betters,” Schoenbeck noted. In parallel to shifting its pipeline focus towards novel modalities, Pfizer has also “revamped” how it advances preclinical and clinical pipeline programs. “Historically, Pfizer has not necessarily been a leader when it comes to rates of progression times in the portfolio. However, over the last three to five years, we've really had a turnaround in R&D by applying a number of steps, including just more rigor in the early stages.” He noted that Pfizer has more recently become a leader when it comes to success rates and cycle times.

Looking at the company's pipeline over time, data from Pharmaprojects shows that Pfizer has significantly reduced

number of early-stage programs it runs, with the size of its in-house preclinical pipeline shrinking over time, in line with its efforts to streamline and work more with external partners (see Exhibit 2).

“As we have seen, sometimes you have to take risks of the unknown mRNA vaccines. You have to take a leap of faith, but this was based on what we felt we saw in the partnership with BioNTech. With the data we had available, we really felt it was the right fit. And as it turned out, it was the right strategy to go after,” Schoenbeck said.

As a result, he thinks Pfizer has built up more confidence, and that even with several novel modalities at play, like gene therapy and RNA, “we are in a good position to make sure we can deliver the portfolio, despite the higher risks of innovative projects.”

Constructing Successful Partnerships

The way in which larger biopharma companies interact with biotech and smaller pharma partners had evolved over recent years, Schoenbeck noted. Thinking back to when he started out in pharma, the “approach in general was more, we give you the funding, you give us the IP and the assets, and then we parted ways.” But he said this approach was not very successful. Over the past few years, big pharma – Pfizer included – has changed. Schoenbeck said Pfizer was able to offer a wider range of investment vehicles to meet the needs of its partners. “We have done research collaborations, licensing option deals, acquisitions, seed investments, equity investments, and so on and so forth. The range of investment vehicles has become much broader,” he said. “We really want to make sure that you bring the best for both parties to the table. And together do something that neither of us can do alone. That is the key motivation behind partnering for us.”

As an example, Schoenbeck noted Pfizer’s 2014 partnership with gene therapy company Spark Therapeutics, for the development of PF-6838435 (fidanacogene elaparvovec) for hemophilia B.

While Pfizer had limited experience in this area, Spark “had some true clinical expertise affiliated with them,” Schoenbeck said. Spark continued to run Phase I and II studies for the gene therapy asset, before Pfizer took on responsibility for Phase III. “We really have worked with the investigators, making sure to bring the best knowledge, the best expertise and the best capabilities into the partnership.”

PF-6838435 is a novel, investigational vector that contains a bio-engineered adeno-associated virus capsid (protein shell) and a high-activity human coagulation factor IX gene. It is hoped that, once treated, hemophilia B patients will be able to produce factor IX themselves, rather than having to regularly inject factor IX. The treatment has shown impressive efficacy data with

an annualized bleed rate below one. Phase III data for PF-6838435 from the BENEGENE-2 trial are expected in the first quarter of 2023. Spark Therapeutics was acquired by Roche in 2019, in a deal valued at \$4.8bn.

“Strong partnerships are the key to success,” Schoenbeck told In Vivo. He noted that more recently, companies had been coming together to focus on particular disease areas or development programs, which was not usual of big pharma in the past. In the oncology space, Schoenbeck noted as an example, combination therapy was a key driver. “Any one company can only run so many Phase II and III studies in their portfolio. If you want to maximize the opportunity for patients from your drugs, you really have to test them in a number of combinations.”

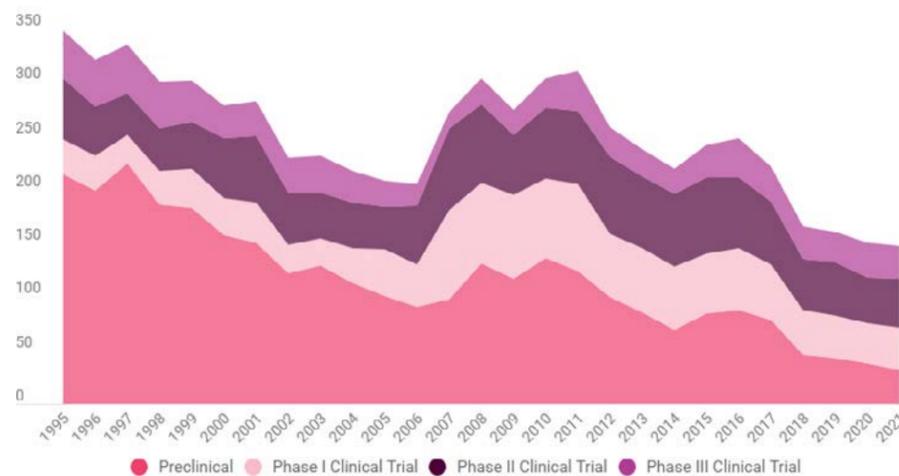
He expects this approach to take hold outside of oncology as well, in areas like autoimmune and cardiovascular disease. “We’ll see more cases where large pharma companies will get together and partner.”

Positive View For 2022

While Comirnaty sales will continue to boost Pfizer in 2022, market experts will also be waiting to see how the company lives up to its successes in 2021, building on a longer-term pipeline that holds risk due to an emphasis on novel approaches. Bank of America has described the big pharma as “transitioning to innovative biopharma,” while JP Morgan analysts have called its pipeline “a work in progress.”

Overall, though, the horizon is bright for Pfizer in 2022, particularly for vaccine sales. JP Morgan analysts, in a 3 November note, said Pfizer’s preliminary \$29bn 2022 outlook for Comirnaty was “conservative.” The company will be able to expand the vaccine’s reach even further in 2022, through additional booster and adolescent vaccination programs – adding more fuel to its R&D pipeline and ability to seek competitive partnerships.

Exhibit 2: Pfizer In-House Development Pipeline Has Shrunk Over Time



Source: Pharmaprojects

Business Continuity And Growth Kept In Sharp Focus At J&J Vision Care

The COVID pandemic dealt a blow to Johnson & Johnson’s Vision Care business, but the company maintained its innovation program and kept customer engagement to the fore. It has started to see a return to positive contact lens buying trends, says Vision Care European business leaders Sandra Rasche and Lisa Ann Hill.



BY ASHLEY YEO, EXECUTIVE EDITOR, EUROPE

Early in the COVID-19 pandemic, Johnson & Johnson’s contact lens business leaders decided to set up regular consumer surveys to gauge the pandemic’s impact on contact lens usage during the lockdowns and quarantine periods. The surveys also allowed the Vision Care business to keep pace with public confidence changes, patients’ ongoing needs and buying habits.

Through its Acuvue portfolio, Johnson & Johnson is the global contact lens market leader, says Lisa Ann Hill, who is managing director for the Western European region of Johnson & Johnson Vision Care. Her territory, which she manages under Sandra Rasche, VP of the EMEA region for Johnson & Johnson Vision Care, includes major markets such as Germany, France, Italy, Netherlands and Switzerland. It excludes the UK and the Nordic countries, which are managed separately.

Vision Care reports through Johnson & Johnson’s medical devices segment, a business which, exposed fully to the negative effects of COVID-19, contracted in 2020 by 11.6% to \$23bn. Within Vision Care, the contact lens (and other) business made revenues of \$2.99bn in 2020, down from \$3.4bn in 2019. Together with the surgical portfolio, Vision Care was a \$3.99bn business in 2020.

Acuvue is a key brand across the company’s portfolio, but Rasche and Hill highlighted two major challenges and opportunities in the contact lens sector: retaining current contact lens wearers to prevent drop out; and carefully re-engaging with potential contact wearers.

While business uncertainty remains a reality for all health care companies, Johnson & Johnson’s Vision Care team has been encouraged by recent consumer survey findings. “We realized early

on we needed to figure out what was happening regarding consumer confidence, and to be relevant to customers and patients in the COVID period,” said Hill.

Contact Lens Usage Up

Vision Care’s July-August 2021 survey of around 3,300 people in France, Germany, Italy, Spain, Belgium, the Netherlands and Switzerland showed that 63% of contact lens wearers were back to pre-pandemic levels of contact lens usage; and 49% of wearers had returned to visiting their optician. Western Europe consumption of contact lenses had increased by 12% in the first eight months of 2021, compared with the same period in 2019.

10% of respondents said they were wearing contact lenses more often, and of those that had stopped wearing contact lenses during the pandemic, 53% claimed they were likely to return to wearing them. Reduced wear was a function of lack of occasions and increased screen-time at home, said Hill, but noted that 61% of wearers were planning to purchase contact lenses within the next three months.

That survey analysis was done before renewed lockdowns and tighter COVID control measures were put in place in certain European markets in November 2021, as a result of renewed levels of infection and circulation of the new Omicron variant. “Now we need to see what happens,” said Hill, against the background of partial lockdowns in Germany, the Netherlands and Austria. Johnson & Johnson expects to run another Vision Care survey before the end of 2021.

Positive Evolution Expected

COVID-19 has influenced wearers’ behavior, “but when it nets out, we expect there to be a

positive evolution, because the contact lens category is naturally a category in growth,” said Hill. “There are so many people wanting to use contact lenses, and yet market penetration is still relatively low.”

Hill estimates that only 10% of people that could wear contact lenses actually do. In turn, Johnson & Johnson products still represent on average only 10% of the portfolios of its eye care professional (ECP) customers. Some countries, such as Switzerland and the Netherlands, are highly penetrated.

“There are a huge amount of contact lens ‘considerers,’ so it is about creating awareness and access to products. That is my primary job,” said Hill. In the wider EMEA area managed by Rasche, contact lens considerers in 2020 numbered 146.3 million.

“The first fit is the linchpin of what our market hinges on, because without new wearers we cannot develop this category. For that reason, eye care professionals are a critical element,” Hill added. In this respect, the method for market building is similar to that of the medical device segment of Johnson & Johnson.

Vision Care uses patient-centric approaches within what it terms a professionally supported model. It is not a direct-to-consumer model, Hill stresses. “It is more an ecosystem where we work together with professionals and consumers. We see ourselves as part of a triangle with them.”

In Hill’s markets in western Europe, Johnson & Johnson’s Vision Care products must comply with CE marking needs under the EU Medical Device Regulation, under which Acuvue is in the IIa risk category. Vision Care applies voluntary codes of conduct, but the segment does not need to comply with pharma-type rules on calling on customers.

But individual rules can be very different according to the market, some of which are regulated and others deregulated. For example, in some countries, a professional fee is applied around contact lenses, which is not the case in all countries.

France is highly regulated, for instance, requiring an ophthalmologist/medical prescription for the wearing of contact lenses. The purchase of contact lenses happens in optical stores, however. “Here, we interact with both parties,” said Hill.

The UK is an optometrist market, where prescriptions are required, but there is no need for patients to visit a separate category of doctors. The eye care doctors work within the High Street retail chains and optical independents.

Germany is a deregulated market, with no prescriptions needed and, in this market, Johnson & Johnson provides support for opticians. Hill notes a relatively higher usage of e-commerce and other sales channels in Germany.

“The business model varies by country. The need to support the stores and sell to consumers adds an element to our business that is more similar to a consumer model,” said Hill. Vision Care will become the wider Johnson & Johnson group’s most obvious touchpoint to the end-consumer, after the company has spun off its consumer arm (personal health care, skin health/beauty products and OTC medicine etc). The decision was made in November, and the spin-off is expected to be completed within 18-24 months.

Innovation Pipeline

Acuvue is Vision Care’s one and only contact lens brand, but innovation in the Acuvue range is fundamental, said Hill, and the business’ innovation pipeline links it strongly to the medical segment of the company. Vision Care leverages synergies through a shared focus on human health, medical devices and pharma, and the unit benefits from being able to work across the company’s R&D divisions and by bringing in talent from other sectors. The contact lens business also works in partnership with the surgical division.

The company responds to evolution in the market precisely by focusing on innovation and value-add products. Moreover, it earns plaudits from customers who appreciate Vision Care’s commitment to R&D. Beside a dedicated R&D department for vision, Johnson & Johnson also operates R&D councils for the sharing of innovative ideas. Furthermore, Hill stresses the value of collaboration with businesses in the regions. “It’s one thing to have R&D, and another to develop what patients really need.”

In 2021, Vision Care launched an innovation in presbyopia in Europe, Acuvue Oasys Multifocal with Pupil Optimised Design, which is a reusable contact lens. Some 50 million eligible people could benefit from such lenses, says Johnson & Johnson, but at present, less than 10% of them actually do. Acuvue Oasys Multifocal was recently launched in the US too.

The innovative technology goes beyond the more traditional elements such as refraction, and adds the dynamic

J&J’s Vision Care Outlook Through The Eyes Of Sandra Rasche



In Vivo: What is your role at Johnson & Johnson Vision?

Sandra Rasche: As a vice president EMEA for Johnson & Johnson Vision Care, I oversee the contact lens business for the region. I’ve been with the Vision Care business for more than seven years and have spent more than 25 years in other parts of Johnson & Johnson Medical Devices, covering general management, business development, sales & marketing, and global strategy.

How has the business model changed over time?

At Johnson & Johnson Vision, we have always been focused and driven by our purpose to change the trajectory of global eye health. WHO World report on vision notes that at least 2.2 billion people around the world suffer from visual impairment, yet 50% have a preventable vision impairment, or one that has yet to be addressed.

Our business model is to support patients with vision and eye health needs, which means supporting and partnering with eye care professionals (ECPs). We work closely with ECPs to help them however we can, whether it is for a better understanding of patient needs, or to consider their business and how we can best engage, retain and nurture contact lens wearers.

of pupil size. This makes it easier for eye care professionals to do a successful fit. The success rate was 97.3%, in two pairs of lenses or less, said Hill.

Sustainability Challenge

Sustainability has rapidly risen to the top of every company’s agenda, and Hill highlights Johnson & Johnson’s efforts around Acuvue in complying with newly accentuated environmental protection needs. Notably, the Johnson & Johnson Credo, which was drafted back in 1943, cites a need to respect and reflect environmental concerns.

Accordingly, the Acuvue packaging has been optimized in terms of materials, and the company has launched a website to help educate consumers on recycling the packaging. The challenge is the actual contact lens itself, which, due to its size, is not suitable for normal recycling methods and needs new approaches.

A system being piloted in the UK sees one thousand opticians helping consumers recycle their lenses. Hill said, “We will look more to those types of methods and efforts in the future, as it will certainly be a consideration in the product pipeline to develop products and packaging that are more sustainable.”

The company is already succeeding in developing wind- and solar-powered manufacturing plants. In spring 2021, it set a new vision for all Acuvue contact lenses to be made using

What impact has COVID-19 had on the business?

The COVID-19 pandemic has had a significant impact on ECPs and the contact lens sector over the past two years. Patients have been wearing contact lenses less, however as the High Street opens again in some markets, we are seeing some encouraging signs of recovery.

Specific to the contact lens sector, we see two key challenges and opportunities. The first is retaining current contact lens wearers to prevent drop out, and the second, to carefully re-engage patients who might be open to contact lenses to come in and be fitted for a trial. How we do this needs to evolve to reflect the current realities in the market, but there remains a huge opportunity for ECPs to adapt their approach to patient engagement.

What trends are you seeing in the market?

The main trends we are seeing are shifts in patient behavior and treatment formats due to the COVID-19 pandemic, along with continued innovations in contact lens technology. While some patients may be wearing contact lenses less, we are working with ECPs to discuss how contact lenses can still support their needs. Choosing the right contact lens can help patients whose eyes might be tired from spending more time looking at digital screens while working from home, for example.

Closed stores and restrictions on patients’ mobility led to significant pent-up demand for overdue eye tests, and ECPs often have less chair time with patients. So, another area we

renewable electricity. “I believe that, in the medical device business, this will become more important as an element in tenders,” said Hill.

While Vision Care does not in general do tenders, customers are clearly valuing sustainability more and more. Even if it is not part of an “official” discussion with customers “certainly we can deliver this sustainability piece to them, and that would be a factor of choice,” said Hill.

The wider company recently announced that 100% of its electricity will come from renewable sources by 2025, and that it will achieve carbon neutrality by 2030. The company is a signatory to the United Nations’ Race to Zero campaign, which sets an ambition of achieving net zero carbon emissions across the value chain by 2045.

Current Market Priorities

In terms of product segments, Vision Care observes a major trend towards daily disposal products – the single-use products that improve convenience for consumers. There are unmet needs in the areas of astigmatism and presbyopia.

For 2022, the priority for Vision Care is to support the market in recovering from COVID-19. “We know that consumers want to come back to buying contact lenses, so we want to enable that access. We also want to enable fittings that were not possible during the pandemic,” said Hill.

are supporting is training and communication tools for remote consultations and digital communication.

In terms of contact lens innovation, there is a lot of exciting work happening. One area we are focusing on is multifocal contact lenses and presbyopia, as there is a significant unmet need, and this represents a growth area for the business.

A second area we are focusing on is myopia (short-sightedness). We see this as one of the biggest eye health threats of the 21st century, as 50% of people globally (4.8 billion) are projected to be myopic by 2050 with significant impact on children. Earlier this year, we launched a comprehensive myopia guide, covering how ECPs can assess, monitor and treat myopia in children, and aim to provide a research-based rationale for providing myopia control. We also have several myopia product innovations in the pipeline, which we hope to launch in Europe in the future.

What are the unique selling points of the business?

Innovation is at the heart of everything we do. Our heritage and expertise allowed us to strongly focus on Vision Care, giving us the opportunity to introduce new products and platforms. If you think about it, soft contact lenses are one of the first examples of wearable technology. The amount of science that goes into each contact lens is incredible. We introduced the world’s first disposable soft contact lens under the Acuvue brand name in 1987, and we continue to be focused on bringing advances to vision care.



Cambrex is the small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. Enjoy working with our experts to accelerate your small molecule therapeutics into the market.

With over 40 years experience and a growing team of over 2,200 experts servicing our global clients from our sites in North America and Europe, we are tried and trusted in branded and generic markets for API and dosage form development and manufacturing.

