Pharma intelligence
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Scrip 100

2018

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ICON
What if there was a way to transform the traditional clinical development model?
There is.
Much of the innovation needed to transform clinical development exists today, and enjoys explicit regulatory support.
ICON's Transforming Trials initiative incorporates a growing range of technology and process innovations to unlock value through fundamental reforms that allow sponsors to move more treatments to market faster.
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Transforming Trials: Reducing Cost and Risk

It is evident that costs and excessive risk are holding back drug development. The total sponsor cost per new drug compound approved in the US now exceeds $2.5 billion, including nearly $1.5 billion for clinical development – a significant 145 per cent jump in just 15 years, according to the Tufts Center for Drug Development. (1). However, only seven percent of first-in-human drugs gained FDA approval in the same period, representing not only great financial cost and great risk, but also a toll in human terms - high drug costs often restrict patients' access to needed therapies, leading to poorer health and possibly, financial hardship.

This inefficiency largely results from a traditional drug development system of three discrete, fixed trial phases. It lacks the flexibility, analytical power and efficiency required to develop complex new therapies targeting the smaller and often heterogeneous patient populations increasingly seen today (2). Antiquated clinical trial processes can slow drug development and force abandonment of promising drug candidates when development costs exceed projected revenues.

Bending the drug cost curve requires more than efficiency gains: we must remove risk from the process entirely. Much of the innovation needed to transform clinical development exists today, and enjoys explicit regulatory support. ICON is addressing this need through our Transforming Trials initiative. This comprehensive rethinking of the entire clinical trials process uses new approaches coupled with existing, tested technologies to substantially reduce the risk and cost of clinical drug development.

DRIVING CHANGE WITH BIG DATA

Big data insights play a major role. For example, developing study protocols with patient inclusion criteria that are shaped by actual

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patient data, automatically harvested from EMRs, reduces the risk of launching a study with unrealistic patient recruitment potential. Access to de-identified live patient data also reduces recruitment costs by knowing how many patients match a trial protocol and where they are located. Automated site monitoring greatly reduces site management costs while ensuring that data are properly collected and validated – reducing the risk and cost of patients lost to protocol deviations.

Remote data links enable data collection directly from patients at home. This not only reduces the number of costly interim office visits required for a trial, it can yield valuable insights into how patients respond to therapy 24/7 in the real world. EMR data allow automated post-market surveillance in Phase IV trials that can vastly expand study populations while actually lowering costs.

Rapid data collection and processing make possible mid-trial insights that support planned adaptive trial changes. These might include homing in on the most effective dose, or enriching a later phase sample with patients who are more likely to respond, or increasing or decreasing sample size to accommodate a drug that has a larger or smaller therapeutic effect than predicted. Real-time data validation technologies support quick data lock for interim analysis and protocol revisions, which is a requirement for successful adaptive design trials.

HARNESSING ADAPTIVE DESIGN

Adaptive approaches also are more efficient and are encouraged by regulatory agencies in Europe and the US. They can be used at every phase of clinical drug trials: modifying study protocols in predetermined ways based on interim patient data and have the potential to eliminate many unanticipated risks that undermine efficacious drugs and unnecessarily extend development timelines. In a single two-year combined Phase II/III trial, adaptive trials can often deliver information that might otherwise require three or more consecutive conventional trials over three or more years. These seamless trials reduce the total sample size needed by using the same patients in more than one stage. We estimate that optimal use of adaptive trials across a portfolio could reduce trial costs by 25 per cent. ICON has successfully designed and executed almost 200 adaptive trials and has an international staff capable of translating and validating patient-centric trial protocols anywhere in the world.

RADICAL PATIENT FOCUS

Improving patients' lives is the ultimate goal of clinical trials. Insight from real-world data supports everything from defining outcomes that matter most to patients, to offering trials to patients identified through EMR in their physicians' office, to minimising control arms using advanced statistical methods and providing study results as soon as they are available.

All of these innovations are already in use sporadically, and their individual potential proven. When implemented fully in a systematic way, we believe they could significantly cut clinical trial costs and reduce time to market by months, if not years.

Expertise in each area, as well as excellent change management skills, are required to fully implement this reimagined clinical trial process. What will make it all worthwhile will be the accelerated delivery of more new drugs to market, saving and improving more patient lives.

www.iconplc.com/transform

1 DiMasi et al., Tufts Center for the Study of Drug Development, 2014
2 Jones DS et al. The Burden of Disease and the Changing Task of Medicine. N Engl J Med 2012;366:2333-2338 June 21 2012, DOI: 10.1056/NEJMp1113569

John Hodgson
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Sales Up, Profits Down – But Is It Real?

Bellwethers tell you something, but to gauge the health of the pharmaceutical industry, you really need the Scrip 100. For FY 2016, it looks like drug sales are up again and profits are down. But is this what's actually going on?

The Scrip 100 examines the financial performance of all companies that sell more than $1m worth of prescription drugs or spend more than $1m on drug-related R&D. Confusingly, the universe of companies we looked at for FY 2016 is more Scrip 1000 than Scrip 100: it encompasses 659 companies (from over 750 researched), mammoths-to-minnows, generics to gene therapy, from Slough to Summit, AB Science to Zynerba Pharmaceuticals, from Seoul to Rockville.

To make things simpler, this introduction focuses on the one hundred companies that make the most revenue from selling prescription drugs, the Scrip 100. Think of the Scrip 100 as a *pro forma* merger of all the world's biggest drug producers (and then breathe out as you imagine the CEO's salary).

Taken together during 2016, the Scrip 100:

- made drugs sales worth nearly $719bn (up 5.8% from $679bn in 2015);
- spent $135bn R&D (up 6% from 2015);
- made $141bn in net profits, down 10.3% from 2015; collectively, their net profit margins fell from 17.8% of sales to 14.8%.

The Scrip 100 is a proxy for the pharmaceutical industry. The 100 companies account for 94% of drug sales ($m), 86% of pharmaceutical R&D and 89% of the employees in the 659 companies in our universe.

Assume that you have friends. More particularly, assume your friends don't work in the pharma industry. To help you convey the magnitude of the industry to these odd people, we have measured the aggregated Scrip 100 in units that are corporate household names.

Thus, for 2016 sales, the Scrip 100 equals Volkswagen, Daimler, General Motors and Ford.

Similarly, for R&D, it spent four times as much per year as those four motor manufacturers and twice as much as Alphabet, Samsung, Apple, Microsoft and Amazon put together.

And for profits, the group of top 100 pharmaceutical companies is equivalent to two-and-a-half Apples, 10 Walmarts or 15 Nestlés.

What's more, the top-slice of the drugs industry makes its money intensely. Each employee in the Scrip 100 generates, on average, nearly $500,000 in revenue and $70,000 in net profit. Walmart employs slightly more people than the Scrip 100 companies (2.3 million versus 2.0 million) but each employee brings in 40% of the revenue ($210,000) and 10% of the profit ($6,400) than staff in the pharma set do. Pharma is far less intense than Apple though, which made $450,000 profit per employee in 2016. A few pharma companies did outperform the iPhone maker – Gilead Sciences Inc. and Celgene Corp. made profits per employee of $570,000 and $630,000, respectively.

COMPARISONS WITH FY 2015

The Scrip 100 headline figures seem to be saying that pharma had 6% higher product sales in 2016 than in 2015 but still ended up making less profit. Its profit margin fell from near 18% to below 15%.

So, is pharma working harder but getting squeezed, or is this an oversimplification? More importantly, are the growing drug sales or shrinking net profits real, or a systematic error within our analysis?

At Scrip, we are convinced that the numbers reflect pharma's reality.

Firstly, 96 members of the Scrip 100 group for 2016 are the same companies covered for 2015.

Four companies dropped out of the list in 2016, and four replaced them. Hanmi Pharmaceutical Co. Ltd. of South Korea and India's Torrent Pharmaceuticals Ltd. were hit by the simple phenomenon of falling drug sales. Hanmi downgraded an arrangement on selling third-party drugs in Korea, while Torrent fell back as its US drug revenues halved after the exclusivity period for an abbreviated new drug application expired in 2015.

Two other, bigger companies went missing in 2016 – Baxalta Inc. and Meda Pharmaceuticals Inc.; they were acquired, respectively, by Shire PLC and Mylan NV during 2016.

Four companies replaced the outgoing firms: Alvogen Inc., Horizon Pharma PLC, Hong Kong's CSPC Pharmaceutical Group Ltd. and Incyte Corp. Alvogen made the list after its acquisition of Country Line in March 2016 added around 25% to its drug revenues. Horizon's

TABLE 1: SELECTED DEALS AND THEIR IMPACT ON SCRIP100 DRUG SALES

ACQUIRER	ACQUIRED ASSET	APPROXIMATE VALUE OF 2015 DRUG SALES ACQUIRED	IMPACT ON SCRIP 100 DRUG SALES TOTAL	REASON
Teva	Allergan generics	$4bn	None	Both companies are in Scrip 100
Shire	Baxalta	$6bn	+ $800m	Merger allows another firm into the Scrip 100
Mylan	Meda	$1.4bn	+ $800m	Merger allows another firm into the Scrip 100
Pfizer	Bind Therapeutics	$0	None	Asset has no drug sales
Concordia Healthcare	Amdipharm Mercury Ltd.	$400m	None	Merger leaves Concordia below the Scrip 100 threshold
Eisai Co. Ltd.	Ajinomoto Co. Inc.'s GI portfolio	$300m	+ $300m	Ajinomoto outside FY 2015 Scrip 100
Nichi-Iko Pharmaceutical Co. Ltd.	Sagent Pharmaceuticals Inc.	$318m	+ $318m	Sagent outside FY 2015 Scrip 100
Takeda Pharmaceutical Co. Ltd.	Ariad Pharmaceuticals Inc.	$112m	+ $112m	Ariad outside FY 2015 Scrip 100

acquisition of Raptor Pharmaceutical Corp. in October 2016 nudged it over the Scrip 100 threshold – $800m well spent! CSPC sales of innovative drugs increased 26% to push it forwards. And Incyte's combined sales of *Jakafi* (ruxolitinib) in the US and *Iclusig* (ponatinib) in Europe grew 47% in 2016.

These changes in the Scrip 100 list make very little difference to the overall sales and profits totals. Replacing Baxalta, Meda, Hanmi and Torrent with Alvogen, Horizon, CSPC and Incyte adds $1.7bn to the annual revenue total, only a fraction of the year-on-year change.

IMPACT OF M&A

Is merger and acquisition a source of year-on-year variability within the Scrip 100? The answer, perhaps surprisingly, appears to be "no, not really."

Mergers between two companies that are both already in the Scrip 100 has little impact. The drug revenue streams of acquired companies such as Baxalta and Meda – around $7.5bn between the two – remain in the Scrip 100 universe, as part of the acquiring companies, Shire and Mylan, respectively in these cases (*see Table 1*). Sales from two companies are compacted into one, thereby allowing the company previous sitting at #101 to enter the Scrip 100 at #100.

Likewise, asset reshuffles between two Scrip 100 companies, do not perturb the system. The sum of drug sales remains roughly the same whether Allergan PLC or Teva Pharmaceutical Industries Ltd., or Mylan or Abbott Laboratories Inc. owns this or that set of generic compounds.

Similarly, any acquisition by a big company of a company without drug sales will have no effect on drug sales totals within the Scrip 100. Pfizer Inc. could acquire a Medivation Inc. or a Bind Therapeutics Inc. many times over with no immediate increase in its drug sales.

Indeed, the only M&A deals that directly affect drug sales totals are those which see a company outside the Scrip 100 (roughly speaking, those with drug sales below $800m a year) merging with a larger firm. Each of those deals could add, by definition, a maximum of $800m into the drug sales pot.

In summation, M&A and asset acquisition can only account for only $2-3bn of the $39.2bn 2015 to 2016 increase in drug sales across Scrip 100 companies. This suggests that the real annual growth in drug sales in 2016 was about 5.3% of the 2015 total.

ARE PROFITS REALLY DOWN?

So, the 5.3% rise in drug revenue is real.

But what about the 10.3% drop in net profits, from $157bn in 2015 to $141bn in 2016? Does that reflect an industry-wide squeeze?

FY 2016 was certainly a tough time for many companies in the generics sector. Concordia, Valeant Pharmaceuticals International Inc., Endo International PLC and Perrigo Co. PLC each registered significant net losses (amounting to $11.5bn between them) while Teva's profit fell 80% and Mylan's over 40%.

Many of those losses or reductions in profit could be attributed to "exceptional" events; they are due to impairments of acquired assets or development programs (if you allow that asset impairment is exceptional among companies that habitually grow through acquisition). In any case, these losses are readily offset in the Scrip 100 set by companies with profits boosted by exceptional circumstances.

The biggest exceptional changes in profitability can be traced to the GlaxoSmithKline PLC-Novartis AG asset swap in 2015. Having both registered exceptionally high net profits in 2015 (nearly $13bn for GSK and nearly 18bn for Novartis), profits fell to more usual levels ($1.4bn and $7bn, respectively) in 2016. The $23bn dive in profitability for these two companies accounts for nearly 90% of difference in 2015-2016 profitability in the Scrip 100. Pharma's profit fall in 2016, therefore, is probably exceptional; a downturn from the previous year when two major pharma companies bartered assets and both came out of it with substantial profits. Now that's how to make money.

THE WORLDS TOP 100 PHARMA COMPANIES BY DRUG SALES ($M)

COMPANY	PHARMA SALES ($M) 2016	CHANGE FROM 2015	RANK 2016 (2015)
Pfizer[1]	49,417.0	8.7%	1 (1)
Novartis[2]	42,706.0	-1.6%	2 (2)
Roche	39,693.8	2.3%	3 (3)
Merck & Co[3]	35,151.0	-2.8%	4 (4)
Sanofi	33,767.4	-0.5%	5 (5)
Johnson & Johnson	33,464.0	6.5%	6 (7)
Gilead Sciences	29,953.0	-6.8%	7 (6)
GlaxoSmithKline	27,961.2	2.5%	8 (8)
AbbVie	25,638.0	12.2%	9 (10)
Teva	21,903.0	11.5%	10 (12)
Amgen	21,892.0	4.5%	11 (11)
AstraZeneca	21,319.0	-9.8%	12 (9)
Bayer	18,166.5	19.1%	13 (15)
Eli Lilly	18,064.0	13.1%	14 (14)
Bristol-Myers Squibb[4]	17,702.0	26.0%	15 (17)
Novo Nordisk	16,610.0	3.4%	16 (13)
Takeda	14,433.0	-3.3%	17 (16)
Allergan[5]	13,348.0	10.8%	18 (19)
Boehringer Ingelheim[6]	13,316.2	7.1%	19 (18)
Astellas	12,620.7	11.3%	20 (20)
Biogen Idec	11,448.8	24.6%	21 (22)
Celgene	11,184.6	22.1%	22 (23)
Mylan	10,967.1	17.1%	23 (21)
Shire[7]	10,885.8	78.5%	24 (28)
Daiichi Sankyo	8,781.4	7.8%	25 (24)

COMPANY	PHARMA SALES ($M) 2016	CHANGE FROM 2015	RANK 2016 (2015)
Merck KGaA[8]	7,584.1	-1.4%	26 (26)
Otsuka Pharmaceutical	6,923.1	-13.8%	27 (25)
Valeant Pharmaceuticals[9]	6,437.0	-10.8%	28 (27)
CSL	5,909.0	5.0%	29 (29)
Eisai	4,873.7	7.7%	30 (30)
Sun Pharmaceutical	4,505.3	9.8%	31 (32)
Servier	4,425.0	2.2%	32 (31)
UCB	4,268.4	9.5%	33 (33)
Endo International	4,010.3	22.7%	34 (37)
Mitsubishi Tanabe Pharma	3,898.0	10.3%	35 (36)
Abbott Laboratories[10]	3,859.0	3.7%	36 (34)
Menarini	3,527.0	-4.4%	37 (35)
Dainippon Sumitomo Pharma	3,383.4	13.5%	38 (38)
Regeneron Pharmaceuticals	3,338.4	24.1%	39 (41)
Alexion Pharmaceuticals[11]	3,082.0	18.4%	40 (42)
Mallinckrodt[12]	3,018.1	5.0%	41 (39)
Fresenius Kabi[13]	2,800.2	3.9%	42 (40)
Actelion[14]	2,448.5	15.4%	43 (47)
Kyowa Hakko Kirin	2,420.7	4.9%	44 (44)
Lupin[15]	2,370.0	32.1%	45 (51)
STADA	2,367.0	0.8%	46 (43)
Lundbeck	2,323.2	7.0%	47 (46)
Baxter International[16]	2,245.0	-2.3%	48 (45)
Dr Reddy's	2,096.2	11.5%	49 (50)
Cipla	1,998.4	1.9%	50 (49)

[1]Excludes $3.407bn in OTC drugs

[2]Innovative Pharma plus Sandoz

[3]Excludes Animal Health, Healthcare Services and Consumer Care

[4]Boosted by Opdivo sales

[5]Includes 7 months of revenue from generics business sold to Teva: Excludes sales of fillers and breast Implants

[6]Prescription Medicines division

[7]Acquistion of Baxalta

[8]Healthcare segment

[9]Excludes OTC

[10]Established Pharmaceuticals

[11]$2843m revenue are Soliris

[12]Excludes oxycodone and hydrocodone API

[13]IV drugs

[14]Before acquisition by J&J

[15]Excludes API sales

[16]Hospital products, Integrated Pharmacy Solutions

COMPANY	PHARMA SALES ($M) 2016	CHANGE FROM 2015	RANK 2016 (2015)
Ono Pharmaceutical[17]	1,970.3	37.7%	51 (60)
Hikma Pharmaceuticals[18]	1,950.0	35.4%	52 (58)
Ferring	1,900.0	-4.9%	53 (48)
Chiesi	1,738.0	6.7%	54 (52)
Santen Pharmaceutical	1,686.8	12.5%	55 (56)
Vertex Pharmaceuticals[19]	1,683.6	68.3%	56 (83)
Apotex[20]	1,600.0	2.2%	57 (55)
United Therapeutics	1,598.8	9.1%	58 (57)
Shanghai Fosun Pharmaceutical Group[21]	1,550.0	8.0%	59 (59)
Gruenenthal	1,537.9	14.3%	60 (64)
Nichi-Iko Pharmaceutical[22]	1,502.0	26.7%	61 (72)
Meiji Holdings	1,485.9	9.3%	62 (63)
Jazz Pharmaceuticals	1,477.3	12.4%	63 (65)
Leo Pharma	1,465.6	16.5%	64 (67)
Zhejiang Hisun Pharma	1,465.2	4.0%	65 (61)
Shionogi	1,452.7	-8.3%	66 (54)
Ipsen[23]	1,408.4	-12.1%	67 (53)
Meda	1,397.9	0.0%	68 (62)
Gedeon Richter	1,384.3	25.1%	69 (77)
Teijin Pharma[24]	1,356.1	11.3%	70 (70)
China Pharmaceutical Group[25]	1,327.0	8.1%	71 (69)
Recordati	1,276.7	9.8%	72 (74)
Glenmark Pharmaceuticals	1,223.9	3.4%	73 (73)
Humanwell Medicine[26]	1,203.0	14.6%	74 (79)
Kowa Pharmaceutical	1,200.0	0.0%	75 (71)

COMPANY	PHARMA SALES ($M) 2016	CHANGE FROM 2015	RANK 2016 (2015)
Galenica AG[27]	1,184.6	34.9%	76 (96)
Cadila[28]	1,171.0	-6.0%	77 (68)
Aurobindo[29]	1,136.2	2.1%	78 (76)
Merz[30]	1,132.0	-11.8%	79 (66)
Sawai Pharmaceutical[31]	1,117.5	21.4%	80 (93)
BioMarin Pharmaceutical	1,110.4	25.5%	81 (95)
Concordia Healthcare[32]	1,081.5	174.3%	82 (134)
KRKA	1,066.2	-1.1%	83 (78)
Akorn[33]	1,053.6	14.0%	84 (91)
Intas Pharmaceuticals	1,050.0	2.5%	85 (80)
Perrigo	1,042.8	4.2%	86 (82)
Sino Biopharmaceutical Ltd.[34]	1,019.0	8.6%	87 (89)
Kyorin	1,007.4	7.2%	88 (87)
Hisamitsu[35]	1,002.7	3.6%	89 (85)
Alvogen Pharmaceuticals[36]	1,000.0	25.0%	90 (99)
Pierre Fabre	996.8	-0.1%	91 (84)
Horizon Pharma[37]	981.1	29.6%	92 (101)
Orion Pharma[38]	952.2	1.4%	93 (88)
Shanghai Pharmaceutical[39]	926.6	0.5%	94 (92)
AlfaSigma	925.2	-8.4%	95 (81)
CSPC Pharmaceutical Group Ltd.[40]	891.0	44.5%	96 (111)
Green Cross	890.0	-3.9%	97 (90)
Taisho Pharmaceutical[41]	883.5	-0.2%	98 (94)
Incyte[42]	882.4	46.8%	99 (113)
Amneal Pharmaceuticals[43]	875.0	0.0%	100 (97)

[17]Boosted by Opdivo sales
[18]Acquisition of Boehringer Ingelheim's Roxane division
[19]Kalydeco, Orkambi and Incivek
[20]Estimated from 2015 data
[21]Estimated (may include some API)
[22]Acquired Sagent Pharmaceuticals
[23]Excludes consumer heathcare
[24]Healthcare segment
[25]Finished drugs and antibiotics
[26]Excludes chemical materials and TCM
[27]Vifor Pharma
[28]Formulations
[29]Excludes API sales
[30]Includes beauty business
[31]Includes ~10% OTC
[32]Acquisition of Amdipharm Mercury
[33]Prescription Pharmaceuticals
[34]Excludes TCM (~ 50% of sales)
[35]Rx segment plus Noven
[36]Acquisition of Country Line
[37]Acquisition of Raptor
[38]Proprietary or specialist pharma
[39]Biologicals and chemical/ biochemical drugs (not TCM)
[40]Finished drugs segment
[41]Ethical drugs
[42]U.S. sales of JAKAFI and European sales of ICLUSIG
[43]Estimated from 2015 data

SCRIP 100: NUMBERS CRUNCHED

The Scrip 100 universe gathers FY 2016 financial performance data on 659 companies selling and developing prescription pharmaceuticals.

Companies: Who Gets In?

$1m

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

2.3m

Employees working within the Scrip 100 universe

659

Companies covered by the Scrip 100 for FY 2016

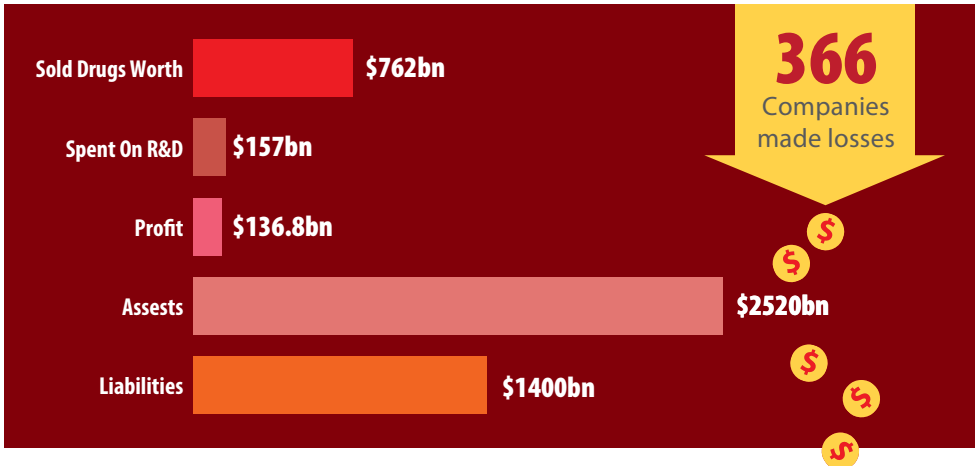
Operational Bases

304
North America

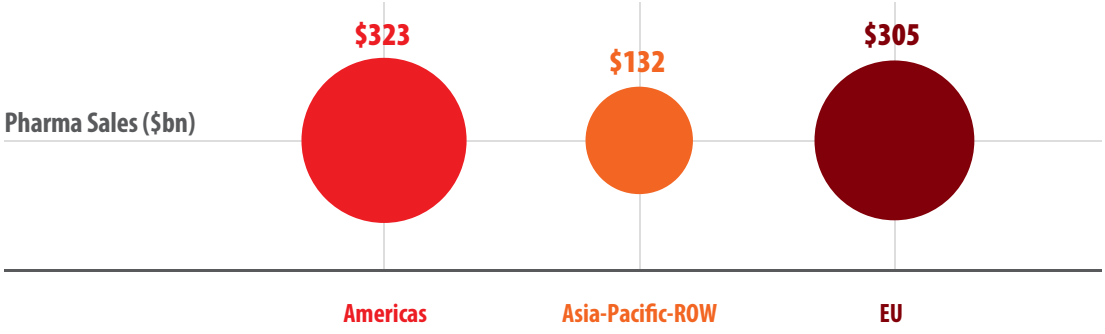
191
Europe

164
Asia-Pacific-ROW

Altogether In 2016, These Companies:



Company Sales By Domicile



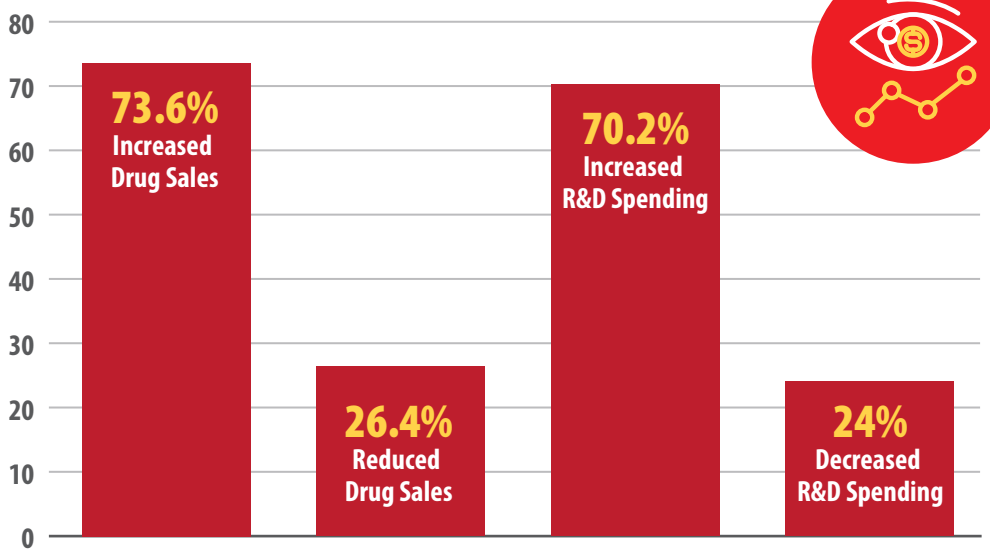
No profit or loss data was available for 74 companies, most of them privately held

Profit & Loss

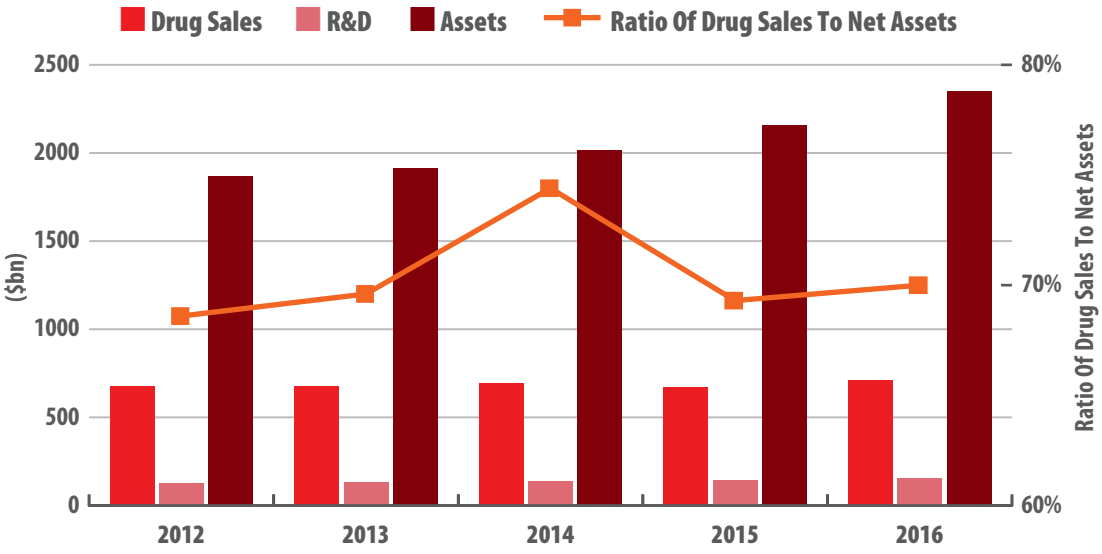
+ $167.3bn
Total profits made by profitable companies

– $30.5bn
Total losses made by loss-making companies

Year-On-Year Company Changes In 2016



5 Year Trends



Change Per Year

+$5.8bn
per annum in drug sales

+$6.8bn
per annum in R&D

+$122bn
per annum in assets

Pharma Remains Very Top Heavy

THE TOP 20 COMPANIES:

GENERATED
66.5%
of drug sales

MADE
87%
of industry profits

EMPLOYED
50.4%
of industry employees

SPENT
64%
of the industry R&D spending

Company Overview

ICON plc is a global provider of drug development solutions and services to the pharmaceutical, biotechnology and medical device industries. We offer a full range of clinical, consulting and commercial services that range from clinical development strategy, planning and trial design to full study execution and post-market commercialisation. With headquarters in Dublin, Ireland, ICON currently operates from 97 locations in 38 countries and has approximately 13,100 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 Cardiac Assessment

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

Functional Services
- Functional Solutions
- FSP (DOCS)
- Government Solutions

Laboratory Services
- Central Laboratories
- Bioanalytical Laboratories

Clinical Research Services
- Project Management
- Clinical Operations/Monitoring
- Patient Centric Monitoring
- Data Management
- Patient Access Solutions
  - Site Feasibility – EMR & Data Analytics
  - ICON owned Site Networks
  - Patient Recruitment Services
  - Site & Patient Digital Solutions
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Mandy Jackson
Managing Editor,
Pharma, US

While The Money Flows, So Will Biopharma IPOs

US initial public offerings by biopharma firms in 2017 have outpaced the number of IPOs completed in 2016 and as investors continue to see big returns the tempo isn't likely to slow in 2018.

Public biopharmaceutical company valuations improved in 2017, prompting more initial public offerings in the US this year than last year. And with better stock performance for this industry than in other sectors of the economy, the market for drug developer IPOs may continue to strengthen in 2018.

The Nasdaq Biotechnology Index (NBI) was up 26% at the end of the third quarter versus the end of 2016 while the broader Nasdaq index increased only 20.7% and the Dow Jones Industrial Average was ahead by just 13.4%. With biopharma companies providing better returns than high-tech firms and industrial heavyweights, it's not surprising that 29 drug developers were able to go public in the US during the first three quarters of 2017 versus 30 for all of 2016.

"Companies that have strong development plans, that will have news flow, that have strong science, and where there's not competition that will not allow them to differentiate no matter how good their data is – and that have a supportive regulatory environment – will always be able to do an IPO," Back Bay Life Science Advisors co-founder, managing partner and CEO Jonathan Gertler told *Scrip*.

However, biopharma IPOs were expected to slow in 2017 after falling from 62 offerings in 2015 to just 30 in 2016, as valuations declined due in part to concerns about a crackdown on prescription drug pricing in the US.

While the NBI slumped 29.6% between its all-time high on July 12, 2015 and the start of 2017, valuations generally have increased this year despite President Donald Trump's promise to cut drug prices. Trump's comments in January that the pharmaceutical industry was "getting away with murder" rang hollow as his administration did not take immediate action on the issue. As a result, the average return for the 29 biopharma IPOs through the third quarter of this year was 35.2% versus 11.2% for last year's new offerings at the end of 2016 (*see infographic*).

"The hot IPO market cooled off and it's heating back up," Gertler said. "The general trend always is that when knowledgeable biotech investors feel the fundamentals are there to get good returns on their investments, then the generalists come in behind them. You can't have a good biotech financing environment without some general investors, but the decisions are driven by the biotech investors."

FINANCING FOR COMPANIES, NOT LIQUIDITY FOR INVESTORS

"I think that people still misinterpret what IPOs are about. They're still financing vehicles, not liquidity vehicles," Gertler said.

Pre-IPO investors typically hold on to their shares of newly public biopharma companies for a while, so the offering isn't necessarily an exit for venture capital firms. It just provides a means for therapeutics firms to occasionally tap the public market to fund drug development.

The 2017 biopharma IPO market is remarkable not only because it exceeded expectations based on the 2016 market's performance, but also because this year got off to a slow start. The first quarter total of just four IPOs represented a four-year low for therapeutics firms, Renaissance Capital noted in its review of the third quarter.

"After hitting a four-year low in the [first quarter], biotechs rebounded in the second quarter and remained active in the third," Renaissance reported.

GOOD NEWS DRIVES INVESTMENT

"As long as the market is going to be out there and warm for IPOs, [life science companies] are going to try it, because they're always going to explore IPOs for financing," Halloran Consulting Group president and CEO Laurie Halloran said in an interview with *Scrip*. "Acquisitions of companies make biotech seem like a bullish industry as compared to others."

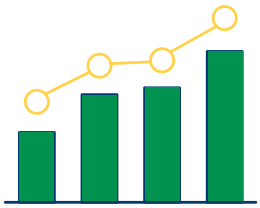
Every company is different in terms of the type of funding they need and when they need to raise it, but Halloran said she tends to point biopharma firms in directions other than the stock market, because of the cost of being a public company and the pressure that trading publicly puts on drug developers.

However, rising biopharma company valuations, increased IPO activity and greater investor interest in the sector helps the industry overall.

"It makes for a whole lot of optimism within the industry as whole. People are willing to take a risk and start companies and continue to progress their development programs, because they don't feel constrained," Halloran said. "Being able to generate data and create even more value makes for a more optimistic industry."

IPO Performance

Through The Third Quarter



29 Biopharma IPOs in the first three quarters of 2017

Average return as of Sept. 29 **35.2%**

Average return for 2016 IPOs at year end **11.2%**

$2.9bn Total raised by biopharma IPOs though the third quarter in 2017

Average gross proceeds **$90.3m**

BIGGEST IPO **$193.5m**

SMALLEST IPO **$6.1m**

PERFORMANCE

20 companies traded above their IPO price and 9 traded below as of Sept. 29

BEST PERFORMER:
Akcea Therapeutics Inc. with a return of **245.9%**

WORST PERFORMER:
Immuron Ltd. with a loss of **47.4%**

HIGHEST SHARE PRICE AS OF SEPT. 29:
Biohaven Pharmaceuticals Holdings Co. Ltd **$37.38**

LOWEST SHARE PRICE AS OF SEPT. 29:
Immuron Ltd. **$5.26**

TOP 5 IPO PERFORMERS

1	Akcea Therapeutics Inc.	245.9%
2	UroGen Pharma Ltd.	142.5%
3	AnaptysBio Inc.	133%
4	Biohaven Pharmaceuticals Holdings Co. Ltd.	119.9%
5	BeyondSpring Inc.	84.4%

WORST 5 IPO PERFORMERS

1	Immuron Ltd.	-47.4%
2	ObsEva SA	-45.7%
3	Ovid Therapeutics Inc.	-42.9%
4	Zymeworks Inc.	-38.6%
5	Aileron Therapeutics Inc.	-10.8%

18 US company IPOs launched

11 Ex-US company IPOs launched

UK	3	China	1
Israel	2	Denmark	1
Australia	1	Netherlands	1
Canada	1	Switzerland	1

Source: Scrip

Mandy Jackson
Managing Editor,
Pharma, US

Celgene's Partnered Pipeline Delivers Successes And Setbacks

Celgene won the first approval for a drug developed under its aggressive deal-making strategy in 2017 and several potential blockbusters in its partnered pipeline are edging closer to the market. Ozanimod will soon face regulatory approval, but the next-in-line acquired asset GED-0301 had a major setback. *Scrip* considers the contribution externally derived products have made – and will make – to Celgene's business.

