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FROM THE EDITOR

LUCIE ELLIS
EXECUTIVE EDITOR

There is much to discuss about the future of the biopharma, medtech and generics sectors as we enter a new year and new decade. Outlook 2020 includes annual league tables for both the top 100 biopharmaceutical and top 100 medical technology companies, as well as analysis of the leading generics and biosimilars businesses. Alongside this performance assessment of the key markets covered by *In Vivo* and its sister publications – *Scrip, Pink Sheet, Medtech Insight* and *Generics Bulletin* – our special issue takes a deeper dive into key themes disrupting today's corporate strategies and paving the way for innovation.

Explore within Outlook 2020 what "company culture" really means in pharma against a backdrop of intense pressure from investors for greater top-line growth. Hear from leaders at Alexion how they have restructured the company's R&D business and rejuvenated the pipeline. And get an expert view on how to prepare for oral explanations for regulatory submissions.

Within the medtech realm, Outlook 2020 outlines the performance of key device and diagnostics players alongside expectations for the coming 12 months. Also featured are articles exploring the changing landscape in China, and how the confluence of health and technology will transform care in the 2020s.

New for 2020 are chapters on Strategy and Digital Transformation and what they mean for the biopharma and medtech industries.

In Vivo's Outlook 2020 edition looks across all of the key health care sectors and connects the dots: pharma, biotech, devices, diagnostics, generics, biosimilars and health tech.

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Transforming Clinical Trials With Digital Tech, And What That Means For The Patient

Many stakeholders within the pharma and biotech industries are witnessing radical shifts taking place in how clinical trials are conceived, designed and conducted. This transformation relies heavily on applying the power of digital technologies.

As new technologies emerge, they will converge through networks and cloud-based platforms to create a new digital health care ecosystem. Collectively, they will have a greater impact on clinical trials than any one technology would achieve separately. At the center of this ecosystem is the patient, demonstrated by the uptick in personalized therapies and a growing emphasis on patient-reported outcomes.

While the mean projected return on new drug research and development (R&D) investments by a dozen large cap biopharma firms fell from 10.1% in 2010 to 1.9% in 2018,[1] an opportunity remains for emerging digital technologies to improve R&D productivity.

We predict the following four technology trends will impact the drug and device development industries and have the potential to transform pharma R&D:

- Rising use of the cloud
- Democratization of artificial intelligence (AI), data and algorithms
- Incorporation of the Internet of Medical Things (IoMT)
- Increased use of digital technology for patient-centered design

Understanding the potential of these emerging trends and technologies to increase returns on pharmaceutical R&D, how they interrelate, and a framework for successfully integrating them needs to be the single biggest priority for every stakeholder in 2020.

RISING USE OF THE CLOUD FOR CLINICAL TRIAL DESIGN AND EXECUTION

Cloud-based platforms offer the ability to access large pools of data that could improve patient recruitment during clinical trials through the enhanced ability to identify, select, onboard and monitor patients who may be eligible for clinical trials. Further, harnessing cloud-based technologies allows sponsors to implement end-to-end data management strategies to transform clinical development life cycles, including data acquisition, storage, aggregation and analysis.

Moreover, cloud-based platforms offer the ability to integrate different applications such as electronic data capture, clinical trial management systems, safety systems and data repositories. A central data storage location provides sponsors and sites access in real time, and increases productivity by allowing information to be quickly shared and managed in a secure fashion.

Additionally, the continuous streaming of data to cloud-based platforms could accelerate clinical trials and decrease protocol amendments, resulting in reduced clinical trial costs. Also, sponsors can use cloud-based platforms for data submission to regulatory agencies, which has the potential to accelerate drug development, streamline regulatory review and enhance regulatory decision-making.[2]

DEMOCRATIZATION OF AI, DATA AND ALGORITHMS

The influx of big data is fueling algorithms that are the building blocks of AI, machine learning and other technologies, such as blockchain. The democratization of data, especially real-world data, is inevitable as its use spreads across every aspect of drug and device development.

As analytic methods improve, these approaches will have a compounding effect on the industry, ultimately increasing efficiency. AI-powered capabilities, including pattern recognition and evolutionary modeling, are essential to gather, normalize, analyze and harness the growing masses of data. In ICON's industry survey, AI and advanced analytics were viewed as the digital technologies with the most potential to improve clinical R&D productivity.[3]

Other AI applications in clinical trials include automating routine data-entry functions, analyzing electronic health record (EHR) data to find suitable candidates and sites for clinical studies, and monitoring and encouraging patient compliance with study protocols. Robotic process automation will streamline or eliminate many costly, time-consuming and error-prone manual steps.

AI can filter and process quality data faster than any human, generating insights to support early decision-making with powerful predictive analytics and statistical models.[1,4–6] Moreover, this function has potential applications in adaptive dose finding, and discovering and modeling new molecules and therapies.

Increased use of machine learning, which is a type of AI, allows for greater power in processing complex data sets. Machine learning applications for increased clinical trial efficiency include remote monitoring

of therapies for adverse events, addressing and adapting to changes in sites for patient recruitment, and using EHRs to reduce data errors.[7]

Meanwhile, blockchain has potential in addressing a key concern in clinical trials – data integrity. Responding to queries from regulatory authorities regarding maintaining the integrity of trial results from data capture is often a time-consuming burden. Designing blockchain into a clinical trial – which can show data from their origin to the final report – has the potential to accelerate the regulatory approval process and reduce costs.[8]

INCREASED USE OF DIGITAL TECHNOLOGY FOR PATIENT-CENTERED DESIGN

Employing digital technologies can also simplify the patient experience in clinical trials. Real-time monitoring of data collected from devices and sensors could mean less frequent study visits for patients. In addition, collecting data points throughout a clinical trial could assist sponsors in making go/no-go decisions faster, saving time and costs.

Within clinical trials, patient data are transactional between stakeholders such as health care institutions, patients and regulators. As more patients become aware of how their data are being used, harnessing blockchain technology could help maintain patient confidentiality – an ethical and legal requirement – and will become more important in engaging and retaining patients.

Blockchain's potential to increase security, privacy and interoperability of health data could make EHRs more efficient and secure. With blockchain, an audit trail is built into the transaction of data, allowing verification of the original source of the information, as well as the ability to detect attempts to tamper with it.

Also, blockchain allows for greater data availability. When data are shared openly within a network, there are fewer issues with data system interoperability. For example, availability and accessibility of patient information could be used for patient feasibility analysis and population studies. Moreover, blockchain allows researchers to submit queries for data that are stored off chain, further protecting patient privacy.[9]

INCORPORATING THE INTERNET OF MEDICAL THINGS

Innovation in medtech has led to an increased number of connected medical devices that can generate, collect, analyze and transmit data. This connected infrastructure of devices, along with their software applications, data and health systems, are creating the Internet of Medical Things (IoMT).

Wearables and imaging are creating diagnostic insights into previously untreatable or undetectable indications. For example, the US Food and Drug Administration (FDA) recently granted breakthrough device designation for an AI technology that can analyze endoscopy images for signs of gastric cancer, a disease associated with a high rate of false-negatives.[10] Further, combining historical information from EHRs with imaging, genetic and molecular test data is driving the development of highly targeted oncology treatments, such as CAR-T.

Clinical trials are increasingly designed with mobile and sensor technologies – such as smartphone applications, wearables and implantables – to capture data. The reliability and accuracy of these devices could mean that real-time monitoring of patients participating in clinical trials could be used to demonstrate the health economic value of protocols, drugs and devices. For instance, a wearable might include an accelerometer. Applying various algorithms to the accelerometer signals could generate data on sleep quality, steps per day and other endpoints that reflects real-world experiences of trial participants.[11]

CONCLUSION

Despite the benefits of digital technologies, leveraging their potential requires the right infrastructure and expertise. In fact, applying advanced statistical and trial design to specific study needs was one of the top-three challenges sponsors identified that requires the skills and knowledge of contract research organizations (CROs) and other clinical trial experts.

CROs can develop platforms to securely capture, transmit and visualize medical device data and can support volumes of data collected by sensors. Identifying and addressing these current study needs using data, AI and other novel digital technologies not only improves trial efficiency significantly in the near term, but also builds competence and confidence in applying the digital technology needed to succeed and increase return on investment in the trial of the future.

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COMPANY	PHARMA SALES ($M)	COUNTRY	2020 RANKING
Pfizer	50,042	United States	1
Novartis	45,752	Switzerland	2
Roche	44,951	Switzerland	3
Johnson & Johnson	40,734	United States	4
Merck & Co	37,689	United States	5
Sanofi	35,197	France	6
AbbVie	32,753	United States	7
GlaxoSmithKline	30,928	United Kingdom	8
Amgen	23,747	United States	9
Bristol-Myers Squibb	22,561	United States	10
Gilead Sciences	21,677	United States	11
Eli Lilly	21,413	United States	12
AstraZeneca	21,049	United Kingdom	13
Bayer	19,777	Germany	14
Teva Pharmaceutical Industries	18,854	Israel	15
Takeda	18,425	Japan	16
Novo Nordisk	17,720	Denmark	17
Allergan	15,787	Ireland	18
Celgene	15,265	United States	19
Shire	15,017	Jersey	20
Boehringer Ingelheim	14,879	Germany	21
Astellas	11,834	Japan	22
Mylan	11,269	Netherlands	23
Biogen	10,887	United States	24
Daiichi Sankyo	8,422	Japan	25
Otsuka Pharmaceutical	7,402	Japan	26
Merck KGaA	7,376	Germany	27
Bausch Health	6,413	Canada	28
Eisai	5,823	Japan	29
CSL	5,674	Australia	30
UCB	5,211	Belgium	31
Servier	4,932	France	32
Abbott Laboratories	4,422	United States	33
Menarini	4,331	Italy	34
Sun Pharmaceutical	4,202	India	35
Sumitomo Dainippon Pharma	4,161	Japan	36
Alexion Pharmaceuticals	4,130	United States	37
Regeneron Pharmaceuticals	4,106	United States	38
Mitsubishi Tanabe Pharma	3,848	Japan	39
Fresenius Kabi	3,230	Germany	40
Mallinckrodt	3,084	Ireland	41
Vertex Pharmaceuticals	3,038	United States	42
Endo International	2,947	Ireland	43
Humanwell Medicine	2,799	China	44
Hikma Pharmaceuticals	2,764	United Kingdom	45
STADA	2,753	Germany	46
Lundbeck	2,727	Denmark	47
Baxter International	2,602	United States	48
Jiangsu Hengrui Medicine Co. Ltd.	2,601	China	49
Sino Biopharmaceutical	2,595	Hong Kong	50

COMPANY	PHARMA SALES ($M)	COUNTRY	2020 RANKING
Kyowa Hakko Kirin	2,460	Japan	51
Sichuan Kelun Pharmaceutical	2,441	China	52
Lupin	2,398	India	53
Cipla	2,397	India	54
Aurobindo	2,367	India	55
Shanghai Fosun Pharmaceutical Group	2,360	China	56
CSPC Pharmaceutical Group Ltd.	2,278	Hong Kong	57
Ipsen	2,273	France	58
Dr Reddy's	2,254	India	59
China National Pharmaceutical Group	2,241	China	60
Santen Pharmaceutical	2,120	Japan	61
Chiesi	2,088	Italy	62
Ono Pharmaceutical	1,893	Japan	63
Jazz Pharmaceuticals	1,869	Ireland	64
Meiji Holdings	1,799	Japan	65
Sawai Pharmaceutical	1,670	Japan	66
Amneal Pharmaceuticals	1,663	United States	67
Leo Pharma	1,650	Denmark	68
United Therapeutics	1,628	United States	69
Vifor Pharma	1,620	Switzerland	70
Recordati	1,597	Italy	71
KRKA	1,573	Slovenia	72
Zhejiang Hisun Pharma	1,527	China	73
Gruenenthal	1,512	Germany	74
Nichi-Iko Pharmaceutical	1,509	Japan	75
BioMarin Pharmaceutical	1,491	United States	76
Incyte	1,467	United States	77
Cadila	1,436	India	78
Teijin Pharma	1,427	Japan	79
Glenmark Pharmaceuticals	1,422	India	80
Yuhan Pharmaceutical	1,381	South Korea	81
Gedeon Richter	1,352	Hungary	82
Indivior	1,342	United Kingdom	83
Hisamitsu	1,268	Japan	84
Asahi Kasei Pharma	1,227	Japan	85
Green Cross	1,214	South Korea	86
Horizon Pharma	1,208	Ireland	87
Shionogi	1,166	Japan	88
Torrent Pharmaceuticals	1,124	India	89
AlfaSigma	1,110	Italy	90
Pierre Fabre	1,063	France	91
Japan Tobacco	1,033	Japan	92
Kyorin	1,029	Japan	93
Mochida Pharmaceutical	993	Japan	94
Orion Pharma	980	Finland	95
Towa Pharmaceutical	952	Japan	96
Daewoong Pharmaceutical	938	South Korea	97
Hanmi Pharm	924	South Korea	98
Nippon Shinyaku	908	Japan	99
Almirall	894	Spain	100

This Scrip 100 ranking is based on Informa Pharma Intelligence's analysis of fiscal year 2018 prescription pharmaceutical sales data for the top 100 biopharmaceutical companies. For more information contact: Lucie.Ellis@informa.com.

SCRIP 100 BIOPHARMA

NUMBERS CRUNCHED

The Scrip 100 universe gathers FY 2018 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 2018

$1M

The threshold on drug sales or R&D spending to get into the Scrip 100

GEOGRAPHICAL SPLIT OF TOP 20 COMPANIES IN SCRIP 100 UNIVERSE

9 Europe

9 US

1 Asia

1 RoW

R&D SPEND

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

$549.4BN

Combined pharma sales of Top 20

$790.9BN

Combined pharma sales of Top 100

1.1 MILLION

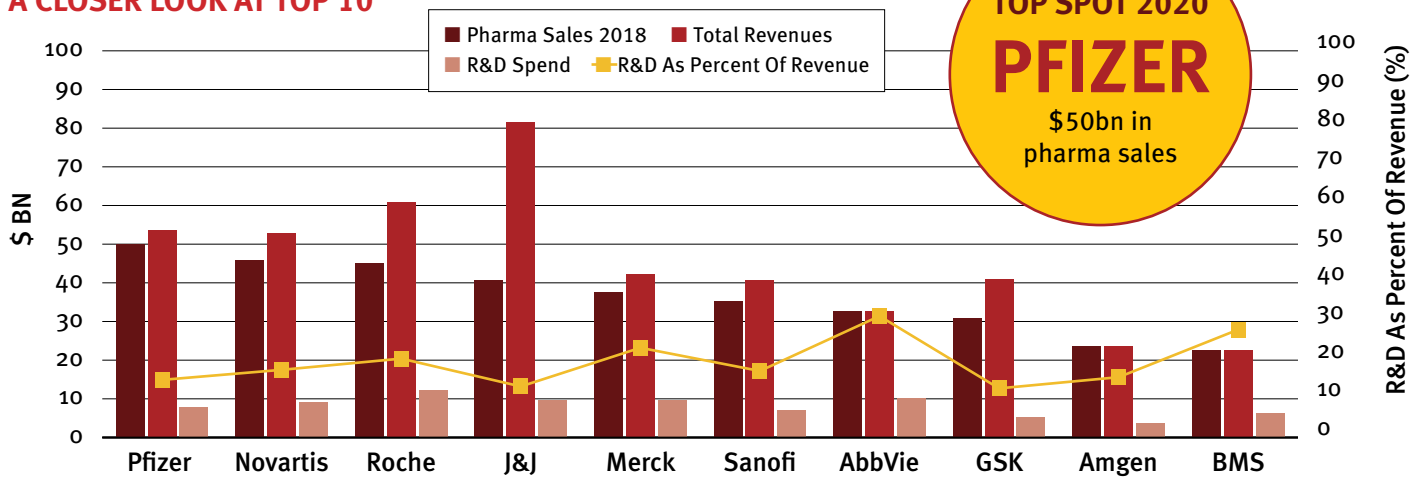
People employed by the Top 20

BMS CRACKED THE TOP 10, UP FROM 14 LAST YEAR

Bristol-Myers Squibb

Now BMS appears poised to continue its upward trajectory even as competitive pressure mounts against Opdivo.

A CLOSER LOOK AT TOP 10



TOP SPOT 2020

PFIZER

$50bn in pharma sales

A Steady Year For The Top Tier In Pharma Ahead Of Major Upheaval

Moderate growth at Bristol-Myers Squibb and Amgen moved the two companies into the top 10 pharma ranks, based on the most recent Scrip 100 rankings, while declining growth at Gilead and Teva moved those drug makers out.

JESSICA MERRILL
SENIOR EDITOR, PHARMA, US

It was generally a steady year for the top pharmaceutical companies, based on full year 2018 pharma sales. There were notable fluctuations, but nothing like what will be in store for the industry if the big deals and M&A that have been announced in 2019 move forward as anticipated. The industry is poised for a major reshaping in the years ahead.

One of the big movers in the Scrip 100 top 10 rankings this year was Bristol-Myers Squibb Co., which has been slowly moving up the pharmaceutical rankings powered by strong growth of blockbuster brands like checkpoint inhibitor Opdivo (nivolumab), blood thinner Eliquis (apixaban) and CTLA4 inhibitor Yervoy (ipilimumab), without the overhang of any big new patent expiration to offset the growth.

With 9% growth and $22.56bn in revenues in 2018, BMS cracked the top 10 pharmaceutical companies in the world, moving up from number 14 last year and number 15 the prior year. Now BMS appears poised to continue its upward trajectory even as competitive pressure mounts against Opdivo. The company's revenues for the first nine months of 2019 grew 8%, and it is on track to close a $74bn merger with Celgene Corp., which ranks number 20 in the Scrip 100, up from number 21 last year.

With the addition of Celgene's revenues of $15.7bn in 2018, BMS will become one of the largest pharmaceutical companies in the world, when compared by sales of branded prescription products.

THE CHANGING FACE OF BIG PHARMA

For two years running, the top six pharmaceutical companies, based on annual pharma sales, have been unchanged: Pfizer Inc., Novartis AG, Roche, Johnson & Johnson, Merck & Co. Inc. and Sanofi. But the leader board will be changing in the years ahead: Pfizer is poised to shake off its big $10bn-sized Upjohn business in a merger with Mylan; and number seven-ranked AbbVie Inc. is working to close the acquisition of Allergan PLC.

The number one-ranking pharmaceutical company in the world will be getting smaller while competitors build up. It will all be a lot for the industry to digest. Pfizer's new base will be around $40bn, an enormous change from where the company was before the loss of Lipitor in 2011, when it generated $67.4bn in consolidated revenues (including non-pharma businesses). CEO Albert Bourla has been clear he does not have an appetite for any big M&A either. Pfizer's chief has consistently informed investors that the company's business development strategy will prioritize mid- to late-stage pipeline drugs.

The new company that absorbs Mylan and Upjohn, now known as Viatris, is expected is expected to have 2020 pro forma revenues of $19bn-$20bn, positioning it as a new top 20 pharmaceutical company. While, AbbVie and Allergan, if merged successfully, stand to become the new powerhouse in the industry, with Allergan's nearly $16bn in annual sales joining AbbVie's roughly $33bn in annual revenues. The companies announced the $63bn mega-merger in June in what could establish a new number one pharmaceutical company, at least until Humira shows substantial signs of erosion.

Another notable change is Takeda Pharmaceutical Co. Ltd. and Shire, which are included separately in the Scrip 100 rankings at number 16 and 19, respectively, because the merger of the two drug makers closed in January and the rankings are based on 2018 pharma revenues. Those companies combined would be positioned to become a top 10 pharmaceutical player, however.

For now, at least, Pfizer holds the number one spot for another year. Amgen Inc. was another winner in the 2019 Scrip 100, moving up to number nine from number 11 last year on revenue growth of 4% and pharma revenue of $23.75bn. It remains to be seen if Amgen can hold onto the position since the first nine months of 2019 have been challenging due to the impact of biosimilar competition with revenues roughly flat.

GILEAD AND TEVA SLIP

Bristol and Amgen also benefited from challenging business environments facing peers Gilead Sciences Inc. and Teva Pharmaceutical Industries Ltd., both of which moved out of the top 10 in the latest Scrip 100 rankings. Gilead slipped from number nine to 11 and Teva moved from number 10 to 12.

Two years ago, Gilead ranked number seven with $29.95bn in pharmaceutical revenues. It has been a very steep decline for the company, which generated pharma revenues of only $21.68bn in 2018. That is a 27% decline in pharmaceutical revenues over two years. The company has just not been able to make up the lost revenues from its maturing hepatitis C business, despite persistent momentum in the HIV business. Gilead is expecting roughly flat revenues in 2019, $21.6bn to $22.1bn.

Teva, meanwhile, has been in something of a revenue free-fall, with 2018 pharmaceutical revenues down 16% over 2017, driven by the loss of Copaxone to generics and a challenging US generic drug market. CEO Kare Schultz has guided that 2019 will be a trough year for the company before it returns to growth in 2020. But the hits have not stopped coming, especially given the uncertainty around Teva's financial exposure to ongoing opioid liability litigation in the US. The top 20 pharmaceutical companies generated pharmaceutical revenues of $534bn in 2018, growth of 2.1% over the $523bn they generated in 2017. These companies make up the vast majority of the industry's revenues. The top 100 pharmaceutical companies generated combined sales of $747bn in 2017.

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COMPANY	PRODUCT SALES ($M)	COUNTRY	RANKING
Medtronic	30,557	United States	1
Johnson & Johnson	26,994	United States	2
Philips Healthcare	20,576	Netherlands	3
GE Healthcare	19,784	United States	4
Abbott Laboratories	18,927	United States	5
Siemens Healthineers	17,145	Germany	6
Becton Dickinson	15,983	United States	7
Cardinal Health	15,633	United States	8
Stryker	13,601	United States	9
Roche Diagnostics	13,168	Switzerland	10
Boston Scientific	9,823	United States	11
Danaher	9,102	United States	12
B Braun	8,159	Germany	13
Zimmer Biomet	7,933	United States	14
Alcon Laboratories	7,149	United States	15
Baxter International	7,131	United States	16
3M	6,021	United States	17
Olympus	5,747	Japan	18
Terumo	5,431	Japan	19
Grifols	5,299	Spain	20
Smith & Nephew	4,904	United Kingdom	21
Fujifilm	4,388	Japan	22
Dentsply Sirona	3,986	United States	23
Fresenius Medical Care	3,877	Germany	24
Intuitive Surgical	3,724	United States	25
Thermo Fisher	3,724	United States	26
Edwards Lifesciences	3,723	United States	27
Shimadzu	2,813	Japan	28
Getinge Group	2,784	Sweden	29
Sysmex	2,659	Japan	30
Hologic Inc	2,644	United States	31
ResMed	2,607	United States	32
Coloplast	2,606	Denmark	33
Teleflex Medical	2,448	United States	34
bioMerieux	2,348	France	35
Align Technology	1,966	United States	36
Drager	1,940	Germany	37
Convatec	1,832	United Kingdom	38
Miraca	1,644	Japan	39
Bausch Health	1,640	United States	40
Nihon Kohden	1,620	Japan	41
Elekta	1,561	Sweden	42
Carl Zeiss Meditec	1,513	Germany	43
Qiagen	1,502	Germany	44
Shinva Medical Instrument	1,495	China	45
Integra LifeSciences	1,472	United States	46
Bio-Rad	1,412	United States	47
ICU Medical	1,400	United States	48
Straumann	1,394	Switzerland	49
DJO Global	1,200	United States	50
AGFA Healthcare	1,186	Belgium	51

COMPANY	PRODUCT SALES ($M)	COUNTRY	RANKING
Smiths Medical	1,176	United Kingdom	52
Fukuda Denshi	1,176	Japan	53
Integer	1,162	United States	54
LivaNova	1,107	United Kingdom	55
NuVasive	1,102	United States	56
Cochlear	1,081	Australia	57
Omron	1,046	Japan	58
Dexcom	1,032	United States	59
Invacare Corp	972	United States	60
Haemonetics	968	United States	61
Guerbet	933	France	62
LePu Medical Technology	925	China	63
Cantel Medical	918	United States	64
Merit Medical Systems	883	United States	65
CONMED	860	United States	66
Masimo Corp	858	United States	67
Myriad Genetics	851	United States	68
Wright Medical Group	836	United States	69
Konica Minolta	824	Japan	70
Diasorin	790	Italy	71
Abiomed	769	United States	72
Globus Medical	713	United States	73
MicroPort Scientific	669	China	74
Cooper Companies Inc	651	United States	75
Jiangsu Yuyue Medical Equipment	608	China	76
Varex Imaging	602	United States	77
Natus Medical	531	United States	78
Quidel	522	United States	79
Hamamatsu Photonics	509	Japan	80
Heraeus Group	472	Germany	81
Ypsomed	464	Switzerland	82
Orthofix Medical	453	United States	83
Accuray	419	United States	84
BTG	365	United Kingdom	85
Hogy Medical	334	Japan	86
Luminex	316	United States	87
RTI Surgical	281	United States	88
AngioDynamics	271	United States	89
CryoLife	263	United States	90
Cardiovascular Systems	248	United States	91
Horiba Ltd	236	Japan	92
Stratec Biomedical Systems	222	Switzerland	93
Meridian Bioscience	214	United States	94
AtriCure	202	United States	95
Orasure Technologies	182	United States	96
Consort Medical	168	United Kingdom	97
Endologix	156	United States	98
Sectra	139	Sweden	99
STAAR Surgical	124	United States	100

This Medtech 100 ranking is based on Informa Pharma Intelligence's analysis of fiscal year 2018 product sales for the top 100 publicly listed medical device technology companies. For more information contact: Lucie.Ellis@informa.com.

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Organic Growth In Medtech Despite Market Disruptions

In 2018, the top 100 publicly listed and reportable medical device technology companies had global sales spanning from over $30bn to some $100m in the lower reaches. As the latest *In Vivo* Medtech 100 ranking shows, many of the major changes in value sales were linked to company restructurings. But there were some impressive organic gains too.

It would be surprising not to say disquieting if, in mature industry sectors, the complexion and composition of the leading companies changed radically year-to-year.

For medtech, a truly unique industry in terms of both the risk assumed by companies and what the ultimate customer – the patient – needs, that would be a pause-for-breath moment. But then, factor in that the medtech industry is itself on the cusp of major disruptive forces, and changes are sure to come as the next decade unfolds.

The consensus is that the industry is readying for the full effects of the digital revolution and potentially new tech industry players; population-based health management, based on big data analytics and patient engagement; alternative methods of paying for innovation based on outcomes; factoring in harder, perhaps much longer regulatory processes during a product's pre-market journey to commercialization; the market's ongoing shift towards outpatient and remote home care; and the need to continually address the explosion of chronic conditions.

Routinely, the US leads the way in much of the significant change that the global medtech environment eventually comes to embrace, for instance tackling value-based health care as a long-term need; and restructuring health care buying and delivery structures to prepare for changing demand patterns. The creation of group purchasing organizations (GPOs) as a response to the ongoing consolidation of the US health care industry, and integrated delivery networks (IDNs) that aggregate buying power for hospital groups, are clear examples.

Developments that disrupt the norm put pressure on medtech selling prices and require changed behavior at the company level. And add to that the fears (at time of writing) that the temporarily-repealed 2.3% US medical device tax is possibly due to restart in 2020, and it is plain that companies in this market must tread ever carefully to maintain competitive advantage. Good managers may well trade on uncertainty and thrive on unpredictability, but uncertainty for medtechs is everywhere right now, from the EU Medical Device Regulation (MDR), to Brexit, to US/China trade standoffs, to wholesale medtech restructuring.

A VACANCY AT MEDTECH RANKING NO. 25

However, in 2018, with isolated episodes of major M&A, the medtech top rankings stayed largely – reassuringly – the same. Absent the acquisition of C.R. Bard by Becton Dickinson & Co. in the dying days of 2017, and the 2018 table lists the same names in the leading 25 companies as in 2017. Robotics pioneer Intuitive Surgical Inc.; Thermo Fisher Scientific Inc., the sixth-largest global IVD player; and Edwards Lifesciences Corp., the heart valve and critical care monitoring specialist, are vying for the vacant slot created by Bard. They all recorded impressive gains in 2018 to reach the level of $3.7bn sales.

None of them used externally added muscle in putting on sales growth of 18.6%, 6.8%, and 8.4%, respectively. They are all at, or ahead, of the average mid- to high single digit-growth of the global market in 2018, which was worth an estimated $425bn (compared with $397bn in 2017; according to Fortune Business Insights).

Fifteen US groups are among the leading 25 medtechs globally, with three from Japan and seven from Europe – across the Netherlands, Switzerland, Spain, the UK and Germany. Their activities span the range of device therapy areas, as shown in our major industry sectors sub-tables, but also extend to dental, ophthalmic, wound care, diabetes and, in the example of Grifols SA, plasma collection and blood diagnostics. In 2018, Spain's largest medtech player consolidated its top 20 ranking by, among other things, completing the acquisition of Biotest US Corp. Grifols had divisional IVD sales of $829m in 2018, and thus remained outside the IVDs top 10.

THE GLOBAL TOP 10: A CURATE'S EGG

Within the top 10 companies, all of which were comfortably in the double-digit billions of dollar-ranked sales, BD was the standout riser in 2018. It added almost a third to its 2017 sales in rising three places to seventh, with 2018 sales knocking on the door of $16bn (including IVD sales, which were up 8.6%). The reason was the $24bn acquisition of Bard, with which BD claims a "unique position in both treatment of disease and processes of care for providers." Clinician satisfaction in terms of device usage and ease of handling has become a much higher-profile USP for many medtech manufacturers in recent years.

BD will hope that incoming CEO and president

Thomas Polen, an internal appointment, will emulate the record of growth under Vincent Forlenza, who is retiring as chair and CEO on January 28, 2020. Recent track records would suggest so: under Forlenza, Polen led the acquisitions of both Bard and, in 2015, CareFusion, which lifted BD into the truly big league.

This pace of growth saw BD rise above Cardinal Health, but still remain $3bn behind fifth-placed Abbott Laboratories Inc., which has also been tearing up the tarmac in M&A in past years. Its 2017 consolidation of St Jude has made it the second-leading cardiovascular group. In 2018, it fully consolidated the October 2017 purchase of diagnostic device and service provider Alere, establishing itself as a leader in point-of-care testing (POCT), and gaining access to new channels and geographies. Overall, it was the second-highest sales climber in the top 10, up by almost 17%. And with its bulked up IVD business – its IVD sales rising by 33% in 2018 – Abbott is now also clearly the second-largest global IVD group by sales. In that industry segment, it sits behind pureplay Roche, whose $13.2bn IVD revenues in 2018 kept it as a top 10 global medtech group.

Fellow European diagnostics player Siemens Healthineers AG made IVD sales of €4.13bn, a rise of 4.3% in the year ended September 30, 2019, and remained the fourth-largest global IVD groups, behind Danaher, in third. Siemens Healthineers' strong imaging (€8.94bn) and advanced therapy (€1.6bn) revenues helped elevate the German group to sixth-largest medtech group in the current Top 100.

The weakest growth among the top 10 came at Cardinal Health Inc., whose merely marginal increase illustrated the "curate's egg" nature of performances in the top 10. Here, it was a case of timing: in fiscal 2018, Cardinal's medical segment revenue grew powerfully, with $1.9bn of revenues coming from new acquisitions, primarily the Patient Recovery Business. That cannot be repeated every year, especially once divestitures – in 2018, it sold its China distribution and the naviHealth businesses – are factored in.

BELOW-AVERAGE GROWTH FOR MANY LEADING COMPANIES

The rest of the top 10 saw average or below-industry-average growth in 2018: Stryker Corp., under 5%; GE Healthcare 4%; and Philips, 2.4%. And that also goes for the global leaders Johnson & Johnson, number two in the ranking, and Medtronic PLC, which is number one. J&J's slim 1.5% medtech segment sales rise in 2018 followed its sale of Codman Neurosurgery to Integra LifeSciences (which increased its sales by 24% and added incremental revenue of $236m). That, plus a loss of spinal market share, led to a 1.9% dip in J&J's orthopedic sales. Its diabetes sales also dropped, by 37.5% to $1bn, as a result of the divestiture of its LifeScan business in Q4 2018, and the Q4 2017 decision to exit the Animas insulin pump business.

In diabetes, the reverse was the case at global medtech leader Medtronic, which, as signaled last year, became the first global $30bn dollar medtech group – albeit on the strength of a lowly 2% sales rise. Its diabetes business (insulin pumps, CGM, insulin pump consumables and therapy management) led the growth, at 12%, recording a business group total of $2.4bn. Next year, Medtronic will be setting group strategy without the deft touch of long-serving CEO Omar Ishrak, whose retirement at the close of the 2020 fiscal year will make way for internal appointee Geoff Martha. The big strategic news for Medtronic in 2018 was its acquisition of robotic guidance systems company Mazor Robotics, for $1.6bn. In 2019, it continued to build its robotics reach.

TRADING PLACES

While at the top of the industry, Medtronic is recording sales upwards of $30bn, the threshold for top 100 status in our listing of publicly held, reporting companies has dropped again, by some $40m, reflecting the ongoing consolidation of the industry. Refractive surgery implantable lens maker Staar Surgical is newly admitted to the top 100, on the strength of a 2018 sales rise of 36%, despite competition from laser vision surgery, where Novartis (Alcon), J&J (AMO), Bausch Health Companies and Carl Zeiss Meditec AG have major strengths. Bespak's drug delivery technologies recorded a small rise in US dollar sales, and franchise owner Consort Medical (UK) was elevated to top 100 status in 2018 (but is now subject to a takeover by Recipharm), as was Swedish imaging IT and digital pathology company Sectra, on the back of a 17% rise in 2018-19 local currency sales.

Making way for these new entrants, besides Bard and Alere, was Analogic Corp, which in 2017 was a $475m revenue group, and remains active in ultrasound, advanced imaging and real-time guidance technologies. In 2018, it was acquired by an affiliate of Altaris Capital Partners, and, now privately held, has been delisted from NASDAQ, and is no longer eligible for inclusion in these tables.

Next year, besides BTG, the US orthopedic and sports medicine group DJO Global will also be a name – if not brand – consigned to league table history. The $1.2bn revenue group was acquired by Colfax Corp for $3.15bn in November 2018 (completed February 2019). DJO will help make Colfax a higher-margin, faster-growing and less cyclical company, says Colfax, which plans to bring DJO within its "CBS" culture – a business management system that uses repeatable, teachable processes to "drive continuous improvement and create superior value for customers, shareholders and associates."

FAST-RISER CLUB

Other eyecatchers in the lower rankings include human tissues supplier CryoLife, whose 39% rise in sales included a full year of revenues from Jotec, a German endovascular and surgical products company. However, the bottom line was a net loss of $2.8m, due largely to the financing needs to integrate that very acquisition.

Microport Scientific's revenues in 2018 were also acquisition-enhanced, growing by 49% (32%, excluding the impact of foreign exchange). Expanded sales on the global market and an improved orthopedics portfolio were augmented by the positive effects of the acquisition of LivaNova's CRM business.

On the contrary, Cardiovascular Biosystems' 14% sales rise (peripheral and coronary products) originated in increased customer accounts, growth in hospital and office-based lab sites, international expansion, and additional product offerings – and all against what it said were modest average selling price declines.

But the Blue Riband for 2018 sales growth should go to IVD company Quidel, whose 2018 revenues increased by 88% to well over half a billion dollars, due primarily the acquisition of the triage and BNP Businesses from Alere in fall 2017. The acquired business represented 51% of Quidel's 2018 revenues.

IV124392

Company Overview

ICON plc is a global provider of outsourced drug and device development and commercialisation services to pharmaceutical, biotechnology, medical device, and government and public health organisations. The company specialises in the strategic development, management and analysis of programs that support clinical development from compound selection to Phase I-IV clinical studies. With headquarters in Dublin, Ireland, ICON currently operates from 98 locations in 40 countries and has approximately 14,600 employees.

Full Service Portfolio: Early Phase to Commercialisation

Early Phase Services
- Clinical Research Unit
- Patient Studies
- Pharmacodynamic Models
- Data Visualisation & Analysis
- NONMEM Software
- PK/PD Pop Software
- Precision Methodology

Drug Development Services
- Non-clinical
- Chemistry, Manufacturing & Controls (CMC)
- Clinical Development

Clinical Research Services
- Project Management
- Clinical Operations/Monitoring
- Patient Centric Monitoring
- Feasibility & Study Start-Up
- Site & Patient Solutions
  - Global Site Network
  - Patient Recruitment, Engagement and Retention
  - Digital Solutions - FIRECREST
- Biometrics
  - Data Management
  - Biostatistics
  - Medical Writing & Publishing
  - Adaptive Trials – ADDPLAN®
- Scientific Operations
  - Medical Imaging
  - Medical Affairs
  - Pharmacovigilance
  - Regulatory Affairs
  - Endpoint Adjudication
  - Interactive Response Technology
    - FLEX ADVANTAGE
- Investigator Payments Service

Commercialisation & Outcomes Services
- Real World Evidence Strategy & Analytics
- Real World Evidence & Late Phase Research
- Global Research Services Hubs
- Access, Commercialisation & Communications
- Patient Centred Sciences
- Strategic Regulatory Services
- Medical Device & Diagnostics Research

Laboratory Services
- Central Laboratories
- Bioanalytical Laboratories
- Specialty Laboratories

Functional Services
- DOCS
- Government & Public Health Solutions

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Rentschler Biopharma's CEO Talks Innovation For The 2020s

Dr. Frank Mathias, CEO of Rentschler Biopharma SE, a contract development and manufacturing organization, explains the company's innovation strategy and updates on its US expansion. He talks broadly about the CDMO landscape in Europe and how Rentschler Biopharma is differentiating itself from the competition.

Founded in 1927, Rentschler Biopharma is an independent, family-owned company headquartered in Laupheim, Germany. Frank Mathias joined the company as CEO in 2016. Since taking the helm of Rentschler Biopharma, Mathias has been focused on preparing the company for the next decade of contract development and manufacturing. In October 2019, Mathias, along with the chairman of the board, Prof. Dr. Nikolaus F. Rentschler, were jointly named Entrepreneur of the Year by Ernst & Young.

One trend Mathias highlighted as an important change and opportunity for the CDMO sector is the move by pharmaceutical companies toward outsourcing R&D arrangements. "More and more we find that companies are deciding not to take on production themselves, but they give it out, and we can profit from this action. It happens that we have more demand for our services than we have capacities available," Mathias said.

In part to answer this growing demand, Rentschler is expanding its business in 2020 by establishing a Center of Excellence in North America. In November 2019, the company announced that it was putting into operation a single-use bioreactor for its new 93,000 square foot facility in Milford, MA, in the Greater Boston area. The system is expected to be client-ready in mid-2020.

Aiming for a larger geographic reach still, Rentschler Biopharma has enhanced its existing collaboration in Japan with Summit Pharmaceuticals International Corporation. SPI and Rentschler Biopharma are working together with Japanese clients to outline projects from early clinical stage up to commercial launch. Japan is an important area of growth for Rentschler Biopharma. Mathias said, "Japanese pharmaceutical companies are playing an important and expanding role in the global health care market, and we are delighted to be continuing this productive collaboration as we grow our client base in Japan."

Despite this positive trend, Mathias noted that Rentschler Biopharma also faces greater competition now than in previous times. "The competitive environment around CMOs and CDMOs will certainly become tougher in the upcoming years. A lot of capacities have been built up around the world, within other manufacturing firms and within pharma companies. There's really a lot ongoing," he stated.

Alongside this, the needs of Rentschler Biopharma's clients are shifting. "The whole market is changing and there are various new therapies coming in. We have cell therapies, we have gene therapies and we have even more complex molecules." Although challenging, Mathias noted that "at the same time this is an opportunity for us because we have a strong track record with such complex molecules, which is not the case for a lot of our competitors." With its innovative and flexible business model, Rentschler Biopharma's new Milford site is already taking on projects, including complex and difficult-to-manufacture proteins, such as multispecific antibodies.

DOING YOUR RESEARCH

When Mathias joined Rentschler Biopharma three years ago, he was asked by the supervisory board to develop a comprehensive strategic outline for the company for the coming decade. While this type of activity can be completed in a few weeks and be centered around financial goals, Mathias said the company decided to go another way. "If we want to know what our company might look like in 2025, we need to first understand how the world might be by 2025. This is not so easy to predict," he explained.

Firstly, the company analyzed 12 so-called mega trends effecting society, including the health care sector, such as the "silver society," Mathias said. "People are becoming older but want to stay healthier. This is a very positive trend for us." Another trend is interconnectivity, how IT and artificial intelligence technologies are changing the world. "We looked at all these mega trends, for each of them we asked ourselves, 'What does this mean for society in general and what does it mean for our company?'" He added that Rentschler Biopharma's leadership team took these trends and assessed how the company needed to adapt.

To further build the knowledge base for its new 10-year business plan, Mathias and his management team sought insights from other experts. For example, Mathias visited venture capitalists. "We asked private equity firms where they are investing their money today. VCs are very interesting trend setters. They put their money in different companies today because they expect a return on that investment in seven or so years."

Mathias noted that the company also visited head hunters to ask them about the upcoming generation of talent in the life sciences sector. "We asked them, 'What do we need to change about our leadership?'" He added that human capital played an important role in Rentschler Biopharma's business plan out to 2025. "In the past people were extremely happy to come to a company that had a good name. Today you need to approach young people totally differently. It is

about what we can offer them as a challenge in their work. How we can develop them. They want to grow with the company," he said.

In 2019, Rentschler Biopharma was featured for a second year in a row on the annual list of Germany's best employers, published by the F.A.Z. Institute. The analysis evaluates the largest German companies from over 150 different sectors for their reputation as employers. Of the 10,000 companies included, 503 were recognized as top employers. Rentschler Biopharma once again ranked number two in the biotechnology sector.

On its fact-finding tour, Rentschler Biopharma also visited hospitals to speak with medical professionals and physicians, asking them questions like: "How are you treating cancer today and how will you treat cancer in 10 years' time?" Finally, Rentschler Biopharma reached out to CEOs of start-ups to ask them about new business models. "We took all this information together and we approached our clients around the world, to ask them what they expected from us. We want to be a company that is really client-oriented," he said, adding that those discussions were "extremely fruitful."

THREE KEY FINDINGS

Mathias said Rentschler Biopharma had learned three key messages from its meetings with peers and clients.

Firstly, quality will remain the main driver for success in 10 years as it is now in 2019. "When I say quality, I don't only mean the API or the finished product, I also mean the quality of everything we do. The quality of the reporting we do; the quality of the consultant work we do; the quality of the dossier we give to clients for registration. All this will be extremely important for success in the future."

Secondly, Mathias said the company had learned more about how communication between clients and CDMOs needed to evolve. "It will be more of a strategic partnership. I predict for companies in our area of business, in the future, we will have fewer clients in total but we will serve those clients in a more strategic way."

Thirdly, Rentschler Biopharma found that full-service solutions would remain favorable. "We were one of the first companies offering this. Our slogan is from concept to market, so we try to offer a service across the entire value chain," Mathias said. Rentschler Biopharma is already thinking about how it can go one step further by providing additional services that go beyond the vial – such as secondary packaging logistics for example.

Additionally, Rentschler Biopharma is striving for simplification for clients. The company has launched a holistic approach in several waves that aims to support efficiency and simplification across the entire organization. Initially, the focus is on operations, increasing productivity and decreasing deviations, for example. But the strategy is expected to extend into other areas of the business, such as project management or business development.

CDMO INNOVATION

Mathias noted that Rentschler Biopharma is keen to keep evolving the company to be an innovative CDMO business, to be able to offer services that its peers cannot. He cited the company's alliance with LEUKOCARE AG as an example of its work to stay novel and ahead of the curve. LEUKOCARE has developed a Stabilizing and Protecting Solutions (SPS) platform, which provides next-generation formulation technology able to increase stability of therapeutic proteins in dry and liquid formulations.

He said Rentschler Biopharma was able to avoid "not invented here" syndrome and accept that there was better innovation to solve a key problem for the business outside of its walls. "We had a formulation department already, but it was not at the level of LEUKOCARE. We closed our formulation department in Laupheim when we entered an alliance with LEUKOCARE. They are now our exclusive partner for the development of formulations, which really brings a competitive advantage to our partners."

Rentschler Biopharma has also appointed a new senior vice president of process science and innovation. Jesús Zurdo joined the company in January 2019. He provides scientific leadership for development and manufacturing services from cell-line through to final product manufacturing and is responsible for managing key strategic collaborations to ensure Rentschler Biopharma remains at the forefront of innovation and technology. Prior to joining Rentschler, Zurdo was senior director of strategic innovation at Lonza.

Rentschler Biopharma has set out a plan to secure its technological leadership by following three innovation horizons: biopharmaceuticals, designer molecules and new therapeutic modalities. Within biopharmaceuticals, Rentschler Biopharma is focused on being "fit for purpose" and improving speed to the clinic. In designer molecules, it is looking at processes for assembly and stabilization, and complex architectures, as well as integrated solutions. Finally, the company is looking at new modalities and seeking partnerships to engage in areas like cell and gene therapy manufacturing. The company is assessing several alliance options, for example, AI technologies that could make production more efficient. Mathias stated, "We are not looking for merger and acquisition opportunities. We would prefer to go into an alliance and to continue to work together in partnership. That's the way we approach innovation."

NEW FACILITIES FOR A NEW DECADE

Mathias said the company's US site was one step on its journey to become a truly global business. Geographic expansion, innovative services and company growth are Mathias' goals for Rentschler Biopharma as it enters the 2020s.