Drug substance	Drug product	Analytical services
<p>Active ingredients Dynamic people</p> <p>From laboratory to commercial supply, enjoy working with the small molecule experts at Cambrex for your custom development, manufacturing or generic API.</p> <ul style="list-style-type: none"> • Custom development • Custom manufacturing • Generic APIs • Specialist technologies • Solid state science • Material characterization 	<p>Drug formulations Expertly finished</p> <p>From preformulation and clinical supply to commercial manufacturing and packaging, Cambrex delivers your complex dosage forms with expertise.</p> <ul style="list-style-type: none"> • Custom development • Clinical supply • Custom manufacturing • Packaging • Solid state science & preformulation development • Conventional dosage forms • Specialist dosage forms 	<p>Analytical solutions Quality assured</p> <p>Trust our analytical development and testing experts to rapidly advance your molecule for the greatest chance of success.</p> <ul style="list-style-type: none"> • Microbiology/chemistry • Cleanroom services • Material characterization • Method development & validation • Compendial & release testing • Stability storage & testing



How can we help you advance? www.cambrex.com



Stephanie Raines
Manufacturing
Technician II

Your molecule Our mission

Discover why we're **the** small molecule experts you'll enjoy working with across the entire drug lifecycle

Contact us today
www.cambrex.com/contact

Drug substance

Drug product

Analytical services

How Science Helps Manufacturing Evolve To Meet The Complex Challenges Of Drug Development

In 2022, the worlds of technology and science will continue to merge at an unprecedented rate, allowing for the faster development and delivery of novel patient-centric treatments, such as cell and gene therapies. But novelty is naturally accompanied by risk. It is critical that biopharma companies collaborate with innovative manufacturing partners in this evolving environment.



Agility and flexibility are the keys to a successful manufacturing system. Almost two decades ago, the US FDA set out its Pharmaceutical Quality for the 21st Century initiative to support a successful, agile and flexible global manufacturing system. While substantial improvements have been made over time,

the COVID-19 pandemic has given rise to a unique period of growth and innovation.

Mitigating Risks Through Scientific And Technological Expertise

Rentschler Biopharma SE is supporting clients as they seek efficient and innovative manufacturing approaches for novel drugs. Dr. Christian Schetter, Rentschler Biopharma's chief scientific officer, highlighted two different kinds of risk to mitigate in order to avoid the costs of failure. "One is a technological risk, which often you cannot avoid because success is determined by trial and error of new modalities or therapies. There is usually no alternative to go through a well-thought clinical development program to ascertain the proper questions to ask. Dr. Schetter noted that execution risks were often the most prominent reason why great ideas fail early in the process, but these can be minimized by expertise. By collaborating with the right partners at the outset, companies are able to focus on where they want to be at the end and develop robust processes for manufacturing.

This is where Rentschler Biopharma sees its role in the industry. The company has built strong foundations based on incorporating technological and scientific innovations into its processes. Assessing the current and future industry outlook, Rentschler Biopharma has integrated digital technologies, single-use manufacturing and flexible production to handle the challenges of today's biopharmaceutical developers. Tailored

processes in bioprocess development and cGMP manufacturing, flanked by strategic expansion, result in optimal timelines while achieving and maintaining high productivity.

Well-versed in combining science and technology for manufacturing success, Rentschler Biopharma is able to minimize risk for clients, as well as assist its partners in asking the right questions at the right time.

There has been a shift in the industry to focus on therapies that require more advanced manufacturing. To remain the partner of choice, Rentschler Biopharma's commitment to staying at the cutting-edge of science means it has noticed significant benefits, such as gains in speed and reliability in processes. Dr. Schetter noted that often clients came to Rentschler Biopharma because of its ability to rapidly develop products. All drug developers are seeking ways to speed up R&D – to get a product from bench to patient faster and in a more cost-efficient manner. COVID-19 vaccines are a prime example of how R&D timelines can be reduced significantly through technology and close collaboration. Dr. Schetter highlighted Rentschler Biopharma's expertise in the manufacture of complex molecules, an expanding area of importance for the innovative drug development sector is it grows away from small molecules toward biologicals and modalities that can be selected and personalized to the appropriate therapy for a patient.

Shaping The Technological Horizon

For the rapid development of groundbreaking therapeutic approaches, standardization within both bioprocess development and manufacturing plays a central role. As the evolution of the biopharma market continues, with a focus on complex molecules, Dr. Schetter saw the greater use of technologies "which digitalize both the production and distribution processes."

The steps can be incremental, such as going paperless and digitizing lab testing records. Besides the initial benefits, "new advances in equipment connectivity allow direct transcription of thousands of data points without any manual data transcription or reviews, and this is clearly reducing the source of manual errors and variability, as well as allowing much faster and effective resolution of problems."



Furthermore, Rentschler Biopharma aims to offer its clients the best technology and solutions along the entire value chain by collaborating with strategic partners that provide complementary services. This sense of collaboration has been an integral part of the company's strategy – as demonstrated in its partnerships with Vetter and Leukocare – and is a growing trend across the life sciences industry. During the pandemic, the life sciences sector saw a number of new collaborations, pairing up big pharma, CDMOs, government and regulators in a new way. Industry leaders have expressed a desire to see this greater collaboration and newly effected lines of communication stay active after the pandemic subsides.

Meeting The Evolving Needs Of Biopharmaceutical Production

Rentschler Biopharma continues to grow in response to the market's increasing demands, by expanding cGMP manufacturing capacity. In August 2021, the CDMO announced a significant expansion of its existing U.S. production site within the Greater Boston area. A new production facility, the Rentschler Biopharma Manufacturing Center US (RBMC US), will add 22,000 square feet to the existing footprint and include four 2,000l single-use bioreactors for easy clinical to commercial scale-up capabilities. The RBMC US has been designed specifically to accommodate future scalability and capacity needs and is due to be operational in 2023.

Looking ahead, Rentschler Biopharma is also evaluating and exploring new modalities with the formation of Rentschler ATMP Ltd. located in the UK. Dr. Schetter explained that this facility is "preparing for cGMP, small scale manufacturing of Adeno-associated virus (AAV), as a means for providing cGMP viral vectors to our clients for gene therapy." A key bottleneck that has previously affected the speed of development and manufacture for gene therapy companies.

Considering innovations in technology and science that will be beneficial to the manufacturing sector, Dr. Schetter offered key insights. He specifically pointed out that the right blend of scientific advancements into technology is necessary to be able to effectively use a modular and flexible

"I think the continuous increase of online and inline monitoring capabilities, in combination with computational modeling, is just a fascinating field which is leading towards a better understanding of how technical limitations may potentially interfere with product quality."

Dr. Christian Schetter, Chief Scientific Officer, Rentschler Biopharma

manufacturing design. "I think the continuous increase of online and inline monitoring capabilities, in combination with computational modeling, is just a fascinating field which is leading towards a better understanding of how technical limitations may potentially interfere with product quality." As this field continues to grow, product quality can be modeled to minimize material waste and time consumption, which are major advantages. Also, as a standard, Dr. Schetter suggested that constantly increasing product titers and quality with the application of next generation cell line development platforms, in combination with new process formats like intensified or fed batch or continuous manufacturing via perfusion, will be the new standard.

Overall, the biopharmaceutical industry is working hard and working together with expert partners to raise known standards while meeting the complex challenges of next-generation drug development.

US Forming Industry Consortia To Prepare For Future Pandemics And Global Supply Chain Disruptions

HHS agencies look to build on COVID-19 experience by developing quicker public/private responses to pandemics and supply chain threats.



BY BOWMAN COX,
EXECUTIVE EDITOR,
US

US authorities are preparing to partner with pharmaceutical companies in 2022 through public/private consortia to lay the groundwork for future pandemic responses and ensure continued production of essential medicines even when global supply chains are disrupted.

The federal government's Health and Human Services Department is encouraging the development of such consortia in the coming months to collaborate on quickening responses to pandemics and disruptions to the supply of medicines.

Concept Emerged From 100-Day Review

HHS initially outlined the consortium approach to shoring up essential medicines supplies as part of the Biden administration's 100-day White House supply chain review in May 2021.

This was a departure from the Trump administration's August 2020 effort to strengthen the domestic industrial base for essential medicines by requiring federal agencies to buy American.

The Biden administration's idea is that public/private consortia will build on the pandemic's massive public/private collaborations to produce COVID-19 vaccines and therapeutics by carving out a new role for the public sector in the pharmaceutical manufacturing process. The government would finance expansions of manufacturing facilities in return for "priority access" to use them in public health emergencies. This would avoid the need to commandeer manufacturing facilities by issuing rated orders under the Defense Production Act, which proved effective but disruptive during the COVID-19

pandemic. It also avoids reliance on boutique specialty contractors whose operations wax and wane with pandemic threats.

An added benefit: the expansion of the domestic pharmaceutical manufacturing infrastructure will increase the US pharmaceutical sector's resilience against interruptions in the global supply chain.

Substantial Funding Expected

Leadership within the HHS' Biomedical Advanced Research and Development Authority, or BARDA, are anxious to get industry's input on how the consortia should work before planning gets too far along.

Mike Angelastro, director of BARDA's Division of Pharmaceutical Countermeasures Infrastructure, told the BARDA Industry Day meeting in November 2021 about "key investment decisions that we need to make as an organization in 2022" because "we've been told by Congress and the administration that there's going to be substantial investments made in this space in the future."

This funding will be in addition to:

- \$3.5bn in the March 2020 CARES Act for BARDA to help industry with the manufacture and purchase of APIs, vaccines, therapeutics and diagnostics; and
- \$10bn in Defense Production Act funding in the March 2021 American Rescue Plan Act, of which \$3bn went to BARDA for expanding the US pharmaceutical industrial base.

However, some \$30bn of additional funding for next-pandemic response and post-pandemic pharmaceutical supply chain strengthening was

Training will play an expanded role in the next iteration of BARDA's pandemic response capabilities.



dropped from President Biden's infrastructure bill before he signed it in November 2021.

But it could reappear in other legislation.

A White House pandemic preparedness report in September 2021 called for \$65bn in funding to be spent over seven to 10 years. About half was for development and manufacturing of vaccines and therapeutics.

Nationwide Vaccination In 130 Days

BARDA, which reports to the HHS's assistant secretary for preparedness and response, or ASPR, is working to transform the industrial supply chain for medical countermeasures as outlined in the White House pandemic preparedness report.

BARDA described its plan in a request for information (RFI) the agency shared at its recent BARDA Industry Day meeting and has since posted on its Medical Countermeasures website. The request outlines an aggressive goal for the consortium: to establish the capability to produce enough vaccines for the entire US population within 130 days, and for the global population within 200 days after recognition of an emerging pandemic threat.

The BARDA infrastructure division's Biopharmaceutical Manufacturing Partnership (BioMaP) branch, which focuses on drug substance manufacturing, will manage the effort, Angelastro said.

CIADMs Re-Envisioned Post-COVID

The effort is a re-envisioning of BARDA's centers for innovation in advanced development and manufacturing program, Tim Belski, BioMaP branch chief, told the BARDA Industry Day meeting.

The CIADM approach, which BARDA developed in the wake of the 2009 H1N1 influenza pandemic, had mixed results with the COVID-19 pandemic.

BARDA ended its partnership with Emergent BioSolutions, Inc. for one of its two centers just as the Industry Day meeting

was getting underway. Emergent had run into difficulties maintaining quality while scaling up for COVID-19 vaccine drug substance manufacturing.

The agency's partnership with Texas A&M University for the other center, which Fujifilm Diosynth Biotechnologies Texas LLC operates for the university, continues.

It Takes More Than Facilities And Equipment

One of BARDA's takeaways from the COVID-19 scaleup experience is that "we don't get there with just capacities and facilities," Belski said. "We really need to have those proven facilities, the proven staffing, and those proven quality systems to get that done in a response scenario."

He said the agency was looking for industry partners to join the Biopharmaceutical Manufacturing Partnership Consortium, or BioMaP consortium, "that are capable and have the capacity to assist us in our next pandemic preparedness efforts so that the next time we have a pandemic, we have a broader list of partners, and we can work with these partners ahead of time to respond even faster."

The Importance Of Workforce Training

Belski underscored the importance of appropriate staffing. "The workforce is key to making sure that we can get these products out in time and ensure the quality of those products when they are needed."

He touted the workforce development aspect of the 2012 CIADM contract with Texas A&M University, which proved key in staffing the Fujifilm Diosynth facility there. The other CIADM, Emergent BioSolutions, told Congress it struggled to hire and train workers for the manufacture of COVID-19 vaccine drug substance.

Training will play an expanded role in the next iteration of BARDA's pandemic response capabilities. "Coming out of the pandemic ... we're looking to team with both industry

and academia and other government agencies to expand the footprint of BioMaP on workforce development,” Belski said.

Toward that end, BARDA has entered discussions with the National Institute of Standards and Technology, or NIST, the National Institute for Innovation in Manufacturing Biopharmaceuticals, or NIIMBL, and others.

A Forum On How To Meet A Challenging Goal

The 130-day goal is very aggressive, and everyone knows it, Belski highlights, which is why the people at BARDA “are very interested in understanding and learning and discussing with you more on what is it that we can do together to get to that point.”

BARDA envisions the BioMaP consortium as not just a funding mechanism, but also a forum for communications between the government and industry, as well as among industry partners to come up with better solutions than any one participant could develop on their own.

Priority Access Sought For Emergencies

One area BARDA hopes to hear from potential partners about through the request for information is their perspective on priority access for the government in public health emergencies.

BARDA had already been negotiating with some industry partners about granting years of priority access in return for investing in their industrial expansion, Belski said. This is a different approach than the government’s heavy reliance on its Defense Production Act authority at the height of the pandemic last year to issue rated orders that compelled manufacturers and their suppliers to stop serving their private sector customers and serve the government instead.

The rated orders proved disruptive, Joe Figlio, Angelastro’s branch chief for pandemic vaccine preparedness capabilities and readiness, noted at the BARDA meeting. “As we prioritize certain raw materials, consumables, needles, syringes, vials, whatever it might be, prioritize them for the COVID vaccines, they are not available for other domestic needs, for cancer medications, childhood vaccines, et cetera.”

The new goal, he said, “is to provide redundancy and additional capacity to be able to handle the extra surge from a pandemic as well as everyday domestic needs.”

Capacity Sustainment Rather Than Warm-Based Support

Asked for the agency’s stance on warm-based support, Belski said it remained uncertain, though he welcomed insight into industry’s view about such an approach, which would require the government to pay for plants to maintain a state of readiness.

The pharmaceutical industry has used this approach, also called “warm start arrangements,” with contract manufacturers selectively, as it is not cheap.

Belski said BARDA is interested in hearing about plans for sustaining production by expanding capacities and capabilities to be available for use in public health emergencies. These would be facilities that have routine commercial operations

as well as the capacity to also respond to public health emergencies when necessary.

“Right now, I think the US government’s position on that is it would be much better if we allowed our industry partners to use that type of capacity,” Belski said. “For commercial reasons, you’d be much more profitable. It would be exercising the capacities, both the equipment and facility itself, but also the quality systems and the personnel that use that facility. That makes the most sense to us. However, we’re certainly willing to, you know, discuss that further and see what makes the most sense.”

The RFI Responses

Belski assured industry day participants that the agency is not looking for anything elaborate in responses to the RFI, which are due 28 February 2022.

“We’re really looking for a brief description of your organization, and what you bring to the table,” he said, as well as feedback on a few questions related to potential financial, technological, legal or other barriers to participating in such a consortium.

An Essential Medicines Consortium In The Works

BARDA also is supporting ASPR’s efforts to implement recommendations from the White House’s June 2021 100-day supply chain review by establishing a consortium for advanced manufacturing and onshoring of domestic essential medicines production.

ASPR’s Program Office for Innovation and Industrial Base Expansion, or IBx, will lead the effort, with BARDA’s Pharmaceutical Countermeasures Infrastructure Division providing expertise in API synthesis and manufacturing, according to Arlene Joyner, chief of the division’s CDMO network branch, which matches prime contractors in BARDA’s medical countermeasures program with contract development and manufacturing organizations and now also suppliers.

As part of the industrial base expansion, Joyner is leading an effort to increase domestic fill-finish capacity. She said the division expects to undertake more than 20 contracting actions over the next two to six months. Because “it’s a lot of work, a big heavy lift,” she said the agency will rely on the Defense Department’s Joint Program Executive Office, or JPEO, for program management, and on the Army Contracting Command for the contracting work.

The ASPR IBx onshoring consortium initiative will build on the previous efforts to improve the availability of essential medicines, including the Trump administration’s potentially \$812m award in May 2020 to Richmond, VA, startup Phlow Corp. for near-term essential medicines procurement and long-term domestic API manufacturing and storage capacity.

News of the award to Phlow, which lacked any manufacturing capacity of its own, discomfited companies that had been manufacturing drugs in the US but had not been approached about the opportunity.

Now they are being approached; the only question is who will answer the call?

Voluntary Limits On Antibacterial Discharges Increase As Fear Of Resistance Grows

Pharmaceutical companies are ratcheting up voluntary efforts to control discharges of antimicrobials from their plants and those of their active pharmaceutical ingredient suppliers so they won’t contribute to antimicrobial resistance. But will it be enough to fend off regulation in countries like India?



BY SHANNON BROWN, REPORTER, US

Pharmaceutical companies are putting more limits on the environmental release of their antibacterial ingredients in liquid waste discharges, the non-profit Access to Medicine Foundation says in an 18 November report.

However, a “huge gap remains” in ensuring standards apply to third-party active pharmaceutical ingredient suppliers, notes the foundation, which is based in Amsterdam, the Netherlands.

The Antimicrobial Resistance Benchmark Report details trends in action against AMR in 17 key pharmaceutical companies and generics manufacturers. It has been published yearly since 2018, and in 2021 removed small- and medium-sized enterprises to focus instead on large organizations.

Among other findings, the report states that more companies are now setting and enforcing limits at their own sites and requiring suppliers to limit the level of antibacterials in their manufacturing wastewaters (*see Exhibit 1*).

The heightened action comes as AMR receives more attention worldwide, including at the 2016 World Economic Forum and this past June’s G7 summit, and may signal industry’s acknowledgement of the topic’s urgency.

The companies are hoping to avoid imposition of regulatory standards by committing to voluntary standards as part of an AMR Industry Alliance initiative, Suzanne Wolf, director of communications at Access to Medicine Foundation, told the *In Vivo*.