Celgene Corp.'s aggressive deal-making strategy could pay off in a big way over the next several years, bringing in billions of dollars in annual sales from new drugs to diversify revenue beyond its multiple myeloma blockbuster *Revlimid* (lenalidomide) and the hematology/oncology franchise that dominates the company's commercial portfolio.

The deal-making strategy has been successful in filling Celgene's pipeline with several high-profile assets at a time when its large biotech and big pharma peers also are putting more emphasis on outside research to boost internal R&D productivity. And as that strategy matures, Celgene should start to see a return on this investment, but after a big bet on GED-0301 (mongersen) in Crohn's disease recently went bust in Phase III, the company lowered its longer-term revenue expectations.

Celgene paid Nogra Pharma Ltd. $720m up front in 2014 to acquire the Crohn's candidate and it hasn't completely discontinued development of GED-0301; it will decide whether to conduct late-stage clinical trials in ulcerative colitis after a Phase II study in this indication. However, GED-0301's Phase III Crohn's disease failure and lower-than-expected sales of the psoriasis and psoriatic arthritis drug *Otezla* (apremilast) are contributing to the company's reduction in 2020 revenue guidance from more than $21bn to about $19bn to $20bn.

Looking at a dozen transactions that may result in new drug approvals between 2017 and 2021, Celgene has spent

CLICK

View Celgene's big buys from the past decade online at: http://bit.ly/CelgeneDeals

more than $13.5bn on upfront fees and acquisition costs to initiate collaborations and acquire companies with therapeutic candidates. In total these assets could deliver as much as $17.5bn in annual sales at their peak – excluding GED-0301 – per the big biotech's and analysts' estimates.

MORE THAN 40 DEALS SINCE 2007

Celgene has entered into more than 40 partnership and acquisition agreements during the past decade, including many preclinical drug development collaborations that still are in the discovery stage. The first approved drug to emerge from those science-based agreements was *Idhifa* (enasidenib), developed with Agios Pharmaceuticals Inc.

Celgene's executive vice president and executive advisor for innovation George Golumbeski, who was previously the senior VP leading business development, highlighted the original agreement signed with Agios in 2010 as the company's first large-scale collaboration where it agreed to make a major investment in a specific area of biology at the preclinical stage. An important feature of the partnership was that it had a three-year initial term and options for subsequent two- and one-year renewals so that the science could be given ample time to mature.

"The reality is that we have had a number of successes with our collaboration program and, as expected, we have had some programs that did not work as planned," Golumbeski said in an interview with *Scrip*. "We always focus on high science, really great work and, in our early-stage collaborations, we have consistently carved out rich areas of biology, given the partner freedom and structured these as multi-year collaborations."

While Celgene recognized years ago that there was a lot of good science going on outside of its labs, the company's own R&D has been very successful. Revlimid, which has become the backbone of most multiple myeloma treatment regimens, generated $6bn in sales during the first nine months of 2017 – 63.2% of Celgene's revenue during that period. Idhifa is likely to be a modest product in comparison, making only a small dent in Revlimid's share of the company's sales, but the next drug candidates approved among Celgene's acquired or partnered assets are expected to generate billions of dollars in annual revenue.

Idhifa was granted accelerated approval by the US FDA in June for relapsed or refractory adult patients with acute myeloid leukemia (AML) and an IDH2 mutation – a small indication with a peak sales estimate of $95m, according to a report on Celgene's pipeline produced by the Informa Pharma Intelligence service PharmaVitae in August.

The next big revenue generator in the company's pipeline is likely to be the oral immunomodulator ozanimod. If that asset – originating from the acquisition of Receptos Inc. – is successful in ongoing Phase II and III studies and approved in major markets, it is expected to be a multibillion-dollar seller across multiple indications.

Ozanimod also will be the first of Celgene's acquired or partnered programs to expand the company's portfolio of commercial immunology and inflammation products beyond Otezla, which brought in $908m in revenue during the first three quarter of 2017.

Celgene acquired ozanimod when it bought Receptos for $7.2bn in 2015. The company entered into a collaboration with Nogra for the development of GED-0301 a year earlier.

Ozanimod is on track to be submitted for FDA approval as a treatment for multiple sclerosis (MS) before the end of 2017, the company confirmed at the end of October after reporting Phase III results that appear to show a safety advantage over Novartis AG's oral MS drug *Gilenya* (fingolimod). Ozanimod is also in Phase III for ulcerative colitis (UC) and Phase II for Crohn's disease.

Celgene's executive VP and president-research and early development Rupert Vessey said the company plans to file an average of eight investigational new drug (IND) applications with the FDA each year between 2017 and 2019, at least half of which will be for drugs developed with partners. "We are creating meaningful, progress-able small molecules and biologics through that partnership network," Vessey told *Scrip*.

> One of the most flexible deal structures of those negotiated by Celgene in recent years is its agreement with Forma Therapeutics

FLEXIBLE TERMS WIN DEALS FOR NEW DRUGS

Celgene has a reputation for being a partner of choice, negotiating creative deal terms that meet the needs and fit the business strategies of its partners. The company's deal-making ways also help it manage the risks associated with investments in novel medicines, keeping preclinical and early clinical development in the hands of partners. The assets often shift to Celgene's balance sheet in later stages of development when those programs have been somewhat de-risked in proof-of-concept studies.

One of the most flexible deal structures of those negotiated by Celgene in recent years is its agreement with Forma Therapeutics Holdings LLC. The relationship began with an initial collaboration and options to add more programs to the partnership. Eventually, the company negotiated an additional option to purchase Forma outright if that makes sense for the smaller firm and its investors.

While acquisitions gave Celgene some of its most anticipated potential blockbusters, such as ozanimod, big purchases also are behind some of the hematology/oncology products that already are on the market.

The $2.7bn acquisition of Pharmion Corp. in 2007, for instance, gave Celgene *Vidaza* (azacitidine) for myelodysplastic syndromes (MDS) and the company paid $640m for Gloucester Pharmaceuticals Inc. in 2009 to gain *Istodax* (romidepsin) for peripheral and cutaneous T-cell lymphoma.

One of Celgene's largest purchases – Abraxis BioScience Inc. for $2.9bn up front in 2010 – brought in *Abraxane* (nab-paclitaxel) for various solid tumors, which has grown to be one of its biggest commercial assets with $741m in sales during the first three quarters of 2017.

"We're generating a lot of opportunities for the company with some good projects, but I'm also looking for new opportunities. There's no way even the largest pharma company can capture everything within their own four walls," Vessey said. He noted that the company is augmenting its own discoveries with complimentary assets, including candidates in adjacent therapeutic areas, such as neuroinflammation.

TITANS OF PHARMA

A snapshot of the industry's top leaders and the businesses they oversee

	Johnson & Johnson US	Pfizer US	Merck & Co US	Gilead Sciences US
				
CEO	**Alex Gorsky**	**Ian Read**	**Kenneth Frazier**	**John Milligan**
Appointed To Role In	**2012**	**2010**	**2011**	**2016**
Previous Position	Chair, J&J Medical Devices	Pfizer SVP, Group President, Worldwide Biopharmaceuticals	President, Merck & Co, Inc	President and COO, Gilead Sciences
Background	Began career as sales rep at Janssen Pharmaceutical, J&J. Defected to Novartis as head of pharma for North America 2004-2008 before returning.	Career spent at Pfizer, joined as an auditor. Has chemical engineering and accounting qualifications.	Legal: joined Merck in 1992 as general counsel.	Joined Gilead in 1990 as research scientist. Studied biochemistry.
2016 Compensation[1]	**$26.9m** (+12.9%)	**$17.3m** (-3.7%)	**$21.8m** (-10.0%)	**$13.9m** (+68.4%)[2]
2016 Company Sales	$71.9bn	$52.8bn	$39.8bn	$30.4bn
2016 Company Net Profit	$16.5bn	$7.2bn	$5.7bn	$13.5bn
Market Cap (June 30, 2017)	$355.9bn	$200.5bn	$175.6bn	$92.5bn
R&D Head	**Paul Stoffels**	**Mikael Dolsten**	**Roger Perlmutter**	**Norbert Bischofberger**
Appointed To Role In	**2009**	**2010**	**2013**	**2007**
Previous Position	Worldwide Chairman, Pharmaceuticals (J&J)	Head of Wyeth R&D, previously at Boehringer Ingelheim and AstraZeneca	Head of R&D, Amgen	EVP, R&D, Gilead
2016 Compensation[1]	**$12.7m** (+18.0%)	**$8.2m** (+35.8%)	**$7.1m** (-14.5%)	**$6.2m** (-11.3%)

[1] base salary, bonus & long-term incentives (including equity awards), [2] assumed CEO position Mar. 10, 2016

AbbVie US	**Roche** Switzerland	**Novartis** Switzerland	**Sanofi** France	**GSK** UK	**AstraZeneca** UK
					
Richard Gonzalez	**Severin Schwan**	**Joseph Jimenez**	**Olivier Brandicourt**	**Emma Walmsley**	**Pascal Soriot**
2013 *(at company inception)*	**2008**	**2010**	**2015**	**2017**	**2012**
Head of Pharmaceutical Products Group at Abbott Laboratories	CEO, Roche Diagnostics	Division Head, Novartis Pharmaceuticals	CEO, Bayer Healthcare	CEO, GSK Consumer Healthcare	COO, Roche Pharmaceuticals
Spent 30 years at Abbott.	Economics, Law degrees, joined Roche as trainee in corporate finance in 1993.	Bachelor's degree in economics then MBA; prior to Novartis had senior leadership roles at HJ Heinz Co.	Physician by training, had leadership roles at Pfizer before Bayer.	Before joining GSK in 2010 was with L'Oréal for 17 years in marketing and general management.	Formerly CEO of Genentech, doctor of veterinary medicine and MBA holder.
$21.0m (+0.8%)	**CHF11.6m** (-2.6%)	**CHF12.0m** (+3.4%)	**EUR9.7m** (-42.3%)	**n/a**[3]	**£9.8m** (+22.6%)
$25.6bn	CHF52.6bn	$48.5bn	EUR33.8bn	£27.9bn	$23.0bn
$6.0bn	CHF9.7bn	$6.7bn	EUR4.5bn	£1.1bn	$3.5bn
$115.4bn	CHF206.7bn	CHF207.3bn	EUR105.6bn	£80.4bn	£65.0bn
Michael Severino	**n/a** **no single R&D chief**	**Vasant Narasimhan**	**Elias Zerhouni**	**Patrick Vallance**	**n/a** **no single R&D chief**
2014	**n/a**	**2016**	**2011**	**2012**	**n/a**
SVP, Global Development and Corporate Chief Medical Officer, Amgen	n/a	Global Head of Development, Novartis Pharmaceuticals	Scientific Advisor to CEO Christopher Viehbacher	SVP, Medicines Discovery and Development, GSK	n/a
$7.2m (+9.7%)	n/a	**CHF3.6m** (from Feb 2016)	n/a	**£0.78m** base salary	n/a

[3] Overall 2017 package will be c.25% less than the £6.8m received by Sir Andrew Witty in 2016

Edward Thomason
Company Analyst,
Datamonitor Healthcare

Japan's Ageing Problem Will Limit Industry Growth

Japanese pharma growth is set to decelerate between 2016-26 as an ageing population and government pressure on drug prices will temper company revenues. PharmaVitae has analyzed eight leading public pharmaceutical companies in Japan to give a snapshot of the wider industry in Japan.

From 2006-2016, drug sales for Japanese pharmas grew at a compound annual growth rate (CAGR) of 2.8%, however between 2016-26, growth will slow to just a 0.7% CAGR. The Japan pharma peerset currently contributes 9% to global pharma revenues, of which sales in Japan make up 44.9% of sales; by 2026, this will fail to 8.6% and 37.9%, respectively. PharmaVitae attributes this decline primarily to increasing challenges facing the healthcare industry in Japan.

Japan's pharmaceutical market is slowing, as it struggles to expand against a worldwide backdrop of growing populations, aging societies, and growing economies in emerging countries. The entire Japanese pharmaceutical market was worth an estimated $70bn in 2016, making Japan the third largest pharmaceutical market having fallen behind the US and now China (ITA, 2016).

In FY2016, healthcare costs, reported by the Ministry of Finance, reached JPY37.9 trillion, and are projected to rise to JPY 54 trillion by 2025. Pressured by a poor economic and an austerity driven environment in Japan, the Ministry of Health, Labour and Welfare (MLHW) have imposed multiple measures to limit healthcare expenditure. Collectively, these measures have successfully driven down the cost of drugs and encouraged the use of generics. This has made the business environment for Japanese pharmaceutical companies increasingly challenging, and will restrain the long-term growth prospective of the Japan pharma peerset.

Facing these headwinds, PharmaVitae expects growth in the peerset will decline to a 0.7% CAGR between 2016-21, before slowing down further to 0.4% between 2021-26, as mature products are affected by the latest government measures. This also threatens to jeopardize Japanese 'inoyaku' (drug development), as alongside rising R&D expenses and an attrition rate associated with new drug development, it risks jeopardizing internal innovation, which will be essential for Japanese companies to overcome headwinds.

TABLE 1: JAPAN PHARMA PEERSET AND 2016 TOTAL REVENUES

COMPANY	FULL YEAR 2016 REVENUE
Takeda Pharmaceutical Co. Ltd.	$13.2bn
Astellas Pharma Inc.	$11.3bn
Daiichi Sankyo Co. Ltd.	$7.8bn
Otsuka Pharmaceutical Co. Ltd.	$6.8bn
Eisai Co. Ltd.	$4.5bn
Mitsubishi Tanabe Pharma Corp.	$3.7bn
Sumitomo Dainippon Pharma Co. Ltd.	$3.4bn
Shionogi & Co. Ltd.	$2.7bn

Source: PharmaVitae, Informa Pharma Intelligence

AGEING POPULATION

Japan faces a demographic crisis of an aging population and population decline, as a result the government is taking significant measures to curb healthcare expenditure growth. According to the estimation from the National Institute of Population and Social Security Research and census data, the Japanese population reached its peak in 2009 and officially entered decline in 2016, having fallen by approximately one million between 2010-2015. Japan's total population in 2017 is projected to be 127,484,000, according to United Nations data, but the pace of population decline is expected to accelerate steadily until 2045, by which Japan will be losing approximately 900,000 residents a year. Presently, UN data forecasts that Japan's population will fall to 108,794,000 by 2050, and to 84,532,000 by 2100.

Simultaneously, the prevalence of noncommunicable diseases is growing as patients survive longer and better treatment becomes available. Noncommunicable diseases are diseases of long duration and generally slow progression, such as cardiovascular disease, cancer, chronic respiratory diseases and diabetes. Together, this poses an opportunity and a challenge for Japan's pharmaceutical companies. On one side, the Japanese healthcare market is growing, we are seeing a shift

towards chronic, age-related disease areas where there is unmet medical need and opportunity for significant advances in the development of new therapies. However, as the size of the market increases it is placing considerable financial strain on the healthcare system.

PRICING BACKGROUND

In Japan, successful pricing outcomes hinge on the product receiving a price premium which can be awarded for added benefit over comparators or innovation. Pricing and reimbursement decisions are made by the Central Social Insurance Medical Council (Chuikyo) within the MHLW. Pricing and reimbursement processes are closely connected, and the majority of medicines are reimbursed, contingent on the successful outcome of pricing negotiations. The medicine is then listed on the National Health Insurance (NIH) reimbursement list and can be used in the country.

For newly launched medicines there are two pricing options. Medicines that are novel and for which there are no similar drugs are priced using a cost-based method where drug development and manufacturing, importation, sales and administrative costs, and profits are taken into account. For medicines that show innovation, the allowed operating profit can be increased by 50-100%, compared to the average operating profit of 18.3% in 2013. The price is then adjusted if a significant discrepancy exists between the calculated price and the drug's foreign price.

For medicines for which there are similar drugs available in Japan, the cost of the daily dose of the comparator is used to establish a base price (similar efficacy pricing method), to which further premiums are added depending on the additional benefit that the new drug offers compared to the similar drug (*see table 2*). In addition, medicines that are awarded innovation, utility or Sakigake designation (equivalent to the FDA breakthrough designation) premiums and that are approved in Japan before any other market are granted an additional 10% premium.

In Japan, there is a system of biannual price revisions for ethical drugs (branded and patent protected drugs), designed to lower treatment costs. In general, the official national health insurance (NHI) prices for ethical drugs are revised once every two years, based on surveys and calculations conducted by the MHLW. In these revisions, the price of a drug is cut according to prevailing market prices using the similar efficacy pricing method, unless protected with a price premium. Products granted an NHI innovation premium are highly valuable for a company because they effectively escape the impact of the price reductions.

Furthermore, as of late, the effect of price revisions has been intensified, as Japanese companies are presently in their second of three consecutive years of price revisions. Companies faced the usual revision in FY16, an irregular revision in FY17 in April 2017 to adjust for a 2% hike in consumption tax, and then another usual revision in FY18. Original plans to change to annual revisions were shelved in 2014, but with three consecutive years of revisions, it will pave the way for Chuikyo to introduce annual revisions from 2019.

TABLE 2. JAPAN PRICING PREMIUMS

TYPE OF PREMIUM	PREMIUM (%)	BASIC RULES
Novelty premium	70-120	Meeting all three conditions: clinically useful new mechanism of action, high efficacy/safety, improvement of disease treatment method
Utility premium (i)	35-60	Meeting two conditions of novelty premium: clinically useful new mechanism of action, high efficacy/safety, improvement of disease treatment method
Utility premium (ii)	5-30	Meeting one condition of above (tier i) or a formulation improvement shows a high medical usefulness
Marketability premium (i)	10-20	Orphan drug, etc.
Marketability premium (ii)	5	Efficacy and effectiveness shows a superiority over comparison drug
Pediatric use premium	5-20	Dosage and usage expressly includes those pertaining to children, etc.
Sakigake designation premium	10-20	Newly entered drugs that have been Sakigake designated, including drugs where pharmaceutical approval was obtained in Japan ahead of other countries, etc.

Sources: JPMA; MHLW

Cost-Effectiveness Assessment Scheme

The MHLW also looks set to introduce in 2018 a new cost-effectiveness assessment (CEA) scheme to revise prices for those drugs deemed 'kyogaku' (best-selling drugs). A pilot program assessing seven drugs, including *Sovaldi* (sofosbuvir; Gilead Sciences Inc.) and *Opdivo* (nivolumab; Bristol-Myers Squibb Co./Ono Pharmaceutical Co. Ltd.), was designed to assess pricing for best-selling drugs with broad labels and establish their cost-effective benefit. Subsequently, based on a products incremental cost-effectiveness ratio or cost per quality-adjusted life year gained, prices for the products in the CEA program will be revised and subjected to a slope-like price adjustments. Chuikyo is expected to add future clarity on the definition of efficacy thresholds, and how to assess products that have more than one indication. Nevertheless, it seems increasingly likely that such a cost-effectiveness program is going to be rolled out throughout all ethical products. If fully implemented, the scheme would transform the business model of the Japanese pharmaceutical industry, appraising innovative new drug developments that demonstrate a real cost-effective benefit, while at the same time reducing further the prices of longer-term listed drugs.

Kevin Grogan
Managing Editor,
Pharma, Europe

Bayer's Weinand On Pricing, Payers And Pipelines

Bayer's pharma president and board member Dieter Weinand talks to Scrip about the importance of big picture thinking when weighing the value of innovative drugs to healthcare systems, the revolutionary potential of big data and how "transparency and open dialogue will further enhance the understanding of our business."

It has been another challenging year for the pharmaceutical industry with a slew of innovative products being approved accompanied by the perennial questions about how they are going to be paid for. Ideally qualified to reflect on this and a number of other issues facing the sector is Dieter Weinand.

With more than 25 years of experience in the pharmaceuticals industry, holding senior posts around the globe with companies including Pfizer Inc. and Bristol-Myers Squibb Co., Weinand took over as head of Bayer AG's pharmaceuticals business in August 2014, joining the German major from Otsuka Pharmaceutical Co. Ltd.

In an interview with *Scrip*, Weinand began with some thoughts on pricing. In a bid to control escalating healthcare costs in Europe, payers are continuing to squeeze the budgets dedicated to new medicines and as such, it is becoming increasingly difficult for pharmaceutical companies to get what they perceive to be a fair price for innovative new products.

Weinand has not seen much evidence of a change in mindset from payers who generally work to an annual budget and tend to focus on price alone rather than value to their healthcare systems as a whole. "I hope to see more such evidence sooner rather than later," he told *Scrip*, saying that payers and governments must take a more comprehensive and long-term approach to understanding the value of innovative medicines and consider the positive impact they have on actually reducing the burden on healthcare systems.

Dieter Weinand, head of Bayer Pharmaceuticals

"A myopic view focused only on a single component of the overall healthcare cost, such as the impact on drug budget alone, not considering the savings associated with avoidance of hospitalization, or more severe outcomes of untreated disease, does not reflect the true value of innovative medicine," he argues. "This silo approach is neither conducive to healthcare cost containment, nor medical progress."

Weinand believes that rather than focusing solely on the cost of an innovative medicine "during a relatively brief period of exclusivity when it first comes to market," one must recognize the value a medicine brings to society for many years at generic prices, "far beyond the initial period of exclusivity." He notes that today, approximately 95% of the drugs included in the World Health Organization's Essential Medicines List are off-patent, pointing out that all these medicines entered the market as patent protected innovative medicines at one point in time, "and they have all been providing good health and value to society for many decades."

He says this system "has worked remarkably well, providing value to society while encouraging continued medical progress." The latter requires a high-risk commitment of innovative pharmaceutical companies over many years of investment in R&D and "against very steep odds."

Weinand cited a 2014 Tufts University study which claimed that it now takes some 14 years and $2.8bn to bring a new medicine to market. "That is more than double what it cost only 10 years earlier and at the same time the risk has substantially increased," he added.

Furthermore, Bayer's pharma chief noted that the probability of a drug that has entered development ever making it to market "is a mere 4.1%." As such, he said that effective patent protection which gives what is

still a limited period of marketing exclusivity has to be maintained to enable continued investment into R&D in the highly-regulated, high-risk life sciences sector.

Weinand also stressed that the pharmaceutical industry has an obligation to work with all stakeholders to contain healthcare costs "and reduce the strain, especially on patients." He added that Bayer places a high priority on patient access when pricing a medicine.

PATIENT TRUST HAS TO BE EARNED

The industry as a whole faces criticism over the cost of its medicines and a number of high-profile examples of price-gouging have not helped attempts to improve its reputation. Still, Weinand told *Scrip* he feels that "the current perception of innovative pharmaceutical companies is somewhat unjustified and does not acknowledge all the positive contributions and impact we are having on patients, their families, and society at large." He added that "we understand that trust can only be earned. We are judged by our business behavior – and rightfully so. With good business practices and exemplary corporate social responsibility, we hope to demonstrate our values and will contribute to improving the current perception of the industry."

Weinand believes that "transparency and open dialogue will further enhance the understanding of our business" and Bayer, as well as disclosing clinical trial information, is "committed to responsible data sharing." He argues that "we are convinced increased transparency, while maintaining patient privacy, will ultimately encourage innovation and benefit patients."

He also believes that greater collaboration is a vital component so that patients can benefit from disruptive technologies earlier. Bayer has significantly increased the number of comprehensive, strategic pacts it has with academic institutions over the past decade, including a collaboration with the Broad Institute, which brings together scientists from Harvard, the Massachusetts Institute of Technology and Harvard-affiliated hospitals.

BIG DATA AND IMPROVING OUTCOMES

Weinand said that big data would also enable a move towards an integrated and outcomes-based healthcare system, where more coordinated health information for tracking outcomes, and metrics are designed to provide a foundation for better decision-making. He added that Bayer also supports "a European health data eco-system, and as such we are engaged in developing digital solutions with public partners through the Innovative Medicines Initiative (IMI)."

Specifically, Bayer is involved in the IMI's Big Data for Better Outcomes program, leading workstreams in the fields of cardiovascular and oncological diseases. The company will also be part of the newly launched IMI project to develop the European Health Data Network, an attempt to provide a harmonized model, rather than the very fragmented systems at present that make data analysis even more challenging.

As for Bayer and specifically its pharmaceuticals division, 2017 has been a successful year yet again. Summing up the highlights, Weinand referenced the results of the COMPASS study, the largest study to date of its Factor Xa inhibitor blockbuster *Xarelto* (rivaroxaban), in some 27,000 patients, which he said "will bring about a change in the treatment paradigm in both chronic coronary artery and peripheral artery disease. This represents a considerable opportunity for our business going forward." *(Also see "COMPASS Sets Course For J&J/Bayer's Xarelto In Unexplored Indications" - Scrip, 29 Aug, 2017.)*

In cancer, he noted that Bayer had successfully established a new dedicated division to the disease, the Oncology Strategic Business Unit, which allows for decisions around clinical progression and resource allotment to be made swiftly. Weinand highlighted the green light in September for the PI3 kinase inhibitor *Aliqopa* (copanlisib) in the US under the FDA's accelerated approval pathway in follicular lymphoma, saying it represented an important milestone in bringing to market an effective therapy in an area of high unmet need.

This year also saw the successful launch of *Kyleena* (levonorgestrel), Bayer's smaller, lower-dose, five-year intrauterine device, contributing to growth in women's healthcare; while *Eylea* (aflibercept), its Regeneron Pharmaceuticals Inc.-partnered treatment for retinal diseases, has achieved market leadership globally. "All in all our strategy of focused leadership is paying off," he said.

While Bayer is still heavily occupied with getting its proposed acquisition of seeds giant Monsanto across the line, the deal is not going to affect the company's R&D spend. It has a rich pipeline with more than 50 projects in clinical development, Weinand told *Scrip*, including a number of exciting new products in late-stage development.

BAYER PIPELINE HOLDS MUCH PROMISE

In cardiology, he highlighted vericiguat, which is in Phase III and is being developed for heart failure with partner Merck & Co. Inc., and finerenone. The latter is also in Phase III for diabetic kidney disease with two studies ongoing, one focused on cardiovascular outcomes and the other on renal outcomes.

In oncology, Weinand has high hopes for darolutamide, Bayer's next-generation androgen receptor inhibitor for males with metastatic hormone-sensitive prostate cancer, and anetumab ravtansine. This MorphoSys AG-partnered antibody drug conjugate failed in a mid-stage trial in July for mesothelioma but the company is confident of success in other indications – it is being investigated as monotherapy and in combination in additional trials, including a Phase Ib multi-indication study in six different types of advanced solid tumors, as well as a Phase Ib combination trial in patients with recurrent platinum-resistant ovarian cancer.

Bayer's R&D spend was, however, not limited to internal projects. In addition, the company is seeking out strategic in-licensing deals and smaller bolt-on acquisitions in order to augment its pipeline inorganically.

One example is the recent exclusive global collaboration with Loxo Oncology Inc. for the development and commercialization of the tropomyosin receptor kinase inhibitors larotrectinib (LOXO-101) and LOXO-195 for upfront and potential milestone payments in the magnitude of around $1.5bn. "This collaboration with Loxo strengthens our presence in this therapeutic area and ideally complements our own oncology pipeline", Weinand said.

Weinand concluded that "these are just a few examples of our very exciting late-stage development products, which is why we are optimistic about our long-term future."

Lucie Ellis
Senior Editor,
Pharma, Europe

Heights And Plights Of Vaccine Development: Tales From The Frontline

Gary Dubin, senior vice president and global medical officer in Takeda Pharmaceutical Co.'s vaccine business unit, talks about the trials and tribulations of vaccine R&D and how it felt to get one of the world's first human papillomavirus injections to market.

Dubin joined Takeda Pharmaceutical Co. Ltd. in 2015 following a long tenure at GlaxoSmithKline PLC, where he was responsible for the clinical development of the UK big pharma's *Cervarix* vaccine – one of the first human papillomavirus (HPV) vaccines, which is now used worldwide to protect women against cervical cancers. Now, Dubin oversees medical affairs and safety activities within Takeda's vaccine business unit and acts as the program lead for the company's Zika virus vaccine candidate.

Q What was your first pharma job?

By background I'm an internist and infectious disease physician; I was in academic medicine before joining industry. I'm also a molecular virologist and have always been passionate about vaccines. When I was working in academia my research focused on trying to develop candidate vaccines against herpes simplex virus (HSV) and my first job in the industry, at GlaxoSmithKline, came directly out of that experience. In 1995, when I joined GSK, I worked on the development of an HSV vaccine and had been working in the lab for many years on this virus. It was really exciting to lead a vaccine development program in an area that I was very familiar with. My laboratory research was very interesting and it was progressing nicely but I wanted to be in a role that had more direct impact on public health.

Two years after I joined GSK to work on the HSV vaccine, I was given a unique opportunity. I was asked to take on a "small" side program for a vaccine that had just been newly licensed by GSK. That program was to develop a human papillomavirus vaccine. I spent the next 10 years of my career leading the GSK HPV clinical development program from initial discovery work to licensure in 120 countries and it is really one of the highlights of my professional career.

Gary Dubin, global medical officer, Takeda vaccine unit

Q What piqued your interest in vaccines early on?

Vaccines are amazing public health tools. When I went into medicine I did not necessarily expect to be doing what I'm doing today but I'm really driven by my passion to contribute to public health. I've had enormous opportunities to aid in the development of many important vaccines. I feel very lucky to have been able to work in vaccine development, and to now continue my work on vaccines at Takeda.

Q You talked about the success of GSK's HPV vaccine as being a highlight of your career: is there one moment of that R&D journey that you would spotlight?

The development of an HPV vaccine required a long and complex program but an event that stands out for me is the presentation of our development program to the FDA Vaccine and Related Biological Products Advisory Committee in 2009. Up to this point, the GSK HPV vaccine had been licensed in many countries around the world but we were not yet licensed in the US. The FDA was quite nervous about licensing a vaccine that had a novel adjuvant, as there had not been a vaccine licensed with a novel adjuvant for 30 to 40 years. The FDA had set the bar very high.

At the brink of licensure, our vaccine program was presented to the FDA Advisory Committee and I had to

present most of the data. At the end of the meeting the Advisory Committee gave a favorable recommendation. This was hugely important for the company and it was also hugely important in terms of making an important vaccine available to women in the US. In front of the committee, I had to address all their questions, which were many. We brought lots of data to the table and ultimately within two or three months, the vaccine was licensed. This became a major milestone, not only for GSK but for the vaccine industry, because suddenly it opened the door for the introduction of other vaccines that were being developed with novel adjuvants. Since then there have been many vaccines that have been licensed in the US with novel adjuvants, but GSK's HPV product was the first.

Q On the flip side, what has been the most difficult moment in your career?

That's easy, surprisingly. I mentioned that I joined industry at GSK to lead a development program for a herpes simplex virus vaccine – and we actually started HPV vaccine development activities several years after the HSV development program was initiated. Within 10 years of starting development, the HPV vaccine was broadly licensed, but to date there are no HSV vaccines that have been successfully developed; we spent 20 years trying to develop that vaccine and ultimately failed. That was the most difficult moment for me, to fail in the development of a herpes vaccine.

However, I learned that some development programs are more straightforward than others. HPV is the prototype of a development program that just went well; in the first efficacy results produced, we saw essentially 100% protection. You don't see that very often. At the other end of the spectrum some vaccine development programs are difficult, because the targets are difficult. I think HIV (human immunodeficiency virus) falls into this category, along with HSV and RSV (respiratory syncytial virus). It doesn't mean that you shouldn't choose challenging targets, but to succeed in some of these challenging programs we are going to need more innovative technologies.

Q Who do you admire in the industry and why?

I really admire what Bill and Melinda Gates have done to support the vaccine industry. The work of the Bill and Melinda Gates Foundation has been transformational; there are many vaccine programs that would not have progressed if the Foundation hadn't created a successful model for public-private partnership. At Takeda, we're excited to partner with the Gates Foundation on the development of our polio vaccine, which will enable us to manufacture and provide access to a Sabin inactivated polio vaccine for developing countries. This will be an important component in the polio eradication endgame.

One of the vaccines that my team at GSK developed was the RTS,S malaria vaccine. This vaccine would likely not have been developed were it not for the support of the Gates Foundation and other groups that were willing to collaborate and help fund the development program. This vaccine is not very attractive commercially but is important from a public health perspective, and because of public/private partnerships it's been successfully developed and licensed, and will soon be implemented in malaria-endemic countries in Africa. This is a shining example of how the Gates Foundation has transformed the industry.

Q What changes have you effected since joining Takeda?

With the recent growth in headcount and the number of portfolio programs in Takeda's vaccine business unit, the company needed to better structure its activities. I and many others like me who have come to Takeda from mature vaccine organizations and who have experience in the development and commercialization of vaccines have been able to put in place structures and processes that will ultimately help ensure that Takeda can achieve its ambitions. Our ambition is not only to develop but to appropriately launch and commercialize vaccines that target important infectious diseases with global impact.

What I've learned is you can't just take the kinds of things that might work in a large company like GSK and apply them to Takeda's smaller vaccine unit: that doesn't work because we're very different. To date, I believe we have been able to find a very good balance and bring the right level of structure while not imposing obstacles to innovation and agility.

Almost every day I find myself thinking, 'Okay, who else do I need to get this decision approved?' because in a large organization there are many levels of hierarchy. But in Takeda we do not have many hierarchical levels and the decision-making process tends to be agile and streamlined. It's very different from what I was used to. We're still developing as a unit but are clearly moving in the right direction. I've been very happy since I joined Takeda.

Q What is your long-term vision for Takeda's vaccine business?

Our midterm vision is to develop the four vaccines currently in our pipeline and see them appropriately commercialized. The pipeline includes candidate vaccines against dengue fever, Zika virus, polio and norovirus. Longer term, I believe that Takeda has the potential to continue to develop as a vaccine organization that will be able to successfully address other infectious disease threats.

For example: our Zika program will help prepare us for, and potentially help position us as a company that can rapidly address emerging infectious diseases. This is an important area because the environment we live in seems to be producing more and more emerging infectious diseases, especially as populations expand geographically into areas that result in more contact between humans and animal virus reservoirs. These are diseases that have been quietly circulating in animals for many years which are now jumping species. That's essentially what we've seen with Zika. I believe we are going to continue to see urbanization result in new emergent infectious disease threats. This is an important and exciting area where Takeda can contribute.

Since joining Takeda, it's been exciting to work creatively and collaboratively in the fight against global infectious diseases. We're keenly focused on forging partnerships with leading institutions and collaborating across our functional areas to identify innovative vaccine development platforms. It's my hope that our culture of collaboration and partnership will continue to expedite the development of potentially life-saving vaccine candidates, as well as their distribution to the populations who need them most.

Lucie Ellis
Senior Editor,
Pharma, Europe

Adapt Or Die: Sanofi CSO On R&D Challenges Within Unstable Industry

Sanofi's chief scientific officer Gary Nabel, who joined the company in 2012 from the NIH, discusses R&D challenges for Sanofi and the wider pharma industry, and highlights the company's biggest drug development achievements and toughest moments over the last few years.