"Until the end of last year, we were a German company, even to say a South German company. However, we have a lot of international clients. Our clients asked about an expansion into the US market and we took this seriously," Mathias said. The Milford facility, which Rentschler Biopharma acquired from an affiliate of Shire plc, represents the first site for the company outside Europe.

The fully FDA-audited facility with a consistently favorable inspection history (from FDA, EMA, and Health Canada) will be qualified as a multiproduct production site to accommodate the growing biologics market. Rentschler Biopharma will be able to support partner projects in the US from early-stage development through clinical and commercial production.

2020 Vision For Biopharma

Crystal ball gazing is a tricky, sometimes futile, endeavor. No one knows what the future holds, but there are consistent scenarios emerging that are being debated by industry leaders as they try to foretell and outsmart key market catalysts expected to ripple across the biopharma sector in 2020. With insights from executives, investors and consultancies, as well as our own experts, *In Vivo* can paint a picture of biopharma wins and woes expected in the new year and new decade.

LUCIE ELLIS
EXECUTIVE EDITOR, PHARMA & MEDTECH, EUROPE

Looking back a century, in 1920, French researchers perfected a tuberculosis vaccine for use in children from infected households. And the first tetanus anatoxin was produced. In the same year, Frederick Banting of the University of Toronto began a development journey that would eventually lead to the successful use of purified insulin in diabetics. Banting, along with John Macleod, was in 1923 awarded the Nobel Prize in Medicine for the discovery of insulin.

One hundred years later, it is a very different world for medicine discovery and development, and for patients in the options they have for the treatment or management of many diseases. In just the last few years, the biopharma sector has witnessed the first approvals of potentially curative cell and gene therapies, significant advances in cancer immunotherapy and a cure for hepatitis C – to spotlight a few radical advancements.

Despite a recent period of success and groundbreaking science in health care, the coming years present their own set of challenges for the biopharma industry. Pricing and the US market, elections, reputation problems and the ability of large companies to return to growth are just some of the issues spotlighted in recent conversations *In Vivo* has had with industry players. Still, taking into account the evolution of modern-day health care and even just the last decade of immense success for biopharma as a community, positivity for 2020 is abundant.

US PRESIDENTIAL ELECTION

Uncertainty is the biggest issue when it comes to the performance of the biopharma sector in an election year for one of its major markets.

The US presidential campaign of 2020 seems likely to include health care as a major focus, and it would be natural for any industry to be concerned about being in the spotlight of political attention. Given pharma's successful track record in previous reform debates, though, history would suggest that drug firms do not necessarily have too much to fear. History could be wrong, however, and the 2020 campaign may turn out to be a no-win scenario for pharma. Regardless of who the Democratic nominee turns out to be and which party wins the election, industry will see an avowedly hostile president inaugurated on January 20, 2021.

That same dynamic was true in 2016, of course, but the climate has only worsened since then, and even if Congress remains divided, industry needs to prepare for the implementation of unfriendly policies either through legislation or executive action.

Roel Bulthuis, managing director at INKEF capital, told *In Vivo*, "For the upcoming US election, one of the topics is bashing the pharma industry. I expect a negative impact on the pricing of stocks and the uncertainty will have an impact on the availability of capital from public markets." Bulthuis said this could have two effects: it could decrease the opportunity for companies to launch IPOs in the US, and it could decrease the ability of large pharma and biotech companies to pursue deals if their share prices are under pressure. "We are concerned about this," he added, "NASDAQ, for us, is the primary stock exchange."

Unsettling outcomes may even come to pass before the election depending on the answers to two questions: how worried is President Trump about drug prices, and how worried about Trump is the Republican Party? So far, the answer to both seems to be sufficiently worried.

"It is an unpredictable space, American politics," Clay Heskett, a partner at L.E.K. Consulting, told *In Vivo*. "The US government has potential power to manage drug prices through Medicare and other mechanisms, such as increasing competition in certain therapeutic classes."

With it being an election year, the biopharma sector could see more aggressive action in the US. "While private payers look after 80% of the coverage in the US market [separate from government reimbursement schemes], I reserve the right to be surprised about the US market in 2020," Heskett said.

President Trump does not want to be outflanked by the Democrats on drug pricing, and his Rx blueprint rolled out last year was designed to show that he could take meaningful action even in the absence of legislation. Trump is pushing forward with Rx importation, and also wants to show that he can get legislation passed as well, appearing to throw his support behind the Senate finance committee's bill.

The bill is bipartisan, but just barely, and does not seem to have enough Republican support to make it through a vote on the Senate floor at the moment.

Exhibit 1

Nobel Prize Awards In Physiology Or Medicine: 1920-1930

YEAR	LAUREATE	WORK
1920	August Krogh	For his discovery of the capillary motor regulating mechanism
1921	The prize money was allocated to the Special Fund of this prize section	
1922	Archibald V. Hill & Otto Meyerhof	Hill: for his discovery relating to the production of heat in the muscle
1923	Frederick G. Banting & John Macleod	For the discovery of insulin
1924	Willem Einthoven	For the discovery of the mechanism of the electrocardiogram
1925	The prize money was allocated to the Special Fund of this prize section	
1926	Johannes Fibiger	For elucidating *Spiroptera carcinoma* and artificially inducing cancer in an animal
1927	Julius Wagner-Jauregg	For his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica
1928	Charles Nicolle	For work on typhus
1929	Christiaan Eijkman & Sir Frederick Hopkins	For the discovery of various vitamins
1930	Karl Landsteiner	For the discovery of human blood types

SOURCE: Nobelprize.org

That is where the second question comes into play.

Republican legislators do not want to draw Trump's ire, lest they draw a primary challenge, but they also worry about his political fortunes. Those dual concerns could lead them to change their minds and support the bill, even though White House domestic policy council director Joe Grogan's declaration that "We're out of time for ideas" does not inspire confidence that this will be a thoughtful piece of legislation.

Pharma might be feeling similarly conflicted, even if the Senate bill is certainly preferable to the House legislation. The tried-and-true arguments about the need to protect innovation no longer seem to be having the impact that they used to. Industry has suffered some surprising, though relatively minor, legislative defeats in the form of increased payment it is being asked to make to the government. And more troubling than the bills themselves is the idea that legislators now seem to feel they can take without even asking.

Industry has, in fact, had to resort to press conferences to get its ideas across. A sure sign that it is getting less backroom traction than it enjoyed in previous reform debates. And when even a candidate as studiously moderate as Pete Buttigieg now has a plan that would direct the government to negotiate drug prices in much the same manner that the House bill would, pharma must know that it is in trouble.

Pharmacy benefit managers are expecting that Rx pricing and rebating practices will return to normal next year, but firms would be wise to keep price increases in check if they want to avoid more intense campaign fury.

Pharma could of course get itself out of this jam if it comes up with some good ideas – it is an industry built on innovation after all. Firms just need to figure out how to make sure they are reimbursed based on the value of their medicines, but with patients only having to pay a small amount because of the considerable savings that pharmaceuticals generate for the health care system.

Come to think of it, it might be easier just to cure Alzheimer's disease.

SHOWING VALUE

More scrutiny over prices and a change in pricing models for new transformative medicines is casting a cloud of ambiguity over the global biopharma sector. But it is the unstable US market that is expected to rock the boat in 2020. "At the moment, the US accounts for somewhere between 70% and 80% of total global value for innovative therapies; that cannot continue forever," said L.E.K. Consulting's Heskett.

"Showing value for money is a key priority" for US drug developers in 2020, said Loic Plantevin, partner at Bain & Company.

Entering 2020, Juliette Audet, a principal at the venture capital group Forbion, said the political discourse on the biopharma industry in the US was relatively worrying. She told *In Vivo* that recent political developments hinted that the US might be comfortable with having less innovation in its biopharma market if it comes with a reduction in drug prices. "Investors will have to grapple with the consequences of such measures if they get implemented. The other side is the public opinion of the biopharma industry, especially in an election year. It is a very popular thing to say, 'We'll have less innovation, but cheaper drug prices for Americans as a result.'"

Audet noted that the understanding outside of the industry of how new drugs are developed, how much it costs and how pricing models work is not necessarily a complete picture. "It's important to keep lawmakers, politicians and the public informed on the challenges of develop-

ing new drugs for patients: we still need to fund innovation so that we can tackle the big diseases," she said. "It is our role to shed some light on the reality of what drug development means and requires, and its impact on public health. Because new efficacious drugs quickly become the new standard of care, there is a tendency to forget the enormous improvements drug development have brought over the last two decades, for example in diseases like rheumatoid arthritis and multiple sclerosis, let alone vast and ongoing improvements in oncology. Without stimulating innovation, these developments will come to a halt."

Maina Bhaman, partner in capital funds at Sofinnova Partners, said her greatest concern entering 2020 was pricing and reimbursement. "We need to be able to anticipate pricing in the future, to make sure the companies we invest in and the drugs they develop will get a price that justifies the investment."

In her role, Bhaman is focused on seed and series A investments. She said Sofinnova did not expect to change its approach to biotech investing in the near future. "We are sticking to our knitting of holding a significant stake in companies." Sofinnova aims for 20% to 25% ownership. This approach is harder to maintain when companies are seeking much larger early-stage funding rounds, but Bhaman said Sofinnova's approach was sustainable in Europe. "In the US, it is potentially unsustainable but we're still looking for good companies where we can make returns here."

Bhaman said Sofinnova "is a big believer in keeping a bit of discipline." There are some areas where large rounds are necessary, she added, such as cell and gene therapy where investment in manufacturing facilities can be needed to reach a critical inflection point.

MANAGING REPUTATION

Aligned with issues around fair and sustainable pricing for new drugs is the challenge of big pharma's bad reputation. Bulthuis noted that recent data for the US market showed the public's opinion of the pharma industry was "lower than that of the people making guns." He said, "The general perception of pharma by the public is still bad and we need to pay attention to this."

Bhaman, though, said it was important to keep perspective when it came to bad headlines. "One or two companies do not make the industry, and pricing disputes do not make for a bad industry. We have had a lot of success in developing new treatments for patients."

A shadow that has lengthened over the industry in 2019 is the ramping up of opioid liability litigation in the US. As several big opioid lawsuits have progressed toward trial or into settlement agreements, the financial impact of the opioid crisis on the industry is becoming less theoretical and more of a reality.

Purdue Pharma LP, the privately held drug company that made billions from the sale of OxyContin (oxycodone) and other opioids over two decades, filed for bankruptcy in September 2019, in a sign of just how severe the toll may be. *(Also see "Purdue Pharma: From Blockbuster Success To Bankrupt Villain " - Scrip, 16 Sep, 2019.)*

Another drugmaker, Insys Therapeutics Inc., filed for bankruptcy in June after reaching a settlement agreement with the US government around the marketing of Subsys (fentanyl sublingual spray).

Investors have been hedging their bets when it comes to public drug manufacturers with liability exposure, including Johnson & Johnson, Teva Pharmaceutical Industries Ltd., Mallinckrodt PLC, Endo International PLC and Mylan NV.

The silver lining for drug manufacturers is that as the litigation progresses and some cases are settled, the results provide greater clarity for stakeholders on the potential financial impact. Teva, for example, entered into a settlement agreement in principle with plaintiffs in a big opioid bellwether trial in Ohio just as opening statements in the trial were about to begin. In that agreement, Teva agreed to a $20m cash payment to the counties plus $25m in supply of Suboxone (buprenorphine/naloxone). But the company also announced an agreement for a global settlement framework to end all opioid litigation for $250m in cash and $25bn in supply of Suboxone over 10 years. In November 2019, though, Teva had not yet secured full approval for the deal.

While such a resolution would still be financial overhang for Teva in the years ahead, it would set the bar for how long the company's financial recovery will take. Teva is already in a precarious financial situation, with billions in debt and a challenging US generic drug environment, and so another uncertain risk factor looming above the company has raised questions about bankruptcy.

J&J, a defendant in several opioid cases, also reached a settlement in Ohio, agreeing to pay $10m to two county plaintiffs, reimburse $5m in legal fees and direct $5.4m in charitable contributions to non-profits connected to opioid-related programs. But in another case, in Oklahoma, a judge ordered J&J to pay $572m, a decision J&J is appealing.

Purdue's bankruptcy was designed to settle litigation with what it called a "critical mass" of plaintiffs, including 24 state attorneys general. It would end more than 2,000 lawsuits alleging the company fueled the opioid epidemic in the US. Purdue said the settlement structure would provide more than $10bn of value to assist the opioid crisis, though the deal has not been finalized.

The impact of the opioid crisis on the sector remains far from certain, but the negative news continues to weigh on the broader industry even as it works to turn the page. In the wake of this situation in the US, many drug makers have committed to rebuilding trust with society.

RETURNING TO GROWTH

The innovative drug development sector continues to feel pressure to grow pipelines as global best-selling drugs, which are responsible for significant revenues, reach the end of their patent lives. "The patent cliff which hit the pharma businesses over the last 20 years will keep going," said Bain & Company's Plantevin. "This cycle will keep eating pharma: the only way to maintain growth is by having your innovation machine deliver those assets which will enable you to provide high-value therapeutic solutions to patients and payers, with an increasing focus on health economic outcomes. Not everything coming through the pharma pipelines right now will be economically viable."

Plantevin sees a future where companies need to work as "launch factories" producing tailored product launches in smaller indications over a series of time points, rather than large commercializa-

tion activities for broad patient populations. "Organizations will need to be able to constantly and continuously launch new products or in new indications. It is a very different engine."

Plantevin cited Regeneron Pharmaceuticals Inc.'s Dupixent (dupilumab), an interleukin-4 receptor antagonist, as an example of this kind of tailored and serial approach to launching a drug in multiple indications in quick succession. Dupixent was first approved in the US in March 2017 for moderate to severe atopic dermatitis in adults. By November 2019, the product had also been approved in asthma, eosinophilic asthma, sinusitis and nasal polyps. There are Phase III trials ongoing for the drug in eosinophilic esophagitis, chronic obstructive pulmonary disease and allergies.

Forbion's Audet said she expected to see more "bolt-on acquisition deals" by big pharma in 2020, in particular to bring early stage assets into their pipeline. "I'm not discounting the value for big pharma companies in building their own pipelines and building a specific expertise," she said. However, Audet believes the big drug developers will continue to mitigate the risks of early stage drug development by outsourcing part of their R&D activities through licensing deals and alliances.

"Pharma companies are doing less in-house discovery," Sofinnova's Bhaman said. "It is a great time to be in biotech. There is a lot of money going into the biotech sector as well and the sector will continue to grow." She added that as a result of more money being available to biotech companies, their activities are expanding into broader therapeutic areas. "We are not limiting ourselves to investments in oncology or inflammation."

BREAKTHROUGH SCIENCE

The biopharma sector has seen a rapid pace of change in the last 10 to 15 years as groundbreaking scientific developments have become realities for treating patients – immunotherapies, cell and gene treatments, and effective cures for the first time in some diseases, such as cystic fibrosis and hepatitis C.

L.E.K. Consulting's Heskett highlighted gene therapy as a critical development area for 2020. "We are on the cusp of substantial launches," he said.

"We have been talking about gene therapy for 20 years in this industry and now it is here," Heskett said. "It is powerful, and it is going to have a big impact on patients. Treatments that are potentially curative really change the game." He noted that pricing and launch strategies for novel gene therapy treatments were going to feature heavily in the industry's top challenges in the first half of the new decade. Heskett added that in the 2020s gene therapies "will also evolve out of the small orphan diseases into larger indications that will come with different pricing challenges."

Despite the potential in this development space, the biggest red flag for the future of gene therapies as viable commercial prospects is duration of therapy. "Is the treatment truly curative? What is the duration of treatment effect? This is what payers want to know and it is information we don't have yet," Heskett said. Treatment effect will differ by therapy and indication but there is potential for gene therapy to cure some diseases. Still, there will be other cases where the patient has to go back and get a gene therapy booster of some kind. "What does that mean for patient monitoring and for the commercial models, etc.? There are unknowns for sure," Heskett said. "Still, the excitement about potential benefit is outweighing a lot of the worries."

Heskett added that he expects the cell therapy pipeline to mature in the 2020s. The first wave of cell therapies has launched to much excitement and fanfare. Heskett said he was positive about their potential and efficacy, but commercial reward has been slow. "Cell therapies have experienced slower uptake than some might have expected because the actual delivery of that therapy is a challenge … The system is not designed at the moment for cell therapies. So, there's effectively a reengineering that has to occur for treatments to get to patients."

Heskett also noted that personalized medicine will mature in the 2020s. "We have worked on an interesting hypothesis, tabled by Nick Johnston at Perella Wienberg, that in the age of personalized medicine large pharma's role will be diminished and that if you can identify the patient based on certain biomarkers, you can design a therapy for that patient and do almost everything – from target identification through the marketing and distribution – on an outsourced basis. If that is the case, is there still a need for large pharma companies?" This theory does raise some provocative questions for the industry as it stands today.

Bulthuis made similar comments regarding the drug development sector's interest in smaller and more explicit patient populations. "At the therapeutics level, in the last decade we went from blockbuster drugs and an emphasis on finding the next blockbusters to a focus on smaller indications and more defined patient populations within those indications," he said. "Think about oncology, cardiovascular – we will move away from disease classifications we have right now and go toward biology and mechanistic-based classifications," Bulthuis said. "I see us moving toward biologically defined populations of patients who will benefit from the same drug. With better technologies for defining these biological populations, we will be better able to treat patients." Bulthuis also highlighted the convergence between health and technology as a trend that will continue through 2020. "More companies are integrating tech into their portfolios," he said.

Heskett said the situation around artificial intelligence and machine learning was a bit chaotic at the moment. "Where and how should AI be applied and is it working?" he asked. Still, he said there was no question in the minds of his R&D clients that there was a role for AI in drug development. "It is not yet optimized and there are a number of approaches being tested to see what works best. We are seeing a range of business models for AI providers, from pure fee-for-service models to classic biotech milestone and royalty structures, as well as some companies using their AI technology to discover and develop their own pipeline candidates."

IV124395

Editor's note: Additional reporting by Nielsen Hobbs and Jessica Merrill.

HOW BIG ARE PHARMA'S GOLDEN EGGS?

Pharma industry sales are heavily reliant on a relatively small number of relatively costly drugs. But what are its biggest golden eggs, how reliant are companies on those products, and how has the situation evolved over time?

How Important Are The Top Selling Drugs?

In 2018, the top 180 companies in pharma (representing > 95% of all drug sales) generated $829bn in pharma sales. Of these sales:

TOP 10
10 drugs sold by
16 companies

11% of pharma sales
$87.154bn

TOP 20
17% $142.598bn

TOP 50
29% $238.281bn

Top 10 Drugs In 2018 – And Top 10 Drugs A Decade Ago, Sales ($m)

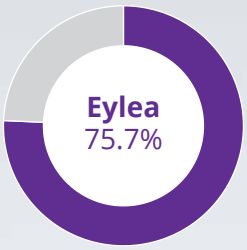
2018		RANK	2009	
20,473	Humira	1	Lipitor	12,653
9,685	Revlimid	2	Plavix	9,804
7,570	Opdivo	3	Advair Diskus	7,877
7,453	Enbrel	4	Remicade	7,103
7,263	Eylea	5	Enbrel	6,691
7,171	Keytruda	6	Abilify	6,392
7,138	Herceptin	7	Diovan/ Diovan HCT	6,112
7,002	Avastin	8	Avastin	5,747
6,903	Rituxan	9	Rituxan	5,622
6,496	Xarelto	10	Humira	5,565

16 Drugs
had sales of
>$5bn in 2018

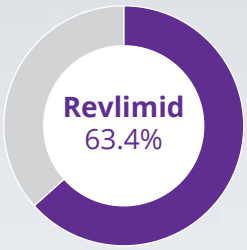
11 Drugs
had sales of
>$5bn in 2009

Drugs in red ranked in top 10 in 2009 & 2018

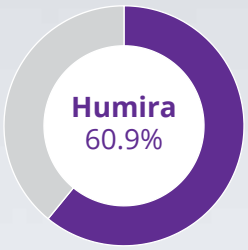
Companies whose revenues depended most on top 10 golden eggs in 2018:



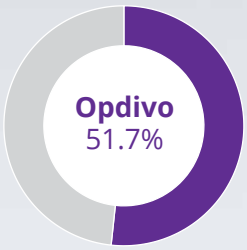
Regeneron, $6.7bn



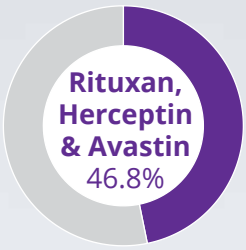
Celgene, $15.3bn



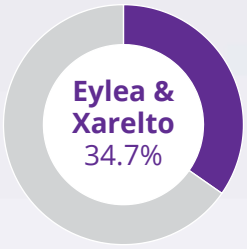
AbbVie, $32.7bn



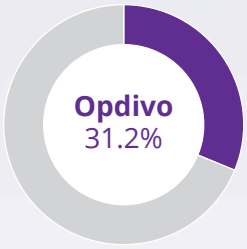
Ono Pharma, $2.7bn



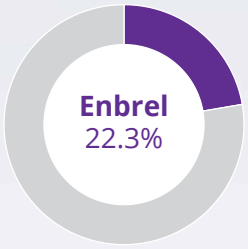
Roche, $44.8bn



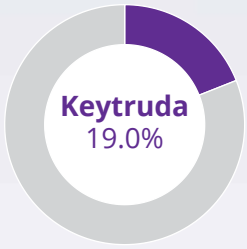
Bayer, $18.8bn



BMS, $21.6bn



Amgen, $22.5bn



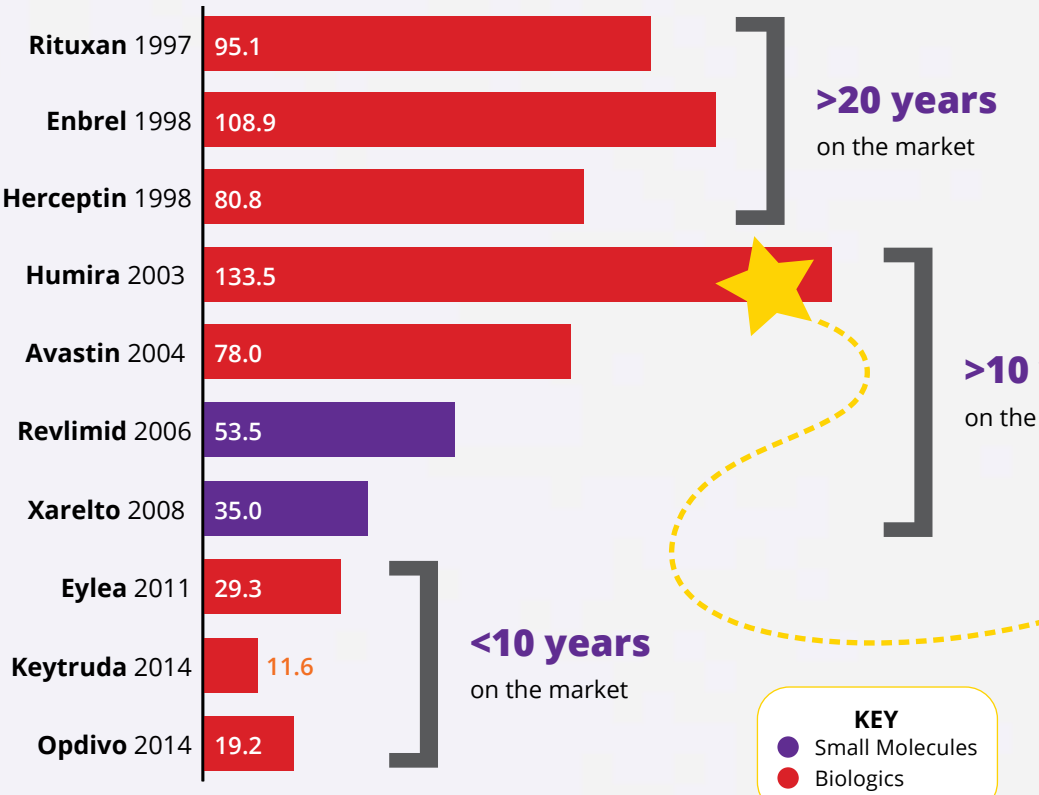
Merck & Co., $37.7bn

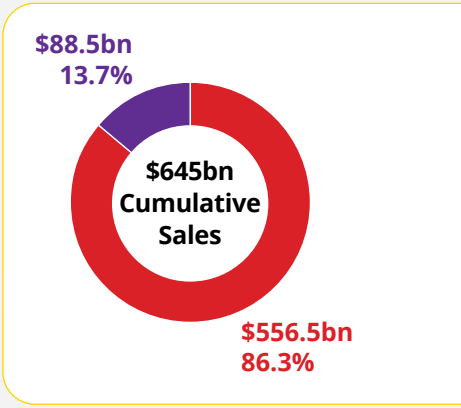
KEY
Company Name,
Total Pharma Sales

Percentage figure = product's contribution to total pharma sales

THE PAST DECADE HAS SEEN BIOLOGICS GROW TO DOMINATE THE BEST-SELLING DRUGS LIST.

Longstanding Autoimmune & Cancer Biologics Drive $645BN In Cumulative Sales For 2018'S Top 10 Drugs



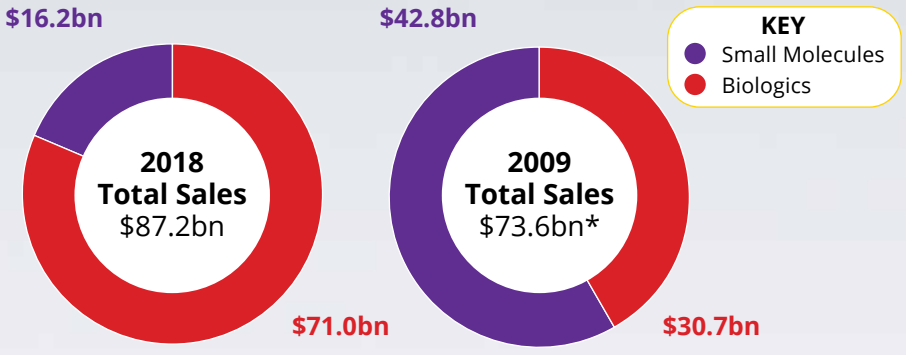


KEY
- Small Molecules
- Biologics

Since its launch in 2003 **Humira** has clocked up sales of **$133.5bn**.

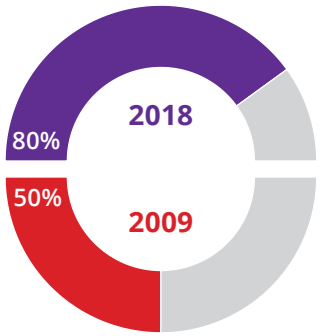
Drug Launch Year **Cumulative sales to 2018 since launch ($bn)**

Sales Of Top 10 Best-Selling Drugs By Molecule Type



*rounding accounts for discrepancy in total figure for 2009

Proportion Of Top 10 That are Biologic Drugs



But The Golden Age Of The First Wave Of Monoclonal Antibodies Is Waning

REMICADE

–35%
Decline in Remicade 2018 global sales

$9.9bn
2014 Sales peak before first biosimilar launches

11th place
In 2018, after being in top 10 since 2006

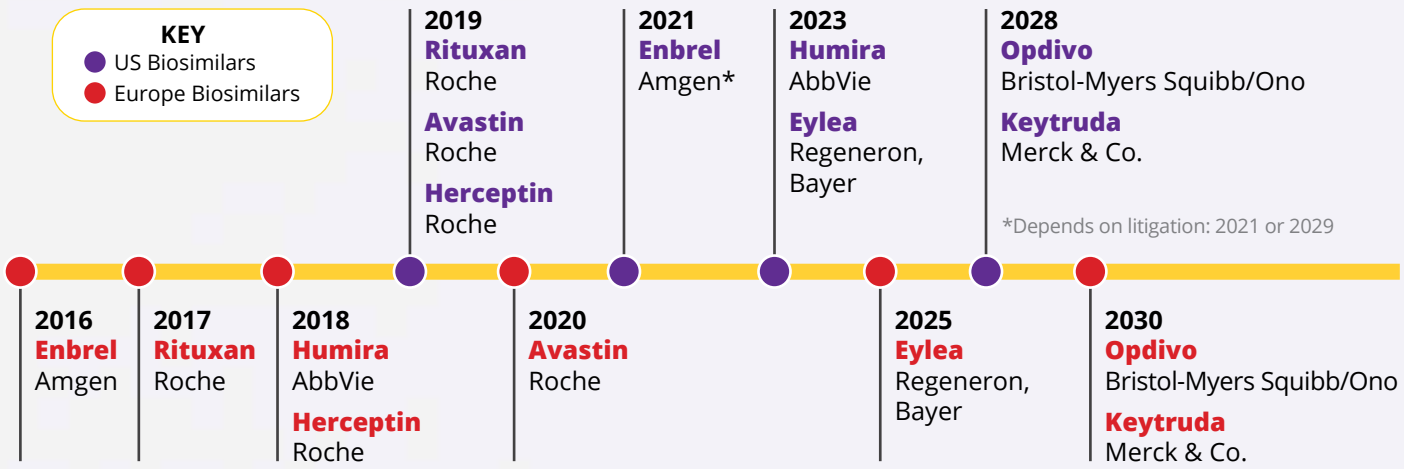
RITUXAN

–47%
Decline in European sales following 2017 biosimilar launches

HUMIRA

–28%
Decline in Q1 2019 ex-US sales following 2018 European biosimilar launches

Biosimilar Launch Dates for 2018's Top-Selling Biologics



Note: NB future launch dates are estimates and may be subject to change.
Sources: Medtrack, company SEC filings, Scrip, Pink Sheet

Design: Janet Haniak / Informa Pharma Intelligence Design Team

Big Pharma's Aging Antibodies Cling To Their Crowns

ELEANOR MALONE
EDITOR-IN-CHIEF,
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The best-seller rankings today are testament to the great success of antibody drug technology developed at the end of the last century, and contrast with the dominance of primary care small molecule drugs that powered big pharma in previous decades. But where did these drugs come from – and where are they going?

A minority of the current generation of best sellers were developed in-house. Myeloma and blood disorder medicine Revlimid (lenalidomide) was discovered and developed in Celgene Corp.'s own laboratories after the firm licensed patents to thalidomide from Rockefeller University in 1992. Antithrombotic Xarelto (rivaroxaban) was also developed in-house by Bayer AG, as was eye drug Eylea (aflibercept) by Regeneron Pharmaceuticals Inc.

Most were acquired very early in their development journeys. Roche came by its three top-sellers through its acquisition of Genentech. The Swiss group acquired a majority stake in Genentech in 1990 long before cancer drugs Herceptin (trastuzumab) or Avastin (bevacizumab) entered the clinic. Roche bought the US firm out completely for $46.8bn in 2009, after Herceptin and Avastin had been launched in 1998 and 2004, respectively. Its other best-seller, Rituxan (rituximab), was developed by IDEC Pharmaceuticals, which merged with Biogen Inc. in 2003. Rituxan was the subject of a collaboration with Genentech in 1995 to take the drug into Phase III for B-cell lymphomas. Rituxan was approved in 1997.

Merck & Co. Inc. and Bristol-Myers Squibb Co. also came by their checkpoint inhibitors before they had delivered clinical results.

BMS picked up what was to become Opdivo (nivolumab) when it was still only just entering clinical development in 2009, through the $2.4bn buy-out of its partner of more than a decade, Medarex. That acquisition was motivated by BMS's appreciation of the latter's antibody technology, which had already yielded late-stage candidate ipilimumab (now Yervoy) and several marketed therapies.

In the same year, Merck acquired future Keytruda, but only as an incidental part of its $41.1bn acquisition of Schering-Plough. The latter had itself acquired the product unintentionally, as it were, when it bought Dutch firm Organon for its CNS and women's health portfolio. Preclinical pembrolizumab was such an unimportant part of the acquisition that in 2009 Merck shut down the project and planned to out-license it. It was only reactivated in 2010 after BMS made progress with Yervoy and Opdivo.

A couple were more advanced when they were acquired. Developed by UK biotech Cambridge Antibody Technology and BASF's Knoll Pharmaceutical Co. unit in the 1990s, Abbott Laboratories Inc. bought what was to become its most valuable asset – then known as D2E7 and already identified as a hot prospect in the industry – when it paid $6.9bn for Knoll in a deal agreed in 2000 and completed in 2001. Subsequently dubbed Humira, it was approved by the US Food and Drug Administration for rheumatoid arthritis the following year, becoming the third TNF inhibitor to reach the market after Remicade (infliximab) and Enbrel (etanercept).

As for Enbrel, the product had already been on the market for two years and was heading for blockbuster status when Amgen Inc. bought Immunex for $9.6bn in 2002.

WHAT NEXT: WINDS OF CHANGE?

All but two of 2018's top 10 best sellers were biologics, and seven had been on the market for more than 10 years. The first generation of antibody drugs have enjoyed a couple of decades of rapid growth but their maturity means that the landscape is ripening for change.

Ex-US sales of the world's best-selling drug Humira dropped by nearly 15% in the fourth quarter of 2018, after biosimilars were launched in Europe in October. Other drugs have already been hit by similar challenges, including for example one-time top 10 best-seller Remicade (infliximab).

Still, antibody drug makers are not giving up on their biggest market – the US – without a fight. AbbVie Inc. books more than two-thirds of Humira's sales in the US. It has managed to keep multiple biosimilar contenders at bay there until 2023 under IP settlement deals. Meanwhile, the drug's US price, already higher than elsewhere, went up by nearly 10% from 2017 to 2018 according to a report by Datamonitor Healthcare.

PRICE HIKES

AbbVie is not the only company leaning on price hikes to up the yield of aging cash cows.

Celgene pushed up the cost of Revlimid not once but three times in the US over 2017-2018, leading to a 16.5% increase in the average wholesale price (AWP). Like AbbVie with Humira, Celgene books two thirds of the revenues from the oral small molecule in the US, where it has been on the market since 2005.

In fact, among the world's 10 best-selling drugs, only Eylea's price did not rise in the US in 2017-2018.

The continuing US patent stronghold and AbbVie's muscular pricing tactics will enable Humira to retain its place at the top of the league table for some time to come.

The past three years have seen the gradual introduction of biosimilars to blockbuster mainstays in some markets. However, the real impact across the all-important US market is yet to unfold. Meanwhile, it remains to be seen if the new age of advanced therapies and personalized medicine will deliver blockbusters of the magnitude of Humira.

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MELANIE SENIOR
CONTRIBUTOR

Behave, Pharma: Why Culture Is Top Of The List

Drug pricing and access issues expose the pharmaceutical sector especially acutely to calls for companies to meet ethical and social goals, alongside commercial ones. Digital is up-ending pharma's processes, its workplaces and its consumers. R&D productivity is spluttering. Amid this turmoil, CEOs highlight company culture – the way an organization behaves – as a crucial ingredient for success. But what is a "right" culture? Organizational culture is neither static nor singular. It is continuously influenced by acquisitions, markets, new technologies and new generations. And pharma's history suggests that culture change cannot happen without sufficient people change.

It is not enough to have the cleverest scientists, the best technology or the fairest prices. These days – perhaps more than ever before – culture may be the most important ingredient in pharmaceutical companies' success. "Defining the kind of culture you want in the organization is absolutely fundamental," said Emma Walmsley, CEO of GlaxoSmithKline PLC, at the FT Global Pharmaceutical and Biotechnology conference in London, November 2019. "Structural changes in R&D are not that significant. Spending time moving around the deckchairs ... can be enormously disruptive."

She did not explicitly mention the multiple R&D reshuffles at GSK, which dragged on for about 15 years after the 2000 merger. The sub-text was clear, though. GSK did not sink to the bottom of the ocean, but it fell behind most of its peers as a result of all the fiddling. Walmsley – who has been in the job since 2017 – hopes that the culture she is trying to instill, captured within an "innovation, performance and trust" trifecta of priorities, will help bring GSK back to the front. *(Also see "GSK Woes Raise Big Pharma R&D Question" - In Vivo, 4 Dec, 2017.)*

Walmsley's changes are around governance and defining clear decision-making responsibilities across R&D and commercial. No more exciting science that cannot translate into a medicine; instead, "single-point decision-making" – individuals who are appointed to make decisions and are held accountable for them. This may sound basic, but in fact is "culturally very new for GSK," she told the FT audience. (Not for want of trying: back in 2012, then-CEO Andrew Witty said "we're not prepared to allow organizations to drift off for 10 years against failing targets or hypotheses."

GSK's chief executive is not the only leader talking about the importance of culture, in a sector that struggles to shake off its reputational challenges amid 24-hour news cycles and with drug pricing at the top of political agendas. Several other big pharma CEOs are also explicitly trying to regain trust and re-build connections with consumers, society and the next-generation of talent through promoting cultures of openness, accountability and sensible risk-taking – alongside dogged patient-centricity. Finger-pointing and hiding from decision-making or setbacks within the layers of corporate bedding are on the way out. The word "culture" was mentioned 22 times in two hours at the FT event – even though none of the session titles included the term.

WHAT IS COMPANY CULTURE?

"Culture" is tricky to define, and even trickier to spread evenly across all corners of a sprawling, international organization. In essence, it is the way an organization behaves – which is inextricably linked to how its employees behave. Organizational cultures are dynamic, and should evolve alongside economic, societal and technological change.

Culture is directed largely by a leader's actions, and by a common goal that is impossible to dispute, like making patients' lives better, or transforming medicine. It may be captured in mantras like "curious, inspired and unbossed" (Novartis AG), or "innovation, performance and trust" (GSK), or in longer guidelines like Johnson & Johnson's Credo.

Such statements can sound trite. They can also sound a bit hypocritical, as accusations of hidden or manipulated data, unjustified price hikes and/or bribery continue to swirl around the industry. But those reputational issues make it even more critical to have a clear direction, for leaders to be "visible and authentic" and to "set the tone from the top," as AstraZeneca's Marc Howells, VP global talent and development, insisted during the FT event. Leaders' words – and, more importantly, their behavior – feed directly into the ethical, social and governance (ESG) priorities that investors, the public, and potential employees are paying increasing attention to.

Persuading tens of thousands of people to behave a certain way is hard. It is harder still, given the

need to marry apparently contradictory qualities within a single, unified culture. Rapid scientific and technological change (including ballooning data) requires agility and flexibility; yet that same fast-moving world demands, more than ever, clear boundaries and strong leadership. A healthy culture must combine creativity and competitiveness with accountability and teamwork; agility with discipline; and hunger for success with the humility to accept failure.

Incentives help. GSK now rewards particular actions – like daring to kill a failing program – rather than actual outcomes. Novartis is moving similarly to endorse scientific failures as wise commercial decisions. Yet incentives are not enough to determine or change a culture. GSK's earlier R&D overhauls included reward structures designed to promote biotech-like behavior, such as annual funding boards and budgets. They did not work as expected. And younger generations may not respond to the same incentives as their elders: social goals and workplace flexibility may speak louder than stock options.

CULTURE CHANGE MEANS PEOPLE CHANGE

The lesson from the last decade or so of big pharma re-jigs is that changing the culture of a large organization is possible only by changing enough of the people. GSK's Walmsley refers to this as a "talent update." The changes she has introduced "have been uncomfortable for some employees," she acknowledged. But the reset is necessary "not because people have not done important work, but because it's about re-designing" for the company's next chapter. It is about developing "fit-for-purpose leaders that embrace the kind of culture you want," she said. (GSK has also cut over 2,000 staff across the US and UK.)

GSK's talent update included the appointment in 2018 of new R&D chief Hal Barron, a Genentech veteran who served as EVP, head of global product development and chief medical officer at Roche. Barron was most recently president of R&D at Google's Calico, alongside ex-Genentech CEO Arthur Levinson.

For Barron, culture is the magic multiplier, alongside science and technology, for drug development success. (He is credited with keeping Genentech's innovation engine going through the biotech's integration into Roche.) If Barron has his way, plenty of GSK's new culture is coming from outside. GSK's $5.1bn acquisition of cancer company Tesaro in late 2018, at a hefty premium, was a "bet on science, but also on people," Barron told an audience at Endpoints News' UK BioPharma Summit in London, October 2019. From here, the challenge is not just catching up on several years' of lost oncology R&D; it is also about how GSK takes Tesaro's culture and "bathes in it and learns from it. We want to achieve that smart, risk-taking" mindset, he said.

FLATTER HIERARCHIES DEMAND GREATER TRUST

At Novartis, too, "we need an environment where teams are not afraid to fail," Marie-France Tschudin, president, Novartis Pharmaceuticals, told the FT audience. The Swiss giant's "inspired, curious, unbossed" tagline means encouraging employees to embrace risk, to take decisions, and to take responsibility for those choices, too. That may sound a reasonable demand for employees in any business, but in fact is "a huge change for so many in pharma, this entrepreneurial way of looking at things," according to Tschudin. For Novartis, the shift from a very hierarchical, rule-abiding Swiss culture to a flatter, unbossed, jeans-and-open-shirt approach will indeed be huge, and will take time.

If leaders are going to devolve more decision-making to lower-down teams, they have to trust them – and their competence. "If you want to delegate risk-taking and have a tolerance for failure, you also need to be very *in*tolerant of incompetence," warned Dan Vasella, who was CEO and chair at Novartis between 1996 and 2010, in a more overtly hierarchical organization with centralized power. You also still need strong leadership and clear rules. "Do not mistake 'unbossed' for 'you can do whatever you want,'" clarified Tschudin. "It's an approach based on principle."

With tens of thousands of employees, across multiple countries (and, in Novartis' case, a steady stream of large acquisitions), the rules will inevitably be flaunted from time to time – with visible consequences in today's always-on media. The furore over hidden, manipulated data surrounding Novartis' gene therapy Zolgensma is one example. The mistake, outed in mid-2019, was eventually pinned to employees within AveXis, purchased by Novartis in April 2018 for $8.7bn. But it shows how being too "un-bossed" may back-fire – and how isolated instances of misbehavior linger longest in many minds.

"It is naïve to think you can control everyone, or that there is no hierarchy. There is always a hierarchy," said one former CEO.

Still, few would dispute that working styles and mindsets need to change within some big pharma – not just in order to innovate fast enough to stay afloat, but also to attract and retain young talent, many of whom may be drawn toward the gig econo-

HANDY TIPS ON CULTURE

Charles Handy (b. 1932) is an Irish philosopher whose ideas about company culture have been influential and appear prescient. He defined four types of organizational culture:

Power culture: characterized by top-down, hierarchical management and centralized decision-making

Role culture: rules- and procedures-driven, bureaucratic, with narrowly-defined roles

Task culture: results- and solutions-driven, with small, flexible, empowered teams

Person culture: focused on individuals' needs and values

Handy argued that corporations have for too long been stuck in the power and/or role culture mode, while changes in education, the economy and in values demand greater emphasis on task- and person-focused cultures. The gig economy, the growth of highly qualified freelancers and changes in what workers seek from their careers are driving a need for more flexible, federal organizations. These are bound by a common purpose, but grant individuals and teams considerable autonomy.

my of professional communities, rather than companies' static hierarchies. "Millennials demand change. They want to move fast. They learn differently, and they have different demands from a job" from those of many older employees, said Tschudin. For example, some millennials seek to broaden their experience-base, rather than to deepen expertise within a given field, she continued.

CHALLENGING NATIONAL CULTURE: SANOFI'S BRITISH CEO

Culture is intertwined with nationality, adding another dimension to pharma firms' culture challenge. Most big pharmas call themselves global companies, with employees of many nationalities and cultures, all over the world. Yet Pfizer is still American, Novartis Swiss, Takeda Japanese and Sanofi French. In some cases, those national heritage ties remain particularly strong.

So the appointment in 2019 of Brit Paul Hudson to Sanofi's helm sent a clear message that the French group needed radical change, and was prepared to swallow some of its Gallic pride in order to achieve that. Hudson (previously head of pharma at Novartis) is not the first non-French CEO – his predecessor Chris Viehbacher was Canadian – but he is the first non-French speaker. Hudson will bring, in the words of one financial analyst, "an Anglo-Saxon mindset" to the task of reviving Sanofi's stuttering R&D engine and deciding what to do with its flagging diabetes portfolio.

Hudson will draw on his background in sales, and a track record sniffing out good products and ramping them up across the globe. He will be based in Paris – still a sensitive issue for the board – but will likely build a more international outlook and partnership base for the group. Like any CEO, he will define and try to propagate his own culture through the organization. It will not be easy; France's strong national identity comes along with strict employment laws and stubborn labor unions. Hudson, who has worked in Europe, the US and Japan, told Bloomberg News in September that his approach to local culture is simply to "immerse yourself in where you go." He will need to do things that make him unpopular in France, though. Hudson revealed a new strategy to drive innovation and growth at Sanofi on December 10, at a capital markets day held in Cambridge, MA. Sanofi will focus on growing Dupixent and its vaccine portfolio, as well as accelerating R&D for six "potentially transformative therapies."

IPSEN PIVOTS TOWARD US

Mid-sized compatriot Ipsen Biopharmaceuticals Inc. is undergoing its own Anglo-Saxon transformation and talent update. "Almost 35% of our headcount was appointed in the last three years," said Harout Semerjian, EVP and chief commercial officer of the Paris-headquartered firm. The update corresponded with the appointment in 2016 of the first-ever non-French CEO at 90-year old Ipsen, which is listed on Paris EuroNext, but majority owned by France's wealthy Beaufour family. David Meek, an American, was head of oncology at Baxalta prior to its acquisition by Shire Pharmaceuticals.