A group of biopharmaceutical, biotechnology, diagnostic and generics companies and some industry associations formed the AMR Industry Alliance after signing an industry declaration on AMR at the 2016 World Economic Forum.

What The Report Found

Typically, solid waste from pharmaceutical manufacturing is sent for incineration or to a landfill, but liquid waste is discharged into environments such as rivers, where APIs can cause bacteria to gain new forms of resistance.

Although the topic of antimicrobial resistance is growing in importance, control of antibacterials in manufacturing waste relies on self-regulation and self-reporting.

The AMR Industry Alliance has guidelines that members can implement on a voluntary basis, which were the standards used in the report, said Martijn van Gerven, a researcher at the Access to Medicine Foundation.

For the benchmark report, the foundation asked the 17 companies to disclose the number of sites they and their suppliers use to manufacture antibacterial APIs and drug products, as well as their environmental practices regarding AMR.

Fifteen companies provided data about their own sites, and 12 also provided information about their suppliers' sites, for a total of 187 directly operated sites (93 brand pharmaceutical companies and 94 generics) and 870 third-party sites.

Some key findings of the report were:

- Twelve of 17 companies apply the voluntary targets laid out by the AMR Industry Alliance;
- At the 187 directly operated sites, two thirds of large research-based companies report compliance at their own sites, while just over one third of generics manufacturers report compliance at their sites;
- Ten of 17 companies now require suppliers to limit the level of antibacterials present in manufacturing wastewaters, an increase from 2018, when only three of 13 companies required this;
- Nine companies in scope actively monitor wastewater antibacterial levels, and request and review per-site discharge levels from third-party suppliers;
- However, only one-fifth of supplier sites actually measure discharge levels; and
- Only 5.2% (45 of 870) of third-party sites were reported as compliant with set limits (see Exhibit 2).

“Setting limits only works if companies are tracking and reporting on compliance with these limits,” the report comments. “It is good news that some pharma companies are now working with their suppliers to improve standards, and that now provides the opportunity to push the remaining 95% of the sites to not only set limits, but to actively monitor and report on compliance,” it continues.

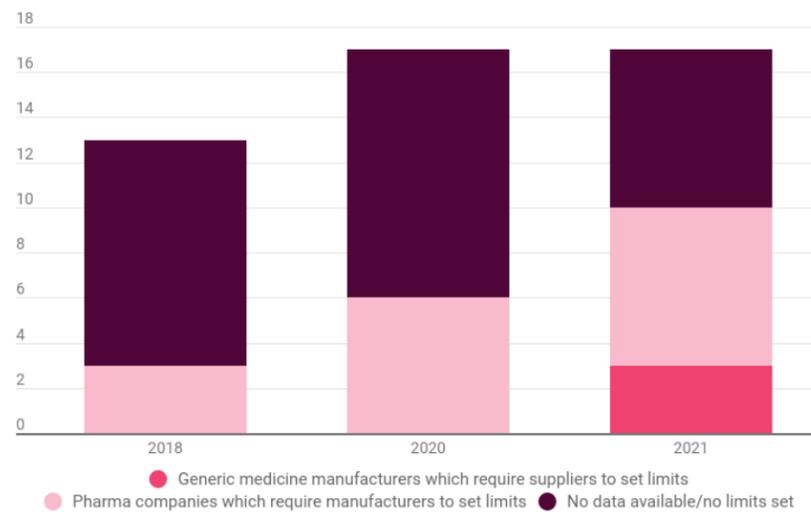
Who's Doing Well, Who's Not

Research-based manufacturers performed well in the benchmarking study. GlaxoSmithKline Pharmaceuticals Ltd. reported that 37 of 39 suppliers' sites are now compliant with set limits, while Shionogi & Co. Ltd. recently announced publicly which of its own sites and suppliers' sites are compliant within limits.

Other leaders included Novartis AG, Johnson & Johnson, and Pfizer Inc., who all reported that they quantify discharge levels against set limits at their own sites, and that they ask their suppliers to set limits and report discharge levels.

Some generics firms also performed well. Aurobindo Pharma Limited was the overall leader, with a risk management

Exhibit 1: Companies That Require Suppliers To Set Discharge Limits



Source: Antimicrobial Resistance Benchmark Report

strategy that involves not just setting limits but also tracking and reporting compliance, both for its own sites and those of its two reported third-party suppliers. Abbott Laboratories Ltd reported having set enforceable contractual provisions related to environmental standards. Abbott introduced a new contract template for API and drug product suppliers requiring them to meet certain antimicrobial environmental standards. Viatrix Inc. requires its zero liquid discharge sites to test recycled waters for antibacterials, and found none.

Cipla Limited's performance dropped on some measures, but it has continued to perform well in stewardship. It sets and checks compliance with discharge limits at some sites and plans to do so for all of its sites by 2022, while extending antibiotics wastewater standards to its API suppliers by March 2022.

Two generics firms trailed the others significantly. The report said Hainan Hailing and Alkem Laboratories Ltd did not share the data required to evaluate their commitment to limiting antibacterials in wastewater.

How Levels Are Quantified

Rather than measuring antibacterial levels in wastewater, most companies use the mass balance approach, which consists of estimating how much of the antibacterial ingredient will end up in waste and how much is removed by on-site treatment. They also may apply dilution factors to account for water flows from treatment plants and rivers, if applicable.

Nine of the 17 companies reported that mass balance calculations were verified by wastewater sampling and chemical analysis, but only when deemed necessary.

Wolf stated that it was not within the report's scope to compare techniques for removing bacterial waste, but that there were pluses and minuses to each method.

For example, incineration of antibacterial waste is great from an AMR perspective but has implications for other emissions such as CO2, she explained.

According to the organization's research, the following methods are generally used, Wolf stated:

For liquid waste, companies mainly apply granular activated carbon filters, membrane filtration, ozone, Fenton's reagent, chlorination, pH treatment and thermal or alkaline hydrolysis.

For solid/sludge waste, companies mainly apply incineration, activated sludge and landfilling. “We do see that companies steer away from landfilling any hazardous waste,” she noted.

Many companies also apply zero liquid discharge (ZLD) systems.

However, Wolf said that some research has questioned the effectiveness of the zero liquid discharge method.

She pointed to a study by the non-profit Changing Markets Foundation, which found extensive antibacterial discharge in Hyderabad, India, despite 40% of pharmaceutical manufacturers in the area claiming to use ZLD technology.

When asked why waste management technology wasn't more widely used by suppliers, van Gerven said cost was likely a barrier.

“Another reason, from our perspective, is that no one is asking them to. We really want companies to ask them. And I think that's where we can start,” he said.

Antimicrobial Resistance Is 'Pandemic In The Making'

AMR is a slower-moving pandemic compared with COVID-19, but still very much a pandemic in the making, said Fatema Rafiqi, a research program manager at Access to Medicine.

Efforts to develop more effective treatments have been hampered by the fact that antibiotics are expensive to develop,

generally requiring around \$1bn per drug, but they then rapidly lose their effectiveness as resistance develops. The drugs therefore cannot stay on the market long enough to be profitable, driving many small- and medium-sized firms bankrupt, said Rafiqi.

Some incentives have been developed, including a subscription model by the UK's National Health Service, in which the NHS pays up front for access to antibiotic medicines.

A similar measure, the PASTEUR Act, has been proposed in the US by Sens. Michael Bennet, D-CO, and Todd Young, R-IN, and Reps. Mike Doyle, D-PA, and Drew Ferguson, R-GA.

In the US model, drug developers can apply for “critical need antimicrobial” designations and receive subscription contracts featuring annual payments once the drugs are approved. The value of the contract will be determined based on the number and value of the favorable characteristics the drug meets upon approval.

Additionally, in 2019, 23 pharmaceutical companies, the World Health Organization, the EU's European Investment Bank, and the Wellcome Trust joined together to invest up to \$1bn in novel, mid-stage antibiotic candidates as a temporary measure to fund development in the area.

Is Self-Regulation Enough?

The report notes that there has been “clear movement in the right direction over the last few years as pharma companies increasingly report setting and adhering to limits at their own sites,” but that companies must now ensure limits are also set at supplier sites.

This is a particularly important goal since so many third-party sites are involved in the supply chain—including 82% of sites covered in the report.

There has been some effort to impose governmental standards.

In India, the Indian Ministry of Environment, Forest and Climate Change in January 2020 announced stringent standards on the concentration of antibiotic waste discharged by pharmaceutical manufacturers.

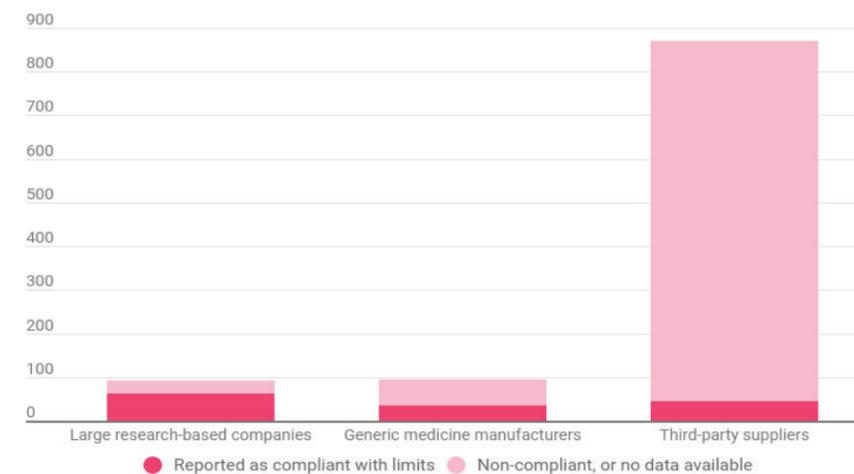
However, the proposed regulation was later dropped from the final rules after pushback from the Indian Drug Manufacturers Association.

The benchmark report offered comments as to what could come next from industry.

Pharma companies should set limits and ensure compliance “via supply contracts and quality agreements, and companies should enforce those agreements when limits are exceeded,” the report said.

Doing so would result in fewer antibacterials being discharged into the environment—“which would be significant progress in the fight against rising antimicrobial resistance,” it concluded.

Exhibit 2: Number Of Manufacturing Sites Reported As Compliant With Discharge Limits (2021)



Source: Antimicrobial Resistance Benchmark Report

MEETING THE
EVOLVING NEEDS OF
BIOPHARMACEUTICAL
MANUFACTURING
THROUGH SCIENTIFIC
EXPERTISE



Rentschler Biopharma is a leading global Contract Development and Manufacturing Organization (CDMO), focused exclusively on client projects. From our headquarters in Laupheim, Germany, and our site in Milford, MA, USA, we offer end-to-end solutions including biopharmaceutical process development and manufacturing as well as related consulting activities such as project management and regulatory support. In Stevenage, UK, we have launched Rentschler ATMP Ltd. dedicated to cell and gene therapies. Thanks to our 50 years of proven scientific expertise in biotechnology and our passion for what we do, we count ourselves among the leaders in the industry and make an essential contribution to the global availability of biopharmaceuticals.

With Rentschler Biopharma, you are in expert hands.

WWW.RENTSCHLER-BIOPHARMA.COM



**YOUR WORLD-CLASS
BIOPHARMACEUTICAL CDMO**

- Experts in bioprocess development and manufacturing
- Family-owned company, globally thinking and focusing exclusively on our clients' projects
- Biopharma pioneer with commitment to advanced technology and innovation leadership
- Extensive track record, almost 50 years of experience and quality made in Germany

YOUR TRUSTED PARTNER FROM CONCEPT TO MARKET

WWW.RENTSCHLER-BIOPHARMA.COM





BY **BARNABY PICKERING**,
REPORTER, EUROPE

Point Of Care Diagnostics In 2022: New Technology But Old Problems

Following a busy year for point of care diagnostics, the industry is facing a period of consolidation. The drive for new technologies is being countered by regulatory and financial issues.

A turbulent year for point of care (PoC) diagnostics, 2021 transformed the industry in the minds of many.

At the heart of this change is a trend towards empowerment. What was once associated primarily with the doctor’s office or emergency wards has now permeated into the home, with vast numbers of people taking rapid at-home COVID-19 lateral flow tests every day.

This permeation has had deep, and what will likely be long-lasting, effects on both the PoC diagnostics market, and society.

Never before have patients been able to test for transmissible disease so easily, and never have patients been so strongly pressured by the social contract to adhere to new rules – all thanks to little plastic testing kits that have been doled out by the millions.

These COVID-19 tests have been a cash-cow

for the point of care diagnostics industry this year, and the resulting revenues have brought renewed attention to the sector from patients, regulators, innovators and investors.

The result has been a merry-go-round of investment, promises, further investment and further promises. Claims have been repeatedly made stating that decades of development have occurred in a matter of months, and until recently evidence of this was sparse.

However, as the industry faces pressure to reapply COVID-19-resultant infrastructure and the financial gains made in the past year to new disease areas, an increasing number innovative companies are revealing new products and technologies to the world. All this builds up the idea that 2022 could be the most exciting yet for point of care diagnostics, as the transformation brought about by COVID is continued.

Out Of Sector Influence

A prime example of a company offering disruptive point of care technology is MeMed. The Israel-based company, which previously received funding from the US Department of Defense, has developed the first US FDA approved test that can differentiate viral and bacterial infections in patients.

The test, called MeMed BV, runs in minutes, and, according to the company’s chief technology officer Kfir Omed, serves as an “accurate and actionable diagnostic” for physicians to begin to tackle the problem of antimicrobial resistance. Something the World Health Organization has described as “one of the biggest threats to global health.”

“One of the biggest challenges facing physicians when not prescribing antibiotics is actually the demands of a patient,” explained Omed. “The patient wants their doctor to do something – just telling them [their illness] is viral is not convincing enough. MeMed BV can show patients in an objective manner that it’s viral. This really empowers physicians to convince patients not to consume antibiotics.”

What makes MeMed’s technology so disruptive is not just its diagnostic capability, but its potential to influencing sectors outside of diagnostics in a way that has not been done so before.

Diagnostics are usually used by a clinician to work out what care path is needed for a patient. This could be surgery or medication, but for the most part, diagnostics indicate further treatment.

MeMed’s BV test is the opposite to this. Its goal is to reduce prescriptions of antibiotics. Given that the US Centers for Disease Control and Prevention claims that 30% of antibiotic prescriptions are unnecessary, should MeMed BV reach the doctor’s office, pharmaceutical companies might see antibiotic revenues dip due to declining sales.

Equally, it is fair to assume that in those 30% of cases where antibiotics are mis-prescribed, some will be viral. By increasing the ability to monitor the spread of viral infections, and actually count the number of patients who suffer them – something that has not been done routinely in the past – demand for effective anti-viral treatments for common colds and flu might be actualized. It is possible that MeMed BV will not just disrupt the antibiotics market, but shift pharma’s focus towards otherwise treatable viral infections.

Lab Grade Tech In The Doctor’s Office

As health care providers, payers, patients and regulators all push for a more “casual” form of health care, where more can be done near to or at the patient’s home, the demand for testing technologies that have not previously been available has soared.

An extreme example of this is genomic testing. The Human Genome Project which commenced in 1990 took 13 years to complete and cost \$2.7bn. Although it did not sequence just one single human genome, the project is viewed as a solid benchmark of the historical price of such technology.

17 years later, James Watson, one of the pioneers of DNA studies, was the first person to have their genome sequenced for less than \$1m. Since then the cost of sequencing a genome has been exhibiting a Moore’s Law-like trend where the cost has been plummeting. It is now possible to sequence a human genome for less than \$500, making it almost affordable for mass use.

Mass genome sequencing would have significant positive impacts on people’s day-to-day lives, argues David Atkins, CEO of Congenica – a UK-based company developing rapid genome analysis tools.

Congenica works primarily with the UK’s National Health Service to screen patients for rare diseases, but the company is looking to develop analysis tools for simpler diseases going forward.

The definition of “rare,” however, is surprising.

“1 in 17 of all newborns has a rare disease, and there are currently 8,000 rare diseases, a number which is growing all the time. The estimate for the number of undiagnosed rare disease patients is massive,” said Atkins.

And for each of these 1 in 17, there are mothers, fathers, siblings, teachers and a whole plethora of other people impacted. The time taken to diagnose a rare disease in the UK – often known as the “diagnostic odyssey” – is far too long, with some of Congenica’s case study patients waiting almost a decade for diagnosis. Atkins described this issue as a “costly error that is messing up the health care system.”

With the price of genome sequencing and then subsequent analysis due to “drop precipitously with new technological entrants,” Atkins believes that there is potential for genomic screening to reach the doctor’s office in the conceivable future.



Source: MeMed

“I can certainly see genomics being used at the point of care level, where a patient sees their physician,” said Atkins. “We’ll get to the point where you only need your genome sequenced once [which still takes several days] and then you can create a portable summary of your genome or attach it to your medical records.”

This, Atkins said, would not only be useful for diagnosing rare diseases in children, but be useful for general practitioners seeing adult patients. Because genomic differences affect drug sensitivities, analysis of a patient’s genome could allow for personalized medicine to be delivered on a patient-by-patient basis, where the optimal dose of the optimal drug is given correctly nearly every single time.

An extreme example Atkins highlighted was a patient Congenica saw through the NHS. “There was a young lady in her twenties, and she had almost complete coverage of psoriasis. One of our clinical team identified that she had a mutation in a gene that encodes an enzyme that just makes an amino acid.”

He continued: “Her condition was totally diet-related, and with a food supplement, her psoriasis went down to about 5% – making it very manageable. It transformed her life, and she could re-enter the workforce. Not all cases are as simple as that, but genome analysis can allow for doctors to identify the underlying cause of a problem, rather than just manage the symptoms.”

Industry Impactors

Whilst innovative technology is serving to drive the PoC diagnostics market, other factors, both regulatory and corporate, are looming on the horizon, threatening to limit its growth.

A prime example is the new In Vitro Diagnostics Regulation (IVDr) in Europe, which has been blighted by a seemingly never-ending series of issues.

Stalling, lack of agreement regarding notified bodies, general administrative incompetence and foot stomping by the poorer nations in Europe has meant that by the time the 26 May 2022 deadline rolls by, at best only 61% of IVDs currently sold in Europe will be certified.