In an exclusive interview with *Scrip*, Gary Nabel, chief scientific officer at Sanofi, talks about the biggest challenges facing innovative pharmaceutical companies and highlights programs to watch within the French big pharma's pipeline.

Sanofi has "a particularly strong emphasis on innovation – on trying to capture the latest in scientific excellence to bring into our company and turn into medicines that make a difference to patients," Nabel said when describing his position as scientific chief at Sanofi.

Having joined Sanofi as CSO and senior vice president in 2012, Nabel said his current position within industry is the "third chapter" of his career. Nabel started within an academic medical center where he was a faculty member at the University of Michigan and a Howard Hughes investigator for about 12 years. He then moved on to the US National Institutes of Health, where he was the director of the vaccine research center working on immunizations against HIV, Ebola and universal flu. After 14 years at the NIH, Nabel made the jump into industry.

"During my career, I have been very lucky and happy to experience how medicine and science work in the academic world, the government world and now industry," Nabel said. He joined big pharma to be able to experience in person the route of a new medicine from the lab, to market and to patients.

Source: Sanofi

Gary Nabel, SVP and chief scientific officer at Sanofi

"As much as I liked the work we were doing at the NIH, advancing knowledge and understanding of disease, I really wanted to see first-hand some of the fruits of our science reach patients. There is no more effective way to do that at scale than through the pharmaceutical industry," he said. Nabel works closely with Elias Zerhouni, the former NIH director who heads Sanofi's global R&D.

In the last four years, Sanofi has brought around 14 new medicines to market. "I really live for those moments of discovery and transformation that we can turn into new therapies – particularly for cancer, infectious diseases or autoimmune diseases," he said, adding that he hopes to get as many new therapies across the finish line before entering another career chapter.

UNSUSTAINABLE INDUSTRY

The greatest pressure facing Sanofi and its peers is the current pace and breadth of the pharma industry, Nabel believes. "The pharma industry as we know it today is not sustainable, certainly not with the number of players we have."

Nabel said the sprawling number of players in the sector means companies have to prioritize near-term wins over long-term visions. "While you might prefer to concentrate your efforts on long-term goals, sometimes you are forced to meet short-term goals to survive."

Nabel would prefer a consolidated industry that allows companies to focus on building up research support and scientific excellence, as well as innovation engines, that take the long-term view rather than the short-term. "But it is what it is, and we have to be smart in the way we work," Nabel said. Despite wishing to take a big-picture view of R&D, Nabel said Sanofi knows it must work with a sense of urgency to serve patients that are awaiting effective medicines and stay ahead of the crowd.

To remain strong in an unstable sector, Nabel said Sanofi is pragmatic about the present while also providing a base for the future. "We are trying to create a culture of scientific excellence, trying to set an example and show how innovation can be harvested. We are encouraging this within the company and we are trying to develop new platforms and broader views on how to approach targets."

As an example, Nabel highlighted the company's tri-specific antibody approach to long-acting human immunodeficiency virus (HIV) prevention and treatment. By binding to three different sites on the virus, this new antibody should be harder for HIV to dodge than natural, single antibodies.

"I think this program shows that we are not afraid to take chances and to innovate," Nabel said. "I really like that this approach is so versatile; we have published data in HIV but it's an approach that can be applied to cancer, autoimmune disorders and more."

R&D HIGHS AND LOWS

As well as the company's early-stage HIV program, Nabel highlighted Sanofi's antibody program against transforming growth factor (TGF) beta as one to watch. "At the risk of sounding late to the party, being an immunologist and virologist by training, I think there is a lot more still to come in the area of cancer immunotherapy," he said. TGF beta is a major driver in immune suppression.

Nabel added that his son has gone into a career in oncology, and "when you see what's happening in the trenches in oncology, the immunotherapies are great but they are still only helping a minority of patients."

As well as the TGF beta program in oncology, Nabel highlighted Sanofi's blockbuster-in-waiting drug, *Dupixent* (dupilumab), the first biologic medication approved by the FDA for adults with moderate to severe atopic dermatitis. Dupixent won US approval for the treatment of atopic dermatitis in March 2017, followed by a European nod in September of the same year.

Dupixent – which brought in sales of €75m in the third quarter of 2017, a figure way above analysts' expectations – is also in development for the treatment for asthma. Nabel said the drug is "showing particular promise in asthma patients that don't respond well to other therapies."

A supplemental new drug application (sNDA) for Dupixent in asthma will be filed with the US FDA before the end of 2017. A European regulatory application for Dupixent – an interleukin 4 receptor antibody, which works by modulating the effects of IL4 and IL13 in allergic conditions – is expected in the first quarter of 2018 for asthma.

In parallel with successes Sanofi's R&D machine has also faced more trying times. Nabel said the most difficult moments for him come when the company cannot pursue a target or disease due to external factors, such as the limitation of resources. "I am trained as a physician and a scientist, so when I see an opportunity to bring the benefits of science to patients and I can't do it, for whatever reason, that's the hardest part – it seems like a lost opportunity."

Since joining Sanofi, Nabel has helped the company to restructure its R&D, which he says is an ongoing process known as "R&D 2.0." Sanofi is now using a project-based strategy with a greater focus on its core areas of interests – oncology, immunology and vaccines for example. "About three years ago, we started the process of revitalizing the system to really turn our R&D organization into a research engine," Nabel said, "prior to this, we were maybe a bit diffuse and unfocused."

Upon Nabel's hiring in Nov. 2012, Zerhouni addressed this need for an R&D overhaul within Sanofi. "Our challenges today require that we re-invent our R&D model. Gary's experience will be invaluable to help us achieve this goal," he said at the time.

PARTNERS & ACQUISITIONS

Nabel is keen to foster collaborations between Sanofi and other drug development groups. "I have really encouraged cooperative research agreements and collaborations with biotech and academia," he said.

He believes collaborations, deals and partnerships are vital to the company's future. Sanofi's annual R&D research budget is around €5bn and early research sees less than €1bn of investment, according to Nabel. In comparison, the NIH has a budget of around $30bn. "If we were only to work within our own walls, we would only capture a small amount of the innovation out there," Nabel noted.

Along these lines, Sanofi completed a $650m acquisition of privately-owned Protein Sciences Corp. in Aug 2017. The purchase brought new technology into Sanofi for the development of vaccines using recombinant proteins produced via the infection of insect cells with engineered baculoviruses. This contrasts with the majority of currently marketed products, which are produced in eggs, a process that takes longer and has the potential to be affected by supply constraints. Protein Sciences won FDA approval for a quadrivalent version of its seasonal influenza vaccine in October 2016. *(Also see "Flu Vax Giant Sanofi Defends Corner With $650m Protein Sciences Buy" - Scrip, 11 Jul, 2017.)*

CRYSTAL BALL GAZING

In 2018, Nabel predicts that more pharma merging is on the cards. "We are going to see, at the large pharma level, more consolidation," he told *Scrip*. "There isn't enough to go around, and when that happens we see restructuring at the large pharma level. We will see a shift in the equilibrium towards there being more small- to medium-sized firms."

Nabel drew parallels between the pharmaceutical industry and the technology sector, which has changed significantly in recent years with the rise of smaller businesses out of Silicon Valley. "We are starting to see it already, with mid-sized companies like Vertex Pharmaceuticals Inc. becoming serious players but not on the scale of big pharma," he noted.

Nabel added that the sector is seeing big biotechs like Celgene Corp. experiment with new R&D models to keep up with the pace of innovation and growth within the industry. Also, more venture capital money is being used to support development. "VCs are taking on more risk and investing in projects that before would have been run by pharma," he noted.

Sanofi's CSO predicts that in 2018 pharma will be an interesting space to watch. "One thing I am pretty sure of is that the industry won't be static, it won't remain in its current form."

Kevin Grogan
Managing Editor,
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What's Best For A Pharma CEO, An MBA Or A Medical Degree?

Novartis's chief medical officer Vas Narasimhan is going to replace Joseph Jimenez as the Swiss major's CEO in February 2018; much has been made of the fact that one of the world's biggest pharmaceutical companies will be led by a scientist.

On the face of things, it is not earth-shattering news that someone with a medical background should be at the helm of a science-centered multinational but the majority of pharma companies have tended to plump for CEOs more noted for their commercial experience. Indeed, a quick glance at the heads of some of the biggest companies show that a legal or business background helps if you are in the running for the top job.

Ian Read, who has been Pfizer Inc.'s CEO for eight years, qualified as a chartered accountant, while Johnson & Johnson's chief executive Alex Gorsky began his career at the healthcare giant as a sales representative with Janssen Pharmaceutica Inc. Kenneth Frazier, who is coming up to seven years as Merck & Co. Inc.'s CEO, was a lawyer representing the firm before he went in-house as general counsel, while Roche's Severin Schwan studied economics and law before being taken on as a trainee in the Swiss major's corporate finance department.

GlaxoSmithKline PLC's new CEO Emma Walmsley has a master's degree in classics and modern languages from Oxford University. Prior to joining GSK in 2010 (becoming head of the consumer healthcare division in 2015) Walmsley worked with L'Oreal for 17 years, holding a variety of marketing and general management roles. And at the end of last year, chemist John Lechleiter stepped down as Eli Lilly & Co. chief executive and was succeeded by Dave Ricks, who has an extensive background in sales and marketing.

The appointment of Narasimhan at Novartis prompted some analysts to ponder whether having a scientist at the top would help the company get even better at selecting compounds for future drug development. Others suggested that he would be able to act as an effective bridge between the research and commercial arms of the company.

So, given the mighty scientific leaps being made by the pharma sector, will we see a shift to more R&D people at the top of the top companies? *Scrip* asked AstraZeneca PLC CEO Pascal Soriot for his thoughts at the European Society for Medical Oncology meeting in Madrid in September 2017.

Soriot's educational background combines science and business. He was a doctor of veterinary medicine before he decided to do a Master of Business Administration (MBA) degree at HEC Paris. He held a number of roles at Aventis before joining Roche as head of marketing and then becoming CEO of Genentech, where he led the latter's merger with the Swiss group. He was chief operating officer of Roche's pharmaceuticals division until 2012 when he was poached for the top job at AstraZeneca.

He said, "There is not one single way to do things, you can manage in different ways and it comes down to personality." In Soriot's case, however, "I feel it is important to stay close to the physicians – personally I have known many of them for years, whether in diabetes or oncology, and each time you listen to them, they give a view."

Talking to clinicians "can really help you think things through about pricing, the risks and opportunities. At the end of the day, as CEO you have to make decisions on where you allocate resources and the prices you'll set – it is useful to have a view that has not only been formed from spreadsheets."

Soriot added that while it is good to have that additional voice of physicians, a CEO must have the ability to listen to the whole range of experts in their company, legal and commercial too. The AstraZeneca chief will remain as one of the few CEOs seen wandering cavernous congress halls, attending sessions and reading posters – "personally, I love it, that's why I'm here," he told *Scrip* at ESMO.

As for Narasimhan, as well as earning a biological sciences degree from the University of Chicago, he got his medical degree from Harvard Medical School and obtained a master's degree in public policy from Harvard's John F Kennedy School of Government. Prior to joining Novartis in 2005, Narasimhan worked as a consultant with McKinsey and at the Swiss giant.

So does an MBA (as well as Soriot, Gorsky and Ricks have one) count for more than a medical degree when it comes to heading up a big pharma company? Probably not, but a mixture of science and business looks a very useful combination – it has certainly worked for Narasimhan.

CLICK

For a table of top CEOs and their educational roots: bit.ly/LeadershipS100

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THE CHANGING ONCOLOGY LANDSCAPE: An Interview with Medpace's Franklin O. Smith

Dr. Franklin Smith, Medpace's vice president of medical affairs and specialist in hematology oncology, reflects on advances in oncology drug development.

Q How has the landscape for oncology treatment changed, given the breakthroughs in cancer immunotherapy and precision medicine?

It is important to understand where we have been and how we got to this point because that lays the foundation for current to future cancer therapy. Over the past one hundred years, cancer therapy has evolved so that it's based upon four modalities: surgery, radiation therapy, chemotherapy, and hematopoietic cell transplantation. These modalities are not going to go away anytime in the foreseeable future, but there are likely very few opportunities for big, significant improvements in each of these four areas.

We are now at an exciting time in medicine where we can harness the full power of science and biology, finding ways to take advantage of science, to develop new therapies for patients, such as immunotherapy or immuno-oncology.

Franklin O. Smith, MD, FAAP, FACP

One of the questions that has intrigued scientists and oncologists for decades has been, 'With this very powerful immune system, why does cancer exist? Why doesn't our immune system just take care of it?' What scientists have found is that cancer has found ways to evade the immune system, so these new immunotherapies are based upon ways to now target those evasive maneuvers to make the cancer "visible" to the immune system.

There are two broad categories of immuno-oncology. One is based upon monoclonal antibodies, which block these signals that hide the cancer cells from the immune system. These are called checkpoint inhibitors. The other are cellular therapies, such as CAR-T (chimeric antigen receptor T-cells), which can be genetically engineered to make them into "angry" T-cells, that can specifically target cancer cells.

Immuno-oncology is not going to necessarily replace chemotherapy, surgery, radiation and hematopoietic cell transplantation, but it is increasingly finding its role in cancer therapy. It is probably now starting to replace some chemotherapy, and I think that for the next 10 years, much of the work we are going to see in cancer research and clinical trials is going to be based upon immuno-oncology approaches.

In addition to an increasingly large number of CAR-T cell and similar immune effector cell therapies, we are going to see different combinations of checkpoint inhibitors and checkpoint inhibitors paired with other types of drugs, such as epigenetic modifiers. The next decade of cancer research will likely be based on combination therapies that are largely based on these exciting checkpoint inhibitors.

In terms of precision medicine, I prefer the term 'increasingly precise medicine' because I think physicians have always used personalized therapy for their patients. As we learn more and more about the biology of cancer, medicine and approaches to the treatment of patients gets increasingly sophisticated, and the treatment of patients becomes increasingly precise.

What we are learning now is that there is great heterogeneity in human beings; there is great heterogeneity in cancers. A lot

of these cancers are driven by a relatively small number of driver mutations. If we can understand what is driving a cancer—what is making it resistant to known forms of therapy—we can offer that patient a treatment that is directed specifically to what's driving the cancer. Understanding more about the patient and his/her cancer's biology, we can now start to identify specific treatments that are targeted to specific abnormalities.

Tying these concepts together, we still have the foundation of cancer therapy with chemotherapy, surgery, radiation, and hematopoietic cell transplant, but importantly, we now are adding onto that foundation better knowledge of cancers and drugs that may be more targeted to specific abnormalities in that patient's cancer. We are now learning how to harness the incredible power of the immune system to seek out and kill cancer cells, where these cancers previously had been "hiding in plain sight" from the immune system.

Q What are the key challenges in designing protocols for oncology studies?

We are moving away from assigning treatment based upon the tissue from which the cancer arose. What we are finding is that by using this approach, we have more drugs to test than we have patients available. In terms of designing protocols, we still must assess safety, efficacy and how a new approach to treatment compares to standard approaches. How do we test the large number of drugs and therapies that are becoming available to us when we have an increasingly small number of patients defined by molecular characteristics? This is a great problem to have, but it is a problem, as the competition for patients to enroll on these exciting clinical trials is becoming increasingly challenging.

In terms of our work at Medpace, this challenge can be overcome by outstanding feasibility work and our ongoing work with dedicated and enthusiastic investigators.

Q How do you think master protocols will impact advances in oncology drug development?

Given the paradigm shift to base treatment on identified molecular targets, master protocols are the wave of the future. These study designs are an efficient and effective way to test numerous targeted agents in the context of a single protocol. I have the honor to serve on the Board of Directors for the Leukemia & Lymphoma Society (LLS), which has a master protocol for acute myeloid leukemia (AML). The LLS serves as an "honest broker" to negotiate with numerous pharmaceutical and biotech companies to have their drugs brought into a common master protocol.

A single protocol testing numerous agents also decreases the burden of scientific review, institutional review board and ethics committee review because everything is embedded within a single protocol.

Given the increasing number of drugs and potential molecular targets, remarkable advances in our understanding of the biology of cancer, and the complexity and expense of executing clinical trials, I think we are going to see an increase in the number of these master protocols over the next decade.

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Sten Stovall
Senior Editor,
Pharma, Europe

Global CRISPR Revolution Gathers Pace, Raising Hopes – and Concerns

CRISPR technology was invented just five years ago but is so accurate, versatile, easy to use, and inexpensive that it has spread quickly through biology laboratories, giving researchers new tools to interrogate biology and make precise alterations to an organism's genetic material, offering its potential use in a wide array of therapies.

CRISPR and similar gene editing technologies are giving researchers new tools to interrogate biology and make precise alterations to an organism's genetic material. The medical and commercial promise emerging from this disruptive technology is huge.

But the speed with which CRISPR techniques are being developed and applied has made mainstream news and led many policymakers and stakeholders to voice worries about whether appropriate systems are in place to govern these technologies and how and when the public should be engaged in these decisions.

CRISPR, which is short for Clustered Regularly Interspaced Short Palindromic Repeats, made headlines in August 2017 when scientists at Cambridge, Massachusetts-based eGenesis Inc. used the gene editing technology to inactivate a family of viruses in pigs, which could pave the way for transplanting organs from those animals into humans.

INACTIVATION OF PERV IN PIGS USING CRISPR/CAS9

Porcine endogenous retrovirus (PERV), found in the pig genome, can infect human cells. Once infected, these cells can pass the virus onto other cells. To fight this, researchers at eGenesis, a recent start-up, used CRISPR to cut the retrovirus out of the genome in primary fibroblast cells taken from pigs. They then cloned the cells, creating retrovirus-free pig embryos that were implanted into surrogate sows. The piglets were the first to be born without active PERVs, and the team will monitor them for any long-term side effects.

While such CRISPR innovations provide concrete examples of the technology's promise, the ethical issues raised by the technology's potential are also fanning concerns.

CO-CREATOR CONCERNS

CRISPR co-inventor Jennifer Doudna, an American biochemist based at the University of California, Berkeley, now openly expresses such worries, while also underscoring the benefits CRISPR offers.

She told BBC radio in September that CRISPR represents "an incredible opportunity and a challenge for human beings."

"The opportunity is that we now have the ability to correct or even if you take it out long enough you could imagine removing very deleterious sequences of DNA from the human population … But what I feel people feel more repulsed by is the whole idea of eugenics that formed around CRISPR," she said, adding: "would we really want a world where we're controlling the genetics of every person?"

The US National Academy of Sciences, an international group of scientists, in June 2016 called for a moratorium on human germline editing until CRISPR's risks had been assessed. But the science is moving fast and such urgings for restraint will be hard to put into practice. Scientists meanwhile say that while CRISPR is not generally ready for clinical use, it is getting there via slow, incremental advances.

The legal drama in which Doudna and others are embroiled - over who owns the underlying IP for the CRISPR approach - continues meanwhile to bubble under the surface, and is likely to do so for years, threatening, in the minds of some observers, to end in a commercial train crash if not resolved in an orderly fashion, given the technology's promise for generating innovative therapies.

CORPORATE CRISPR IP

Despite that legal uncertainty, however, companies are motoring on with their CRISPR activities, with some saying they are focused on the so-called second level of IP rights, to avoid being caught up in future litigation.

One of the pioneers harnessing CRISPR/Cas9 to develop human therapeutics, Switzerland-based CRISPR Therapeutics AG is confident its lead program in sickle cell disease and beta-thalassemia therapies will generate a product launch by 2022, and that the ongoing global patent wrangling over the technology won't get in the way of that objective.

It is one of four companies working with the gene editing CRISPR/Cas9 technology - the others being Intellia Therapeutics Inc., Caribou Biosciences Inc. and ERS Genomics Ltd. - that have made a pact with each other and with the three owners of their intellectual property to manage the patent prosecution work, share the associated costs and cross-license necessary IP.

Sam Kulkarni, CRISPR Therapeutics' CEO, spoke to *Scrip* about the company's preclinical work on sickle cell and beta-thalassemia therapies, and about the importance of IP within academia and the corporate world.

He stressed in an interview that companies need to distinguish between two things with regards to IP: "If you are a company, the first is the freedom to operate, and the second is the ability to protect your IP and your drug from competition."

"Essentially all the legal wrangling that is happening is around the legal foundation – who owns the rights to CRISPR to develop medicines … There are many possible outcomes here. It may turn out that one side wins; it may also turn out that there's a settlement of sorts, and it's also possible that there's some IP that one party gets and some IP that another party gets, but which would need to be resolved so that all parties are satisfied," Kulkarni explained.

Regarding second-level IP, beyond the foundational IP, he believes "the way to win in that space is through continuous innovation. CRISPR itself as a tool is great at cutting DNA or making double-stranded breaks. The real art and the science of it in developing drugs is going to be in how to apply and how to deliver CRISPR into the right cell types or organ types; how do you understand the pharmacology of the drug? Or the DNA editing? And then how do you manufacture it in the right way to make it available to patients in a high-quality fashion? All those aspects require a lot of innovation. And as we go along and we for example develop our drugs in sickle cell and beta-thalassemia, there are a number of things that we'll continue to patent along the way. And that's going to be helpful to protect our IP position as we continue to invest in that drug," he said.

There's another type of second-level IP, around how scientists make their CRISPR gene-editing platform perform better.

"CRISPR itself is good enough for 70% to 80% of the applications as we perceive them today but there may be applications where you need a smaller Cas9; there may be applications where you need a more specific Cas9; there may be applications where you need to reduce the immunogenicity. And we're doing a lot of the work to improve the platform - that that's where our joint venture with Bayer AG comes in."

"Bayer are investing heavily to improve that platform. So, we'll wait to see how the foundational IP legal wrangling turns out but we will continue to innovate along the way in the meantime."

Kulkarni and other experts say the pace of Cas9 development is only accelerating. Researchers are enhancing the functionalities of the approach at phenomenal speed, making it more specific, efficient and easier to use in a variety of biological contexts. It is already one of the most powerful and precise genomic engineering tools to date and more exciting developments are ahead, as scientists continue to unravel the CRISPR-Cas9 system.

CRISPR Therapeutics is confident its lead program in sickle cell disease and beta-thalassemia will generate a product launch by 2022.

Amanda Micklus
Principle Analyst,
Pharma Insights

Gene Editing: A Powerful, Growing Modality In Regenerative Medicine

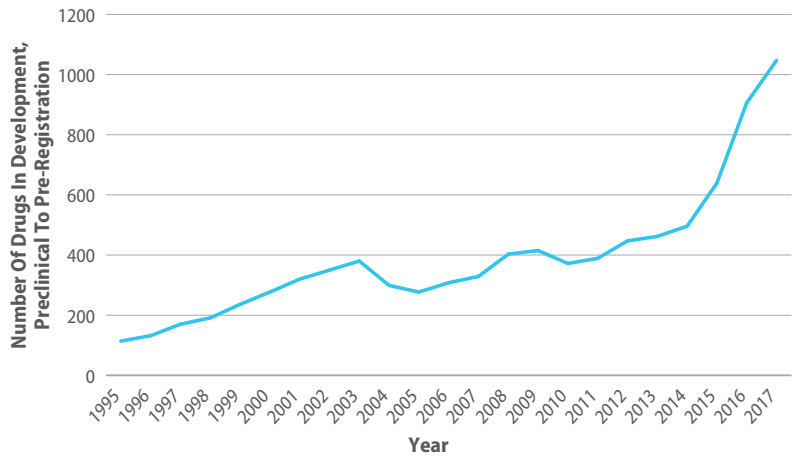
Regenerative medicine has made advances in recent years to emerge as one of the key fields with a chance of addressing, and even curing, diseases that until now had few or no treatment options.

These regenerative methods have far-reaching potential and mark an important next wave of research targeting genetically defined diseases, as well as chronic or life-threatening disorders that are underserved or not yet addressed.

Broadly defined, the regenerative medicine market encompasses a wide range of treatment modalities that help to repair, replace or regenerate lost functionality in tissue that has been damaged because of disease, injury or aging. How regenerative medicine is specifically characterized can vary, but it generally includes therapeutic- or pharmaceutical-based treatments, devices or types of engineered materials.

Government initiatives have been helping to move the regenerative medicine field forward, including the 2007 regulation introduced in the EU to govern advanced therapy medicinal products (ATMPs), and most recently, the creation of the regenerative medicine advanced therapy (RMAT) designation in the US under the 21st Century Cures Act.

EXHIBIT 1. GROWTH IN REGENERATIVE MEDICINE PIPELINE, 1995–2017



Source: Pharmaprojects

In parallel, there has been exponential growth in the regenerative medicine therapy pipeline. In 1995, there were 114 drugs from preclinical through to pre-registration phases in development; by 2017, that figure had increased to over 1,000. The volume has been steadily growing year on year since 2010 *(see Exhibit 1)*. A sharp uptick starting in 2015 was the result of an investment resurgence in this area, particularly in gene therapy, which had dropped off following patient deaths in clinical trials at the end of the 1990s. This revival was also prompted by the promise of the field following several product launches outside of the US.

The regenerative medicine pipeline is led by *in vivo* gene therapies, which account for 30% of the volume. The next generation of these products has improved in safety over initial treatments. Gene therapy developers have become more targeted when it comes to the patient populations being treated and more niche indications, and by focusing in on parts of the body that are somewhat separated from the immune system and antibodies that might attack. There have also been improvements in the delivery vectors used. Altogether, the potential for gene therapies to offer single-treatment cures of genetically defined diseases will ultimately continue to move this class forward.

In the current pipeline, approximately 3% of the volume of candidates are gene editing therapies. While the proportion is small, gene editing presents a unique and potentially paradigm-changing opportunity in the regenerative medicine market. The underlying principle of gene editing is to make precise changes to DNA in a cell. As opposed to gene therapy – which essentially provides a gene or genetic instructions for the cell to use – gene editing permanently and more precisely changes a cell's genome. There are high hopes this modality will provide a way to radically impact how diseases are targeted. Across the gene editing therapy pipeline, the most active companies range from discovery-stage biotechs to large pharmaceutical companies. The

key clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9) companies are well represented, including Editas Medicine Inc. and CRISPR Therapeutics AG, which each have 10 candidates in development (either as an originator or licensee). Among the big pharma (companies with annual revenues in excess of $15bn) and mid pharma peer sets, Shire PLC, Pfizer Inc. and Bayer AG have stakes in gene editing *(see exhibit 2)*.

The pipeline of gene editing drug candidates is dominated by clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (Cas9) technology. There are nearly 60 gene editing therapies currently in development from preclinical through Phase II (the most advanced stage for any gene-edited candidate in the pipeline presently), and 74% of them use the CRISPR/Cas9 method. It is a clear indicator of the interest and investment in this latest generation of gene editing technologies for the long term, and companies' vision that it has the most potential for producing new therapies as a result. At much smaller proportions, zinc-finger nuclease (ZFN) therapies account for 14% of the pipeline (all of these exclusively owned by Sangamo Therapeutics Inc.), and transcription activator-like effector nuclease (TALEN) candidates take a 10% share (sourced solely from Cellectis SA).

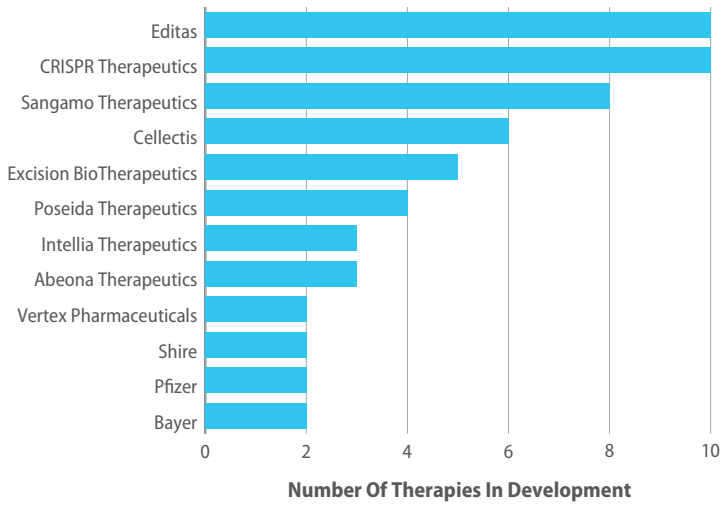
While CRISPR/Cas9 candidates are the most abundant in the gene editing pipeline by volume, they are further back in development, reflecting the relative newness of this method in gene editing drug development. All of the CRISPR/Cas9 therapies are in preclinical studies, although there is ongoing academic research to test the application of CRISPR/Cas9 in humans. In contrast, ZFN, which has been in practice a lot longer by Sangamo, is incorporated into more advanced programs. The majority of ZFN candidates (those from Sangamo) are in Phase II.

Similar to CRISPR/Cas9, there is a higher volume of TALEN therapies in the preclinical setting, although Cellectis has two candidates in Phase I, including programs partnered with Pfizer and Servier.

Rare diseases, many of which are genetically defined, are the primary targets for gene editing candidates in the pipeline *(see Exhibit 3)*. The same holds true when filtering down to most gene editing methods. For both CRISPR/Cas9 and ZFN technologies, the volume of therapies in development is higher for rare diseases than for any other therapy area. Other primary therapy areas where overall gene editing is active include oncology, blood and clotting diseases, and infectious diseases. (It is worth noting that these therapy area categories also include rare diseases that are counted in the separate "rare disease" category.) CRISPR/Cas9 therapies have a broader reach, with development in several other areas. In contrast, TALEN editing candidates to date have been focused on cancers, many of which are rare diseases themselves.

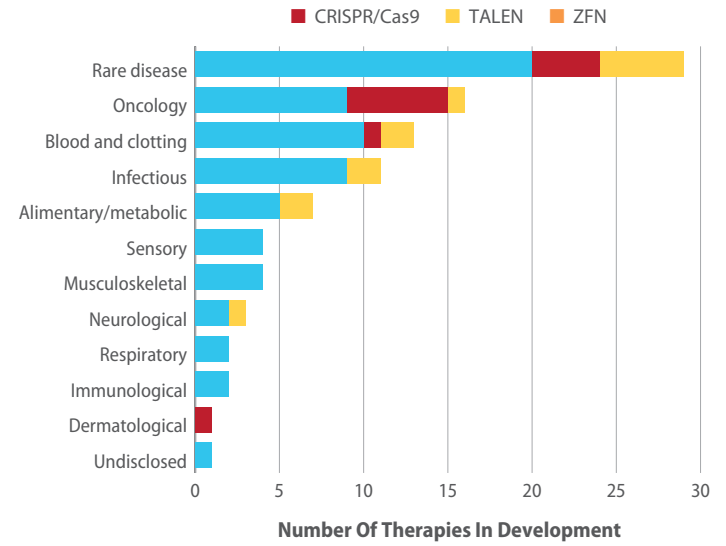
Within the broad category of rare diseases are several unique indications that are active in development. Leading that group of rare disorders is thalassemia, for which four preclinical therapies are in the pipeline. Both Poseida Therapeutics Inc. and Editas are working on candidates themselves, while CRISPR Therapeutics and Sangamo Therapeutics have secured bigger partners: Vertex Pharmaceuticals Inc. and Bioverativ Inc., respectively.

EXHIBIT 2. MOST ACTIVE GENE-EDITING COMPANIES



Source: Pharmaprojects

EXHIBIT 3. MORE GENE-EDITING THERAPIES FOR RARE DISEASES



Source: Pharmaprojects

John Hodgson
Executive Editor,
Pharma, Europe

Impairment And Youth Boost R&D Spending

Spending on R&D increased substantially in 2016; but the picture is complicated and more than half of the increase is due to accountancy updates following drug program failures, one large company's commitment to new projects and young companies fuelled by generous financial markets.

The Scrip 100 universe contains around 750 companies. In looking at research and development expenditure, the study focuses on data from 621 companies for which the R&D expenditures are known both for FY 2016 and FY 2015.

In that set:

- R&D spending in 2016 was up 7.5% on 2015 at $157bn;
- two-thirds of companies increased their R&D spending from 2015 to 2016;
- and R&D spending as a proportion of drugs sales increased slightly from 20.33% in 2015 to 20.63% in 2016.

Within the largest 100 companies by sales (the Scrip 100):

- R&D spending was 18.81% of drugs sales in 2016, virtually unchanged from 2015;
- the top 100 spenders account for 88% of total R&D spending;
- and the top 20 account for over two-thirds (68%) of total R&D spending.

These headline numbers paint a picture of a dynamic industry, devoting the same high proportion of its product sales to finding new drug-based fixes for disease while simultaneously satisfying shareholders demands for a return on their investments. However, R&D expenditure, as accounted for in company annual reports, is not everything that it seems.

EXHIBIT 1: GROWTH ACROSS THE INDUSTRY, LESS SO AMONG THE BIGGEST COMPANIES

	R&D SPENDING ($BN)			
YEAR	ALL COMPANIES*	TOP 100 R&D SPENDERS	TOP 20 R&D SPENDERS	COMPANIES WITHOUT SALES
2016	157.0	138.9	101.7	13.72
2015	146.0	132.0	96.5	10.76
Change (2016 as % of 2015)	+11.0 (+7.5%)	+6.9 (+5.2%)	+5.2 (+5.4%)	+2. 96 (+27.5%)

*Data from 621 companies with R&D spending in both 2015 and 2016

Firstly, not all R&D is equal. In younger and more naïve companies, R&D expenditure in the account may reflect the costs of trying to establish the practical reality of the research phenomenon. As companies progress, most expenditure is devoted to confirmatory experiments – late-stage clinical trials that are essential to commercial progress but lack significant scientific value. As a company's products hit the market, R&D spending is increasingly focused on projects that straddle the fuzzy border between product development and marketing. Some development – such as comparative studies involving rival products – is rarely undertaken. When a company draws up its account, all these different aspects of R&D are lumped into the same reporting line.

One other, rather odd, dimension also contributes to R&D spending totals: the concept of R&D impairment. R&D impairments represent value that is written off when a project (often one that has been acquired) fails or underperforms.

The impact of impairments is nicely illustrated by the fluctuating R&D expenditure reported by some of the world's largest pharmaceutical companies (*see Exhibit 2*). At the top is Merck & Co. Inc., last year the fifth biggest spender of R&D dollars. In 2016, it rose above Roche, Novartis AG, Pfizer Inc. and Johnson & Johnson to take the top spot following a $3.4bn (51%) increase in R&D spending. However, its $10.12bn figure includes $3.6bn in R&D impairments, most of which ($2.9bn) was associated with a re-evaluation of uprifosbuvir, an HCV nucleotide prodrug. Uprifosbuvir was one of the HPV assets Merck acquired in 2014 when it bought Idenix Pharmaceuticals Inc. for $3.7bn net of cash. *(Also see "Merck's Write-Down Of Phase II Nuc Illustrates Current Reality In HCV" - Scrip, 24 Feb, 2017.)*

Since then, uprifosbuvir has sat around in Merck's accounts either as "goodwill" or "intangible assets" that balanced the outlays used to buy Idenix. Since 2014, Merck has piled in more money to bring the drug to the market. A year after the HCV drug sales of market leader Gilead Sciences Inc. peaked, recognizing that its compound could not be competitive in a market closed off by Gilead's

EXHIBIT 2: COMPANIES WITH THE LARGEST CHANGES IN R&D SPENDING, 2015-2016

COMPANY	PHARMA R&D ($M) 2016	CHANGE FROM 2015	NOTES	DIFFERENCE FROM 2015
Merck & Co	10,124	51.0%	IPR&D impairment charges of $3.6bn	3,420
Gilead Sciences	5,098	69.1%	$430m impairments; Vigorous programs in cancer and inflammation	2,084
Celgene Corp.	4,470	20.9%		773
Teva Pharmaceutical Industries Ltd.	2,111	38.4%		586
Bristol-Myers Squibb Co.	4,940	-16.6%	Completion of some large Opdivo trials; absence of 2015 $160m R&D impairment	-980
GlaxoSmithKline PLC	4460	-11.6%	Sale of cancer portfolio to Novartis and Brexit	-586

success, Merck reduced its holding value of uprifosbuvir to just $240m, and piled the expense onto the R&D line.