Ipsen had expanded into the US before Meek's arrival, but cautiously. The American ramped that up, moving the company's US headquarters from New Jersey to Kendall Square in Cambridge, MA, in 2018, and acquiring Canadian rare diseases focused Clementia Pharmaceuticals in early 2019 for over $1bn.

Meek described Ipsen's transformation as "profound and ambitious" and, guess what, as "instilling a biotech mindset and nurturing a culture of external innovation." To help with that: American Howard Mayer, previously CMO of Shire Pharmaceuticals' neurosciences division, began as Ipsen's EVP and head of R&D on December 1, 2019. Almost 30% of Ipsen's €1.2bn ($1.3bn) sales during the first half of 2019 were from North America, up from 24% just two years earlier.

CHANGE IS THE CULTURE

Big pharma has been notoriously slow to change, sometimes with good reason. It was slow to embrace digital, just as it was a decade ago in ditching "not-invented-here" syndrome from the halls of R&D.

Now, though, sluggish sales growth and pricing pressures bring a sense of urgency. Several of these giants are now transforming along multiple dimensions in a bid to kick-start innovation and R&D efficiency. They are having to become more patient-centric, more digital and data-driven. They need financial success, but also to be responsible with drug prices. Some have to adjust to being more American, most have to tackle becoming more Chinese. All need to embrace partnerships.

Bundling all this under the umbrella term "culture-change" – with an emphasis on refreshing workforces – is convenient and mostly fair. The shifts underway will be gradual, despite their urgency. Changes to decision-making at GSK "will take years to gain traction," conceded Barron. And there is no fixed destination. Culture is dynamic; it will respond to some external circumstances, just as it builds on each company's history and strengths. Devolved decision-making, acceptance of failure and teams bound by trust and a shared mission are popular directions today; just like immuno-oncology and rare diseases are popular therapy areas. Yet these are not absolutes – and winds may change.

Defining a company's values and direction, behaving according to those values, and creating the best environment for workers to do the same, are all part of the complex role of today's pharma leaders. So is deciding when to be flexible, and when to hold firm. "Culture can be a fantastic accelerator," said GSK's Walmsley. "But it can also be a complete de-railer if you get it wrong. It can lead to paralysis, or churn, or worse."

Pharma CEOs have their jobs cut out.

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CAN PHARMA BE BIOTECH-LIKE? NOT REALLY

The pharma industry has mostly failed to imbibe biotech culture, even as its need for innovation has grown more acute. Biotechs are typically smothered by the pharmaceutical giants that buy them. Most recently, Sanofi's 2018 acquisition of Belgium-based Ablynx resulted in an employee exodus to nearby independent biotechs such ArgenX and Galapagos. (Galapagos is effectively under Gilead Sciences' wing, however, following an expansive R&D collaboration in mid-2019.)

Roche was credited for many years with keeping Genentech at arm's length, but even that did not last – although Roche is widely believed to have handled Genentech's jewels more wisely than most other biotech buyers.

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Welcome To Alexion 2.0

In an exclusive interview, Alexion R&D head John Orloff takes *In Vivo* on a tour around the company's rejuvenated pipeline and explains how the business is innovating to pre-empt the Soliris-shaped hole in its balance sheet.

JO SHORTHOUSE
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Two years ago the board of directors of Alexion Pharmaceuticals Inc. began a seismic overhaul of its leadership, strategy and pipeline. The Boston-based rare disease specialist had success with Soliris (eculizumab), its blockbuster first-in-class complement inhibitor, but needed to prove to shareholders where the next revenue streams were coming from.

A less-than successful $8.4bn takeover of Synageva BioPharma Corp. in 2015, which brought in the slow-selling Kanuma (sebelipase alfa), had made investors question Alexion's direction. The follow-on complement inhibitor to Soliris, Ultomiris (ravulizumab), helped plug the revenue gaps, but it was not going to be enough.

MANAGEMENT MERRY-GO-ROUND

A fundamental part of "Alexion 2.0" is the plan to broaden and diversify its R&D pipeline, both through external business development and organic innovation. John Orloff joined the company two years ago, during the tumultuous but necessary re-imagining of the drug company.

After some 2016 reporting irregularities, the senior management team of CEO David Hallal and chief financial officer Vikas Sinha reportedly lost the confidence of the board of directors. Both execs resigned, leaving ex-AstraZeneca PLC CEO David Brennan, a member of the Alexion board, in place as interim CEO, alongside Honeywell CFO David J. Anderson as the company's financial head. Speaking about Brennan's position at the time, Doug Norby, lead independent director at Alexion, said the company was "fortunate to have someone of his caliber guide us during this transition."

Just three months later, in March 2017, Alexion's founder, Leonard Bell, who had formed the company in 1992 and was CEO until 2015, announced his retirement as chair of the board. Brennan took his place as chair to spearhead the search for a new executive management team and said in a statement that the company was "working hard to drive significant, long-term growth that benefits all of our stakeholders."

The search for a new CEO did not take long. By the end of March, the head of Baxalta, Ludwig Hantson, was announced as CEO. This appointment was swiftly followed by a number of important management changes including a new CFO, chief commercial officer and heads of compliance and human resources. Notably, Martin Mackay, head of R&D, retired from the company to be replaced by Hantson's Baxalta colleague John Orloff.

"I thought I could bring my experience from big pharma but also, more recently, smaller companies, to bear on the challenges that Alexion faced that needed to be rebooted," Orloff told *In Vivo* in an exclusive interview.

Six months later, with the new executive management team in place, Alexion announced more major strategic changes. It aimed to save the company $250m with a 20% reduction in the workforce, an investment of $100m to rejuvenate the pipeline through business development and add-on complement indications, a new headquarters in Boston, MA, and a new Research Center of Excellence in New Haven, CT.

Orloff chose to de-prioritize programs such as cPMP

replacement therapy ALXN1101 and samalizumab, as well as partnerships with Moderna Inc., Blueprint Medicines Corp. and Arbutus Biopharma Corp. The speed with which Orloff could move to reposition and focus the Alexion pipeline was helped by the size of the firm. "I've found that coming into a smaller company focused on rare disease there's a great opportunity to have an impact more quickly and to make decisions faster. There is less bureaucracy, and so for me it's more fun."

Orloff had been head of R&D at Novelion Therapeutics Inc., a small Boston-based biotech employing around 200 people. Prior to that he was chief scientific officer and global head of R&D at Baxalta, and previously held executive R&D roles at Baxter International Inc., Merck Serono SA, Novartis AG and Merck Research Laboratories.

Despite Alexion making sweeping changes throughout the company there was still immense pressure from activist investor Elliott Management, which did not believe the firm was doing enough to increase its stock price. In December 2017, after the company's market capitalization dipped below $24bn, it was widely reported that the hedge fund manager was urging the biotech to think about selling, while also insisting on more biotech experts on the board of directors.

And the management merry-go-round may not be completely over. In late-September CFO Paul Clancy, who is well-respected among the investment community, announced his intention to leave the company. Replacing him is Aradhana Sarin, the current chief strategy and business officer. "He has contributed materially to the rehabilitation of Alexion's reputation, and in no small measure ensured that the company's stock became investable again after the difficulties of 2016," said SVB Leerink in an investor note discussing Clancy's departure. "By comparison, Dr. Sarin is largely an unknown quantity, reportedly a capable individual, but one with no C-suite experience, no significant public exposure to investors, and a reputation for active advocacy for transactions. It will take some time before she builds the confidence that Clancy has among investors."

Investors will be encouraged by Clancy's intention to remain with one hand on the tiller for the next few months, but by year-end there will be a new hand at the helm of this frequently challenged biopharmaceutical company. "At this stage, despite Dr. Sarin's strong reputation, in our view there's no basis for arguing this transition will be positive for the stock or for investors' interests," said Leerink analysts.

BUSINESS DEVELOPMENT

Discussing the picture before he joined the company, Orloff said, "There was a heavy reliance on Soliris, the pipeline needed to be expanded and for me that was thrilling." Despite the immense pressure by investors to turn the company's pipeline around, Orloff told *In Vivo* that this was "the best place to be, as an R&D person, to come in and be charged with building a new pipeline."

In the two years that Orloff has been with the company he has made swift and decisive changes. "Our goal has been to rechart the vision of Alexion: Alexion 2.0 we're calling it," he said. Focusing on the unmet needs of patients with rare diseases, Alexion has four approved medicines, covering six different diseases. But Orloff insists it is not stopping there. "We're looking for transformational impact, we're looking at all therapies in our core business but beyond that, that really have an impact on lives."

The Alexion management team has created four franchises in hematology/nephrology, neurology (a new growth driver), metabolic and the neonatal Fc receptor (FcRn) opportunity that, Orloff said, can branch in a number of different directions.

Orloff is pleased with the progress he has made since 2017. He has catalyzed eight clinical-stage business development deals, and the company has "capacity to look at new assets" that fit within the four franchises. He also highlighted that moving the firm's therapeutic focus from ultra-rare to rare disease would "allow us to expand even beyond the current footprint." He added that continuing to build the pipeline was a "chief priority for us." Such is the pressure to perform, and importantly not to miss opportunities for growth. The Alexion business development committee, which consists of the executive management team, meets weekly, sometimes more frequently to evaluate opportunities on a continuous basis, explained Orloff.

Orloff's first big addition to the Alexion pipeline was the $855m takeover of Wilson Therapeutics AB to add the Swedish biotech's sole asset, WTX101, to its pipeline. WTX101, now called ALXN1840, is a first-in-class oral copper-binding agent with a unique mechanism of action and ability to access and bind copper from serum and promote its removal from the liver. Wilson's disease is a rare inherited disorder caused when copper absorbed from food accumulates in the body, particularly the liver and brain. It is characterized by neurological disability, progressive hepatic impairment and death in the absence of treatment.

Orloff became familiar with the liver disorder during his hospital residency in the 1980s. There have been no new products approved for it since then. SVB Leerink analysts believe the market could be worth $1bn by 2027. Current products are fraught with multiple adverse events leading to adherence issues, progressive liver disease and eventually liver transplant. "We think that this is going to be a transformative therapy for those patients," Orloff said. Enrollment for the trial is going well, he noted. Alexion hopes it will be fully enrolled by early 2020.

This was the first M&A activity for the company since Alexion's $8.4bn purchase of Synageva in 2015 for the sluggish Kanuma (sebelipase alfa) for lysosomal acid

lipase deficiency (LAL-D). This move badly damaged shareholder value and investor opinion of Alexion's business development capacity, said analysts at the time. However, investment analysts reacted well to the Wilson Therapeutics deal. At the time, Barclays said, "Overall, we think this acquisition helps to diversify away from Soliris and provides investors with near-term, de-risked clinical catalysts, to help shift sentiment."

Analysts at SVB Leerink believe that the asset, if successful in the clinic, will launch in 2022, generating revenue of $470m by 2025, growing to $760m by 2027.

The $400m acquisition of Syntimmune in September 2018 was also well received by Alexion shareholders. The deal brought in the company and its mid-stage immunoglobulin G (IgG)-targeting candidate, SYNT001, which is being studied in three rare disorders and which moved Alexion into the neonatal FcRn arena. SYNT001 is in Phase Ib/IIa for warm autoimmune hemolytic anemia (WAIHA), pemphigus vulgaris (PV) and pemphigus foliaceus (PF).

"We have capacity to do additional deals, both from an organizational expertise perspective and a resource perspective, as well as financial flexibility to do additional deals to expand the pipeline," said Orloff. He also noted that the company was committed to "organic expansion as well as external innovation."

FcRn

The FcRn arena is of interest and importance to Alexion. A $25m up-front deal inked with Swedish biotech Affibody in March 2019 saw the company agree to take the clinical lead in developing ABY-039, a bivalent antibody mimetic targeting the FcRn, which moved into a Phase I study in UK healthy volunteers in March 2018.

Despite a host of potential competitors developing FcRn antagonists, including argenx SE, Immunovant, Momenta Pharmaceuticals Inc. and UCB Group, Orloff believes the molecules have the potential to be very fruitful.

While discussing SYNT001, he described the molecule as an "exciting new target and mechanism" that has proof of concept in pemphigus vulgaris. Its initial indication will be in WAIHA, first with an intravenous and later a subcutaneous formulation. Although he remained coy about how this full-length antibody could differentiate from others in development. Orloff did note that the "product has some features that potentially can be differentiated from competitor FcRn molecules."

"The ABY-039 molecule is a little different," he continued. Although it targets the FcRn, it is not a full-length antibody: it is a smaller package at 19 kilodaltons, compared with the typical antibody, which is 150-160 kilodaltons. The Affibody molecule could be packaged into a smaller volume "with the same punch" in an autoinjector for at-home subcutaneous administration.

> *"I can't make any promises about deals beyond the end of the year, but we have a lot in the works, and I can tell you that we're not finished and we want to continue to push that envelope."*

JOHN ORLOFF, ALEXION'S HEAD OF R&D

This chance to have a "second shot on goal" was a large part of the attraction of the Affibody deal. Alexion believes that the molecule has the potential to be a best-in-class product in terms of route of administration and acceptability to certain segments of patients, especially those with neurological disorders. "This is a target that offers us the opportunity to pursue a wide range of IgG-mediated autoimmune diseases within hematology, nephrology, neurology and potentially new areas for us like dermatology and beyond," explained Orloff, saying that there are "at least a dozen IgG-mediated autoimmune diseases on our radar that we could pursue."

DIVERSIFICATION

The company is not interested in buying only late-stage assets for P&L gains. Diversification takes many forms, said Orloff. "We want to diversify by risk and stage, so we want to have a portfolio that has a steady

flow of new INDs and CTAs filed, as well as products in Phase II and Phase III development so we continue to have a steady flow of launches over the next several years and into the future."

Orloff is certainly putting his money where his mouth is. There has been a steady stream of research partnerships signed with companies since his arrival at Alexion, including the $25m collaboration with Zealand Pharma on novel peptides, a €14m ($11.4m) deal with Complement Pharma to co-develop the preclinical C6 complement inhibitor CP010 for neurodegenerative disorders and the $22m collaboration to discover and develop RNAi therapies for complement-mediated diseases with Dicerna Pharmaceutical Inc.

A January 2019 collaboration with Caelum Biosciences diversified the company's clinical-stage rare hematology portfolio. The $60m development deal pivots on CAEL-101 for light chain amyloidosis. CAEL-101 is a first-in-class amyloid fibril targeted therapy designed to improve organ function by reducing or eliminating amyloid deposits in patients with AL amyloidosis, a systemic disorder that causes misfolded immunoglobulin light chain protein to build up in and around tissues, resulting in progressive and widespread organ damage, most commonly to the heart and kidneys. Patients are currently treated with chemotherapy, a "blunt instrument," Orloff said, and there is a need for new treatments.

Despite the flurry of deal-making, Orloff is not resting on his laurels. "I can't make any promises about deals beyond the end of the year, but we have a lot in the works, and I can tell you that we're not finished and we want to continue to push that envelope," he said. "If something comes along, lets says it's a gene therapy or a cell therapy, we would look at that. We are agnostic to the modality and the technology," he said. "As long as its fits within our mission to pursue rare disease and have an impact on patients."

UPS AND DOWNS OF THE C5 FRANCHISE

But of course, it is not just new additions to the pipeline to which Orloff dedicates his time and resources. He inherited a strong C5 complement inhibitor franchise in the blockbuster Soliris and its successor and possible better, Ultomiris.

With four indications in the US and EU: in paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD), plus three in Japan (PNH, aHUS and gMG), Soliris is still undoubtedly the star of Alexion's show. Along with the longer-acting C5 complement inhibitor Ultomiris, it contributed $1bn to the company's $1.2bn second-quarter earnings in 2019.

Ultomiris is indicated in PNH in the US, Japan and Europe and is awaiting regulatory approval in those geographies in aHUS. With Ultomiris having a potential further than Soliris, Orloff is determined to trial the drug in as many indications as could be applicable, such as thromboembolic microangiopathy associated with stem cell transplants, PNH in children and adolescents, primary progressive multiple sclerosis and amyotrophic lateral sclerosis.

Competitors such as Omeros' narsoplimab and Akari Therapeutics' nomacopan are already in trials in thrombotic microangiopathy associated with hematopoietic stem cell transplantation (HSCT-TMA), but Morningstar analysts said that Alexion's "experience with clinical development compared with these small competitors suggests the company could catch up quickly and further expand the addressable patient population for Ultomiris." The firm is also working on a weekly subcutaneous version of Ultomiris in PNH and aHUS, and a high concentration dose.

The complement inhibitor franchise is growing rapidly. According to investment analysts the newest US approval for Soliris in NMOSD should earn around $700m by 2024. The company is expected to reach a 70% conversion rate of US PNH patients from Soliris to Ultomiris before the end of 2020, and with recently secured approvals in the EU and Japan, Alexion is "expected to establish the new standard of care globally with Ultomiris in the next few years," said SVB Leerink in a 24 July note.

With enzyme replacement therapies Strensiq (asfotase alfa) and Kanuma also contributing double-digit year-on-year growth in the second quarter, one would think the company's forecast was fair set. However, where there are peaks there are also troughs and the significant trough for Alexion's immediate future is the impending patent cliff for money spinner Soliris.

In September the European Patent Office declined to grant patents that would extend Soliris's exclusivity for a few more years. While Alexion continues to future proof its hold on Soliris indications through switching patients to Ultomiris, competitor biosimilars and new chemical entities (NCEs) such as Ra Pharma's zilucoplan or Apellis' APL-2 will inevitably cause price erosion up to 20%, and market loss when competitors enter the market as early as 2021-2022.

In the US, Alexion has a second family of Soliris patents issued with expiry in 2027 that are currently being challenged by Amgen, and if Alexion loses in the Patent Trial and Appeal Board's (PTAB) inter partes review (IPR) process, patent protection for Soliris ends in March 2021. Amgen's biosimilar to eculizumab, ABP-959, started Phase III studies in EU PNH patients in April 2019 with a completion date of April 2021.

Considering the US patent challenge, SVB Leerink's US Soliris revenue forecast decreases by 4% in 2022, and by up to 21% beyond 2025. As Alexion faces uncharted waters, the importance of Orloff's success in the clinic cannot be overstated if the company is to overcome the patent loss bumps and continue its journey to becoming Alexion 2.0.

IV124349

JOHN HODGSON
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Gender Diversity In Pharma: Caught Between Desire And Reality

Charting the executive gender mix across 384 companies from mid-2014 to mid-2019 demonstrates that C-suite gender balance in pharma is moving towards a point that more closely reflects its total workforce, but that progress has been slow and that there is a long road to travel before the transformation is complete.

Pharma as an industry suffers from cerebral dysmorphia: the structure of its head does not always match its body. The industry is struggling to align its executive management layer with the diversity in its workforce. There are short-term, symptomatic fixes for the condition but curative therapy is a protracted process that, at current rates, will take until 2050 to complete.

Beth Crowley is now senior vice president and chief product development officer at Celldex Therapeutics Inc., a clinical-stage antibody and immuno-oncology company in Hampton, New Jersey. But she started her pharmaceutical career in 1992 at a much bigger firm, Bayer AG.

Crowley stayed with Bayer until 2005 and found it to be a very family-friendly company. It fostered a culture where parents could strike a balance between their work life and home and family life. "There was corporate day care, which we regarded as a luxury," said Crowley. "I was never told that I couldn't do it all."

Yet, in the wider pharmaceutical environment, there was an anomaly, she recalled: "Women with children could be found in middle management; corporate executives had chosen not to have children."

That was how things were. But in 2019, most companies in the pharmaceutical industry recognize that commercial success depends on full mobilization of all their resources, and that talent does not reside solely within the confines of one gender, color, ethnic background or reproductive status. Pharma and its research tributary and competitive collaborator, biotechnology, are proven equal-opportunity hirers, at least as far as gender is concerned: across the industries and around the globe, around 50% of pharma employees are women.

But the upper echelons of pharma still echo with an older order. Charting the executive gender mix in each of 384 companies from mid-2014 to mid-2019 (*see box for method*) demonstrates that C-suite gender balance in pharma is moving towards a point that more closely represents its workforce, but that progress has been

Exhibit 1
Tracking The C-suite Tortoise

	TOTAL EXECUTIVES	FEMALE EXECUTIVES	GENDER BALANCE (FEMALE/BOTH GENDERS)	COUNT*
2014	2778	546	19.7%	384
2019	2745	660	24.0%	384

*Number of companies for which data was collected in both 2014 and 2019

Exhibit 2
Executive Roles For Women, 2014-2019

ROLE	COUNT 2014	COUNT 2019	2014	2019
Human Resources	58	94	10.6%	14.2%
Legal	52	77	9.5%	11.7%
Finance	59	63	10.8%	9.5%
QA/Regulatory Affairs	46	53	8.4%	8.0%
Drug development	56	51	10.3%	7.7%
Business Development/ Strategy	30	46	5.5%	7.0%
Operations/General	30	42	5.5%	6.4%
Medical	32	41	5.9%	6.2%
Comms/Investor Relations	27	35	4.9%	5.3%
CSO	23	33	4.2%	5.0%
Head of Unit	20	30	3.7%	4.5%
CEO	27	28	4.9%	4.2%
Commercial	28	27	5.1%	4.1%
Other Research/Technical	19	21	3.5%	3.2%
Clinical	17	16	3.1%	2.4%
Chair	4	1	0.7%	0.2%
Other/Unknown*	18	2	3.3%	0.3%
TOTAL	**546**	**660**		

Exhibit 3
Percentage Of Firms Increasing Or Decreasing Gender Balance In 2019 From 2014 Levels

	GENDER BALANCE (WOMEN/TOTAL) IN 2014 (# COMPANIES)	
Gender balance direction in 2019	Below average 2014 (192)	Above average 2014 (192)
Decrease	8.3%	54.2%
Same	32.3%	10.4%
Increase	59.4%	35.4%

slow and that there is long road to travel before the transformation is complete (*see Exhibit 1*).

In the pharmaceutical industry, reassortment of executive team members is a constant process, the nuances of which are not captured by snapshot data collection methods used here. However, the net result of this churn is that the number of female executives within a broad sample of 384 firms rose between 2014 and 2019 from 546 to 660, a 20.9% increase. Over the same period, the number of male executives fell from 2,232 to 2,085, a drop of 6.6%.

While the percentage increase in the number of female executives is impressive, the industry's starting point was low. The bottom line is that in five years, in these 384 companies at least, increase in the percentage of women in the executive team – from 19.7% in 2014 to 24% in 2019 – is measurable but not striking. "We need to do better," said Beth Crowley, "and focus on the pipeline [of female managers below the executive team]."

The five-year change is equivalent to the removal of a third of a man and adding a quarter of a woman per company. At the current rate of improvement in the industry's executive gender ratio – 0.86 percentage points per year – it would take another 30 years or so before for gender equality in pharma is achieved. By that time, most people currently in the industry will have retired.

The roles in which female executives are deployed has its own pattern, as Beth Crowley noted: "It's still clear that the majority of women in pharma-biotech are still in the more traditional roles: drug development, regulatory [affairs]; human resources: There are some women CSOs, but it's rare."

Crowley's observations are largely borne out by the survey data (*see Exhibit 2*). Human resources roles constitute both the single biggest category for female pharma executives in 2019 and the fastest growing category. Drug development and regulatory affairs make the top five, although legal and finance functions take the second and third spots. As Crowley anticipated, female CSOs are rare – 33 in the sample – only just ahead of CEOs (28).

The top three – HR, legal and finance – account for 35.5% of the female executive roles in pharma. The link between them might be that, along with communications/ investor relations and possibly business de-

Exhibit 4
Mean Gender Balance Increases Whether Companies Grow Or Shrink

	CHANGE IN EMPLOYEE NUMBER 2014-2019	GENDER RATIO (FEMALE/BOTH)		CHANGE IN MEAN GENDER RATIO 2014-2019 (IN PERCENTAGE POINTS)
Class (# firms)*		2014	2019	
Reduced (85)	Cut by 10% or more	18.4%	22.0%	+3.6
Even (76)	-10% to +20%	19.0%	22.6%	+3.6
Expanded (99)	+20% to +100%	21.0%	23.6%	+2.6
Doubled (100)	Over + 100%	20.7%	24.6%	+3.9

*Companies with employee number available for both years

velopment, industries other than pharmaceuticals and biotechnology act as "feeder layers" for the executive talent pool. While sector-specific experience would undoubtedly remain an advantage, it might be less common and less vital in, say, legal or HR roles than in scientific or clinical jobs.

COMMITMENT TO CHANGE

"Overall, the growth rate in gender diversity is insufficiently high," said Karl Simpson, CEO of Liftstream, an executive search firm that specializes in the life sciences. "I'm not surprised that things haven't gone far." He pointed to two practical obstacles to progress. "Companies can't just start kicking people out in order to put women in place and, [for the change in gender balance] to be sustainable, you need a healthy pipeline of people that can fill the posts, which requires progress at all levels and a change in how you look for and evaluate leaders."

Sustainability, as Simpson sees it, is a question of building the drive for equality and full use of resources "into the memory muscle of the organization." There is some evidence from the survey that that inflection point has not been reached in many companies in the pharmaceutical sector: that gains in the past are reversible rather than built upon.

Exhibit 3 shows the percentage of firms increasing or decreasing gender balance from 2014 levels. The 384 companies in the sample were divided into two groups – those above or below the mean gender ratio in 2014. If companies were embedding sustainable change, the direction of change would continue, outperforming firms would continue to outperform.

However, only in around a third of the firms with an above-average proportion of female executives in 2014 did gender balance increase further by 2019: in over half (54%), the gender ratio fell below its 2014 level.

In contrast, nearly 60% of firms with below-average female representation had raised their game by 2019.

That below-average group, of course, includes 126 companies with no female executives at all in 2014, firms, therefore, with only one way to go; slightly over half of them twisted, the rest stuck.

The other below-average group – companies with at least one female executive in 2014 – appears to have done better: in 71% of those firms gender ratio increased (albeit from a below-average level) by 2019.

Disappointingly perhaps, over half (57%) of the underperforming companies that improved their representation of women between 2014 and 2019 did so by reducing the number of men rather than adding female executives. Indeed, 54% of above-average firms that improved their executive gender ratio also did it by cutting out men.

It appears from this analysis that there is little momentum, if any, towards executive team gender equality. Rather there is, in most companies, oscillation around a lower, preset figure that represents a currently accepted level of female presence.

DIVERSITY APPEARS

Despite the slow progress on executive gender balance and recidivist tendencies, Liftstream's Simpson said life science companies remained very conscious both of the need to address their diversity issues, and of the need to be seen to be doing so.

A 2017 report on gender diversity that Liftstream undertook with MassBio, the biotechnology umbrella organization for the state of Massachussetts, noted among other findings that 45% of female candidates are deterred from seeking interviews at companies that they perceive as not having appropriate levels of gender diversity (all-male board, all-male management team, all-male interviewing panel).

METHODOLOGY

Scope: 384 public companies in pharma and biotech, the majority (379) from North American and Europe (including Israel).

For each company included in the survey, counts by gender were made manually of the executive team members, member of the boards of directors and members of scientific or clinical advisory boards. The information was extracted in the main from the parts of corporate websites dealing with 'leadership', often found within 'about us' or 'corporate governance' sections. Infrequently (in less than 10% of cases) data were also obtained from corporate filings, such as 10-K and annual reports.

Gender assignments were binary (male/female) and made based on the presence of photographs, highly gender-specific forenames or gender-specific pronouns or possessive pronouns in associated biographies. For female executives, job titles were noted.

The data are snapshots (with a slow shutter speed): data were collected in September and October 2014 and again in August and September 2019. Caveat: companies, their websites and their executive teams are not static entities.

Exhibit 5

Mean Gender Balance Increases More When Size Of Executive Team Increases

CHANGE IN EXECUTIVE TEAM SIZE 2014-2019	GENDER RATIO (FEMALE/BOTH)		CHANGE IN MEAN GENDER RATIO 2014-2019
	2014	2019	
Decreased	20.9%	21.7%	+0.8%
Stayed the same	21.2%	25.1%	+3.9%
Increased	16.2%	24.3%	+8.1%

In a competitive job market, prospective candidates at all levels will glean information about company culture from their websites, said Simpson. Some companies have "got savvy" to this fact and may include profiles of more peripheral leadership team members to appeal to diversity candidates. "Its not a scam," insisted Simpson, "they simply want to get the best applicants and know that diversity plays well in hiring."

In regions where the competition for biotech and pharma talent is most intense, representing diversity can be even more important. In 257 pharma companies in the US, the percentage of female executives was 23.9% in 2019, up from 20.1% in 2014. Both figures are slightly higher than comparative numbers outside the US. But in companies from the hubs of California and Massachussetts, which represent just under half of the US sample, that number went from 23.1% in 2014 to 26.4% in 2019. In the rest of the US, progress was more modest, from just 17.1% in 2014 to 21.4% in 2019.

Simpson argued that it may not matter much whether the exhibition of greater management diversity in companies based in life science hubs is real or for show. "To some extent," he said, "companies have been forced into looking toward more diverse candidates because the competition for talent is so fierce. But having more diversity means you can attract more going forward."

DRIVERS OF DIVERSITY

The pharma industry is nothing if not a dynamic employer. Several factors contribute to the churn of executives in the industry: one is the accumulation of individual decisions about self-furtherment and another is the serial nature of merger, acquisition and growth in response to clinical progress, setbacks and external funding.

At the end of 2014, Alameda, CA-based cancer drug developer Exelixis employed around 100 people. Now it has over 500 and is still growing rapidly. "Growth provides an opportunity for hiring and retaining the most talented employees," said Gisela Schwab, Exelixis's president of product development and medical affairs and chief medical officer. Along with the company's growth spurt, the proportion of female employees now exceeds 50%. A third of Exelixis's senior management team are women (3/9), lagging the workforce a little but not much.

Growth and the demand for highly skilled personnel bring the possibility of accelerating renewal and gender-balancing within the employee base up to very senior levels. However, the executive teams may not always reflect that change. Doubling the research and development base, for instance, is not necessarily a reason to appoint an additional chief scientific officer. Unless corporate progression opens up new responsibilities (as when late-stage clinical approvals turn the spotlight to sales and marketing) there may be no reason to expand the C-suite.

The survey data bear this out. Exhibit 4 divides companies into four groups based on the change of employee numbers between 2014 and 2019. Whether companies cut their workforce, or expanded it substantially or something in between, the proportion of women on executive teams increased by the same amount, 2.6-3.9 percentage points.

Experiences at Incyte Corporation, based in Wilmington, DE, help explains why. FDA approvals for the company's drug Jakafi (ruxolitinib) in 2011, 2014 and 2019 (for different indications) and the acquisition of European rights to Iclusig (ponatinib) in 2016 were clear catalysts for the expansion of the company. It grew from just under 600 people in 2014 to nearly 1,500 in 2019. "We have been constantly filling posts," said Paula Swain, Incyte's executive vice-president human resources. "We have hired a lot of senior people and at least half of the open positions on our executive team were filled by women."

But Incyte's executive team remained much as it had been in 2014 with Swain as the only woman member, until Maria Pasquale joined in April 2018 as general counsel. In February 2019, Christiana Stamoulis came in as CFO. With those appointments, the gender ratio at Incyte's executive team shot from 12.5% to 33.3%, but the opportunities for change arose only when members of the management group departed for new challenges, said Swain: "Changing things at the very highest level of management is not easy, and the opportunities to do so are less frequent." Growth and success preserve the status quo as often as they promote it.

While the growth of companies is a double-edged sword when it comes to increasing the proportion of female executives, growth within management teams themselves is strongly associated with improved executive diversity. For the group of companies where executive teams were smaller in 2019 than in 2014 (200 in the sample), the mean gender ratio moved less than one percentage point (from 20.2% to 21.0% over five years). In expanding teams (from 153 companies), gender diversity went from 16.2% to 24.3% over the 2014-2019 period (*see Exhibit 5*).

Thus, the diversity in the pharma's upper management is likely, ultimately, to reflect the changes in the broader workforce, but changing the C-suite requires its own catalysts, and company growth may not be one of them.

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Immuno-Oncology Continues To Draw Pharma Companies To The Deal Table

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Immuno-oncology development trends are revealed through an analysis of deals between cancer drug developers over the past five years.

Five years out from the initial approvals of programmed cell death protein 1 (PD-1) inhibitors Opdivo (nivolumab) from Bristol-Myers Squibb Co. and Keytruda (pembrolizumab) from Merck & Co. Inc., the field of immuno-oncology is still evolving.

The IO space has seen approvals of new therapies, additional indications for existing products and their combinations, continued development of the pipeline, and new modalities emerging (such as chimeric antigen receptor T-cell, or CAR-T, therapies and tumor infiltrating lymphocytes) which have shown great promise with durable responses in clinical trials. First-generation efforts into IO have now been recognized. Notably, groundbreaking research by James Allison, PhD, and Tasuku Honjo, MD, PhD, into the inhibition of checkpoint proteins as cancer therapies was awarded the Nobel Prize in Physiology or Medicine in 2018.

Currently there are 25 IO therapies (including monotherapies and combinations with chemotherapies or other products but excluding biosimilars) launched throughout the world (*see Exhibit 1*). These treat a wide range of solid and hematological tumors and cover several different mechanisms, not only checkpoint inhibition but also:

- targets of ganglioside antigen GD2;
- signaling lymphocyte activation molecule F7 (SLAMF7);
- chemokine;
- CD20; and
- CD38

IO is also additionally encompassing gene therapies, vaccines, and T-cell engagers. There are over 2,000 IO therapies currently in active global development (from preclinical through pre-registration stages). The pipeline in 2019 represents a six-fold increase compared with five years earlier in 2014 when the pipeline first began to significantly grow.

As one of the great breakthroughs in cancer care, IO continues to be a strong force in business development efforts. In a review of IO deal-making by big pharma and mid-pharma companies between 2014 and 2018, these peer sets established 435 IO collaborations, including traditional licensing deals as well as collaborative clinical trial agreements in which products from two or more companies are being combined and evaluated in a clinical trial.

Deal volume varied over the five-year time period, with a peak in 2015 of just over 100 collaborations, then slightly decreasing over the next two years, potentially a result of a "wait and see" approach by deal makers for efforts thus far, including clinical data readouts, with existing IO efforts. Deal-making rebounded in 2018 and featured big pharma companies transitioning from combination collaborations to full-fledged licensing deals (*see Exhibit 2*). Bristol-Myers Squibb and Merck & Co, arguably the biggest players currently in the immuno-oncology market, signed the most deals over the five-year period, followed by AstraZeneca PLC, Roche and Pfizer Inc.

The potential for synergistic effects of combining multiple therapies to address larger patient populations and those who have not responded to monotherapies, and to be implemented in earlier lines of therapy, is driving IO deal-making. Overall, combinations were involved in nearly three-quarters of the total deals done during 2014-2018, and as of 2017-2018 combinations were part of over 80% of agreements.

Deal economics on IO collaborations have been strong. Of the 21% of deals with a disclosed value (93/435), in aggregate, $97bn was pledged in total deal value, $12bn of which was spent upfront (*see Exhibit 3*). Average deal values have generally increased over the five-year time period. In 2014, the average paid upfront was $101m, and that jumped to $214m in 2018. Similarly, the average total deal value has also increased, from $945m in 2014 to $1.6bn in 2018.

Within the last two years of the five-year time period (2017-2018), average values increased significantly compared with previous years. Drivers behind these deal values were alliances around combinations with leaders in the PD-1/PD-L1 class, among those, formalized deals stemming from clinical trial combination collaborations. In the largest IO transaction of all of 2014-2018 (*see Exhibit 4*), Merck & Co. paid $1.6bn as part of a total $8.5bn value in 2017 for co-development and co-commercialization rights to the PARP inhibitor Lynparza (olaparib) as a monotherapy and in combination with other therapies including Keytruda, as

Exhibit 1

Currently Approved IO Therapies In Solid Tumor Indications

	Bladder	Breast	Cer	CRC	EC	GI	GJ	H/N	Liver	Lung	MCC	Mel	Mes	Na	Ne	NSCLC	Pr	Pa	Renal	SC	SCLC
CTLA-4																					
Ganglioside antigen GD2																					
Gene therapy																					
PD-1/PD-L1																					
Vaccine																					

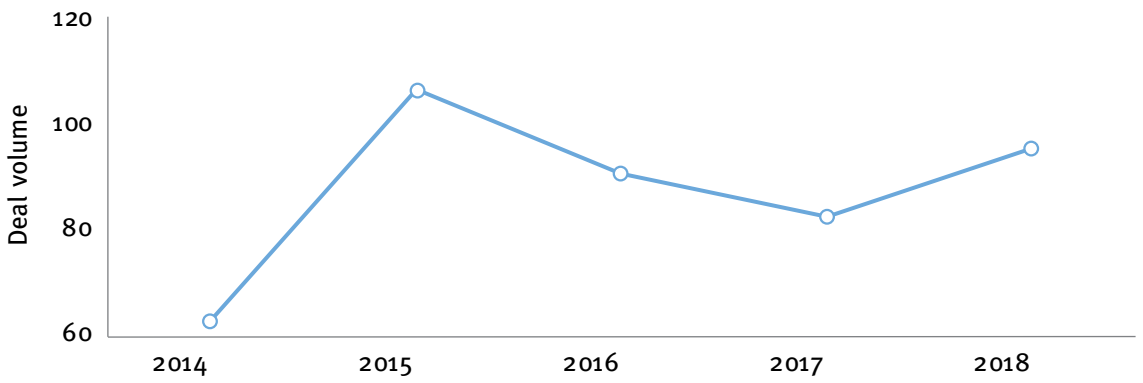
Yervoy	Unituxin	Imlygic, Oncorine	Bavencio, Imfinzi, Keytruda, Libtayo, Opdivo, Tecentriq, Tuoyi	GemVax, PIKA vaccine, Provenge, Rigvir

Cer = cervical; CRC = colorectal cancer; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; EC = esophageal cancer; GI = gastrointestinal, stomach; GJ = gastroesophageal junction; H/N = head and neck; MCC = Merkel cell carcinoma; Mel = melanoma; Mes = mesothelioma; Na = nasopharyngeal; Ne = neuroblastoma; NSCLC = non-small cell lung cancer; Pr = prostate; Pa = pancreatic; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; SC = squamous cell; SCLC = small cell lung cancer

SOURCE: Pharmaprojects

Exhibit 2

IO Deal Volume By Big Pharma And Mid Pharma Peer Sets, 2014-2018



SOURCES: Medtrack; Strategic Transactions; Trialtrove

Exhibit 3

Top-Level Metrics On IO Deals By Big Pharma And Mid Pharma Companies

2014 - 2018

21%	$12bn	$97bn	$1bn	$162bn
Proportion of deals with disclosed financials (93/435deals)	Total up-front aggregate	Total potential deal value aggregate	Average potential deal value	Average up-front payment

SOURCES: Medtrack; Strategic Transactions

Exhibit 4

Top 10 Big Pharma And Mid Pharma IO Deals By Total Deal Value

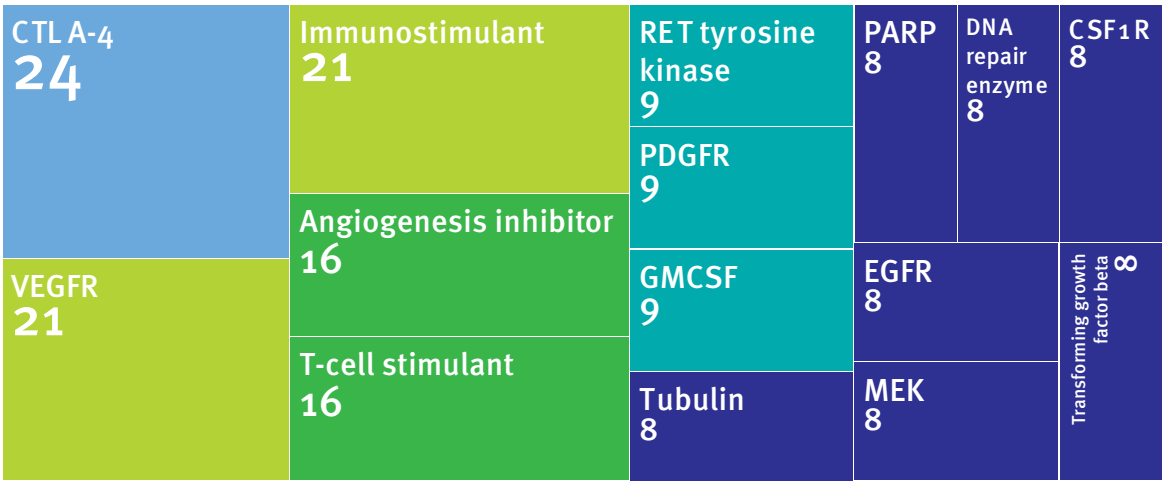
DATE	LICENSER	LICENSEE	DEAL FOCUS	UPFRONT ($M)	TOTAL MILESTONES ($M)	TOTAL DEAL VALUE ($M)
July 2017	AstraZeneca	Merck & Co	AstraZeneca's Lynparza plus combinations, including with Merck & Co's Keytruda	1,600	6,900	8,500
February 2014	Ablynx	Merck & Co	Bi- and tri-specific Nanobodies directed toward up to 17 immune checkpoint modulators	41	6,724	6,779
March 2018	Eisai	Merck & Co	Co-development/ commercialization of Lenvima alone and in combination with Keytruda; stemmed from 2015 clinical trial combination collaboration	300	4,355	5,755
August 2018	Affimed	Genentech	Innate immune cell immunotherapies, including NK and T-cells for solid and hematological cancers	96	4,950	5,046
February 2018	Nektar	Bristol-Myers Squibb	Combinations of Opdivo and NKTR-214 (bempegaldesleukin), and Opdivo+Yervoy and NKTR-214 in 20 indications; stemmed from 2016 clinical trial combination collaboration	1,850	1,780	3,630
February 2018	Sangamo	Kite/Gilead	Zinc finger nuclease gene editing in autologous and allogeneic T-cell and NK cell therapies	150	3,010	3,160
June 2014	Pfizer*	Cellectis	Allogeneic CAR-T immunotherapies against 15 targets*	80	2,775	2,855
November 2014	Merck KGaA	Pfizer	Merck KGaA's PD-L1 inhibitor Bavencio (avelumab) in multiple tumor types	850	2,000	2,850
July 2016	Jounce Therapeutics	Celgene	Options on Jounce's preclinical ICOS antibody JTX2011 plus up to four additional projects from a set group of B-cell, T regulatory cell, and tumor-associated macrophage targets	261	2,300	2,561
June 2016	Xencor	Novartis	Preclinical XmAb bispecific antibodies XmAb14045 (targeting CD3 and CD123) for acute myeloid leukemia, and XmAb13676 (targeting CD3 and CD20) for lymphomas	150	2,410	2,560

*Pfizer divested its CAR-T assets to Allogene in April 2018.

SOURCES: Medtrack; Strategic Transactions

Exhibit 5

In Partnerships, PDx Inhibitors Paired With CTLA-4 Inhibitors At The Highest Volume



SOURCES: Medtrack; Strategic Transactions; Trialtrove

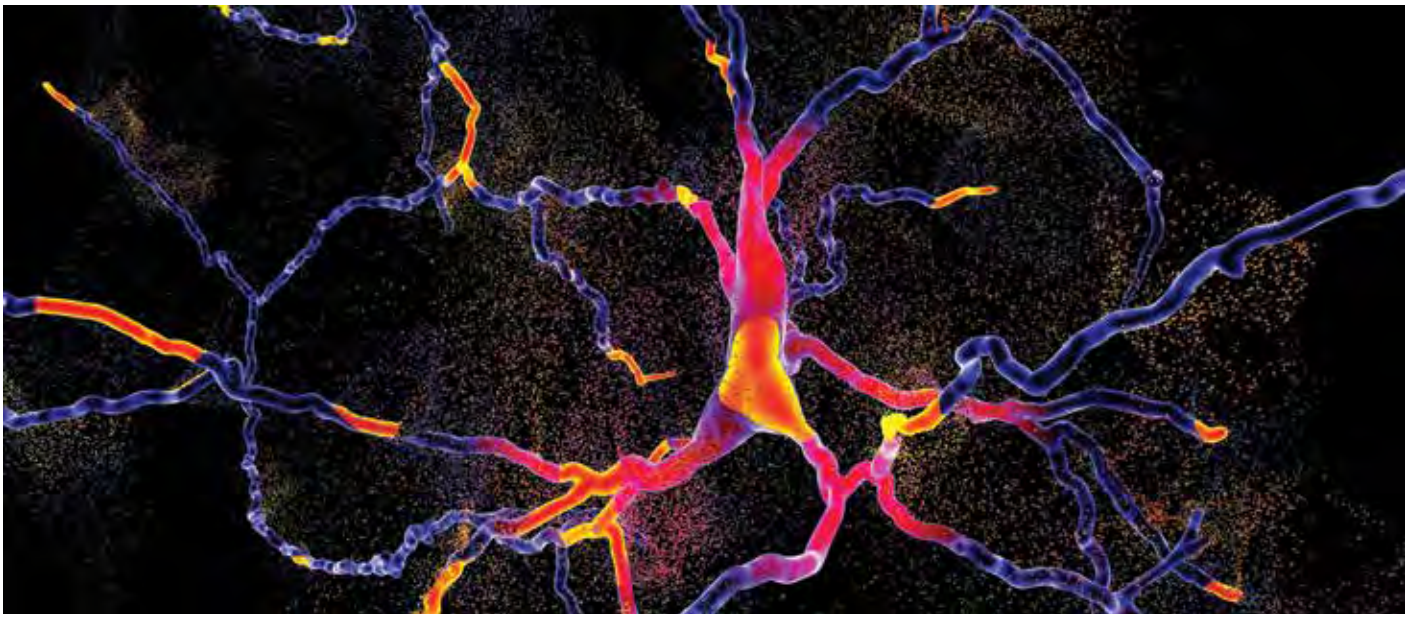
well as combinations of Keytruda with AstraZeneca's MEK inhibitor selumetinib, and Imfinzi (durvalumab)/ Lynparza and Imfinzi/selumetinib combinations

Also, Merck and Bristol-Myers Squibb individually settled big licensing arrangements that came about as a result of earlier combination agreements. Merck and Eisai Co. Ltd. first teamed up in 2015 to develop a combination of Keytruda and Lenvima (lenvatinib) in solid tumors, including endometrial cancer and renal cell carcinoma. In 2018, as part of an official deal, they expanded the scope to 11 indications across six cancer types and agreed to co-commercialize the combination if successful; Merck also receives co-development rights and cost/profit share on Lenvima monotherapy. Similarly, Bristol-Myers Squibb was working with Nektar Therapeutics under a 2016 arrangement to study an Opdivo combination with bempegaldesleukin, an IL-2 agonist. The companies ended up terminating that agreement and replacing with a new alliance in 2018 that carved out commercialization rights and cost and profit splits for the Opdivo/bempegaldesleukin combination as well as Opdivo plus Yervoy(ipilimumab)/ bempegaldesleukin in more than 20 indications across nine tumor types.