A worst-case scenario could, in fact, cripple the industry with a MedTech Europe survey finding that potentially only 24% of IVDs will be certified in time.

In response to this, the European Commission has backtracked slightly, and whilst IVDr will still fully apply on 26 May 2022, a tiered system with prolonged transition periods has been created to allow many products more time to be certified before being withdrawn from the market.

Fundamentally though, if the European Commission does not prioritize certification of IVDs, innovators in the industry will likely move elsewhere. Europe faces a slowdown in development of a range of point of care IVDs covering coagulation, glucose monitoring, cardiac testing, pregnancy and infectious disease.

Money, Money, Money

Much like every other industry worldwide, supply chain, personnel and structural issues are affecting the PoC diagnostics market.

A recent survey of diagnostics companies – both imaging and in vitro – ran by Simon Kucher, found that 80% of internal barriers facing diagnostics companies are related to organizational structure, resources and simple lack of staffing.

Gerald Schnell, senior partner in Simon Kucher’s life sciences division, highlighted pricing as the core underlying issue impacting diagnostics. He noted that poor pricing strategies prevent companies having the money to combat the issues they face.

“If you look towards pharma, you’ll see that pricing is one of their most important commercial pillars,” Schnell said. “A pharma company will have pricing managers at all levels. However, in diagnostics, even larger companies do not have pricing managers – there just aren’t the resources.”

Michael Keller, partner elect in Simon Kucher’s global medical technology practice elaborated

further. “The IVD industry is complaining – internally for the most part – about eroding prices. 70% of health care decisions are based on diagnostics, but diagnostics only receive about 2% of the budget. Diagnostics [companies] feel like they don’t get what they deserve,” he said.

“In the eyes of the payer though, it’s still the pill, the pharmacological treatment that makes the impact,” he said. Adding that the pharma industry has mastered value-based pricing detached from the base product. The diagnostics industry is struggling to follow suit. Payers in this space are not used to evaluating the “value” of an innovative biomarker and what it can bring to the health care system. They often fall back and – worst case – relate diagnostics to the “the cost of putting a couple of liquids together.”

Schnell agreed. “I think the [diagnostics] industry totally underestimates its pricing power. They are in a comfortable position where they can always differentiate their offer with various reagents, equipment, technical services and digital solutions.”

“It is this that will be top on the radar for companies in the next year,” Schnell said.

“A pharma company will have pricing managers at all levels. However, in diagnostics, even larger companies do not have pricing managers – there just aren’t the resources.”

Gerald Schnell, Simon Kucher

Big Cardio Medtechs Are Moving ESG Agenda To Center Stage In 2022



In Vivo outlines major trends shaping the top 15 cardiovascular device companies included in the latest Medtech 100 rankings. They include a growing need to reach underserved patient populations, ongoing staffing and other challenges created by the COVID-19 pandemic, and reimbursement obstacles.



BY REED MILLER, MANAGER, US COMMERCIAL AND R&D, US

The top 15 cardiovascular device makers included in the most recent Medtech 100 rankings are on track to return to their pre-pandemic growth rates and strategies by the end of 2022, but COVID-19 has had a lasting impact on the industry.

The pandemic has highlighted persistent structural inequalities in the health care system, especially in the US, and the large medtech companies see an opportunity to lead their industry’s efforts to address these problems.

“This past year-and-a-half brought global challenges that tested each of us in new ways, highlighting how important good health is to the foundation of our global society,” Medtronic president and CEO Geoff Martha said during a 13 October 2021 investor meeting to discuss its environmental, social, and governance (ESG) initiatives.

Medtronic – the biggest medtech company overall and biggest cardiovascular device company – recently announced a series of ESG goals, with aggressive targets for diversity and inclusion, as well as environmental-impact targets.

The company maintains that it must be a global leader in these areas to recruit the best talent. “Our employee [satisfaction] scores remain high despite all the burnout and everything affecting employees [during the pandemic],” Martha said during Medtronic’s sales and earnings call on 23 November. “We’re getting

“Traditionally clinical trials, especially in the medical device space, have selected sites in high volume locations, not necessarily reflecting communities of color.”

Laura Mauri, Medtronic

attractive talent like never before – we’ve had a 50% spike in people applying for jobs at Medtronic.”

While it tries to promote diversity and inclusion within its own organization, Medtronic is also trying to diversify the population who benefit from its technology by reaching out to historically underserved groups. “Traditionally, clinical trials, especially in the medical device space, have selected sites in high volume locations, not necessarily reflecting communities of color,” Laura Mauri, Medtronic’s chief clinical and regulatory officer, said during the 13 October meeting.

Martha added, “Every single [physician and health administrator] wants to talk about health disparities and how we can partner [to reduce them].” He cited heart failure, hypertension and diabetes as the three most common chronic diseases that impact people of color disproportionately.

“We want to have a longer-term impact on global health. This is about sustainability.”

Nick West, Abbott

Expanding access to clinical trials is also a priority for Abbott, the number two company on the Medtech 100 list of biggest cardiovascular device makers.

Abbott recently announced a series of clinical trial diversity initiatives, including the creation of the Diversity in Research Medical Advisory Board. The company also plans to fund about 300 scholarships to encourage more physicians and nurses to specialize in clinical research in underserved communities. These diversification initiatives are part of Abbott’s overall long-term strategy to extend the benefits of medical innovations to more people worldwide.

Abbott currently serves two billion people worldwide, but it plans to serve three billion by 2030, Nick West, chief medical officer for Abbott’s vascular business, told In Vivo. “We want to have a longer-term impact on global health. This is about sustainability.”

COVID-19 Is Still With Us

The dominant theme for all medtech companies in 2021 was “recovery.” Demand for almost every type of medical procedure – aside from care of COVID-19 patients – dropped dramatically in the middle of 2020 as hospitals and clinics focused most of their resources on mitigating the pandemic.

Sales of cardiovascular devices have since rebounded and most cardiovascular device sectors are growing. However, the emergence of the “Delta variant” and widespread hospital staffing shortages have forced cardiovascular device companies to temper their previously aggressive growth expectations for the end of 2021 and early 2022.

Boston Scientific, the third biggest cardio device company included in the Medtech 100 table, announced on 27



October that its third-quarter 2021 sales missed its previous projections. The company attributed the disappointing result to a recent decline in procedure volumes.

“July was pretty good, and then we saw a slowdown in August and September,” CEO Michael Mahoney said.

In a 22 November 2021 report, Credit Suisse reported that the US’ surgical capacity was standing at almost 94%, representing a 6% improvement over the prior eight weeks, but COVID-19 hospitalization had crept up in the preceding month.

The biggest threat to the recovery in procedure volumes are acute staffing shortages at many hospitals, especially in the US. “The hospitals do hustle, and they figure out ways to get things done, but it does create a bit of a headwind,” Boston Scientific’s Mahoney said.

But the CEO believes these challenges will not stop the overall trend toward recovery and procedure-volume growth in 2022. “We think COVID impacts will be less in 2022 than in 2021 based on the vaccination rates and the improvement in Asia, Europe, and hopefully the US as well,” he said.

Edwards Lifesciences, the leader of the transcatheter aortic valve replacement (TAVR) market and the fourth biggest cardiovascular device company, reported that some hospitals were postponing valve-replacement procedures because of staffing shortages. Still the company expects TAVR sales to grow about 20% in 2021.

The company is cautiously optimistic that TAVR procedure volumes will be “normalized” in 2022, Edwards’ chief financial officer Scott Ullem said. “If COVID is playing a more meaningful role in certain regions or there are hotspots that are more noticeable, then that’s going to impact our growth overall,” Ullem said. “That’s probably the biggest uncertainty that we have going into 2022, [but] overall we feel really positive about the growth prospects for TAVR in the US, in Europe, in Japan, and then the rest of the world.”

Abiomed, the number 10 cardiovascular company in the Medtech 100, has also found that staffing shortages remain a major challenge at many hospitals in the US.

“The staffing shortages are a bit of a challenge – the hospitals do hustle, and they figure out ways to get things done, but it does create a bit of a headwind.”

Michael Mahoney, Boston Scientific

Abiomed markets the Impella line of percutaneous blood pumps for multiple indications, including circulatory support during high-risk cardiovascular interventions. The company adapted its sales and service strategy to accommodate the COVID-related restrictions in hospitals and recovered rapidly from the worst days of the pandemic in 2020.

However, that recovery has slowed down since the emergence of the Delta variant of COVID-19. “In Q2, the shortage of hospital staff, especially nursing, was a new dynamic that we had not experienced during the COVID pandemic,” Abiomed CEO Michael Minogue said on 28 October. “Overall, hospitals today are managing the treatment of the pandemic better, but Impella usage in the cath lab is still impacted by ICU-capacity limitations. Hospital staffing shortages in the US caused some health systems to reduce cardiac procedures or temporarily close facilities.”

Abiomed reported that the staffing problems are concentrated in about a quarter of the hospitals that use Impella and will likely be resolved soon. “Despite these headwinds faced within the quarter, the majority of US regions remained resilient and recorded growth,” Minogue said.

Will Connectivity Be Hindered By Reimbursement?

The cardiovascular monitoring industry has been rapidly consolidating over the past year with a series of major acquisitions, including Boston Scientific’s \$1.25bn deal for Preventice, Connect America’s merger with 100Plus and Philips’ acquisitions of Cardiologs, BioTelemetry, and Capsule Technologies.

Advances in artificial intelligence, sensor technology and digital communications infrastructure could dramatically change how cardiologists and patients detect and manage cardiovascular disease in the future, but the pace of this progress will depend largely on the support of third-party payers.

iRhythm Technology, a recent entry in the Top 100, is an example of a company that is working around the constraints of public reimbursement for new technologies. The San Francisco-based company markets the Zio XT 14-day electrocardiogram monitoring and diagnostics system and is part of a consortium of device companies and cardiology groups trying to secure national Medicare pricing for its long-term remote monitoring.

Currently, iRhythm depends heavily on one regional Medicare carrier, Novitas, which drastically cut its payment rate for continuous long-term continuous electrocardiogram earlier this year. The cut was so drastic that the company briefly considered discontinuing sales to Medicare beneficiaries before eventually agreeing to continue providing Zio XT to those patients while it tries to work out a better deal with Novitas.

Despite the reimbursement challenges and hospital-staffing shortages, iRhythm is growing 20% annually as more and more cardiologists adopt Zio XT to diagnose cardiac arrhythmias. “We have the opportunity to continue to capture more share, grow the overall market, and expand our addressable market,” iRhythm CEO Quentin Blackford said during a 4 November 2021 sales and earnings call.

The Lasting Impact Of The Pandemic On Pharmacovigilance

Despite the critical importance of pharmacovigilance (PV) activities, two years ago it was a concept with which most people outside the life sciences space were largely unfamiliar. Since the onset of the COVID-19 pandemic, however, this has changed immensely. Drug safety has become a topic frequently featured in mainstream media coverage, increasing public awareness substantially.



Along with bringing pharmacovigilance to the front of public consciousness, COVID-19 has had a significant impact on the way these activities are conducted. Annette Williams, vice president and global head of lifecycle safety at IQVIA, witnessed this first-hand. “There was complete disruption to the drug development ecosystem in the early stages of the

pandemic. As in-person activities were no longer possible, the industry witnessed clinical trials being halted and delayed, and similar difficulties arose in pharmacovigilance.”

Despite the challenge of having to adapt rapidly, there have been positive consequences for pharmacovigilance, in the form of automation initiatives, adoption and streamlined processes that can be carried forward well beyond the pandemic for adverse event (AE) reporting.

A New Era Of Adverse Event Reporting

The task of inoculating the global population, along with the speed at which manufacturers were able to mass-produce vaccines, meant that the potential scale of data resulting from AE reporting was well beyond anything the pharmacovigilance sector had previously experienced. “We very quickly realized that historical vaccine AE rate models simply did not apply to the COVID-19 situation. Working collaboratively with our vaccine manufacturer partners, IQVIA conducted significant analysis in the early days of the vaccination rollouts to build forecasts and refine AE modelling as vaccination data became available in real time,” Williams states.

These predictions have materialized in 2021, Williams continues, “We have looked at the number of AEs being

reported to the European Medicines Agency (EMA) in totality and expect a 50% increase in their total annual volume by the end of the year. While adverse events associated with the COVID vaccines is relatively small, one has to consider the actual total size of the universe of patients inoculated this year, which has led to this large increase in total number of cases processed in 2021. Even though it’s a very small subset of patients that might experience an AE, it’s a large amount of information to process and analyze.”

Traditionally, most AE reports are reported by patients and health care professionals to the manufacturers initially, who would then relay this information to regulators. Regulators anticipated that there would be a need to change the way they received AE information for the COVID vaccines, so they could assess the emerging safety data in near real-time, and ultimately enable them to take quick action should that have been necessary. For example, the UK Medicines and Healthcare products Regulatory Agency (MHRA) invested in artificial intelligence (AI) to update their Yellow Card scheme: the UK’s system for collecting and monitoring safety concerns through voluntary reporting, including possible side effects or AEs. This use of technology made it easier for patients and health care professionals to provide such information associated with vaccine administration directly to the UK agency.

In the US, the Centers for Disease Control and Prevention (CDC) implemented the v-safe tool. This allowed patients to opt in for personalized follow-ups following their COVID-19 vaccination, along with giving them the ability to report side effects should they have been experienced. While the extent to which the public adopts these programs long-term remains to be seen, now that the technology is in place, it offers the potential for wider application to medication reporting not related to the pandemic.

The outcome of this reporting paradigm shift for companies, like IQVIA, resulted in a data flow flip (now from regulators to industry), and companies had to be prepared to accept large volumes of information almost immediately. This required effective, connected systems and processes capable of managing significant amounts of information within the necessary timeframes. All of this was critical to reassure the public of the efficacy and safety of the vaccines.

As the acceptance by the public to proactively report adverse events grows, there is also a desire to simplify the process for reporting as much as possible. Williams predicts that “there is potential for further consolidation of how people report AEs versus the myriad of ways that currently exist.” Doing so lowers barriers to patients’ involvement in the reporting cycle, ultimately providing manufacturers and regulators with increased drug safety data.

Digital Disruption Here To Stay

While there were, of course, challenges in processing AE data, those working in PV stepped up to maintain safety standards. COVID-19 has been a catalyst for implementing exciting innovation that has been in the cards for many years but had yet to be fully realized.

IQVIA seized this opportunity, implementing technology such as AI to support automated AE report intake and retrieval, and robotic process automation (RPA) bots to support automated case processing. Auto-translation tools have also been indispensable for the management of non-English AE cases which need to be handled with as much speed as those coming from other regions.

The implementation of AI bodes extremely well for the future, as its benefits transcend the reporting of COVID-19 vaccine-related AEs. “We’ve additionally employed AI-enabled virtual agents to support medical information queries, which has helped enormously when we were experiencing very high call volumes,” Williams notes. “In the longer term, this is allowing us to enhance the customer experience, by having improved out of hours coverage, but we also found that 15–25% of live calls that humans used to answer can be fielded by these virtual agents. Removing this workload allows human experts to focus on more complex queries.”

As confidence in AI grows and it is applied to more PV tasks, staff can turn increased attention to oversight and management of the safety data generated.

AI and automation have created significant strategic opportunities for IQVIA and their clients. Williams says, “For one client alone, we developed and implemented more than a dozen different instances of automation to streamline their end-to-end case handling process. By looking at how this innovation can apply across the wider safety landscape, we are future-proofing our organization.”

The Evolving Role Of Humans In Pharmacovigilance

As AI utilization grows, so does the need for skilled staffing. “In less than six months, we doubled the number of staff in our organization. While it was immediately clear that AI and automation were going to feature prominently in our COVID plan, we still needed to ramp up our team numbers because the amount of work was enormous and could not be completed by technology alone,” says Williams. Remote working capabilities meant that the pool of candidates for these roles was expanded, as companies like IQVIA could focus on hiring wherever the talent was, without being limited to those within a certain proximity to offices.

Nonetheless, it was and still is pivotal to meet the urgent need for human resources without compromising on the quality of onboarding. While training was accelerated for those joining IQVIA, an onboarding compliance database was built to proactively monitor the progress of new hires and intervene early if they seemed to be struggling. Moreover, Williams notes, “Because we’re talking about patient safety, it is key that we can monitor and measure their knowledge uptake to ensure that patients continue to have confidence in our industry and the safety of medications.”

Improving Patient Prospects Beyond COVID-19

COVID-19 has disrupted pharmacovigilance like nothing before it, fundamentally changing the role of people, processes, and technology. However, despite the great challenges the industry has had to contend with, Williams is proud to say that everyone came together to ensure safety standards were maintained. “First and foremost, patient safety was never sacrificed. There was no relaxation of standards by regulatory agencies, and our reporting clocks for AEs did not change. We remained laser-focused on quality and compliance because we needed to maintain the confidence of the public.”

“There is potential for further consolidation of how people report AEs versus the myriad of ways that currently exist.”

Annette Williams, IQVIA

Instead, the industry’s rapid implementation of new frameworks and technologies is what allowed compliance and safety to be upheld. Williams notes that COVID-19 forced many industries to bring forward their planned tech investments for 2025 into 2020 and 2021, leading to pharmacovigilance processes and infrastructure that is robust and is future proof.

Finally, the industry will be forever changed by the new surge in public interest in drug safety. While there are still challenges surrounding misinformation spreading via word of mouth and on social media platforms, overall patients have a deeper understanding of the importance of providing feedback when taking medication or receiving vaccines. When combined with more accessible reporting systems, quicker AI-enabled processes, and more staff to deal with complex queries, there is great potential to further engage patients in the pharmacovigilance process well beyond COVID.

Operation Warp Speed: What The Logo Can Tell Us About Successful Pandemic Preparedness

Operation Warp Speed’s seal was a combination of ’70s design, au courant clip art, and 18th Century militarism, but just like the oddly assembled organization that it represented, the thing worked.



BY NIELSON HOBBS,
EXECUTIVE EDITOR,
US

Operation Warp Speed has not been called “Operation Warp Speed” since the beginning of the Biden administration, but as the one-year anniversary of the authorization of the first COVID-19 vaccine passes by, *In Vivo* is reflecting on what is widely considered the most effective aspect of the US government’s pandemic response.