In essence, Merck's ill-fated investment in Idenix has taken two years to find its way onto the company's income statement.

Gilead's 69% increase in R&D spending also contains $430m worth of R&D impairments on terminated compounds even though most of its $2.1bn increase in R&D spending represents its next clinical thrust in oncology and inflammatory disease. In 2016, it doubled spending on outside clinical studies (e.g. CRO-managed clinical work) from $1.6bn to $3.2bn.

Other companies' rises or falls in R&D spending didn't match the magnitude of the changes at Merck and Gilead (*see Exhibit 2*).

Celgene Corp. added nearly 21% to its R&D spending, partly through a $300m increase in early discovery and development programs. R&D spending at Teva Pharmaceutical Industries Ltd. rose 38%, reflecting an extension of late-stage clinical trials and increased up-front fees in its collaborations with Regeneron Pharmaceuticals Inc. and Celltrion Inc. The big reductions reported by Bristol-Myers Squibb Co. and GlaxoSmithKline PLC were due largely to the completion or disposal of expensive late-stage clinical programs although, for BMS, $160m of the decrease in R&D spending was attributable to an R&D impairment recognized in 2015.

The two R&D-related impairments from Merck and Gilead (and the absence of BMS's) account for nearly $3.9bn of the $5.2m additional spending reported for FY 2016 by the top 20 biggest drug companies. For this group, in effect, nearly 75% of the apparent increase in R&D spending is just accountancy mop-up after failed development projects; real growth in R&D spending in pharma's top tier was just 1.4%.

INVESTOR-FUNDED R&D

Another major source of variability in R&D spending between FY 2015 and FY 2016 is the expansion of activity reported by companies without pharmaceutical sales. This "drugless" set of companies, often self-styled as "development-stage" companies, all have research and/or development programs oriented to pharmaceuticals.

Drugless companies are, perhaps, an odd group to highlight in the context of the Scrip 100, which usually is about firms with prescription drug sales. However, they provide an additional engine for the generation of new drugs. R&D spending among drugless companies rose to $13.7bn in FY 2016 (8.7% of the total spend in the sector) from $10.8bn in FY 2015.

Within the drugless set, firms that underwent an initial public offering in the 2013-2016 window accounted for $7.9bn (57%) of drugless R&D spending in FY 2016 and 77% ($2.2bn) of the rise in spending among the drugless group. Around 87% of the R&D spending among development-stage firms occurs in US or Canadian companies.

SUMMARY

Two factors distort what appears to be a healthy $11bn (7.5%) increase in spending on drug R&D of in FY 2016 compared with FY 2015.

One is the exceptional level of R&D impairment. Myriad impairments to R&D assets usually balance each other out in year-on-year comparison. But in 2016, two R&D impairments stood out; they were responsible the transfer of around $4bn worth of lost value in R&D project from lines on the balance sheets of Merck and Gilead to lines of expenditure.

The second distorting factor for 2016 is the level of increased R&D activity amongst development-stage public companies without drug revenues. These are companies that, in effect, are being bankrolled with investor money, much of it from the public financing glut of 2013-2016. This accounted for $2.2bn of the apparent increase in overall R&D spending between 2015 and 2016.

Adjusting for these factors, therefore, a better estimate might be that R&D expenditure rose $4.8bn in FY 2016 over FY 2015, a change of just 3.3%.

Eleanor Malone
Editor-In-Chief,
Pharma, Europe

Joerg Moeller, Bayer Development Chief, On R&D Consolidation

Joerg Moeller, Bayer's current head of development for pharma, who takes the helm for the wider R&D group from January 2018, talks about the German firm's R&D consolidation strategy.

Q Tell me about the motivation for the consolidation of the R&D activities at Bayer Pharmaceuticals.

We have come to realize that we can improve how seamlessly we work together in research and development. We will have a smoother hand-off between the various functions by having it all under one roof, we can think about integrated project management, and there are a number of ideas that we want to implement in order to further drive efficiency in the research and development organization.

Q How long have you been planning it?

In my view there's never an ideal organization. You have an organization that you think addresses what the company needs. It typically never addresses 100% of what a company needs. If you are good it addresses 90%. As for the remaining 10%, over time you realize there's a problem we want to address, and you start thinking 'ok, maybe now it's time to get into a different set-up.'

Q How does the oncology strategic business unit fit under this new umbrella? I've seen some speculation that this change brings it back in.

No, no, no. The strategic business unit for oncology is not affected by this. Oncology research has always been part of the research organization and that will not change, but there is no effect of this reorganization on oncology.

Q Do you have preserved budgets for each therapeutic area?

No, we always look at what our key priorities are. I don't believe in fixed budgets because they don't give you the flexibility to shift according to your needs. So while of course we have a budget plan and we also have an allocation to functions, it is important that we maintain some flexibility to potentially react to shifting priorities.

Q But there is some kind of strategy plan going to come out this year?

Bayer was a €10bn pharma organization around 2010, and we are well on our way to being a €20bn sales pharma company around 2020. That alone requires a different R&D engine to support a €20bn business compared to where we were some time ago.

Q Bayer's pharma pipeline currently has 20 Phase I programs, 14 Phase II programs and 14 Phase III programs. Is that about the right number for now or are you looking to expand that?

Well we don't have a certain number right now. Actually, if you look at an R&D portfolio, yes, you have number of projects, but you also have to consider how many of these projects will survive the various stages. And you can have maybe a smaller number, but if you have the ability to really have good quality in these projects and therefore a higher percentage of them survive, then it also addresses the portfolio needs. So there's different ways to play the game.

Q Can I ask you about the complexity nowadays of R&D – it's not just moving molecules through trials. How have things changed in terms of building factors like reimbursement, payers, rapidly changing landscape of comparators (especially in oncology) into planning?

It has fundamentally changed the R&D process. At the very early stages of clinical development we now start thinking about market access. And what it also means is that the level of innovation that you need to target for has increased. When I started in this industry in 1993 you could still have a good economic case when you were number seven or eight in a compound class. Those days are over. So you need to drive your speed, you need to drive your efficiency, but most importantly, we need to set ourselves really ambitious goals and speculate where the standard of care will be maybe 10 years down the road. And I prefer to aim high, because you don't want to invest all the time and resources and find out that what you bring to the table is not really perceived as attractive innovation – because innovation is not defined by us, it's defined by prescribers, by patients and by payers.

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Daniel Chancellor
Lead Analyst,
Datamonitor Healthcare

Will J&J TRANSFORM Esketamine Into A Viable Depression Treatment?

In early 2018, Johnson & Johnson is expecting to announce the first data from its long-awaited pivotal clinical trial program for esketamine in treatment-resistant depression; a successful result will open a lucrative commercial opportunity for J&J and give the wider depression market a new direction for growth.

Esketamine efficacy is already well established, with the main hurdle to overcome being to demonstrate that a recreational drug can be safely formulated into an appropriate prescription therapy, controlling the risks for abuse, addiction, and bladder toxicity.

J&J is developing an inhaled, intranasal formulation of esketamine as a potential adjunctive treatment for major depressive disorder patients who do not respond adequately to conventional antidepressants. The development of esketamine is a direct result of previous data suggesting the rapid and large antidepressant effect of the recreational drug ketamine. Ketamine is a racemic mixture that acts as an N-methyl-D-aspartate (NMDA) receptor antagonist. It is thought that the NMDA receptor and glutamatergic signaling mediate the delayed response of conventional monoaminergic-based antidepressants, and that blocking the NMDA receptor would result in a rapid antidepressant effect. Esketamine is the S-enantiomer of ketamine, with a three-to-fourfold higher affinity for the NMDA receptor than arketamine.

Treatment-resistant depression represents a big unmet need as existing therapies are completely ineffective in one third of patients and only partially effective in another third. This leaves many patients with a chronic, debilitating condition and few viable treatment options. It is among these patients that esketamine is being tested, and where regulators may be more likely to approve a drug with potential safety considerations. Ketamine is a popular recreational drug owing to its dissociative effects, leaving J&J with the challenge of mitigating the risk of abuse and addiction. Ketamine is also associated with severe bladder and urinary tract side effects in regular users, which at worst can necessitate surgical intervention.

SIX PHASE III TRIALS COMPLETING IMMINENTLY

Having successfully demonstrated that a single dose of esketamine, given intranasally, could yield an unprecedented improvement of 6-9 points on the Montgomery-Asberg Depression Rating Scale (MADRS) in the Phase II SYNAPSE trial, J&J initiated an extensive Phase III clinical trial program. These studies, which include short-term placebo-controlled trials among patients already receiving background antidepressant therapy (TRANSFORM-1, -2, and -3), as well as longer-term safety and efficacy studies (SUSTAIN-1, -2, and -3), are completing imminently. According to *clinicaltrials.gov*, TRANSFORM-2 and -3 completed this summer, although J&J's latest guidance is that it intends to disclose the first trial results in early 2018.

ADJUNCTIVE MARKET COULD BE WORTH BILLIONS

Positive data from the TRANSFORM and SUSTAIN clinical trials will position esketamine as a long-term option for treatment-resistant major depression in patients who have failed to respond adequately to their standard antidepressants. In this setting, esketamine would be competing with the atypical antipsychotic class, as well as other common adjunctive antidepressants such as mirtazapine, which in 2015 equated to an estimated $3.2bn segment of the depression market in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK).

Considering the sheer number of patients who are not getting adequate benefit from their treatments, and the shortcomings associated with common adjunctive therapies, esketamine has a large market opportunity.

The increase in the use of atypical antipsychotics for the treatment of depression has been one of the rare commercial success stories for psychiatry in recent years. Spearheaded by the approvals of *Abilify* (aripiprazole; Otsuka) and *Seroquel* (quetiapine; AstraZeneca/Astellas), in addition to considerable accompanying direct-to-consumer promotion, physicians and patients have added depth to the treatment algorithm should

EXHIBIT 1. ESKETAMINE PHASE III TRIALS IN DEPRESSION

TRIAL	SAMPLE SIZE	TARGET PATIENTS	STUDY DESIGN	TREATMENT ARMS	PRIMARY ENDPOINTS	START DATE/PRIMARY COMPLETION DATE
TRANSFORM-1	348	MDD patients with inadequate response to antidepressant therapy	Double-blind, placebo-controlled, fixed-dose	Esketamine 56mg, 84mg, or placebo, adjunctive to standard antidepressant therapy.	Change from baseline in MADRS	August 2015/ April 2018
TRANSFORM-2	196	MDD patients with inadequate response to antidepressant therapy	Double-blind, placebo-controlled, flexible-dose	Esketamine 56–84mg or placebo, adjunctive to standard antidepressant therapy.	Change from baseline in MADRS	August 2015/ June 2017
TRANSFORM-3	148	Elderly MDD patients with inadequate response to antidepressant therapy	Double-blind, placebo-controlled, flexible-dose	Esketamine 28–84mg or placebo, adjunctive to standard antidepressant therapy.	Change from baseline in MADRS	August 2015/ August 2017
SUSTAIN-1	333	MDD patients receiving stable esketamine and antidepressant	Double-blind, placebo-controlled, flexible-dose, relapse-prevention	Esketamine 56–84mg or placebo, adjunctive to standard antidepressant therapy.	Time to relapse	October 2015/ April 2018
SUSTAIN-2	1,071	MDD patients receiving stable esketamine and antidepressant	Open-label, long-term extension	Esketamine 28–84mg, adjunctive to standard antidepressant therapy.	Change from baseline in BPIC-SS; CogState computerized cognitive battery domains; HVLT-R, and incidence of withdrawal symptoms	September 2015/ October 2017
SUSTAIN-3	330	MDD patients receiving stable esketamine and antidepressant	Open-label, long-term extension	Esketamine 28–84mg, adjunctive to standard antidepressant therapy.	Number of participants with treatment-emergent adverse events	June 2016/ August 2021

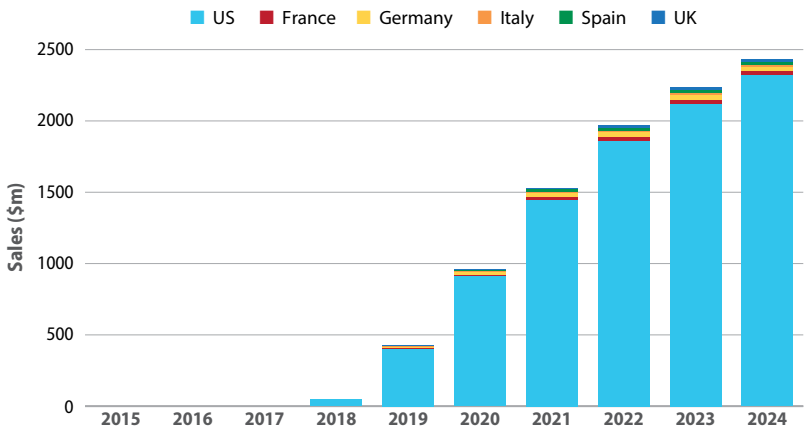
BPIC-SS = Bladder Pain/Interstitial Cystitis Symptom Score; HVLT-R = Hopkins Verbal Learning Test – Revised; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder

Source: Datamonitor Healthcare; Trialtrove; clinicaltrials.gov

standard serotonin-based antidepressants prove inadequate. This has established combination therapy as a common treatment strategy for difficult-to-treat depression, accounting for around 30% of patients at later lines of therapy. However, atypical antipsychotics can have limiting side effects, commonly including weight gain, akathisia, and somnolence. The additional improvements in depression symptoms, which may only be modest, must therefore be considered against the increased tolerability burden.

In esketamine, J&J is aiming to develop a treatment that greatly supersedes the efficacy of common adjunctive therapies, therefore allowing for greater leniency in the trade-off between its added benefit and any associated risks. The TRANSFORM studies, and in particular the relapse-prevention SUSTAIN-1 trial, will provide clues as to whether the risk-benefit profile will be acceptable for regulators. Ultimately, the potential approval of esketamine may provide to be a difficult-to-predict binary event. Assuming esketamine does reach the market, Datamonitor Healthcare projects sales of $2.4bn by 2024, placing the drug as the highest selling for depression (see Datamonitor Healthcare's Forecast: Depression), and providing the wider market with an avenue for growth. However, should J&J be unsuccessful in its attempts to develop esketamine, the market will continue its historical decline and other developers with projects targeting the NMDA receptor, such as Allergan, may be implicated.

EXHIBIT 2. ESKETAMINE SALES FOR DEPRESSION ACROSS US FIVE MAJOR EU MARKETS



Source: Datamonitor Healthcare

About Medpace

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its physician-led, high-science, and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective. Headquartered in Cincinnati, Ohio, Medpace employs approximately 2,500 people across 35 countries.

A Full-Service Clinical Research Partner

Throughout the development life cycle, Medpace provides medical and regulatory leadership and guidance, with efficient, disciplined operational execution of your studies around the world. Our unique global partnering philosophy emphasizes an uncompromising commitment to clinical research and to the highest level of ethical standards and performance in our jobs. We are selective about the projects we engage in because we are devoted to quality and providing our partners with best-in-class service.

Medpace's dedicated teams serve as an extension of your team – we engage quickly and provide strategic thinking – ensuring quicker start-up times, superior quality, and the most efficient delivery of every phase of your clinical trial. Our therapeutic and regulatory experts are committed to streamlining your path to approval so every partnership is designed to create research solutions focused on your critical needs.

Driven by a full-service CRO model, Medpace provides an accountable, seamless, integrated and efficient platform for executing clinical research – increasing quality and speed while significantly reducing the need for duplicate management oversight. Our disciplined processes, site relationships, and technologies enable us to execute even the most complex global studies.

Explore our full range of integrated services:

- Medical Affairs
- Regulatory Affairs and Medical Writing
- Clinical Monitoring
- Clinical Trial Management
- Biometrics & Data Sciences
- Safety & Pharmacovigilance
- Quality Assurance
- Proprietary CTMS

Global Laboratories

Fully integrated labs facilitate efficiency and collaboration.

- Medpace Central Laboratories: wholly owned and purpose built laboratories around the world
- Medpace Bioanalytical laboratory: experience working with small molecules, biologics, and biomarkers across a wide variety of technologies and therapeutic areas
- Imaging Core Lab and Cardiovascular Core Lab further support studies with imaging and safety requirements

Physician Led - Therapeutically Focused

Increasingly complex clinical research demands that you engage a team of medical experts to navigate the challenges. Medpace is unique in its physician-led approach to clinical research. The Medpace model gives you the advantage of early and ongoing insight and guidance from therapeutic experts (MDs and PhDs) throughout trial design and execution. Your project team will be led by medical, regulatory and operational experts with deep therapeutic experience who are fully engaged throughout your study, proving guidance and averting potential roadblocks by staying close to the project.

Therapeutic Areas:

- Cardiovascular
- Endocrine & Metabolic
- Hematology & Oncology
- Infectious Diseases and Vaccines
- Neurology & Psychiatry
- Nephrology

Specialty Areas:

- Pediatrics
- Rare and Orphan Disease
- Advanced Therapies

Accelerate your drug, biologic, or medical device clinical development with a full-service, highly disciplined and therapeutically-focused model.

For more information email info@medpace.com

MEDPACE

Therapeutically Specialized Clinical Development

North America Latin America Europe Asia Pacific Middle East Africa

Celebrating 25 Years as a Global, Full-Service CRO

This year, Medpace marked its 25th year as a company. Founded in July, 1992 by Dr. August J. Troendle, Medpace has grown from a small group of dedicated people looking for a better way to conduct clinical research to a publicly-held, global community of 2,500 employees.

Much has changed over the past 25 years. What hasn't changed is our dedication to the mission of accelerating the global development of safe and effective medical therapeutics.

MEDPACE

Therapeutically Specialized Clinical Development

North America Latin America Europe Asia Pacific Middle East Africa

Don't Let Go

HOW WORKING WITH A CRO HELPS EMERGING BIOTECH COMPANIES AVOID RISKS AND GENERATE MORE VALUE FROM THEIR DRUG DEVELOPMENT PROGRAMS

Clinipace experts, Nik Burlew, EVP of RSD Global Consulting and Brian Travers, SVP for Asia Pacific explore the challenges that emerging biopharma companies face bringing new drugs down the development pipeline, and how they can overcome those obstacles.

Emerging biopharma (EBP) drug programs are energizing the pharma industry. Much of the biopharmaceutical industry is made up of small, emerging companies, and their projects represent a significant percentage of the global industry pipeline. These smaller firms have huge opportunities to generate value and establish their brands. Smaller companies also benefit from limited bureaucracy and less overhead, which makes them more agile than their larger and better-funded peers.

As the benefits of this agility become increasingly apparent, smaller firms are being pushed by investors to generate more value in their projects and to drive their drugs further down the development path. However, when they lack the necessary financial and human capital, regulatory expertise, geographic reach, and/or general clinical trial experience, they may be forced to sell or out-license their asset earlier than they would like.

But there is an alternative path. When small firms partner with a global contract research organization, such as Clinipace, which specializes in supporting emerging biopharma clients, they can avoid many of the obstacles that add time and cost to the development process. Working with a CRO gives small companies access to clinical, therapeutic, manufacturing, regional and regulatory expertise to de-risk their project without giving up control of their asset.

EXPENSIVE MISTAKES

In our experience, one of the biggest obstacles many emerging biopharma companies face is a leadership team that does not have strong business development experience, which can put the project at risk. This lack of experience can cause small firms to set overly optimistic expectations about the time, money and manpower it will take to get a drug development project up and running. It can also cause them to make decisions that may deliver short-term benefits but create problems later on.

One common mistake small firms make is to work with multiple low-cost vendors for different aspects of their research. This may lower their initial costs, but often results in mismatched data that cannot be integrated. In other cases, companies fail to make decisions that support the long-term needs of the project. For example, we recently worked with a small biotech company that had not thought through the long-term commercialization goals for their drug. That led them to develop essential documents and protocols that did not align with international guidelines in the countries where the drug would ultimately be marketed. They also lacked manufacturing experience, which resulted in incomplete chemistry, manufacturing, and controls (CMC) documents. This lack of long term strategic planning delayed start-up by a full year and increased their costs by more than 25 percent.

We regularly help firms address these kinds of early missteps – though they can be avoided all together by partnering with a skilled CRO from the outset of development. These outside experts provide the necessary balance of clinical, regulatory, and strategic expertise as well as global coverage to ensure risks are addressed proactively. When small companies partner with a CRO, and take the time to collaboratively develop a sound clinical strategy and detailed risk management plan, they hang onto that asset into Phase 2, Phase 3, or take it all the way to commercialization.

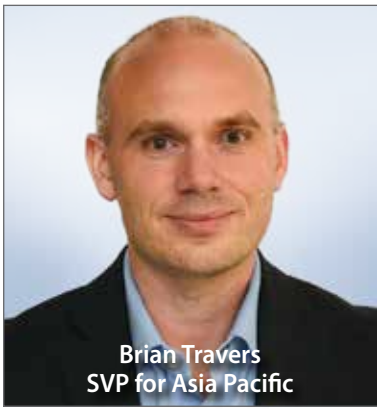
Such early due diligence can also put them in a better position to secure funding from one of the many venture capital funds interested in this space. Biotech companies saw a record amount of venture financing deals in 2015 and 2016, and 2017 looks to be another banner year for small firms. But to secure those deals, companies need both a promising drug candidate and a team that has experience developing innovative new drugs and devices for a global market.

ADVICE FOR EBPS: HOW TO BUILD A PLAN

When we work with emerging biopharma companies, the first and most important step we take is helping them devise a holistic end-to-end clinical strategy. This process includes the following steps:

1. **Define the end goal.** Deciding whether you want to out-license the drug or take it all the way to commercialization will affect many development decisions. For example, if you plan to out-license, you need to know what data will make the asset attractive to potential buyers, whereas if you plan to commercialize, you need know what geographies have the greatest patient-need and what sales strategy will be most effective. A global CRO can help you answer these questions and craft a plan to maximize value at key milestones in the development process.
2. **Schedule gap assessments.** Gap assessments should be conducted at key milestones throughout the development lifecycle to keep the project on track. Conducting assessments prior to every clinical research phase ensures all pharmacology and toxicology documents are sufficient, CMC documents are in order, any dose escalation and safety concerns are addressed, and all global regulatory expectations will be met. It is important to work with a CRO that can provide clinical and research expertise and that has intimate knowledge of the asset and progress to date so that assessments are as strategically specific as possible.
3. **Create a central repository for data that align with global standards.** To avoid data gaps, work with your CRO to ensure all data meets CDISC formats, and that it is stored in a central location. This will help streamline data collection, audits and reviews, and prevent data losses and manual entry errors.
4. **Build a regional plan.** Having a geographic strategy is critical if you plan to market the product globally, because it directly impacts where trials are conducted, the types of data you collect, and the key opinion leaders you'll need to support your efforts. For example, Asia Pacific is one of the fastest growing markets for innovative new drugs, but countries in the region each have their own regulatory authorities and often hold strict requirements for the percentage of ethnic data required for market authorization.
5. **Research regulatory expectations.** Having a clear understanding of what data and documentation regulators will expect to see is critical to crafting a clinical strategy that is well positioned for approval. Having regulatory expertise through the CRO will ensure small companies make better choices about development strategies, protocols, manufacturing, and other key decisions. They can also help the team engage with regulators to consult on their development plan and to answer specific scientific questions to further shape those strategies.


Nikolas Burlew
EVP of RSD Global Consulting


Brian Travers
SVP for Asia Pacific

CLOSING KNOWLEDGE GAPS

Taking a holistic approach to clinical research with a view to the entire development life cycle is key to a successful program. Having the support of a global CRO with experience and resources to support novel drug development can give small firms the confidence to take their drug further down the development path.

But to get the most value from these relationships, small firms should think carefully about what kind of CRO will best represent their interests. It is important to choose a partner who has relevant therapeutic expertise, a global footprint, and strong site relationships to ensure patient recruiting goals can be met. But small companies should also look for a CRO that fits their culture and values.

The best way to find that fit, is to look for firms that take the time to listen to their needs, and are willing to brainstorm solutions at a high level before pushing contracts and NDAs. They should also look for a partner who will view them as a premiere client, whether they are spending $30,000 or $3 million. It can be easy for emerging companies to get lost in big CROs where they are competing for resources against larger customers and projects. Whether the goal is to make it through phase two, or to become an established pharma company, having the right CRO partner can help these firms generate the most value from their drug candidates.

At Clinipace, we specialize in supporting emerging and mid-sized biopharma companies, and we are steadfast in guiding our clients through all of the clinical development and regulatory challenges they face in bringing innovative therapies to patients that need them the most.

Emily Hayes
Senior Editor, Pharma, US

ASCO's Richard Schilsky On State-of-the-Art Oncology Trials

Richard Schilsky, chief medical officer of the American Society of Clinical Oncology (ASCO), as well as senior vice president of its Center for Research & Analytics and principal investigator of the Targeted Agent Profiling and Utilization Registry (TAPUR) study, weighs in with current thinking on innovative trial designs, FDA programs that speed drug development, and room to improve with ASCO's Value Framework.

Q **Is the traditional way of studying drugs working in oncology today?**

Schilsky: To a great extent, the whole drug development paradigm in oncology is rapidly changing. In essence, what it boils down to is that in the past we followed these discrete phases of drug development: Phase I, where we attempted to learn mostly about dosing and safety and maybe some information on pharmacokinetics; Phase II, where we would try to determine initial efficacy; Phase III, where we are trying to determine clinical benefit and so on. Because in many cases the drugs are now more effective or because we are better able to identify patient populations in whom drugs are likely to work using biomarkers, a lot of these phases of drug development are collapsing.

Oftentimes, the drugs are less toxic than traditional cytotoxic chemotherapy. So the dose-finding tends to be a little bit easier. We are seeing more and more seamless designs where one can transition rapidly from Phase I to Phase III without necessarily doing a lot of Phase II studies in between, or alternatively where one only does a Phase II study and that provides sufficient information for a regulatory approval. Although there still then needs to be some confirmatory studies being done.

In general, our oncology drug development is becoming faster, more efficient and we are gathering information throughout the whole drug development process that we ultimately need to know to determine how to use these drugs for patients.

Now, immuno-oncology drugs – the checkpoint inhibitors, specifically – have presented some challenges. On the safety-side, they present with a number of rare but potentially life threatening toxicities. And sometimes it is difficult to identify that those toxicities are happening, because they present clinically with common symptom complexes.

The bigger challenge that many people have identified is that the traditional clinical trial endpoints may not apply well to some of these drugs. Tumors can enlarge before they shrink, so response rate maybe isn't the optimal endpoint. Tumors can progress before they resolve, so progression-free survival may not be the optimal endpoint. Overall survival is still a pretty good endpoint, but of course it takes a long time in many clinical settings to wait for that endpoint. There is a lot of discussion right now in the field about can we develop better more precise, more reliable endpoints for clinical activity and clinical benefit, I don't know that the field has yet settled on any particular endpoints or group of endpoints.

Q **Has the field moved forward enough in learning how to test immunotherapy combinations?**

I am sure there are hundreds of clinical trials that are evaluating these approaches. The issues are going to be not only how do you combine the drugs – what are the right doses to use – but what is the sequence of drug administration. For example, if you wanted to combine a small molecule tyrosine kinase inhibitor with a checkpoint

UPDATE ON TAPUR

ASCO has sponsored its own adaptive trial, which uses next-generation sequencing to map patient's tumor genetics and match them to targeted therapies. *(Also see "Genomics-Driven Trials Built To Be Fast And Flexible" - Pink Sheet, 21 Sep, 2015.)*

"We don't really have major learnings just yet because the trial is still ongoing," Schilsky said. The Phase II basket trial is looking for signs of activity for already-marketed drugs in off-label indications "where there is a specific genomic alteration thought to be a target for the drug," he explained. There are now 19 drugs in the study from seven different companies, with about 450 patients receiving treatment and the study still enrolling at about 100 sites around the US. "We are hoping to have initial results by the end of the year that we will be able to announce or publish in some way."

inhibitor should you give one first or [give them] together? There could be a rationale to giving the small molecule therapy first [to] get rapid tumor response, then a checkpoint inhibitor to try to sustain that response for as long as possible. These are all things that need some scientific rationale and then an appropriate clinical trial design to test them. And it is going to be the usual kind of problem in that there will be many more ideas that could be tested than patients available to actually test them.

Q Has guidance from the FDA on co-development of two or more novel drugs been helpful guiding industry in combination studies?

There is still a lot of uncertainty. What I hear, just talking to colleagues, is that there still is some uncertainty as to the best strategies to use with respect to combining these drugs. Particularly in circumstances where one drug in a sense might be more of an adjuvant to another, meaning if you have two drugs, one of which doesn't actually have much anticancer activity in its own right but perhaps in some way enhances the anticancer activity of the second drug, then it can be challenging to prove the utility of the combination without doing some big, huge multi-arm clinical trial that nobody wants to spend the money to do these days. There needs to be more thinking and discussion about those kinds of things in particular.

Q We have seen more and more master protocols, umbrella trials, basket trial designs, in recent years. How do you think those designs advance oncology drug development?

Most are really designed to improve the efficiency of trials in the way in which patient resources are used, particularly in circumstances where you are studying therapies that are directed against rare tumor subtypes and you have to screen large numbers of patients to find the appropriate population.

I think one of the advantages of these types of trials is that by bucketing patients into various groups you can study multiple tumor types with the same alteration simultaneously or multiple alterations within a tumor type simultaneously and you only have to screen the population once to figure out which arm of the trial a patient goes into as opposed to conducting multiple trials and screening thousands of patients each time.

Many of them are set up as signal-finding trials. Some of them can be designed as more definitive trials. The original design of the NCI LungMAP trial was an umbrella trial in squamous cell carcinoma in the lung – that was designed initially as a randomized trial where each arm of the trial was randomized against a control treatment. Ultimately, they decided that not was not a very efficient design… But it is technically possible to incorporate a randomized trial design in an umbrella trial. What might be more efficient is to follow the example of I-SPY and other trials where there is an initial efficacy evaluation that is not based on randomization against a control, and [if] the activity level exceeds some prespecified threshold, indicating a drug is sufficient promising – then you can move into the randomized setting.

Q Is development as efficient as it can be in oncology?

It all depends on how good the drugs are and how good our ability is to identify patients likely to benefit from the drugs. For any drug, whether oncology or not, there are certain key pieces of information that need to be known about the drug. …

> "The bigger challenge that many people have identified is that the traditional clinical trial endpoints may not apply well to some of these [immuno-oncology] drugs.

There are examples where drugs entered the market and the dose is ultimately shown to be too high or too low, but if you have a dose that seems to be safe and has a certain level of activity in a population of patients for whom there is a medical need, you can develop and get that drug to market quickly. That doesn't mean when the drug enters market that the medical community and regulatory authorities know everything that needs to be known about the drug. There still is a lot more information to be learned. One of the concerns of course in the way drug development is going today is that drugs are entering market with far less information about them than has been typically the case in the past. Drugs are getting approved with datasets of 200 to 300 patients instead of 2,000 or 3,000 patients. Oftentimes what is known about dosing, the potential rare side effects, the true benefit of the drug is not really well understood at the time drug is introduced in the market, so the burden then is on the medical community as well as the commercial sponsor to continue to develop information about the drug so we can all learn how to optimally use it once it's available.

Q Have the new value frameworks developed by ASCO and other organizations been effective for capturing the value of oncology drugs?

The ASCO Value Framework is a way of integrating information from a randomized trial about the relative efficacy and toxicity of the treatments compared in a trial and integrating that into what we call the net health benefit score as a single assessment overall of the relative benefit of a new therapy. Our approach so far does not provide for a comparison of two drugs available in the same indication but never compared head-to-head to each other. We are working to improve our methodology to see if we can accommodate these sorts of comparisons in the future.

The ASCO framework was develop primarily with the goal of facilitating shared decision making between doctors and patients. We heard informally that both insurance and pharma companies are using our framework and others to calculate the net health benefit score or other value assessments for their drugs. How that information is being used in pricing or coverage decisions I don't know at this point. The whole concept is still in evolution and time will tell what their real utility is in the oncology community.

Editor's Note: This interview has been edited for length and clarity.

Emily Hayes
Senior Editor, Pharma, US

IO BIOMARKERS: Where Do We Stand In 2017?

A survey of recent literature shows the breadth and quality of early research activity aimed at developing biomarkers to predict response to PD-1 and CTLA-4 checkpoint inhibitors.

The wide variety of biomarkers being explored as measures to help predict response to cancer immunotherapies – including tumor mutation burden and gut microbiota analysis – is encouraging, though the field is still a long way from relying on any of them as predictive tools, experts say.

Biomarkers are in demand to help predict which patients won't respond to PD-1/L1 and CTLA-4 checkpoint inhibitors, in order to save money as well as toxicity, and help guide patients to combination therapy where appropriate.

PD-1/L1 and CTLA-4 inhibitors are extremely effective for some patients. Response rates for PD-1 inhibitors vary depending on the tumor type, Yale University pathologist Kurt Schalper noted at the American Society of Clinical Oncology (ASCO) meeting in June 2017. In some tumor types they can be quite high, like 56% for Merkel cell carcinoma and 81% for classical Hodgkin lymphoma. But others are lower: e.g., non-small cell lung cancer (17% to 23%), renal cell carcinoma (14% to 29%) and melanoma (25% to 45%).

Thus, there has been significant focus on finding a biomarker to predict response. The use of PD-L1 expression (on tumor and/or immune cells) has been the only option in clinical practice, but its value in guiding treatment decisions has been a topic of perennial debate.

Tumor PD-L1 expression, which reflects the influence of tumor infiltrating T-cell activation, has historically been associated with controversy because clinicians feared that patients testing negative would be unfairly denied treatment – as the drugs can work even in patients with low PD-L1 levels. PD-L1 expression also can change over time, in response to treatment, for example, so the timing of when a biopsy is taken has an effect on the testing results. It may also vary within individual tumors. Complicating matters further, PD-L1 assays used by the major checkpoint inhibitor sponsors are also different, which makes it hard to compare results.

Roche has advocated using the PD-L1 biomarker as a way to identify high-expressing patients who should receive PD-1/L1 monotherapy, or if patients are low, using that as a signal that they may benefit from combination therapy.

THE NEXT GENERATION OF BIOMARKERS

Sponsors have declared an openness to testing a range of alternative biomarker approaches. Merck & Co. Inc. was first to market using mismatch repair deficiency, a marker of mutational burden and production of new antigens, as a selective biomarker. Merck's PD-1 inhibitor *Keytruda* (pembrolizumab) was approved for patients with microsatellite instability (MSI)-high or mismatch repair (MMR)-deficient solid tumors in May, marking the agency's first approval of a cancer drug across tumor types. Bristol-Myers Squibb Co.'s PD-1 inhibitor Opdivo (nivolumab) was approved for MMR-deficient colon cancer on Aug. 1.

The demand for the drugs themselves has necessitated a different approach to biomarker development, as the drugs are moved quickly to market and the biomarkers must catch up – rather than being thoroughly vetted in pre-market trials.

At ASCO, Jeffrey Weber, deputy director of the Perlmutter Cancer Center at the NYU Langone Medical Center, presented a review of biomarkers, noting the breadth of development, including analyses of gene expression profiles and microbiota in the gut, but concluded that none is ready for prime time in terms of helping to rigorously predict which patients will respond to treatment. *(The field is slow-moving and Weber said that there were no significant developments from recent conferences - Ed.)*

The early studies of biomarkers are typically small, involving fewer than 50 patients, and most biomarkers may be prognostic and not predictive.