Lung cancer and melanoma are lead indications in IO deal-making, not surprising given the responses of patients with these cancers to marketed immunotherapies. Lung cancer by far is the strongest focus, represented on 93 deals, including several of the highest-values ones such as the Merck/Eisai and Bristol-Myers Squibb/Nektar partnerships involving Keytruda and Opdivo, respectively.

Among hematological tumors, different forms of leukemia and myeloma were most often part of IO deals, at 35 and 34 alliances, respectively. In the largest among the leukemia deals, Novartis AG's Novartis Institutes for BioMedical Research Inc. gained ex-US rights to Xencor Inc.'s bispecific antibody XmAb14045, which interacts with CD3 and interleukin-3 (CD123) and is now in Phase I for AML, ALL, CML. Concurrently, Xencor also licensed Novartis rights to the CD3 and CD20-targeting antibody XmAb13676 for B-cell lymphomas. Altogether the deal is worth $2.6bn. Unlike several other big pharma and major pharmaceutical companies, Novartis has not jumped into the PDx inhibitor market yet. Still, the company has made headways in immunotherapy through not only deal-making such as the transaction with Xencor, as well as earlier acquisitions of Admune and CoStim, but also through its marketed *ex vivo* gene therapy Kymriah (tisagenlecleucel), the first CAR-T therapy ever approved, for leukemia and lymphoma indications. In addition, Novartis is developing in-house the PD-1 inhibitor spartalizumab, in Phase III trials for melanoma. The company is studying the candidate in combination with its lymphocyte-activation gene 3 (LAG-3) antagonist LAG525.

Overwhelmingly, immunotherapies targeting PD-1 or PD-L1, particularly the marketed inhibitor products, either as single agents or as the backbone in combination treatments, are the most popular subjects of deals – represented on 270 collaborations. In clinical trial combination agreements, most often, PD-1 or PD-L1 inhibitors were combined with CTLA-4 inhibitors *(see Exhibit 5)*. These deals were primarily done by Bristol-Myers Squibb and involved testing Opdivo or Yervoy plus a partner's candidate. Recent examples include collaborations between Bristol-Myers Squibb for Opdivo/ Yervoy combinations with products from Checkmate Pharmaceuticals Inc. (CMP-001, a TLR9 agonist; metastatic colorectal cancer with liver metastases), Syndax Pharmaceuticals Inc. (entinostat, an HDAC inhibitor; renal cell carcinoma), and Gritstone Oncology (T-cell stimulant GRANITE001; advanced solid tumors).



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Parkinson's Disease: Novel Science And Collaborations Fuel Progress

Novel therapeutic strategies for Parkinson's disease have brought a renewed sense of optimism to those researching this neurodegenerative disorder. Numerous treatment avenues are being explored, including small molecules, gene therapy, cell therapy and medical devices to stimulate nerves deep in the brain. Digital also gets a look-in, being useful for analyzing gait and other symptoms, and addressing both mental and physical issues.

The development of therapies for Parkinson's disease should have been a triumph long ago for medical science. Degeneration of dopaminergic nerves in the central nervous system (CNS) was identified as a key process in the condition; drugs, such as levodopa, that alleviate symptoms were identified back in the 1960s; and high-profile charities were set up to support patients and impel research into new therapeutic discoveries.

It comes as some surprise, therefore, that in past decades attempts to develop new therapies were rather frustrating experiences, really useful biological markers to help assess the progression of Parkinson's were not identified and new pharmaceutical approaches were found wanting. Meanwhile, experts were warning about the increasing threat of a "pandemic" of Parkinson's disease, as populations age and no longer succumb to other diseases. Deep brain stimulation devices have been found to alleviate some of the symptoms, but they do not affect disease progression. Currently, there are no therapies that slow or halt the progression of Parkinson's.

But more recently, a more optimistic vibe has permeated the Parkinson's disease field, following a steady accumulation of scientific progress in unpacking the biological processes involved in the condition. "Over the past 10 years or so, some of the genes, biological pathways and pathological processes thought to be involved in Parkinson's disease have been discovered and defined, leading to a number of good ideas which are now being picked up by biotech and pharmaceutical companies," noted Arthur Roach, director of research at the disease charity Parkinson's UK. "We are now at the point where some ideas are reaching the clinic; some are further behind, but the opportunities are really exciting," Roach explained.

A similarly upbeat assessment has come from Todd Sherer, CEO of the US charity the Michael J. Fox

Foundation for Parkinson's Research, who noted it was a "great time to be working – and investing – in this field," during the PD Therapeutics Conference in New York in October 2019. Many opportunities exist in Parkinson's research and many more are on the way, Sherer told the meeting attendees.

Mutations in several genes, including PINK1, PARKIN, LRRK2 and GBA have been linked to the development of Parkinson's disease; PINK1 and PARKIN are linked to the turnover of mitochondria, LRRK2 codes for a protein kinase and GBA codes for a glucocerebrosidase. And a protein, alpha-synuclein, has been linked to the disease because of its presence in Lewy bodies, the aggregates of proteins found in the nerves of affected individuals.

So, although the underlying causes of Parkinson's are still to be fully defined, and the condition may involve numerous sub-types much like in cancer, the identified genes and proteins are powering new approaches to therapy. For example, LRRK2 inhibitors are in development, including at the one-year-old Pfizer Inc. spin-out Cerevel Therapeutics LLC.

Venture capital-backed Cerevel is a rarity among biotech companies, one focused on neuroscience, but it is already developing another candidate Parkinson's disease therapy, tavapadon, a once-daily orally active dopamine D1 and D5 agonist, which in Phase II studies has been found to improve motor symptoms and be well tolerated in patients with early-stage disease. The company plans to initiate a Phase III clinical trial program in 2020. Current approaches to alleviating motor symptoms are often associated with troublesome side effects or limited efficacy, the company noted. An indication of the interest now being shown in the neurosciences is demonstrated by Cerevel's series A round of financing in October 2018, which raised a hefty $350m.

More recent work, from Tim Greenamyre and colleagues at the University of Pittsburgh and supported by the Michael J. Fox Foundation, suggests that LRRK2 is overactive in Parkinson's patients with and without LRRK2 mutations, and is linked with dysfunction of neuronal lysosomes, while LRRK2 inhibitors improve lysosome function and prevent the accumulation of alpha-synuclein.

It should be noted that alpha-synuclein is also a therapeutic target, with companies like ProMIS Neurosciences in the "lead selection" stage of developing antibodies that bind to toxic forms of alpha-synuclein, and Lausanne, Switzerland-based **AC Immune SA**, which is also engaged in identifying small-molecule inhibitors of alpha-synuclein.

Several other companies are targeting alpha-synuclein, including Enterin Inc. with ENT-01 (Phase IIb), Biogen/Neurimmune with the Mab, BIIB054 (Phase II), Roche/Prothena with prasineuzumab (Phase II) and AbbVie/BioArtic with the Mab, ABBV-0805 (Phase I), according to drug development database, Biomedtracker.

San Francisco, CA-based Denali Therapeutics Inc. is one of the pioneers of the development of LRRK2 inhibitors, with a small-molecule LRRK2 inhibitor, DNL201, being evaluated in a Phase Ib study in patients with and without the LRRK2 mutation. Others active in this area include Servier SA and Dijon, France-based Oncodesign SA, which entered into a collaboration in March 2019 to develop LRRK2 kinase inhibitors. *(Also see "Servier To Tackle Parkinson's With Oncodesign Pact" - Scrip, 13 Mar, 2019.)* The research push has attracted biotech heavyweight Biogen Inc.; in August 2019 it dosed the first patient in a Phase I study of BIIB094 (ION859), an antisense oligonucleotide targeting LRRK2.

One factor that could limit clinical studies of gene-related strategies: early-stage Parkinson's disease patients will need to know their genotype before they are admitted into clinical studies. As a result, a number of Parkinson's charities around the world are considering educational programs to encourage or facilitate genotype testing for early-stage patients, thereby giving those patients the opportunity to participate in trials that may slow the progress of their disease.

ASAP INITIATIVE

A US-based group, the Aligning Science Across Parkinson's (ASAP) Initiative, is taking collaboration a step further, by calling for and funding a new approach to basic research, which it believes needs to be supercharged to find a cure.

Set up in 2017 and financially backed by Google co-founder Sergey Brin, and with Nobel Laureate Professor Randy Schekman as scientific director, the ASAP Initiative began in October 2019 to call for preliminary research proposals from collaborative teams that are: international in scope, embrace openness, have an interdisciplinary approach, include early-career and non-Parkinson's disease investigators and are focused on specific areas of basic research.

The proposal areas include evaluating potential disease biomarkers, particularly in early disease before the onset of symptoms; identifying and characterizing Parkinson's disease-associated genes; delineating the molecular mechanisms underlining neuro-inflammation; and the role of neuromodulatory dysfunction beyond dopamine and the substantia nigra (the area of the brain where dopaminergic neurons are lost). The research program is being administered in collaboration with the Michael J. Fox Foundation, with support from the Milken Institute and financial backing from the Sergey Brin Family Foundation.

ALPHA-SYNUCLEIN IMAGING

The Michael J. Fox Foundation is an active funder of Parkinson's research, and its Fox Trial Finder lists more than 700 clinical studies that are currently underway around the world. Additionally, in September 2019 it set up the $10m alpha-synuclein imaging competition, to deliver a PET tracer for use in clinical studies to measure progression of the disease. The foundation already supports the efforts of AC Immune to develop an alpha-synuclein targeted PET imaging tracer; it entered clinical studies earlier this year.

DIGITAL TECHNOLOGIES

Digital technologies such as "wearables" may also allow the progression of symptoms to be measured in clinical trials, and the data collected to be used in the regulatory drug approval process. Pharmaceutical companies have recognized the potential, and a group of them have taken part in a pre-competitive collaboration, the Critical Path for Parkinson's Consortium (CPP), a public-private partnership set up in 2015 by Roche, Biogen, Lundbeck Inc., Merck & Co. Inc., Takeda Pharmaceutical Co. Ltd., UCB Group and GlaxoSmithKline PLC, along with the Michael J. Fox Foundation and Parkinson's UK.

In 2018, the WATCH-PD study began, to generate objective digital measures to complement clinical assessments.

VIRTUAL BIOTECH

Parkinson's UK is attempting to accelerate development of new therapeutics by addressing the funding gap it sees between academics conducting basic research and the pursuit of late-stage development. It has set up a "Virtual Biotech" program, in particular for symptoms affecting patients such as psychosis, hallucinations, sleep disorders, balance and posture dysfunction, and constipation.

"It's like a venture fund; we are providing very-targeted injections of funds for virtual and small companies," noted Roach. These funds should move the research to a point where projects are taken up by more established biotech and pharmaceutical companies, or are quickly discontinued because of lack of promise. The program is "exceeding expectations," and other funding bodies and charities are interested in joining, he added.

The most recent research to be supported is a Phase II study of cannabidiol for Parkinson's-associated psychoses. There are currently no drugs approved for Parkinson's-related psychosis in the UK. The Virtual Biotech program is also supporting the US/European biotech Neurolixis Inc., to move its 5HT1A receptor activator, befiradol (NLX-112), into a Phase II study for levodopa-induced dyskinesia; in animal studies, the administration of NLX-112 inhibited the dyskinesia caused by repeated doses of levodopa.

Another company supported by the program is UK-based Keapstone Therapeutics, which is looking to use KEAP1 (Keclh-like ECH-associated protein-1) inhibitors to counter the negative effects of KEAP1 on transcription factor protein, NFE2-related factor-2 (NRF2)-activated mitochondrial function. NRF2 is thought to activate a battery of genes that combat neuronal oxidative stress and reduce inflammation.

Separately, the US firm Cerespir Inc. has a Phase II-ready candidate, itanapraced, which acts as an inhibitor of AICD (amyloid precursor protein intracellular domain), which is involved in neuronal death due to oxidative stress, and which also blocks the expression of LRRK; it is considered a promising candidate as a disease-modifying agent in Parkinson's. Researchers have suggested that slowing Parkinson's progression by 50% would yield a 35% reduction in excess health care costs – the economic burden of Parkinson's disease is $14.4bn a year for the US alone, related to cognition decline and mobility issues requiring patients to enter long-term care.

GENE AND CELL THERAPIES

With the first cell and gene therapies now entering commercial use in other diseases, researchers are considering applying such approaches to Parkinson's disease. US/Switzerland-based Axovant Gene Therapies Ltd. is evaluating a lentivirus vector containing three genes, AXO-LENTI-PD, in a Phase II study, SUNRISE-PD, and in August 2019 said the candidate was well tolerated and showing signs of clinical benefit in the two patients studied. The vector contains genes for three enzymes involved in the synthesis of dopamine – tyrosine hydroxylase, cyclohydrolase 1 and aromatic L-amino acid decarboxylase (AADC). SC124320

Cambridge, MA-based Voyager Therapeutics Inc. is also developing a potential gene therapy for Parkinson's, in its case called VY-AADC, which involves delivering the gene for AADC into the CNS. The work is under a collaboration signed in January 2019 with fellow US company, Neurocrine Biosciences Inc..

Patients with Parkinson's gradually lose AADC activity, and neuronal dopamine levels go into decline. It is thought that the addition of the AADC enzyme, via an adeno-associated viral vector, will help lift dopamine levels. In results from a Phase Ib study reported in August 2019, VY-AADC improved the mean "on" time (when patients have a positive response to levodopa therapy) by 1.7 hours, and reduced mean "off" time by 2.2 hours. A Phase II study, RESTORE-1, is ongoing. *(Also see "Voyager Nabs Neurocrine As Partner In CNS Gene Therapy" - Scrip, 29 Jan, 2019.)*

Other companies with gene therapies in clinical development include New York-based Prevail Therapeutics Inc., which raised $125m in a US IPO in June 2019 and is using REGENXBIO Inc.'s NAV AAV9 vector to deliver genes. It is collaborating with the Silverstein Foundation for Parkinson's with GBA – patients who are glucocerebrosidase (GBA1) mutation carriers. It is hypothesised that GBA1 leads to a deficiency in the lysosomal enzyme, beta-glucocerebrosidase (GCase), leading to an accumulation of glycolipids that cause inflammation and cytotoxicity. The company's Phase I/II study, PROPEL, to evaluate an AAV9 viral vector delivering the GBA1 gene, is underway.

The lead program at Cambridge, MA-based BlueRock Therapeutics is an engineered cell therapy for Parkinson's disease, which was expected to enter clinical development by the end of 2019. BlueRock, which is being acquired by big pharma Bayer AG, is developing master cell banks of universal pluripotent stems cells (PSCs) that can be expanded, differentiated and engineered. They can become dopaminergic neurons that release increased amounts of dopamine and in preclinical studies restored motor function. The aim is no less than to "reinnervate the human brain and reverse degenerative disease," the company says.

Another group making a concerted effort to pursue PCS transplantation in Parkinson's is Jun Takahashi and colleagues at the Center for iPS Cell Research and Application, based at Kyoto University, Japan. One patient has already had millions of stem cells reprogrammed to be neuronal cell precursors transplanted into the front part of his brain. The patient will be followed for up to two years to see if he responds to the regimen.

Research groups are evaluating transplanted human fetus-derived dopaminergic neurons, including in the TRANSEURO study taking place in the UK and Sweden.

And finally, another UK-based charity, the Cure Parkinson's Trust, set up 2005 by patients to find disease-modifying therapies, often through the re-purposing of marketed medicines, is taking part in a Phase III study of the GLP-1 agonist, exenatide, which recently started, after a Phase II study suggested the compound slowed the progression of motor symptoms of the disease.

The study is also supported by the US-based Van Andel Institute through the Linked Clinical Trials Initiative, a group of researchers who regularly evaluate emerging evidence of the potential role of various compounds in Parkinson's. The process has led to several marketed drugs being evaluated, including ambroxol, simvastatin, deferiprone, liraglutide and lixisenatide. The program, if successful, would add another treatment strategy to the future anti-Parkinson's armory.

IV124374

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Denmark Offers One-Stop-Shop For Clinical Trials

Denmark's Trial Nation Portal was established in 2018 with government backing and the aim of luring clinical trials to the country.

STEN STOVALL
SENIOR EDITOR,
PHARMA, EUROPE

Denmark has become the envy of its Nordic neighbors by building a joined-up "one-stop-shop" approach to attract pharma companies to the small Scandinavian country to conduct their clinical trials.

The initiative – called Trial Nation – was founded last year with the backing of regional and state government and from a group of Danish life sciences companies. It offers a single, national entry point for biopharma companies, patient organizations and clinical researchers wanting to sponsor, participate in, and conduct clinical trials in Denmark.

It took just four years to create Trial Nation, a process that benefited from a strong desire within the country's government and parliament to boost Denmark's life sciences industry, which already benefits from a thriving medical and academic ecosystem. The assumption is that a single point of entry helps to better identify relevant subjects and facilitates contact with leading clinical centers of excellence at Danish hospitals nationwide.

PUBLIC-PRIVATE COOPERATION

An important component for this project is the public ownership of universities and university hospitals in Denmark, which presents big possibilities for the integration of research and clinical care. It is further supported by substantial public and private investment in medical research in universities and industry.

Another key factor is that many large Danish companies are foundation-controlled – a unique ownership model, whereby a founder irrevocably donates the majority of shares in a company to an independent legal entity, called a foundation, with certain rights and responsibilities. No person or legal entity will thereafter own the foundation's assets and the foundation needs to have a non-selfish purpose. The foundation typically maintains control over the company.

Two thirds of all listed companies in terms of value on the Danish Stock Exchange are of this type, including the four biggest life science companies: Novo Nordisk A/S, LEO Pharma A/S, Lundbeck A/S, and Coloplast A/S.

Big data and its collation nationwide is another advantage for Denmark. The country has electronic health care data going back more than 40 years, bolstered by 170 clinical databases and the Danish Biobank Register, which connects 25 million biological samples.

The result is a life science industry that today generates more than 17% of Denmark's total export of goods. The sector's ambition – supported by government policy – is to double that export contribution by 2025. Integral to that aim is attracting more clinical trials to the country.

Denmark's share of applications for clinical trials within the EU increased from 9% in 2015 to 12% in 2017. The Danish Life Science community and government hope Trial Nation – which opens doors to labs and clinics throughout Denmark – can help maintain that momentum.

There are currently 384 recruiting clinical trials occurring in Denmark. Their details can be found at ClinicalTrials.gov. Many are being conducted by companies not headquartered there, including AbbVie, AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Pfizer, Roche and Sanofi.

Switzerland-based Roche said the Trial Nation approach should help to push for better timelines. "This initiative also creates an awareness of the importance of clinical trials which does make life easier for companies," said Nicolas Dunant, head of media relations at the Swiss drugs group, told *In Vivo*.

Although it is still early days for the Trial Nation project, Roche is optimistic that it will be a success.

"This is a long-term initiative where we work on simplifying, standardising and approving things. Having the private-public partnership and the governmental involvement and support does make things much easier," Dunant said.

By attracting clinical trials to Denmark, the stakeholders behind Trial Nation hope to continuously provide patients at Danish health care facilities with state-of-the-art treatments. The portal's services include investigator identification, a coordinated feasibility process with a national response from hospital sites within five days, estimation of patient numbers eligible for a specific trial and access to established partnerships with hospitals, scientists and patient networks – all free of charge.

At present, there are Trial Nation centres in operation for oncology and hematology, dermatology, respiratory diseases, infectious diseases and dementia. Additional research centres are in the pipeline.

The Danish Medicines Agency has set a goal to process all clinical trial applications within a maximum

of 30 working days, corresponding to 42 calendar days. On average, more than 90% of all trial applicants receive a first reply within 42 days – around 95% of applications are accepted, according to Trial Nation.

Denmark's single-entry testing hub was the result of a four-year public-private partnership called the National Experimental Therapeutic Partnership (NEXT) and its merger in 2018 with the country's state-owned regional service clinical trials office. Britta Smedegaard Andersen, an experienced clinical trial manager, was NEXT's project director and a driving force behind the initiative. She said that Danish government backing had been crucial for the project's advancement.

"NEXT was started in 2014 and ended in 2018 when its activities were passed to Trial Nation, which is now a state-funded initiative, single port of call for industry to come to in and organize clinical trials in Denmark," she told *In Vivo*. "The involvement of the Danish state in this was key, and means the government wants to be involved in the life science strategy for Denmark going forward," Smedegaard Andersen said.

AN ENVIABLE SETUP

Trial Nation is a Danish success story that neighboring countries clearly envy.

"All the Nordic countries are studying what we're doing in Denmark because somehow we've succeeded in joining the various ends and making it happen using the public-private approach to attract more clinical trials here," Smedegaard Andersen said. It would be in Denmark's interests if similar initiatives could be set-up in Sweden and Norway, as that could bring "critical mass" to the region in the form of expertise and infrastructure, she added.

Such a development is not likely anytime soon, however. Norway's life sciences sector is not yet adequately advanced for an initiative like Trial Nation.

In Sweden, the national life sciences sector is highly efficient and innovative, but the central government has not made promoting clinical trials a distinct policy objective. Sweden's position is that such an activity should be led by academic institutions and regional hospitals, which in turn say they are already overstretched and underfunded.

Smedegaard Andersen said this should leave the field open for Denmark's regional play for attracting clinical trials. "We would like to have a bigger Scandinavian initiative in future, because Denmark is such a small country. But that won't be possible until each of the Nordic countries are sorted on the national level. That's what they are struggling with in Sweden, for example," Smedegaard Andersen said.

"Sweden's regional university hospitals and the Karolinska Institute are top quality and doing very well independently, but they are having difficulties taking the broader national view."

DENMARK'S LIFE SCIENCES SECTOR BY THE NUMBERS

ALMOST
1,500
life sciences companies make-up the Danish Life Sciences industry

COMPRISED OF
47,300
EMPLOYEES

Life sciences companies account for more than a third of all private R&D projects in Denmark

60% Investment growth in life sciences within Denmark since 2008

Subsidiaries of major multinationals employ more than a quarter of all employees in the Danish life sciences industry

SWEDEN STILL SIDE-LINED

Clinical trial expert Arvid Soderhall says making that happen in Sweden will take time and necessitate a number of changes to occur first.

"I authored a report and project in 2014 at the Royal Academy of Engineering Sciences which was very much inspired by what was going on in Denmark. It got some traction within the Swedish government, but it did not go very far," Soderhall told *In Vivo*.

He said lack of commitment from central government in Sweden was a major stumbling block to getting a joined-up approach to attracting more clinical trials to the country.

"The decline in the number of clinical trials being conducted in Sweden is seen by the central government as being essentially an academic problem for academics to sort out, not an economic problem that's is undermining the life sciences sector's overall contribution to the national economy," said Soderhall.

That is not the only barrier, however. "We are in discussions in Sweden between the pharma industry and the regional hospitals aimed at promoting co-operation within clinical trials. But these efforts are being hindered by a number of factors, one of which is a long-standing lack of trust between the two sides, which goes back many years," Soderhall explained.

"We are now trying to build up trust again between the two sides with the hope of creating cooperation between the two sides and ideally to the extent that we're seeing in Denmark right now. But that will take time."

IV124386

Could A Type 1 Diabetes Immunotherapy Be In Reach?

Promising data from the likes of Provention Bio and Diamyd Medical suggest that treatment for the autoimmune disorder type 1 diabetes could soon move beyond insulin.

KEVIN GROGAN
MANAGING EDITOR, PHARMA, EUROPE

While some autoimmune diseases such as rheumatoid arthritis and psoriasis have benefited from drugs that target components of the immune system, efforts to come up with something similar for another one – type 1 diabetes – have not progressed smoothly. However, a number of companies are moving closer to finding an effective immunotherapy for the disease.

Type 1 diabetes, in which immune system cells attack and destroy the insulin-producing beta cells of the pancreas, accounts for around 8-10% of patients with diabetes, but the advancement of innovative therapies compared to type 2 diabetes has been slow. One of the issues is that insulin has been used fairly successfully to treat type 1 patients for nearly 100 years and that success has blunted the push for new drugs.

Colin Dayan of the University of Cardiff in Wales and a key figure in the T1DM UK Immunotherapy Consortium (set up in 2015 with funding from Diabetes UK and the type 1 diabetes charity JDRF) said that "insulin is good but it has hidden us from the reality" of how bad the disease is and "we haven't thought of anything else."

The Consortium noted that previously, only around 30 of every 3,000 eligible people diagnosed with type 1 diabetes each year took part in an immunotherapy trial. To put this into perspective, one early-stage trial to test the safety of a new drug could require all 30 of those to take part. This lack of participation has held back progress.

Another problem had been that clinicians were unwilling to refer patients onto immunotherapy trials amid safety concerns, Dayan said. "When we talk about immunotherapies, we don't mean ciclosporin, we don't mean anti-rejection drugs and the things in the 1980s that gave you opportunistic infections, we are talking about modern biologics" with strong safety profiles.

So while type 1 diabetes patients can live a relatively normal life on insulin, relying on multiple insulin injections or pump infusions every day is tough. JDRF highlights that a child diagnosed at the age of five faces up to 19,000 injections and 50,000 finger prick blood tests by the time they are 18.

Having a treatment that could be injected every couple of months would make life easier but there have been a number of high-profile failures in the type 1 diabetes immunotherapy space. Back in 2011 GlaxoSmithKline and Tolerx's Phase III DEFEND-1 study of the anti-CD3 monoclonal antibody otelixzimuab did not meet its primary endpoint in patients with new-onset autoimmune type 1 diabetes.

After years of slow progress, 2019 has seen a reignited enthusiasm around attempts to re-program the immune system to stop it from attacking working cells in the pancreas. A report from Diabetes UK in November saw the charity claim, "We believe a licensed immunotherapy can be achieved within the next five years, bringing us closer to a cure for type 1 diabetes."

One drug that may hit that target is Provention Bio Inc.'s anti-CD3 monoclonal antibody, PRV-031 (teplizumab). The drug caused a stir at the American Diabetes Association meeting in San Francisco in June 2019 after showing that a single 14-day course significantly delayed the onset and diagnosis of type 1 diabetes by a median of two years compared with placebo. The median time to clinical diagnosis of type 1 diabetes for placebo participants was just over 24 months. In comparison, the median time for teplizumab-treated participants to clinical diagnosis was just over 48 months.

During the Phase II 76-patient trial, 72% in the placebo group developed clinical diabetes compared with only 43% of the teplizumab group. Since June, the drug has been granted breakthrough therapy designation from the US Food and Drug Administration and in November, it became the first investigational treatment for diabetes accepted onto the European Medicines Agency's PRIME (priority medicines) scheme, which aims to get drugs for unmet medical needs to patients faster. *(Also see "EMA Accepts First Diabetes Drug Onto PRIME" - Pink Sheet, 4 Nov, 2019.)*

The results represented a change in fortunes for teplizumab. Originally developed by MacroGenics and licensed to Eli Lilly & Co. in 2007, a Phase III study of the drug in type 1 diabetes patients with recent-onset disease failed in 2010. Lilly handed back the rights to the drug to MacroGenics but it was licensed to Provention Bio in May 2018.

The Phase II study was published in the *New England Journal of Medicine* and while an editorial in the journal acknowledged that the trial showed a marked delay in the onset of overt diabetes, "the results should not be taken to imply that immune modulation constitutes a potential curative approach. Rather, these data provide strong albeit indirect evidence about the pathogenesis of beta-cell destruction and the potential to modify the course of type 1 diabetes with newer biologic agents."

The enthusiasm around teplizumab has also been extended to Diamyd Medical's type 1 diabetes vaccine. However, like Provention Bio's drug, the antigen-specific immunotherapy has had a troubled past.

CEO Ulf Hannelius told *In Vivo* that the project dated back to 1991 when the Swedish biotech's founder Anders Essen-Möller's youngest daughter was diagnosed with type 1 diabetes. After linking up with Johnson & Johnson, the vaccine was progressing well until a European Phase III trial failed to meet its primary endpoint of preserving beta cell function at 15 months. After that failure in 2011, which saw J&J exit the deal, Diamyd's stock sank but the firm continued with "smaller, investigator-initiated trials to see how to enhance the effect of the vaccine because we know it works," Hannelius said.

One key change was to switch from subcutaneous administration to injecting the compound directly into the lymph node, he noted. Regrouping after the Phase III setback, Diamyd began the Phase I/II DIAGNODE-1 trial which involved 12 patients who were injected in the superficial lymph nodes with very small amounts of the vaccine three times one month apart, Hannelius said. This method "seems to have increased the efficacy quite considerably compared with when we injected underneath the skin," he added. Intralymphatic administration "really seems to do the trick," Hannelius said, noting that 11 out of the 12 type 1 diabetes patients in DIAGNODE-1 were in partial remission mode 15 months after treatment.

DIAGNODE-2, a European Phase IIb trial, began enrolling at the end of 2017 and is now fully recruited with 109 patients from Spain, the Czech Republic, Sweden and the Netherlands, aged 12-24 years. The patients are given the Diamyd vaccine or placebo directly into the lymph node in combination with oral vitamin D and followed for 15 months to evaluate the remaining insulin-producing capacity.

Hannelius noted, "We recently got approval from all the medical authorities in the different countries where we have clinics to offer patients an additional nine months to be part of the same trial. This longer follow up will further increase the regulatory strength in that trial, especially to get even more safety data collected." To date, more than 1,000 patients have been given the vaccine either subcutaneously or directly into the lymph nodes with no safety concerns being observed.

The company also recently carried out a feasibility study based on interviews with selected radiologists and nurses participating in DIAGNODE-2, which showed that the procedure of intralymphatic injections is considered simple and safe to perform and is associated with very little discomfort for the patient. The study also showed that portable ultrasound devices could be used to guide the injections, giving support for performing the procedure outside of specialized radiology departments.

Hannelius said that the topline results will read out in about a year, adding that the longer follow up "will further strengthen our case with regulators and our aim is to apply earlier for marketing approval." Diamyd's confidence is based on its own analysis and advice from regulatory experts. In 2020 the company will be busy interacting with agencies and getting feedback.

Hannelius pointed out that getting conditional marketing approval is based on a treatment addressing significant unmet medical need "which is clear in type one diabetes" and showing clear benefit versus risk ratio. "We have a very good safety profile, we don't put the patients at risk and it looks like we are benefiting them quite considerably, and they don't have anything today besides insulin. Based on this, we believe that there is a very good chance to go for early marketing approval," Hannelius added.

He went on to say that it is because of the support of investigators from all around the world "that we are where we are today. We only have six employees, it's a typical virtual biotech business model with clinical trials outsourced to CROs and clinics, and we have researchers and universities who do some of the preclinical work. It's been a long journey and a huge team effort, but it's looking very promising now."

The promise is such that big pharma is looking at Diamyd. Hannelius noted that the firm is in discussions with potential partners "and some of those discussions are under confidentiality agreements." He added that "big pharma are experts in pricing and making sure all the preparations for marketing are in place so we want to do it with the right partner with the right level of engagement, interest and the resources to make sure that this reaches as many patients as possible."

With the likes of Diamyd, Provention Bio and a number of other companies progressing through the clinic, it looks as though Diabetes UK's hopes of a licensed immunotherapy for type 1 diabetes by 2025 could well be in reach.

IV124388

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It's Time For Regulatory And Safety To Speak The Same Language

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Regulatory and Safety teams share the same goal: ensuring patients have access to products as quickly and safely as possible. Yet the language, processes and systems these two groups use to achieve that goal have diverged over the years. This siloed approach has complicated data reconciliation, created delays in getting products to market and blocked opportunities for these teams to effectively leverage predictive analytics.

Fortunately, companies no longer have to accept these limitations. To generate the most value from their teams' solutions, Regulatory and Safety leaders have to adapt their workflow and collaborative strategies to bring these vital processes back together.

> "It is possible to link current generations of Regulatory and Safety platforms today, enabling shared data and more streamlined communication.

TWO ROADS DIVERGED

Historically, Regulatory and Safety were a single team working jointly toward a shared focus and goals. However, as volumes grew and activities became more specialized, the industry split Safety and Regulatory tasks, especially when the focus was on individual cases rather than mining holistic data and maintaining complete products. This caused the industry to start treating Safety as a stand-alone team that dealt with routine maintenance of a product, whereas Regulatory handled the overall strategy of the product.

Their different priorities and skills justified the separation, but dividing the functions led to unintended consequences. It put them on different paths, resulting in unique taxonomies, acronyms, processes and ways of holding products within their systems. This created efficiency barriers and led to sometimes conflicting views and priorities for product maintenance and management.

For example, if the Safety team could easily view the entire Regulatory intelligence of a product, it could efficiently assess cases and signals, and conduct risk management. However, the diverging workflows mean Safety rarely has access to data in the Regulatory Information Management (RIM) system. This forces each department to manually request information that ideally it would investigate itself, and to interpret even basic information, like which product sits in which market. This not only wastes the team's time, it creates risks for the organization on current products and delays patients' access to new medicines.

These are problems that no longer need to exist. When companies integrate Safety systems with their RIM platform, the teams are reunited, able to share information, communicate and collaborate in ways that benefit both functional areas, bringing safer drugs to market faster.

For example, when these solutions are used in concert, Safety reports can be created in the RIM system using Safety system data via a single workflow. This eliminates the need to create aggregate reports and then share them by email or document management systems, eliminating time and risk from the process.

Linking the two platforms also gives the Regulatory team access to all the Safety system data, which can facilitate more robust predictive analytics to inform the Regulatory strategy structure.

REUNITING REGULATORY AND SAFETY

The goal for Regulatory and Safety to once again work together is a long way from the reality on the ground today, but most pharma companies recognize it is the path they need to follow.

System integration is the first step to bridging the chasm, and identifying the commonalities that have become obscured by the lack of a shared language. Once integrated, the RIM system can drive every team's understanding of products to ensure seamless information sharing and alignment. The convergence will allow a shared language to reemerge, creating a common platform for discussions between Regulatory and Safety. This will make it easier to identify joint interests and share information that will drive benefits for all stakeholders.

The good news for companies that want to realize these benefits, is there are currently no technical barriers to integrating systems used by Regulatory and Safety. It is possible to link current generations of Regulatory and Safety platforms today, enabling shared data and more streamlined communication.

Once these connections are made, companies can make the leap to a single Regulatory-Safety system that supports the development of more rational processes, further streamlining both functions. In

this environment, business and process barriers will be to easier to overcome, and everyone will work from a single data environment.

THE BENEFITS OF INTEGRATION

IQVIA has already partnered with a number of companies to bring the Regulatory and Safety teams together through shared technology and integrated processes. By eliminating the barriers created by outdated technology, their systems can finally talk to each other in real time.

In these environments, the processes aren't just aligned – they are integrated, allowing both groups to work on each other's systems as strategy requires. The taxonomies and time frames are jointly approved, ensuring teams can work seamlessly together while also meeting their own team goals.

This has led to two significant benefits:

1. **A single viewpoint across the product life cycle.** Integration provides Regulatory and Safety teams with a consistent, harmonized view of the product. Companies can currently achieve this level of harmonization but only through considerable manual activity. By bringing Regulatory and Safety information and knowledge together through a single, shared platform, manual activities are eliminated while collaborative capabilities are enhanced.
2. **Accelerated time to market.** The ability of teams to speak the same language and share data eliminates unnecessary delays and miscommunication. As a result, products come to market sooner with a better understood and described profile. Our clients have found that housing all product information in a single location creates clarity about a product's population and potential risks, making it easier to monitor safety and performance over time.

SEIZING THE OPPORTUNITY

The current split between Regulatory and Safety is so entrenched that the idea of structuring the two groups as a joint team feels impossible in some quarters. This rigid thinking is holding Regulatory and Safety back. Denied a common language, the functions are unable to capitalize on the commonalities and shared purpose that led them to be grouped together in the past.

But when companies acknowledge the downsides of the divergence within Regulatory and Safety processes, and are willing to transform their technology and workflows to address these issues, they are rewarded with a more efficient operation that brings products to market sooner.

Solutions such as the new IQVIA™ RIM Smart and IQVIA™ Vigilance Platform were specifically designed to tear down these siloes and drive efficiencies that benefit all industry stakeholders. They were created by life sciences experts who understand how to best integrate data and analytics in ways that transform compliance beyond just following the rules. Our modern approach delivers compliance more effectively and more efficiently, so our clients can focus their resources on efficiently delivering valuable products to market.

However, achieving this transformation requires more than technology investments. Challenging entrenched thinking and bold action are required to seize opportunities and tear down barriers that prevent Safety and Regulatory from working in concert. When companies embrace the technology and culture change necessary to bring these two teams back together, time and cost benefits will quickly follow, ensuring pharma, biotech and providers can deliver the right therapies to patients in need as soon as possible.

IQVIA RIM Smart and IQVIA Vigilance Platform integrate Regulatory and Safety, simplifying their processes while boosting speed, accuracy and efficiency. Visit iqvia.com/globalcompliance to learn more.

> “When companies embrace the technology and culture change necessary to bring Regulatory and Safety teams back together, time and cost benefits will quickly follow.

NEENA BRIZMOHUN
MANAGING EDITOR, PHARMA, EUROPE

The Stakes Are High So Get It Right

The stakes are extremely high for companies called before EU or US regulators and scientific experts to answer queries about their new drug applications at the later stages of the review process. How they perform is critical. Consultant Kate Dion highlights to *In Vivo* helpful tips for companies facing this daunting situation.

Providing an oral explanation to the European Medicines Agency's drug evaluation committee, the CHMP, or presenting before a US Food and Drug Administration advisory panel has to count as one of the most important and possibly most stressful tasks that drug companies might face.

These meetings are where drug sponsors get a final chance to address questions and concerns regulators have about their marketing authorization applications. Whether it's at the CHMP or the FDA, each meeting brings with it specific challenges, according to regulatory consultant Kate Dion.

During a CHMP oral explanation, for example, sponsors have only an hour to make their case. After this, they are dismissed from the room and have limited ability to influence the committee's ensuing debate and vote that will likely determine the fate of their product, said Dion, communications lead at regulatory consultancy firm 3D Communications.

Sponsors at an FDA advisory committee (AdCom) meeting are given more time to speak and spend all day in the room. That said, they "don't have much opportunity to respond or react to" what the regulator says because they deliver their presentation before the FDA does.

It may not feel like it, but there is a lot companies can do to exert control, said Dion, who gave a presentation on how companies can optimize their preparation for both meetings at the Regulatory Affairs Professionals Society (RAPS) 2019 Europe conference.

There are similarities and differences between the two meetings that "really do matter in terms of how to prepare and how likely you are to succeed."

In both cases, companies should prepare thoroughly, have a clear presentation and know how to answer questions and use back-up slides. "You really need to understand who your audience is and what it is that is bothering them, because they have legitimate concerns." Dodging questions "is just going to alienate people."

Most importantly, Dion warned, "a high-stakes regulatory meeting is the wrong time for an original thought. You do all the thinking before you get in the room. It's not a time for improvisation."

A BRIEF BACKGROUND

CHMP oral explanations and AdCom meetings are only convened for certain marketing authorization applications that have reached the end of the regulatory review cycle.

Companies usually get called to an oral explanation when one or both of the CHMP rapporteurs want to settle major objections they might still have about an application. AdCom meetings are normally required if the drug under review is a new chemical entity or if the FDA has concerns over a product relating to such things as trial conduct, endpoints or missing data that warrant independent, outside input. Both the EMA and the FDA usually follow the recommendation of their respective committee.

Sponsors are usually notified around two to three months in advance of an oral explanation, and four to six months before an AdCom meeting. "In both cases that's really not very much time to prepare," cautioned Dion.

CHMP oral explanation meetings tend to comprise around 40-50 members (who are mainly pharmacologists and therapeutic area experts), of which 28 (one CHMP member – or their alternate where applicable – from each of the EU member states) cast a vote. Sponsors submit their draft presentation slides to the agency a week in advance but are not required to submit briefing materials. They can have around one or two presenters and a maximum of 10 people from their organization in the room. They are allowed 20 minutes to make their presentation and 40 minutes for Q&As, after which they are dismissed while the rapporteurs deliver their presentation and the committee discusses and votes on the product. In some cases, the committee might not vote until much later on at a subsequent CHMP meeting.

At an AdCom meeting, the FDA convenes a panel of 15 or so independent experts, who are the ones who vote, and there is also an open public hearing before their votes are cast. Sponsors send their briefing book to the FDA two weeks in advance. They normally have around five to six presenters, and another 15 responders and/or triage leads who help locate the necessary slides. They remain in the room for the entire day and have 60-90 minutes to present, followed by 15 minutes to answer questions. There is a raft of different AdCom panels, and companies present to the one that aligns most closely with the FDA review division for their product.

HOW YOU TELL YOUR STORY IS CRITICAL

A similarity between the two meetings is "that the people who are voting on your product, which has taken you many years to get to this stage, may not know very much about it," Dion said.

CHMP members are likely to be familiar with a product, having spent the best part of a year reviewing it. However, there is no guarantee that all of the "people who have been really thinking about it are going to be in the room on the day of your meeting," Dion explained.

Similarly, with an AdCom meeting, the product will be familiar to the FDA members at the meeting but not necessarily the independent experts sitting on the advisory committee. "So, it's really critical how you tell your story. It matters how you put your information together, how you structure it and how much information you're delivering to these people."

DIFFERENCES IN TRANSPARENCY

A big difference between the two meetings – before, during and after – is transparency.

"CHMP oral explanations are private, all done behind closed doors," Dion said. There is no public transcript and only a brief summary of the meeting is posted online afterwards. It is therefore "really difficult to know how other companies have solved issues in the past."

With AdCom meetings, everything is public. The meetings end with an open public hearing, where patients, physicians, advocacy groups and anyone else who wants to talk about the product in question – either for or against it – can speak up at this stage of the proceedings.

The FDA also posts the sponsor's and the agency's briefing books online 48 hours before the meeting takes place. And a full transcript of everything that is said during the meeting is published afterwards.

TACTICAL EXECUTION

When it comes to tactical execution, there are differences again.

The focus for sponsors at a CHMP oral explanations should be on "message retention," Dion said, while at an AdCom "it's all about controlling the microphone." Because companies speaking at an oral explanation only have an hour in the room, they really need to make their "message stick." It is not clear how much of what they have said is retained by the people who discuss and vote on their product after they have left the room.

With an AdCom meeting, companies can engage with the advisory committee during the discussion period, and "should think of themselves as a member of the conversation that's going on," Dion advised. "You have every right if you feel they are going off track or it's not going in a particularly helpful direction to break into that conversation and take control of where it's going and make sure that you're bringing people back on to the path that you think they need to be focusing on."

The room set-up for each meeting is something else that companies should bear in mind. Both set-ups are daunting, according to Dion, but an AdCom meeting is even more so, partly because "you're going to be presenting to people [of whom a] half to two-thirds

have their back to you." While this is "not really conducive to effective communications," these things can be overcome "as long as you think about it first."

SAYING IT LIKE YOU MEAN IT

When it comes to choosing their presenters and responders, companies need to be selective. "You want to make sure that you've got somebody who has both a command of the data and the ability to communicate clearly, confidently and politely. We don't want anybody getting into arguments. This person should be able to answer questions credibly and take control of the message."

Before going into a meeting, sponsors must ensure they understand and are able to address the issues that the regulators are concerned about.

Presenters should make sure they answer the questions asked of them during a meeting, "because it's amazing how many people go straight to bridging," moving from a difficult question to a prepared key message.

Presenters should "say it like [they] mean it" and take care not to "break into jail" by bringing up information or data during the Q&A that might make the meeting members ask more challenging questions.

In addition, Dion recommends that the people who present the data and proposed risk management plan should be from the company itself. This task should not be given to the external key opinion leaders (KOLs) that sponsors sometimes hire to speak during these meetings.

The consultant said that KOLs should focus on clinically relevant content such as why the product is necessary and how it is going to be used in clinical practice. Doing so helps a company build credibility, especially since the CHMP and the FDA are aware that they have paid their KOLs for their services and there may be a risk for bias. "Again, try to make sure that even if this is the most highly esteemed KOL in a given space, don't let him or her get into an argument with the people they are talking to. That's not going to end well for anyone. They need to be very respectful, very polite and keep themselves in check."

As a rule of thumb, Dion advises sponsors to use American KOLs in America and European KOLs in Europe. "There will be exceptions, but that is a good guiding principle."