Launched by the Trump administration as an effort to collaborate with private industry to develop vaccines, diagnostics and therapeutics in record time, Operation Warp Speed exceeded everyone’s expectations except their own it seems. OWS’ description of its mission was to “deliver 300 million doses of safe and effective vaccine by 1 January 2021.”

They got close – shots were going in arms by December, though there was not widespread availability of vaccine until the spring – but the perception that the Trump administration had fumbled the initial distribution was among the reasons that the Biden administration opted to change the name from Operation Warp Speed, along with a desire to move away from their opponent’s slogans.

The Biden Administration briefly rebranded the program as the Federal COVID-19 Response when it took office in January, and the effort is now called the Countermeasure Acceleration Group.



Neither of the names has the pizzazz of Operation Warp Speed, taken from the term for the propulsion method in Star Trek – the utopian “space Western” franchise about a society where money is obsolete, interspecies romance is no big deal, and yet people still find themselves in life-threatening predicaments before nearly every commercial break.

Credit for the OWS name has gone to Peter Marks, director of the US FDA’s Center for Biologics Evaluation and Research. Speaking at a meeting in November 2021, Marks said, “Contrary to what some people said, I am not a diehard Trekkie, but I did watch my fair share of Star Trek when I was a kid.” CBER had been calling its activities and other regulatory accelerations for vaccine candidates Project Warp Speed, and the term was then applied to the larger effort as that got underway.

As part of the that expansion, the Department of Health and Human Services began sharing responsibly for the effort with the Department of Defense, and it was a DOD staffer who developed the seal of Operation Warp Speed.

The combination of public health officials, Army logicians and pharmaceutical companies produced surprisingly quick triumph.

Operation Warp Speed’s seal was a combination of ’70s design, au courant clip art, and 18th Century militarism, but just like the oddly assembled organization that it represented, the thing worked. The emblem includes aspects of the seal of HHS which dates to its evolution from the Department of Health, Education, and Welfare, a rendering of SARS-CoV-2 itself with the spike proteins accented in red, and five-pointed stars which have been a symbol of American military might since Betsy Ross’ day.

Similarly, the combination of public health officials, Army logicians, and pharmaceutical companies produced surprisingly quick triumph with the three vaccines now available in the US. OWS was so successful, in fact, that FDA has indicated it will

not authorize any more vaccines through its emergency use pathway; there’s no longer a need for that shortcut.

To Boldly Go

And yet the pandemic is far from behind us. After a late-summer lull in 2021, case counts are back on the rise driven by the rapid spread of the Omicron variant. Those 300 million vaccine doses may now be available, but only just over 70% of people five and up have gotten at least one shot. Things have not wrapped up tidily like they tended to at the end of a syndicated TV show.

The divisions within the Republican party are a factor in the less-than-salutary state of affairs. Some argue Trump deserves all the credit for ending the pandemic while the majority of the Republican caucus in the House refuses to say whether they have been vaccinated.

But part of the disappointing denouement for Operation Warp Speed was a function its design itself. Reinventing public health communications did not seem to get the attention that overhauling vaccine discovery did, and the resulting vaccine hesitancy allowed the delta variant to exploit that weakness.

“Heart and minds” seems to have been a military slogan for as long as armies have been unable to win them, but if the government wants to prepare for a stronger pandemic response, that likely needs to be part of its strategy as much as faster vaccine creation and manufacturing.

Developing a needle-free, Star Trek-style hypospray would not hurt either.

The Continuing Mission

Chances are, there will not be a “next time” – a global pandemic – for another few decades, but the Biden administration wants to create a system for more rapid response, including the availability of significant manufacturing capacity.

The cycle of panic and neglect that has been familiar with past infectious disease scares does not seem like a good approach, but had the system that the Biden team envisions been in place 15 years ago, the government would have probably been seen as “overreacting” to Zika and Ebola, and mass vaccination fatigue could become as big a challenge as vaccination hesitancy.

That is assuming the government can find willing pharmaceutical partners. Moderna and the US government could end up in court over vaccine patents, a development that threatens to sour future industry-NIH collaborations. And liberal activists continue to pressure the administration to force the company to offer more vaccines to developing countries using the previous development funding as leverage.

The situation seems enough to make any shareholder-minded company hesitant about a future collaboration.

Policy makers should take those concerns to heart and develop new solutions, not focus on the previous glories of the COVID-19 success. Star Trek can offer a cautionary tale here in addition to some appealing terminology. The main series streaming now is a prequel; for a franchise about the future, it is stuck in the past.

Listen Up! Big Things Happening In The World Of Audiology

From innovation to legislation, the US audiology market is being shaped by cutting-edge technology from device makers and legislation from the Biden administration to get more hearing aids to those that need them.



BY BRIAN BOSSETTA, SENIOR WRITER, US

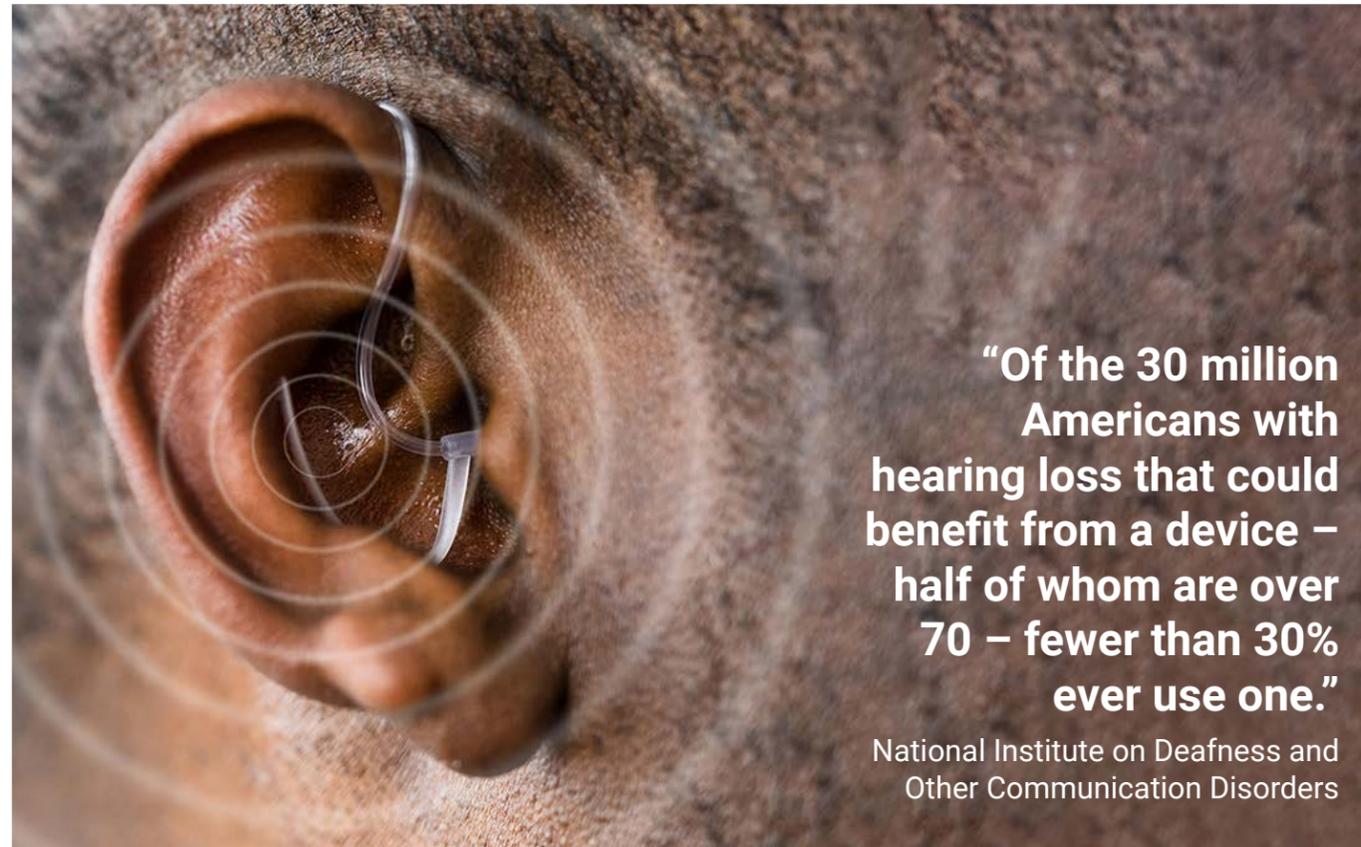
If you have not heard, there has been a lot of noise in the US audiology market lately, from advancements in hearing aid technology to a Biden administration policy allowing the direct sale of some hearing aid devices to consumers without a prescription.

Manufacturers in the audiology device space are capitalizing on artificial intelligence, smartphone apps and the latest audiological science to create hearing aids that are smaller, more user friendly – and, well, simply better than hearing aids of old.

And while all this innovation has improved the hearing for many suffering with hearing loss, it has also improved the bottom lines of manufacturers and distributors who compete in this space. Estimates valued the US audiology market at around \$10bn in 2020, with expectations it will reach \$20bn in the next decade. Globally, the market for hearing aids is on pace to reach \$11bn by 2023, according to a recent report by Meddevicetracker, growing at a compound annual growth rate of 7.4% from its \$7.7bn market value in 2018.

“The hearing-aid manufacturers continue to do amazing work in research and development, which provides the audiologist with sophisticated solutions for their patients.”

Catherine Palmer, American Academy of Audiology



“Of the 30 million Americans with hearing loss that could benefit from a device – half of whom are over 70 – fewer than 30% ever use one.”

National Institute on Deafness and Other Communication Disorders

Tapping into technology to meet this growing demand, hearing-aid manufacturers are becoming more popular with patients and audiologists, both of whom are benefitting from higher quality hearing devices. Because of all these advancements, audiologists are in a better position to satisfy their individual needs of their patients when it comes to improving their hearing.

As Catherine Palmer, president-elect of the American Academy of Audiology and an associate professor at the University of Pittsburgh, told *In Vivo*: “The hearing-aid manufacturers continue to do amazing work in research and development, which provides the audiologist with sophisticated solutions for their patients.” And there are a lot of patients out there.

Scott Longval, president and CEO of medical device manufacturer Intricon, told *In Vivo* his research indicated more than 38 million Americans experience some degree of hearing loss and only 14% of them use a hearing aid. “Based on our research, we estimate approximately 30 million individuals in the US have mild-to-moderate hearing loss,” said Longval, adding that on a global scale the problem is much worse. “Hearing loss is one of the most prevalent health conditions, and it is

the third most common medical condition in the US – more prevalent than both diabetes and cancer.”

Globally, some 466 million people, according to the World Health Organization, suffer from disabling hearing loss, including 34 million children. That number is expected to reach 630 million by 2030 and more than 900 million by 2050. Roughly 72 million people globally could benefit from using hearing aids or cochlear implants. Most people who have hearing loss live in developing countries and are unable to afford hearing aids or do not have access to audiological care.

Sound Competition

Growth in the US audiology market is also being fueled by a rise in those with hearing loss. Aging baby boomers, for example, are providing manufacturers with a steady stream of consumers as is the rise in hearing loss among the general population. Roughly 14% of the US population suffers hearing loss every year, according to John Hopkins Cochlear Center for Hearing and Public Health.

At the same time, companies in the audiology space draw consumers to their brands through solid networks of audiologists and retailers to sell their products.

Some of the leaders in the audiology market include Sonova, which pulled in a massive 31% of the market share in 2018 according to Meddevicetracker, and revenues of nearly \$2.5bn. William Demant Group (24% of the market), WS Audiology (16%), GN Group/GN Store Nord A/S (11%), Starkey Hearing Technologies (8%), are other key impact players in the increasingly competitive field.

Small, But Making Noise

But the big fish are not the only ones making waves. Smaller companies, such as Audicus, Arphi Electronics, Audina Hearing Instruments, Eargo, Horentek Hearing Diagnostics, Microson, Miracle-Ear, Ovation Pharma SARL and Rion all together accounted for somewhere between 1% and 2% of the market – or roughly \$100m to \$150m in hearing-aid revenues.

But as Palmer points out, whether large or small, all the major audiology companies are producing top of the line products featuring the latest technology and innovation. So, what it ultimately comes down to is finding the right type of hearing device for each consumer, which means focusing on lifestyle, work status, income and what that consumer’s goals are in purchasing a hearing aid.

For instance, a retired, home-bound patient might prefer a hearing aid that is simple to operate with less concern over how it might appear when worn, whereas a younger patient working in a professional environment might opt for a more nuanced device that can be operated via an iPhone while remaining undetected when in place.

But above all, sound quality is by far the most important quality any consumer looks for, no matter the type of hearing device. And, of course, reliability.

Most hearing aids today range in their levels of sophistication – from entry-level, standard, high and premium – with premium devices featuring more bells and whistles, such as more bandwidth, which allows audiologists to fine tune the device for a specific wearer and to make it more comfortable and effective all around. And this is where the expertise of an audiologist comes in handy.

While engineers design the devices that manufacturers make and sales reps sell, audiologists are the ones that listen to the patients to pinpoint the right devices for their individual needs.

A prime example of how cutting-edge products are shaping the audiology market is the Eargo 5 from Silicon Valley-based hearing aid manufacturer Eargo, Inc. Designed for mild to moderate hearing impairment, the company offers the device on its website, along with a complimentary digital hearing checkup and the opportunity to speak with a hearing specialist.

After receiving the device, the patient downloads the Eargo app to set up a personalized hearing profile using test tones emitted from the device. This innovative feature allows the patient to find the perfect pitch, and to further customize hearing preferences for different environments, such as when in crowded spaces, outdoors, in meetings or listening to music.

Wells Fargo equity analyst Larry Biegelsen said the Eargo 5 was the most significant launch in the company’s history and would “transform and disrupt” the hearing aid market. The device’s improved output, sound quality, user-friendly pitch adjustments, lithium-ion battery that holds better charge than traditional batteries, and 10% smaller size, and improved water resistance, are some of the features Biegelsen highlighted in his assessment.

The Eargo 5, Biegelsen also noted, breaks new ground in that it is contactless and 100% inductive, a first in the world of hearing aids.

I Can't Hear You

But for many Americans with trouble hearing, all this talk about hearing aid innovation is nothing but background noise. That is because many who need hearing help never do anything about it.

According to the National Institute on Deafness and Other Communication Disorders (NIDCD), of the 30 million Americans with hearing loss that could benefit from a device – half of whom are over 70 – fewer than 30% ever use one.

Several factors play into this. For one, there's stigma often associated with hearing loss, especially for seniors – the “doddering old person” for example – or that hearing impairment equates to a lack of intelligent or makes someone appear less attractive. Of course, none of these is accurate, but nevertheless they often stick.

But the main obstacles are the high cost of hearing devices and the hoops one must jump through – exams, fittings – to get them. Also, hearings aids are not covered under Medicare or most private plans, which means most Americans must pay for them out-of-pocket. And with the average cost of a single device around \$2,400 – and a pair nearly \$5,000 – that's simply out of reach for a lot of people.

However, some of these barriers are about to get knocked down.

OTC Hearing Aid Act Will Disrupt Market

In October, the FDA issued a proposal that would allow for the direct over-the-counter sale of some hearing aids to consumers without a prescription or prior test. This means consumers could walk into their local pharmacy or drugstore – or go online – and pick them up as easily as getting their vitamins.

Though the proposed regulatory category for OTC hearing aids is somewhat restrictive, applying to class 1 hearing aids for those 18 and older with mild to moderate hearing loss and not more complex devices for severe impairment, proponents of the new regulations say they will go a long way in getting more hearing aids to those that need them most, primarily by driving down costs.

“If you look at other regions in the world where they have removed cost as a barrier to entry, such as the UK and Scandinavia, penetration rates are double that of the US,” Longval said. “We're confident that the OTC channel will provide greater convenience, increased value, and easier access.”

Momentum to get hearing aids sold OTC gathered renewed steam in July when President Joe Biden signed an executive order directing the Department of Health and Human Services to come up with a plan to offer the devices directly to consumers.

In a speech after signing his July executive order, President Biden said needing to see a specialist prior to getting a hearing aid not only made it more inconvenient, but more expensive. Biden said direct sale of hearing aids would foster competition and would make them more affordable. The status quo, Biden argued, made it hard for new companies to compete, innovate and sell hearing aids at lower prices. “As a result, a pair of hearing aids can cost thousands of dollars, which is a big reason why only one in seven Americans with hearing loss use a hearing aid.” Biden added that his order would result in

“As a result, a pair of hearing aids can cost thousands of dollars, which is a big reason why only one in seven Americans with hearing loss use a hearing aid.”

President Biden

a pair of hearing aids costing hundreds, not thousands, of dollars.

The initiative for direct sale goes back to 2017 with the Over-the-Counter Hearing Aid Act, which gave the FDA until 2020 to establish guidelines for direct sales of hearing aids. The agency, however, did not meet that timeline and those regulations were never advanced.

But now, with the FDA's draft rule published in October, it looks like advocates that have been pushing to get hearing aids sold directly to consumers will finally get their way. Though not yet finalized, hearing aids could be available at drugstores and retail pharmacies, and online, as early as spring 2022.

The FDA, which is accepting comments on the OTC proposal until 19 January, says the proposal will “promote the hearing health of Americans by lowering barriers to access and fostering innovation in hearing aid technology.”

Longval believes seniors in rural areas, where access to hearing aids – and health care in general – is limited, stand to benefit the most from the new regulations, especially being able to purchase their hearing aids directly online. “Many people in rural areas go untreated or use assistive devices rather than hearing aids,” he said. “The proposed OTC regulation enables greater accessibility, by bringing hearing health care to the consumer's home.”

Whenever consumers are finally able to grab a pair of hearing aids off the shelf, or click on a pair, it is likely to cause major market upheaval, as hearing aid manufacturers rush to fill vacuum by creating hearing devices that fit within the new OTC category.

Longval also feels the new regulations can make difference with the other obstacles to wearing hearing aids, mainly the stigma. “We believe that more people wearing hearing aids will make them more common and inspire others to wear them ... much like glasses.”