"These are, frankly, biased and highly selective cohorts," and no immune biomarker has yet been proven as a predictive biomarker with benefit in a large, randomized study, he said.

Still, the science underpinning many of them is of very high quality and with more validation they could find their way into routine clinical practice. Weber said he believes that in the future, every patient will receive personalized immunotherapy determined by the presence of baseline biomarkers.

WEBER'S TAKE ON CURRENT IO BIOMARKER RESEARCH

BIOMARKER	COMMENTS
Gene expression profiles: Analysis of pathways associated with patients' response to checkpoint blockade, such as the innate anti-PD-1 resistance (IPRES) signature	Response is associated with mutations in the DNA repair gene BRCA2. Resistant tumors have the IPRES signature, with up-expression of genes involved in regulation of mesenchymal transition, cell adhesion, extracellular matrix remodeling, angiogenesis and wound healing. The study included roughly 40 patients. Published by W. Hugo *et al*. in *Cell*, March 24, 2016.
Interferon receptor signaling pathways regulating PD-L1 and PD-L2 expression in immune cells	Pathways can be categorized according to response. Analysis of biopsy specimens from patients with melanoma confirmed interferon signature enrichment and upregulation of gene targets for STAT1/STAT2/STAT3 and IRF1 in anti-PD-1-responding tumors. The pathways clearly varied between responders and non-responders, but the study only involved five patients. Published by A. Garcia-Diaz, *et al*. in *Cell Reports*, May 9, 2017.
Mutations in the interferon signaling pathway	Loss-of-function JAK1/2 mutations can lead to acquired resistance to anti-PD-1 therapy. Authors conclude that JAK1/2 loss-of-function mutations are a "genetic mechanism of lack of reactive PD-L1 expression and response to interferon gamma, leading to primary resistance to PD-1 blockade therapy." Study only included 8 patients. Published by DS Shin, *et al*. in *Cancer Discovery*, February 2017. JAK1/2 mutations are associated with acquired resistance to treatment due to the inability to signal through the gamma interferon pathway. Onset of clones with JAK mutations seen in circulating tumor DNA is sign patient is about to become resistant to PD-1 blockade. Published by J. Zaretsky, *et al*. *New England Journal of Medicin*e, July 13, 2016.
Gamma interferon copy number alterations in the genome, association with resistance to CTLA-4 blockade	Anti-CTLA-4 therapy enhances T-cell responses, including production of interferon gamma, a critical cytokine for host immune responses. Patients identified as non-responders to anti-CTLA-4 treatment with ipilimumab have tumors with genomic defects in the interferon gamma pathway gene. Loss of the interferon gamma signaling pathway is associated with primary resistance to anti-CTLA-4 therapy. Association shown between having gross alteration of gamma interferon genes, which prevents interferon gamma signaling from occurring acutely, and lack of response to CTLA-4 blockade. An easy biomarker to measure, but interferon gamma signaling is a double-edged sword; acute loss of signaling is associated with lack of response to checkpoint inhibitors, but chronic gamma interferon signaling might also be associated with lack of benefit for patients. Small study with 16 samples. Published by J. Gao, *et al*. in *Cell*, Oct. 6, 2016.
Tumor mutation burden	Higher mutation burden in NSCLC tumors associated with improved response, durable clinical benefit and progression-free survival (PFS). Study included 20 patients in a discovery cohort and even fewer in a validation cohort. Biomarker does not allow a cut-off where you could tell a patient they should definitely get a PD-1 inhibitor or definitely shouldn't, based on mutation burden, making it a problematic biomarker. Published by N. Rizvi, *et al*. in *Science*, April 3, 2015.
Neoantigen expression: Mutation associated neoantigens are linked with good response to PD-1 blockade, while resistance is associated with elimination of neoantigens	Multiple biopsies show neoantigen expression prior to treatment and loss as patients progressed. Impressive study, but with current technology it is unlikely in clinical practice that whole genome sequencing will be done for every patient with multiple biopsies over time to identify all of the neoantigens and keep track of them. There is also the risk of heterogeneity within a tumor on biopsy. Unlikely to make it to prime time. Published by V. Anagostou, *et al*. in *Cancer Discovery* (AACR), March 2017.
TCR clonality	Deep molecular profiling in melanoma patients, including T-cell receptor sequencing and whole-exome sequencing in the same cohort, demonstrated that a more clonal T-cell repertoire was predictive of response to PD-1 but not CTLA-4 blockade. Study shows that patients with good clonality do better with PD-1 inhibitors, but there isn't an absolute cut-off that could be easily used to select patients. Published by R. Whijae, *et al*. in *Science Translational Medicine*, March 1, 2017.
PD-L1 expression	In large melanoma study (451 patients evaluable for PD-L1 expression), response to anti-PD1 pembrolizumab correlated strongly to PD-L1 expression (p-value <0.0001). There are reams of data across tumor types showing the higher level of PD-L1 expression, the better the response. But in a review of results from eight major Phase III bladder cancer trials, PD-L1 expression was only a predictive marker for response in three studies. Good but not optimal biomarker. Published by A. Daud, *Journal Of Clinical Oncology*, December 2016.
CD8 cell infiltration: Patients who respond tend to have preexisting T-cell infiltration within tumors and at the margin adjacent to normal tissue	In small study, T-cell infiltration goes up at the margin and in tumors in responders. Promising biomarker, though based on analysis of small number of patients. But it would require a biopsy of every patient and defining of where the margin is and whether T-cells are in the tumor. Consequently, probably not an easy biomarker to utilize clinically. Published by P. Tumeh, *et al*. in *Nature*, Nov. 27, 2014.
Tumor-infiltrating lymphocytes	Researchers looked in tumor microenvironment, did core or excisional biopsies, isolated CD8 T-cells and looked for PD-L1+ CTLA-4+ expression on infiltrating cells. Those who did not respond all had low PD-L1, low CTLA-4 expression on the CD8 T-cells infiltrating the tumor, with strong p-value. Study was in 40 patients and there hasn't been a follow-up yet – but very promising and needs to be validated. Published by A. Daud, *et al*. in *Journal of Clinical Investigation*, Aug. 15, 2016.
Immune profiling during treatment with checkpoint inhibitors	In metastatic melanoma initially treated with CTLA-4 blockade and then PD-1 blockade at progression, immune signatures in tissue samples collected early in therapy were highly predictive of response to immune checkpoint blockade. However, a pharmacodynamic on-treatment marker rather than predictive marker. Published by PL Chen, *et al*. in *Cancer Discovery*, June 14, 2016.
Myeloid-derived suppressor cells (MDSC) at baseline	In 92 ipilimumab-refractory melanoma patients who went on to have nivolumab, high numbers of MDSC were associated with poor survival. Prospectively evaluating MDSC numbers before treatment could help assess the expected benefit of nivolumab; most likely a prognostic marker. Published by J. Weber, *et al.* in *Cancer Immunology Research* (AACR), Feb. 12, 2016.
Mass spec protein serum signature	Test of 209 proteins in serum associated with response versus non-response to PD-1 blockade in melanoma patients. Initial results look promising. Presented by J. Weber at Society for Immunotherapy of Cancer meeting, 2016.
Composite biomarker of tumor burden and PD-1-positive CD8 T- cells	Composite of circulating CD8 T-cell phenotype and tumor burden helps identify the minority of patients who will respond, but not that useful for identifying who will not respond. Published by A. Huang, *et al*. in *Nature*, May 4, 2017.
Microbiome/microbiota composition	Microbiota composition with more *Bacteroidetes phylum* is associated with decreased risk for colitis with CTLA-4 checkpoint blockade. Research activity with the microbiome likely to expand dramatically. Published by K. Dubin, *et al*. in *Nature Communications*, Feb. 2, 2016.

Doro Shin
Thought Leadership Manager, Pharma Intelligence

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A Status Check Of The Alzheimer's Trial Landscape

Despite high-profile failures, including the recent disappointing results for Axovant Science's Phase III MINDSET study, the trial landscape remains active for Alzheimer's disease.

Outside of the oncology research that dominates pharma R&D, Alzheimer's disease (AD) is one of the more active indications according to the clinical trials database Trialtrove. Undeterred, the industry continues to seek insights from prior failures, incorporating new strategies and tools, in an attempt to address the unmet needs in within the large AD market.

As of Oct. 2017, a total of 240 Phase I to III trials are ongoing for AD – 78% of which are still actively recruiting – exhibiting a healthy level of continuing interest in the area. Most of the remaining trials are closed to enrollment, while three trials are temporarily suspended (*see Exhibit 1*).

Among the open trials, Phase I activity slightly edges out Phase II with 67 and 63 trials, respectively. Phase III counts are nearly half that and only 34 late-stage trials are actively seeking patients. However, Phase II is the most active development phase for closed trials, which could fuel new opportunities for late-stage research if all goes well for the various drug candidates.

Six Phase III trials are closed to enrollment with varying durations until follow-up for primary endpoints are expected to complete. Most projects date from mid-2018 until 2019, but one trial is expected to continue until July 2022. This long-term trial is Eli Lilly & Co.'s A4 study, taking place in older individuals who have evidence of amyloid plaque build-up to evaluate solanezumab's effectiveness in preventing AD, continuing development of the antibody that missed its primary endpoints in the Phase III EXPEDITION3 trial.

All three temporarily closed trials are in Phase II, none of the sponsors for which have publicly disclosed a specific reason for their suspensions. The sponsors, and drugs, for these trials are: Boehringer Ingelheim (BI 425809), Daiichi Sankyo's *Plexxicon* (pexidartinib), and Fogangren Bio-Pharma and Star Lake Bioscience Co. Inc.'s memantine hydrochloride.

Within AD research, there has been a call to treat patients earlier, or even move toward disease prevention. Patients with mild AD has, and continues to be, the most common patient population included in Phase I to III clinical research. In recent years, this has been coupled with a growing interest in prodromal patients as well as decreasing activity in moderate to severe AD populations. Currently, a total of 54 ongoing trials target patients with mild cognitive impairment and/or prodromal AD, 21 of which only recruits this population. In contrast, seven trials only seek patients with moderate to severe AD, with an additional 12 that include patients with moderate to severe AD, as well as those with mild stages of the disease (*see Exhibit 2*).

KEY PLAYERS DRIVING CURRENT EFFORTS

Industry companies, excluding those solely focusing on generics, are fueling the majority of ongoing AD clinical research – a total of 144 trials include at least one industry sponsor, or 60%. Academic centers are also prolific and are involved in 100 of the 240 ongoing Phase I to III trials, while

government organizations and cooperative groups are only linked to 33 and 18 trials each. Generic developers contribute a modest level of activity with 25 ongoing studies.

Focusing on the top industry sponsors, the key players are a mixture of top 20 pharma companies, based on annual revenue, as well as other smaller companies (*see Exhibit 3*). This cohort is responsible for a total of 53 trials, evaluating 31 different drug candidates. The beta amyloid protein persists as a major target for AD with eight different beta amyloid protein antagonists, targeting the protein directly, included in 21 trials. Another mechanism of action (MOA) targeting the amyloid pathway is the beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitor, also known as the secretase beta inhibitor. This is the second most common MOA by both drug and ongoing trial count – five BACE inhibitors are being evaluated in 12 ongoing AD trials.

Eli Lilly is the leading sponsor with 14 trials involving nine different drugs, followed by Roche (nine trials for three drugs). The bulk of Lilly's activity falls in Phase I (eight trials) while the remaining studies are primarily late-stage evaluations of a BACE inhibitor, lanabecestat, and the previously mentioned beta amyloid protein antagonist, solanezumab.

Roche, on the other hand, has nearly half its trials in Phase III, splitting activity between two beta amyloid protein antagonists: crenezumab and gantenerumab. Crenezumab is also included in a Phase II prevention trial, partnered with AC Immune, which targets PSEN1 E280A mutation carriers who are in the preclinical phase of AD.

Other active top 20 pharma companies include Johnson & Johnson (J&J; six trials for three drugs) and Boehringer Ingelheim (four trials for two drugs). Meanwhile, smaller players with robust ongoing activity include Otsuka Pharmaceutical, AC Immune and Capo Therapeutics. Biogen and Eisai are also key players, with four collaborative trials ongoing between the two companies. This partnership started in 2014 to develop and commercialize two of Eisai's candidates, elenbecestat (E-2609) and BAN-2401. Both are in one closed Phase II trial each, with projected primary completion dates in 2018. Elenbecestat is also in two recruiting Phase III studies that initiated in 4Q 2016 and are both expected to complete in 2020.

ON THE HORIZON

In addition to this ongoing clinical research, 90 further trials are waiting in the wings and remain in planning phases. Sponsors for planned activity include a familiar cast of players, such as Biogen, J&J, Lilly, and Roche, as well as companies looking to increase their involvement. Although companies have faced setbacks and unexpected results within the field, the industry seemingly remains committed to identify effective drug interventions to combat, or prevent, this devastating disease.

EXHIBIT 1. ONGOING PHASE I-III ALZHEIMER'S TRIALS BY STATUS AND PHASE

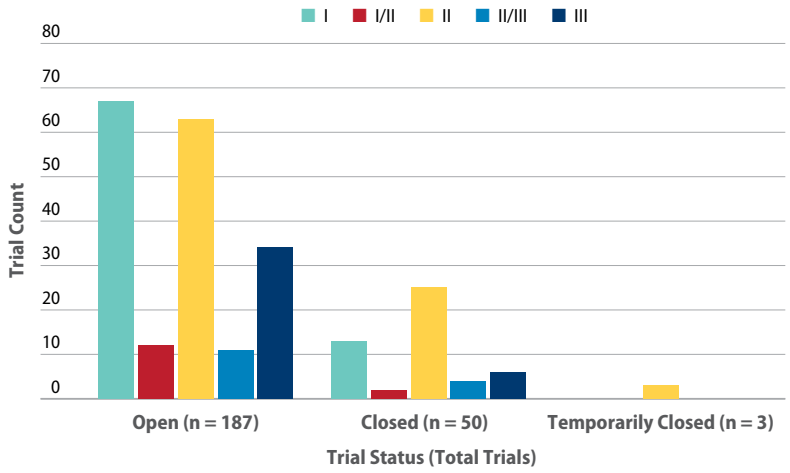


EXHIBIT 2. PATIENT POPULATIONS IN ONGOING TRIALS

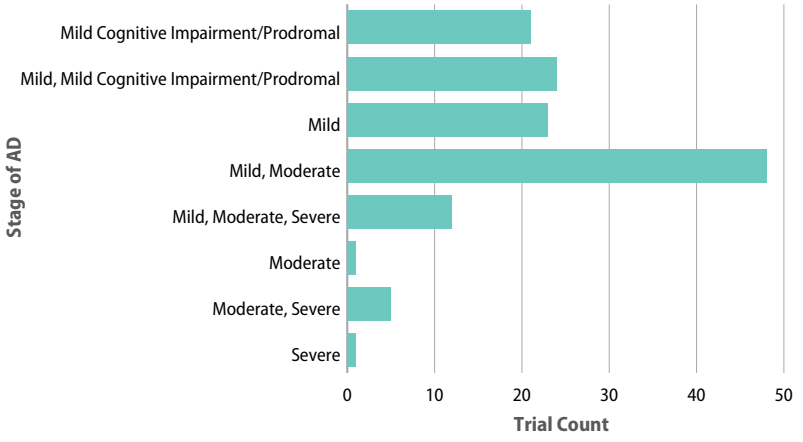
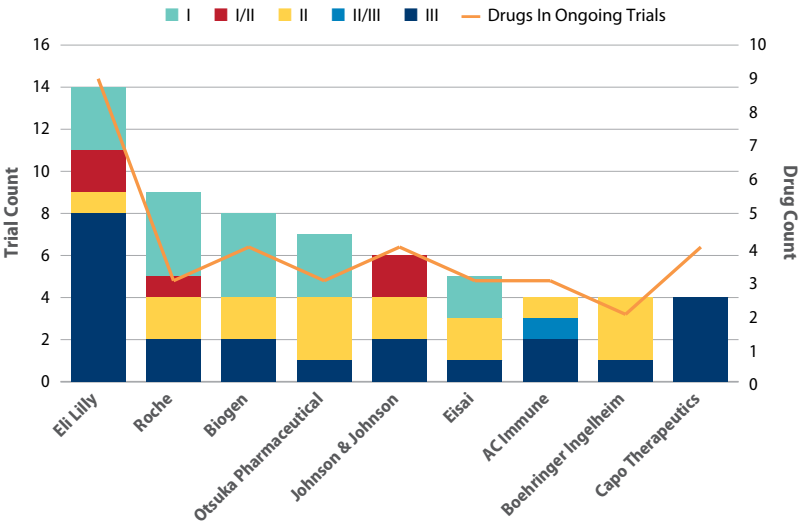


EXHIBIT 3. TOP INDUSTRY SPONSORS OF ONGOING TRIALS



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Francesca Bruce
Senior Reporter,
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Brazil's Spiraling Access Suits And The Potential Impact On Companies

Spending on medicines as a result of litigation against health authorities is soaring in Brazil. Scrip investigates the challenges firms may face in future, including greater pricing pressure, a more NICE-like health technology appraisal system and increased scrutiny over any perceived industry wrongdoing.

Lawsuits brought by patients to enable them to access medicines and other healthcare products have been a fixture in Brazil for some years. This is because Brazil's constitution gives all citizens the basic right to healthcare. However, it does not stipulate how this should work practically and fails to establish any limits on the provision of healthcare. If a product is made available on the national health system, the SUS, in theory it should be accessible to everyone. In the wake of this phenomenon pharmaceutical companies active or pursuing business in Brazil must adapt quickly.

Most court cases arise when a product is not available on the SUS, either because it has been excluded from the system or because it has not been assessed. In some cases, patients seek unregistered, experimental or off-label drugs. In other cases, patients sue for drugs that are provided on the SUS, perhaps because they are unaware that the medicine is available. Many of the drugs sought are orphan drugs for rare diseases.

Success rates in such lawsuits are high, and companies, lawyers, patient groups and healthcare professionals have been accused of exploiting and profiting from the system. "Growth in the bill for medicines acquired through the courts seems to indicate that stakeholders are finding ways to circumvent the lack of reimbursement, possibly by enabling clinicians to make their patients aware of this funding route," says RJW &Partners, a market access consultancy firm.

IMPACT

The health ministry says it has spent R$4.5bn ($1.4bn) on complying with court orders to supply medicines and other health products over seven years, and that spending soared by 1010% between 2010 and 2016. In 2016, spending levels reached R$1.6bn, 90% of which went on just ten drugs. The ministry says that Alexion Pharmaceuticals Inc.'s *Soliris* (eculizumab) represented the biggest expense, costing R$613m.

By August 2017, the ministry had already allocated R$721.1m to comply with lawsuits seeking access to specific medicines. Of that total R$666.8m was set aside for 13 medicines: Alexion's Soliris for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, and *Kanuma* (sebelipase alfa) for lysosomal acid lipase deficiency; BioMarin Pharmaceutical Inc.'s *Naglazyme* (galsulfase) for MPS VI, or Maroteaux-Lamy syndrome, *Aldurazyme* (laronidase) for mucopolysaccharidosis I (MPS I) and *Vimizim* (elosulfase) for Morquio A syndrome; Shire PLC's *Replagal* (agalsidase alfa) for Fabry disease, *Myozyme* (alglucosidase alfa) for Pompe disease and *Fabrazyme* (agalsidase beta) for Fabry disease; Shire PLC's *Elaprase* (idursulfase) for Hunter syndrome and *Cinryze* (C1 esterase inhibitor) for prophylactic treatment of hereditary angioedema; PTC Therapeutics Inc.'s *Translarna* (ataluren) for Duchenne muscular dystrophy; and Novelion Therapeutics Inc.'s *Myalept* (metreleptin) for generalized lipodystrophy and *Juxtapid* (lomitapide) for homozygous familial hypercholesterolemia.

An audit by Brazil's General Accounting Office (TCU) attributes the increase in cases and costs to factors such as speedier market entry and the revolution in information technology that quickly spreads reports abut of new technologies to countries where they are unavailable. It also highlights networks connecting patients, lawyers, doctors and the pharmaceutical industry that try to encourage more cases. The lawsuits spell bad news for the healthcare system, says the audit. "Resources are diverted away from elsewhere in the public health system to the detriment of planning and managing budgets… This loss has the potential to destabilize the public health network, leading to even more judicialization of products that should be provided regularly by SUS."

The cases are likely to remain a feature in Brazil, a fact to which the health ministry seems resigned. "There is no deadline for ending judicialization. Every day new drugs enter studies and new diseases appear worldwide.

The government's role is to guarantee access to health," it says. According to RJW, a real solution would require an amendment to the constitution, which it says is very unlikely.

However, there are ways in which authorities can try to control the situation. For example, RJW believes that the Brazilian system for making funding decisions will evolve to become more like England's health technology assessment body, NICE, which uses a strict ICER (incremental cost-effectiveness ratio) threshold range of between £20,000 and £30,000 per quality adjusted life year. Indeed, a bill putting more emphasis on cost-effectiveness and setting out ICER thresholds in health technology assessments is in the legislative pipeline. The bill's supporters hope it will cut the number of lawsuits by establishing clear and transparent rules for listing products on the SUS.

Change in the way orphan drugs are appraised could also be imminent. Alexion says that rare disease patients "often resort to the judicial system in order to obtain access to needed treatment otherwise denied them by the government, exercising their constitutional right to health by bringing forth legal proceedings." It believes better policies on orphan drugs and other treatments for rare diseases would both improve access to these medicines and stem the number of lawsuits. Several bills that could tackle this issue are moving through congress. One bill sets out how orphan drugs should be dealt with and recognizes that orphans require a different evaluation process owing to the very small patient populations affected.

There could also be more pressure on pricing. According to JRW, drugs accessed through the courts are charged at the maximum retail price if the drug has been awarded a price in Brazil, or at the price of the drug in the country of origin if it has not. JRW believes that "payers will increasingly become more focused on these prices and will try to contain them more."

According to Bennie Spiewak, from the Brazilian law firm Zancaner Costa, Bastos and Spiewak, measures are already being taken. "Legislators have become stricter when issuing pricing regulations. CMED, the pricing authority, has issued a rule requiring compulsory discounts for sales aimed at meeting court orders."

Companies could also see more focus on managed entry agreements, says RJW. However, enforcing conditional reimbursement or restricting eligibility could be difficult within the SUS. Such agreements will be used more widely in the private sector, it adds.

Meanwhile, the health ministry acknowledges that investing more in access to medicines is important and says that six of the 10 most sought-after medicines between 2014 and 2016 are now listed on the SUS. The ministry also points to product development partnerships (PDPs) as a means of improving access. These deals typically see a manufacturer, often a multinational, sign a technology transfer agreement with publicly and privately owned Brazilian companies that will eventually be the main supplier of the drug in question for a fixed period. The originator company will continue to supply Brazilian authorities with the drug until local production is fully up and running.

These PDPs aim to expand access to strategic products and boost local capabilities. Eighty agreements involving 67 products are now in place. "The partnerships will mean savings of at least 30% in the acquisition of medicines and health products, in addition to R$6.4bn in investments in the sector," the health ministry says.

However, Spiewak is more cautious about the immediate benefits of PDPs. "Brazil is at least two decades away from effectively benefiting from such arrangements."

SCRUTINY

It also looks as though the pharmaceutical industry will come under greater scrutiny for any perceived wrongdoing. RJW warns that "companies manipulating the system can expect to be investigated and sanctioned."

Alexion is being investigated in relation to Soliris and the company says it is co-operating with the investigation. Separately, a 2015 SEC filing by Aegerion (now part of Novelion) revealed that federal and São Paulo authorities in Brazil were "conducting an investigation to determine whether there have been any violations of Brazilian laws related to the sales of Juxtapid in Brazil." The drug is not approved in Brazil but it is authorized for marketing in the US. The filing also pointed to a separate investigation by Interfarma, the industry association representing R&D-based companies in Brazil.

Novelion says that Brazilian law allows patients to seek access to imported, unapproved treatments through the court system, as permitted by the Brazilian Federal Constitution, although the company itself doesn't have any involvement in this process. It says it is "aware of individual former employees under investigation, but not the company itself… The company is aware of an ongoing investigation, which is being conducted in secrecy, and we will continue to make ourselves available to discuss it and cooperate with the authorities."

It says Aegerion does not market or promote its products to doctors or patients and that employees "are trained to only conduct disease awareness activities that educate doctors on rare diseases and to respond to unsolicited medical information requests from physicians about our products in compliance with local laws and industry codes." It will file its products with medicines regulator ANVISA after it establishes itself as a pharma company in Brazil.

Nevertheless, the SEC filing from Aegerion highlighted the consequences of suspicion, warning that it could be prohibited from further named patient sales. It said the scandal led to delays in orders and re-orders of Juxtapid and reluctance among doctors to prescribe the product.

"Recently, we have observed an increase in the drop-out rate of patients on Juxtapid in Brazil, and we believe that part of the reason for the increase is due to the investigations," Aegerion said. "These issues could negatively affect our ability to generate product revenue consistent with our expectations, and may impact our ability to achieve and maintain profitability or maintain cash-flow-positive operations."

According to Spiewak, companies are already adapting and taking care in their interactions with doctors and healthcare professionals. "It looks better from both a legal and compliance perspective not to push the judicialization agenda forward. While in the past it looked like an alternative, it is currently construed as an illegal practice, which can harm the company on so many levels, including regulatory and self-regulatory penalties and criminal investigations," he says. Meanwhile, Interfarma has been critical of such lawsuits and has changed its code of practice to prohibit companies from encouraging them.

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Projects In Sub-Saharan Africa Propelling Drug Approval Procedures

Sub-Saharan Africa has been firmly in the regulatory spotlight over the past year or so, with east and west Africa making progress on projects to speed up drug regulatory procedures through greater cooperation and information sharing at the regional level.

The projects are part of the African Medicines Regulatory Harmonization (AMRH) initiative, which was set up in 2009 to establish and bolster regulatory standards across sub-Saharan Africa with the goal of improving patient access, to safe, high-quality medicines. The initiative is gaining momentum, with the setting up of regional regulatory agencies or even a pan-African body being mentioned as part of a longer-term vision.

Here *Scrip* looks at some of the projects that are under way or in development.

EAST AFRICAN COMMUNITY PROJECT

Implementing regulatory reform is a daunting challenge in sub-Saharan Africa, where countries have limited human and infrastructure capacity, varying standards of regulations, and often lengthy procedures for getting new medicines onto the market. Moreover, there is often a lack of clarity over the roles of the various national regulatory bodies and ethics committees in clinical trial authorizations. Nonetheless, the harmonization efforts are starting to bear fruit. One of the biggest AMRH success stories to date is a project run by the East African Community (EAC), which has been pioneering joint assessments and collaborations between pharma and local regulators, resulting in faster drug approvals and the prospect of even closer cooperation in future. The EAC consists of Burundi, Kenya, Rwanda, Tanzania, Uganda and South Sudan.

Among the aims of the joint EAC Medicines Registration Harmonisation (MRH) procedure, launched in 2012, are to develop a common documentation package for new drug approval applications, streamline processes, and conduct joint dossier assessments and manufacturing site inspections.

The first edition of the "EAC Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products" were published in 2014, setting out procedures and requirements for drug approvals based on ICH CTD (common technical document) guidelines.

A joint assessment pilot was conducted in the EAC in 2015-16 focusing on high-priority medicines, with a CTD, a team of assessors conducting assessments, and a framework for mutual recognition of regulatory decisions. The result was a reduction in the median time from dossier submission to national marketing authorization to seven months, compared with the one to two years that would normally have been the case with separate national applications – a reduction of 40-60%.

EAC AGENCY IN PROSPECT?

On the basis of this and other similar pilots, the intention now is to look at establishing an EAC Medicines and Food Safety Agency whose activities will be funded by industry fees – although the EAC is at pains to stress that the agency will not replace national regulatory bodies in its member countries.

The idea of an agency was discussed in May 2017 when a delegation of EAC and other representatives visited the European Medicines Agency in London to see whether the EMA might provide a suitable model.

A report on the meeting published in August said the EAC agency would be "self sustaining through fees and technical expertise from partner states." It would have regulatory oversight of selected medical products as well as promoting cooperation, convergence, harmonization, reliance and mutual recognition of regulatory decisions, and enhancing work and information sharing.

According to John Mwangi, Regulatory Affairs & Cluster Quality Head, Middle Africa, at Bayer East Africa Ltd, the agency is expected to be "a platform where applicants can access the EAC services without necessarily being required to go through individual agencies to fulfil administrative requirements, as is currently the case."

However, it's still early days, and such a body is unlikely to be formed any time soon. Still, efforts are

continuing to extend the EAC initiative and to bring more products – including new innovative medicines – into the joint assessment procedure and to implement a full system of mutual recognition of national assessments. According to Mwangi, this is being done in collaboration with the industry.

Also under discussion are plans to include assessments of new biologics and vaccines, the drafting of guidelines on variations, and the establishment of pharmacovigilance systems, the Bayer executive said. "There is also in the process of finalization a technical cooperation framework which is to act as a precursor to the future mutual recognition framework."

To back up the joint regulatory procedures, there are plans to set up a regional fee structure. Little progress seems to have been made on this front, however.

Some see the EAC approach to regional cooperation as a model for other sub-Saharan regional communities to follow.

ZAZIBONA

Meanwhile, another collaborative medicines registration initiative has been established in the ZaZiBoNa area (Zambia, Zimbabwe, Botswana, Namibia and – since June 2016 – South Africa), which is part of the South African Development Community (SADC). The aim here is to slim down approval times, reduce the workloads of the national medicine regulatory agencies (NMRAs), and develop mutual trust and confidence.

In the ZaZiBoNa collaborative project, one rapporteur is assigned to evaluate the sponsor's dossier and produce an assessment report that then acts as the basis for approval decisions by the individual NMRAs. Again this approach is not intended to replace the NRAs, but is more akin to the decentralized or mutual recognition procedures established in the EU. As noted by Sinah Selelo of the Drugs Regulatory Unit at the Botswana health ministry, approvals are issued nationally and there is "no central single submission – yet."

WHO CRP

In a related global initiative that also affects Africa, the World Health Organization is seeking to set up a voluntary "collaborative registration procedure" that would allow NMRAs in countries with limited resources to approve drugs more quickly by relying on assessments conducted by "stringent regulatory authorities" (SRAs).

The proposal was outlined in a March 2017 working document based on the results of a pilot that tested the initiative between 2015 and 2017, and on feedback from regulators and manufacturers. The idea is to allow NMRAs to base their regulatory decisions on assessment and inspection reports from an SRA such as the EMA or the US Food and Drug Administration. The agencies would be expected to take an approval decision within 90 days of receiving an application from a sponsor. Registration dossiers would have to be in the ICH CTD format.

The responses to a second consultation on the working document were due to be presented to the 52nd meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held in October.

AN AFRICAN MEDICINES AGENCY?

These and other regional projects and regulatory collaboration efforts are gradually paving the way to more harmonization at both regional and continental level. The logical conclusion might be a to set up a pan-African Medicines Agency (AMA), and indeed plans for such a body to be established under the AMRH are fairly well advanced.

The AMA is intended to be an organ of the African Union with the aim of increasing the availability of affordable, quality, safe and effective medicines and other health products. This would be achieved through coordinating national and sub-regional regulatory systems, providing regulatory oversight of selected products, and promoting cooperation, harmonization and mutual recognition of regulatory decisions. The 57-page business plan for the AMA says the agency, as a continental organization, would be able to draw on technical support, expertise and resources from various countries and regional economic communities (RECs) at a scale that cannot be matched at national or regional level.

A stakeholders' consultation held in February 2017 resulted in a revision of the legal and institutional frameworks and business plan for the AMA.

The aim is to launch the agency in 2018. This is a seemingly ambitious timeline, but the fact that its role would be limited to coordinating the activities of NMRAs or sub-regional drug regulatory authorities established by RECs could make the chances of success more likely.

RENEWED PARTNERSHIP PROJECT

A separate initiative, again involving the WHO, has just ended and the results are now being assessed. This is the five-year Renewed Partnership project between the European Commission, the African Caribbean and Pacific group of states (ACP) and the WHO, which began in 2012 with €10m in funding from the commission.

The aim of the partnership is to build up pharmaceutical systems in 15 African countries. According to the WHO, it has already made progress, such as wider availability of child-friendly medicines, particularly for HIV, TB and malaria, faster registration times for some vital medicines, and a degree of progress towards achieving coverage of health expenditure for the whole community.

There remains a lot of work to do because of issues relating to governance, lack of infrastructure and limited resources and capacity. Suzanne Hill, WHO director for essential medicines and health products, said that many medicines are missing from pharmacy shelves, especially in rural areas, and there are "problems of substandard and falsified medicines entering distribution chains" while many households go without other necessities in order to pay for medicines.

The project partners were due to meet in Zanzibar in September to take stock of achievements and devise a way forward. "We need our countries to set up stronger health systems and ensure that all communities are accessing the medicines they need, when they need them, at an affordable price," said Matshidiso Moeti, WHO regional director for Africa. "Basically, we need African governments to take access to medicines seriously and invest time and resources into the issue, and we need technical and financial support."

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How J&J Scientist Koul Hopes To Reboot R&D At India's IMTECH

Anil Koul, part of the Johnson & Johnson team that discovered and developed TB drug Sirturo, is currently on a sabbatical to head up IMTECH, an Indian R&D institute. Koul shares with *Scrip* the ups and downs of Sirturo's development journey and outlines what he hopes to achieve at IMTECH.

For any top-notch scientist, shifting from a frontline innovator firm to a government R&D institution in an emerging market like India is, as some industry watchers say, akin to moving from Hollywood to local theatre. Smaller budgets, technology constraints, scale limitations and inefficiencies are just some of the general variances that you may have to deal with.

But Dr. Anil Koul, part of the Johnson & Johnson team that discovered and developed tuberculosis (TB) drug *Sirturo* (bedaquiline), sees that the big picture, at times, warrants taking the challenges that come with such choices. After all, the development journey of Sirturo, the first new TB medicine in more than 40 years and a poster child in the war against multidrug-resistant (MDR) tuberculosis, had its share of significant troughs and peaks.

Koul, a senior director and head of respiratory infections discovery group at J&J in Belgium, is currently on a sabbatical and now heads the Chandigarh-based Institute of Microbial Technology (IMTECH), a research institute of India's Council of Scientific and Industrial Research (CSIR).

Koul tells *Scrip* that initially, the scientific community was "skeptical" about the bedaquiline discovery, particularly its target. Very few people believed it was possible to target ATP synthase – the enzyme involved in energy synthesis that is also present in humans – as was published in an earlier *Science* paper by Koen Andries *et. al.* Dr Andries led the bedaquiline discovery team.

Dr Anil Koul
Director CSIR-IMTECH

"However, subsequently, we were able to prove categorically, through various biochemical and biophysical means, that the target was ATP synthase of TB bacterium (*Nature Chemical Biology, 2007*). We also established the selectivity of the target ATP synthase in mycobacterial as compared to its human homologue," Koul said.

CHALLENGES AND 'ANOTHER CHANCE'

But bigger challenges lay ahead: the first TB patient trial with the drug did not show "exceptional" results. It was a seven-day treatment trial to measure the early bactericidal activity and bedaquiline "did not perform as well as expected," raising questions at the time around the program's future.

Koul said there was a period of "great uncertainty," not knowing whether the project would "move forward or be stopped." However, a subsequent two-month multidrug-resistant TB treatment trial was a "phenomenal success." Sirturo, as we now know, inhibits mycobacterial ATP synthase, an enzyme which is essential for the generation of energy in mycobacterium tuberculosis.