Regarding company team size, she said that this would be slightly different according to whether it was an AdCom or CHMP meeting. "For both you're going to need a regulatory liaison, a moderator, presenters, subject matter experts/responders, triage support to help with slide, medical writers and statisticians."

For AdCom meetings, companies also need people to staff the "backroom," which is another room at the FDA where the sponsor has two members listening to the proceedings by video conference who can prepare new analyses, data or new slides that the company can show, as necessary.

MEANINGFUL AND MEMORABLE CONTENT

Creating meaningful and memorable content for both meetings is critical. But even here there are nuances, Dion said. Discussions at CHMP oral hearings, she explained, focus on issues, whereas the vote itself is on the benefit-risk profile of the product. When dealing with these issues, Dion advised sponsors to put the CHMP's concerns and objections into perspective "with some clear and concise messages and credible data" that establish the favorable benefit-risk profile for their product.

"You have to address the rapporteurs' major objections. It's not about convincing them that they're wrong and you're right. At this stage in the game it's about coming forward with sensible, innovative, effective strategies to make sure that you're addressing their concerns."

With an AdCom, the focus was on benefit-risk, Dion said. Companies that bear this in mind when they prepare their presentation are much more likely to keep benefit-risk "in the front and center" of the people they are speaking to "even though the discussion may end up going onto very specific issues."

AVOID DATA DUMPING

When it comes to framing and delivering the message, the rules are the same for both AdCom and CHMP meetings.

"Don't data dump," Dion said. "People are not going to remember anything you've said if you give them way too much information and they do not know what the context is or how to put it in context. They are just going to be lost."

She described a simple, four-level pyramid format that companies can use to pull their messages together. The tip of the pyramid is where you want to get to the point as soon as possible, so start with a headline or a summary statement, Dion said. The second level down should include the data and facts that support the statement. The third level is where you can visualize the importance of the data by establishing an emotional connection between yourselves and your audience. You might explain, for example, what the data mean to a child with cystic fibrosis, or to a mother of two with breast cancer. "That helps to really drive home the message," Dion said.

The final level, or bottom line, is where you reinforce your headline so that the meeting members "are in no doubt as to what it is

you are trying to get across. This is really important, especially for the CHMP meeting when you're not in the room anymore."

Regarding slides, Dion reminded companies that these visuals should support and not compete with the verbal messages. "People remember information a lot better when they see it and hear it at the same time. So again, this will dramatically increase the odds that they will remember what you said, and they will agree with it when it comes to the voting." Each slide should focus on one main idea, have a meaningful headline, and contain concise, bulleted text. Any graphs or charts should be bold and easy to understand.

Regarding briefing books, Dion noted that while the FDA requires these of companies, the CHMP does not. Nevertheless, she advised that sponsors submit a briefing book to the CHMP. These books "are critical" as they provide your perspective ahead of the meeting, she explained, adding that they should be to the point and easy to navigate. "Make sure each section of the briefing book has a clear key message and you're reinforcing what's going to be in the content of your core presentation, so you're not hearing it for the first time on the day of the meeting."

PRACTICE MAKES PERFECT

Once a company has pulled its messages and slides together, it needs to make sure these are going to work. For this, Dion advises that companies run realistic mock meetings and practice. "This is a really fundamental part of your preparation and is going to give your team a lot more confidence as they go into these two quite tough meetings." Because the regulatory audiences are different, the mock membership should be as well, she said. "You really want to choose mock members who are going to best represent the voting members you are trying to persuade. Give them a specific identity and make sure you stay in role."

Dion noted that a common frustration for sponsors with AdCom meetings is that the FDA provides short notice regarding who the sitting and temporary voting members are going to be. Nevertheless, she said that "having to present and answer challenging questions to external people who have been hand selected to represent your CHMP or AdCom audience is a great way to focus the mind and improve the speaker's credibility."

The consultant also encouraged companies to practice Q&As several times a week. "This really helps you to identify, prioritize and organize questions. It means it's easier to create clear, memorable answers and back-up slides" and that "you are able to pull up the right slides at the right time." This, Dion said, was particularly important for AdCom meetings "because you can be looking at 1,000 to 1,500 back-up slides that you need to pull up in an instance during the meeting."

Similarly, for CHMP oral explanations, it is critical that during the Q&A you have the appropriate slides again "because your verbal message being supported by visual will help with message retention."

On the topic of back-up slides, Dion noted that because the CHMP often uses a single PowerPoint file to present data, some companies have tended to answer questions without any stand-by slides because they do not want the committee to see them. "That's OK, it's not wrong, but it does lessen your ability to really make a message stick," she cautioned.

Dion included in her presentation advice for companies that she had received from the regulatory community and industry.

The following is from former CHMP chair Tomas Salmonson:

- make sure all slides are clear, transparent and credible – don't jeopardize losing the trust of the CHMP members;
- ask for clarification if you don't understand a question – English isn't most peoples' first language; and
- don't speak too fast – be aware of potential language barriers.

Meanwhile, Alan Moses, a former chief medical officer at Novo Nordisk, said:

- be ready for push back at both meetings – and when it comes, don't take it personally;
- for the FDA, be ready for that surprise question, or perspective or issue; and
- for the CHMP be "extra" succinct, since you only have 20 minutes to present.

STAGGER PREPARATION TIMELINES

Dion also had advice for companies that have to attend both meetings.

They should take control of the timelines, she said. "Try to either delay the FDA or the EMA submission, or at least stagger preparation timelines. You don't want to be preparing for the two meetings at the same time, it's just too much."

Companies should focus on one goal at a time. "Your team will otherwise be completely overwhelmed with different information requests" from the two agencies. To ensure continuity and consistency, the same individual should oversee all the documents for both the FDA and the EMA, and other agencies if necessary. Sponsors should set realistic expectations with their senior management and their team. "Let them both know it's going to take a lot of time and a lot of energy and resources to really excel."

In addition, they should have enough statistical support and medical writers to help with all the requests for information they are going get. Dion concluded her presentation for companies preparing for oral explanation and AdCom meetings with a quote from Albert Einstein: "If you can't explain it simply, you just don't understand it well enough."

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What's Next After 20 Years Of NICE?

Meindert Boysen, head of NICE's Centre For Health Technology Evaluation, shares advice for companies aiming to get their medicine to patients. His golden rules: engage in early advice and be more realistic about pricing.

In 2019, the National Institute for Health and Care Excellence (NICE), the world-renowned organization that conducts health technology appraisals for England, celebrated its 20th anniversary. Meindert Boysen, who heads NICE's Center For Health Technology Evaluation, spoke to *In Vivo* about the ups and downs of the past 20 years and how the institute is preparing for a future with an increasing number of highly priced individualized treatments.

That NICE still exists 20 years on is no small feat, said Boysen. Indeed, he lists this among the institute's biggest achievements. "It might not sound that exciting, but we're still here and still central to the debate about what is true value."

The importance of the institute is apparent in the National Health Service (NHS) Constitution, first published in 2009 and which tells patients they have the right to drugs recommended by NICE if their physician believes they are appropriate. In addition, the NHS is obliged to make sure treatments recommended by NICE are available within three months of NICE publishing guidance.

But with that status have come challenges, not least the need to publish timely guidance, said Boysen. "Patient rights depend on whether we produce guidance. It means we have to be on time," he said. "So the focus has been on ever faster, ever more in parallel with the regulatory approval, therefore ever more relying on less evidence."

FROM ACADEMICS TO COMPANIES

NICE has responded to the challenge over the years by evolving its processes. The major sea change in speeding up the process was the shift from appraisals based on submissions made by independent academic groups to ones based on scrutinizing submissions from companies. Boysen views this change as one of the institute's biggest achievements because it allows decisions to be made much closer to the point of marketing authorization. "We turned what was a tanker that would take ages to develop guidance into a very agile program that can achieve first signals to market within 90 days of marketing authorization. That is really quite amazing," he said.

A more recent development to speed up the appraisal process is to encourage more early engagement with companies through the institute's Office for Market Access with a view to cutting the number of appraisal committee meetings down from two to one. The idea, explained Boysen, was to help companies build their submissions and crucially address key issues much sooner in the process – before the first meeting – rather than letting the committee thrash these out at the meeting. Such issues could include reviews of the evidence and increasingly whether the price on offer can get through the committee, said Boysen.

It is early days, however, and many companies still seem reticent to take the early advice, something Boysen wants to see change. "You can react in two ways. You can say … 'I'm going to wait for the committee to tell me,' which creates the delay. Or you say, 'NICE advisors have the experience; we absolutely understand that there will be a committee meeting and the committee may decide differently, but we're happy to go along with your instincts and judgment.'"

Nevertheless, Boysen is satisfied with how the institute is performing in terms of speed, given that 80% of its recommendations are in some way positive. And despite the trend of regulators awarding early approval for some drugs that address unmet need, making the appraisal process too fast would be counterproductive. Though companies may feel they can put a case together for marketing authorization, putting a value proposition forward may prove difficult. "We're already experiencing companies that say, 'We want some more time please,'" he noted.

CDF – 'AMAZING SUCCESS'

One area that has proved difficult for NICE appraisals is oncology, and there has been much debate over whether its methods are suitable for evaluating cancer drugs. Critics have claimed that NICE processes cannot deal with the incremental benefits and uncertainties attached to end-of-life drugs for very ill patients. They have also argued that NICE processes are unsuitable for determining the cost-effectiveness of a new drug compared with older generic competitors.

So, in 2010, in response to England's comparatively poor uptake of new cancer drugs, a Cancer Drugs Fund was launched to provide access to drugs rejected by NICE or which had not undergone a review. It was supposed to be a stopgap measure until a new value-based pricing system was up and running. The new pricing system never materialized and the fund itself came under fire for its big overspend and failure to tackle

any of the fundamental problems. Among other things, it was claimed there was little follow-up for drugs that had benefited from funding to determine whether their initial promise was borne out in clinical practice.

There was a second iteration of the fund in 2016, which Boysen described as "an amazing success." It allows NICE to recommend promising oncology treatments, around which there exists some uncertainty, for interim funding. During this period, more evidence is gathered to help assess whether the treatment should be recommended for routine NHS funding. Two main data sources are the NHS' Systemic Anti-Cancer Therapy Dataset and new or ongoing clinical studies. Between June 2016 and June 2018 there were 28 CDF recommendations.

Boysen put the fund's success down to its allowance of a conversation with industry on the basis of "plausible value." Though there remained uncertainty around the products, there is at least a "baseline" for a drug's potential clinical and cost-effectiveness, he said.

There has been some criticism that data collection under the new CDF will be unlikely to resolve long-term uncertainties, such as gains in overall survival and comparative effectiveness. However, according to Boysen, the new CDF is essentially "allowing companies some extra time." The institute believes this is the right approach. "The alternative would be to say no and companies research further. They would no doubt do that, but then we would be behind all the other countries where these drugs are available."

Boysen believes that the model for conditional reimbursement could be extended to some other areas, albeit only to "the really difficult ones." The vast majority of drugs should go through the standard process, he said. Extending the model to other types of drugs would also depend on a company's willingness to engage with the system, for example by organizing data collection.

FUTURE PROOFING?

Since NICE's inception 20 years ago, the pharmaceutical industry has shifted its focus away from a one-size fits all approach to ever more individualized treatments for smaller patient populations. The growing number of personalized medicines and of gene and cell therapies is therefore no small challenge for an institute that focuses on overall patient benefit. "It does raise questions about our approach to decision-making, which is not about individuals. It's about the mean benefits and the mean costs, and what, on average, we are displacing," said Boysen.

Nevertheless, as far as personalized medicines are concerned, the institute does claim to have tools to accommodate such medicines. For example, it has a diagnostics assessment program to evaluate tests required for personalized medicines.

Also, within the health technology appraisal programs there are tools to look differently at challenging drugs, including also cell and gene therapies, for example, through the Highly Specialized Technologies program. Boysen added that the NICE methods review that is underway would likely consider some complex issues relating to certain technologies, including histology-agnostic cancer drugs.

Early, collaborative approaches between companies, NICE and NHS England are also crucial in getting these medicines to patients. Such collaboration should involve not just discussion on value access, but in addition the services that may be required to deliver treatment and what contractual arrangements may be necessary. This was exemplified through the agreement struck between Novartis and NHS England for the company's CAR-T therapy, Kymriah (tisagenlecleucel), said Boysen. The agreement came just 10 days after EU marketing authorization and was one of the fastest funding approvals in the 70-year history of the NHS.

Boysen also pointed to plans for a new commercial and managed access program operating between NICE and the NHS in England that would come up with templates and structures for the "pre work" necessary for such access arrangements. "This will allow next-generation cell and gene therapies to just slot into an already developed thinking. That ought to be the way we do it rather than just chasing the next one as it comes."

More generally Boysen is likewise open to different forms of managed access agreements such as risk-sharing agreements and outcomes-based deals that generate learning about any new technology. Not only do they help in developing a better understanding of how effective a product is, but also of how it is used with the health service. There is increasingly more uncertainty over this and how some services relating to treatment are paid for.

In addition, forewarned is forearmed. Boysen wants to appeal to companies to engage with the NHS horizon scanning service to identify relevant topics. "What we're trying to do is to predict what might come and perhaps that's also one of the messages to industry: if you don't tell us that these things are coming and don't actively involve us in thinking about how we might handle them, then we will be on the back foot."

Boysen is also calling on companies with promising but challenging products, such as tumor agnostic drugs, to come to NICE earlier on alongside their competitors to discuss a way forward. Any such meeting would offer a safe harbor where sensitive information like pricing need not be discussed. "I get all the competition and market sensitivities, but still it's much better if we can develop something together."

Another big project is NICE Connect, which aims to digitize and combine advice offered by NICE currently in the form of guidelines, technology appraisals and quality standards. The goal is to make the information far more accessible to patients and physicians and enable better decision-making.

METHODS REVIEW

NICE's ongoing review of its methods and processes has attracted much attention, with some wondering how far it will go to prepare for the future and address big issues. However, Boysen is keen to manage expectations. The review will not involve a big overhaul of NICE processes, such as resetting cost-effectiveness thresholds, but instead will focus on clarifying current methods.

Companies sometimes focus on NICE's appraisal methods but forget that the institute operates within the constraints of a wider health system, Boysen remarked. "To just single us out and hope that our methods, let's say, will provide a solution to all of their pains [is] never going to work."

Topics to be covered in the methods review include how uncertainty is explored and quantified, and what can be done to reduce that uncertainty, with a potential role for real-world evidence and modifiers used in decision-making. It will also look at criteria for appraising highly specialized technologies. Proposals will be put out for consultation next summer.

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Brexit To And Fro Continues Into Fresh Decade

Three Brexit deadlines have come and gone, and the UK is still a member of the European Union. It will remain so until it agrees a withdrawal deal or leaves without one at the end of January 2020. Alternatively, it could secure yet another extension to the Article 50 period beyond January 31.

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For the life sciences industry, the latest delay to the Brexit process spells a further period of regulatory and trade uncertainty. Companies poured time, energy and money into preparing for the possibility of a no-deal exit on October 31, only to see that date pass uneventfully by when prime minister Boris Johnson reluctantly requested another extension, this time to January 31, 2020.

The industry certainly does not want a no-deal outcome, but it does crave some form of stability. The feeling was summed up by Steve Bates, CEO of the UK BioIndustry Association: "The UK life sciences sector has spent significant time, effort and resource in preparing for a no-deal Brexit," Bates told *In Vivo*. "Companies have faced considerable costs in finding and securing space at warehouses, understanding the impact of the possible new regulatory environment the UK will operate in, and securing freight on new supply routes."

"We should be under no illusions," Bates added. "Despite assurances from government, Brexit has meant extra red tape and cost to British business." It had seemed that some sort of resolution might be in the offing when prime minister Johnson's Withdrawal Agreement Bill passed its second reading on October 23, but Johnson unleashed yet more disruption when he plumped instead for a general election on December 12, 2019. The election saw the Conservative Party win a clear majority, so the UK is now expected to leave the EU by January 31, 2020, with a withdrawal bill that includes a transitional period to the end of the year.

Still, it is important to remember that a no-deal Brexit remains the legal default.

CARRY ON PREPARING

In the meantime, businesses have been advised by the government to assume the worst and maintain their no-deal readiness as the clock ticks away towards yet another potential Brexit cliff edge.

Companies based in the UK have already made substantial preparations, such as transferring centrally authorized products to marketing authorization holders in the EU, a process that is now all but complete. They have also had to ensure that they have a Qualified Person for batch release, QP for pharmacovigilance and pharmacovigilance safety master safety file in the EEA, which in many cases has required the creation of new facilities.

At the behest of the government, companies built up an extra six weeks' worth of buffer stock to avoid shortages, and in many cases had to buy more warehousing space to house it.

They were also urged to book places on new freight routes organized by the government away from the Channel ports, where supply blockages were widely expected in the event of a no-deal Brexit.

All this, of course, comes at a cost. Companies are reluctant to reveal specifics, but it is generally accepted that for a large pharma firm the price of preparing for Brexit will already have run into millions of pounds.

The question is, what happens now? Such is the unpredictability of the Brexit trajectory that nothing is certain. A number of possible scenarios could emerge, including a withdrawal deal, a no-deal exit on January 31, another Article 50 extension, a "people's vote" on deal versus remain, or revocation of the Article 50 notification.

BENEFITS OF A WITHDRAWAL DEAL

For a highly regulated industry like life sciences, the advantage of a withdrawal deal and the accompanying transition period for businesses is that, trade and regulation-wise, things would pretty much stay as they are.

The UK would no longer be a member of the EU, but it would still have to abide by its rules and would make to make its contribution to the budget and other financial commitments during the transition period. It would remain part of the customs union and single market, so trade with EU countries would be unaffected. EU centralized marketing authorizations would still be valid in the UK, and companies could continue to use the EU centralized and decentralized approval procedures.

Mutual recognition of manufacturing and distribution licenses and good practice inspections would continue, and the UK would be treated as an EU member state for the purposes of international agreements such as MRAs during the transition period.

However, during the transition period the UK could not act as rapporteur for EU procedures, and although representatives of the Medicines and Healthcare Products Regulatory Agency (MHRA) could continue

to attend EU committee meetings, the UK would have no voting rights.

Moreover, ratification of the withdrawal deal could bring regulatory complications because it includes special arrangements for Northern Ireland. Under the deal the UK would leave the EU customs union, while Northern Ireland would remain aligned with the EU's rules on goods and to some extent on customs. This would effectively place a customs border down the Irish Sea, rather than along the border with the Republic of Ireland.

Bates pointed out that because the MHRA is the medicines regulator for both Northern Ireland and Great Britain, under the withdrawal deal the agency would have to "operate two sets of rules: EU rules in Northern Ireland, and GB rules in GB."

He said it was "hard to see that the UK would be a pure third country to the European Union in term of medicine regulation, so there now needs to be a detailed technical discussion on how this would operate."

THE FUTURE RELATIONSHIP

The agreement of a deal and the triggering of a transition period would also see talks kick off on the future UK-EU relationship. In the life sciences sector, industry has always insisted on the importance of having a close trading and regulatory relationship in order to avoid possible barriers to trade and divergences in UK and EU standards that could impact innovation, the science base and trade in pharmaceuticals between the UK and its nearest neighbors.

Bates said that "for the UK to stay at the frontier of global innovations and treatments, we must ensure the UK's health and care sector is in the strongest possible position once the UK leaves the EU. Maintaining regulatory and customs cooperation on medical devices and medicines as well as ensuring maximum levels of participation in European research is a must."

A framework for the negotiations is outlined in the Political Declaration that accompanies the withdrawal deal. This calls for "an ambitious, wide-ranging future economic partnership" but leaves many details to be decided during the negotiations and keeps a range of options open.

The BIA says that priorities for the negotiators should include continued participation in, and cooperation with, EU regulatory regimes, bodies and networks, as well as the preservation of a "level playing field" with EU member states. This would ensure that the UK industry is not faced with undue regulatory barriers to R&D, marketing, manufacturing, distribution, import, export and vigilance requirements, or any weakening of intellectual property rights.

It is likely that the life sciences industry will want to press for a sector-specific annex or protocol in the Political Declaration that ensures maximum alignment between UK and EU pharmaceutical legislation, while allowing the UK to adopt new laws where appropriate. There is no desire among UK companies for adding costly regulations that duplicate those of the EU.

Industry would also like the MHRA to be given as big a role as possible in the EU regulatory network, saying that the lack of input from the agency and other UK bodies would significantly impair the EU's ability to be competitive at a global level in this sector.

The Association of the British Pharmaceutical Industry said that because of the complexity of customs declarations and inspections and the highly integrated nature of medicine supply chains, it was vital for companies to be able to continue moving pharmaceuticals and medical supplies, as well as capital, across borders with the EU.

As well as continued regulatory alignment, it wants to see continued UK access to long-term EU funding and collaborative science programs, and agreements that make it easy for highly skilled life science personnel to move between the UK and the EU.

NO-DEAL STILL THE DEFAULT

The alternative to a deal-based Brexit, of course, is a no-deal Brexit, a prospect that industry wants to avoid at any cost. A no-deal scenario was again averted in October, but it remains the legal default. And a no-deal exit could happen in two ways.

If the Withdrawal Agreement Bill is not ratified by January 31 and there is no further extension period, the UK will leave the EU on World Trade Organization terms. The implications of this for the life science sector are well known. Existing ties with the EU would be cut overnight, and the UK's participation in trade deals negotiated by the EU would fall away. The UK would have to set up its own freestanding drug regulatory, marketing authorization and pharmacovigilance system, and would play no further part in the EU regulatory network. Trade in medicines between the UK and the EU could be hit by customs and tariff barriers, with many predicting widespread supply disruptions at Channel ports.

But a different type of no-deal Brexit could happen if a withdrawal deal is agreed but negotiations on the future UK-EU relationship are not completed by the end of the transition period. Again, the UK's relationship with the EU would fall onto WTO terms.

The transition period is currently set to last until the end of 2020, but the value of that period has been gradually eroded as the deadline was originally set on the basis that the UK would have left the EU on March 29, 2019. If the UK exits on January 31, a bare 11 months will remain in which to negotiate the

entire future relationship, which in practice is likely to take many years.

Michel Barnier, who was the EU's chief Brexit negotiator and has now been given the job of negotiating the future relationship, suggested in early November that an extension of the transition period beyond December 2020 would be necessary to allow talks to conclude.

The UK government replied, though, that MPs would not be given a vote on an extension, thereby going back on a pledge it had made the month before. A spokesman for Johnson said: "We aren't extending the implementation period. There is no reason whatsoever why we will not secure a deal by that date."

Critics, though, have pointed to the repeated extensions of the Article 50 period, most notably Johnson's failure to honor his "do-or-die" pledge to "get Brexit done" by 31 October. In any case, the UK does have the option of extending the transition period by up to two years to allow negotiations to be completed, although any such extension would have to be agreed by the UK and the EU before July 1, 2020.

In the meantime, the government has said that registration for the no-deal freight services will remain open and civil servants will remain in readiness mode. The "Be Prepared for Brexit" campaign is likely to kick off again in January.

Bates said the government would probably ask industry to continue its own no-deal planning, including stockpiling, supply rerouting and planning for new customs and border arrangements. He also advised companies that if they had any warning signs of supply disruptions that might appear inJanuary they should share them as early as possible.

According to Tim Sarson of KPMG, companies should not be tempted to rest easy following this latest extension. He points out that there could be another "cliff edge" in January, and that companies should continue to do all they can to prepare for it.

Sarson said in October that he had worked with a wide range of life science companies over the past few years and that "every single one" had a no-deal Brexit as its "core scenario." This is mainly because while such an eventuality obviously brings many uncertainties, there is much that is predictable, particularly for highly regulated industries like the life sciences.

"You know what the paperwork changes will be and you can get yourself prepared. No deal remains the default outcome, it means changes happens on day one, and in my view it is the only viable scenario." Until there is the certainty of a withdrawal deal, he said companies "should be planning for an unmitigated no-deal scenario, and if things turn out better than that, then great."

In the meantime, Sarson had some advice for companies wanting to reduce their exposure to a no-deal scenario, such as verifying the security of their supply chains. The smaller those companies are, the less likely they are to have done any serious no-deal planning and "the more financially vulnerable they are going to be."

If companies manufacture in the UK, for example, they need to understand what is happening at the level of their suppliers, he said. "The first thing you need to do is really understand the environment you are working in and which suppliers you are dependent on. It is incredible the extent to which many companies, including multinationals, have outscored responsibility for their supply chain to companies of which they know very little."

"I can't emphasise enough the importance of mapping out your supply chain in detail and really understanding who owns what, where they move it from and to, where stuff is stored, and which third parties you are relying on."

The BIA's Brexit Lead, Michael Warren, said, rather worryingly, that there were many life science companies that were still not ready for a sudden exit. He said many businesses were "either partly prepared or not at all prepared," and that many still had questions in areas like batch testing, regulation, clinical trials, people and employment, and potential border arrangements.

A US FREE TRADE DEAL?

Whenever Brexit happens, and whatever form it takes, the UK will also need to negotiate its future relationships with other countries that have trade or other arrangements with the EU. Government ministers and other Brexit supporters have made much of the opportunities that pulling out of the EU customs union could bring, in particular the UK's ability to strike its own independent trade deals.

The government has depicted a US trade deal as a glittering Brexit prize, pointing to the close ties between the two countries, although the image was sullied somewhat by President Donald Trump's declaration in November that the deal negotiated by Johnson might hinder a UK-US trade deal.

Negotiating a trade agreement with the US, particularly in a no-deal scenario where the UK is on the back foot, will in any case be no walk in the park. The smaller partner is likely to come under strong pressure to lower some regulatory standards and concern has been expressed that it may have to make other concessions such as higher drug prices, changes to the role of the HTA body NICE, and wider access to the NHS by US health care corporations.

Certainly, the US favors change in the area of pricing, reimbursement and access to the UK drugs market. In its final negotiating objectives released in February, the US Trade Representative said it planned to "seek standards to ensure that government regulatory reimbursement regimes are transparent, provide procedural fairness, are non-discriminatory, and provide full market access for US products."

In its submission to the USTR, the US pharmaceutical industry body PhRMA said UK market access policies were characterized by "rigid health technology assessments, government price controls, insufficient health care budgets, and increasingly punitive and proactive national procurement initiatives and local barriers to uptake."

It said the UK system "significantly undervalues innovative medicines and restricts patient access to those medicines" and that drugs should be priced "either through a market-based system... or some type of equivalent system."

These, of course, are opening positions, and whether the NHS will be "on the table" of the trade negotiations with the US, as Labour and many others claim, remains to be seen. The government insists it will not, and has also denied reports of "secret" meetings between UK trade officials and US pharma firms to negotiate higher NHS prices for US drugs.

But with the chaos and polarization wrought by Brexit, and the high level of distrust in politicians it has generated, it is difficult to take any such reassurances at face value. We will just have to wait and see.

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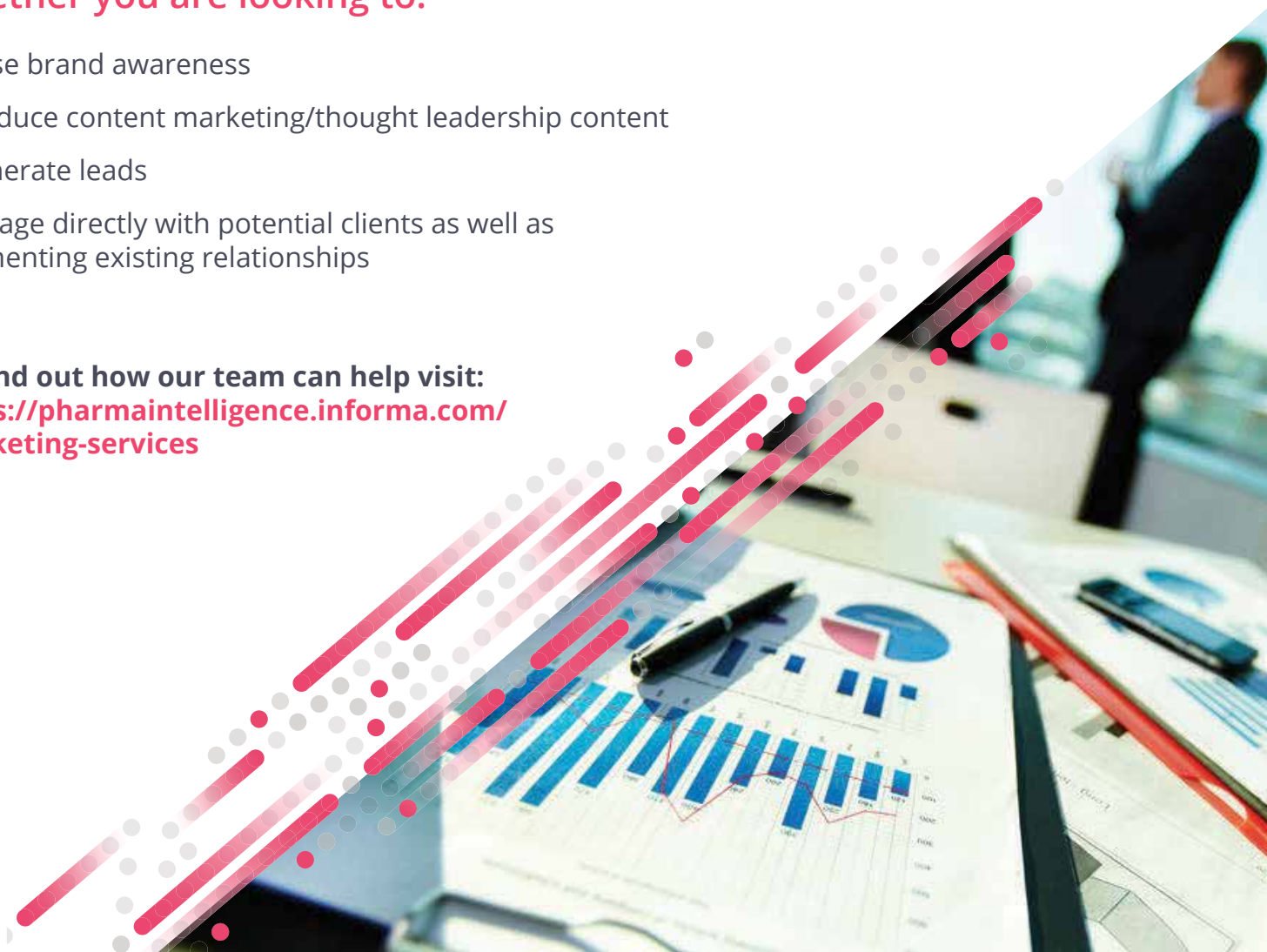

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With the steady rise of FDA Abbreviated New Drug Applications (ANDAs) approvals and continued generic competition and global pricing pressures, speed to market and frequent evaluation of go-to-market strategies are imperative to generic drug manufacturers.

Go-to-market strategies may include a greater mix of generic drug products to balance manufacturers' overall product portfolios. Some strategic approaches may include the launch of branded generics, submission of 505(b)(2) filings in the US or evaluation of the regional/global footprint to diversify the inherent risk in their product portfolios. No matter which strategic approach is employed by a generic drug manufacturer, controlling costs is paramount to the strategy.

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This year, West enhanced the program further with the addition of plungers to the AccelTRA *Select* product line. Additionally, West also launched the new AccelTRA *RTS/RTU* product line for non-North American customers who have a premium domestic need that requires a high-performing elastomer with commercial quantity lead times of 6 weeks. The full repertoire of Ready-to-Sterilize (RTS) configurations will be available in Q1-2020, while the Ready-to-Use (RTU) gamma irradiated elastomer configurations are expected to launch in Q2-2020.

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AIDAN FRY
EXECUTIVE EDITOR, GENERICS & BIOSIMILARS, EUROPE

Generics Leaders Trade Places At The Top

In 2019, Mylan moved up to become the world's leading generics, biosimilars and OTC player, according to Informa Pharma Intelligence's latest global rankings. Sandoz has surpassed troubled Teva into second place but is set to surrender that position following the sale of its US solid-dose and dermatology business to India's Aurobindo.

Mylan NV has faced a couple of fallow years financially, stemming from difficulties in its home market – particularly around manufacturing issues. This led the US-headquartered company to report a 4% slip in group turnover last year.

Nevertheless, it was able to claim top spot in the latest rankings of the world's leading generics, biosimilars and OTC players compiled annually by *Generics Bulletin*, based on calculations from official sales disclosures made by companies for the full year 2018.

According to *Generics Bulletin*, a sister publication of *In Vivo*, Mylan's turnover from generics, biosimilars and OTC products matched the group's performance in slipping by 4%, falling to $10.017bn. That figure includes any active pharmaceutical ingredient (API) sales to third parties made through its Matrix operation, but excludes around $1.25bn of turnover from respiratory and allergy brands such as EpiPen (epinephrine), Perforomist (formoterol) and Tobi (tobramycin).

Mylan's move into the leading position globally comes by virtue of Teva Pharmaceutical Industries Ltd.'s double-digit decline. A 12% slide in generics, biosimilars and OTC sales to $9.859bn was due in large part to a 22% tumble to $4.056bn in North America. Still, Teva highlighted, "In 2018, we led the US generics market in total prescriptions and new prescriptions, with approximately 504 million total prescriptions, representing 13% of total US generic prescriptions."

The company added, "Our generic products pipeline in the US includes, as of 31 December 2018, 297 product applications awaiting US Food and Drug Application approval, including 92 tentative approvals." Approximately 70% of Teva's pending applications include a paragraph IV patent challenge and "we believe we are first-to-file with respect to 107 of these products, or 132 products including final approvals where launch is pending a settlement agreement or court decision."

TOP US PLAYERS ARE PULLING PRODUCTS

Such were Teva's travails in the US generics arena that the Israeli group was pushed into third place in the latest rankings by Sandoz International GMBH. Like Teva with its Ratiopharm range and Mylan with its Meda portfolio, Sandoz does not split out sales of its OTC products under labels like Hexal separately from its generics offering. Thus, this ranking includes OTC products alongside prescription generics and biosimilars, the effect being 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 – renders it a top-five global player when combined with the Prescription Pharma unit that it is considering selling or spinning off.

The global top three's falling sales in the US generics arena have not been entirely inadvertent. Faced with declining margins in light of a heavily consolidated customer base intent on exercising its considerable purchasing power, leading players are increasingly choosing to exit the least profitable profit lines rather than to stay in the market, potentially at a loss.

Former Sandoz head Richard Francis said in late 2018 that pruning the firm's US portfolio of less profitable products was essential if the firm were to continue growing. "It gets to a point where the maths can never work out – your base business is so big that you cannot fill it in enough with new products. When you get to a critical mass," he cautioned, "you cannot launch your way out of a price decline."

Francis pointed out that the consolidated buying groups had chosen largely to run procurement processes on a molecule-by-molecule basis, rather than striking deals for entire product portfolios or baskets of products. Thus, he said, customers understood why manufacturers were choosing to pull certain products from the market and were focusing less on offering the most comprehensive portfolio possible.

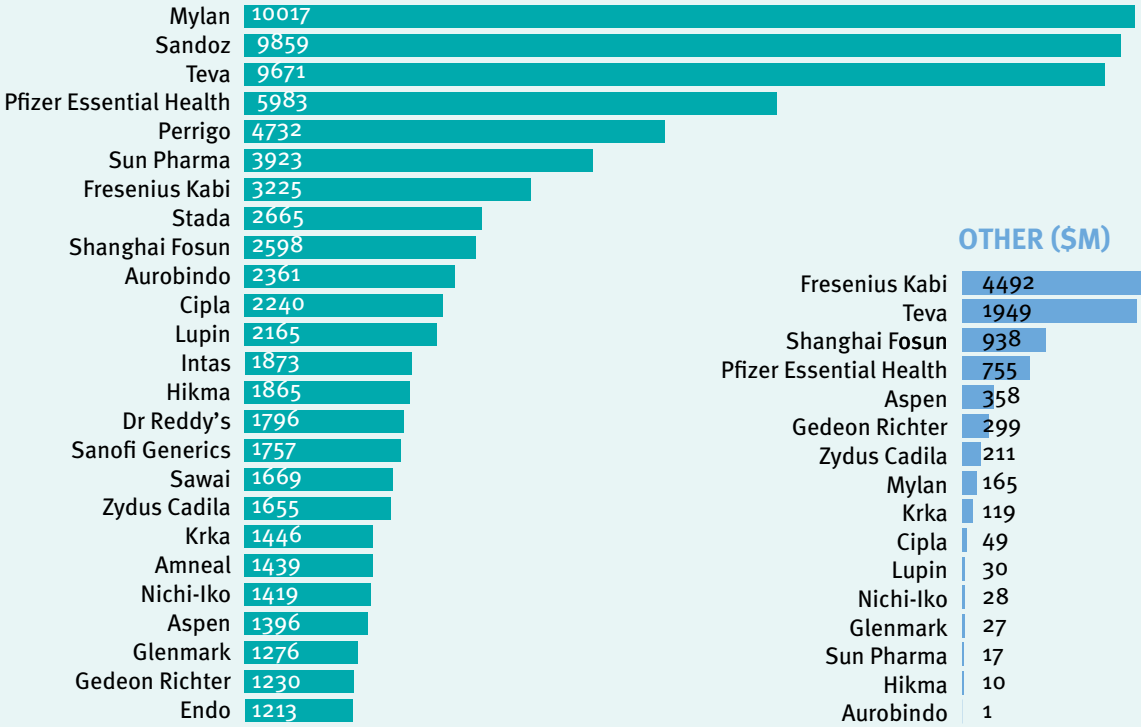
US APPROVALS ARE NOT TRANSLATING TO LAUNCHES

Lupin – one of a host of major Indian players looking to capitalize on the leading lights' increasing focus on profitability, rather than portfolio breadth – referred to FDA disclosures to highlight how Mylan had raised its number of drug discontinuations last year by more than six-fold to 64. At the same time, Teva and Sandoz had lifted their withdrawals from a handful in 2017 to 28 and 13, respectively, in 2018.

The 25 Leading Generics, Biosimilars And OTC Companies

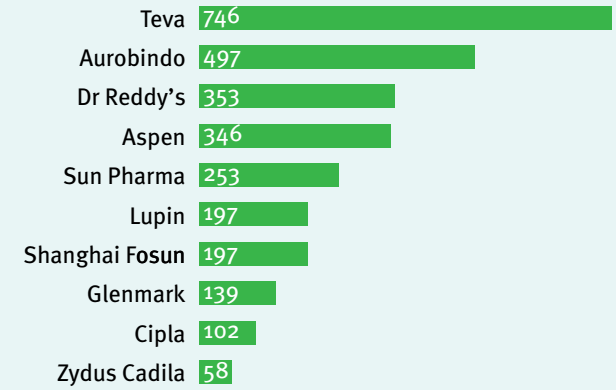
Leading companies by annual sales of generic, biosimilar and OTC medicines, according to an analysis of annual sales data reported by each company.

GENERICS/BIOSIMILARS/OTC ($M)

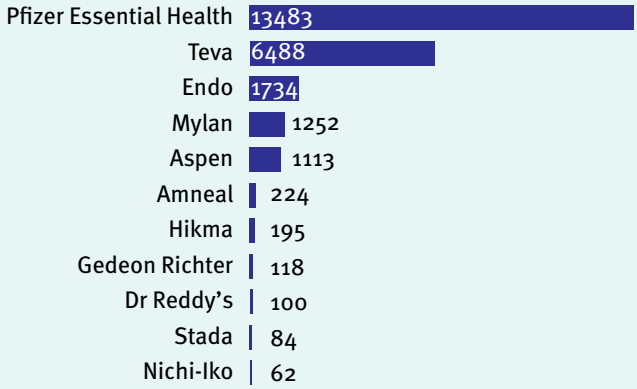


OTHER ($M)

APIS ($M)



PRESCRIPTION BRANDS ($M)



Sales data is for calendar 2018 or for each company's most recently completed financial year; sales are categorized as per corporate divisions and discretionary calculations by Generics Bulletin; where firms report in currencies other than US dollars, figures have been converted into dollars at prevailing average exchange rates as calculated by the US Internal Revenue Service

Based on its performance in its financial year ended March 31, 2019, Lupin fell just outside the global top 10, slightly behind its compatriot Cipla that ranked 11th on the same basis. Just behind the Indian pair was Hikma, which produced a steady growth profile across its generics operations in the US, Middle East and North Africa, as well as from its global injectables division. In total, Hikma's global generics, biosimilars and OTC turnover rose by 8% to $1.865bn.

Part of that growth was due to a strong performance from the UK-listed company's non-injectable Generics division in the US.

> *"Notable performances among companies ranked between 26th and 50th in our list included Torrent Pharma's impressive 30% increase in generics, biosimilars and OTC sales."*

Citing IQVIA data, Hikma observed that just 261 – or barely a third – of the 723 ANDAs approved in 2018 had been launched onto the US market as of December 2018. While price erosion in the US market had eased slightly last year, conditions remained challenging, it said.

Sun Pharma – which is increasingly looking to differentiated and branded therapies in the US – bucked the general trend by raising its US Formulations sales by 12% in its financial year ended March 31, 2019. This contributed to the Indian group's global generics, biosimilars and OTC turnover increasing by 9% to $3.923bn, ranking Sun sixth behind Perrigo and Pfizer Essential Health.

PFIZER STRUGGLES WITH LEGACY HOSPIRA ISSUES

Pfizer's generics, biosimilars and OTC figure of $5.983bn reflects largely its legacy Hospira operations, both in small-molecule injectables and biosimilars such as Inflectra (infliximab). The 4% decline was attributable in part to shortages of legacy Hospira injectables in the US as the firm continued to struggle with its large-scale plant in McPherson, KS. Mature brands such as Celebrex (celecoxib) and Lipitor (atorvastatin) are classified as Prescription Brands in our ranking.

Two German companies, Fresenius Kabi and Stada, fared somewhat better – each reporting 1% rises in generics, biosimilars and OTC sales year. Both were somewhat hampered by adverse exchange-rate fluctuations, but that setback was tempered by not being exposed to fierce price erosion and competition in the US retail generics sector: Kabi by virtue of its focus on intravenous drugs, an area in which it benefitted from Pfizer's supply problems; and Stada by focusing its operations largely in Europe.

A Chinese company, Shanghai Fosun, this year appeared in the top-10 for the first time on the strength of a 48% surge in generics, biosimilars and OTC sales to $2.598bn from drugs such as enoxaparin, febuxostat, pitavastatin and quetiapine.

DEAL WITH SANDOZ POISED TO PUSH UP AUROBINDO

Aurobindo rounded out the top 10, having overtaken compatriots Cipla and Lupin with 19% growth that was fuelled by double-digit turnover rises across its finished-dose formulations business. And with a $1.0bn deal for Sandoz' US solid-dose and dermatology operations scheduled for completion, the Indian company looks likely to rise further up our rankings in 2020.

Heading in the opposite direction is Sanofi's Generics division, which will next year not benefit from a nine-month contribution from the European Zentiva business that the French group sold to private-equity investor Advent International at the start of October 2018.

Acquiring Impax and Gemini in May 2018 gave Amneal double-digit growth that masked a small decline on a proforma basis in generics, biosimilars and OTC sales.

INDIA' INTAS CONTINUES UPWARD TRAJECTORY

Intas continued its recent growth trajectory, not least through its Accord affiliates in Europe and North Africa, while fellow Indian firm Dr Reddy's also gained ground on many of those above it. The opposite was true for Endo, which tumbled to the bottom of our top 25 ranking as it suffered from competitive pressures on its Par operation in the US generics arena, as well as from divesting certain non-US operations.

Notable performances among companies ranked between 26th and 50th in our ranking included Torrent Pharma's impressive 30% increase in generics, biosimilars and OTC sales, which was attributable in part to the Indian company having bolstered its domestic activities by acquiring Unichem Laboratories' business in India and Nepal at the end of 2017. Torrent also registered double-digit rises in countries including Germany and the US.

Having seen its proposed takeover by Fresenius thwarted by manufacturing compliance concerns, Akorn endured a difficult 2018. This is reflected in its 17% turnover slide that year. Advanz Pharma and Mallinckrodt saw similar sales falls, but Bulgaria's Sopharma was among the stronger performers, as were Indian players Alembic and Biocon.

Private companies that do not disclose detailed sales information – from Alvogen and Apotex, through Polpharma and Prasco to Xantis and Zentiva – are not included in the rankings due to the lack of verifiable data.

Also excluded are companies that do not split out generics, biosimilar 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.

To find a place in the ranking, generics, biosimilars and OTC products must be a major part of a company's operations. Had Biogen been included on the basis of its 2018 sales of the Benepali, Flixabi and Imraldi biosimilars marketed through its Samsung Bioepis joint venture that totalled $545m last year, the biotech specialist would have been placed between 30-50th.

On the same basis, a case could be made to list originator Eli Lilly considering turnover from its Basaglar follow-on insulin glargine brand, which was approved through the hybrid 505(b)(2) regulatory pathway in the US and is tracking towards $1bn in annual sales.

US Generics Market Continues To Seek Stability

As the US generics market continues to experience turbulence, the industry's largest players are adopting a wide range of strategies to cope with the uncertainty as signs of stabilization begin to emerge.

DAVID WALLACE
MANAGING EDITOR, GENERICS & BIOSIMILARS, EUROPE

At the start of 2019, the chief executive of one of the generics industry's biggest players set out a bold claim: that the severe US pricing pressures experienced over the past few years had stabilized, bringing an end to a period of misery for many generics producers.