BY DERRICK GINGERY, SENIOR WRITER, US

When It Comes To Sponsor Meetings, FDA Is Getting A ‘D’

New “Type D” meetings will be added as part of PDUFA VII, one of a spate of changes under the next version of the user fee program that will begin in October 2022.

Beginning next fall, drug sponsors favorite letter might be “D.” That's the term for the new type of meeting being created to help developers ask clarifying questions after a formal meeting with the US FDA.

The new kind of meeting is one of a number of changes that will be implemented as part of the seventh iteration of the Prescription Drug User Fee Act (PDUFA) that barring some calamity on the way to congressional reauthorization will go into effect on 1 October 2022, the beginning of the federal government's fiscal year.

The FDA's meeting alphabet already includes Type A (helping an otherwise stalled product development program proceed), Type B (end-of-phase meetings) and Type C (none of the above).

Type D meetings – designed to be limited in scope so they can happen faster than Type C and aimed at critical elements of a drug's development – are in keeping with many of

the adjustments to the user fee program that sponsors and the FDA negotiated over the past year. The agency will develop best practices for issues ranging from chemistry controls of investigational products to safety oversight of long-marketed ones through meetings and guidances, but the overall speed of reviews will not change except for one pilot program.

In exchange for those additional interactions and clarifications from the agency, sponsors will be paying higher fees to support more FDA staff, but, in keeping with the relatively modest aims of this PDUFA, it is not expected to be a big bump.

Below is a guide to some of the changes that drug developers can expect in the regulatory landscape, from soaring pilot programs to arguably more pedestrian shifts in postmarketing surveillance that could nonetheless help sponsors have a more pleasant day.

Pilot Programs Aim To Get Rare Disease And RWE Flying

Rare Disease Could Be Lifted By Endpoint Development Pilot

The Rare Disease Endpoint Advancement (RDEA) pilot program will be implemented to increase FDA-sponsor communications and help develop novel endpoints for rare disease clinical trials.

- Participating sponsors will be allowed up to four focused meetings with agency staff.
- Sponsors also must allow the agency to discuss endpoint proposal information publicly.
- One sponsor will be accepted into the pilot in FY 2023 and up to three per year from FY 2024 through FY 2027.

Putting Wind Under Real-World Evidence

The Advancing RWE pilot program will identify approaches for generating real-world evidence that meets regulatory requirements.

- The program will aim to support labeling and efficacy or post-approval study requirements, develop agency processes promoting consistent decision-making and shared learning, and promote awareness of the RWE characteristics necessary for regulatory decisions by allowing public agency discussion of study designs.
- Applications will be solicited twice per year.
- One to two proposals will be accepted for the program each proposal cycle in FY 2023 and FY 2024, followed by one to four proposals from FY 2025 through FY 2027.



More Meetings Mean More Productivity

“D” Is Detailed Advice

Type D meetings will allow sponsors to ask more clarifying questions after a formal meeting.

- The meeting is limited to two focused topics and should not require input from more than three disciplines or divisions.
- Background packages will be required at the time the meeting request is submitted.
- The FDA goal is 14 calendar days to respond to a meeting request and 50 days from the receipt of the request to schedule the meeting or written response.



CDER Will Start INTERACTing With IND Sponsors

Initial Targeted Engagement for Regulatory Advice on CBER/CDER Products (INTERACT) meetings will be formalized for CDER, in addition to CBER, and available for novel questions and unique development challenges prior to IND filing.

- IND-enabling toxicology study designs, complex manufacturing technologies or processes, innovative device development for use with a drug or biologic, or a cutting-edge testing method are appropriate topics.
- Background packages must be submitted at the time of the meeting request.
- The FDA goal is 21 calendar days to respond to a meeting request and 75 calendar days to schedule the meeting or written response.

Post-Marketing Requirements To Be Discussed Earlier

The FDA will communicate details on anticipated postmarketing requirements to sponsors no later than eight weeks prior to the user fee goal date for standard applications and six weeks before the goal date for priority applications.

- The agency will be required to meet the goal for 60% of applications in FY 2023, 70% of sponsors in FY 2024, and 80% of sponsors in FY 2025 through FY 2027.
- All relevant Manual of Policies and Procedures (MaPPs), Standard Operating Procedures and Policies (SOPPs) and guidances on PMRs must be updated by the beginning of FY 2023 and finalized by the end of FY 2027.
- Staff training on updated PMR processes also will begin in FY 2023.
- A new formal process also will be established to request the release of a PMR, along with the ability to appeal a non-agreement letter stating a PMR should remain in place.
- The process will be incorporated into all FDA MaPPs, SOPPs and guidances by the beginning of FY 2023 and finalized by the end of FY 2027.

Some Applications Will Get To Be STARS

The Split Real-Time Application Review (STAR) pilot program will allow sponsors of qualifying supplements to send application information in two parts about two months apart.

- The goal is to shorten the time between the date of a complete submission and the action date.
- Application assessments will begin when the first part of the supplement is submitted, but the PDUFA clock will not start until the second portion is received.
- The agency also will act on the application at least one month earlier than the goal date.

Manufacturing Oversight Could Be Reshaped By Pre-Inspection Communications

CMC Development And Readiness Pilot

In FY 2023, CDER and CBER will offer a CMC Development and Readiness Pilot to facilitate expedited CMC development of products with an IND.

- The program will be based on the anticipated clinical benefit of earlier patient access, and CMC readiness for CDER and CBER products with accelerated development timelines.
- Participation criteria may differ between centers due to product complexity.
- The FDA will provide sponsors in the program specific CMC advice during development through two additional CMC-focused Type B meetings and additional limited CMC-focused discussions based on readiness and CMC milestones.

Pre-License Inspection Communications

When the FDA determines a pre-approval or pre-licensure inspection will be needed for an NDA or BLA, its goal will be to communicate its intent to inspect the facility at least 60 days in advance of the visit.

- It will inspect the facility no later than mid-assessment cycle.
- Supplements will be not included in the goal.

Alternative Inspection Tools

The agency must issue draft guidance on the use of alternative tools to assess manufacturing facilities in pending applications by 30 September 2023.

- Guidance must be finalized within 18 months of closing the public comment period.

Innovative Manufacturing Technologies

The FDA will issue a draft strategy document outlining actions it will take to facilitate use of innovative manufacturing technologies and address barriers to adoption.

- MaPPs, SOPPs, guidances and other documents may be updated or created.



Postmarket Changes Could Make Safety Surveillance Feel Like A Walk In The Park

REMS Assessments Changing

The FDA will improve REMS assessments by incorporating assessment planning into REMS design and establishing performance goals.

- The FDA goal to provide feedback and comments on REMS methodological approaches and study protocols used to assess a REMS will be within 90 days of receipt.
- The FDA must meet the goal for 50% of sponsors in FY 2024, 70% of sponsors in FY 2025, and 90% of sponsors in FY 2026 and FY 2027.

Pregnancy Postmarket Safety Being Standardized

The FDA will develop a consistent approach to postmarket requirements and commitments related to assessing outcomes in pregnant women.

- The agency will clarify the value of pregnancy registries and electronic health data for determining pregnancy safety.
- By 30 September 2023, the FDA will hold a public workshop on postmarket safety studies in pregnant women to help determine the ideal study design.
- The FDA will initiate five demonstration projects to address knowledge gaps about study design performance, including the performance of pregnancy registries versus electronic health record database studies to detect safety signals.



Sentinel Getting Upgrades

By 30 September 2023, the FDA must hold a public workshop on using negative controls for assessing the validity of non-interventional studies for treatment and proposed Sentinel initiative projects.

- Two methods development projects must be initiated by 30 September 2024 and a report on the results of the projects must be published by 30 September 2027.
- By the end of FY 2025, the FDA will publish an update on facilitation of public and sponsor access to Sentinel data to conduct safety surveillance.
- It will also analyze and report on the use of Sentinel for regulatory purposes, such as labeling changes and PMRs.

Allergenic Extracts Moving To PDUFA-topia

Allergenic Extract Products

Allergenic extract products licensed after 1 October 2022 will join the PDUFA program.

- These products will enjoy all relevant performance goals, as well as pay application and other fees.
- Products licensed before 1 October 2022 along with “standardized allergenic extract products submitted pursuant to a notification to the applicant from the Secretary of Health and Human Services regarding the existence of a potency test that measures the allergenic activity of an allergenic extract product licensed by the applicant before” that date will remain excluded from PDUFA.

The FDA will communicate details on anticipated postmarketing requirements to sponsors no later than eight weeks prior to the user fee goal date for standard applications.

IQVIA Integrated Global Compliance.

Intelligent.
Automated.
Integrated.



We believe “what’s possible” can always go further. That’s why we do things differently at IQVIA. By simplifying and automating safety processes, regulatory information management and tech-enabled services, we are transforming compliance across your portfolio’s complete lifecycle. Increasing speed and accuracy. Reducing cost and complexity. It’s how we look beyond what’s expected to see what’s possible.

*Others may offer a way forward.
IQVIA gives you a way further.*



Compliance reimagined.

IQVIA has a vision that goes beyond simply optimizing individual safety, regulatory, quality, and commercial compliance functions.

Using cloud-based technology combined with advanced analytics—including artificial intelligence and machine learning—we are bringing together global regulatory intelligence and information management, safety data and processes, product quality information and legal/ethical guidance on an integrated platform.

For customers, this means:

- **Faster** cycle times
- **Improved** compliance performance at lower cost across all functions
- **Better** predictive planning, throughout the product lifecycle
- **Visibility** across your complete compliance landscape



Contact us: [IQVIA.com/globalcompliance](https://www.iqvia.com/globalcompliance)





BY DANIEL CHANCELLOR, DIRECTOR OF THOUGHT LEADERSHIP, EUROPE

Biotech's Cambrian Explosion

An increasing number of sophisticated tools are on offer to address new therapeutic challenges and remaining unmet needs.

Approximately 540 million years ago in a condensed period of evolution, almost all major animal classifications started to appear and be preserved in the fossil record. This so-called Cambrian explosion produced the foundations for the evolutionary diversity that remains to this day. There are certainly parallels with the science-led innovation within the biotech industry, particularly over the last five years, delivering several new and differentiated drug platforms and greatly advancing the range of potential treatments today and in the future.

An increasing number of sophisticated tools are on offer to address new therapeutic challenges and remaining unmet needs. Within the last 10 years, the sector has seen the emergence of cell

therapies, gene therapies and RNA therapies, with multiple approved treatment options within these modalities. Most recently, gene editing has started to emerge as a precise take on gene silencing with applications extending to off-the-shelf cell therapy. While messenger RNA (mRNA) has shown itself to be a powerful and lucrative weapon against the COVID-19 pandemic.

Of these, the cell therapy class has the most activity, tracking just shy of 2,000 active candidates under investigation according to the 2021 snapshot from the global R&D database Pharmaprojects. This number has tripled within the last five years, moving well clear of gene therapies. But the hottest area in terms of recent growth involves gene editing using techniques

such as CRISPR, which has increased eight-fold over the same period and become a notable standalone drug class, distinct from classical gene therapy (see Exhibit 1). Pharmaprojects is tracking around 200 gene editing drugs in active development, similar to the number of mRNA-based vaccines and therapeutics – the other emergent drug platform over recent years.

This is not science for science's sake, but rather to yield meaningful clinical advances that have provided valuable treatments for underserved patients. Continued development of next-generation versions of these drug platforms will provide a long tail of therapeutic opportunities. For monoclonal antibodies (MAbs), for example, the first 50 drugs were approved over the space of three whole decades, while the next 50 were condensed into just five years.

The current iteration of cell therapy is led by CAR-T cells, used in refractory blood cancers and requiring autologous manufacturing. Considerable effort is going into off-the-shelf production, alternative cell types such as natural killer cells and macrophages, while the true potential of cell therapy in oncology will depend upon successful management of solid tumors, which are 10 times more common.

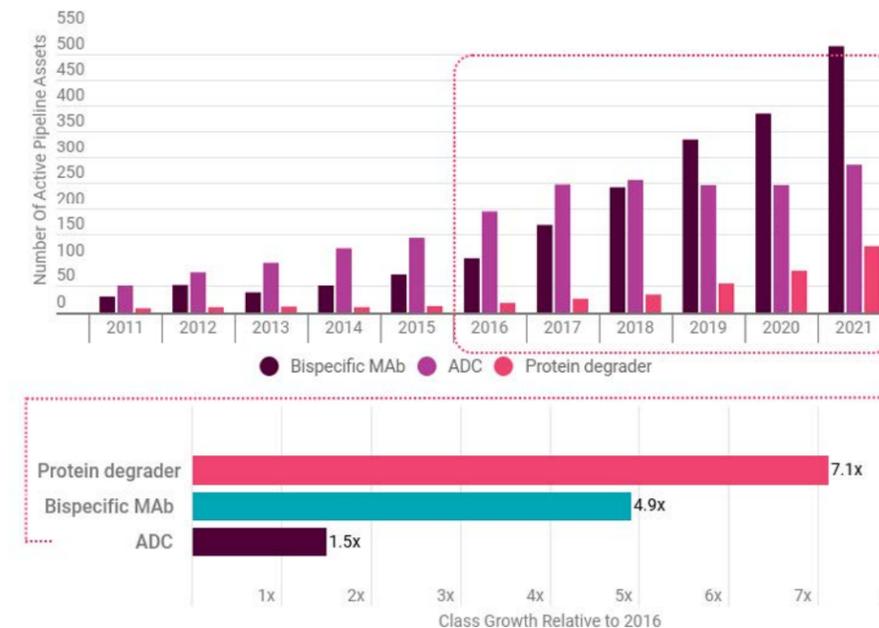
Gene therapies are only available for a tiny group of patients with spinal muscular atrophy or rare inherited retinal disorders, although companies in this space are sequentially targeting broader patient populations and more prevalent diseases. The long-term potential of gene silencing depends heavily on improved delivery platforms, allowing RNA interference and gene editing to occur in tissues outside of the liver such as the brain and the lung.

For mRNA, COVID-19 vaccines from Moderna and Pfizer/BioNTech have been incredibly successful, but the legacy of the technology will extend to vaccination against more complex infectious diseases and cancer, not to mention its potential role as an intermediate in producing therapeutic proteins.

Existing Technologies Provide Prolonged Therapeutic Options

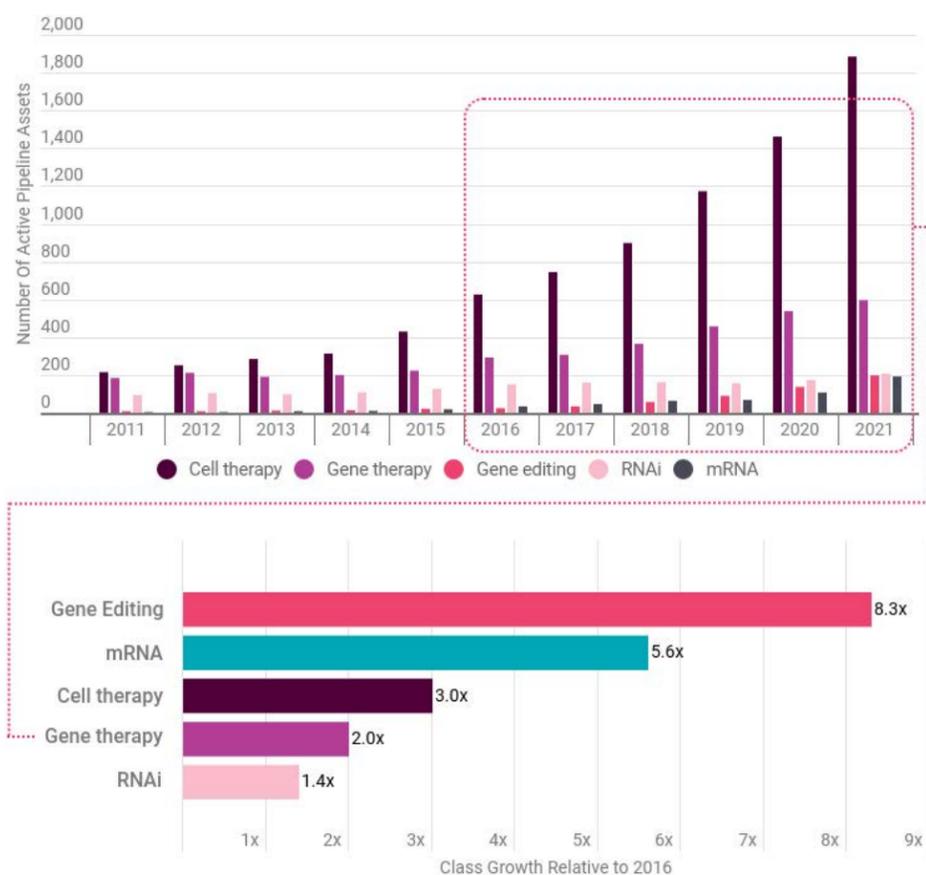
Tracking next-generation MAb technologies such as bi-specific, tri-specific and antibody-drug conjugates (ADCs) shows that existing drug platforms can have long developmental runways. Pharmaprojects shows over 500 bi-specific MAbs in active development, in addition to almost 300 ADCs as of 2021. While ADC growth has remained rather shallow, the technology is notable for recent high-value licensing deals signed, in addition to

Exhibit 2: Growth In Existing Modalities



Source: Pharmaprojects, October 2021

Exhibit 1: Growth In New Modalities



Source: Pharmaprojects, October 2021

therapeutic breakthroughs such as the HER2+ breast cancer drugs Kadcyla (trastuzumab emtansine) and Enhertu (trastuzumab deruxtecan). By contrast, bispecific MAbs are showing considerable growth, expanding five-fold between 2016-2021 as the technology is positioned as an off-the-shelf alternative to CAR-T cells. Furthermore, Roche's hemophilia drug Hemlibra (emicizumab) shows the therapeutic and commercial potential (\$2.4bn in 2020) of MAbs is not limited to oncology.