Importantly, Koul underscores that the "lack of commercial opportunity" for TB treatments was "balanced" by the support of J&J senior leadership, which had a "strong commitment and desire" to make an impact for those suffering from this neglected disease. In particular, he refers to leaders like J&J's chief scientific officer, Paul Stoffels, who backed the drug giving it "another chance" in a larger trial in multidrug-resistant TB patients; a decision clearly changed the course of bedaquiline's history.

J&J-IMTECH COLLABORATION

Significantly, Stoffels on a visit to India in February 2017, told *Scrip* that he hoped a potential J&J-IMTECH alliance

could "pull off something special" in India and jointly progress the science for a new medicine in TB. Koul was perhaps just the right man to steer things. Stoffels, at the time, also mentioned how Koul has "very good insight on what it takes to get from science in the lab to a product." Koul is a recipient of the 'Johnson Medal,' the highest award for R&D excellence within J&J, for his contribution to the discovery and development of Sirturo.

Months later, in August 2017, J&J announced a partnership with IMTECH, to accelerate R&D for innovative new treatments for TB in India. The partners expect to explore "more effective, safer, all-oral treatment regimens" for multidrug-resistant TB and also develop new molecular entities to treat all TB patients. "The idea is to work on a synergistic combination of drugs working in same biological pathways as bedaquiline," Koul explained.

The collaboration aims to develop a completely new all-oral combination therapy with a significantly shorter treatment duration that could be used by anyone, regardless of their drug resistance indications, and has a better safety profile.

While CSIR-IMTECH expects to provide expertise in areas of bacterial energy metabolism – which is the target of combination therapy – J&J brings its broad preclinical and clinical development resources and experience. "By bringing together the best of India's TB scientists with a global team of experts in drug development from Johnson & Johnson, we aim to deliver on the national strategic goal of ending TB by 2025," Koul declared. The collaboration hopes to move a potential new therapy into clinical testing by 2020/21.

BELGIUM TO CHANDIGARH

But surely the shift from Belgium to Chandigarh in India, where IMTECH is based, is a huge contrast, to say the least. Koul said his friends reacted with "shock to sheer disbelief and even a bit of sympathy" when he informed them that he was headed to India to work in a government R&D outfit, though it was apparently no less than India's Prime Minister Narendra Modi who invited the Sirturo scientist back to his homeland. Speculation suggests that Koul has the ear of the Indian PM, though the scientist isn't saying much on that front for now.

Koul says that as president of the Council of Scientific and Industrial Research, PM Modi's commitment towards Indian science and the ability of scientific innovation to deliver positive results and solve some of the national problems is "quite big." India's scientific leaders believe that IMTECH's mandate of doing more product-related and translational science is important for delivering value out of India's R&D investment, especially in areas such as neglected diseases, he adds.

Koul's goal is to enable scientists at IMTECH to translate their basic biomedical research into early products and technologies with a greater emphasis on collaborative industrial research. "Such developments should ultimately strengthen and support efforts to address India's healthcare challenges, bring value to the country's R&D investments and give taxpayers greater value for money." He also wants to promote an "open-innovation model for drug discovery" in order to address the diseases of developing countries. *(Also see "INTERVIEW: Janssen India Boss On Sirturo Pricing And Real World Evidence" - Scrip, 10 Apr, 2016.)*

DRUG DISCOVERY ENGINE

Koul hopes IMTECH can establish "excellent science" which acts as a platform for it to be the "drug discovery engine" for neglected diseases and also the first to bring new drug and diagnostic approvals, be it in biopharmaceuticals or the human microbiome. There is already an "intended engagement" with Nobel Laureate Prof. Roger Kornberg from Stanford University around dengue fever drug development.

Other partnerships have also been identified, especially in the field of the human microbiome where Koul hopes to treat childhood sepsis, which is a big challenge in India, with a "microbial cocktail." Sepsis in early infancy results in one million deaths annually worldwide, most of them in developing countries and no efficient means of prevention is currently available.

IMTECH, Koul adds, is looking to collaborate with the University of Nebraska Medical Center in the US and local Indian medical schools to develop a synbiotic that can be used in an Indian clinical setting. "For multidrug-resistant pathogens, we have identified some efflux-pump inhibitors that can be used as adjunctive therapy in treatment of serious hospital-based infections." Koul added.

Published literature in the area refers to a trial of an oral synbiotic preparation (*Lactobacillus plantarum* plus fructooligosaccharide) in rural Indian newborns by a group of researchers including those of the University of Nebraska Medical Center, though *Scrip* could not immediately verify if the synbiotic is the one under consideration by IMTECH.

GOVERNANCE STRUCTURE

While a focus on delivery of solutions – especially in neglected diseases like TB and dengue, and in biotherapeutics – ranks high on Koul's agenda at IMTECH, he hopes his shift to India will act as a catalyst in bringing about "some essential change."

"The bigger challenge is the improvement in our governance structures within our publicly-funded R&D institutions, ensuring that individual scientific accountability is linked to measurable deliverables and incentives. The key is how to incentivize R&D productivity, discourage mediocrity and introduce some corrective measures for under-performance," Koul explained.

He rues how India, despite being considered the pharmacy of the world, supplying generic medicines globally, has very little to flaunt when it comes to discovery research. No wholly-India developed new chemical entity, which in itself are few, has yet reached close to blockbuster status internationally, though there are quite a few promising projects underway especially in the private sector.

While India's chemistry and formulation expertise has been the backbone of its strong generics industry, Koul believes that India's drug discovery has been limited due to "risk-averse attitudes" as well as "lack of good talent" in discovery biology and clinical development. Only time will tell if Koul's stint at IMTECH can help shift gears for R&D at the promising Indian R&D establishment.

The spotlight will certainly be on the J&J scientist, who ventured to don a new role in a challenging setting. Going back to the Hollywood analogy, talented theatre artists are known for their versatility and ingenuity in using available resources to their fullest potential to make an impact.

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What's Behind The Success Of Korean Biosimilars?

Celltrion and Samsung Bioepis are moving fast to grab leading positions in the global biosimilars space, but how have these two firms got to where they are now? Scrip takes a look at what is driving their success and where they are heading next.

South Korean biosimilar companies are entering their prime. One after another, Celltrion Inc. and Samsung Bioepis Co. Ltd. are making headlines and receiving approvals for their biosimilar products in major markets; the products they have launched are leading their markets, or have potential to do so.

This scene was not expected by many industry players several years ago because, at that time, South Korea had a limited focus on innovation and R&D investment, and the country's pharma and biotech companies had not yielded notable outcomes in global markets.

"Celltrion focused on the high growth potential of the antibody biosimilars market, sought development of biosimilars earlier than others, and is now leading the market," said Dong Won Sung, senior analyst at the Export-Import Bank of Korea. "Samsung has entered the market late but it is quickly catching up with Celltrion based on the ample capital and strong drive frequently seen in large conglomerates."

Various factors, including savvy clinical trial and collaboration strategies, have played a part in the recent stellar performance of the two South Korean firms.

"One of the key factors contributing to the success of Samsung Bioepis and Celltrion in the MAb biosimilar space is the fact that they are conducting global clinical trials in key regions of interest such as the US and Europe, and the firms are tailoring their clinical development to the expectations of the regulatory authorities in those respective regions," Datamonitor Healthcare's analyst Hristina Ivanova told *Scrip*.

CELLTRION'S EARLY DAYS

Celltrion started out as a contract manufacturing organization (CMO) in South Korea, but it is now a pioneer in antibody biosimilars. When multinational pharma firms monopolized global markets with antibody drugs, many of them believed development of biosimilars would be difficult. But Celltrion had different thoughts and became the first mover in this field. Celltrion focused on the potential of the biotech industry and the value of biosimilar business, as patents of several blockbuster biologics were set to expire soon.

When Celltrion began global clinical trials of its first biosimilar product *Remsima/Inflectra*, a version of Janssen Biotech Inc.'s *Remicade* (infliximab), the concept of biosimilars was still unfamiliar and South Korea was little known in the global biotech industry. The company had to pioneer the process and pave the way for regulatory approval in Europe. "At that time, there were no global guidelines on biosimilars. We had to pioneer the process by persuading the EMA [European Medicines Agency], but our folks continuously challenged and succeeded. This has become the driving force of our first mover and first launch status," said Celltrion CEO Woo Sung Kee in an interview with *Scrip*.

Celltrion's Remsima now controls more than 40% of the European market. The biosimilar product launched in the US late last year and the company expects to repeat its success in the world's biggest market as it has accumulated prescription data and various clinical data needed to earn doctors' trust and boost recognition of its brand name.

Celltrion's biosimilar rituximab, known as *Truxima*, has also launched in various European countries. Truxima and *Herzuma*, its biosimilar version of *Herceptin* (trastuzumab), are undergoing regulatory approval review in the US.

Meanwhile, Celltrion received a US FDA Form 483 in early 2017 after the FDA's regular GMP inspection of the company's biomanufacturing site in South Korea. But by September the company had already completed improvements for the list of demands the US regulator made. It added that none of the issues directly impacted the company's drug quality; as a result, there were no disruptions in its drug production or global supply and there will be no changes in its products' approval schedules.

SAMSUNG CATCHES UP

Samsung Bioepis entered the biosimilar business several years later than Celltrion but it is quickly catching up. Backed by Samsung Group's ample capital and strong drive for the biotech business though, Samsung Bioepis is swiftly progressing global clinical trials of its broad biosimilar candidates.

"When we started out five years ago, biosimilars were still new to many in the industry. We had the confidence that our development platform and scientists could

capitalize on the level playing field, thereby allowing us to compete from the start and positively impact patients' lives sooner rather than later," Samsung Bioepis told *Scrip*. "Since then, we have relied on our agile biologics development platform to transform and enhance the way therapies are brought to patients from conception and development through regulatory approval by replacing legacy processes with new and innovative ones. In so doing, we have been able to develop arguably the industry's most expansive and rapidly advancing biosimilar pipeline."

Samsung has launched its infliximab biosimilar *Renflexis* in the US, only several months after Celltrion's Inflectra. With the latest EU approval for its adalimumab biosimilar *Imraldi*, Samsung has become the first company to receive EU approvals of three biosimilar anti-tumor necrosis factor products. Samsung is selling *Benepali*, its biosimilar version of *Enbrel* (etanercept) and *Flixabi*, its biosimilar version of Remicade, in Europe, through its partner Biogen Inc. Samsung's biosimilar to Herceptin, *Ontruzant*, is also under regulatory review by the EMA. Ontruzant (formerly known as SB3) received a positive recommendation for approval in Europe from the EMA's scientific committee the CHMP in October 2017.

As a late comer, Samsung Bioepis, which is a joint venture between Samsung BioLogics and Biogen Inc., has largely benefited from the pioneering work of Celltrion. While Celltrion had to spend much time in the beginning creating approval guidelines in global markets, Samsung could receive approval in a shorter period. Renflexis could get FDA approval without review by an FDA advisory committee thanks to Inflectra, which had to earn the green light of the advisory committee as the first mover, NH Investment & Securities said.

Unlike the EU market where Remsima had a significant head start and dominated the biosimilar infliximab market, some South Korean analysts predict it could be a closer match between Inflectra and Renflexis in the US where the launch time gap between the two is only several months. In addition, Renflexis's list price was 35% below its reference drug price, while Inflectra's list price was at a 15% discount to the innovator.

BUILDING ON PARTNERSHIPS

Another factor that contributed to the South Korean companies' success is their robust collaborations with global companies. Celltrion and Samsung Bioepis both have created a network of collaborations with a wide range of companies for the development and marketing of their biosimilar MAbs, said Datamonitor's Ivanova.

For example, Celltrion has a partnership with Hospira Inc., now a subsidiary of Pfizer Inc., for the marketing of Inflectra in the US, and has partnered with Mundipharma International Corp. Ltd. for the commercialization of Remsima and Truxima in Europe, benefitting from the local presence their partners have in US and Europe, Ivanova noted.

In addition, South Korean companies' ability to construct high quality manufacturing facilities required for manufacturing biosimilars and governmental policy support are likely to have made it easier for them to have a head start in the biosimilar business.

Helped by the South Korean government's policy support, Celltrion and Samsung Group could successfully build large-scale bioreactors in the beginning. From early 2000s, the government has been considering the biotech industry, including biosimilars, as the next-generation growth engine, while other countries had slightly different visions. For example, Japan focused much more on novel drug development, overlooking the biosimilars sector, while Singapore opted to attract the production facilities of multinational pharmas such as Roche and Lonza Group Ltd., according to NH Investment & Securities.

INCREASING GLOBAL COMPETITION

As South Korea is aiming to develop global blockbuster drugs in the coming years, its success in biosimilars could serve as a basis for accumulating and building technology and knowhows to reach its goal.

Although the global biosimilars market is poised to grow sharply for now, EXIM Bank of Korea's Sung stressed the importance of novel drug development amid the toughening of competition in the biosimilar space.

Competition in the global biosimilar market is set to become fiercer as multinational pharmas such as Pfizer Inc. and Merck & Co. Inc. as well as leading generic companies Teva Pharmaceutical Industries Ltd. and Sandoz Inc. are actively pursuing the development of biosimilar businesses via ways such as M&As. As a result, the global biosimilar market could turn into a "red ocean" with limitations in growth, Sung said.

According to the database, Trialtrove, in 2017 there were more than 1,060 clinical trials of biosimilars ongoing worldwide and 158 trials in the US alone. By therapeutic area, there were 299 clinical trials of biosimilars in oncology and 291 trials of biosimilars in autoimmune and inflammation.

As part of their overall plans, Celltrion is already progressing a novel antibody drug pipeline including a new antibody influenza drug. It is targeting becoming a global top 10 biopharma after 2020 once it launches three biosimilar products in global markets, and after that plans to aggressively invest in the development of novel drugs.

Samsung is also stepping up efforts to diversify into new drug development. In August, Samsung Bioepis has joined with Takeda Pharmaceutical Co. Ltd. to develop novel biologics, moving beyond its core focus on biosimilars. The partners will initially focus on acute pancreatitis and jointly develop Takeda's preclinical candidate in the segment.

In 2017 there were more than 1,060 clinical trials of biosimilars ongoing worldwide and 158 trials in the US alone, according to TrialTrove.

Opening a New Era in Rare Disease Medicines

HELPING PAYERS AND ADVOCACY GROUPS SEE EYE TO EYE

In criticizing high orphan drug prices, some payers disparage ties between manufacturers and patient advocates. Jeanine O'Kane and Marie Emms, senior executives at Syneos Health, argue these relationships foster innovations that lower prices over time. In creating registries, assisting trial recruitment, and gathering real world evidence, patients and advocacy groups form the front line in our battle against rare diseases.

Health insurers whose plans include families struggling with rare disease often express empathy for the patients, and I believe they are sincere. Why? Because, in 2017, my company conducted many hours of interviews with medical and pharmacy directors at managed care organizations and integrated delivery networks representing 47.2 million covered lives. In these conversations, many payers expressed deep concern for patients on their plans—especially for children whose lives are in peril, and for parents who battle bravely to save their lives. But, in at least two respects, payers took stances on the economics of rare diseases that were at odds with what advocacy groups in rare disease believe.

First of all, payers and advocates don't see eye to eye on how to interpret the patient's experience of an illness when calculating the value of an orphan drug. They also disagree on whether the rapid proliferation of expensive treatments for rare diseases poses an existential threat to the U.S. healthcare system.

The first area of discord—valuing the patient's experience—makes it hard to figure out what role advocacy groups should play in debates about orphan drug pricing. In short, payers welcome the opinions of patient organizations when those groups take a stand against high prices. But, when rare disease advocates defend the pricing of drugs developed by companies with which they collaborate, payers say the groups have been manipulated.

Likewise, when advocacy groups become activists in the regulatory process, pressing for the speedy approval of promising medicines, insurers worry emotions will overrule evidence. One insurer we spoke with described a case in which "an FDA director reversed his decision after meeting with advocacy groups, calling into question the credibility of [the agency's] decisions across the board."

Payers, even though they are sympathetic to patients, are not swayed by encounters with the families, said another executive—the managing director of a regional affiliate. "On a scale of one to ten, where ten is clinical efficacy, [the voices of] these groups are a 3-to-5. They are out there, and they are a consideration, but we try to go beyond them to the evidence."

To gain a fair and balanced picture, we discussed key takeaways from our payer interviews with several prominent advocacy leaders. "I understand where payers are coming from," the director of one patient organization told us. "But remember, patients are not the payer's customers. "That role is filled by employers and the government, she explained.

"Payers serve companies that run employer-funded plans," the advocacy leader said. "At the end of the day, those companies serve employees, who are now, or may become, patients. Payers must integrate patients and treat them as customers."

The second area of dispute concerns sustainability of the pharmaceutical business model when it comes to rare diseases. Many payers interviewed by Syneos Health believed manufacturers are abusing the incentives and intent of the Orphan Drug Act of 1983—especially when the high price assigned to an orphan indication remains unchanged when the drug is later used to treat common illnesses. And nearly all payers said the high prices of orphan drugs jeopardize the healthcare system's stability.

Yet, the healthcare system is not in jeopardy, said the founder of a rare disease advocacy group who examined anonymized summaries of the payer interviews. "Payers need to recognize that orphan drug prices will come down drastically over time," she said. Many factors will contribute to price adjustments. Competition among multiple products treating the same rare conditions will have an impact. And, on the patient side, digital and social tools will enable people with rare diseases to work with researchers and accelerate patient identification and enrollment in clinical trials, which amount to one of the biggest cost burdens in drug development [See sidebar]. Such tools will also help patients participate in more accurate registries, which will yield exactly the kinds of real-world performance and outcomes data payers have told us they seek.

Technical innovations in the private sector will also affect the cost equation in fundamental and positive ways, the advocacy leader said. She was surprised that some payers view genetic advances fueling personalized medicine with alarm. In interviews, payers worried these advances signal a future where each personalized condition is treated like a rare disease, with a pricing borrowed from the orphan drug playbook. But many advocacy organizations take a more optimistic stance.

Advocates argue that next-generation drugs, including gene therapies, promise to replace costly medicines the patient takes for years, or decades, with a single, curative shot. Even if the treatment is expensive, the cost over a lifetime will be far less, the advocacy leader said. "Scientific breakthroughs, innovation in contract services, the ability to bring clinical trials right to the patient's home, and to monitor them in the real world—all of these innovations and forward momentum will cooperate to drive down costs."

The last two decades of technical innovation in diverse but related fields, from biotechnology, to electrical engineering, to computer science, artificial intelligence, and the internet, suggest optimists in the advocacy camp have a strong case. Current pricing structures paint a grim picture, from the payers' vantage point—but that is nothing more than a portrait of the moment. It pays to remember that rare diseases are a landscape of constant change, and advocacy groups hold the paintbrush that brings it all to life.

To view the full report titled, How Payers and Manufacturers Can Find Common Ground in Rare Disease visit: SyneosHealth.com/Rare.

PROMOTING TRIAL ENROLLMENT BENEFITS ALL STAKEHOLDERS

The challenges of recruiting and retaining patients in clinical trials are well known. A 2013 report from the Tufts Center for the Study of Drug Development noted that clinical trial timelines typically double in length as investigators struggle to complete enrollment. Only 39 percent of sites in a given clinical trial meet the sponsor's enrollment targets, according to Tufts, while 11 percent fail to enroll a single patient.[1]

These hurdles translate into delays and higher R&D costs, which are reflected in elevated prices once medications reach the market. Payers are certainly aware of these correlations. Yet, when Syneos Health asked insurers how they would deal with rising prices of rare disease treatments in the future, some proposed measures that, in the long term, would slow the development of new treatments and put upward pressure to prices.

For example, some payers said that if a sponsor excluded patients from a trial because of health conditions, such as cardiovascular complaints or impaired kidney function, the payers might deny coverage to patients with such conditions once the drug was commercialized. "If patients are excluded from a trial," one payer told us, "maybe they shouldn't be on the drug."

It's not unusual for payers to restrict coverage when biomarkers or test data show that certain patients are unlikely to benefit from a drug. Pegging insurance coverage to clinical trial inclusion, however, conjures a very different logical framework—one that could bring adverse, unintended consequences.

Today, when a child with a rare disease is excluded from a clinical trial for health reasons, the parents don't give up hope of accessing the new treatment. In many cases, they work harder than ever to inform other parents and get other children enrolled, knowing there's a chance the treatment will benefit their own child once it's approved. Word of mouth is a potent communication channel in rare diseases where patient populations are small and widely dispersed. More and more, trial sponsors depend on this channel in trial recruitment.

But, if parents and family members believe exclusion from a trial carries a high risk of being denied insurance coverage down the road, many won't even try to enroll their children, and they certainly won't encourage other parents to take the risk. Suddenly, the tough challenge of recruiting patients becomes that much harder, and the prospect for speeding new treatments through the pipeline dims in proportion.

Advocacy groups can help sponsors navigate these and other uncertainties—and, in rare diseases, they already do so. Using social media and other tools, they often assist in identifying patients, building registries, and constructing natural histories of diseases that are of vital interest to researchers. Advocacy also plays a critical role in educating families, recruiting patients, and keeping them compliant with challenging drug regimens in a trial.

Unfortunately, many payers interviewed by Syneos Health expressed mistrust of advocacy groups working with these conditions. Because such organizations often receive funding from clinical trial sponsors, payers say they can't count on objective input. This issue comes to the fore when patients or families working with advocates describe positive responses to medications via patient-reported outcome measures (PROs). In reality, payers must learn to peer beyond the complex industry-advocacy relationships and recognize, wherever possible, the authenticity of patients' voices.

Without the collaboration of advocacy groups, it's hard to envision manufacturers creating life-altering treatments of the sort that turned HIV/AIDS from a death sentence to a manageable condition. What's more, in the case of HIV, patients and advocacy groups earned the trust of payers.

The model of strong collaboration between payers and advocacy already exists, and we all need to learn from that model. For the sake of patients and families living with rare diseases, shoring up trust is a top priority in rare diseases today. It may be the best strategy for averting unintended consequences as payers and manufacturers grapple with pricing of rare disease medicines.

Read the Syneos Health Rare Disease Payer Report here: SyneosHealth.com/Rare.

1 http://csdd.tufts.edu/files/uploads/jan-feb_2013_ir_summary.pdf

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Right-To-Try Legislation Must Narrow Spectrum Of Patients, Gottlieb Says

The Senate's right-to-try legislation should be narrowed to specify patients who are "terminally ill" as a criterion for experimental drug eligibility from its current language of "a life-threatening disease or condition," US FDA Commissioner Scott Gottlieb told an Oct. 2017 House hearing.

Testifying before the House Energy and Commerce Subcommittee on Health Oct. 3, Gottlieb cautioned that Sen. Ron Johnson's (R-Wisc.) right-to-try legislation, known as the Trickett Wendler Right-to-Try Act (S.204), would encompass too broad a patient population. The bill in its current form could apply to patients with chronic illnesses such as diabetes or other diseases that don't immediately set a patient on a terminal course, but that are still life-threatening, the commissioner said.

"If you look across the state laws in states that have passed right-to-try laws, the language typically speaks about a patient being terminally ill to qualify for consideration under the right-to-try provisions," Gottlieb said. "Congress, in consideration of some of this legislation … has broadened that to include diseases that are either terminal or life threatening. The component of a life-threatening disease is a broader definition. … There are a lot of illnesses that are certainly life-threatening, but not immediately terminal."

In his prepared remarks, Gottlieb recommended defining a terminal illness as "a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months."

Johnson's right-to-try law has the goal of increasing access to investigational drugs in accordance with state right-to-try laws. The Senate passed the bill by unanimous consent the same day it voted to pass the FDA Reauthorization Act (FDARA).

The Senate, however, may not be welcome to any changes the House makes to the bill. Rep. Greg Walden (R-Ore.), who chairs the full Energy and Commerce Committee, explained that at least one Senate sponsor of the bill told him that the upper chamber is not looking for any changes "out of fear it may fail if it goes back with changes."

Gottlieb explained that the broad "life-threatening" diseases definition could force the FDA to interpret the bill "expansively," and that it could "sweep in a whole range of conditions for which it didn't intend."

"The more we broaden this provision, and the more we potentially sweep in conditions for which we might be exposing people to unwanted side effects from experimental therapies, the more we risk undermining the whole venture that we are trying to engage in here, which is to narrowly tailor something to people who really don't have good options from available therapy," Gottlieb said.

In addition to the Senate legislation, Rep. Andy Biggs, R-Ariz, is sponsoring the Right to Try Act of 2017 (H.R.878). Bigg's bill uses the phrase "terminal illness" instead of "a life-threatening disease or condition." The bill defines terminal illness in accordance with state laws.

The House bill has 43 co-sponsors, which includes four Democrats. Other Democrats, however, such as subcommittee Ranking Member Gene Green (D-Texas), have raised concerns about right-to-try legislative efforts taking the FDA out of the equation.

The fate of legislative efforts remains unclear. Subcommittee chair Rep. Michael Burgess (R-Texas) closed out the hearing noting that the conversations "set the stage for perhaps our second hearing in this regard," adding that "clearly, this is not the end of the story."

AVAILABILITY, SAFETY ALSO ISSUES

The commissioner maintained the FDA's usual stances on the issue of expanded access, noting that the agency approves 99% of requests, and that it can approve emergency requests over the phone within 24 hours.

For the requests that were denied, Gottlieb explained that roughly half have been due to the experimental drug not being available.

"The biggest reason is that when companies do clinical trials, they don't have continuous manufacturing," Gottlieb said. "They don't have large facilities online pumping out endless supplies of drugs. They will do what we call 'discontinuous batches.' They will do runs just to create batches of drug supply and active pharmaceutical ingredient sufficient for the clinical trial."

Gottlieb said that drug makers could be incentivized to produce more product in the pre-approval setting through a change in clinical trial design, but stressed that the issue is not addressed in the bill.

In other cases, Gottlieb said, the denial comes as a result of a clinical hold, which the public doesn't know about since the hold is confidential information.

NOT A PERFECT SYSTEM, BUT A VERY GOOD ONE

Gottlieb noted at the hearing that though the FDA's expanded access system over the years has not been perfect, it has been remained effective.

In an Oct. 3 *FDA Voice* blog post, the commissioner touted several measures that the agency has taken to remove hurdles that delay or discourage expanded access applications. He announced that physicians now only need approval from one Institutional Review Board (IRB) member – either the chair or another "appropriate" member – at their facility to treat a patient under expanded access. Previously, physicians were required to obtain approval from the full board.

IRB requirements were clarified in both the "Form FDA 3926" guidance, as well as the "Waiver of IRB Requirements for Drug and Biological Product Studies" guidance. "This is an important step to protect the rights, safety and well-being of human subjects in clinical research – but assembling the full board may cause delays because they may not routinely meet," Gottlieb wrote. "I believe the simplified IRB process will facilitate access while still protecting patients."

He also announced in the blog post that the FDA has its June 2016 Q&A guidance with clarifications about how sponsors should report adverse event data for expanded access investigational new drug applications (INDs). The updated guidance specifies that sponsors are only required to report adverse events "if there is evidence to suggest a causal relationship between the drug and the adverse event."

Sponsors have often been hesitant to provide drugs under the expanded access program with the uncertainty about how the FDA will view the product's adverse event data in the review process. Gottlieb worked to assuage these fears at the hearing, however, pointing to a Government Accountability Office (GAO) report that found that have only been two instances where adverse events from expanded access use contributed to a decision to put development of an investigational drug on a partial clinical hold.

The commissioner added in his blog post that more "simplifications and clarifications" regarding the expanded access program are on the way.

INDUSTRY REP NOT A FAN

An industry representative at the hearing, Cognition Therapeutics Inc. president and CEO Kenneth Moch, was the harshest critic of the right-to-try legislation at the hearing.

Along with Gottlieb, Moch explained that the legislation cannot force drug makers to provide their experimental products to patients. Moch added that the FDA has never been a hindrance to granting expanded access requests, and that the legislation also does not take into the account the complexities of drug development.

"No ethical company that I know of would ever release an experimental medicine outside of the FDA's regulatory process. A basic mantra is that 'all drugs have side effects.' And cutting scientific corners creates unbounded risks."

Moch further criticized anecdotal arguments in favor of right-to-try legislation, and stressed that taking the FDA out of the equation does nothing to address the reasons as to why drug makers don't provide access to experimental treatments.

"You have to look at the totality [of data]," Moch said, also referring to the bill as "feel-good legislation."

The FDA approves 99% of expanded access requests and it can approve emergency requests over the phone within 24 hours, Gottlieb said.

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Do Accelerated Approval Pathways Mean Earlier Patient Access?

Accelerated access mechanisms that aim to get medicines to the market more quickly do not necessarily mean earlier access for patients, according to interim findings from a London School of Economics study.

Accelerated assessment mechanisms aimed at getting medicines to market more quickly do not necessarily provide earlier access for patients, according to the preliminary analysis of a study being conducted by the London School of Economics.

Patient access to products that have passed through accelerated approval mechanisms is still dependent on the data requirements of health technology appraisal bodies. "Despite the early regulatory approval schemes, HTA agencies do require robust clinical and economic evidence that would allow a positive coverage recommendation," said LSE's Mackenzie Mills, who presented the findings at the ISPOR 20th Annual Congress in Glasgow on Nov. 8, 2017. Nevertheless, he added that social value judgements could act as modifiers to allow HTA agencies to arrive at positive – albeit mostly restricted – recommendations.

The ongoing study is funded by an unrestricted grant from AstraZeneca and has two main priorities. These are to map early access programs in 25 countries across the world and to explore the impact of these schemes on coverage or funding decisions. The final results of the studies will be published in June 2018.

FOUR MAIN TYPES OF ACCELERATED APPROVAL MECHANISMS:

- Most commonly these include accelerated reviews (like the FDA priority review or the EMA accelerated assessment) which shorten the review period by two to four months and which have evidence requirements that are the same as those of standard marketing authorization reviews.
- Marketing Authorization with lower evidence requirements (like the EMA's Conditional marketing authorization, of the FDA accelerated approval).
- Abridged verification reviews that are based on approvals by trusted regulators such as the US Food and Drug Administration or the European Medicines Agency.
- Other mechanisms based on early engagement with regulatory authorities, such as adaptive licensing or the PRIME scheme in the EU, or breakthrough designation in the US.

The study found there were four main types of early access mechanisms *(see box)*. The study looked at 16 drug indications across lung cancer, melanoma and hematological cancers, and the interim results presented focused on recommendations by HTA authorities in England (NICE), Scotland (SMC), Australia (PBAC) and Canada (PCODR).

The results point to a "huge range" in the time it takes HTA bodies to publish their reimbursement decisions following marketing authorization. For example, NICE took between 42 days and 1,707 days to publish recommendations on early access scheme drugs, while the SMC took between 44 and 1,216 days. Meanwhile, PBAC took between minus 71 days to 1,048 days and PCODR took between minus 95 days and 725 days to publish recommendations. The Australian and Canadian authorities allow a parallel review process that means HTA applications can be made before marketing authorization, which allows for the possibility of a negative date.

Times between authorization and HTA recommendations also vary widely for the same product. For example, Seattle Genetics' *Adcetris* (brentuximab vedotin) for refractory CD30 positive Hodgkin lymphoma won conditional marketing approval in the EU in October 2012. NICE recommendations came 1,707 days later in June 2016. The SMC published recommendations 680 days after approval in September 2014. Meanwhile, authorization of the same drug in Australia came in December 2013.

Another example is AstraZeneca's *Tagrisso* (osimertinib) in locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer, which won EU conditional marketing approval in February 2016 (and full approval in April 2017). NICE recommended that the drug be available through the Cancer Drugs Fund in October 2016, some 245 days after EU approval. The SMC took 377 days to publish recommendations in February 2017. Meanwhile, in Canada PCODR recommended the drug in April 2016, 95 days before it won conditional marketing authorization in April July 2017 from Health Canada.

Pfizer Skeptical About Value-Based Contracting In Current Environment

Cathy Kelly
Senior Editor, Pharma, US

Pfizer has around 18 different projects underway but has achieved only one value-based deal in the US because the system is not constructed to do value-based contracting, says CEO Ian Read.

Pfizer Inc. has been slower than some of its peers in executing value-based contracts with payers because it believes meaningful deals aren't very workable in the current system, chair and CEO Ian Read suggested during a 2017 Washington, DC, policy discussion on healthcare system value.

"We've been struggling to do value-based contracting with payers and providers," he said during the Sept. 19 meeting. "We have about 18 different projects underway but we've achieved [only] one." A company spokesperson would not disclose what drug is covered by the contract but said it involves a "major" Medicare Part D plan. Read maintained that Pfizer has been unable to complete more contracts because "the system is just not constructed to do value-based contracting." The meeting was sponsored by the Pharmaceutical Research and Manufacturers of America as part of its Value Collaborative policy initiative.

Pfizer's chief also pointed to policy and operational barriers to value-based contracts that are often cited by industry, such as FDA restrictions on communications with payers, federal anti-kickback laws, and concerns that discounted prices provided under such deals would trigger Medicaid "best price" requirements. Biopharma has urged the Trump Administration to address those barriers to enable innovative contracting that would ultimately help lower drug costs.

At least some of those arguments are finding traction. CMS announced plans in Sept. 2017 to develop value-based purchasing models for prescription drugs through its Center for Medicaid and Medicare Innovation and requested input from stakeholders on how to approach such arrangements. The initiative could lead CMS to remove barriers to contracts related to price reporting requirements in Medicaid and Medicare.

Other obstacles may take longer to clear away and some might need legislation. For example, changes in the FDA's communications policies may eventually come under the leadership of Commissioner Scott Gottlieb, but stakeholders don't anticipate relief in the short-term..

Pfizer's Read said that in some cases, there is an additional barrier: insurer priorities are not aligned with some value-based models, and that stands in the way of progress. For example, he said that insurers may not be interested in promoting the use of smoking cessation drugs (say *Chantix*) because they are concerned about attracting smokers to their plan. That worry that adding smokers will boost their costs because smokers often have more health problems than non-smokers.

It's "really about getting incentives and risks aligned," he emphasized. "I think the risks and incentives have to be with the providers and that's how you get the best healthcare."

Read's comments about value-based contracts are less optimistic than public statements by other companies, such as Novartis AG, AstraZeneca PLC and Amgen Inc., which have disclosed their involvement in several outcomes-based arrangements. For example, in Aug. 2017, Novartis announced it was working with the Centers for Medicare and Medicaid Services on outcomes-based payments for its new gene therapy for cancer, *Kymriah* (tisagenlecleucel).

The development of value-based purchasing models for drugs has become an important industry narrative in response to criticism over drug pricing. Nevertheless, the reality remains that value-based contracting is still in the early stages and no hard evidence has yet emerged that it lowers costs for payers or patients. In the near-term, manufacturers and payers see more modest benefits in the arrangements.

Johnson & Johnson executive vice president and pharmaceuticals chair Joaquin Duato, who also spoke at the policy event, cited a few of those other advantages in discussing an outcomes-based contract with Aetna Inc. for its diabetes drug, *Invokana* (canagliflozin). Under the contract, J&J agreed to provide the insurer with a rebate if a pre-specified percentage of members taking Invokana need to add another diabetes drug to meet their treatment goals, he explained.

"The good thing about this value-based arrangement is that it forces the parties to collaborate," Duato said. In addition, "in most of these value-based arrangements you follow an… evidence-based practice and pathway that guarantees the patient will have very high-quality care."

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Maureen Kenny
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EU Regulatory Review – What Pharma Should Remember From 2017

You could be forgiven for thinking that Brexit was the only story in town on the European regulatory front in 2017, but there were of course plenty of other important developments during the year.