"The whole pricing dynamic in US generics [has] changed," Teva Pharmaceutical Industries Ltd. president and chief executive officer Kåre Schultz told attendees of the 2019 J.P. Morgan Healthcare Conference at the start of the year. "We no longer have this death spiral of price declines, but we have a much more stable situation." *(Also see "US Pricing Pressures Have Stabilized, Insists Teva Chief" - Generics Bulletin, 9 Jan, 2019.)*

Schultz' comments surprised many, coming against the backdrop of pressures that had been cited by US off-patent industry body the Association for Accessible Medicines as "sustained historic levels of price deflation."

As a wave of consolidation among generics suppliers has continued to be the prevailing trend of recent years, so too with buying groups, which have concentrated through consolidation. And now, the buying power of these purchasers that together control a vast majority of the market has enabled them to push down prices, devaluing portfolios of products.

A good example is the portfolios of products divested by Teva itself in the wake of its purchase of Actavis in 2016, on which many of the purchasing companies were subsequently forced to register writedowns due to the falling value of these product baskets. Teva also took a substantial hit on the value of the purchased portfolio.

"Increasing consolidation among pharmaceutical purchasers represents an increasing threat to maintaining a stable supply of generic medicines," noted AAM president and CEO Chip Davis in late 2018. "In fact, today roughly 200 generic companies compete to sell to three purchasing groups that collectively control 90% of the market," he pointed out, referring to Red Oak Sourcing LLC, Clarus One and Walgreens-Boots Alliance Development. *(Also see "Pressures on US industry go beyond current price squeeze" - Generics Bulletin, 2 Nov, 2018.)*

However, Schultz was clear in his early 2019 prediction that the US generics market would "in absolute value" be stable throughout the second to the fourth quarter, adding, "I'm also predicting that to be the case for the future."

But while Teva has continued to maintain that it has seen "an overall stabilization of the pricing environment" in North America – partly due to the firm's deci-

sion to prune its portfolio of non-profitable product lines where prices had dropped below sustainable levels – not all of its peers may agree with its perception of the US generics market as one that has reached a new equilibrium.

In fact, the generics industry has seen a wide range of coping mechanisms employed by its biggest players, as all seek to weather the storm of continued pricing pressure and market instability.

Mylan NV, another of the largest generics players in the US market – and according to Pharma Intelligence's own ranking, the world's leading generics, biosimilars and OTC player – entered 2019 under the cloud of an ongoing board-level strategic review.

> *"If you want stable supplies, you need to have a price point to support that stability.*
>
> *– Kåre Schultz"*

leading the firm's share price to fall to a five-year low. *(Also see "Wait For Strategic Decisions Weighs Heavily On Mylan" - Generics Bulletin, 17 May, 2019.)*

Its eventual decision to merge with Pfizer Inc.'s Upjohn off-patent business to create a brand-new company, Viatris GMBH, was a dramatic move that demonstrated the extent to which even the generics industry's biggest actors are willing to shake up their business model to address US pressures.

SANDOZ ABANDONED ORAL SOLIDS BUSINESS

On the other hand, some major players have simply chosen to pull out of large chunks of the market altogether. Novartis AG generics unit Sandoz International GMBH in mid-2018 struck a deal with Aurobindo Pharma Ltd. for the Indian company to acquire Sandoz' dermatology and oral solids businesses in a deal worth $1bn.

Sandoz' new CEO, Richard Saynor, was frank when he took the lead of the company, declaring in one of his earliest appearances on behalf of the generics firm in mid-2019 that "we haven't seen yet a stabilization in the core generics business in the US." *(Also see "US Generics Market Isn't Stabilizing Yet, Sandoz Says" - Scrip, 18 Jul, 2019.)*

And more recently, Saynor continued to express caution over the US market, telling *Generics Bulletin* in late October that there was still "huge uncertainty" in the US and "an awful lot of change happening very rapidly."

"Having a leaner, more nimble, smaller business in the US at this time I think is actually a benefit," Saynor outlined, maintaining that "the core retail business is still declining quite strongly."

"Clearly it will reach the bottom at some point," he said, "but I'm not sure when that will be," especially given that "prices are still eroding very rapidly."

"All the reasons [why] Novartis made the decision to divest the business to Aurobindo are still there today," Saynor explained. "It doesn't mean over time, that we won't choose to come back into some of those spaces if we see the right opportunities. But then clearly, the more attractive segments of the market are biologics, the harder to make ophthalmics, sterile injectables, respiratory. Those are really far more sustainable, rather than commodity products for which pricing inevitably will collapse very rapidly."

AMNEAL FELL BACK ON FORMER MANAGEMENT

While Mylan has chosen consolidation with Upjohn and Sandoz has decided on divestment to Aurobindo as ways to address the ongoing US pressures, another major player has sought to weather the storm through a management overhaul.

Amneal Pharmaceuticals LLC – which became the fifth-largest US generics player after completing in mid-2018 its merger with Impax Laboratories Inc. – dramatically slashed its earnings forecasts in mid-2019, citing a highly competitive local generics market. It launched a wide-ranging restructuring plan to cut costs and staff, calling the move "a difficult but necessary step forward to position Amneal for future success."

However, investors were not convinced, downgrading their valuation of the firm, which ultimately lead to the resignations of president and CEO Rob Stewart and chairman Paul Bisaro and the return of the co-founders of Amneal, Chirag Patel and Chintu Patel, to the position of co-CEOs.

Amneal hopes that Chirag Patel and Chintu Patel's experience and leadership skills will be enough to turn the company's fortunes around. And joining Amneal in seeking new management is Endo, which recently revealed plans to look for a new chief after CEO and former Par head Paul Campanelli announced plans to step down for personal reasons. *(Also see "Endo Starts Search For Campanelli's Successor" - Generics Bulletin, 8 Nov, 2019.)*

UNCERTAINTY PLAGUES PERRIGO AS IT PURSUES PRESCRIPTION SPLIT

Even decisive actions to address the uncertainty in the US market can themselves fall foul of the changing landscape for US generics.

For Perrigo Co. PLC, a move announced in August 2018 to separate the company's Prescription Pharmaceuticals (Rx) US generics business has now been pushed back indefinitely from the original planned separation date of the second half of 2019.

The firm's new president and CEO, Murray Kessler – a consumer goods veteran whose experience is in line with Perrigo's shift to a consumer-focused strategy – said he agreed with the strategy to separate the Rx unit, as it was "a distraction to our core Consumer businesses, even though it is a good and profitable business in its own right."

But even though Kessler had in early 2019 pointed to "sequential improvement in the Prescription segment during the fourth quarter [of 2018], as downward pricing pressure eased," the Perrigo chief was forced to concede later in the year that it was pushing back the move while it evaluates timing amid uncertainty and tumult in the US generics market.

"The Rx separation continues to be a strategic priority," said Kessler, "and we continue to work on effecting a separation. But uncertainty in the market and generic pharmaceutical industry generally right now requires us to re-evaluate timing so as to optimize value for our shareholders."

"We have not backed off," Kessler insisted. "But I have to be aware of what's going on in the marketplace. For this spin, I need to create as much value as I possibly can."

As well as pricing issues affecting the stability of the US market, supply problems are also having a major impact, with shortages rife especially among generic injectables.

Hikma Pharmaceuticals PLC has lately been one of the firms to benefit from these opportunities, recently telling *Generics Bulletin* that helping to alleviate shortages of critical US injectables, including controlled substances, had strengthened the firm's relationships with its hospital customers in the US.

With ongoing shortages in the US market foreseen by Hikma, the firm expects to report strong results in 2019 in US injectables, while it has adopted a strategy of differentiation in US generics that it says will help it hit the top end of its forecasts this year.

However, Hikma's injectables rival, Fresenius Kabi AG, recently told investors that the financial upside from stepping in to supply injectables that were in shortage had all but been exhausted as Pfizer's Hospira brought manufacturing capacity back online.

JAPAN'S SAWAI AND NICHI-IKO SLIDE BUT INDIAN FIRMS SEE UPTICK IN US

Japanese investment in the US generics market has been seen in recent years by both Sawai Pharmaceutical Co. Ltd. and Nichi-Iko Pharmaceutical Co. Ltd., via their respective acquisitions of Upsher-Smith Laboratories and Sagent Pharmaceuticals.

However, both of these businesses have also suffered from the industry headwinds seen in the US market, with Upsher-Smith citing a "severe competitive environment" as the cause of its 7% sales decline in Sawai's financial first quarter, and Sagent's turnover plummeting by almost a third in the same period, also reflecting "intensified competition in the US market."

However, Indian generics players with a major presence in the US market have seen slightly better fortunes over the last year.

Sun Pharmaceutical Industries Ltd. saw its finished-dose sales in the US rise by 6% in the firm's financial first half, while Aurobindo has pointed to "robust growth" of 27.3% in its own US formulations business in its most recent financial quarter, as it prepares to take over the Sandoz business. Meanwhile, Cipla Ltd. saw its US business grow by 25% in the second quarter of the year. *(Also see "Momentum Is Back At Cipla In Q2" - Generics Bulletin, 8 Nov, 2019.)*

Lupin Ltd. has also seen sales continue to rise in the US, with 8% growth in the firm's financial second quarter. "Relative to the erosion of in-line businesses seen over the last few years, from 2015 to 2018," Alok Sonig, CEO of Lupin's US Generics business told *Generics Bulletin*, "we have seen signs of stabilization this year."

Many of these firms have benefited from an increased pace of abbreviated new drug application approvals at the US Food and Drug Administration, as the agency seeks to deliver on ambitious programs to drive generics uptake.

For example, Dr. Reddy's introduced eight new products in the US in the second quarter alone, with the firm remaining on course to launch over 30 new products in the current fiscal year.

SUSTAINABILITY MUST GO BEYOND PRICING

Returning to Teva, the firm's president and CEO recently reiterated his belief that the Israeli firm is "seeing the operational stabilization we've been talking about."

But according to Schultz, the key to stability more broadly in the US would be the market reaching an equilibrium that not only rewarded low prices, but also non-price aspects such as security of supply, as well as quality and compliance considerations. This, he said, would not only help to curtail the problem of shortages but would also offer suppliers a more stable pricing environment.

> *"Uncertainty in the market and generic pharmaceutical industry generally right now requires us to re-evaluate timing so as to optimize value for our shareholders."*
>
> *– Murray Kessler*

"If you want stable supplies, you need to have a price point to support that stability," said Schultz, emphasizing that this should not be only based on the cheapest price available.

Pricing has to be sustainable, Schultz insisted, and supplies should be drawn from reliable firms, not only the lowest offers. Moreover, he said, "quality and compliance should be number one in the minds of the regulators," as without such an approach the whole market is put at risk.

Globally, Schultz concluded, "the overall pharmaceutical value chain is ticking along and working well."

However, the AAM's Davis sounded a more cautious note. "Sustained price deflation has now continued for 36 of the past 38 months," Davis warned, "on top of harmful marketplace changes such as purchaser consolidation and lack of formulary access for new generics...The challenges facing generics continue."

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DUNCAN EMERTON
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How The Promise Of Biosimilars Has Evolved

There is no doubt that biologics are the leading growth engine of global medicine spending. According to recent figures, revenues from biologics increased by 70% during 2011-2016 to reach $232bn, accounting for roughly 20-22% of total pharmaceutical spending. But as to the question of whether biosimilars can offer a solution to this affordability issue, that is tougher to answer.

In 2019 the biosimilars market became a teenager, having been 'born' in April 2006, following the European Medicines Agency's (EMA) approval of its first biosimilar, Omnitrope, Sandoz's growth hormone biosimilar.

In certain regions such as Europe, biosimilars have begun to deliver on their promise of making high quality, safe and effective biologic treatments more accessible to patients at a lower cost. This is not to say biosimilars have solved, or can solve, all the issues related to the ever-expanding cost of medicines. But like generics before them, there is little doubt that biosimilars are helping.

Fast forward to October 2019; we now have multiple biosimilars approved around the world, ranging from simple peptides, such as growth hormones, to highly complex proteins like monoclonal antibodies (mAbs). In Europe, 61 biosimilars have received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) and subsequently been authorized by the European Commission. Of these 61 approved biosimilars there are currently 54 valid biosimilar marketing authorizations covering 15 distinct reference molecules.

The pace of approvals is also increasing in the US. Since 2015, when the US Food and Drug Administration (FDA) approved its first biosimilar – Zarxio, Sandoz's filgrastim biosimilar – the agency has approved 23 biosimilars.

In both regions, biosimilars have been approved via the "totality of evidence" (ToE) paradigm. What this means is that biosimilar developers are required to accumulate comparative data of the proposed biosimilar with the reference medicinal product from analytical, non-clinical and clinical studies gain regulatory approval.

CHALLENGES REMAIN IN EUROPE, DESPITE EARLY SUCCESS

There are many reasons to be cheerful about how things are progressing with the European biosimilars market; the statistics speak for themselves. With more than 60 biosimilars approved and others expected soon, cost savings already in bag up to the end of 2017 came to roughly €1.5bn-€2bn ($1.6bn-$2.2bn) across the five major European markets of France, Germany, Italy, Spain and the UK.

Future cost savings could be much higher, with some estimates suggesting that the use of biosimilars will result in overall savings of between €11.8bn and €33.4bn between 2007 and 2020 in several key European markets, including France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK, according to an article by the *Generics and Biosimilars Initiative Journal*.

Medicines for Europe, the off-patent industry association, told *In Vivo* its views on the successes with biosimilars seen in Europe. Improvements in patient access, stakeholder acceptance of biosimilars and changes at the country-level, in terms of changes to procurement and treatment practice to support their uptake, are considered clear successes, it said.

Commercially, biosimilars have performed well in Europe. For some product classes, there has been a complete switch from the brand to the biosimilar. For example, IQVIA claims market shares for EPO-alfa and filgrastim biosimilars at the end of 2017 reached 100% in certain Central and Eastern European markets. The biggest commercial success, albeit from the perspective of biosimilar developers and payers in Europe, has been the launch and strong uptake of biosimilar versions of AbbVie Inc.'s Humira (adalimumab).

Humira was the biggest selling drug at the end of 2018, with worldwide sales coming in at just under $20bn. Whereas most of Humira's sales are in the US, a significant proportion come from Europe where Humira has topped the drug spending charts in several markets. In the UK, for example, during the 2017-2018 financial year, the National Health Service (NHS) spent over £400m ($520m) on Humira. Suffice to say, interest in cost-effective biosimilar versions of Humira has been high for several years.

So, when Humira's European patent expired in October 2018, a quartet of Humira biosimilars were ready to launch, comprising Amgevita (Amgen Inc.), Hyrimoz (Sandoz International GMBH), Hulio (Mylan NV) and Imraldi (Biogen Inc.).

In the UK it is important to note that NHS England took the lead on procurement and implemented a unique strategy that focused on two key objectives: plurality of supply (i.e. to ensure reliable supply of adalimumab over the longer term), and best price (i.e. to enable NHS England to achieve competitive prices from suppliers with guaranteed shares for more competitive bids). Experts have applauded NHS England's efforts in developing an innovative procurement strategy for Humira biosimilars.

And the results speak for themselves. NHS England expects to save more than £300m ($370m) in its current financial year (2018-2019), equivalent to about three-quarters of its historical spending on reference brand Humira. This is supported by robust adoption of biosimilars across each of NHS England's key regions.

Despite these successes, certain challenges remain. In Europe, at the time of writing this article, Belgium's competition authority had launched a probe designed to investigate "restrictive practices" aimed at stifling biosimilars; the Dutch competition authority had published a sector inquiry warning that originators may be breaching competition law by making discounts on biologic list prices conditional on hospitals not switching treatment to anti-TNF biosimilars; and French draft legislation setting out proposals to tackle an originator tactic of using low prices for biologic brands in hospitals to get patients set on a course of treatment that would then be much more expensive when they transition to out-patient care had just been announced.

Medicines for Europe raised other concerns about biosimilars in Europe. Biosimilars are only having a negligible impact on improving patient access to biologic therapies in certain Central and Eastern European countries, a region where restrictions on biological therapies are the most severe. There is also a remaining need to counter misleading information surrounding biosimilar medicines in relation to their approval, safety and efficacy – even after 13 years of significant educational outreach.

Medicines for Europe also has concerns that changes to more sustainable procurement practices are not being implemented quickly enough across Europe. Countries such as the UK, Denmark, Italy and Norway have either adopted or will adopt multi-winner tenders for biosimilars but single-winner tenders are still being used in other countries, thereby forcing health care systems to move from one monopoly to another.

In the future, Medicines for Europe believes that biosimilar medicines represent a strategic asset for policy makers in reaching their access objectives for healthier communities, but to simply focus on uptake or price is not a good indicator of the functionality of the market today, or of the perspectives for future access to biologics. On that basis, policy implementation road maps and the monitoring of key performance indicators beyond price and volume will be instrumental in the coming years. The ability of European health care systems to adjust policy frameworks based on recent experience will have a significant impact on countries in realizing the full potential of biosimilar medicines.

DOES THE US BIOSIMILARS MARKET NEED MORE TIME?

Perhaps there are not as many as from Europe, but we do have some reasons to be cheerful about the US biosimilars market. Since the FDA approved its first biosimilar in 2015, the agency has approved 23 biosimilars. It would be quick to assume that the FDA's performance has lagged the EMA's, but if you look at the average number of biosimilars approved per year, both agencies are approving between four and five biosimilars a year based on current data. On that basis, the FDA's approval rates should be applauded (*see Exhibit1*).

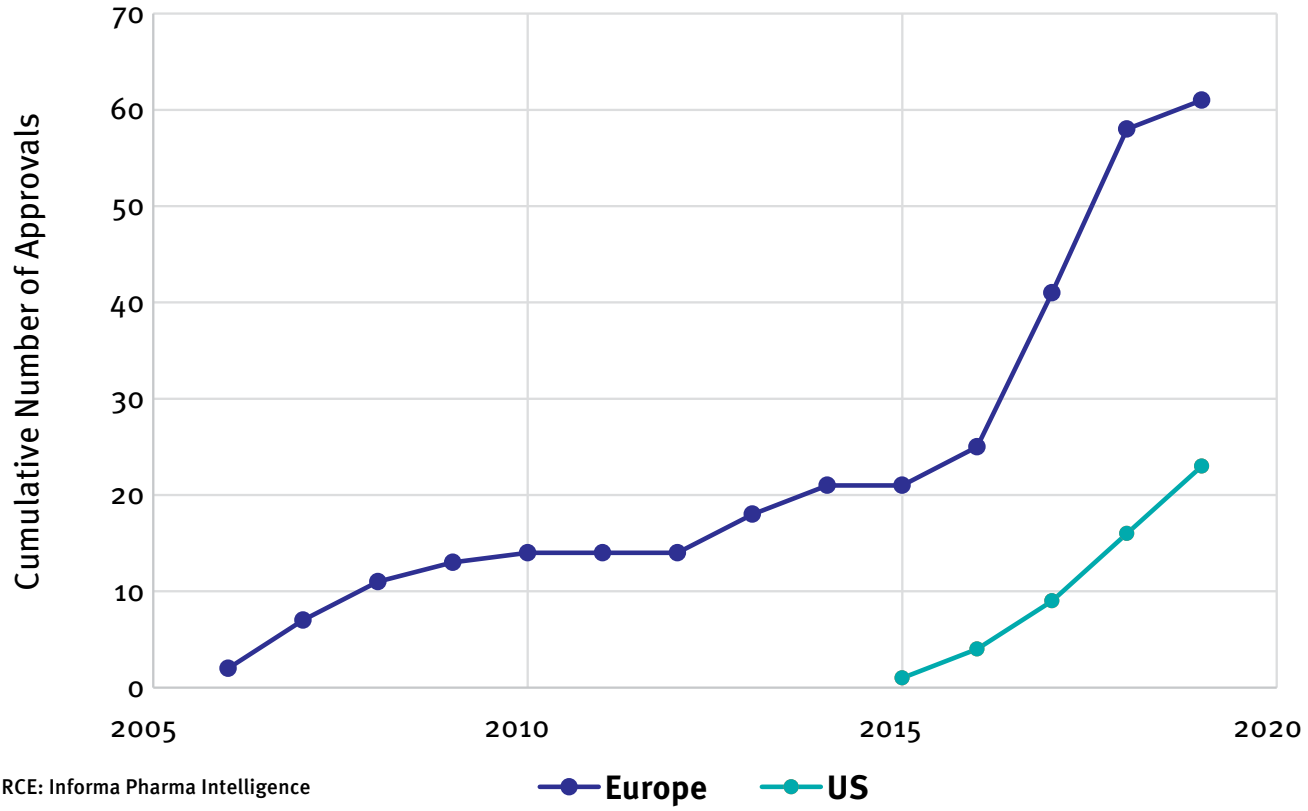
In addition to this regulatory success in the US, there have been some limited commercial success stories, argued Stan Mehr, principal at Biosimilars Review & Reports: "With only nine products launched [as of October 2019], US market successes have been extremely limited. That being said, Sandoz's Zarxio (filgrastim-sndz) was the first biosimilar approved in the US and has gained more than 50% market share. Coherus BioSciences Inc.'s Udenyca (pegfilgrastim) has also gained some traction since it was launched in January 2019."

Despite these small pockets of success, many believe that the US biosimilars market is a failed one. In 2018, the US spent $126bn on biologics, less than 2% of which was on biosimilars, according to IQVIA. A key barrier in this regard, according to Bernstein analyst Ronny Gal, is that payers are not preferring biosimilars over originator products, with many simply blocking or step-editing biosimilars.

Others believe that more time is needed to get the US biosimilars market to the same point as the European market. Richard

Exhibit 1

Cumulative Biosimilar Approvals In Europe And The US



SOURCE: Informa Pharma Intelligence

Saynor, CEO of Sandoz, told *In Vivo*'s sister publication *Generics Bulletin* that US policymakers and health care stakeholders must not give up on biosimilars, but rather build on some promising recent developments and trends that could unlock vast savings.

Reacting to a *Wall Street Journal* article in which oncologist Peter Bach and colleague Mark Trusheim argued that biosimilar competition would harm innovation without creating meaningful health care savings, Saynor pointed out that the same doubts about the ability of competition to drive savings were voiced loudly when the US generics market was effectively created by the Hatch-Waxman Act in 1984.

Saynor commented: "Today, as biosimilars look increasingly like the 'new generics,' it is fascinating to watch the same tactics being deployed against them." He pointed out that generics now make up 90% of all US prescriptions filled but account for just 22% of medicines spending, saving $2tn over the past decade.

Right now, however, the US market has perverse incentives that do not compel physicians and hospitals to adopt biosimilars. This essentially means that physicians are incentivized to use the more expensive, branded, reference product because the economics favor the established originator. This is despite the costs to the health care system being more for the higher-priced product. This dynamic needs to change to drive better adoption for biosimilars in the US. The FDA's Biosimilars Action Plan has been developed to try to remove these incentives to use the higher-priced medications.

CHANGES EMERGING IN THE BIOSIMILARS MARKET

From a regulatory perspective, there is no doubt that the ToE paradigm works, but many are now calling for changes to the approval paradigm for biosimilars. At the core of the argument is an assertion that the current ToE paradigm is "burdensome and inefficient." A new paradigm has been suggested by experts that emphasizes the demonstration of analytical resemblance between the biosimilar candidate and its reference product and permits the conclusion of biosimilarity on this basis.

This "confirmation of sufficient likeness," or CSL paradigm, does not include bridging studies, *in vivo* non-clinical studies, or powered efficacy studies and is, according to the experts who have suggested it, more efficient than ToE while maintaining equivalent scientific rigour. It is also based on evidence from the current biosimilar approvals.

From a procurement perspective, deep discounting in countries such as Norway where infliximab biosimilars were initially offered at a roughly 70% discount have set the benchmark. The subsequent focus was all about price, regardless of what this meant to the sustainability of the biosimilars market.

It would seem, however, that a more sustainable approach to biosimilar procurement is emerging in Europe. As previously discussed, NHS England has adopted a new strategy for Humira biosimilars in the UK, seeking to ensure competition but also to gain the best price. A key driver of this innovative strategy was a desire to create a sustainable market for Humira biosimilars and not just focus on the lowest-cost product.

Looking to the future, it remains to be seen if other countries will adopt the same sustainable approach. As Warwick Smith, director general of the British Biosimilars Association (BBA), said at Medicines for Europe's 2019 biosimilars conference in Amsterdam, "There was a recognition that we needed a competitive system, not a race to the bottom where the lowest-price manufacturer takes everything. There has been a learning that if you just drive competition on price, it eventually drives out competition."

In terms of market-level policy as it relates to driving biosimilar adoption, an acceptance of the need to switch patients from originator products to biosimilars has had a significant impact in relation to cost savings and improving patient access to biological therapies. Although several studies have been conducted to support brand to biosimilar switching, no clinical data exists that supports biosimilar to biosimilar switching.

This is not stopping countries from switching patients from one biosimilar to another to save money, and there is no reason to expect any problems with this in practice. In markets that operate "winner-takes-all" national tenders, such as many of the Scandinavian countries, biosimilars have begun to be treated as effectively interchangeable with other biosimilars and the reference product.

Notwithstanding the big biosimilar launches expected in the US over the next decade, the second wave of biosimilar launches is reaching its climax. In many countries around the world we now have biosimilar versions of Remicade, Enbrel, Rituxan/MabThera, Herceptin, Avastin and Humira. All eyes are now on the next wave of biosimilar opportunities (i.e. those branded biologics that lose patent protection in key markets beyond 2020). These include checkpoint inhibitors, such as Keytruda (pembrolizumab; Merck & Co.), which are used in the treatment of various cancers; anti-interleukins, such as Stelara (ustekinumab) and Cosentyx (secukinumab; Novartis), which are used to treat various autoimmune conditions; the anti-VEGFs, such as Lucentis (ranibizumab; Roche/Novartis) and Eylea (aflibercept; Sanofi/Regeneron), used to treat various ophthalmologic conditions; and biologics used in the treatment of multiple sclerosis, such as Tysabri (natalizumab; Biogen).

CREATIVE STRATEGIES NEEDED FOR THE FUTURE

First, companies must always seek to understand what they are going up against. A critical element of any biosimilar commercialization strategy is a deep understanding of the actual and potential barriers to biosimilar adoption, and ways to mitigate these barriers. Many barriers exist, including logistical, regulatory, commercial, competitive and legal barriers, to name only a handful. Commercial issues have become one of the most significant types of barrier in the US and have the potential to influence competitive dynamics today and in the future. Informational barriers also present themselves as key blockades against the successful commercialization of biosimilars.

Second, the strategic vision for any biosimilar needs to be defined as early as possible, and it is critical that the views and insights of multiple stakeholders are included. These insights and views are crucial to assessing the prospective biosimilar's position from all perspectives.

Third, and perhaps most surprising, companies must continue to educate, even when they do not think they need to. In Europe there has been 13 years of mainly positive experience with biosimilars, but as experts from Medicines for Europe have commented, much more education is needed to convince key stakeholders of the benefits of biosimilars. Similar comments are being made by US groups.

Finally, and perhaps most importantly, all interested stakeholders must work with national governments to ensure the future sustainability of the biosimilars industry. Serious questions are now being asked about the impact of massive discounting from biosimilar manufacturers on the longer-term sustainability of the market. While deep discounting has supported robust biosimilar adoption rates in some countries, many are now concerned that if this continues, competition in the future will be limited to only a select few companies that have the financial power to remain. It is now the national payers, regulators and policymakers – not biosimilars themselves – that hold much of the power to influence the longer-term sustainability of the biosimilars market. Procurement strategies focused on future market sustainability are being seen in some key European markets, so it is over to the biosimilar companies to support these initiatives and help shape the next wave of biosimilars for future generations.

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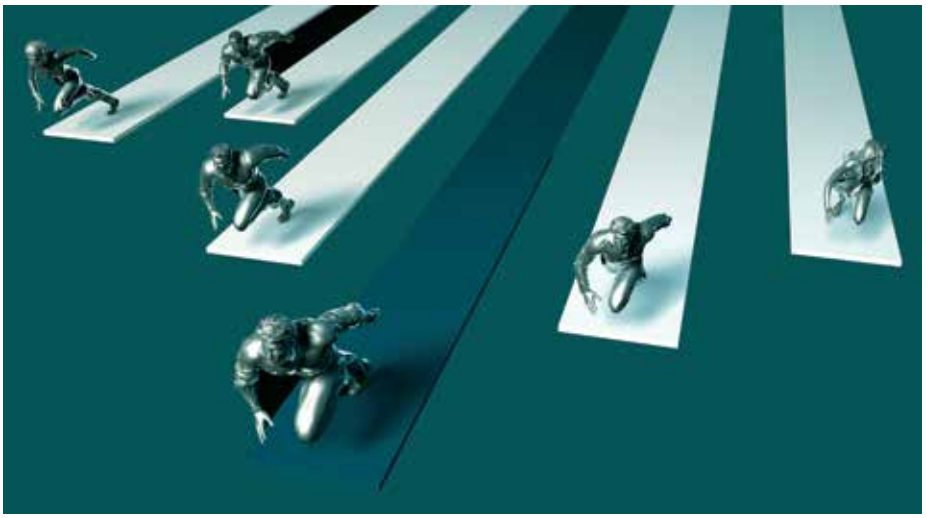

"There was a recognition that we needed a competitive system, not a race to the bottom where the lowest-price manufacturer takes everything. – Warwick Smith"

Indian Firms May Want To Slow March Into China

New markets are opening up for Indian firms and China appears to be the flavor of the season, but gaining a strong foothold there is not expected to be even "half as easy" as in the US.

ANJU GHANGURDE
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Indian pharmaceutical firms are flocking to China, after the Asian giant opened its doors to generics and unveiled a raft of favorable regulatory reforms including accepting foreign clinical trial data to support new drug approvals.

More than half a dozen front-line Indian firms including Sun Pharmaceutical Industries Ltd., Dr. Reddy's Laboratories Ltd., Cipla Ltd., Aurobindo Pharma Ltd., Alembic Pharmaceuticals Ltd., Glenmark Pharmaceuticals Ltd., Biocon Ltd. and Strides have outlined plans for China recently, signaling their growing ambition in the world's second largest market, which saw pharmaceutical spending touch $137bn in 2018.

These plans arrive against a backdrop of tough market conditions in the US, a traditional bastion that has accounted for a significant chunk of revenues over the years for many Indian generic companies. Growth in the US market has been hit, in part, by price erosion amid buyer consolidation and intense competition for key products. Prices of generics in the US declined by about 8% annually between 2015 and 2018.

Salil Kallianpur, a former executive vice president at GlaxoSmithKline PLC in India, now running a digital health consultancy, said that China is a huge market and attractive in size and opportunity – especially as Indian companies are seeking to "de-leverage" from US exposure. "Indian companies have all but 'maxed' out the US opportunity – at least for the time being before differentiated generics and biosimilars are ready to be launched – and Japan and the EU don't have the penetration rates of generic medicines to make them as attractive. China then becomes a very attractive market for Indian generic players," Kallianpur told *In Vivo*. The Chinese market is projected to reach $140-170bn by 2023, as per IQVIA data, though growth is expected to taper to 3-6%.

FAVORABLE REFORMS AND EMERGING OPPORTUNITIES

Industry's focus on China has been propelled by a range of market-changing reforms rolled out by the Asian giant to support and drive innovation, and improve insurance access to both the rural and urban population as well as expand the hospitals system and primary care services.

Opportunities for the supply of cost-effective and high-quality generics under China's mammoth centralized '4+7' drug procurement scheme, have also raised the interest of several Indian firms. The 4+7 scheme was initially rolled out in large hospitals in 11 major cities, including Beijing, Shanghai and Tianjin and is now be-

ing sharply expanded. *(Also see "What's At Stake As China Expands '4+7' Scheme: An Infographic Snapshot" - Scrip, 19 Sep, 2019.)*

Experts say it is important to look at the underlying context for China's volume-based procurement policies in the backdrop of its efforts to promote innovation and that driving innovation requires better regulatory approval processes as well as improved affordability and reimbursement. "And with that it also requires more funding to support that level of reimbursement. The government believes it is important to free up funding from one part of the system in order to fund the drive for innovation. And one of those parts is the off-patent originator market or the generics market," Gaobo Zhou, partner (Hong Kong) at McKinsey & Company, told *In ViVo*.

The McKinsey executive said it was the "right direction to go" and generally in sync with the evolution of the pharma markets in other parts of the world, like the US and Europe, where generic players typically take over the production of a drug once the originator product goes off patent.

EQUAL OPPORTUNITY

Zhou highlighted the ongoing initiatives in China to provide significant opportunities for generic players, but noted that the Chinese government had never really specified whether it preferred locally-produced generics or imported generics from other multinational players. "For them it's all about ensuring low cost, high quality generic products to the market and also supply consistency. The opportunity is equally relevant for local Chinese generic manufacturers as well as leading generics players across the world," Zhou said, adding that for Indian companies successful in different parts of the world, China certainly represents an opportunity.

There are, however, already some concerns around procurement policies that lean towards local Chinese firms, currently seen in the medical devices space. The EU Chamber of Commerce in China recently sought "competitive neutrality" that would end such distinction between foreign and local ownership.

Ex-GSK executive Kallianpur maintained that China was not going to be "half as easy" as the US to crack. He said the domestic Chinese industry had evolved into a formidable one of late and that while Indian firms enjoyed a large share of the US generics pie, the Chinese "will not offer theirs on a platter."

"The recent Indian pivot of moving away from vanilla generics to specialty drugs is also not expected to give it too much leverage since Chinese companies have advanced their capabilities to manufacture biologics, biosimilars, new formulations and difficult to make complex generics – at scale. This is a capability that India still lacks," Kallianpur explained.

The "silver lining" for Indian firms, however, is that blockbuster innovative molecules are yet to come out of China, he added.

PARTNERSHIP MODEL

For now, most Indian firms tapping into China appear to be opting for the partnership route. Earlier this year, Cipla firmed up an 80:20 joint venture with Jiangsu Acebright Pharmaceutical Co. Ltd. for the Chinese market at a combined investment of $30m. The venture, upon incorporation, will set up a local manufacturing facility for respiratory products – a segment that has been Cipla's forte. Peer Aurobindo had similarly sealed a deal with Shandong Luoxin Pharmaceutical Group Stock Co., Ltd to establish a joint venture in China with manufacturing facilities. The venture plans to make nebulizer inhalers and other products for China, the US and Europe.

Elsewhere, Strides has teamed up with Sun Moral International (HK) Ltd, a wholly-owned arm of Sihuan Pharmaceutical Holdings Group Ltd. The Indian group has initially licensed four products with an option to expand the portfolio in due course. Meanwhile, Alembic entered into joint venture pact with SPH Sine Pharmaceutical Laboratories Co Ltd and Adia (Shanghai) Pharma Co Ltd to promote and sell pharmaceutical products for the Chinese market. More recently Biocon signed a license-and-supply deal with China Medical System Holdings Ltd. for certain generic formulations in greater China.

McKinsey's Zhou underscored that the "key success factor" for a China thrust was local presence. This includes a local presence in terms of regulatory affairs – people who understand the regulatory environment, government affairs and market access and also those familiar with the nuances of the policy environment and not just at the national level but also at the provincial level, "which can almost operate as mini markets and have their own policy system." A localized commercial and medical team to engage with customers is also vital.

"Local presence will be very important for companies wanting to capture China's potential. Whether that presence is organic – greenfield – or it is through some form of partnership, that is all open and many companies have tried different approaches," the McKinsey executive said. A greenfield initiative would, however, be expensive and challenging especially for companies with a limited portfolio, since it would not provide economies of scale, he added.

Companies like Dr Reddy's Laboratories have a head start in more ways than one in China, with a long-standing presence through subsidiary Kunshan Rotam Reddy Pharmaceutical Co. Limited and a joint venture with the Rotam Group of Canada. In 2017, Dr Reddy's incorporated another subsidiary, Dr Reddy's (Wuxi) Pharmaceutical Co. Limited in China.

"Being there for the last 20 years, selling about $100m, about 10 products, we never left China even when it was hard and hopefully now, we can reap the benefit of it," Erez Israeli, Dr Reddy's then-chief operating officer, who has now been elevated to CEO, said at the JP Morgan Healthcare Conference in January 2019.

Dr Reddy's believes that an estimated 70 products from its US portfolio can meet China's new regulatory requirements and registration is already underway of some of the products. The Indian firm recently won a bid for olanzapine 10mg in China, setting the ball rolling as it aims to "go big" in that market. Plans also appear to be afoot in the biosimilars segment. Dr Reddy's senior vice president and global head of the firm's biologics business unit, Raymond De Vré, indicated that the company is actively looking at how to get into China for biosimilars. "It is likely that as in the case of small molecules where we started with a joint venture, we may probably have to do this with a partner," De Vré said in a recent interview. *(Also see "Dr Reddy's De Vré On Momentum In US Biosimilars Market, Interchangeability" - Scrip, 3 Oct, 2019.)*

SYNERGY AND DIVERSE STRENGTH

For those Indian firms just logging into China (though most Indian firms have long been sourcing APIs from its neighbor), there appears to be ample scope for synergy between the two sides.

McKinsey & Company senior partner Vikas Bhadoria noted that, in general, Chinese companies had built very strong sales and marketing capabilities especially around localized aspects on how to get listed, access next tier hospitals in provinces, in addition to a generation of firms that were pursuing the R&D agenda. Operations, however, has not been a major area of focus.

"If you look at the core competence of Chinese companies it is either sales and marketing or R&D, much more than operations. That's where they would find maximum synergy with Indian companies that are focused on operations and probably well developed on those capabilities versus their Chinese counterparts," Bhadoria, who leads McKinsey's pharmaceutical and medical products (PMP) practice for India and the PMP operations practice in Asia, told *In ViVo*.

Some of the licensing deals struck by Indian firms perhaps recognize the core strengths that the Chinese partners bring to the table. For instance, India's top-ranked drug firm Sun firmed up licensing deals for its psoriasis asset tildrakizumab and the dry eye therapy cyclosporine A 0.09% (CsA) with a subsidiary of China Medical System Holdings Ltd. (CMS) for greater China (including mainland China, Hong Kong, Macau and Taiwan). The deals, sealed for an initial tenure of 15 years from the first commercial sale of the products in greater China, involves an initial upfront payment to Sun and the Indian firm is also entitled to regulatory and sales milestones and royalties on net sales. CMS will be responsible for development, regulatory filings and commercialization.

Similarly, Glenmark inked a licensing deal for its early stage immuno-oncology asset with China's Harbour BioMed. The agreement for the greater China territory covers the development, manufacture and commercialization of GBR 1302, Glenmark's bispecific antibody targeting HER2 and CD3 for the treatment of HER2-positive cancers. Harbour will lead the clinical development and commercialization effort of GBR 1302; it has, among other aspects. the option to manufacture GBR 1302 for the greater China market.

MARGINS SQUEEZED

Still, the promise of the Chinese market notwithstanding, supplies under the volume-based procurement system are expected to see margins squeezed and then there is the general unpredictability around the regulatory regime in China, alongside ongoing uncertainties precipitated by the trade war with the US.

Kallianpur said the very reasons Indian firms cite for considering China as an opportunity – i.e. a decline in US market growth, pressure on margins and prices bottoming out via channel consolidation – could potentially be worse in China given the health system is entirely state controlled.

"Margins in the China market are also not expected to be high given that the procurement is through government tenders and is volume-linked," he said, adding that it could be "a déjà vu moment" for Dr Reddy's after its experience in Germany in 2006-2007 following the acquisition of betapharm Arzneimittel GmbH when the government there took over the drug procurement system completely, driving down margins to unfeasible levels.

McKinsey's Zhou, however, said that because of the unmet needs for patients in China, the volume potential was significant and with lower prices, more patients were expected to seek the "right medication" for their treatment. Because of this companies will benefit from a volume perspective even after they lower their price. "With volume-based procurement which guarantees the level of volume for manufacturers, the need for sales and marketing spends reduce significantly. Companies no longer need to have a large sales force or significant marketing spend as part of their business. So that part of the cost base could reduce and therefore, to some extent, it offsets the margin erosion," Zhou added.

POLICY UNPREDICTABILITY

While some uncertainty in the overall China policy environment remains, Zhou explained that it was important for companies focused on the underlying government priorities that were driving these policies and "then a lot of things become clear and predictable." These priorities, he said, were focused around the drive for innovation and improving health care facilities; efficient use of health care resources and improving both the quality and outcomes of care delivery; and delivering a sustainable and efficient system through greater cost efficiencies.

"Most of the policies that we have seen fall under one of those priorities and if we believe that the those priorities are here to stay at least in the foreseeable future, then it's not a matter of unpredictability of policies, rather it is about speed and pace at which policies are rolled out, refined and implemented," he said.

McKinsey's Bhadoria added that as long as Indian firms had a strong quality and cost proposition, they would be able to tap emerging markets either directly or through a partnership. "It's important to push the boundary on compliance and quality and stay cost competitive while doing that."

But others urged caution. Kallianpur underscored that China was not an opportunity that had suddenly come up. While the market size has expanded considerably and the government has made "all the right calls" by creating infrastructure, focusing optimally on leveraging manpower and technology, and now shining a spotlight on making drugs and services affordable, the size of the market and the opportunity always existed.

"Despite all this, India's contribution to China drug supply is just 0.1%. This surely cannot be because Indian firms didn't see the market opportunity. Also, India has been lobbying actively with China to ensure easy entry and quick clearances for several years now, but it has not worked, at least so far," Kallianpur said. There is also the aspect on whether China will accept US FDA audit reports or insist on new ones and/or additional requirements, which then can up costs of Indian firms.

Kallianpur said it was perhaps too early to suggest that "all roads lead to China" given its regulatory unpredictability and that Indian companies do not understand the market very well.

One top executive with an Indian firm told *In Vivo*, "You have to approach China with a healthy dose of cautiousness and not go 'berserk.' I won't go and write a check for a huge amount of money in China but will do it progressively."

Clearly, China offers huge opportunities for Indian pharma but the path ahead could be tricky and tough. A measured approach could perhaps be ideal, at least for now.

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Medtech's Move To Business Process Orchestration

Today's Patient-Centric World Driving Continued Transformation

Medtech companies have always been patient-centric organizations. Yet today, with the point of care moving from hospitals to homes and physicians evolving from authorities to guides, what it means to make patients the focal point of operations is changing. These changes interweaved with market access, value-based pricing and reimbursement, digital health, new regulations and the pursuit of innovation are forcing transformation for companies looking for global excellence. Addressing these changes, companies need to orchestrate across their business processes to thrive.

The role of patient-centricity is further evident with the rise of digital health. Breaking digital health into its component parts, which include connected devices, software as a device, patient data and real world evidence, and personalized devices shows the central role patients play and the importance of human data science in a digital health world.

USING DIGITAL HEALTH TO BENEFIT PATIENTS

Connected devices that can be modulated to facilitate personalized care and remote monitoring are a direct manifestation of patient-centricity. Treatment can be monitored and tailored to the specific needs of the patient and the continued growth of 3D-printed devices exemplifies ways in which companies are leveraging innovation to meet both speed-to-delivery and patient-specific care. Patient-centricity is also evident in connected devices that can constantly gather data on patients. When combined with data captured by software as a device products, such as medical apps, which can include geo-centric and other physical and personal data, the output of connected devices in our IoT (Internet of Things) world we operate in today yields unprecedented insights into the day-to-day health of individual patients and can be used to identify clinical trial populations and even support virtual trials.

Importantly, patients are increasingly in charge of the data behind these insights. Ownership of data is shifting from institutions to consumers, putting patients in control of how their information is aggregated for population-level analyses that improve care. Analysis of digital health data is part of a broader effort involving real world evidence (RWE). That effort is based on four main sources of longitudinal data: medical records, prescription data, hospital encounters, and claims from payers, hospitals and drug plans. While RWE is typically thought of in the postmarket context, the value of its insights extends across the value chain. RWE informs everything from device concepts and trial designs to health care professional training and the generation of evidence to support premium pricing in a value-based health care environment. Thus, it is a concept to consumer and back again environment that requires business process orchestration to fully leverage the benefits.

Business process orchestration permits such company-wide use of RWE by breaking down silos while overlaying quality, regulatory, safety and other functions from clinical to commercial that span the entire product life cycle. That means people working at each step in the value chain from concept to market have access to information both upstream and downstream of them.

Each component of digital health is powerful in isolation. However, their full potential only becomes apparent and fully realized when they are combined. Together, the components are facilitating virtual trials by enabling sponsors to remotely identify participants and collect data from them, streamlining the process of generating evidence to support claims about a device.

INNOVATION IN THE BIG DATA DIGITAL HEALTH ERA

The proliferation of data is happening in unison with a related expansion in advanced analytic capabilities. Faced with the need to analyze data from sources such as connected devices and other external data sources, medtech companies are leveraging the power of cloud computing along with machine learning (ML) and artificial intelligence (AI). These advanced technologies are enabling companies to get insights from big data and perform predictive analytics and better risk management.

Medtech companies have always innovated faster than their pharmaceutical counterparts. The rise of data and advanced technologies is further accelerating that pace by equipping companies to quickly make data-driven and risk-based assessments of what patients need and develop products that address them. Patient-centric digital transformation is mirrored by changes in physical products, which can now be personalized to individuals.

New products are only one part of the innovation story, though. To meet the needs of patients around the globe, medtech companies also need to understand the regulatory pathways and requirements to get existing devices into new markets. Orchestration across regulatory intelligence data (RID) and regulatory information management (RIM) along with enterprise quality management (eQMS) solutions are the backbone of getting products more quickly and efficiently into new markets. In some cases, medtech companies can enter additional markets with minimal new trial efforts or trials and approvals from other markets, thereby quickly bringing benefits to millions of patients. Where trials or data are required for market approval, business process orchestration and real-world evidence will facilitate accomplishing this more effectively without adding significant costs.