The emerging field of targeted protein degradation is perhaps the ultimate example of using old methods of designing drugs in an increasingly sophisticated manner. Targeted protein degraders harness the natural ubiquitin-proteasome system to achieve knockdown or silencing of a given protein, recasting simple small molecules as being far more than inhibitors occupying a binding pocket. Rather, a typical molecule has two separate binding moieties that co-localize an E3 ubiquitin ligase with the desired target protein, effectively tagging it for degradation. Led by biotechs such as Arvinas, Kymera and C4 Therapeutics, there are now more than 100 active targeted protein degraders in development. Its seven-fold growth since 2016 (see Exhibit 2) makes this new class one of the hottest areas of drug discovery, with therapeutic potential across a range of human diseases.

Abundant Biotech Sector With Plentiful Resources

Much of these scientific and clinical advances are originating from the laboratories of biotech companies, specifically those investing in drug platforms. While the pioneering biotechs may eventually get acquired and folded into big

pharma, as has been the case with cell and gene therapies – think Kite, Juno, AveXis, Spark – there are always new platform companies emerging to further progress the science. RNA biotechs and the gene editing field remain entirely independent, with the market capitalizations of mRNA leaders such as Moderna and BioNTech having risen to such a level that any acquisition is prohibitively expensive for even the largest pharmaceutical companies.

More generally, biotech valuations have enjoyed a long run of steady growth since 2016. The NASDAQ Biotechnology Index has risen 63% over the last five years, even when including a recent 10% correction. Over this period, the number of biotechs with a \$5bn+ valuation has more than tripled to almost 100 companies. This has happened alongside a proliferation in the number of publicly listed biotechs, doubling within a five-year period to more than 700 companies by the end of 2020. The estimated annual cash burn of these 700 publicly listed biotech companies exceeds \$55bn; this total is beginning to rival the collective ~\$100bn R&D spend of big pharma.

On the private side, financing continues to rise, setting new thresholds in particular for venture capital. As shown in Exhibit 3, VC funding of private biotechs in the first six months of 2021 eclipsed the total value of 2020, which itself was a record year. What began as a pandemic-related influx of capital into the sector to progress COVID-19 treatments and vaccines has translated into broad support for biotech start-ups across a spectrum of therapy areas and drug discovery platforms. This promises to support scientific innovations and advances, led by the biotech sector, for many years to come.

Deal-Making Implications For Pharma Players

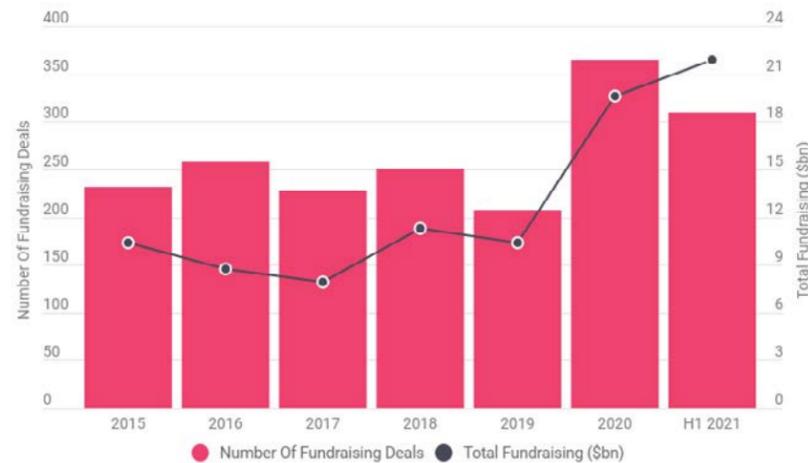
As the biotech sector explores the tremendous opportunities afforded by this Cambrian explosion, there are some major implications for traditional pharma companies. For several years, the vogue has been to balance pipelines and portfolio strategy with a mix of internal R&D and in-licensed or acquired assets with an oft-cited 50:50 ratio. Pipelines that did not reach this number were deemed too insular and failing to capitalize on the degree of external innovation on offer. As the biotech engine continues produce new breakthroughs, and platform companies can further invest the fundamental science, then even this aspirational ratio may be suboptimal and insufficient.

Another consequence of the availability of capital within biotech is the abundance of choice. In times of capital constraint, investors place considerable selection pressure whereby biotechs with weaker science, management or data are unable to secure funds to progress development. In today's abundant biotech sector, it falls increasingly to pharmaceutical companies to conduct due diligence on an ever-larger

scale. It is therefore essential to have world-class business development teams that are close to the science in order to successfully tease apart the winners and losers from the large volume of potential partners. This is especially the case as deal-making shifts increasingly towards early-stage assets and scientific platforms.

Lastly, with the growing number of ways in which a drug can be designed against a given target, pharma companies should retain flexibility and follow a modality-agnostic approach. Rather than being heavily wedded to a particular drug type such as cell, gene or RNA therapies, the decision about how to approach a given disease should be weighed against a range of factors. Expected clinical profile, unmet needs, patient preferences, competing drugs and the reimbursement landscape all need to be considered. It is therefore advantageous for a modern biopharmaceutical company to have the full range of potential modalities at its disposal and match the right drug for the right opportunity.

Exhibit 3: Private Biotech Venture Capital Fundraising Continues To Rise



Source: Pharmaprojects, October 2021

This article is based on a series of presentations prepared by Daniel Chancellor, thought leadership director at Pharma Intelligence, in collaboration with colleagues Duncan Emerton, Ly Nguyen-Jatkoe and Timothy Pang in October 2021. 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: Daniel.Chancellor@informa.com.



COVID-19 R&D: Pharma's Path Ahead

Global research and development for preventative vaccines and therapeutics to treat COVID-19 have progressed at a rapid pace. Still, key issues remain and to dampen the effects of the virus in 2022, even greater collaboration is needed.



BY **ANDREW ODAME-KWAKYE**, GRADUATE FELLOW, EUROPE

The therapeutic solutions and vaccines developed by the biopharma industry during the pandemic have allowed society to start imagining life after COVID-19. However, more tools and treatments are needed to control the virus. COVID-19 has become a leading cause of death worldwide and continues to profoundly affect patients, families and societies and strain health care systems.

Three pressing issues stand out and require the collaborative efforts of the biopharma industry to slow the pandemic, reduce deaths and hospitalizations and return life to something resembles normality: understanding long-COVID, growing the arsenal of anti-infectives and tackling virus variants.

SARS-CoV-2 is a highly infectious, rapidly mutating virus that has claimed over 5 million lives. Vaccines, such as those developed by AstraZeneca, Pfizer/BioNTech, Moderna and Johnson & Johnson, have mitigated the virus's catastrophic impact. Available vaccines have been distributed and administered to a large segment of the world's population but, as a long-

term solution there are issues. Particularly, the varying efficacy of approved vaccines against new variants such as Delta and Omicron.

An unexpected consequence of the pandemic is post-COVID-19 syndrome or "long-COVID," meaning that some people experience a range of symptoms that last weeks or months after the infection has gone. The prevalence of this phenomenon is widespread but defining and developing treatments for post-viral syndrome has proven difficult for experts within the life sciences industry. More research needs to be done so the medical community can agree upon a commonly accepted definition of the disease.

Clinical Landscape For Long-COVID

Long-COVID is defined by the World Health Organization as a condition that "occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis."

According to one of the major studies of the virus financed by the UK government, nearly 2 million people in England have had one or more COVID-19 symptoms lasting at least 12 weeks. The research is based on self-reported data from 508,707 people aged 18 and up, who participated in REACT-2 clinical trial rounds 3-5 between September 2020 and February 2021. Long-COVID symptoms can include breathlessness or shortness of breath, fatigue, persistent cough, heart palpitations, “brain fog,” joint or muscle pain, and changes to your sense of smell or taste.

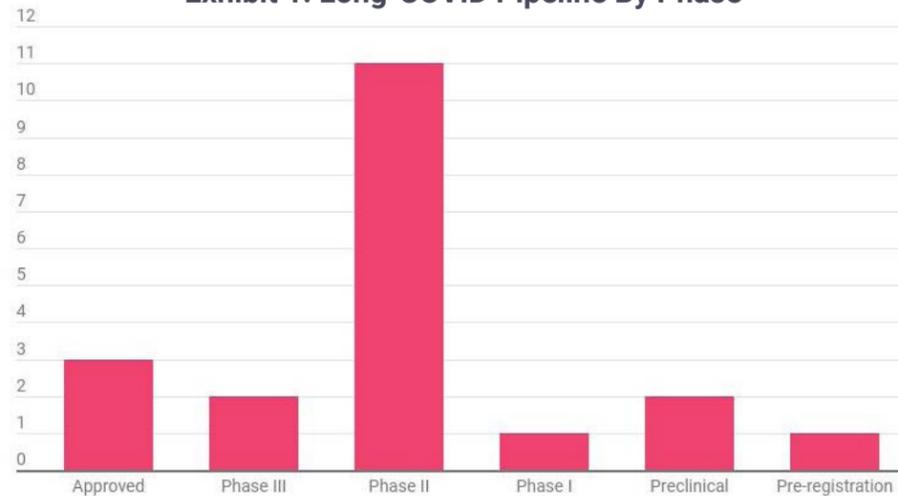
Ashok Gupta, neuroplasticity expert and founder of the Gupta Program told *In Vivo* several of the long-COVID symptoms tracked closely with other chronic conditions were often dismissed, misdiagnosed, or untreated by the medical community. “As such, I believe the research and medical communities need to be more vigilant in paying attention to the possible signals that long-COVID could be more prevalent than currently estimated.”

Exhibit 1 illustrates the development phases of drugs in the pipeline for treating symptoms of long-COVID. This handful of pipeline programs demonstrates that it may take some time before long-COVID receives higher levels of investment and interest from the pharmaceutical industry.

Pharma Intelligence’s Daniel Chancellor believes in the future, long-COVID will be replaced by a range of more narrowly defined consequences such as post-viral fatigue, post-viral interstitial lung disease and post-viral myocarditis. Drug development may be concentrated on these narrower patient populations. Arguably, long-COVID is one dimension of the pandemic that has been overlooked, as rolling out vaccinations and launching other preventive measures and policies for society have been prioritized.

In the future, long-COVID could be replaced by a long range of more narrowly defined consequences such as post-viral fatigue, post-viral interstitial lung disease and post-viral myocarditis.

Exhibit 1: Long-COVID Pipeline By Phase



Source: Phmaprojects (Data correct as of Dec 2021)

Novel Therapeutics For Treatment of COVID-19

The biopharma industry has quickly stepped up to the plate to develop therapeutic treatments for patients with COVID-19. Working in parallel with vaccines that aim to prevent circulation of the virus and limit its effects, companies have taken different approaches to therapeutic treatment. *In Vivo* has highlighted four drug candidates with interesting modalities.

In November, the UK became the first country in the world to issue a marketing authorization to Merck & Co’s (known as MSD outside of the US) Lagevrio (molnupiravir), the first oral antiviral for COVID-19.

The UK’s Medicines and Healthcare products Regulatory Agency found that the antiviral was safe and effective at reducing the risk of hospitalization and death in people with mild to moderate COVID-19 who are at increased risk of developing severe disease. The drug is being keenly awaited around the world as many countries continue to struggle with the huge numbers of patients being admitted to hospital, even in regions where a large segment of the population has been double vaccinated.

The MHRA recommends the drug is taken as soon as possible following a positive COVID-19 test and within five days of symptom onset. Eligible patients should have at least one risk factor for severe COVID-19, which may include being aged 60 or over, obesity, diabetes or heart disease.

In a Phase III trial, Merck and its partner Ridgeback Therapeutics showed the drug cut the risk of hospitalization or death by 50% compared with placebo, from 14% to 7%.

Pfizer’s pipeline drug paxlovid is also an oral antiviral for the treatment of patients with COVID-19. The SARS-CoV-2-3CL protease inhibitor is designed to prevent viral replication. A Phase II/III trial in 1,219 adults found that the probability of COVID-19-related hospital admission or death from any cause was shown to be 89% lower in the paxlovid group than in a placebo group among patients who received treatments within three days of the onset of COVID-19 symptoms.

The drug could be prescribed more broadly as an at-home treatment to help reduce illness severity, hospitalizations, and deaths, as well as reduce the probability of infection following exposure, among adults. Paxlovid has shown effective antiviral action *in vitro* against other coronavirus variations as well as other known coronaviruses, suggesting that it could be used to treat a variety of COVID-19 infections. Subject to regulatory approval, Pfizer’s drug could be available in 2022.

Appili Therapeutics is developing favipiravir, an oral COVID-19 antiviral, for mild-to-moderate COVID-19 infection. Favipiravir is a tablet-based, broad-spectrum antiviral that had previously been in development for influenza. The agent targets single-stranded RNA viruses, like coronaviruses, by inhibiting viral RNA-dependent RNA polymerase (RdRP). Appili announced in October 2021 that enrolment in its Phase II PRESECO trial was complete. Topline data from the trial are expected imminently.

Elsewhere, Synairgen is working on an inhaled therapy for COVID-19, SNG001, that uses interferon beta, a protein that helps the immune system coordinate its response to viral infections. Inhaled interferon beta is being tested in hospitalized COVID-19 patients in a Phase III study. The National Institute for Health Research in the UK has designated the trial as an Urgent Public Health Study. In the US, the FDA has given SNG001 fast track status. As a broad-spectrum antiviral, SNG001 could have uses against other respiratory viral infections. Top-line data from the Phase III SPRINTER trial are expected in the first quarter of 2022.

What Now For COVID Vaccines?

Vaccine developers such as AstraZeneca, Pfizer, Moderna, Johnson & Johnson and others have been at the forefront on the world’s journey out of this pandemic. But what is next for the development of vaccines to get the world back to normal?

Moderna is in the process of developing a single vaccine (mRNA-1073) that combines a booster dose against COVID-19 with its experimental flu shot. This is designed to be a multi-respiratory vaccine in a single dose, which could potentially tackle 12 strains of the virus. The goal of this development is to reduce hospitalizations and death from respiratory illnesses. The innovative vaccine could reach the market as early as fall 2023.

Cuban researchers at Finlay Vaccine Institute have also developed a single-dose vaccine called Soberana Plus (Soberana 02). The institute has specifically tailored this vaccine to people who have had previous infections with COVID-19. This strategy could help prevent reinfection, reduce mutations of the virus, and limit the spread of new variants. Soberana Plus entered Phase III trials in March 2021.

These examples showcase a sustained effort within the biopharma industry to develop innovative solutions to move past the pandemic. But COVID-19 evolves quickly.

On 26 November 2021, the World Health Organisation designated the variant Omicron (B.1.1.529) a variant of concern. It is unclear how effective existing vaccines will

be against this new variant. There are 50 mutations in the Omicron variation, 32 of which are on the COVID-19 spike protein. As a result, the area of the spike protein that antibodies attach to may become less recognizable, thereby decreasing the efficacy of available vaccines. Pharma companies have already begun developing Omicron-specific vaccines, with Pfizer and Moderna estimating that their jabs will be available within 100 days.

“Leveraging patient-reported information from vaccinated individuals will allow us to understand how well these vaccines mitigate the seriousness of getting COVID-19.”

Nancy Dreyer, IQVIA

Nancy Dreyer, chief scientific officer and senior vice president at IQVIA, told *In Vivo*, “Total eradication of any virus is a long-game strategy. We all want to improve our chances of not getting seriously ill and returning to normal life. Leveraging patient-reported information from vaccinated individuals, including those who have been infected, will allow us to understand how well these vaccines mitigate the seriousness of getting COVID-19.”

The novelty of the Omicron variant means that there are great unknowns about transmissibility, health outcomes and mortality rate. Pharma Intelligence’s Davinderpreet Mangat believes a major concern of this new variant is whether global vaccination campaigns will be substantially set back, and whether vaccines will need to be reformulated against the new variant – presenting a new set of challenges for the biopharma industry. Researchers in South Africa and around the world are conducting studies to better understand many aspects of Omicron and will continue to share the findings of these studies as they become available.

Ultimately, the COVID-19 pandemic has created a complex web of obstacles for the biopharma industry. The transformation from attempting to understand what this virus is to generating viable vaccines to people in a short timeframe has been a fantastic win for the sector. There is a sustained effort across the industry to tackle these issues from various angles. But, as we learn more about the virus, how it changes, and the long-term consequences of infection, biopharma will need to come up with more innovative approaches to keep pace.

Exploring Life Sciences Stories From Across The Globe

Navigate through *In Vivo* features from around the world. Read more about venture capital activities in Chile, data protection laws in China or the expanding pharma markets in South Korea and Kazakhstan.