The landmark mutual recognition agreement between the EU and the US on pharmaceutical inspections finally became operational. The European Commission published its long-awaited report on ten years of the EU Paediatric Regulation, but the implementation date of the new EU Clinical Trials Regulation was put back yet again. PRIME, the European Medicines Agency's priority medicines scheme for speeding up access to medicines for unmet medical needs, is now well and truly a fixture on the EU regulatory scene.

The EMA's policy on the proactive publication of clinical data passed its one-year anniversary, and patient involvement in the medicines evaluation process reached a new level when the EMA held its first ever public hearing on drug safety, focusing on Sanofi's anti-epileptic, valproate. EU regulators got serious over how big data should be used in the drug development and assessment process, and the European Commission launched a consultation that could result in changes to the supplementary protection certificate rules.

In terms of product approvals, there has been considerable action in the biosimilar space this year. The first biosimilar version in the EU of Roche's blockbuster breast cancer drug, *Herceptin* (trastuzumab), may well be approved before the year is out, after Samsung Bioepis Co. Ltd.'s *Ontruzant* received a positive opinion from the EMA in Sept. The first EU biosimilar of Roche's Avastin (bevacizumab) received a positive opinion in Nov. Also approve this year were the first EU biosimilars of other major products, including AbbVie Inc.'s *Humira* (adalimumab) and Eli Lilly & Co.'s insulin analog, *Humalog*.

EU/US MRA

On the international front, the mutual recognition agreement between the US and EU on pharmaceutical good manufacturing practice inspections – which entered its operational phase on Nov. 1 – will allow regulators from the two jurisdictions to better focus their inspection resources on manufacturing sites in other countries around the world where there may be greater risk. Industry is hoping the agreement will among other things result in more uniformity in the reporting of inspection findings by EU and US regulators.

This is a significant development. The agreement is an amended annex to the EU-US MRA which was signed in 1998, and some aspects of the revised agreement took effect on March 2, the day after its signing was completed.

Other aspects took effect on Nov. 1, such as the cessation of routine inspections by EU authorities in the US and routine FDA inspections in the eight recognized EU countries: Austria, Croatia, France, Italy, Malta, Spain, Sweden and the UK. The EU had recognized the FDA in June and added it to its list of recognized authorities in August. The FDA must recognize the other 20 EU member states by mid-July 2019 for the agreement to remain in effect.

The FDA and the EU had been working together since May 2014 to evaluate how they each inspect drug manufacturers and assess the risk and benefits of mutual recognition of drug inspections. The European pharmaceutical industry body EFPIA issued a statement that said: "EFPIA has maintained consistently that uniformity in the reporting of inspection findings by the EU and US will be of significant value to global health authorities, industry, and the general public. On this basis, informed comparisons can be made of the relative compliance statuses of different facilities or the same facility at different points in time… A clearer understanding of inspection results and the compliance status of a facility will mean that health authorities are able to dedicate limited inspectional resources to those facilities that need the greater regulatory oversight."

EU PEDIATRIC REGULATION REVIEW

In October, the European Commission published its keenly-awaited report on how the controversial EU Paediatric Regulation (Regulation (EC) No 1901/2006) has been working since it was introduced 10 years ago.

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The commission and other proponents of the legislation accept the legislation has its faults, but their underlying belief is that it has had a considerable impact on the development of medicines for use by children over the past decade. Not everyone is convinced, though, and the EU research-based pharmaceutical industry has long complained the legislation is overly prescriptive, onerous and unnecessarily bureaucratic.

The report includes concrete actions that the commission will take to streamline the application and implementation of the regulation.

A key issue for industry was whether the report would lead to revisions to the regulation. It will, but change won't happen any time soon. It turns out the commission will not be proposing any amendments before 2019, when the results of a new study evaluating the combined effects of the legislation and the Orphan Regulation are expected to become available.

NEW CLINICAL TRIALS REGULATION

The new EU Clinical Trials Regulation is a key piece of legislation that should improve the environment for conducting clinical trials in the EU but it will be at least another year-and-a-half before the new system it introduces is up and running.

Among other things the regulation will harmonize the assessment and supervision procedures for clinical trials across the EU via a single application portal and trials database that will be run by the EMA. It is also expected to bring greater transparency of trial data and higher safety standards for trial participants.

The CTR replaces the unpopular and widely criticized Clinical Trials Directive. The new legislation is in fact legally in force, but its provisions will not apply until six months after the portal and database system has been confirmed to be fully functional. It was announced recently that the system's go-live date had been delayed and so the CTR provisions would not apply until the second half of 2019, rather than 2018 as had earlier been expected.

PRIME

Industry interest remained strong this year in PRIME, the EMA's priority review scheme for potentially truly innovative medicines. The scheme was launched in March 2016 and its popularity is easy to understand. The focus is on SMEs, and successful applicants are guaranteed early and enhanced support from the EMA to help them optimize their development plans. They also have the chance of having their eventual marketing authorization application (MAA) reviewed under the accelerated access pathway, which can cut the assessment timeframe from the standard 210 days to 150 days.

There is disappointment for many, though, as almost four out of every five applications for entry to the program are rejected. Only 31 of the 137 applications that were submitted to the EMA between March 2016 and October 2017 have been accepted.

To be deemed eligible for entry onto PRIME, a medicine must show its potential to address an unmet medical need based on early clinical data. Given that drugs are accepted onto the scheme at a very early stage in their development, it will be years before we know whether PRIME is in fact a success. In July, Kite Pharma Inc. issued what appeared to be the first public disclosure by a company that an MAA for a product in PRIME had been submitted and granted accelerated assessment. Kite's announcement relates to its CAR T-cell therapy, axicabtagene ciloleucel, for treating relapsed/refractory diffuse large B-cell lymphoma (DLBCL).

The vast majority of applications relate to the therapeutic area of oncology (11 applications granted as of October, 34 denied). Other therapeutic indications being targeted include Alzheimer's disease, postpartum depression and transfusion-dependent beta-thalassemia.

A key reason for rejection is insufficiently robust data. Rejected applicants sometimes try again but no second attempt has been successful. As of late September, the EMA had processed ten resubmissions – one was considered to be out of scope of the scheme, and the other nine were assessed but rejected. The submission deadlines and review timetable for PRIME applications in 2018 have been published. There's no reason to believe the scheme will be any less popular next year.

VALPROATE HEARING

In September, the EMA process of assessing medicines in the post-marketing phase was opened to the wider public for the first time when the agency organized a public hearing on the safe use of Sanofi's anti-epilepsy drug valproate during pregnancy and in women of childbearing age.

Public hearings to assess the safety of marketed medicines are a new tool that was made available to the EMA in 2012 under the new EU pharmacovigilance legislation; the agency waited a long time to identify an ideal case where public input would really benefit its regulatory decision-making.

At the request of the French medicines regulator, the ANSM, the EMA initiated a review to ascertain the effectiveness of existing measures to minimize the risk of harm from valproate to unborn babies, and to decide whether more could be done to prevent harm. The public hearing was organized as part of this review.

The hearing took place at the EMA's London headquarters on Sept. 26 and generated huge interest among stakeholders. It was attended by 65 people, including 28 patients and patient representatives, 19 healthcare professionals and academics, 11 pharmaceutical industry representatives and seven media persons. At the hearing, patients gave personal and sometimes emotional accounts of how existing risk minimization measures for valproate had in some cases failed miserably, resulting in thousands of children being born with developmental disorders. The patients said these failings were still happening because of variations in how the drug is prescribed and dispensed across EU member states.

As a next step, the EMA's pharmacovigilance committee, the PRAC, will issue recommendations on the safe use of valproate, which will be sent to the EU Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which is responsible for ensuring harmonized safety standards for medicines authorized via national procedures across the EU.

With additional reporting from Vibha Sharma, Neena Brizmohun and Ian Schofield.

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US Payers Like Biosimilars, But Rebates Remain The Bottom Line (For Now)

The US launch of Pfizer's Inflectra has been an early case study for the US biosimilar market, and some biosimilar manufacturers and payers say market access challenges are worrying.

The launch of the first biosimilar monoclonal antibody in the US, Pfizer Inc./Celltrion Inc.'s *Inflectra* (infliximab-dyyb), is raising questions about how biosimilar manufacturers can gain traction in the market when the innovator is willing to compete on price and play hardball in contract negotiations with insurers – and payers are willing to shake on the deal.

Nearly one year after the launch of Inflectra, Johnson & Johnson's *Remicade* (the original infliximab) has held onto to the lion's share of the market despite the entry of what is meant to be a cheaper competitor. J&J has successfully defended Remicade by offering steep rebates and discounts, tying rebates in some cases to other important portfolio products and, according to a lawsuit filed by Pfizer in September, coercing payers into agreeing not to reimburse Inflectra in exchange.

"Payers are all looking at the dollars and cents, and the dollars and cents for biosimilars don't make sense right now," said Roger Longman, the CEO of Real Endpoints, a reimbursement intelligence firm. "There's got to be something else that encourages the use of biosimilars."

Aggressive contracting along the lines of the tactics being used by J&J happen in the brand market, with drug manufacturers looking to block their competitors' access to the market, but what's unique in this instance is that Inflectra and other biosimilars to follow are intended to act more like a generic competitor, with the aim of lowering overall healthcare spend.

Exclusive contracts involving brand products usually include a provision that voids the agreement if and when a generic comes to market, but that language doesn't exist for biosimilars, which are harder to replicate and manufacture than small molecule generic drugs and are expected to have less price erosion.

Pfizer has turned to the courts for relief, arguing that J&J's contracting tactics are anti-competitive and could set a worrisome precedent for how innovators respond to the launch of a biosimilar rival. But Pfizer isn't the only stakeholder concerned about the long-term impact on what is an emerging new business area. At a presentation in September, FDA Commissioner Scott Gottlieb acknowledged that the adoption of early biosimilars has been slow and wondered if biosimilar manufacturers might dismiss the viability of the products if adoption rates don't improve.

Kaiser Permanente's national pharmaceutical contracting leader Ambrose Carrejo said the market access challenges will be concerning if they persist. "If [the US market is] not able to produce movement … to the biosimilars and generate a return for those manufacturers that have gone down this biosimilar pathway and invested in those molecules I think they will just realize over time that they have to close up shop and move on," he said in an interview. "America would have missed a very significant opportunity." Kaiser is one of the few payers that has put Inflectra on its formulary in place of Remicade.

Mylan NV president Rajiv Malik said the company was optimistic about the biosimilar opportunity but closely watching the market. "We are placing bets that rationality will prevail," he said. "Otherwise, people will run out of the stamina to invest the significant dollars required to bring these products to the market, if they don't see the return, and then you will see no one investing in this space and the costs to the healthcare system will continue to go through the roof."

Novartis AG's Sandoz International GMBH is not particularly worried by the early challenges, and the generic drug group has experience selling several biosimilars in Europe as well as *Zarxio* in the US, the first biosimilar version of Amgen Inc.'s *Neupogen* (filgrastim). "We believe our healthcare system will ultimately embrace biosimilars," head of biopharmaceuticals-North America Sheila Frame said. "We've already seen formularies prioritizing biosimilars."

VOLUME EQUALS LEVERAGE

J&J has an upper hand in contract negotiations with payers when it comes to Remicade because the infused anti-TNF is so entrenched in the market and so many patients are already taking it for a range of autoimmune

conditions. The high prescription volume gives J&J leverage to hand-tie payers into accepting the contract terms because Inflectra, being new, is not as frequently used. Lower prescription volume means the potential cost-savings in the form of rebates will be lower no matter what discount Pfizer offers.

Patients, physicians and payers are still benefiting from a steeper discount and they get the product they know and want, so J&J says its strategy as a win-win, and payers, for now, are mostly accepting J&J's offer. The concern is if the market for biosimilars fizzles over the long-term.

Pfizer said it expected J&J to aggressively defend its blockbuster franchise, but that it was taken aback by J&J's effort to block Inflectra from the market entirely.

"We were surprised that J&J would seek to abuse its dominant market position to thwart competition," a Pfizer insider said.

J&J, for its part, eschews the allegations, arguing that Pfizer just hasn't demonstrated a strong enough value proposition for Inflectra. In an interview, Janssen Biotech immunology president Scott White insisted the company hadn't significantly changed its contracting strategy since the launch of Inflectra, other than to offer steeper discounts.

"When we provide a contract with a payer, we provide a bid, and the bid looks at different contracting or pricing terms for a preferred position, a parity position, a step-through position in terms of a variety of discounts we provide," White said.

Competing against an entrenched and trusted product like Remicade isn't easy for any new entrant, White said, noting that he expects it will take time before biosimilars gain more traction in the market.

"I wonder if the effort was premature," he said of Pfizer's lawsuit.

PAYERS PLAY THE REBATE CARD

For now, some payers are siding with J&J, despite their enthusiasm for biosimilars to help lower their specialty health care spend.

"If you talk to payers and various folks within payer organizations about can we be doing something to promote the use of biosimlars, most payers will say that makes sense but then do whatever is the most tactical thing at the moment," said Edmund Pezalla, formerly national medical director for pharmaceutical policy and strategy at Aetna Inc.

"It's hard to have a long-term strategy, and part of the problem is that the price of the biosimilars isn't low enough yet," Pezalla said.

Express Scripts Holding Co.'s chief medical officer Steve Miller agreed. "One problem is that the discounts have been relatively shallow," he said. "We've told all the main actors that shallow discounts aren't going to be adequate. The discounts are going to have to become greater."

The pharmacy benefit manager isn't in the middle of the Remicade debate specifically because the drug is administered in physician's offices and mostly reimbursed through insurers' medical benefit rather than the pharmacy benefit. Bigger discounts are expected to become more commonplace when more than one biosimilar in a category reaches the market. Ironically, that is the case with infliximab, as Merck & Co. Inc.'s *Renflexis* (infliximab-abda) – launched in July.

Merck hasn't commented much on the initial uptake but said in an email: "We expected that the first months of our launch would be used to educate customers about the product and for negotiations with them."

Pfizer insists the size of the discount is not the reason for excluding Inflectra from the market altogether. "We know clearly that our ASP [average sales price] is lower than J&J's Remicade, which continued to rise since Inflectra's launch without a substantial loss in volume or share of sales – counter to what should occur in a truly competitive market," Pfizer said. J&J's White confirmed that the ASP for Remicade under Medicare has increased this year, but also pointed out that reporting of ASP has a time delay, so it is not necessarily reflective of what is currently going on in the market.

Kaiser's Carrejo said the decision to put Inflectra on Kaiser's formulary was financially motivated after the payer's physician review board agreed the safety and efficacy data supported adoption. "It became a financial decision much like therapeutic alternatives or generic alternatives," he said.

Carrejo acknowledged the decision to switch might be "untenable" for some payers. "Your business has to come in on budget. Taking a significant loss on a biosimilar that could be a $100m or $200m part of your business, taking a 10% cut, could mean not making budget."

It's impossible to know exactly what discounts Pfizer and J&J are offering on their products since that information is closely guarded. Pfizer set the wholesale cost (WAC) Inflectra at a 15% discount to Remicade at launch in November 2016, but offered rebates and discounts to payers on top of that discount. In its lawsuit, Pfizer said it offered to guarantee payers that the price would be less than the price of Remicade. J&J has said the actual cost of Remicade after rebates and discounts is about 30% below the WAC, though that was prior to the entry of biosimilar competition. Merck's Renflexis also launched at a 35% discount to the Remicade WAC. (*Also see "Merck's Second-To-Market Renflexis Biosimilar Priced Below The First" - Scrip, 24 Jul, 2017.*)

The reality is that J&J can offer substantially greater value to payers through steep discounts on a widely-used product like Remicade, at least as long as automatic switching is not an option.

Some payers say they want to see discounts of up to 40% versus the original brand, but Real Endpoints' Longman pointed out that a race to the bottom on price could present a business conundrum for biosimilar manufacturers because the originator company can compete effectively with a goal of retaining some value from its franchise. "Remicade has very low cost of goods right now. Their unit cost is relatively low. That gives [J&J] significant margin to increase their rebates or increase the discounts," Longman said. "They might not be growing the brand, but they are keeping the competitors from coming in."

Sandoz's Frame also urged against a race to the bottom on price. "If prices drop too quickly, there is no incentive for biosimilar competitors to join the marketplace, leaving room for reference product manufacturers to increase prices indiscriminately," she said. "Additional discounts will happen naturally as new biosimilar competition enters the market."

It's still early days and some payers are likely taking time to survey the landscape, measuring their patient and provider communities' willingness to accept biosimilars and watching to how the discounts will shake out over the long term. But the pharma industry is investing in biosimilars – sometimes hundreds of millions of dollars – for the promise of seeing a return on that investment. That promise will have to be fulfilled if the biosimilar market is going to flourish.

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Getting To Grips With International Reference Pricing

International reference pricing has become something of a fixture as payers around the world grapple with rising healthcare costs. The landscape is becoming more complex as the practice spreads further into emerging markets, reference baskets get bigger, and calls for pricing transparency grow louder. *Scrip* examines some of the problems companies face and some of the ways they can adapt, including through new technology, revised approaches to launching new products and better relations with stakeholders.

International reference pricing – the practice of setting a benchmark for price setting in a given market by referencing the price of the same medicine in other countries – has long been used to control pricing but is becoming more complex in a number of ways. It came of age in Europe, but it has been widely adopted elsewhere, particularly in emerging markets that see it as a relatively simple way of setting a competitive global launch price. Nearly half the countries in the world now use reference pricing, and reference baskets can include countries from across the world, according to Voytech Sudol, director of life sciences product marketing at Model N, which provides revenue management solutions to the life sciences industry.

This means a bad price in one country can have a domino effect across continents. For example, France is referenced by 39 countries, including Japan and the United Arab Emirates, says Sudol. A drop in price can send ripples even further. "The problem is that as soon as the United Arab Emirates lowers the price, other surrounding countries, including Saudi Arabia and Kuwait, do too. And now we have the entire region lowering their price tremendously," says Sudol.

Companies therefore need to think about how to limit price erosion. According to Sudol, without any active intervention to protect prices, they typically fall by 15% over the lifecycle of the product.

Reconsidering launch strategies is one way to manage this. Traditionally companies launched first in the US and then Western Europe, where the bulk of pharmaceutical sales are generated, initially going to countries that offer the highest prices, says James Robinson, Model N's director of solutions. However, this strategy needs rethinking. "In many cases, by the time you have launched across Europe, you have taken four years out of the patent life and you may have eroded the price down to the point where a launch in the emerging markets does not look economical," he says. Companies need a more global approach to launch strategies, not least because the bulk of market growth is set to come from Asia, Africa and Australia by 2020, adds Sudol. "They really, truly have to have a global strategy," says Sudol.

With a more globalized approach it is also possible to weave around reference pricing, says Robinson. Companies can launch very early into countries, such as Mexico, that might be perceived as having less to spend, but which in fact have large middle-class populations and vibrant private health insurance markets that pay good prices, he explains. "You can operate outside the realms of price referencing into these kind of niche, smaller markets and get a good return at the same time, as opposed to simply going through the usual channels, like in Europe, where it is all generally public players and you have to suffer the ravages of international price referencing."

Companies also need fluidity and the ability to quickly change their launch plans. Conventionally, companies have stuck rigidly to a pre-determined plan, even if prices end up lower than expected, says Robinson. However, this is changing. "From being very top down, companies are becoming much more agile because of all the variables and different outcomes that arise as you launch. Companies need to understand any big changes, for example what would be the impact if we accept X price in Belgium?"

Robinson notes also that firms are increasingly using new technologies to respond to these challenges to accurately monitor prices and run simulations. "Companies are becoming very good at using the tools to construct models to simulate how a launch price in one country, or a price change in another can impact the price elsewhere." So, if a company secures a disappointing launch price, technology can help it decide whether or not to launch. And if an authority demands a price reduction, companies can more easily see if they should comply with the request or withdraw from the market.

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Indeed, the impact of IRP on patient access is something that a study (Study on enhanced cross-country coordination in the area of pharmaceutical product pricing) commissioned by the European Commission acknowledges: "With regards to patient access, [IRP] is likely to have a negative impact since it incentivises the pharmaceutical industry to first launch in higher-priced countries and delay, and refrain from entering the market in lower-priced countries, and may also inhibit them from offering medicines at lower prices in lower-priced countries."

Companies are also adapting by becoming more tightly coordinated when it comes to pricing, says Robinson. This helps prevent a local affiliate from agreeing to a price that would have negative consequences elsewhere. This is something that companies such as Pfizer Inc. recognize. "We work closely and are efficient at making the right decisions for both local and global business needs… companies need to be adept at working across regions and geographies, reflecting the nature of some of the 'baskets' that countries reference and the rules they apply," says Sam Taylor, Pfizer's head of global pricing.

INCREASING COMPLEXITY

There are other challenges for companies. According to a study conducted by Pfizer and the London School of Economics, the baskets of countries that are used for benchmarking are growing to include more reference markets, says Taylor.

Egypt, for example, has 35 countries in its basket, and this leads to a big administrative burden for companies. "It takes time and effort to gather the data from each country, to make sure all the data is accurate and validated before we can share a correct price externally," says Taylor. However, he points out that bigger baskets do not necessarily mean lower prices. "Smaller baskets can provide similar prices through IRP, but with significantly less administrative burden on all parties," he says.

Another complication is fluctuations in exchange rates, which according to Taylor can lead to distortion in IRP models. "This is something that should be recognized when developing a model that includes countries with varied currencies. Calculations can then be made to reflect currency fluctuations, exchange rates and inflationary adjustments in a symmetrical way, and a tolerance band applied to help minimize distortions."

The frequency of referencing can be a headache for companies too. This varies from country to country. For example, some markets only reference at launch, while other markets re-reference throughout the lifecycle of a drug at different intervals. The more often prices are re-referenced, the bigger the burden for companies. Furthermore, the European Commission study found that the more often a country re-references, the lower the price it can achieve. As such, it proposes regular price reviews. "There is room for improvement since several Member States do not seem to perform regular (i.e. bi-annually, annually or at other defined time intervals) price re-evaluations even if provided for in the legislation," says the study.

A key way that companies can tackle such issues is to develop good relations with stakeholders, says Taylor. For example, Pfizer works with health ministries to help them understand the impact of fluctuations on both company and country. "From this shared understanding we are better placed to develop mitigation strategies." Taylor also adds that the company tries to open dialogue with payer earlier in a drug's lifecycle to ensure the value of innovative medicines is understood and that they reach patients.

Another issue set to complicate matters even further is transparency. Payers are increasingly aware that the prices they are comparing do not include confidential discounts, for example. As such, authorities are looking at how to change this. Sharing of discounts already happens unofficially, but there are moves to make it more formal.

THE FUTURE

It looks like IRP – also known external price referencing – will be around for a while at least. However, there is already growing recognition of its limitations. For example, Morse Consulting's Mani points out that in Canada the global rise of managed entry agreements has "severely curtailed the effectiveness of IRP" as markets are not benchmarking real prices. And according to Taylor, the LSE/Pfizer study showed a move away from IRP as the sole price-setting mechanism as countries add other processes to aid their decision-making. It's also not clear how new approaches, such as indication-based pricing, will fit with IRP. Robinson hopes authorities will reference according to indication rather than selecting the lowest price available for a product.

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Capacity Shortages Unlikely To Hold Back Cell And Gene Therapies

The pharmaceutical industry's manufacturing capacity for cell and gene therapies is under pressure from an ever-increasing number of life science companies wanting to exploit rare expertise in the sector, but CMOs and government-backed facilities are rapidly coming on-stream, hoping to develop local clusters of companies to deliver the complete "living medicines" supply chain.

Stunning clinical trial results with chimeric antigen receptor (CAR)-T cell-based therapies and virus-based gene therapies, and approvals of the first pioneering medicines in these categories, has given a boost to the hundreds of biotech companies working in the sector, and led to concerns about how contract manufacturing organizations and other third-party manufacturing suites will be able to meet the burgeoning demand for their services.

"There's a real lack of manufacturing capacity for cell therapy companies, and they are block-booking suites in CMOs even if they don't have any patients," noted one commentator, adding that the time-consuming nature of using viral vectors in the manufacturing process has been a particular concern. Gene therapy companies face similar issues: "The capacity and expertise to make GMP gene therapies has been tight, but the industry is catching up fast," said an investor in the sector.

If you are a multinational pharmaceutical company, it probably makes sense to build your own manufacturing facility, thereby keeping control of the manufacturing process and its costs, and reducing "IP leakage," the loss of industrial secrets about methods and techniques that represent a competitive advantage in this sector. That's what Novartis AG and Gilead Sciences Inc. have done.

Novartis gained US approval for its chimeric antigen T cell (CAR-T) therapy *Kymriah* (tisagenlecleucel) for B-cell precursor acute lymphoblastic leukemia in August 2017, with the requirement that only certified hospitals should administer the therapy, and that a post-marketing observational study to assess its long-term safety should continue for 15 years. The therapy is being manufactured in Novartis's own facility in Morris Plains, New Jersey, where white blood cells are sent, genetically modified with a new gene, and then sent back to the treatment center.

The $11.9bn acquisition of the gene therapy company Kite Pharma Inc. by Gilead at the start of October 2017 was a signal, if any was needed, that the sector was now attracting serious money, and the US approval of Kite/Gilead's CD19-directed CAR-T immunotherapy, *Yescarta* (axicabtagene ciloleucel), in October 2017 for relapsed or refractory large B-cell lymphoma showed why Gilead was prepared to engage in such high-value M&A. Yescarta, which also has a 15 year-follow-up requirement, will be made in Gilead's manufacturing facility in El Segundo, California, and administered, after training, in up to 90 specific treatment centers. Additional manufacturing sites are being sought elsewhere in the US and in Europe.

Moreover, the first gene therapy for inherited blindness, Spark Therapeutics Inc.'s *Luxturna* (voretigene neparvovec), has been recommended for approval by an advisory panel in the US, with approval expected in January 2018.

Nonetheless, the manufacturing strategies of big pharma are unlikely to be cost-effective for biotech companies, whose investors would likely be unhappy if they started spending capital on "bricks and mortar," at least until a product shows some success in the market. And the pioneering nature of the sector means there are manufacturing hurdles throughout the process – autologous therapies require cells to be removed from patients who are severely ill, so the quality of the removed cells can vary enormously between patients. Lentivirus or retroviral viruses are then used as vectors to modify patients' cells, but techniques to produce those viruses are small-scale, manual, and of course expensive.

Another drawback of pioneering a new therapeutic sector is that investment must be made in a raft of products and services needed in the supply chain to support a therapy designed around removing cells from patients, modifying them in some way, and then returning them to patients. Services required include secure logistics, the preservation of cells via cryogenics or some other method, the laboratory and manufacturing facilities, and suitable tracking software.

PARADIGM-SHIFTING TECHNOLOGIES

Kymriah is "paradigm shifting in that it is not an off-the-shelf therapy but is generated on demand, and therein lies the technical, logistics, reimbursement and policy challenges," contends Bruce Levine, professor of cancer gene therapy at the University of Pennsylvania's Perelman School of Medicine. Levine and colleagues at the university and at the Children's Hospital, Philadelphia, led the R&D and clinical trials with Kymriah, and highlighted the therapy as a "one and done" medicine, in a recent interview for *Scrip*.

Levine believes the scientific equipment industry is, however, catching up fast with potential opportunities in the cell processing sector. "I have been in the field for 25 years, and we had equipment and reagents in the early period, and then some companies said there was not a market and stopped making them, and we had to find other suppliers and were at a loss about how to find substitutes," he remembers.

"But in the past five years, we've seen a difference, we see companies investing in new systems and materials that we only dreamed of 20 years ago. So, I think the pace of the evolution of technology is on an accelerating curve now," Levine said. He noted there were now around 40 companies developing redirected T cell or other cell types for therapeutic use, and more than 800 cell therapy clinical trials are currently underway.

AUTOMATION MAY BE POSSIBLE

Levine is a member of the International Society for Cellular Therapy (ISCT), and the Society's chief commercialization officer, Miguel Forte, believes there are a lot of options to start automating the manufacturing process for cell therapies. "Automation will make cell processing easier, will lower the cost and allow the transferability of the process," he remarked, comparing the situation now in the cell therapy sector with the early days of monoclonal antibody treatment, when the cost of production was high, there were supply chain issues, and monoclonal antibodies were only administered in specialized medical centers.

Alternatives to viral vectors are being explored. "Flow electroporation is the only technology in cell therapy able to scale from early R&D all the way to patient treatment," argues Doug Doerfler, president and CEO of MaxCyte Inc., a US biotech focused on developing such technology. Maxcyte's process uses an electric field to allow molecules to move across membranes, and its instruments and processing assemblies are now being used by big pharma companies.

Overcoming technical barriers and bottlenecks in manufacturing processes is the aim of translational research facilities like the UK's Cell and Gene Therapy Catapult, the Fraunhofer Institute for Cell Therapy and Immunology in Germany and Canada's CCRM. These facilities often act as incubators for startup companies as well as technical advisers, but their managers understand they may have to take a more holistic approach. "These 'living medicines' are different… to treat people at scale with cell and gene therapies, the actual supply chain, particularly for autologous products, is going to have to be re-invented," claims Keith Thompson, CEO of the UK's Cell and Gene Therapy Catapult

KEY ISSUE FOR INVESTORS TOO

The manufacturing of cell and gene therapies has been a key issue for investors too. "From the very start we've been thinking about how we deliver the technology into the market," said Syncona's Chris Hollowood. The Wellcome Trust-backed long-term investing VC has targeted disease areas where new technology has only just been proven, and where companies can be built to take products all the way to market.

"You can choose to make products in your own clean room or in somebody else's clean room, but you have to have control of the manufacturing technology," Hollowood said. "Each company makes its own investment choice." He noted the hiring of manufacturing experts has been an important activity for the cell and gene therapy companies that Syncona supports and, from an investor's point of view, there's still a lot of space in the CAR-T and gene therapy field.

France's muscular dystrophy association, AFM-Téléthon, is also involved in supporting manufacturing efforts for cell and gene therapies through its affiliation with Yposkesi, a French company set up with a dual business strategy and €121m in investment from AFM and the governmental investment bank, Bpifrance. "We have a dual plan, to act as the development and commercialization partner for the two AFM-Téléthon research institutes, Genethon and iStem, but also to act as a contract manufacturer for third parties," said CEO Alain Lamproye.

Yposkesi currently has a 5,000 sq m production facility, and intends to increase this to 13,000 sq m by 2021.

THE CHAIN OF CUSTODY

The rather worrying possibility that patients' cells might be lost in transit, mixed up or damaged in some way has led to the growth of a new breed of company that uses cloud-based software solutions to provide an almost forensic "chain of identity and chain of custody." The head of one of these, Ravi Nalliah, CEO of the UK's TrakCel, pointed out that because the therapy is patient-specific, cells have to be tracked throughout the process from collection, through logistics, manufacturing and back to infusion.

Cell therapy companies have to know who has handled the cells, when and where, because if there is an adverse event, they will have to trace where it occurred; was it in manufacturing, or a mistake during transportation, or somewhere else, Nalliah said.

EXTRA CAPACITY ON HORIZON

You would expect investors to scent a business opportunity, and you'd not be disappointed. For example equity firm Ampersand Capital Partners is an investor in Brammer Bio, a rapidly growing Cambridge, Mass.-based cell and gene therapy contract development and manufacturing organization. Brammer Bio has snapped up unwanted manufacturing assets from Biogen, and has invested more than $50m in capacity expansion in 2017, in Alachua, Florida and in Cambridge, Massachusetts.

The multinational CMO, Lonza Group Ltd., is near to completing a new US cell and gene therapy manufacturing facility in Pearland, Houston. With an initial 9,200 sq m facility and a subsequent 14,000 sq m expansion, it is expected to become the largest such facility in the world and will open in the first quarter of 2018.

And finally, Merck KGAA announced in October 2017 that its Carlsbad, California-based manufacturing facility for cell and gene therapies had passed inspection by the US FDA and Europe's EMA. The facility is to cover 65,000 sq ft and have 16 modular viral bulk manufacturing cleanroom suites.

Lucie Ellis
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The Rise Of The Digital Factory – Sanofi's Story

As digital continues to take hold within the pharma industry's clinical activities, *Scrip* explores how technology enhancements are being put into practice in another area of the drug development cycle – manufacturing.

Jakob Harttung, Sanofi's head of digital and the leader of Factory 4.0, a new initiative that was launched by the French pharma at the end of 2016, and Brendan O'Callaghan, Sanofi's global head of biologics within industrial affairs, talk about manufacturing challenges and trends, as well as the big pharma's digital factory setup and the future for this strategic manufacturing development.

Harttung, who is responsible for driving the digital transformation of Sanofi's industrial affairs, leads a small team that operates like an incubator within the company for new opportunities and projects. He is creating a set of programs by building the initial digital capabilities and then connecting these to operational activities across the board.

He said the term 'digital factory' is used within the business to describe how Sanofi is revolutionizing its manufacturing. "We are moving from a past generation where we leveraged automation to improve performance within a plant to an environment where we are connecting the physical and digital, and putting intelligence, flexibility and adaptive capabilities into the plant," Harttung said.

Using these built-in technologies, the company's manufacturing units can manage different activities at a faster pace with more agility. "And we are able to ensure quality and performance for any environment," Harttung added. He said Sanofi is now leveraging technologies from a new era, "Industry 4.0."

"We are using advanced automation and robotics, new tools around data and advanced analytics; we are moving to artificial intelligence and using other tools like virtual reality to increase capabilities," Harttung said.

Industry 4.0 is a name for the current trend, not just within the pharma sector, of automation and data exchange in manufacturing technologies. Industry 4.0 has seen the rise of cyber-physical systems, the Internet of Things, cloud computing and cognitive computing.

Harttung is working on three key topics as part of his overall aim of digitizing industrial activities within Sanofi, these are:

- **Operational performance:** for which there is a specific initiative within the business aimed at upgrading the digital aspects already within operations.
- **Digital by design:** this concentrates on new investments to make sure they can work within Sanofi's digital infrastructure.
- **Information management:** Harttung wants to improve information management across the life-cycle of products, from R&D into production, by creating a digital continuum of information.

O'Callaghan, who is also the industrial affairs business partner to Sanofi Genzyme, the company's specialty care business, added that the company is trying to leverage advances in technology to improve the efficiency of operations and better integrate biologics drug development with manufacturing, to help speed access of treatment options for patients. "When we make investments in this space we want to do it in a way that uses the latest thinking in terms of technology and capability," he said. "Digital Factory 4.0 is driving better efficiency and higher levels of manufacturing excellence." As well as speeding up processes, Harttung said that lowering production costs was one of the critical benefits of using a digital manufacturing strategy across the business. He also noted that greater flexibility and agility within drug manufacturing gives Sanofi an edge over others that are using more traditional methods. "Having this digital overlay makes it easier to adapt to different conditions or change product strategies," Harttung said.

"Digital technologies allow us to capture and make use of the vast amounts of data that we collect as part of a manufacturing process," O'Callaghan said. He noted that this kind of data analysis can lead to better product optimization across all aspects of the product life-cycle.

O'Callaghan also highlighted that digital manufacturing technologies used by Sanofi today mean the company can more easily connect its global facilities. "Connecting operations across different sites and being able to compare in real-time … enables us to spot issues and avoid complications or look to optimize performance based on strengths seen at other sites."

Sanofi has developed proprietary digital manufacturing technologies based on best practices, all of which are designed to enhance performance. "We want to be leaders in manufacturing performance but in a sustainable way," O'Callaghan said.

Using digital technologies to push products to the market earlier is the end goal, "to benefit both the top- and bottom-line," Harttung added.

Hurricane Maria Tests Pharma Business Continuity Plans

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bit.ly/HurricaneMariaS100

Puerto Rico's slow recovery from Hurricane Maria provides insight into what happens when disaster strikes a node of the global pharmaceutical manufacturing network.