Entering new markets extends the life cycle and overall profitability of products and maximizes the benefits they provide to patients. However, the effectiveness of innovation and compliance strategies rests on a company's ability to operate from an overall business process orchestration perspective globally across traditional functional and geographic silos. Integrated solutions implemented in a business process orchestration fashion in concert with one's clinical, compliance and commercial operation systems and processes can quickly identify the best opportunities, improve decision-making and facilitate operational excellence.

HOW PATIENTS ARE RESHAPING REGULATION

Changing regulations are also driving companies to relook at how they orchestrate compliance across their operation. Patient-centricity underlies changing regulations and product innovation and improved safety is a by-product. The focus on further enhancing patient safety, manifested in new and constantly evolving regulations, will require medtech companies to capture and report additional data on their products. These regulatory changes may create challenges related to product reclassification and approvals through notified bodies in the near term, but medtech companies that adapt effectively to the new regulatory environment will be best positioned to reap the benefits long term.

Those benefits stem from the fact that companies as well as regulators will have more and better data on their products. Regulators glean insights from the data that enable them to take a more informed, risk-based approach to oversight, reducing auditing of some companies on the grounds that the data provide confidence in their compliance. That too will benefit patients by increasing scrutiny of high-risk products and companies. Medtech companies, in turn, can use data captured in orchestrating their business processes from research and development and clinical trials through commercial operations and service providers for not only compliance but additional evidence and analytic capabilities to further innovation and operational excellence.

WHY BUSINESS PROCESS ORCHESTRATION?

Companies will, and are, moving past a focus on simply integrating disparate systems and siloed groups to one that fosters and operates in a true cross-functional and extended enterprise collaborative fashion. Operating across business processes, including the systems and technology to support the needed business process orchestration illustrates how leading companies will further adapt to the transformation and leverage being driven by digital health, regulatory change, and patient-centricity.

To achieve this entails taking a business process view of the full medtech product life cycle, from concept to market, and bringing together the technology, products, services, consulting, data and technology-enabled managed services necessary to combine each link in the value chain. In practice, these changes will require medtech companies to use the collective resources and industry expertise they possess and that of their trusted partners.

Business process orchestration is a new way of working for many medtech companies but it is a necessary change. Companies that make this transformation with be best positioned to emerge from these times of change as industry leaders. As patient-centricity, digital health and regulatory changes are behind many of the forces reshaping the medtech industry, companies that put the patient and data at the center of their innovation will be the long-term winners.

Successful companies will leverage deep and unmatched domain expertise, transformative technology, unparalleled data and advanced analytics while adopting business process orchestration, equipping them to improve their operations while keeping patients at the center of every decision.

ASHLEY YEO
EXECUTIVE EDITOR,
MEDTECH, EUROPE

Medtechs Enter The Decade Of Digital, Consumers And Wellness

For providers and medtech manufacturers alike, the decade ahead will be a time of coming to terms with digital technologies and integrating new methods of payment. Quality of service delivery remains the market entry criterion, but companies will have to adapt to evolving health care delivery models. The stakes are implausibly high. Will they be able to capitalize on the changes in a market that is more competitive and unpredictable than ever?

The patient is increasingly the focus of the combined efforts of health-care stakeholders, dictating more and more how the broad concept of value must be integrated into health care delivery. Digital technologies will expedite the process. Yet critics unfairly claim health care is too slow to transform. 2020 will be the year when the industry shake-out from the EU Medical Device Regulation will become fully visible; until now, it has mainly been silence and speculation. The MDR has united medtech executives on one thing: it must not slow down access to innovation for patients. But is it a failure in waiting? Innovation will remain the spine of the industry, but disruptive forces are telling manufacturers the old business model will not suffice.

"Digital is no longer a vertical, it cuts across all sectors. It is a horizontal." Andy Fish of AdvaMed was explaining to the press in late fall 2019 that, in medtech, companies will come to incorporate digital as a means to an end, not as an end in itself. "Digital is now the coin of the realm," he said, explaining the rationale behind the US industry's decision to invest time and resources in a new Center For Digital Heath.

It is a further recognition of the health care value of digital, now and in the future, and another step on the road to the integration of modern methods of care delivery. It is also a reflection of the transition in health care industries from supply push to demand pull.

Innovation tends to spawn early adopters with their own jargon, but they are not the real market for medtech companies of any size. Delegates were reminded of this truth at the French annual medtech start-ups meeting, in spring 2019. In such a fast-moving climate, there can be a tendency to overplay the early prospects of a technology – digital or "traditional." Later in its lifecycle, the continual, incremental and perhaps less visible changes that make a real difference tend to be underplayed.

This applies to the value-based health care arena too, where much is happening, even if progress here is not as fast or as major as expected. That is the view of Boston Scientific's Eric Thépaut who gave *In Vivo* a brief tour in mid-2019 of how health care will change in the future. VBHC, he said, "is a long-term initiative, and a step-by-step approach is needed." It is a delivery concept that one day will become more mainstream, similar to how once disruptive medical tools like nanotechnology, molecular diagnostics, POCT and telehealth are now part of the medtech routine.

Elsewhere for the medtech industry, some routines are changing fast. 2020 will see the biggest change to EU medtech regulation since the 1993 Medical Device Directive (93/42/EEC), when the EU Council's Medical Device Regulation (MDR, 2017/745) comes fully into force. That is the promise. But as the clock ticks down to implementation day on May 26, the magnitude of the task has been starting to cause a few jitters. Will there be realization at EU level that, while the MDR is generally welcomed, it is coming too soon? It is certainly the right thing to do, but it is arriving too fast, so it is the wrong thing to do, to paraphrase ResMed CEO Mick Farrell during MedTech Europe's MedTech Forum panel discussion, in Paris, in May 2019. There are still not enough notified bodies accredited to do the work required by the MDR (seven under the MDR, and two under the IVDR, as of November 8, 2019). Under the previous EU directives, there were latterly 58 such organizations. This prospective shortage of resources makes the new regulation work *against* high-quality patient care – the very thing the MDR promises to strengthen.

The first signs of a more flexible European Commission approach were seen in October 2019, when talk emerged of some Class I products additionally being able to use the MDR's four-year grace period, remaining under MDD oversight until 2024. There was also a proposal for a two-year delay in Eudamed. These moves open the door to possibly further concessions from the commission in 2020, which would suit most of industry very well. Brexit – effectively sanctioned by the December 12 UK general election result – throws a considerable spanner in the works, and may yet be the catalyst that allows the commission to do a more concerted rethink on MDR timetables without sacrificing the EU policy line.

FAVORABLE DEMOGRAPHIC TRENDS ARE THERE TO BE EXPLOITED

On a broad scale, the outlook for medtech business is good, with global health care expected to benefit from continued favorable demographic trends. The

world's population is anticipated to grow by more than 1 billion by 2030. The number of people over the age of 60 is forecast to rise by 500 million, to 1.4 billion, with the prevalence of cancer, cardiovascular (CV) diseases and other long-term conditions rising in tandem. Health care spending is expected to increase annually by 4% to 5% on average through to 2021 when around half of all health care spending – some $4 trillion – will be targeted at cancer, and CV and respiratory diseases, according to Deloitte's Global Healthcare Sector Outlook.

This is good news for medtechs, but there is a complication: innovation is changing. Big-scale innovations in the traditional device areas are becoming fewer. An increasing amount of innovation is coming from digital iterations and advances. For example, Abbott's Merlin 10.0 app (CardioMEMS HF sensor system), which keeps heart failure patients out of hospital and allows physicians to communicate directly with patients.

The US FDA is fully behind mobile apps, which can help individuals manage their own health and wellness, and gain access to useful information when and where they need it. The US, arguably the most fertile and receptive market for medtech innovation, is once again leading the way in a new cornerstone of the industry, just as in did in fall 2013 when it broke the turf on device UDI implementation.

It seems mobile apps are being adopted almost as quickly as they are developed: in 2017 alone, 325,000 health care apps were available on smartphones, according to FDA-reported industry estimates. The agency posted an updated Policy for Device Software Functions and Mobile Medical Applications Guidance (MMA guidance) in fall 2019.

INTO THE DATA-DRIVEN ERA OF THE 2020s

Apps are where the medtech and digital confluence is at its most obvious. Digital is prompting a rethink among those medtechs who are reviewing whether they should be targeting consumers and wellness, or patients and sickness. The simplistic view is that there is a clear marketing advantage, at least, to seek consumer/wellness branding, as ZS principal Brian Chapman explained to *In Vivo*. But as a rule, medtech has yet to view patient-consumers as its real customers; its efforts are still focused largely on provider systems. *(Also see "MedTech Forum 2019: Consumers And Wellness, Or Patients And Health Care?" - In Vivo, 17 Jul, 2019.)*

"Digitization is going to completely transform health care, albeit later than has happened in the consumer world"

Boston Scientific's Eric Thépaut

Nevertheless, medtech is "truly beginning to acquire the tools and capabilities that will allow it to enter a data-driven, personalized new era," said Kevin Lobo, chair and CEO of Stryker, and the current AdvaMed chair. EY's latest annual Pulse Of The Industry report (2019) quotes Lobo as saying that data-driven medical devices will be at the forefront of health care's transformation. Digital and AI are currently the standout features in an industry that has seen "generally conservative activity" in the past year.

Boston Scientific's Thépaut agreed, there was no changing course now. "Digitization is going to completely transform health care, albeit later than has happened in the consumer world," he said, alluding to the type of criticism often flung in health care's direction. But there are clear reasons for this to be so. "We are focusing on patients in a highly regulated industry, and health care will always be unique." Commoditizing it would not be good for the ecosystem or the patient; however, it will evolve significantly.

Patients were arguably already "at the center," but now they are going to be even more so, with device-derived information more fluid and available more quickly. At present, the European industry remains focused on products and therapeutic value, but what is required, in Thépaut's view, is a very open dialog with patients. FDA guidance seems to acknowledge this shift. Indeed, at the 2019 MedTech Forum, it was sobering to find both that the medtech industry was unable to define precisely the benefits that "digital" could bring; and that it was open about that.

DIGITAL IS 'BLURRING EVERYTHING'

The medtech industry is still very much at the digital learning stage, as underlined by AdvaMed with its rebooted Center For Digital Heath (CDH). The center will look at adoption, regulation and reimbursement of digital tools across the industry. In the UK, the BIVDA diagnostics industry association is going along the same path. BIVDA chair Darren Stenlake (Sysmex) told an association meeting in early October

that "digital is blurring everything," and highlighted the UK industry's plans to focus a new working group on IT infrastructures, cybersecurity and malware.

AdvaMed has highlighted that digital cuts across the whole medtech industry, and digital products are not the rare commodities they were just three years ago. Hence the need to pool resources in one center. The big medtech names and certain software manufacturers are already members of the CDH. How its membership changes and grows, and how its agenda shifts will be very telling in terms of how health care will be delivered in the 2020s, and by whom.

TECHNOLOGY TRENDS

Digital will continue to hog the headlines in 2020, but not to the total detriment of traditional medical technologies.

Indeed, innovation levels are currently at seldom-reached heights, to judge from activity at the FDA, which broke its new novel medical devices approval record in 2018: at 106 new devices (PMS, panel-track supplements, de novos, breakthrough 510(k)s; and HDEs.) Generally, as an investment proposition, medtech is currently perceived as less favorable than biopharma, and the intense competition means a clear run on innovation does not last for very long. However, the appetite for and pace of innovation in medtech cannot be matched, as seen, for example, in ...

MINIMALLY INVASIVE TECHNOLOGIES

The consensus is that massive opportunities are available in medtech, as seen in Abbott's significant breakthrough with MitraClip. Abbott's structural heart franchise rose strongly to $1.2bn in 2018. The next-generation MitraClip percutaneous mitral valve repair system was perhaps the single most eye-catching "traditional" medical technology in 2018. A rich year for Abbott, 2018 also yielded the HeartMate 3 LVAD as a destination (long-term use) therapy, and the XIENCE Sierra drug-eluting stent system. The group was able to boast healthy cardiovascular sales, and is now the fifth-leading medtech group by sales, after Medtronic, Johnson & Johnson, Philips and GE Healthcare.

PATIENT CENTRIC CARE

Indeed, devices for minimally invasive procedures will likely gain increasing momentum in the more patient-centric 2020s. PAD micro-catheters, small incision radiation-therapy devices in breast cancer therapy, and urology drainage catheters that significantly reduce UTIs are the types of technologies touted for future success. Thus, a clear driving theme is becoming visible for medtech R&D departments, which are now able to more rapidly determine if their technology has what it takes to gain acceptance in the value-based era.

> *"Improved patient outcomes and cost-savings for provider systems have long been the obvious yet all-too-easily overlooked benefits of IVDs and other diagnostics technologies."*

IMPLANTABLE INNOVATION

Fellow cardiovascular company Edwards Lifesciences Corp. expects revenues from its transcatheter mitral and tricuspid valve therapies to double to $80m in 2020. The global market for mitral and tricuspid repair and replacement therapies will reach $3bn by 2024 – but it will not stop there, according to Edwards' CEO Michael Mussallem. The Sapien TAVR system will continue to drive the group's revenues – by 20-25% to over $4bn in 2019.

More recent technology breakthroughs that will continue to command attention in 2020 and beyond include diabetes technology group Senseonics' implantable Eversense CGM. The group has become the third to receive the non-adjunctive indication, which allows a CGM to be used for insulin dosing in place of a fingerstick glucometer.

CONNECTED HEALTH CREATES NEW MARKETS

The global market for hearing aids is expected to grow to $11bn by 2023, a CAGR of 7.4%, according to Informa's Meddevicetracker. This is on the back of the rising aging population worldwide experiencing hearing loss, and a younger population looking for more sophisticated devices. Into this market will come Bose's direct-to-consumer hearing aid, a device that does not need to be fitted by physicians, and can be sold online. This is a disruptive challenge to the majors, like Sonova, William Demant and GN Store Nord.

And of course, Apple's every move in medtech is scrutinized, and never more so than when the de novo-classified Apple Watch gained FDA approval in fall 2018 for an app that functions as an electrocardiogram (ECG).

MEDTECH FOR WHERE PHARMA CANNOT SUCCEED

There is a consensus that light-therapy-based devices will attract more market interest in the coming years. Philips' VitalSky delirium-recovery technology, which will challenge traditional pharma approaches for a condition that costs $150bn per year in the US alone, is one such technology. It does not attract greater direct reimbursement, but it helps reduce in hospital stay length, and thus generates a secondary reimbursement effect.

It is another example of the value-based, holistic care approach that will be the subtext of medtech providers in the coming decade.

M&A AND START-UPS

A cautious mood has settled in regarding M&A targets, especially given the strong valuations at present. In our annual table of major M&A, the list of purely medtech-focused $1bn+ acquisitions is shorter than usual. It is a cautious environment at present that will extend into 2020, but this will be seen negatively by start-ups, which provide the traditional fuel for the majors' medtech innovation.

The EU MDR will also have a telling effect on those who succeed, which companies will be acquired and when, and which companies will decide to bite the bullet and cut programs and products. Companies are now increasingly expected to gain reimbursement before they can make an exit. And all this against an environment of overall industry financing levels declining for the second consecutive year in 2018, according to data from EY. However, venture capital continues to flow into medtech.

A good indication of where there are new seams to be exploited is provided by Cleveland Clinic Innovations in its Top 10 Medical Innovations, the annual showcase from the US hospital group that was voted US News & World Report's "2019-20 Best Hospital." CCI predicted in fall 2019 that the following technologies, procedures and trends would gain ground in 2020:

• Minimally invasive mitral valve surgery. This will further expand in the US, to individuals with secondary or functional MR, despite optimal medical therapy. The mitral valve is defective in around 1 in 10 individuals over the age of 75, causing regurgitation, so this is seen as an important new treatment option.

• Closed-loop spinal cord stimulation. Chronic pain is a reason for prescription of opioid medication, but spinal cord stimulation also provides electrical stimulus to the spinal cord. Closed-loop stimulation allows for better communication between the device and the spinal cord, and can reduce unsatisfactory outcomes due to subtherapeutic or overstimulation events.

• Biologics in orthopedic repair. Cells, blood components, growth factors, and other natural substances are increasingly finding their way into orthopedic care, allowing for the possibility of expedited improved outcomes. To facilitate biologics license approvals, the FDA has opened new pathways to expedite reviews.

• Antibiotic envelopes for cardiac implantable device infection prevention. Some 1.5 million patients receive an implantable cardiac electronic device every year. Antibiotic-embedded envelopes can encase these cardiac devices, effectively preventing infection or even potentially life-threatening complications.

Exhibit 1

Largest Medtech M&A Deals In 2019*

BUYER	TARGET	INDUSTRY SECTOR	PRICE	ANNOUNCED 2019
3M (US)	M*Modal	Health IT	$1bn	February 4
J&J (US)	Auris Health (US)	Robotics surgery	$3.4bn	February 13
Danaher	GE's Biopharma business	Drug discovery tools	$21.4bn	February 25
Smith & Nephew	Osiris Therapeutics	Regen-med – wound care	$660m	March 12
3M	Acelity	Wound care	$6.7bn	May 2
Boston Scientific	Vertiflex	Orthopedics – spinal implants	$465m	May 9
Dassault Systems	Medidata	Clinical trials software (mainly pharma)	$5.8bn	June 12
Abbvie	Allergan	Pharma deal, incl. medical aesthetics	$63bn	June 25
Exact Sciences	Genomic Health	Cancer diagnostic tests	$2.3bn	July 29
Siemens Healthineers	Corindus	Vascular robotics	$1.1bn	August 8
Stryker	Mobius	Imaging Robotics	$500m	September 4
Cantel Medical (US)	Hu-Friedy (US)	Dental devices	$719.4m	October 2
Stryker	Wright Medical	Extremities orthopedics	$4bn	November 4

* Correct as of November 8, 2019; deal value $450m and above

SOURCES: In Vivo And Medtech Insight

INVESTMENTS IN DIGITAL HEALTH

US investment in digital health start-ups was up 16% at over $11bn in 2018, according to a new Top 150 Investments report and interactive research briefing from CB Insights (New York). Genomics company Grail secured a total of $1.6bn, disease diagnosis company 23andMe, $795m, and health care services delivery company Babylon Health, $635m. The big rounds went to companies innovating across health insurance – Clover Health raising $500m in a series E, and genomics company Ginkgo BioWorks, $290m (series E), for instance.

Notable in this list of 150 was how many Chinese firms occupy top rankings. The world's second-largest economy is investing significantly in health care, a national priority as the population ages and demands better options. The Chinese health care market is growing at 17% CAGR, according to the World Health Organization.

The report showed that China's tech giant Tencent was a top three investor in digital health start-ups (based on the number of portfolio companies), alongside Google and Microsoft – these three representing over 70% of digital health deals made by the key big tech companies. Google is the undisputed leader in digital health investment, according to CB Insights, mainly in genomics, clinical research, and insurance and benefits. Its subsidiaries and investment vehicles include Alphabet, Google Ventures, CapitalG, Gradient Ventures, Verily Life Sciences, and incubators such as Google Launchpad Accelerator. In November 2019, Google said it was acquiring

FitBit for $2.1bn, boosting its presence in the wearable technology market. Intel, Samsung, Alibaba, Amazon, and Comcast have likewise reached household-name status in digital health care.

These groups' top targets are not medtech *per se*, but data management, wellness, diagnostics, remote patient monitoring, drug delivery, telemedicine and chronic disease management, as well as genomics and the other leading targets listed by Google (above). The clinician expertise resides in the major medtechs, which the big techs do not have access to, and maybe do not want. But there is no hiding from it: these developments show how the health care delivery model is undergoing huge change.

RISING ROLE OF GENOMICS IN HEALTH CARE MANAGEMENT

The awakening of minds to the potential of genomics is arguably the biggest single positive development in the success of targeted therapy in the decade ahead. Genomics is one of three new industries (alongside digital and diagnostics) that the UK Life Sciences Industrial Strategy (LSIS), and NHS England's second "sector deal" aim to establish in the coming years. *(Also see "UK Plugs Into 'Golden Period' For Medtech Innovation" - Medtech Insight, 17 Jun, 2019.)*

The LSIS was authored by Sir John Bell, Regius Professor of Medicine at Oxford University, who is a champion of genomics and of the power it brings to identify at-risk individuals with greater precision. Genomics is expected to have a profound impact on the development of diagnostics and on new ways of treating disease, he said. The biggest genomics company, Illumina, which has built its genomics reach around the 2007 purchase of UK DNA sequencing firm Solexa, is of the same mind.

Illumina CSO David Bentley told In Vivo that if genetic testing followed the trend of wearables, becoming readily accessible and filling in gaps like phenotypes and medical indicators, such as pulse and blood sugar level, it will become very popular. *(Also see "Illumina CSO Bentley Paints A Vision For The Future Of Precision Medicine" - In Vivo, 2 Sep, 2019.)*

Many key genomics organizations already use Illumina technology, such as 23andMe and Grail, illustrating its pivotal role in individuals' health care management. Things to come for Illumina include the completion of the$1.2bn acquisition of Pacific Biosciences of California Inc. (PacBio), giving it both long- and short-read technologies; and projects on sudden cardiac death and neurological diseases.

ELEVATING EARLY DIAGNOSIS

Improved patient outcomes and cost-savings for provider systems have long been the obvious yet all-too-easily overlooked benefits of IVDs and other diagnostics technologies. Conditions such as cancer, stroke, heart disease and diabetes can be supported or prevented through early and regular use of diagnostics. But despite widespread recognition of their value, diagnostic services have suffered from chronic underinvestment in health care systems, and slow or even non-availability of IVD tests in mainstream medicine.

The message of "the earlier and the more targeted, the better" has become more understandable with the success of AI and machine learning, and the power of big data. Diagnostics' true value is thus becoming more visible, and the importance of early diagnosis is being elevated in initiatives like the NHS Long Term Plan (LTP) in the UK. Technologies are being developed faster too. The LTP states that by 2021, pathology networks will deliver quicker test turnaround times and improved access to more complex tests at less overall cost.

IVDs are the biggest subsegment of the world medtech market (including dental and ophthalmic) of $426bn in 2018. IVDs accounted for almost 13% or $55.4bn. By 2021, the overall IVDs market will have risen to $70bn, according to IQVIA Medtech in a 2019 global IVDs industry outlook white paper.

M&A DEALS IN MEDTECH

M&A spending increased in the 12 months to June 2019, according to EY, but the uplift came from a larger number of smaller deals. The 2019 batch of major disclosed deals reveal significant spending from a limited number of acquirers (*see Exhibit 1*).

The eye-catching deal-makers were: 3M, with $7.7bn-worth of spending in two major deals; Stryker, whose deal to buy Wright Medical for $4bn will combine the third and ninth largest orthopedic groups in 2020; and Exact Sciences, a colorectal cancer diagnostics and services company, in purchasing Genomic Health. Exact Sciences had sales of just $1.8m in 2014, rising swiftly to $454m in 2018, spurred by an ACS recommendation that colorectal cancer screening should begin at age 45, not 50.

But while deal numbers are smaller on average, valuations are getting higher. Medtechs are seemingly prioritizing tuck-ins and portfolio optimization, rather than opting for larger, more adventurous targets.

ROBOTICS MARKET GROWTH TEMPTS INNOVATORS

Competition in robotics is picking up, as many want a bigger piece of the action that the robotics pioneer Intuitive Surgical has done so much to create. They also know that space is limited in a market with very high entry barriers, hence the rapid attention to targeted M&A in the past two to three years. CMR Surgical, Verb Surgical, Olympus Corp., Samsung, TransEnterix Inc. and Wego Holding Co., all serious contenders, now have even greater competition from Medtronic, with its Hugo RAS system that will rival Intuitive's Da Vinci system in gynecologic, urologic, cardiothoracic surgery, head and neck and general surgery. The market for robotic minimally invasive surgery systems is growing at some 20% annually and is worth about $4bn, according to Medtronic. The global market for RAS systems is expected to reach $5.3bn by 2021.

Medtronic also markets the Mazor robotic system for spine surgery. NuVasive Inc. and Globus Medical are now developing orthopedics platforms, and Auris Health is also expected to compete with Intuitive in the area of robotic-assisted bronchoscope devices, by means of its endoluminal system for minimally invasive biopsies in the peripheral lung. It follows DePuy Synthes' purchase of Orthotaxy's robotic technology for orthopedics in 2018, which some saw as a belated entry into the sector.

Siemens and Johnson & Johnson made the largest robotics M&A deals in 2019. Stryker was in there too, with an imaging robotics purchase (Moebius). This large-scale move into robotics is a further illustration of how medtechs in 2019-2020 are becoming immersed in disruptive technologies and practices that go beyond the technology alone.

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Changing China Is Opening Up For Health Care Entrants

The potential of China's vast health care products market is alluring. It has proved off-limits to most of the global medtech industry, and is rarely in the early launch strategies of global companies. Government-led initiatives want that to change, as evidenced in the latest Five-Year Plan and the recent Healthy China 2030 report.

ASHLEY YEO
EXECUTIVE EDITOR,
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The barriers for health care industry entrants into China are lowering, but still not as quickly as many medtech companies would like. Recent structural health care delivery plans are instilling more confidence in a market and industry that in the past have been regarded with suspicion. Much of the change is down to the new climate for business being overseen by PRC president Xi Jinping. Global law firm CMS' China expert Nick Beckett explained what is changing and why western companies should monitor developments.

Of the four Chinese companies that feature in *In Vivo*'s Top 100 medical device companies by revenues for 2018 (Lepu Medical Technology (Beijing) Co. Ltd., cardiovascular products and services, Beijing; MicroPort Scientific Corp., orthopedic and cardiac products, Shanghai; Jiangsu Yuyue Medical Equipment & Supply, Zhenjiang; and Shinva Medical Instrument Co., Shandong), only Shinva, a sterilization and disinfection equipment manufacturer, is in the top 50 of global medtech companies by US dollar-ranked revenues.

Chinese manufacturers are under-represented at this level, and so are foreign companies and their medtech innovations in China. But China is changing as demand is growing for the technologies that western patients already have access to. Changing attitudes about the value of health care will help transform China's health care industry and market in the decade ahead. Mindful of the need for quality health care for the vast local population, Chinese decision makers, from Jinping down, are overseeing an ongoing process of support and investment in the sector.

The overall framework is set out in the 13th Five-Year Plan for economic and social development of the People's Republic of China 2016-2020, listing China's strategic intentions and major objectives, tasks, and measures for economic and social development. By the end of the plan, for a national population anticipated to reach 1.42 billion in 2020, the major aims are for: China's GDP and per capita personal income to have doubled from 2010 levels; industrial production to have moved towards the medium-high end; and for visible outcomes of the support being given to foster innovation-driven development, business start-ups and internationally-competitive enterprises.

In a section dedicated to promoting a healthy China, the Plan promises deepened reform of the health care system, an emphasis on prevention, and strategies to control of chronic diseases – cardiovascular, brain, and vascular diseases, diabetes, cancer, respiratory disease, and mental illness. It speaks of a tiered medical diag-

nosis and treatment system and general practitioner capacity improvements, with the number of active physicians targeted to reach 2.5 per 1,000 people.

Enlarging the scale of the national health industry, and perfecting the health care services systems, are two of the five specific goals of Healthy China 2030: A Vision for Health Care, released in October 2016 by Jinping as a blueprint for the changes China should make in the coming decade. With innovation at its center, it advocates a role for market mechanisms, and recommends, in 29 chapters, 13 indicators and four core principles, how China must factor in reform in key areas, including in the areas of public health services, food and drug safety and the Chinese medical industry.

The ground is increasingly fertile and the population ready for the health care reforms and delivery improvements of the kinds detailed in these two reports. That is the view of CMS' Nick Beckett, the law firm's co-head of life sciences and health care, and head of Asia-Pacific IP, who spends much of his time in Beijing and greater China. Speaking to *In Vivo*, he observed that, in health care, China is indeed at a turning point. The markets may have heard that before, but the sense now is of real change to come.

One reason for increased optimism that China is more ready now to turn the corner is that the youth of the country, more connected through social media, international travel and foreign education and experiences, have a greater awareness of what goes on beyond China. Other parts of the world have access to innovative devices and drugs, and China's millennials are now demanding them too. Overseas companies are monitoring this, factoring in the impact it will have. Beckett observed that these companies will need to be more patient – and consumer – focused, and ready to bring their technologies, new or yet-to-be-developed, into China to provide information and support local patients.

This comes at the same time that AI, machine learning and the advantages offered by big data – a major focus in the Five-Year Plan 2016-2020 – are being brought to bear. For health care, AI is seen as a transformational step, and the next few years will be truly fascinating in terms of who will drive developments in the digital health care ecosystem. China is a global leader in AI, alongside the UK and US. Its homegrown major tech groups, Tencent and Alibaba especially, continue to make huge strides in digital health care delivery. In some ways, the traditional big pharma companies, especially, seem to be relatively unprepared – a surprise, given the accelerated pace of developments over the past four to five years.

The uptake of AI in China is one of the focus areas of a CMS "legal perspectives" document, "AI in Life Sciences," which quotes a government prediction of the value of the Chinese AI industry in 2025: RMB400bn, according to the national "Plan for the Development of a New Generation of AI." The slight puzzle, still, is that pharma and to an extent medtech too, while talking up the prospects of AI, are still grappling with the hows and whys in terms of monetizing it and bringing it into business models. They more often talk about specific bolt-ons only, but by contrast, China's Tencent, for one, is not waiting around (see below).

AWARENESS OF HEALTH CARE ON THE UP

The sense that China is ready to open up for health care entrants is boosted by the knowledge that while the population has traditionally had a low fundamental awareness of health, greater awareness of that very fact means that remedial action is unavoidable. The millennial generation's attitudes will be a contributory factor to the speed of change ahead.

Historically, as a very poor country, China has lacked a health care infrastructure. No or low primary care availability and no local GP interface, have forced patients to head off to usually crowded hospitals to seek an appointment. With no yardstick about their ailment, patients have been prone to overreact to very simple issues, and so there remain big challenges around educational issues, and about patients being able to seek appropriate health care attention for perhaps minor health issues. Here is an area where awareness, from an albeit low base, is set to rise markedly.

Coupled with that, China's new vision of itself as a "strong and growing country" in turn fosters notions that it should rightfully have good health care. That is still not the case in the large rural areas, but there, too, a better basic understanding of health is developing. The advent of technology, and personal health care information apps that give basic information about conditions, are facilitating and driving that.

In view of this, medtech companies should be providing support to those patients who are more receptive to it and maybe even more demanding of it. This will lead to demands for better basic health care provision. Healthy China 2030 and its recommendations are central tenets of the administration, which now finds it must provide in the large rural communities the standard of health care enjoyed by the slightly more affluent people in Shanghai or Beijing, say. "The government had to up its game in terms of quality of health care services, and, tied to the opening up of the market to private investment, it's apparent that it is all coming together," said Beckett.

ONE CHINA

China's policies are built around a "one country" approach for health care, and good provision across the provinces and into the remote rural zones. The use of remote monitoring technology, such as telecare/telemedicine systems, is seen as increasingly critical in rural China. Allowing private investment is one of the strategies to develop health care provision in China's the second and third-tier cites.

The Five-Year Plan underlines the "one country, two systems," approaches for Hong Kong and Macao. Hong Kong's current protests against its government over China's drive for more influence there are being watched closely for potential effects on business. China also seeks to build cross-Straits cooperation with Taiwan, under the One China approach.

Private health care, although still very small-scale, has been making inroads in China in the past three to five years, manifesting itself in the establishment of specialist clinics for respiratory disease, for example. "The ground work has been done to allow greater investment now in both private and public private hospitals," said Beckett, adding however, that while China can "move at the speed of light" for building projects, etc, in policy, law and regulation it sometimes moves much more slowly.

PILOT ZONES

Using pilot zones is a common approach of the Chinese authorities. A prime example in summer 2019 was the way it tested the new

marketing authorization holder (MAH) tool for medtech. The MAH is a very significant concept that until recently did not exist in China. Medtech product license owners were typically the manufacturers, and only they could own the MA, and could only transfer it to another manufacturer.

This led to difficulties, with so much economic activity tied to manufacturing capability. The MAH system, first used in three zones, then in a further 21 this year, makes matters much easier and will lead to contracts being set up in manufacturing development. CROs and CSOs etc are expected to flourish in what will become a wider outsourcing environment.

But such processes often take several years, as the Chinese need to be totally comfortable before rolling out their scheme nationwide.

> *"The market is there, the infrastructure is being put in place, and there is a move towards a more consumer-led, innovative economy."*

The medtech MAH rule is also seen as a boost for local innovation. "It will be a move from basic and mid-level devices, to higher-end and probably higher-price devices, and thereby will help Chinese commercial operators be better able to compete globally," said Beckett.

Jinping's "One belt one road" trade outreach project focuses on improving connectivity and cooperation across Asia, Africa and Europe. Though not primarily a tool for medtech projects, if China were to develop large medtech champions, they too could use the OBOR to develop trading routes and find trading partners, eventually helping their global health care trading plans.

SLOW CHINA

Critics would argue that "eventually" has too often been a signature word for Chinese policy initiatives. The long-awaited amendment to the PRC Drug Administration Law came into effect on 1 December 2019. It is a second major systematic and structural amendment to China's drug-administration framework since the implementation of the last significant amendment in 2001. But the amendment has been in the works since 2015.

The catalyst was the China's State Council's issuance in October 2017 of the Opinions on Deepening Regulatory Reforms to Encourage Drug and Medical Device Innovation. This proposed fundamental changes to regulatory systems, including the simplification of clinical trials, implementing the Drug Marketing Administration Holder (MAH) system, establishing a patent-linkage regime and perfecting the drug-registration process. The MAH system for medtech is slowly and carefully coming into place now.

"Politically, China tries to do things in such a way to get everyone on side with it; not to do anything suddenly," Beckett observed. A frustration is that several of China's regulatory authorities are often involved in looking at the same issues at the same time (three were studying China's anti-trust and competition law), which does not make for swift passage of regulatory instruments.

In the medtech domain, the NMPA (National Medical Products Administration), the Chinese agency for regulating drugs and medical devices, has been mulling the dropping of the country of origin (COO) certification requirement for "priority" devices that qualify for its "Green Channel," fast-track innovation approval pathway. But nervousness of making big decisions among individual regulatory executives has led to a situation where no decision has yet been taken. The culture is such that regulatory officers would rather not make a decision than make a wrong decision. In terms of the COO, the nervousness is at individual level, not at a state level. "Looking at it through the lens of the Chinese state, it's clear China's not in a hurry, I feel," said Beckett.

The Green channel, the fast-track system for both innovative and priority devices, has not so far been called into action as much as had been anticipated. It was set up in 2014, but five years on, use of this route to expedite devices remains underused by manufacturers. The consensus is that the initiative has value, however. And on the regulator's side, it is a sign of preparedness to expedite the right products, Beckett noted. From a western company's perspective, as an initiative, it ties in with foreign clinical trials exemptions, quicker regulatory reviews, and products getting to market much faster, and indeed, coming to market first."

REACHING OUT

The regulations and infrastructure being put in place now in China are more internationally aligned, and so are more acceptable to companies in the west, which are no longer worried quite so much about each and every step they take. In the area of IP, China has formalized dialog with US judges, the UK and Japan, which is also making China more internationally accepted. "The lens is slowly changing, and we may soon have data exclusivity and a patent linkage system. "We already have patent recognition and special courts protecting companies' rights," said Beckett.

The standards are changing, and the infrastructure is being put in place that allows investors in China to have more confidence. From China's perspective, there is a drive to elevate domestic life sciences companies to "national champion level," so that they can eventually compete globally. However, although there is a long way to go in the life sciences and health care spaces, where there are outstanding learning requirements, and the ongoing need for talent and know how. This makes China receptive to foreign investment and assistance in ways which, other industries, for example telecoms, simply do not need.

The recent development in the Drug Administration Law (see above) also answers in some ways the need in China to align more with international standards. The authorities are looking at bringing in a pharmacovigilance standard, and are changing the emphasis from pre-approval to more post-approval. The pre-approval stage in pharma is much faster now, enabling companies to bring products to market more swiftly, but at the same time, with increasing liabilities on them. China is on the same basic path in devices, making strides in exemptions from local clinical trials. "It all fits," said Beckett.

Clearly, China is more prepared to use a

mix of international and Chinese standards in its regulatory infrastructure. It is developing its own UDI system for medical devices, but using ISO-based, China-specific standards, GB (the code for national standards, issued by the Standards Administration) and YY (the code for medical devices, issued by the NMPA). The medtech industry follows both sets of standards, says Chao Xu, co-founder of Chinese consultancy J-Medtec (Berlin, Germany).

IMITATION TO ACHIEVE GREATER GOALS

"China is not afraid to copy – historically seen as a high form of flattery in China," said Beckett. The law, for example, is very heavily based on European law, and the patent linkage system is partially derived from the US system.

The same principle applies in the case of WeChat, the multi-purpose messaging, social media and mobile payment app, owned by Tencent Holdings. Tencent specializes in internet-related services and products, has become bigger than the concept it imitated, Facebook, and is increasingly important in digital health care. It was the first Chinese firm to have a market valuation of over $500bn. Of the three big tech players in China, including Alibaba and Baidu, Tencent is the fastest growing in health care.

Tencent Trusted Doctor now claims to connect 440,000 certified doctors with more than 10 million patients online. It collaborates with Germany's Merck KGaA, and it also operates WeDoctor, a web-appointments, education, diagnosis, and consultation tool. Alibaba is developing services to support China's primary care system through online doctor consultations.

PRIMARY CARE ISSUE TO BE SOLVED

Such tools are gaining a lot of ground in the relative absence of primary care in China, where there are some very early-stage plans to install primary care services in hospitals and a push to establish smaller clinics that integrate technology.

At the same time, China sees the need to increase the standing and social status of general practitioners, who believe they are perceived as inferior to specialists. A 2017 survey by the Chinese Academy of Medical Sciences and others revealed that Chinese physicians bear heavy physical, mental, and financial stress. Low confidence, trust and respect in them from wider society are some of their other complaints. Soberingly, over 70% would not encourage their children to follow their career path.

TALENT BEING BROUGHT IN

China is encouraging foreign talent into the country, including in Nanjing, the heart of the Chinese pharma industry, to leverage the knowledge to innovate and help advance the local industry. Nanjing University is a leading university in the pharmaceutical field in China. The country is welcoming new, innovative products in the life sciences domain, but it will ensure that it retains the firm hand of control over any decisions.

Another tool for developing health care and local health care business is the special zones, such as Hainan province, where the aim is to create a free trade zone and medical tourist pilot zone. It would be able to take advantage of its position to maximize the huge trading potential with Vietnam, the Philippines, and Thailand, among others.

The changing environment under Jinping has also seen a big push to rid the country of corruption at all levels over the past five or six years. The historical problem with corruption partly lies in the multiple layers of distributors, and the power of money. The GSK kickbacks episode and 2014 judgement scared companies and individuals alike, and everyone redoubled compliance and auditing activities, set up proper local training, and reviewed their procedures.

But the involvement of third parties still presents challenges, as it means manufacturers losing sight of what happens and possibly losing control. The government has tightened up this whole area by reducing distributor numbers, slimming down brands, introducing invoice controls, and generally tidying up the system. "It was built in, and changing it has been a big challenge, but Xi Jinping has taken strong action and it's now a lot better than it was," said Beckett.

The tariff issues between the US and China have done nothing to help China's global trade ambitions, but the effects are being seen in the US too, where providers are having to consider finding alternative sources for Chinese imported devices. VC funding has been impacted recently by the US trade tensions, after a big VC funding uptake in 2018.

STRATEGIC SIGNPOSTS POINT TO MORE HEALTH CARE

The Five-Year Plan and Healthy China 2030 initiative are strategic signposts for massive change, and a strong indication of where China is focusing.

They acknowledge that Chinese role model names in medtech and pharma are not there as yet, and at present, aspiring innovators in China are looking at companies like Johnson & Johnson as models to emulate.

They underline the critical nature of partnerships to success in China. And they encourage companies to "be the first in China," under the package of measures being developed for the health care products industries. China has not yet featured in the launch strategies of global companies at an early stage: it used to be at the very end of such plans. Now, it's getting to a point where companies might consider to launch in China first. "But it's very early days there, and that notion needs more time," said Beckett.

Locally, investment is being improved, as seen, for example, in the new health care incubator fund in Shenzen, in the Greater Bay Area. It is a government-funded initiative, and does not yet involve huge figures, but it is an attempt to encourage start-ups from all over the world to come to China.

Conservative China's plans make it one to watch in health care in the next five years. Its plans are centrally-government led. This is a critical initiative for the Chinese government, targeting an area of great need, and providing opportunities for western and Chinese companies alike. The market is there, the infrastructure is being put in place, and there is a move towards a more consumer-led, innovative economy. China may play the long game, but western minds can probably see there is growing confidence – and a little less nervousness – about future medtech and pharma business with China.

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Gene Therapy Manufacturers Are Highly Sought Acquisition Targets

Given the transformative nature of regenerative medicines, treatments yielding greatly improved patient responses that now exist as viable products on the market, cell and gene drug developers over the past several years have been drawing deal attention. Not only through collaborative partnerships, but also as acquisition targets.

In the first half of 2019 attention-grabbing headlines such as Roche's acquisition of Spark Therapeutics Inc. for $4.8bn, Biogen Inc.'s $877m play for Nightstar Therapeutics PLC, and Vertex Pharmaceuticals Inc.'s double deals for Exonics Therapeutics Inc. (up to $1bn) and Semma Therapeutics Inc. ($950m) exemplify the demand to enter or expand in this sector.

But 2019 deal-making has also been notable for another critical piece in the cell and gene therapy modality: manufacturing. Therapeutic cells and genes are unique products requiring special scale, and technical and logistical considerations. A popular saying in the regenerative medicine industry is that "process *is* the product," because inherent in the final medicine are the critical manufacturing steps that take place to make that medicine. In 1H 2019, there were at least six major acquisitions involving cell and gene therapy manufacturing companies.

In the largest of these transactions, Danaher Corp. paid $21.4bn for GE Healthcare Life Sciences' biopharma business, which brings with it a cell therapy and analysis portfolio including an end-to-end (from development through commercialization) bioprocessing and manufacturing platform.

Thermo Fisher Scientific Inc. now owns one of the largest US contract development and manufacturing organizations (CDMOs) in the gene therapy market after buying Brammer Bio Inc. for $1.7bn. Brammer conducts clinical- and commercial-stage current good manufacturing practice (cGMP) manufacturing of viral vectors used to deliver *in vivo* and *ex vivo* gene therapies, specializing in adeno-associated viral, adenoviral, lentiviral, retroviral, and herpes vectors.

In addition to consolidation among manufacturers, private equity buyouts have also played a role, with the purpose of these transactions presumably to further enhance value for shareholders. The majority of plasmid DNA supplier Aldevron was purchased by EQT

Exhibit 1

Gene Therapy Manufacturing Deals In 1H 2019

JANUARY — $86m

Apceth Biopharma
Hitachi Chemical

Apceth is a leading European CDMO for ATMPs, with state-of-the-art facilities in Munich, Germany. It has expertise in GMP manufacturing for autologous and allogeneic cell types.

FEBRUARY — $21.4bn

Danaher
GE Healthcare Life Sciences

This acquisition gives Danaher a cell therapy and analysis portfolio including an end-to-end bioprocessing and manufacturing platform

MARCH — $1.7bn

ThermoFisher Scientific
Brammer

Brammer Bio is one of the biggest contractors in process development and manufacturing of viral vectors for cell and gene therapies.

APRIL — Not Disclosed

Catalent
Paragon Bioservices

Paragon specializes in viral vector development and manufacturing for gene therapies, specializing in AAV, as well as DNA plasmids and lentiviral vectors.

MAY — Not Disclosed

Ampresand
Vibalogics

PE firm Ampersand's investment is expected to expand Vibalogics' capabilities. Vibalogics is a CDMO that performs process development and manufacturing for gene therapies

JULY — Not Disclosed

EQT
Aldevron

EQT took majority ownership of Aldevron to support investment in additional production capacity, R&D, and growth initiatives. Aldevron is a global supplier of GMP and research-grade plasmid DNA used in commercial, clinical and research stage gene therapies.

SOURCES: Medtrack, September 2019; Strategic Transactions, September 2019; company press releases

VIII Fund, while Vibalogics, which performs cell-based virus production for gene therapies, was acquired by Ampersand Capital Partners.

Panelists at the 2019 Cell And Gene Therapy BioProcessing And Commercialization conference in Boston, MA, and on Informa Pharma Intelligence's webinar Manufacturing Challenges Facing Cell And Gene Therapy, held on 19 September 2019, discussed factors driving such acquisitions. According to Wouter Van 't Hof, the cord blood bank director at the Cleveland Cord Blood Center, these deals can bring in additional capacity and enable further iterations of existing capabilities. They also signal that acquirers are looking to diversify their portfolio offerings.

Bob Preti, president and CEO of Hitachi Chemical Co. Ltd., agreed, saying these acquisitions add important services, allowing customers access to a harmonized network that is more efficient than working with separate providers or a loosely affiliated network. Preti said another key advantage to building through M&A is geographic expansion, giving therapeutic developers access to multiple regions in the world. There was consensus among the panelists that the pace of acquisition activity for manufacturing companies will continue in the future. "I expect to see this consolidation trend really increasing. The biggest players will be snapping up other parts to make more complete offerings," said Preti.