1 Canada

As of April 2021, the European Medicines Agency and Health Canada had proactively released regulatory data for 123 and 71 medicinal products respectively, while the US FDA had disclosed data for only one drug. This was among the findings of a US study that found that EU and Canadian regulators had “greatly expanded the public availability of regulatory data over the past decade.” [Read More](#)

2 Chile

While Latin American countries have suffered the world’s sharpest economic reversal due to COVID-19, some enterprising local investors think it is time to put serious money behind the region’s nascent market in biotech and life sciences. The driver is the way that structural changes exposed by the virus actually work to the advantage of Latin America and other developing countries. [Read More](#)

3 Brazil

Brazil has established an accelerated pathway for approval of drugs for ultra-rare diseases, encouraging development activity – but the definition of qualifying drugs is narrow. Expansion to include more treatments could boost clinical trials activity and companies’ overall development presence. The Brazilian health regulatory agency, ANVISA, approved 11 rare disease drugs in 2020. About the same as awarded in 2018, but half of the number for 2019. [Read More](#)

4 Switzerland

Swiss medtech is transitioning into the next era of innovation. A survey of 261 companies run by the Swiss Medtech industry association in 2020 showed the top reasons for medtechs setting up operations in Switzerland to be: access to qualified technical staff and capital; good support for R&D; a stable economy; ease of doing business (including setting up, building approvals, utilities supply etc.); and levels of corporation tax (current average, 14.9%). [Read More](#)

5 Lithuania

The Baltic state saw its life sciences sector grow by 62% according to government agency, Enterprise Lithuania. The goal is for life sciences to represent 5% of Lithuanian GDP by 2030, a figure which now looks to be on the conservative side. The sector is already at 2.9% with around 600 companies and, even before the pandemic, was growing on average by 13.9% per year. [Read More](#)

6 Kazakhstan

Kazakhstan’s pharmaceutical market showed positive dynamics in 2020. In the first 9 months of 2020, market size for finished pharmaceutical products grew to KZT460bn (\$1bn), up 22% year-on-year. Other areas of the Kazakhstan pharmaceutical market have also shown high growth increases: the volume of purchases for outpatient drug provision over the past year increased by 41%, and purchases for hospitals grew by 30%. [Read More](#)

7 China

China ambitiously wants to champion domestic medtech manufacturers in the global market. It also needs to ensure foreign manufacturers do not sustainably dominate its home market – while also benefiting from their technical expertise. Against that backdrop, new Chinese data laws are being eyed by global medtechs with a certain trepidation. [Read More](#)

8 Vietnam

Vietnam’s pharma market has seen constant growth over the last decade, driven by rising incomes and an aging population. Spending on drugs is expected to rise more than 10% by the end of 2021. The sales revenue of Vietnam’s pharma market has been growing constantly over the last decade, reaching \$6.4bn in 2020, 2% up year-on-year. Top 5 growth contributors in 2020 were immunosuppressants (40%), vaccines (36%), topical anti rheumatics (34%), antineoplastics (13%) and diabetes treatments (11%). [Read More](#)

9 South Korea

South Korea is the 10th largest economy in the world with a population of 51.3 million. Alongside fast growth of the region’s technology-driven economy, its pharma industry has been expanding significantly too. According to the Korean Ministry of Food and Drug Safety, the domestic pharmaceutical market hit KRW24,310bn (\$21.8bn) in 2019, up 5.2% year-on-year, while exports surged by 11.2%. The domestic biopharmaceutical market and export expansion focused on biosimilars has contributed largely to the growth of the South Korean market. [Read More](#)

10 Australia

Legislation aimed at mitigating drug shortages in Australia by requiring suppliers to hold additional safety stocks of certain medicines, while at the same time establishing a price reduction floor for cheaper drugs, has been welcomed by the Australian Generic and Biosimilar Medicines Association. Responding to the draft legislation, the GBMA said the bill represented a “watershed moment in the security of medicine supply for Australian patients” after “months of collaborative negotiations.” [Read More](#)



BY ANJU GHANDURDE, EXECUTIVE EDITOR, ASIA

CEO Pay Packages Expand In India But Ratio To Employee Earnings Hurts

Top executives at leading local and foreign drug firms in India by and large earned more in 2020-21, while differentials in CEO to median employee remuneration remained stark. With increasing scrutiny by shareholders and lawmakers, experts suggest that pharma should be more mindful of balancing “adequate” C-suite compensation and glaring inequalities.

C-suite remuneration across a dozen leading pharma companies in India rose in 2020-21 as top executives steered their organizations through pandemic-related disruptions and challenges to keep things moving. CEOs and managing directors of domestic firms continued to draw sizeably higher earnings overall versus their peers in foreign-listed entities in India.

Cadila Healthcare’s managing director Sharvil Patel, the son of chairman Pankaj Patel, led the earnings chart yet again, taking home

INR262.50m (\$3.5m) in 2020-21, up 5% over the previous year, data on front-line listed companies showed.

Patel junior was the top earner among the group of companies last year as well, though notably Cadila executive director Ganesh Nayak, a company long-timer, received remuneration of INR289.60m for fiscal year 2021, which refers to the 12-months ended 31 March this year.

Aurobindo Pharma Limited’s outgoing managing director N Govindarajan took home

INR193.9m, a jump of almost 15%, while Cipla Limited’s global CEO Umang Vohra followed with earnings up almost 34% to INR181.2m in 2020-21. Govindarajan, who resigned in October, will leave the firm effective from the close of business on 31 December 2021.

The increase in Govindarajan’s remuneration is after considering the commission for FY2020-21, while the percentage increase in Vohra’s remuneration for the period includes the perquisite value of stock options exercised during the financial year. If that had not been considered, the percentage increase in Cipla CEO’s earnings would have stood at 11.3%.

Dr. Reddy’s Laboratories Ltd. co-chair and managing director GV Prasad’s remuneration for the period rose 9% to INR156.1m and includes commission, salary and perquisites.

Lupin MD Takes Less

Notably, Dilip Shanghvi, founder and managing director of India’s top-ranked drug firm, Sun Pharmaceutical Industries Ltd., received remuneration of INR46m for FY21, the least among the local company CEOs on the list.

While a comparison of remuneration as per Form 16 of FY20 and FY21 reflects a jump of 37.2%, the company explained that the actual increase in Shanghvi’s total remuneration (basis CTC) for FY21 was 7%. This since the bonus of the previous year was paid in the current year and has been reflected in the current year’s Form 16.

“However, no such component was there in the Form 16 for FY20 as in the year previous to FY20 (i.e. FY19), Dilip Shanghvi was paid only INR1 towards remuneration,” the company said. Form 16 is the certificate of deduction of tax at source and issued on deduction of tax by the employer on behalf of the employee.

Lupin Limited’s managing director, Nileshe Gupta, is the only top executive on the list who saw a decline in remuneration to INR57.67m (-3%), while earnings of his sibling and CEO Vinita Gupta were flat at INR127.87m (she is an employee of Lupin Management Inc, USA, a wholly-owned arm of Lupin).

Top Exec Pay At Foreign-Listed Firms

Among listed foreign firms covered in the compilation, GlaxoSmithKline Pharmaceuticals Ltd.’s managing director, Sridhar Venkatesh, who took over the top job at the UK multinational’s Indian arm in April 2020, received remuneration of INR82.1m. Pfizer Ltd. (India) managing director S Sridhar followed with earnings of INR50.2m, which was an increase of almost 14%.

There are, however, some caveats to the data. First, large multinationals like Merck & Co., Inc., Eli Lilly and Company, Johnson & Johnson and Roche, whose operating firms are unlisted in India, are not covered. Besides, some executives - for

instance Abbott India Ltd. managing director Anil Joseph - took charge effective 1 July 2020, implying that the remuneration figure is not for a full 12-month period.

Furthermore, some top bosses may receive stock options directly from the parent firm, which may or may not be reflected in the local annual report. Pfizer India chief S Sridhar’s remuneration covers benefits and perquisites and performance-linked incentives, which include stock options/restricted stock units granted by the parent company, Pfizer Inc. US. Similarly, Abbott’s Joseph also received during the year, as part of a “Long-term Incentive Program,” restricted stock units of Abbott Laboratories, USA.

Sanofi India Ltd. said that it does not have a scheme for grant of stock options but 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. Accordingly, the amount accrued in the financial statements for the year ended 31 December 2020 for stock options/performance shares granted to managing director Rajaram Narayanan stood at INR17.88m.

In addition, the higher earnings of MDs/CEOs at leading Indian firms compared with the bosses of foreign companies need to be viewed against a wider backdrop – some local firms, in which the founding group is also the largest shareholder, are led by members

of the founding family and so a direct comparison of their remuneration with peers at foreign entities may not entirely be like-to-like.

That is not meant in any way to take away from the fact that scions at the helm of most family-controlled Indian firms are well equipped and qualified for the top job.

CEOs Deserve A ‘Decent’ Pay Hike

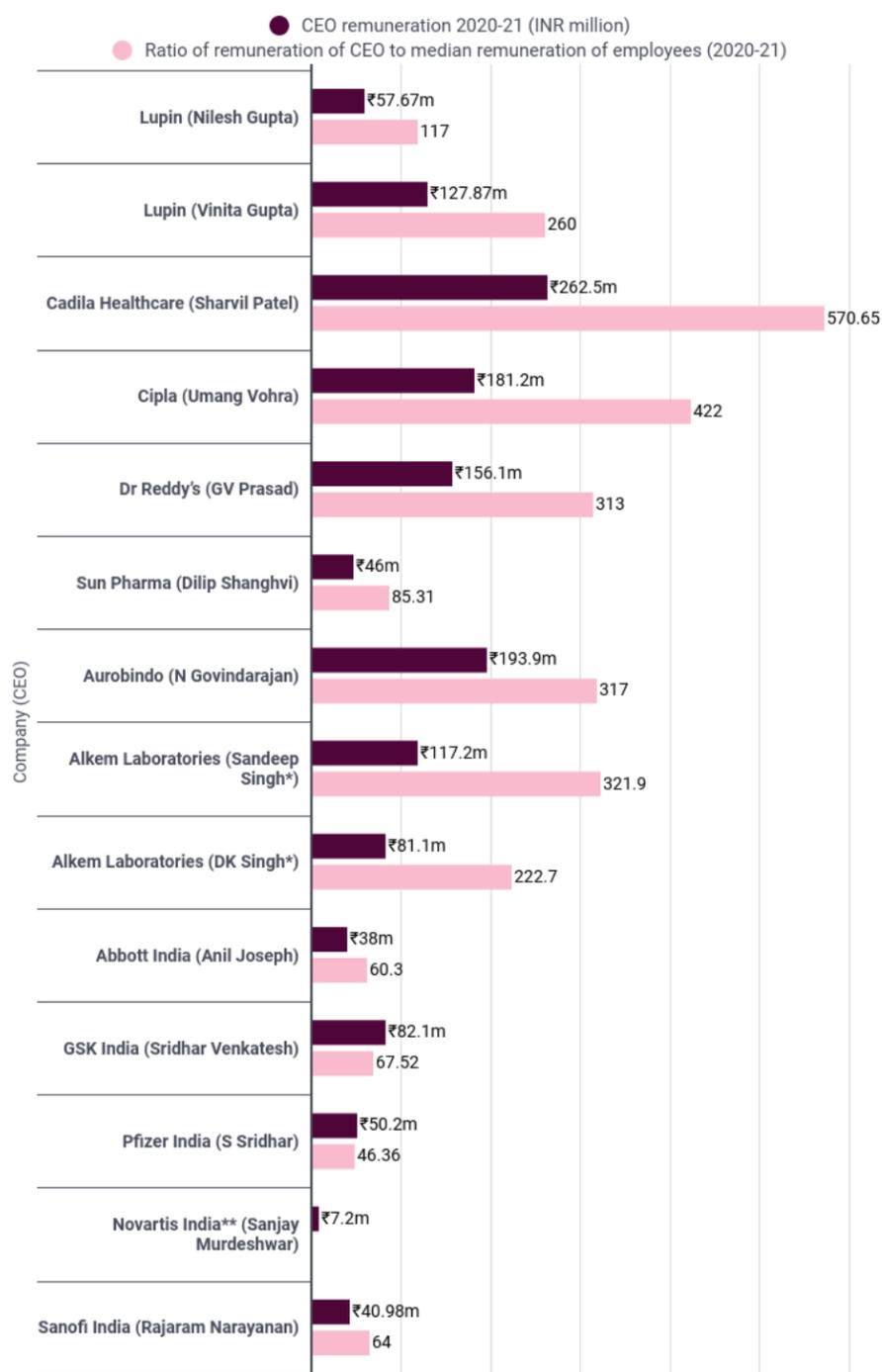
Meanwhile, industry experts noted how, despite severe business disruption caused by the pandemic, the Indian pharmaceutical industry had shown resilience. The domestic market clocked growth of 18% in September 2021, as per moving annual total data from IQVIA.

“Hence Indian pharma CEOs do deserve [a] decent pay increase. The ultimate value of CEO compensation will depend on the ability of the CEO to achieve predetermined performance goals such as revenue growth, profitability and changes in the stock price for listed companies,” said Dr Ajit Dangi, president and CEO of Danssen Consulting.

Dangi, a former president and executive director of Johnson & Johnson in India, also explained that increasingly the concept of a “triple bottom line and meeting ESG [environmental, social and governance] goals” are also becoming part of the compensation process. The whole objective is to “attract, inspire and retain high-performance executives” who can

Lupin Limited’s managing director, Nileshe Gupta, is the only top executive on the list to see a decline in remuneration.

Exhibit 1: CEO/MD Salaries In India (2020-21)



* Sandeep Singh and DK Singh are MD and Joint MD of Alkem respectively.
 ** Novartis' 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.

Source: Company Annual Reports

deliver superior results in spite of several challenges, he said.

“As such, the job of the Indian Pharma CEO is quite challenging considering issues such as intense competition, rigid price control, unpredictable government policies, weak IPR [intellectual property rights] enforcement and generally ‘not so favorable’ ease of doing business.”

Others also highlighted how pharma reacted swiftly to opportunities. Salil Kallianpur, a former executive vice-president at GlaxoSmithKline plc in India, referred to how pharma was broadly less impacted due to some organizations leveraging portfolios well (over-the-counter, chronic brands), while others launched “very timely products” such as remdesivir and favipiravir, he noted and have more or less managed the balance sheet better than CEOs in “less fortunate” industries.

“The rise in salaries correlates to the ability of the company to grow during the pandemic through some agility and market-focused action (as in the case of some J&J executives internationally) versus organic growth that is less rewarded,” said Kallianpur, who now runs a digital health consultancy.

Globally, Alex Gorsky, CEO of Johnson & Johnson, was the top paid CEO of the 17 largest pharma companies in 2020. Gorsky's leadership has been recognized as the US firm developed a COVID-19 vaccine, managed supply chain turbulence and protected employees during the pandemic.

Gorsky is set to hand over the baton to J&J veteran and current vice-chairman Joaquin Duato, the company said in August.

Resistance To Excessive Packages

While there's widespread recognition of the role of pharma and its personnel in the fight against COVID-19, it's increasingly clear that shareholders are keeping close tabs on C-suite remuneration aspects, as was amplified in the controversy around the reappointment of Eicher Motors' managing director in India. Pharma, some experts indicated, may want to pay heed to these signs.

Danssen's Dangi said that shareholder actions pertaining to the reappointment of the Eicher MD can perhaps be viewed as a “signal” to the remuneration and compensation committees of many companies to be more mindful of such acts, as there is increasing resistance to “excessive packages”, particularly in a country like India where close to quarter of the population lives below the poverty line.

Kallianpur, however, maintained that while the issue was initially derived as the meaning of the shareholder action, it doesn't seem to be the case, given the fact that the employees union of Royal Enfield (a unit of Eicher) backed the reappointment of the Eicher MD. “Also, it was clarified that the issue wasn't his remuneration but a lack of transparency in the percentage of profit paid to him under it. When that was made more transparent, the issue subsided and he was re-appointed as managing director,” Kallianpur observed.

Earlier this year, shareholders of Eicher Motors in India were reported to have rejected a proposal for the re-appointment of Siddhartha Lal as managing director for a period of five years, effective May. Some shareholders at the time also blocked a proposal pertaining to the increase in Lal's remuneration. On 23 August, the motorcycles and commercial vehicles maker said that Lal had been reappointed as managing director and that the board would go back to shareholders for approval via a postal ballot.

The company also maintained that the primary concern with investors was not the managing director's reappointment or the proposed compensation but the “lack of clarity” regarding the enabling provision that potentially allowed payment of remuneration up to 3% of profits. “Over the last four years, we have had the same limit of 3%, but in reality have paid only a fraction of that amount. The actual remuneration during FY2021 was at 1.04% of profits, with the preceding years being at a lower percentage,” Eicher explained in a notice to Indian stock markets at the time.

Nevertheless, the board said that given the background of actual remuneration paid to the managing director in preceding years, it had cleared a revised remuneration structure for Lal, with a maximum cap of 1.5% of profits as per Section 198 of the Companies Act.

Balancing Adequate CEO Remuneration And Inequalities

Significantly, while pharma CEO compensation in India inched upwards in 2020-21, one area that continued to draw attention was the stark ratio of the remuneration of CEO/managing directors to the median remuneration of employees. It was as high as 570.65 in the case of Zydus Cadila among Indian firms, while for the foreign companies on the list it ranged between 47 and 68.

Ex-GSK executive Kallianpur said that the huge differentials in CEO to median remuneration are unacceptable and while CEOs must definitely receive remuneration according to the role, responsibility and status of the positions they hold, commanding such huge differentials is “ridiculous”. The idea is to strike a balance between adequate CEO remuneration and glaring inequalities, he asserted.

“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 British and American CEOs earn 331 times that of median salaries in their organizations. Indian companies certainly don't seem very different.”

But the other extreme are public sector companies in India, where CEO salaries are only three-four times that of median salaries, though it isn't clear if this includes all the perks that come with public sector jobs - but “those salaries do seem low,” he added.

Dangi, however, explained that the high ratios are more or less a global phenomenon and “fortunately, such issues are being addressed at board level” and there is a realization that the excessive gap between CEO pay and median remuneration needs to be moderated.

“Additionally issues such as gender equality, diversity etc. are also increasingly becoming a priority for HR [human resources] departments and company boards. There is a concerted effort in most companies to address these issues,” said Dangi, also an ex-chairman of Merck & Co subsidiary, Fulford India Ltd.

The Tax Route To Check Executive Pay

The huge differentials in CEO to median employee remuneration has also been a political talking point in other countries. Earlier this year, a group of US senators including Bernie Sanders and Elizabeth Warren proposed the Tax Excessive CEO Pay Act, to take on what they termed as “corporate greed” by raising taxes on companies that pay their top executives at least 50 times more than the pay of a median worker.

Dangi said that while such pronouncements make catchy headlines, in a free market economy such proposals are “unworkable”, particularly in a country like the US which has the highest number of dollar billionaires - 724 according to Forbes World's Billionaires list 2021. “Even communist China has the second-largest number of dollar billionaires at 698. Such pronouncements, therefore, will remain as mere election campaign rhetorics,” Dangi declared.

Kallianpur was emphatic too, noting that he was “no fan of the government/lawmakers deciding CEO salaries” and that they have “no business” doing that.

“Half-baked laws like this one overlook the fact that increased corporate tax rates most affect the job of blue-collar workers when companies move business to overseas markets. Since laws cannot impact CEO salaries, the focus should be on increasing workers' wages. Instead of raising minimum wage, the focus should be on driving up company productivity which translates into better bonuses and raises for workers.”

A statement from the US senators at the time of the introduction of the Tax Excessive CEO Pay Act maintained that a nationwide survey suggested the typical American would limit CEO pay to no more than six times that of the average worker. About 62% of all Americans – 52% of Republicans and 66% of Democrats – favor capping CEO pay relative to worker pay.



Intelligence to Impact.

ICON is a clinical research organisation powered by the strategic application of healthcare intelligence. We're evolving clinical research, creating impactful outcomes for our clients and their patients.

Intelligent insights. Impactful results.

[ICONplc.com](https://www.ICONplc.com)