Companies that have drawn big acquisition dollars, such as Brammer Bio, Paragon Bioservices Inc., and apceth, are attractive because they play key roles in the development and manufacturing processes of gene therapies. Many developers choose to outsource the manufacturing piece as opposed to introducing and broadening that capability in-house. Steve Oh, director of stem cell bioprocessing and institute professor at A*Star, said partnering was a viable option for those short on cash who cannot invest in internal manufacturing. When scouting and evaluating an outsourcing partner, there are several important characteristics that developers should take into consideration, such as understanding the volume of products to be produced, the complexity of those products and accessibility to high-end equipment, including large-scale bioreactors that enable scale-up for vector manufacturing. From the developer's side, having a good understanding of the process and critical quality attributes of the product is critical to establishing a robust manufacturing process. Partnering with a contract manufacturing organization (CMO) or a CDMO

Exhibit 2
Advantages Of Partnering With A Cell And Gene Therapy CDMO/CMO

ADVANTAGE	DETAILS
Therapy Development	Potential to reduce development risk
Scale	Secure a scalable supply of product so that developers can transition from enablement to sustainability
Access To Capital/Infrastructure	CDMO/CMO has capital, infrastructure, logistics, information systems, and an already built/presumably high-quality facility; access to this enables developers to avoid making a long-term investment in a facility
Reduction In Cost Of Goods	Potential to reduce cost of goods, increasing the chances for producing a viable product
Speed To Market	CDMO/CMO partners have the capacity to increase speed of product to market; partners can offer additional value on commercial manufacturing/high volume
Geographic Considerations	Ability to put manufacturing footprint in parts of the world that would otherwise not be accessible
Expertise	CDMOs/CMOs already employ trained personnel to handle manufacturing for highly specialized cell and gene therapies

SOURCES: Conference panels at Cell And Gene Therapy BioProcessing And Commercialization conference; Informa Pharma Intelligence's Manufacturing Challenges Facing Cell and Gene Therapy webinar

comes with multiple advantages, according to the panelists at the conference (held on 10-12 September 2019) and on the webinar.

Overall, to take the best path forward, proper alliance management should be in place – the manufacturer and developer would benefit most from a true relationship, where each partner is working toward a unified goal, with strong communication in place, including identification and discussion of bottlenecks that arise. Both Van 't Hof and Oh agreed that entering discussions with a CMO or CDMO partner as early as possible was an advantage. It is also important to begin that relationship with the ultimate use of the end product in mind, and to work backward to understand the goals needed to produce that end product. Having a target product profile, said Van 't Hof, was a major factor for success, especially having a good grasp of the mechanism of action, potency and stability. "Manufacturing capability or scale is no replacement for the need to understand the fundamentals of the product," he said. Developers should approach CMOs already having a well-understood development process, a clear understanding of protocol and, for gene vectors, provide the CMO or CDMO with the source of the virus or plasmid. Another critical factor is face-to-face time, with developers having a presence at the actual manufacturing site to, for example, be able to physically see the clean room and observe. Geographic location between the partners is also an important consideration.

Outsourcing, however, might not be the best approach for all companies. Some of the advantages to outsourcing – including access to quality, scale and automated systems – may also be reasons why a company would want to retain manufacturing internally. Chris Gemmiti, Sentien Biotechnologies' vice president of operations, highlighted that automation in manufacturing was unique to each developer, so this may be more appropriate to keep in-house. According to Lior Raviv, Pluristem's vice president of development, a change in environment, such as manufacturing or process development, can alter the end product, which was another reason that a developer may not wish to outsource. In addition, because there is such a high demand from developers for manufacturing in cell and gene therapy, and a finite number of CDMOs and CMOs that specialize in this area, backlogs and long wait times are inevitable.

Developers do not necessarily have to choose one option over the other. Some could take a hybrid approach. This might be appropriate in situations of curative therapies, said Preti. When a product first goes on the market, a company needs to ensure that the pace of manufacturing can keep up with demand, because there will initially be a backlog. Based on the estimated patient population, a developer may want to outsource with a CDMO to meet, for example, half of those patients, because it is a known volume of patients. For the remaining patients, the developer may choose to build out its own manufacturing to handle the capacity because it will be highly variable, given that the product is a curative therapy, and eventually the number of patients theoretically will decrease over time as patients are cured. In this strategy, a developer can avoid overproducing while meeting the demand of the market and reaching patients.

To partner, or build-out manufacturing, or to do a combination of both, remains highly individualized to each company and the status of a project. The wave of deal-making around cell and gene therapy manufacturing players indicates that companies are looking for services that are broad in terms of capabilities and geographic reach. Understanding manufacturing challenges, introducing innovative technologies and planning for future demand are all key to ensuring success in the cell and gene therapy industry.

IV124344

Regulators Seek Solutions To Manufacturing Woes

ED SILVERMAN
CONTRIBUTOR

Over the past few years, frustrating instances of shortages and recalls – particularly generics – have been blamed on inferior quality control at countless suppliers of active pharmaceutical ingredients and finished products, especially those based in India and China.

In early 2017, a US Food and Drug Administration inspector visited a factory run by Changzhou Jintan Qianyao Pharmaceutical in Changzhou City, China, and asked the company to produce a list of raw materials and sampling requirements. But he received a curious response. Rather than handing over documents, the company explained there were no procedures for testing or sampling incoming materials. Instead, warehouse employees kept the information "in their heads."

In late 2018, an inspector visited a Centurion Laboratories facility in Gujarat, India, and found the company failed to follow written procedures for cleaning and maintaining equipment. The company explained the deficiencies by saying a nine-day dancing festival and government holiday caused a manpower shortage. While this was an important event on the Hindu calendar, no reason was given why the holiday prevented the company from following procedures before and after the celebration.

And earlier this year, an FDA inspector visited Strides Pharma Inc., one of the largest purveyors of generic drugs, and found discarded documents, including batch records, in a 55-gallon drum in its scrapyard in Puducherry, India. Multiple bags of documents pertaining to production, quality, and laboratory operations were waiting to be shredded, but when asked about the documents, a Strides employee insisted the bags were placed there "inadvertently," according to an FDA warning letter.

Although these were isolated incidents, each episode is part of a larger – and increasingly troubling – tale about the questionable state of pharmaceutical manufacturing and its debilitating effect on the global supply chain.

From early 2018 until August 2019, the FDA's Office of Manufacturing Quality issued 75 warning letters to drug makers that violated its safety or quality standards. Half of these warning letters – 49% – were sent to companies based in China or India, according to a recent analysis by *The Pharmaceutical Journal*. During the same period, the European Medicines Agency published 22 compliance notices, of which 14, or 64%, were sent to manufacturers in India or China.

"These are challenging times, to say the least," said David Gortler, an associate professor of pharmacology at Georgetown University and a former senior medical analyst and medical officer at the FDA. "And it poses problems for everyone, whether you're a regulator, lawmaker or patient. You have key suppliers concentrated in two countries where oversight is hard to maintain and cultural differences can exacerbate the problem. And at the same time, regulatory resources are not what they should be."

Much of the problem, however, is blamed on old-fashioned economics.

"Unfortunately, incentives today are not high enough for many manufacturers to establish mature quality management capabilities," Janet Woodcock, the director of the Center for Drug Evaluation and Research at the FDA, wrote in a recent blog post. "Drug manufacturers are more likely to keep costs down by minimizing investments in manufacturing quality, leading to quality issues that can trigger supply disruptions and shortages."

The fallout is especially acute in the US, where generics account for 89% of all prescriptions, according to market researcher IQVIA. India supplies approximately 25% of finished generics and China supplies about 9% of the generics entering the country, according to Rosemary Gibson, a health care and patient safety expert at bioethics non-profit The Hastings Center and co-author of *China Rx: Exposing the Risks of America's Dependence on China for Medicine*.

At the same time, the number of ongoing shortages has been steadily rising — reaching about 150 this past fall — after previously peaking in 2011. And shortages are becoming more persistent with a growing portion lasting longer than five years, according to the FDA. Some occur because a company decides a product is no longer profitable, but the agency found quality issues accounted for 62% of 163 drugs that went into shortage between 2013 and 2017.

The trend accelerated in recent years as global manufacturers cut back on production following mergers or simply to reduce overall costs. As a result, fewer of these companies continued to operate plants, notably in Puerto Rico, where US tax incentives dwindled. Instead, more outsourcing is being done, especially in China. The number of registered facilities making active pharmaceutical ingredients in China more than doubled between 2010 and 2019, according to the FDA.

"The mantra is that generics reduce costs, but the

situation we have now drives API production to China and then we get poor quality. This is the problem with long supply chains that are located thousands of miles away," said Gibson. "It's a deep systemic problem that we have. These products are viewed as commodities. Unfortunately, the FDA has to make trade-offs by allowing products that don't meet US standards on the market, because otherwise there would be a shortage. Pick your poison."

Perhaps no recent episode has typified this quandary more than the contamination of blood pressure medicine valsartan. A controversy erupted in July 2018 after the FDA and EMA found contaminated ingredients used to make valsartan were sold to numerous drug makers, including many in India. The discovery prompted a steady stream of product recalls, which alarmed patients and led to shortages.

In its last public communiqué in August, the FDA acknowledged that it was still investigating the "root causes" to explain how traces of a possible carcinogen known as N-Nitrosodimethylamine, or NDMA, was detected in so many lots sold by different manufacturers.

The contamination prompted lawmakers in Washington DC to press the FDA to explain its oversight of the pharmaceutical supply chain. While a May 2019 report from the FDA Office of Pharmaceutical Quality found the percentage of inspections in China and India was on a par with the number of facilities in those countries – at 22% and 23%, respectively – one US Senator complained this ratio suggested regulators did not apply the scrutiny needed to address the issue.

Since then, things have gotten still more worrisome.

This past fall, the FDA and EMA began grappling with traces of NDMA found in heartburn medicine ranitidine, used in Zantac. An online pharmacy that analyzes medicines prior to shipments contends the impurity is due to molecular activity that occurs in the stomach. But after running simulated testing, the FDA maintained there was no evidence that the medicines form a possible carcinogen in patient stomachs or small intestines.

Still, this marked the second consecutive year in which wildly popular medicines taken for common ailments posed some level of risk, leaving regulators scrambling to find the cause as they tell manufacturers to issue recalls while trying to calm consumers. Given that many of the suppliers are based in China and India – and the concurrent rise in warning letters issued to ingredients and finished dose manufacturers based there – some experts say that the current oversight system is lacking.

"Actually, this is not so much a manufacturing issue. It's really a compliance issue," said Dinesh Thakur, a public health activist and a former director and global head of research information and portfolio management at Ranbaxy Laboratories Ltd., who exposed data manipulation at the generics company. "It's basically an honesty system. We send inspectors to these facilities, most of which are given advance notice, and we have to take a lot of data at face value."

It is not only generic manufacturers that have quality control problems.

In 2017, a Pfizer Inc. unit that makes the EpiPen device for Mylan experienced a quality-control meltdown that included a failure to investigate serious problems associated with an unspecified number of patient deaths. The same year, a Bayer AG facility in Leverkusen, Germany, that was doing contract manufacturing work failed to properly clean equipment and thoroughly investigate batches. A warning letter noted that its customer had to recall several lots of tablets due to contamination.

Then there was an episode in 2013, when the FDA approved Gilead Sciences Inc.'s revolutionary hepatitis C treatment Sovaldi. An FDA inspection report found a testing facility had numerous quality control problems, including samples that were improperly stored and cataloged, failures with batches that were not adequately reviewed, and testing results that were susceptible to tampering that could hide problems.

But the number of such instances pales by comparison to the steady march of difficulties associated with generics. "The big global companies have corporate quality assurance staff and travel to different overseas sites continuously to make sure every supplier is complying with their demands. That may be the reason there are fewer recalls from these companies," said Charles Ahn of Aegis Beacon Consulting, who is a former FDA compliance officer and assistant country director in China.

But Sudarshan Jain, the secretary general of the Indian Pharmaceutical Alliance, maintained that the domestic industry had made "significant investments" in manufacturing infrastructure and technology, along with improvements in documentation practices, data integrity and process validation. And with more than 550 facilities approved by the FDA, it is not surprising that the agency has been issuing more Form 483 inspection forms to local drug companies.

However, he argued, a 483 form "con-

tains observations and, therefore, not every 483 form means that there is a quality issue. Some of observations could be procedural or administrative in nature and may require minor corrections."

Nonetheless, the quality problems plaguing generics are prompting a lot of hand-wringing as regulators and lawmakers seek to find a fix. Last summer, for instance, a bipartisan group of House Energy and Commerce Committee lawmakers asked the US Government Accountability Office to investigate how the FDA conducts inspections, including a "risk-based" approach the agency uses to sort out which plants require attention.

For its part, the FDA points to a "mutual recognition agreement" with the EU, which allows regulators in nearly three dozen countries – including the UK, Germany and France – to harmonize inspections. The idea is to save time and money that comes from avoiding duplicate inspections. However, there are no publicly available metrics to illustrate the extent to which this arrangement may be saving time and money, or increasing the ability to more aptly identify quality control problems at manufacturing facilities.

Nonetheless, the FDA claims to be working harder to oversee manufacturing plants beyond the US. At a recent conference, agency officials explained that the number of facilities inspected in foreign countries had increased 20% over the most recent five-year period. Specifically, the agency inspected 993 foreign plants in fiscal year 2014 compared with 1,245 in fiscal year 2018, not including biologics.

Nonetheless, finding a solution is proving elusive.

For one thing, most regulators are apparently not equipped to do their jobs. In fact, fewer than 30% of the world's medicines regulatory authorities are considered to have the capacity to perform the functions required to ensure medicines, vaccines and other health products actually work and do not harm patients, according to the World Health Organization.

A key issue involves inspections, and on a number of different levels.

A 2016 report by the US GAO found that almost one-third of foreign plants had not been inspected by the FDA, although the agency said the backlog has since diminished. And inspecting facilities does not come cheap. In recent US Congressional subcommittee testimony, the FDA's Woodcock noted that a foreign inspection costs the agency about $76,000. But while "we have the funding, [we] are having trouble bringing people on board," she testified.

Then there are cultural issues that can crop up during inspections. "A lot of times investigators don't have what I call cultural intelligence," said Steven Lynn, a former director of the FDA Office of Pharmaceutical Quality, who has subsequently worked in global quality compliance for both Novartis AG and Mylan NV before leaving to start his own consulting firm.

"Investigators have to know the culture of the country so they can find issues they're looking for," he explained. "You have to know the way managers and employees think and do things, because misunderstandings occur. Very often, foreigners may not appreciate what they're hearing or seeing. But if they know the culture, it can help them interact better."

Staffing and cultural considerations aside, another regularly debated point is whether regulators should more aggressively pursue unannounced inspections. Most ordinary surveillance inspections are "pre-announced," which means that foreign manufacturing plants are typically given two to three months advance notice. Given the growing number of quality control problems, this is controversial, because a company has time to conceal important data or plan how to divert an inspector's attention.

But the FDA offers a heads-up to plant management for a couple of reasons. One is to ensure that the plant is running when an inspector visits. Sometimes, holidays, bad weather or employee issues can unexpectedly hinder staffing to the point where work is briefly stopped. But unannounced inspections do occur when there are known issues at a plant.

"We are doing unannounced inspections right now," said Francis Godwin, director of the Office of Manufacturing Quality in the FDA's Office of Compliance. "There are pros and cons to both. If nobody is there you may have wasted time. There are other instances where you want a pre-announced inspection, such as with a pre-approval, because you want to see a drug being manufactured, so the inspector can witness that directly."

Ahn, meanwhile, argued that focusing mostly on suppliers in China and India allowed others to escape scrutiny, especially since APIs are made all over the world. Yes, China's share of API production plants has doubled in the past decade, but the EU accounts for 26% of all API manufacturing plants, while the US accounts for 28%. "Chinese or Indian companies take all the blame. But some of the major players located in Europe also control the flow of APIs and drug products," he said.

To remedy the situation, the FDA is proposing a system to rate manufacturing facilities run by drug makers. The idea is that group purchasing organizations for hospitals, in particular, would reward manufacturers that consistently make drugs that conform to quality standards. These steady sales could provide incentive for further investment in facilities and lessen the likelihood that quality issues would develop, mitigating recalls and shortages.

Whether the idea sees the light of day is uncertain.

"All of this underscores the immense complexity of the global supply chain," said David Light, chief executive at Valisure, an online pharmacy that tests batches of medicines before shipping to customers. The company made headlines recently after alerting the FDA to traces of NDMA in ranitidine. "A rating score could be useful, but not all medicines are made equal."

"To an extent, this could be considered somewhat similar to the rating systems we have for a used car – thousands of miles have been driven, components were made in different places. And with medicines, the active ingredients and inactive ingredients can be supplied from different locations. So is the packaging. But pills are not simple products," Light said. Any system that relies primarily on self-reporting might not capture enough of the potential quality problems.

Ultimately, Gortler argued that regulators need to test each batch of medicines and ingredients arriving in their respective country. And incentives are needed to somehow increase manufacturing in countries where production standards and concurrent oversight lessens the risk of quality problems. "We should bring drug manufacturing back to places like the US," he said. "But that's easier said than done."

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From Human To Machine: AI And RPA Are Kick-Starting Productivity To Fuel Medical Breakthroughs

The life sciences industry is barreling toward a breaking point. Productivity is in long-term decline, generics are cannibalizing blockbuster drugs and regulators are applying new pressures. Something must change quickly to turn the industry around.

Faced with these challenges, forward-thinking companies have recognized that artificial intelligence (AI) and robotic process automation (RPA) are ready and able to transform their operations. Automation Anywhere, the world's most widely deployed, intelligent Digital Workforce platform, is facilitating these improvements.

The improvements cannot come soon enough. Deloitte calculates the cost of bringing a new drug to market increased from $1.2bn in 2010 to $2.2bn in 2018.[1] From 2010 to 2016, pharma R&D spending in the US increased by 29%.[2] Returns on these investments are under threat. Patent expirations will expose biologics, with sales of $194bn, to competition from 2017 to 2022.[3]

Medical device companies have other problems, such as the need to spend billions to adapt to legislation that "significantly modifies and intensifies the compliance requirements."[4,5] Such problems are created or exacerbated by the use of skilled staff on low-value processes. By one estimate, 40% of biopharma R&D costs are tied to paper-based processes.[6]

The problems continue once products come to market. Pharmacovigilance, the monitoring of safety post-approval, accounts for 11% of all R&D spending, in part because of its administrative burden.[2]

WHY AI AND RPA ARE A GOOD FIT FOR LIFE SCIENCES

These trends cannot continue. If the life sciences industry is to thrive, it must swiftly control costs and improve productivity. Ideally, the approaches will also improve quality. That is a tough set of criteria to meet. Yet, there is a large body of evidence showing technology available today can clear that high bar.

Boston Scientific, Eli Lilly and other companies have run pioneering projects proving AI and RPA enable transformative change, driving down costs while improving accuracy and freeing up staff to perform higher-value work.

RPA bots emulate staff by executing manual, repetitive tasks and making decisions. Companies tailor bot capabilities to their needs, assigning some bots to limited, rule-based activities while empowering others with AI so they learn and manage semi-structured data. The breadth of capabilities possessed by bots and their ability to automate processes involved in any system or application mean they can help across the value chain, from drug discovery to regulatory compliance.

That broad applicability of the technology is evident in the real-world use of intelligent automation. Working with Automation Anywhere, Boston Scientific initially looked to intelligent RPA to improve four processes involving a device used to read a cardiac implant.[7] The processes were performed manually or impossible to handle before RPA.

Now, Boston Scientific has a bot that monitors an email address related to the device and notifies the inventory team when it receives a request, facilitating timely responses and deliveries to customers. Other bots upload transmission summaries to support billing, inform sales staff of device inventories and periodically produce invoices using data from an SAP enterprise resource planning system.

The ease and speed with which bots can be deployed enabled Boston Scientific to quickly put an intelligent RPA system in place. The company has since deployed bots to automate more than 50 processes, resulting in zero errors and savings of $240,000 a year.

AI and RPA are also transforming biopharma companies. Eli Lilly, for example, used intelligent bots to automate payment confirmation and notification letter processing in Japan, saving $1.5m and 3,850 hours and encouraging it to automate more complex, highly regulated job functions.[8]

Such quantifiable benefits are only part of the story, though. AI and RPA also improve the working lives of human employees by eliminating the robotic parts of their jobs. That change frees people to apply their creativity to important, high-value work such as development of the next wave of medical breakthroughs.

HOW TO GET STARTED WITH AI AND RPA

Life sciences companies can start making their employees' lives better today. With 3,500 customer entities and 1,900 enterprise brands using its solution, Automation Anywhere is well placed to help companies get started with AI and RPA, guiding them past potential barriers and ensuring they quickly start realizing the benefits of automation.

"Our intelligent RPA technology helps you save time and resources to accomplish goals like no other automation technology

we've ever seen. As a result, our customers in life sciences are experiencing unprecedented success and faster time to market," Catherine Calarco, senior director, industry strategy and marketing for life sciences at Automation Anywhere, says.

Some companies leap into RPA, leveraging the experience of specialists such as Automation Anywhere to roll bots out in weeks to address urgent needs before tackling other processes in a more measured manner. This approach has proven successful, both in addressing the urgent problem and in leading to long-term, large-scale use of RPA.

Yet, for companies that have the time, Automation Anywhere's experience shows there are benefits to planning. By engaging multiple teams early, a company can address employee concerns, overcome conceptual barriers and establish an implementation model tailored to its circumstances. Assigning a senior employee with influence over the budget as an RPA champion ensures the use of bots is supported by groups across the organization and aligned with their needs.

Planning enables rigorous vendor selection, too. Companies should assess whether the vendor will innovate as technology advances, is able to deliver enterprise-grade security and can provide intuitive software so staff can create and run their own bots.

The next step is to identify initial use cases. Companies should avoid low-risk, low-reward projects as they fail to provide the evidence needed to support widespread RPA use. Rather, businesses are best served by targeting high-value processes that touch multiple major systems and tracking predefined markers of success, such as cost savings, increased compliance and higher productivity.

Generating proof of concept in a high-value process tests business case assumptions and validates the implementation model, positioning the organization to start a wider pilot test before moving into the scale-up phase. Ultimately, organizations reach a point where AI and RPA are embedded in their culture, making intelligent bots a go-to option for manual tasks and workflows and thereby freeing employees to do higher-value work.

A fast-growing number of life sciences companies have been through this process and are reaping the rewards. Now is the moment for the rest of the industry to follow their lead and begin the digital transformation needed to thrive in the face of rising costs and commercial pressures.

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The Drug Hunter's Assistant: Accelerating Drug Discovery With AI

The hype around artificial intelligence has been deafening in recent years, but real progress can only come when drug discovery culture and regulators catch up with the technology.

Excitement about the potential of artificial intelligence (AI) to transform drug discovery has been building for several years. Millions of dollars have been poured into AI-based drug discovery start-ups in the US, Europe and beyond, who are all racing to reach the first true proof-of-concept for the approach.

Big pharma has also been investing in the field, both internally and in partnership with new AI-focused platforms. There is no doubt that AI in drug discovery has become one of the most hyped technologies in the sector. What the field needs is evidence of concrete proof and 2019 saw two companies lay claim to a major milestone: the first AI-discovered drug.

But before looking closely at those claims, let us consider the very real and pressing need for greater productivity in biopharma R&D. The return on investment in R&D is rapidly deteriorating. A report in 2018 from consultancy group Deloitte, calculated that the average cost of R&D for the top 12 biopharma companies was $2.17bn per drug – double the $1.19bn calculated in 2010. At the same time, the average forecast peak sales per late-stage asset declined to $407m in 2018, less than half the 2010 value of $816m. As a result, the expected return on investment declined from 10.1% in 2010 to 1.9% in 2018.

Improving the efficiency and cost-effectiveness of bringing a new drug to the market, which still takes 10-12 years, is of critical importance. The promise of AI is clear – it could help sift through vast amounts of data far quicker than traditional automated and manual processes, cutting down the time to drug discovery and lead optimization. But can AI really fulfill this promise, and contribute to greater productivity across the full research continuum? And what is the best strategy for the industry in integrating AI into its R&D organizations?

AI MILESTONES

Oxford, UK-based Exscientia Ltd. was the first of two companies to make a breakthrough announcement in 2019. In April, the company declared it had delivered its first selective and potent in vivo active lead molecule to partner GlaxoSmithKline PLC.

Exscientia said the molecule, targeting a key pathway for the treatment of chronic obstructive pulmonary disease (COPD) had been discovered with five cycles and only 85 compounds tested – far fewer than in conventional drug discovery processes. Andy Bell, chief research officer of Exscientia, said: "Our AI platform and approach have advanced significantly over the past few years and have been constantly refined and optimized through real-world projects for our pharma partners. With the productivity improvements we are seeing, we believe that our Centaur Chemist approach is proving itself to be the industry's leading AI-drug discovery platform by achieving far superior results to what conventional discovery techniques have historically delivered."

Then in September, Toronto, Canada-based Deep Genomics declared a similar achievement. The group announced that its AI-based drug discovery platform had identified a novel treatment target and corresponding drug candidate for Wilson disease, a rare and potentially life-threatening genetic disorder. "This is an important milestone for patients affected by Wilson disease and it represents a significant advance in the drug discovery community more broadly," said Brendan Frey, founder and CEO of Deep Genomics.

Frey said the company's researchers had identified a genetic mutation that causes the disease within 18 months, as well as the chemical properties needed in a molecule to target the mutation, and a compound that warrants further investigation. Deep Genomics will develop the candidate, DG12P1, for the treatment of patients with Wilson disease who harbor a genetic mutation that impairs the body's ability to remove copper, which can cause life-threatening organ damage.

Frey has specialized in combining machine learning with genomic biology research over the last 15 years and set up Deep Genomics three years ago. One of its chief advisors is Arthur Levin, current executive vice president of R&D at Avidity Biosciences and a drug development veteran of more than 30 years. "Our expectation is that, going forward, Deep Genomics' platform will enable them to go from known target to first patient dosed in less than half the time of the industry standard, and they may be able to do this even faster with subsequent programs," said Levin. He added:

"Developing new therapeutics is full of unknowns, but I am certain that we are witnessing a new era of drug discovery."

THE DRUG HUNTER'S ASSISTANT

Of course, Exscientia and Deep Genomics are just two of the dozens of firms working in AI-based drug discovery, and more announcements like these are sure to follow in the coming months.

While claims about reaching this milestone naturally have to be taken with a pinch of salt, they are nevertheless evidence of progress in the field. At the recent FT Global Pharmaceutical and Biotechnology conference in London, a panel of experts in the field convened to discuss the state of progress. Badhri Srinivasan, head of global development operations at Novartis AG, is an exponent of AI in R&D, but nevertheless wanted to put claims about machine learning-discovered drugs into context.

At the FT event, Srinivasan said AI was augmenting the existing decision-making process, not simply replacing it – making it not the drug hunter's master, but more his or her assistant. "It's the process. So [it's about] failing fast, making decisions faster, making more robust decisions, rather than AI actually helping find a drug. I think we're not at a level of maturity where we can say human intervention is not needed. Human intervention is needed."

Srinivasan added: "It's the intersection of humans and machines where the most innovative things will happen." Still, he cautioned that there was much progress to be made, including a change in drug regulator's rules, and in pharma's own culture.

"I think there's also the ecosystem that has to come along, i.e. the regulators bringing other constituents along on this journey, which is a big task in itself," Srinivasan said. There are many substantial issues that are currently holding back progress towards creating a truly data and AI-driven biopharma industry.

DATA INTEROPERABILITY

Interoperability refers to how easily, or otherwise, a range of systems and data silos can exchange data. It is one of the biggest stumbling blocks within health care systems looking to provide joined up care based on electronic patient records, but also in biopharma companies. The industry needs to pool its knowledge, gathering diverse datasets to inform drug discovery and development, and other functions, to unlock the potential of AI.

Developing interoperable systems across global operations and being able to collect high quality data from clinical trials are huge tasks for the sector – but these activities are essential. AI-enabled systems will not be able to support high quality decision-making if they are being fed low-quality, fragmented datasets in the first place.

One company that has identified this need to generate the very best and most interoperable data is Roche. It has gone down the M&A route to bolster its in-house data expertise, buying up electronic health record specialist Flatiron Health for $1.9bn and spending $3.4bn on genomics and personalized medicine-focused Foundation Medicine. It is now implementing a company-wide approach to validating its data, highlighting the need to work towards having Findable Accessible Interoperable Reusable (FAIR) data.

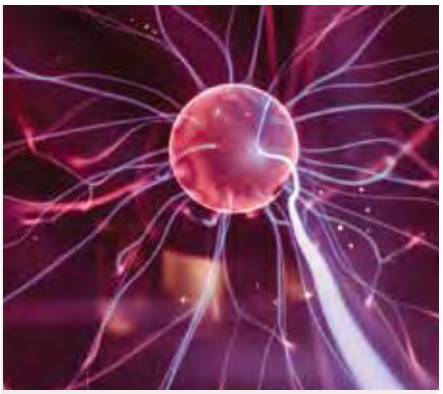
Reservations around the AI hype has lead to a variable uptake of the technology in drug discovery across the industry. Jackie Hunter, chief executive, clinical and strategic partnerships, at UK-based BenevolentAI, confirmed that some big pharma companies had been more enthusiastic about AI's potential than others. "There are companies like AstraZeneca PLC and Novartis who have made digital and AI absolutely core to their success going forward. And there are others that are kind of dipping their toes in the water," she said.

Hunter said the pharma sector was over the worst of the AI-hype, but many industry leaders still want more evidence that it can bring major benefits to R&D productivity.

CHANGING THE R&D CULTURE

Srinivasan highlighted that many in big pharma were still wrestling with how to integrate AI into their R&D organizations. "I think it's a struggle to say 'How should I do this? What does this mean? What model should I used to work with nimble start-ups or smaller companies – and how can I create that environment in-house?'"

He said an experimental field such as AI in drug discovery would inevitably bring some early failures and disappointments



NOVARTIS AND MICROSOFT STRIKE AN AI ALLIANCE

Novartis is also investing heavily in following up on its pledge to "reimagine medicine" by becoming a "data-driven" company. In October 2019 it unveiled a major new collaboration with Microsoft to allow data to flow more easily within its organizations, applying AI and new computational power to a huge range of business challenges.

The Microsoft alliance will start with a few targeted projects: helping to develop personalized therapies for macular degeneration, as well as projects in cell and gene therapy and drug design.

More broadly, the alliance will focus on two core objectives, called AI Empowerment and AI Exploration. Novartis said AI Empowerment will be led by its new AI lab, which will "bring the power of AI to the desktop of every Novartis associate." This will involve bringing together a huge range of isolated datasets across Novartis using Microsoft platforms. This will allow new AI models and applications to be developed to "augment" the work of employees across different disciplines.

Meanwhile, AI Exploration will focus on the hardest computational challenges in life sciences drug discovery and development. Novartis said this will begin with "generative chemistry, image segmentation and analysis for smart and personalized delivery of therapies, as well as optimization of cell and gene therapies at scale."

> *"The difference between a problem a computer can solve and one it can't is a very thin line."*

– but these should be seen as part of the process, rather than a sign that AI drug discovery is fundamentally flawed. "That's part of a failure cycle that should happen. That's where I think the ability to understand that [in pharma] is still maturing."

WHAT AI CAN AND CANNOT DO

Andrew Radin, co-founder and CEO of AI specialists twoXAR, was also on the FT conference panel. He indicated that in order to get the most from AI in drug discovery, there needed to be a sound understanding of how to frame the tasks given to it. He said this required integrating biomedical informatics into the drug discovery organization. "Having separate biologists and computer scientists is a real challenge."

Radin said, "If a biologist goes to a computer scientist and says 'Here's a question I have, what's the answer?' that's not optimal because computation is very complex. The difference between a problem a computer can solve and one it can't solve is a very thin line. If you change the definition just a little bit. It goes from impossible to trivial."

He added: "I'm a trained computer scientist, studying biomedical informatics. That's just a fancy way of saying using computers to solve medical problems ... On our team, we have both of those capabilities in that lead science team. And so we're thinking about it from the perspective of not what's the biological question I want to answer, but as a computer scientist." Radin said this was an approach that allows the company to get the most from the technology.

Andrew Garrett, executive vice president scientific operations, ICON, said navigating a way through the hype and inflated expectations of what AI can do is itself one of the biggest challenges. Making a slightly tongue-in-cheek comparison, he said there was a danger of "digital obesity" i.e. where the industry indulges too much in digital innovation without balancing out its "diet" of organizational change and management. "You need to have the right amount of AI, the right tool, but not so excessive. On the one hand, you have to be an evangelist. On the other side, you have to be a healthy critic, and it's trying to get that right balance."

REGULATORY GUIDANCE

The industry is now looking to regulators, in the US and Europe particularly, to address uncertainty about how to use AI tools within drug development and to develop a regulatory framework and standards.

In April 2019, then-FDA commissioner Scott Gottlieb launched a consultation on how to update regulations on medical devices that use AI. The US regulator approved the first ever such device in 2018, IDx-DR, developed by IDx, which helps detect diabetic retinopathy earlier than can be diagnosed by humans. Since then, around 30 devices have been added to the list, including the electrocardiogram (ECG) technology in Apple Watch Series 4.

This could lead to the FDA creating a pathway for formal qualification of AI-based drug-development tools to ensure they meet agreed standards.

The FDA is considering a "total product lifecycle-based" regulatory framework for AI technologies, allowing for modifications to be made from real-world learning and adaptation, while still ensuring that the safety and effectiveness of the software as a medical device is maintained. The consultation closed in June 2019, and the regulator is expected to announce initial conclusions in 2020.

DRUG DEVELOPMENT

As the first "AI-discovered" molecules enter clinical trials over the next few years, the ultimate test will be just how much the technology contributes to upping the overall efficiency and hit rate.

Many companies are now also exploring how AI could help them make better decisions in their clinical trial programs. This ranges from improving trial design and patient recruitment to analysis of trial results and real-world evidence, and many other applications.

Despite all the obstacles, limitations of AI, and indeed hype, there is no doubt it will play a central role in the future of biopharma R&D. The adoption of the best technologies, twinned with an organization's ability to integrate AI and adapt its culture, will be a competitive advantage.

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Global Health Systems Are Learning To Embrace AI As A Force For Good

ASHLEY YEO
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The term artificial intelligence was coined at the Dartmouth Summer Research Project in 1956, but it is only in very recent years that it has been consistently at the top of the agenda in discussions on the future direction of health care. As a tool to improve both the quality and speed of care, AI is now increasingly seen as a realistic solution to the demand overload on clinicians. At the same time, techno-fears are abating. This confluence will transform health care radically in the next two decades.

"AI will change the world of health care." So said Siemens Healthineers AG CFO Jochen Schmitz, addressing a room full of investors at the Jefferies Global Healthcare Conference in November 2019. The IVDs and imaging group had posted comparable 2018-2019 sales up 5.8% that same month, and Schmitz was looking ahead to future reporting periods when AI would be having a clear and identifiable influence on revenues. "The health care industry can and will benefit from digital and AI, and imaging and radiology are the clear and obvious doors of entry for AI," he said.

The requirement for support for physicians during radiological routines is compelling: with more patients needing more examinations and CT images, clinical staff are prone to being overloaded, and tight turnaround times and fatigue can lead to anomalies being overlooked. Artificial – or augmented – intelligence, on the other hand, works at a constant level of performance. Predictable and reliable, it can offer certainty to physicians who are used to manually scanning data sets of fifty to a thousand images in a single CT for abnormalities.

At its most simple, AI has the potential to improve efficiency, reduce cost and/or deliver better products and services. National health care systems are broaching how to integrate machine learning and AI into health care delivery either locally, as seen in the newly-unveiled NHSX in the UK, led by Matthew Gould; or supranationally, as described in German health minister Jens Spahn's opening address to the 11th World Health Summit, on October 27, in Berlin.

There, Spahn spoke of the need to implement, at national level, the "Global Action Plan for healthy lives and well-being for all." The plan was launched in September at the UN High-Level Meeting on Universal Health Coverage in New York. Germany will assume the EU presidency in the second half of 2020, and its main focus will be "digitization, big data and AI." In Germany, Spahn – who has not concealed ambitions of one day being German Chancellor – will harness the ongoing digital revolution, making the electronic patient record available across the population by 2021. He will also implement telemedicine and AI capabilities to improve health in under-served regions.

ETHICAL AND LEGAL CONSIDERATIONS

The core ethical issue with AI and big data is how to make the best use of it for both the individual and wider society, while ensuring that the patient retains choice and control. Publicly funded, national health care systems should be able to embrace AI affordably and effectively for the broader population, but crucially, individuals' rights to privacy are paramount. This has led to much soul-searching over how fast and how far patient data can be used, as the AI wheel picks up pace.

AI-based patent filings have risen rapidly, especially in the US and Asia. In the EU, the European Patent Office (EPO) in 2018 included a section on AI and machine learning in its Guidelines for Examination, with advice on how to assess AI patents. Law and tax firm CMS notes that AI inventions are subject to the same criteria as any other inventions implemented by computers. But it is a learning curve for AI patent assessors just as it is for health care stakeholders: they must reflect on whether such inventions satisfy novelty in terms of patentability. Applicants seeking patent protection in the EU need to establish a causal link to technical purpose.

AI has already been applied in major disease areas, such as cancer, cardiology, neurology, and stroke – where wearables are being used to recognize the movements of a person undergoing a stroke. The liability issues in cases where an AI-supported assessment is inaccurate, or when algorithms produce false positives and negatives, need to be broached. One huge question is: how should cases where no human is at fault be handled?

AI solutions research is not confined to the larger

companies, and hard-to-treat neuro diseases are a particular sweet spot for the small and medium enterprises as well as start-up innovators. For instance, there are still no effective therapies available to slow the progression of Alzheimer's disease, yet there is realization that new ideas are needed. Better-targeted success has been an aim in neurological disease clinical trials for some time, and AI could be key in meeting that challenge.

INNOVATION IN MEDTECH SPACE

While it is clear that governance is needed to create a trustworthy framework for digitization of the system where AI is a major component, especially with regard to data availability and ownership, these apparently thorny issues have not dissuaded the medtech sector, where a lot of innovation is underway.

IVD major Roche – the world's 10th leading medtech group by sales in 2018 – is paving the way in unlocking the potential of AI to develop truly personalized health care. The group believes that the industry is at a pivotal moment, with the real convergence of medical knowledge, technology and data management science. It is combining data from multiple sources and using machine learning to further its understanding.

AI is already used in diagnostics, imaging and pathology, but some very recent cases reported in *In Vivo* and sister publication *Medtech Insight* show where pioneering companies are rolling back the barriers across medtech. They include:

• Abbott Laboratories Inc.'s myocardial ischemic injury index (MI3) AI algorithm, to risk-stratify patients with suspected myocardial infarction. Using gradient boosting, doctors can get a better estimate of the probability that a patient is having a myocardial infarction than with cardiac troponin testing alone.

• Medtronic PLC's GI Genius, an AI-enhanced endoscopy system for recognizing pre-cancerous polyps. The system's algorithm was validated with a data set of white-light endoscopy videos. It acts as a virtual second observer during the endoscopic exam by detecting anomalies of the intestinal mucosa in real-time. The endoscopist is alerted to anomalies via an on-screen visual marker and alarm.

• Ixico Ltd.'s work on neuroimaging methods that provide more accurate and richer brain structural and functional information. The company can also capture, analyze and measure digital biomarker data supplied by wearable biosensors or mobile devices. These are for parameters such as sleep, activity and heart rate. (*Also see "IXICO Targets Go-To Status In Neuro Data Analytics Space " - In Vivo, 25 Mar, 2019.*)

• Cognetivity's sensitive visual categorization platform that uses advanced AI algorithms to cluster test neurological disease patients' performance in terms of accuracy, speed and image properties. Its test can predict dementia up to 20 years before symptoms appear. (*Also see "A 'Blood Pressure Test' For Dementia" - In Vivo, 17 Jun, 2019.*)

WHERE TO NEXT?

Precisely where medtech's association with AI is going in the coming five years was the theme of a panel discussion at the 2019 Medical Design & Manufacturing East (MD&M East) meeting, in New York City. Johnson & Johnson delivered the view that sensors and wearables are clearly a huge opportunity for the medical device industry, but the question is how to develop technologies that take advantage of the data that devices such as FitBits and Apple Watches deliver. J&J collaborates with Apple in research on the use of wearable technology on early detection of atrial fibrillation.

AI can be used in all areas of work, from the disruptively innovative to the more prosaic, such as ensuring health care staff clean their hands before and after touching patients. This particular project is owned by Radius Innovation, which used an AI application to synchronize the number of hand sanitizing events across a hospital, resulting in proactive uptake and more hand-washing. *(Also see "Medtech's AI Pioneers – Where Are We Headed?" - Medtech Insight, 21 Jun, 2019.)*

Regulatory pathways for AI-based devices have been the focus of US FDA attention, which sees the compliance landscape as continually evolving as technology advances. That, and reimbursement, are huge outstanding issues for an industry that once again is seemingly ahead of government and central decision-makers on pivotal medtech market access themes. But clearly, AI comes under the headings of "value generation" and "reduced overall health system burden." The theory is that driving for better outcomes and cost-effectiveness at an early stage early will deliver a clear-cut value proposition.

AI DEFINED

Just as there is no single definition of what digital health care comprises, the parameters for artificial intelligence are equally difficult to establish. In its recent "AI in Life Sciences" compilation, law and tax firm CMS suggests that, for a program to claim AI capability, it should demonstrate behaviors associated with human intelligence, such as planning, learning, reasoning, problem-solving, knowledge representation, perception, motion and manipulation. It also involves, to a lesser extent, social intelligence and creativity. AI covers a number of technologies, primarily machine learning, deep learning, neural networks, natural language processing and computer vision.

THE FIELD OF PLAY

Generically, AI has many applications in health care for reducing costs and improving outcomes. But the industry is not free to move as quickly as other industries in AI adoption. The notions as to why include: many other economic sectors are profit- not budget-based, and do not partner so intensely with government departments on decision-making; the volumes of data needed are so much greater in health care than in other industries, and, for physicians, too much data can also be as big a hurdle problem as too little; there is a greater cost and higher risk of failure in health care, likely affecting downstream investor decisions; life-and-death decisions, or at least quality of life, are the central and the day-to-day remit in health care; and health is personal, and wellness is an intangible that has a purely subjective value and cannot be resold.

Nevertheless, according to CMS' AI In Life Sciences report, the list of areas where

AI can have an impact is impressive:

- Accurate personalized medicine – where AI platforms can "interrogate" the patient to determine the therapy that will have the greatest chance of success.
- Patient records – where natural language processing tools can ensure information is captured in a standardized way, allowing better understanding of the risk of future illness in a patient, based on historic health data.
- Real-world evidence – which is being used to enable health system to pay for therapies based on outcomes, and also reducing waste.
- Image recognition – an early AI success in the making.
- Supply chain and logistics automation – where forecasting tools enable manufacturers to plan production volumes around predicted demand.
- Data tracking of patients' vital signs to apply tailored doses of therapy, such as insulin pumps that monitor blood glucose levels and inject insulin when needed.
- Clinical trial design and data interpretation assisted by AI, for more efficient clinical trials.
- Drug candidate selection and remodelling of therapies while they are on the market.

WHAT ABOUT THE HUMAN FACTOR?

As little as 1-2 years ago, the approach of AI into health care routines was met with a modicum of fear on the part of providers and physicians. Augmented intelligence was being used as a more acceptable description of a technology that clinical staff suspected would be either making them unemployed or dictating their day-to-day agenda. Those notions are now seen as exaggerated, and a new confidence – or at least acceptance – has tended to suffuse the sector, which is now generally aware of the huge benefits and that clinical jobs are not the target sights of AI.

Studies show that if physicians have 50% less time to evaluate medical images, error rates rise by 17%, according to Siemens Healthineers' global marketing manager for AI, Ivo Dreisser. Interviewed for the medica.de portal ahead of the 2019 Medica conference (November 18-21), Dreisser said that physicians become faster and more accurate by replacing manual image analysis with AI analysis. AI saves 5-10 minutes per patient, and, moreover, AI automatically examines not just the target organs, but the wider area around them and coronary vessels, for example.

Physicians are now finding support from AI to be very helpful. Algorithms don't tire of doing the same thing time after time. AI can also be used to train staff in new skills.

US-based gastroenterologist Michael Wallace said of AI in fall 2019 that the technology has come to help, and it was important to recognize that it was not going to replace gastroenterologists. That said, he added that there was a need to be careful so that these tools did not replace what physicians do. Crucially, "it will enable us to be better doctors, to spend more time doing a very good examination of a patient and talking with patients – things that AI will never be able to do."

The inescapable advance of AI and digital was clear to see at Medica 2019, where the Tech, Connected Health and Health IT Forums drew standing-room-only crowds to presentations on all aspects of these particular transformative elements of the evolving health care industry. As to digital, "in 20 years' time there will no longer be sectors," Techniker Krankenkasse's sickness fund deputy chair Thomas Ballast said during one panel. This was an observation that digital and AI will blur the boundaries of care settings. Rapid care delivered by digital technologies will mean an increase in day cases, Doris Pfeiffer, GKV (statutory health insurance) sickness fund chair, added. This will have positive effects on overall health system costs.

AI is fast coming into practical use in health care. Evidence of the need for this rapid and predictive tool was given by Germany's Spahn, at the World Health Summit when he observed that cancer, diabetes and heart disease and other non-communicable diseases are globally on the rise, leading to 15 million premature deaths every year across all countries. This is just one example of health care needing all the help that it can get.

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