Hurricane Maria's Sept. 20 takedown of Puerto Rico's power grid is testing the business continuity plans of the US territory's dozens of pharmaceutical plants, particularly those making generic injectables that sell for the price of a latte.

The threat to US supply of 14 critical drug products made only in Puerto Rico is a reminder that when disaster strikes a node in the global pharmaceutical manufacturing network, resilience depends on how willing and able companies have been to invest in redundancy.

In Maria's aftermath, generic sterile injectable mainstays of healthcare proved least resilient, their prices and hence manufacturing capacity depressed by longevity in a US market that prizes innovation over enduring value.

The jury is out on an initiative FDA Commissioner Scott Gottlieb launched in July to stir up competition and resilience among older generic drugs by revisiting the 1984 Hatch-Waxman amendments.

CLOCK IS TICKING

But even the most resilient manufacturing operation won't last in Puerto Rico if the island's aging, damaged infrastructure isn't restored soon. If electrical crews haven't restored power to Puerto Rico's pharmaceutical manufacturing plants by the first quarter of 2018, the US could face shortages of multiple critical drug products, Gottlieb told Congress Oct. 24.

Much depends on how quickly the debt-laden Puerto Rico Electric Power Authority (PREPA), which filed for bankruptcy in July, and federal and state partners coordinate the resurrection of downed electrical transmission and distribution lines across the island.

The Federal Emergency Management Agency Sept. 30 asked the US Army Corps of Engineers to help PREPA restore the grid. The corps told Congress Nov. 2 it was on track to restore 50% of the grid's pre-storm load by Nov. 30 and 75% by Jan. 31, 2018. Meanwhile, Gottlieb wrote Congress that FDA is urging local and federal partners to give sole or primary sources of medically important products earlier access to the rebuilt grid.

To help drug makers avert shortages, FDA secured diesel for power generators, medical gases for blood-related products, and landing rights for planes to take drug products rescued from flooding warehouses. Recognizing that the generators powering most plants at 20% to 70% of capacity will break down, FDA has helped some facilities obtain secondary units so they can maintain directional airflow and keep stored batches refrigerated whenever primary generators must be repaired.

BAXTER PULLS OUT ALL THE STOPS

One generic injectables firm quickly ran into difficulty staving off shortages despite extra measures. Before Hurricane Maria hit, Baxter International Inc. moved product to secure off-island storage. In the first week after Maria, Baxter put many sterile injectables on allocation, which can guard against hoarding.

Baxter resumed limited production at its three Puerto Rico plants with power from diesel generators and connectivity from satellite communications, while ramping up production elsewhere to maintain supplies of 0.9% sodium chloride and 5% dextrose mini bags, which providers use to compound or admix hundreds of medications for intravenous delivery. FDA agreed to let Baxter temporarily import mini bags from its plants in Ireland, Australia, Canada and Mexico.

Meanwhile, the two other manufacturers of these products, B. Braun Medical Inc. and ICU Medical Inc., are doing what they can to keep up with increased demand.

Because these measures won't bridge the supply gap in the fourth quarter, Baxter CEO José Almeida told investors Oct. 25 to expect a $70m reduction in quarterly revenues.

AMGEN BENEFITS FROM STRONG PLAN

Meanwhile, Amgen Inc. CEO Robert Bradway said on an Oct. 25 earnings call that Amgen is not expecting any impact to product supply, an outcome he attributed to employee dedication and contingency plan robustness.

There will likely be $75m to $100m of fourth quarter expenses for facility recovery, but no supply-gap revenue reduction, and no significant impact to 2018 results.

The company is generating its own power for now. "But that doesn't create any risk of our ability to produce," CFO David Meline said. "So it's come out very well, I'd say."

The way Amgen weathered the storm reflects an Amgen motto, "every patient, every time," that makes sense for prescription brands but not generics. With generics, shortage prevention is a shared responsibility among manufacturers and FDA. A better motto for this sector might be "another crisis averted every time."

Lubna Ahmed
Reporter, Pharma, Europe

Timothy Pang
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TEXT MINING AND MACHINE READING

The Answer To Pharma's R&D Drought?

How to make the most of the wealth of raw data in pharmaceutical R&D is an increasing challenge for the industry. The digital revolution is already having an impact in areas like clinical trials, and pharma is also starting to embrace new technologies in drug discovery.

Technology is expected to revolutionize parts of the life science industry, and slowly but surely pharma is embracing digital features in different aspects of its operating models – with clinical trials and disease management being the most popular starting points. But can technology prevent drug developers' early-stage pipelines from drying out?

As industry's "big data" buzz has intensified over the last few years, programs for "data mining," "machine reading," and "machine learning" have become increasingly popular.

Jane Reed, head of life science strategy for natural language processing (NLP) provider Linguamatics, told *Scrip* that text mining and machine reading have been around for over a decade. The advancement of technology, as well as increased access to online research, is making such tools more relevant. Machine learning, however, is the next step up in Reed's opinion.

Machine learning is the process by which a machine ingests bodies of data, text or numbers to analyze patterns within the information and form conclusions to apply to other sets of data. Machine reading, however, is the step before the learning; the machine is not yet learning, but scanning the large bundles of data and spotting any patterns.

WHAT IS MACHINE READING?

Timothy Pang, Informa Pharma Consulting's senior director, believes machine reading is a tool that can aid pharma's R&D productivity and help it source new targets amongst masses of information that would be impossible for humans to filter through accurately and quickly.

"Machine reading has the advantage of being not only quick, but also free of bias. And it has the potential to free up scientists to do more interesting things than literature reviews and related tasks," Pang said.

The first step in drug development, choosing a target, is of critical importance highlighted GlaxoSmithKline PLC's head of computational biology and stats, Philippe Sanseau. If not done right, it could be harmful in the long run – wasting money and time. "Attrition is a problem for GSK and many other companies… if you can use data to predict which targets are more likely to be successful, based on certain characteristics, they may be less likely to fail later – this reduces the chances of wasting money on projects," Sanseau said.

He underlined the potential of artificial intelligence (AI) and machine learning in parts of the pharma industry, including target discovery. Pharma is dealing with an increasing volume of data at all stages of development and Sanseau believes AI techniques could lighten the load, increase efficiency and confidence.

Lon Cardon, GSK's senior vice president of target sciences, said in a statement about the company's Open Targets collaboration that, "Discovering and developing new medicines is exciting and innovative but also time consuming, high risk, and incredibly difficult. Anything we can do to choose better starting points in that journey can have a massive positive impact on our success rate in developing innovative new medicines for patients."

Open Targets was established by GSK, the European Bioinformatics Institute, the Wellcome Trust Sanger Institute and biotech company Biogen Inc. to propel open-access. The collaborators have created an open access Google-type search engine that extensively searches, evaluates and integrates the mountain of genetic and biological data being generated. The aim of this platform is to provide detailed data, including genetics and genomics, for drug target selection and evidence of links between known and potential drug targets and diseases. The information put together derives from public domain data sources.

"We believe that harnessing the potential of big data and genome sequencing through this collaboration could help us dramatically improve our success rate for discovering new medicines," Cardon said.

Historically, when searching for a new R&D direction, pharma companies would rely on humans to perform literature reviews and other manual secondary research,

but realistically for a person to read masses of information objectively and accurately is nearly impossible.

"The degree of human error, even before you think about bias, is huge," Pang said, adding that even using multiple researchers to perform literature reviews or other secondary research doesn't rule out bias. "A machine, however, in an impartial way, can look at relationships between different points in a data set."

SCOUTING TARGETS

At the simplest level, when examining a body of data, a machine reader can be used to count frequencies; the number of times a word, phrase, or other item is mentioned in a body of data. By analyzing the relationships between different key items in a body of data, patterns and trends can be used to highlight indications, mechanisms of action, or biological targets of most relevance or greatest potential.

"The idea behind this is that we assume there is wisdom in the crowd," Pang said. Even relatively simple machine reading can be used to highlight the relationship between, for example, indications, biological targets, and mechanisms of action in large information sets. By doing this, areas of potential success or failure based on previous research are accumulated in a quick and orderly fashion, rather than waiting a long time for a human to examine papers and collate information.

"This can be particularly useful when starting out in a new area of research or where research has stalled and direction is required to guide further work," Pang said.

Reed added that the benefit of text mining/machine reading extends to any decision point along the drug development process, not just target spotting. She noted that customers use such tools to ensure regulatory submissions are correct, to harbor information on designing clinical trials, and for data on the real world use of drugs.

MACHINE LEARNING: ALL ABOUT MEMORY

Machine learning in this area of research occurs when relationships, rules and characteristics are remembered and applied to new sets of data. The machine learns to identify specific points using prior information.

Sanseu revealed that GSK has been experimenting with machine learning to pinpoint target areas. "We are investing in more innovative approaches and analytics when thinking about how to pick good drug targets," he told *Scrip*. As one example, he said successful indication characteristics were gathered from Informa's Pharmaprojects database, which provides information on pipeline drugs; including successful, ongoing and stalled products. Those characteristics were gained through machine learning and deployed on the Open Target database to create predictions of potential successful targets.

"We are dealing with massive datasets using the Open Targets database and it can be difficult to understand the patterns ourselves. Machine learning or AI are much better at recognizing patterns, they can keep learning and are able to deal with that large volume of data, which is very hard for a human being," Sanseau said. "Of course, drug discovery is a long process, right now we are at the early stage of identifying potential interesting targets."

REPURPOSING AND RECYCLING

BenevolentAI CEO Jackie Hunter told *Scrip* that an advantage of using AI technologies is access to a wealth of data. She underlined that with such tools, it is not only possible to discover new R&D directions but also repurpose stalled products.

Lingumatics' Reed added: "Within every pharmaceutical company's backyard cellar there is a whole load of compounds that have got through development and then because of various reasons, been put on the backburner – text mining can pull out information of other possible uses for such products,"

And Hunter believes it is essential that pharma considers the potential of this new technology. "We don't use anywhere near the amount of evidence we should – there is so much complex data that no human could ever assimilate it. To be able to assimilate it in a way that is easy to understand and interrogate – you need artificial intelligence," she said. BenevolentAI uses technology to identify new targets and repurpose existing drugs that might have been unsuccessful in one area but harbor potential in others. The company licenses assets from pharma companies for repurposing.

GOING ALL IN

There are challenges still for pharma companies trying to use machine reading in drug discovery. Hunter highlighted that while it is encouraging GSK is active in AI, the company may not be going about it the right way. "Ideally you would want to embed AI into the whole organization at every level, not just a division of your company. It's good to see GSK doing something in the AI space, by establishing a unit, but doing this in a silo rather than embedding it into the whole business makes it harder for bench scientists to truly drive discovery using AI," she explained.

"The real effort is in the curation of the data – cleaning these up and annotating the results," Hunter said, she added that the company has spent two years developing its scientific dictionaries that allow its technology to recognize characteristics and relationships between targets and diseases.

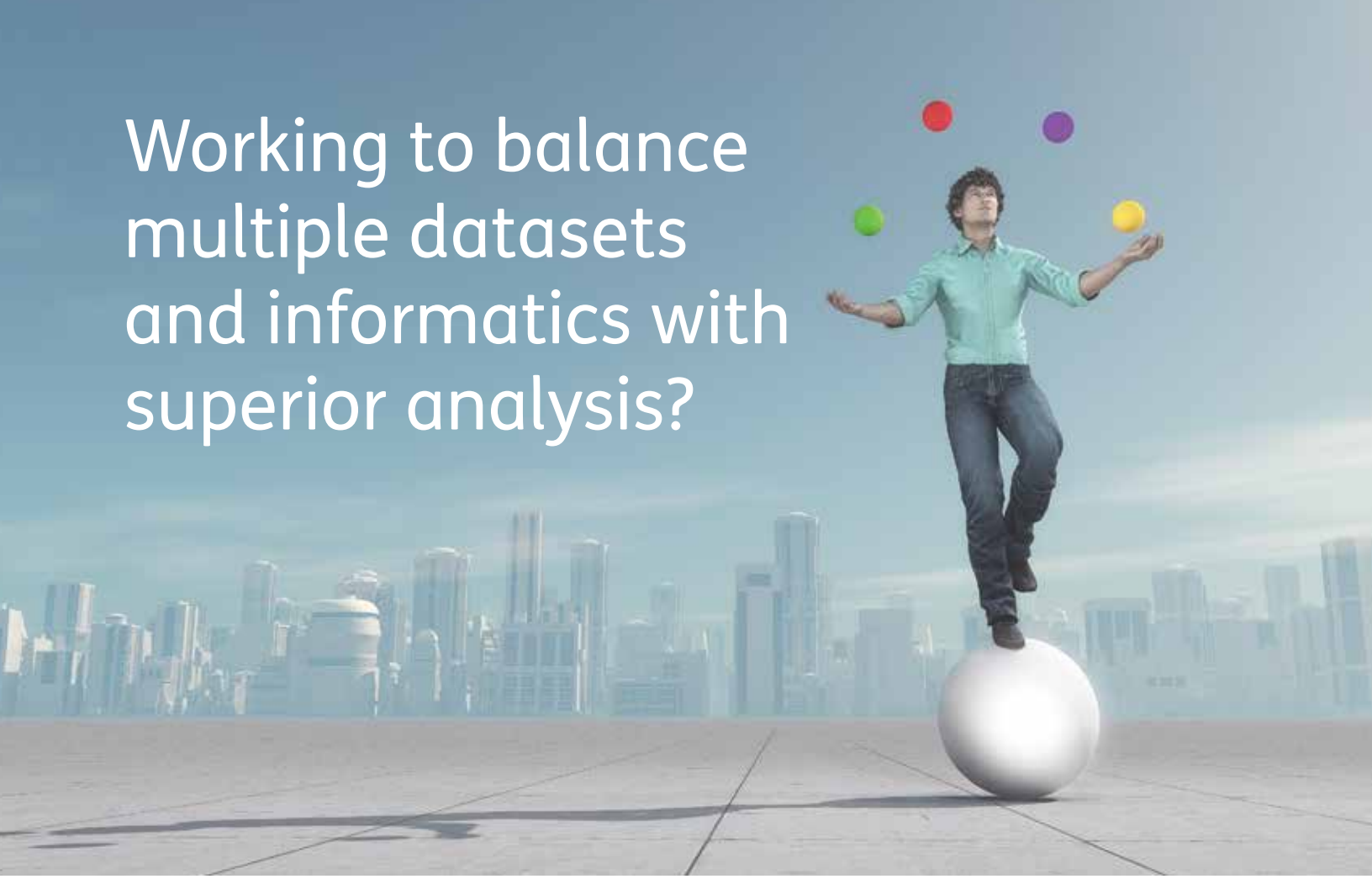
It's the fear of the unknown that Pang believes is the cause of pharma's hesitancy towards implementing data mining and other big data approaches. He said, "Pharma now has the opportunity to embrace big data and the possibilities that it brings to improve the pharma business model, thus creating value for patients and shareholders alike. Some companies are cautious, but those whose fear of the unknown gets in the way are likely to be left behind as the tidal wave of big data washes through the industry."

There are certainly pitfalls for the unwary, and companies must be careful about asking obvious questions, or asking too much – big data is no use if the questions asked are not specific enough or if the answers are too obvious, he added.

Above all, pharma companies need a clear goal – an image of what they want to achieve through data mining and other big data efforts. "Companies that keep these principles in mind will be the ones positioned to thrive in pharma's emerging big data era," Pang said.

For more information on machine reading, text mining and big data initiatives, please contact Timothy Pang at Informa Pharma Consulting: timothy.pang@informa.com.

Working to balance multiple datasets and informatics with superior analysis?



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What's Next For Artificial Intelligence In The Clinic?

Lucie Ellis
Senior Editor,
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Numerate CEO Guido Lanza talks to *Scrip* about how artificial intelligence has been used in the background by some drug developers over the last decade and why this trend has evolved and rocketed recently.

There is an artificial intelligence boom happening in the life sciences sector, according to Guido Lanza, president and CEO of AI biotech company Numerate Inc., but pharma and biotech are playing catch-up to other industries where this technological advancement is already being successfully applied.

Numerate has been using an algorithm-centric process to drive its preclinical drug discovery and development decisions for several years – but Lanza said the company chose to act under a more traditional biotech façade in its earlier days in order to secure funding. He told *Scrip* that until recently the industry has not been ready to listen to a story about AI in drug development and the world was not interested until some success stories emerged.

GlaxoSmithKline PLC is one big pharma that is starting to put more emphasis on AI in drug design. The company signed a discovery deal with AI-firm Exscientia Ltd. earlier this year.

Lanza said the pharma industry has "decided to stop ignoring the impact that AI has made in other industries." He added that the sector has started to realize that while it is "very data rich, it is algorithm poor."

Lanza noted that early activity in applied AI within pharma was focused on using large datasets to answer questions such as, 'Can I use AI to help me identify a target for a disease?' or 'Can I use AI to help me define a patient population?'.

Numerate has been focusing instead on the translational aspects of AI in drug development. "Our view is that the biggest impact AI can play is on changing those attrition rates that are the biggest issue in our industry," he said. Numerate is looking to answer questions like, 'Can we change the rate at which we transform an exciting emerging target into drug program and then the rate at which that drug program becomes a clinical candidate?'

In the past, AI in pharma was seen as a computer-aided drug design tool, said Numerate's chief technology officer Brandon Allgood. This time, he hopes that the technology is viewed as a solution for managing and reading complex data and designing complex models.

Allgood highlighted the pairing of data and the right technology as a huge challenge for the use of AI in drug development. "Right now, there are large amounts of data sitting in big pharma but the current cutting-edge AI algorithm development is not happening within pharma; it's happening outside of the industry," he said. Allgood highlighted a separation issue between the people with the data and the people with the algorithms. "The drug development industry is going to have a hard time seeing very big advances in the application of AI in this space, unless those two things come together."

However, Allgood noted that movement is happening in this area. GSK, for example, is about to start its ATOM collaboration – a data sharing initiative.

The gaps that still exist in the understanding of human biology will be another task for greater use of AI in drug R&D. "We know more about the universe, about galaxy formation, than we do about the biology of our own bodies," Allgood said. "It will be challenging to think about algorithms, about different types of AI models, and how to best apply them in biology."

Finally, Lanza highlighted the complexity of AI technologies as an issue in drug development. "A clinical example: you have the big tech companies saying, 'I can pick patient populations from the whole genome.' And then you have the pharma companies, or the pharma researcher, saying, 'Yes, but I must explain why I picked these patients to my head of development and, at some point, I'm going to have to sit in front of the FDA and explain something that I don't even understand.' Everybody calls it the black box problem."

Lanza notes that if AI technologies only predict things researchers could immediately understand, then the programs are not digging deep enough. "The interesting things to predict are the higher-level phenomenon," Lanza said.

The only way to know if algorithm predictions can improve research is to test the technologies, he believes. "There was a very similar cultural resistance to the self-driving car," Lanza noted. "At some point, you have to allow those cars to drive on the roads."

Numerate's CEO and CTO believe the early pharma movers, such as GSK and one of its own partners Takeda Pharmaceutical Co. Ltd., will start to see early positive returns from their AI investments over the next year. These successes will push the idea that AI needs to be a part of drug development stories in the future.

William Looney
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HACK ATTACK: Biopharma Cyber Chiefs Fight Back

A global ransomware attack earlier in 2017 that affected US pharma giant Merck & Co. hit home the increasing importance of cybersecurity for the industry; in response, information security officers discuss how to prepare for the growing threat of cyberattack.

The threat of cyberattacks on biopharma's extensive information assets is moving to the top of the list of business risks confronting senior C-suite management. *In Vivo*'s roundtable panel of leading biopharma chief information security officers (CISOs), whom got together in May 2017, review what to do and what it will take to convince others in senior management to buy into a challenge that still remains largely below the surface.

As an information-rich industry, biopharma faces a growing threat to the integrity of the data it holds on patients, products and research. The threat stems from a disruptive new wave of tech-inspired cyberattacks originating from unfriendly governments; organized crime syndicates; opportunistic, networked groups and individuals, sometimes from within the company itself; and anti-business "hacktivists" with political or policy grievances.

In May 2017, WannaCry's ransomed malware attack on major businesses and public institutions in 150 countries – including the UK National Health Service – demonstrates the growing technological sophistication and geographic reach of this emerging, still murky community of cyber rogues. WannaCry and other, less publicized breaches of industry data defenses have focused attention on a relatively new member of the biopharma C-suite: CISOs. Long a mainstay in historically vulnerable sectors like banking and finance, the CISO post in biopharma is evolving from a technical, "check the box" compliance-oriented function to one that is strategic and integrated, managing sensitive data issues across the commercial base to support business performance and deliver value to shareholders. More important, the biopharma CISO is leading the transition to an enterprise-wide approach to evaluating and controlling exposure to risk.

On May 11, in conjunction with the NH-ISAC 2017 Spring Summit in Orlando, FL, a meeting of cyber security professionals, In Vivo convened a Roundtable discussion to explore the strategic, operational and policy issues involved in this area with CISOs from four companies in the health and biopharma industries, as well as experts from the professional services and industry association fields.

Looney: It's been said that the healthcare sector is particularly vulnerable to cyber threats due to the sheer diversity of entry points for hackers and other illicit players. Where is that "soft underbelly" located in healthcare? Is it also correct to say there are few protections in place to control the proliferation of bad actors?

Rice: We are highly exposed. It's estimated that three-quarters of healthcare delivery is provided by practices with less than 10 physicians. They lack the resources to invest in the systems and devices necessary to protect confidential data, especially since any small practice can serve as an entry point for cyber criminals to bring down entire networks. There are also all those biotech start-ups with sensitive IP data, who face the same issue over a lack of scale and resources commensurate to the threat.

Shields-Uehling: With reference to fighting the bad actors, prevention and control standards have been carefully drawn up through SAFE-BioPharma, NH-ISAC and other venues. However, while the standards are good, implementing them in the field is slow. The issue is not the lack of standards; it's the collective will to execute around them that is absent. You need a commitment to change management from all the players that Terry Rice just mentioned as well as a willingness to address the issue of legacy systems in IT. A lot of money and investment is at stake. We shouldn't forget it took 20 years to realize the full potential of the Internet.

ROUNDTABLE PARTICIPANTS

Hosted by William Looney, executive editor, Informa Pharma Insights

- **Denise Anderson**, president of the National Health Information Sharing Analysis Center (NH-ISAC)
- **Greg Barnes**, global chief information and security officer at Amgen Inc.
- **Krishnan Chellakarai**, director of IT security and privacy at Gilead Sciences
- **Valmiki Mukherjee**, executive director of cyber advisory services at EY
- **Terry Rice**, VP of IT risk management and CISO at Merck & Co.
- **James Routh**, Aetna chief security officer
- **Mollie Shields-Uehling**, president and CEO of SAFE-BioPharma Association

Looney: How would you characterize the current cyber threat landscape in healthcare?

Routh: Our industry is extremely vulnerable, due to the size of the attack surface. This means the number of entry points that enable a bad actor to penetrate and compromise a data system. The size of the attack surface is exponentially greater in healthcare compared to financial services, the other sector with a history of exposure to the cyber challenge. Healthcare is highly decentralized; there are thousands of small organizations with few resources to mount a cyber capability against the bad actors.

Mukherjee: Sources of cyber threat are proliferating… [Bad actors] have a formidable offensive edge because they can set the rules of the game in terms of the threat, vulnerability and consequences. They only need to find one way in to collapse our defenses, while industry must protect literally thousands of entry points in a single information network. Healthcare companies have only recently begun to prepare for this.

Looney: What are the actual consequences of recent cyberattacks on industry? Although such attacks are widely reported, there is rarely any assessment of the seriousness of a data breach – it's business as usual the next day.

Rice: Reporting on cyberattacks tend to be characterized as a privacy and confidentiality of information issue. But the impacts are far wider. Consider the effect of manipulating health records or a product manufacturing line – giving a sick patient the wrong prescription, or changing production software to 50 cc of an API instead of 5 cc, causing patients to overdose. We've seen ransomware shutting down entire hospitals because of the scrambling of patient records. This issue – patient safety – is the big differentiator when it comes to health care versus other business sectors.

Anderson: A big driver in understanding the importance of information sharing came at the time of the cyberattacks by a rogue nation state [author's note: media reports at the time attributed the attack to Iran] on several US finance and banking institutions in 2012–2013. The attacks received wide attention in the press, from CEOs and at the White House. As a result, cybersecurity suddenly became a board-level issue within finance. While recent ransomware attacks have raised the level of interest in the life science and health care delivery sector, I don't think we are seeing yet the same level of C-suite attention or support as is the case in finance.

Looney: Of the cadres of bad actors in cybersecurity, which one is causing the biggest problems in healthcare companies?

Anderson: It depends. Nation states that coordinate attacks on IP or trade secrets tend to focus on pharmaceuticals, while opportunistic criminals using ransomware and credential theft are motivated by money – they show the most interest in smaller hospitals and clinics, which are easiest to enter and lack the defense capabilities that will raise the costs of penetration to the invader. A trend we have not mentioned is the rise of the "hacktivist" – individuals motivated by a cause or an issue, who use disruption to bring attention to their grievances. This cadre is growing and is particularly worrisome to biopharma due to the industry's poor public image. To date, hacktivist targets have been unpredictable.

Hacktivists – individuals motivated by a cause or an issue, who use disruption to bring attention to their grievances.

Looney: Is there an "insider" threat within the healthcare industry?

Mukherjee: Most big companies today operate in a "virtual" environment in which day-to-day human interaction is declining. People move around a lot, and the millennial generation is particularly restless in terms of job tenure. Company affiliation and identity is thus not as strong, which provides an opening to cyber threats coming from within the organization. It's a company culture issue at base.

Looney: Can the group recommend a specific business or policy change that would support the mandate of the CISO function and/or make the health care sector safer against cyberattacks?

Routh: For Aetna, a key "want" is limiting use of the individual social security number as a unique identifier in data systems. It's pervasive throughout healthcare and, in some cases, is even mandated by the federal government. All this does is increase the potential attack surface for cyber criminals, who regard the social security ID as a highly marketable asset, especially on the darknet.

Rice: Companies have to move decisively from debating whether cybersecurity is a priority issue, to taking action, preferably in coordination with others. Most CEOs today understand there are big issues in cybersecurity that have to be tackled. But are the business units and the cybersecurity folks in our companies ready to sit down and outline the specifics of what must be done?... We will not solve the growing vulnerabilities from cyber criminals unless everyone pulls their weight across the company.

Anderson: I would like to see a repositioning of cybersecurity away from treating it as a compliance problem. It's much bigger than that, with enormous strategic consequences for how healthcare is delivered and paid for. The sector needs to shift from the reactive mind-set of compliance to a focus on enterprise risk management, a more proactive approach.

Chellakarai: Another change that's necessary is considering how to coordinate with the outside vendors who manage large parts of the industry supply chain. One option is to establish a register for vendors along with performance standards, where cyber threats can be assessed and resolved. Coordination with vendors provides the opportunity for expanded information sharing too.

Lubna Ahmed
Reporter, Pharma, Europe

Adherence Issues Add Weight To Digital Trials Push

Technology advancement has brought a wave of change in healthcare, with an increasing number of key pharma players now recognizing the potential of digital – particularly in clinical trials.

Companies like GlaxoSmithKline PLC, Bayer AG, Novartis AG, AstraZeneca PLC and Teva Pharmaceutical Industries Ltd., are extending their hands to those in the technology industry, establishing partnerships to explore this uncharted area. From developing wearables and applications to building portals to gather data, pharma is exploring the usability of tech in R&D processes.

GSK's head of digital innovation and strategic partnerships, AJ Ploszay, told *Scrip*, "The capabilities a pharmaceutical company now needs are not organically found within a traditional company." He emphasized that pharma needs to enter more "buy, build or rent" partnerships to stop its early digital dreams from sinking.

There is enormous potential for digital technology in clinical trials, says ICON PLC's director of product innovation, Marie McCarthy**.** She believes new technologies, like apps on mobiles and other handheld devices, can provide pharma with a means of connecting directly with patients to understand outcomes that are meaningful to them, as well as improving the quality of the data obtained in studies.

Players in the pharma space are still in the "exploratory phase," said John Reites,chief product officer at THREAD, a company that helps pharma, contract research organizations (CROs) and researchers to conduct remote studies. However, the industry has progressed in the past few years: more companies know what they want when it comes to digital trials and are already using easily accessible tech, such as mobile apps.

THREAD, which has worked with several of the top 20 pharma companies, aids in building components of digital trials, including patient-facing apps, web portals, data clouds, eConsent forms, surveys, ePROs (electronic patient reported outcomes) and medical devices. "We're not just using digital because it's the cool thing to do, we're using it to capture endpoints and data that are valuable to a researcher," Reites told *Scrip*.

REAL-WORLD DATA

Digital clinical trials can provide real-world evidence to increase a manufacturer's confidence in their products and answer questions payers, healthcare professionals and regulatory bodies might have about effectiveness and usability. Instead of assessing patients in the clinic, technology offers the option to remotely assess them and understand how therapies affect patients in their day-to-day lives. For example: rather than a six-minute walk test for physical activity in the clinic, patients can be monitored whilst walking to the bus stop.

The way clinical trials currently work is "very archaic," according to Elin Haf Davies, founder and CEO of Aparito**.** Researchers rely on snapshots and episodic data captured during hospital visits. Davies believes that these results can be inconsistent, unreliable, incomplete and not a true reflection of the reality a patient faces outside of the clinic. She feels that using technology to capture continuous data will improve the quality of the data collected. "Technology is allowing patient-generated data to be available in a compliant and real-time way, avoiding center bias or memory recall that may compromise the accuracy," Davies said.

Aparito provides wearable devices and mobile apps for remote patient monitoring outside the clinic, with the aim of reducing the cost of trials. Davies has 20 years of clinical, academic and regulatory experience and worked as a regulator for six years; she founded Aparito because of her frustration at seeing bad or inconsistent data from clinical trials. The company is one of four start-ups that received funding this year via Bayer's Grant4Apps scheme – a program promoting technologies that can improve clinical studies and the quality of data.

ADHERENCE ISSUE CONTINUES

Though endpoints may be hit in clinical trials and the results may seem positive, clinicians in the real world do not always see the same results. Ploszay explained that this is not always down to the underlying mechanism of the medicine but because of the way it is being taken – or not taken – by the patient. Even in the clinical trial setting, adherence is not always achieved, which skews efficacy data. Tracking adherence would be useful as it could provide an insight as to why the patient is not taking the drug, which could be because of side effects.

Dave Allen, respiratory R&D head at GSK, explained that with electronic diaries – something GSK is looking to incorporate into its trials – there is opportunity to

gather useful metadata. "In a COPD (chronic obstructive pulmonary disease) study where activity is important, it is useful to know whether a patient's arthritic knee was playing up on a given day – there's not much point measuring the efficacy of your lung drug if the patient has been immobilized because of their knee," Allen pointed out.

Vodafone has also been active in clinical trial data gathering and has been working with top 10 pharma players. The company's IoT (internet of things) network provides connectivity, storage and management portals that handle data obtained from various devices in clinical settings. John Lee-Davey, Vodafone's IoT health lead, told *Scrip* the pharma industry needed to tackle adherence issues in a different way. Now is the right time as "connectivity is available, technology is cheap enough and peoples' attitudes have changed," he said.

Chronic respiratory disease is one area where companies, including Novartis, Teva and AstraZeneca, have concentrated their initial efforts for digitally monitoring patient adherence.

AstraZeneca is using Adherium Ltd.'s Smartinhaler, a device that can be clipped onto any prescribed inhaler to treat asthma or COPD. It is rolling out Adherium's technology in five countries across Europe, as well as Australia. Meanwhile, GSK entered a partnership with Propeller Health in 2015 for the development of a custom sensor for GSK's Ellipta inhaler. The sensor, which logs when the inhaler is used, was cleared by the FDA a year later.

DIGITAL BY DESIGN

Mobile apps have the potential to relieve the burden of administrative work on clinical trial sites and persuade patients to join studies because of their ease of use and familiarity. Companies use such apps to schedule visits and conduct ePROs, reducing the need for spreadsheets and questionnaires.

McCarthy emphasized that such technology can reduce the number of times patients are required to visit sites, with the technology capturing relevant parameters continually. This could be more appealing to patients who may be put off by long, frequent clinic visits.

Furthermore, the fact that patients could be given an insight into their activity at the end of a study might also be an incentive to join a trial. Allen said that in the same way that people love to use Fitbits and view how many steps they have taken, participating in a study that may help them keep track of their disease might be motivational and result in them adhering to a medical regimen more consistently.

Reites noted that some companies are moving towards a 'BYOD' (bring your own device) model instead of providing patients with devices, because this is scalable and cost-effective.

Digital trials also present the opportunity to create new endpoints that are more relevant to patients. For example, the number of days taken off work or the number of days a patient is pain-free and able to leave the house. Such information can be obtained through wearables or electronic diaries.

"With the devices and sensors, we can aggregate data which can allow us to create more responsive endpoints," McCarthy said.

Still, selection of trial endpoints should be considered carefully and should always start with patients and what is relevant to them, noted Pam Tenaerts, executive director of the Clinical Trials Transformation Initiative (CTTI). "Mobile tech has great promise for clinical trials but some parts of the industry are not sure how to use it for data capture in trials," she pointed out.. The device should be chosen once the endpoints have been defined. "It's logical when you say it, but some get enamored with the device and then think of what to do later," Tenaerts said.

The CTTI is a public private partnership established in 2007 by the FDA and Duke University. It aims to understand current practices, explore alternative approaches, recognize barriers and offer recommendations for trial design. It is running four projects in the mobile clinical trials space, in the areas of legal and regulatory, mobile devices, stakeholder perception and novel endpoints.

OUTSIDE OF THE CLINIC

George Savage, Proteus International PLC's chief medical officer, provided an alternative view, telling *Scrip* that while there is a huge value of technology in the clinical development setting, the focus should be on medicines that are already on the market. He believes a treatment system that creates a flow of digital information and allows collaboration between manufacturer, patient and physician is needed to increase current therapies' effectiveness.

Proteus aims to merge the digital world with traditional medicine and has created an ingestible sensor that can be taken with a medicine to track adherence *(Also see "Digitizing The Pill: Proteus Pioneer Explains How" - Scrip, 14 Dec, 2015.)*. In November 2017 the FDA approved *Abilify MyCite*, a version of Otsuka Pharmaceutical Co. Ltd. 's atypical antipsychotic *Abilify* (aripiprazole) incorporating the Proteus sensor, which is ingested with the pill and sends a message to a wearable patch. *(Also see "FDA Approves First Digital Pill: Otsuka/Proteus' Abilify MyCite" - Scrip, 14 Nov, 2017.)*

According to Savage: "We need to get more value out of medicines that are already approved and already on the market as people aren't getting the full benefit of these drugs because of adherence issues. Coming up with a better molecule won't change that problem."

Some companies are moving towards a 'BYOD' (bring your own device) model instead of providing patients with devices.

Ian Schofield
Executive Editor
Pharma, Europe

Time Is Running Out For Industry To Prepare For Brexit, Firms Begin to Feel Staffing Effects

Nearly 18 months after the UK voted to leave the European Union, pharmaceutical companies and regulators are still in the dark as to what kind of regulatory arrangements will exist between the two parties after Brexit takes place in March 2019.

Stakeholders are worried that a failure to ensure post-Brexit regulatory alignment between the UK and the EU could hit drug approvals, clinical research, trade and many other areas. It could also force the UK to set up its own regulatory regime in parallel with that of the EU.

Brexit negotiations have been proceeding at a snail's pace since the UK triggered Article 50 in March 2017, formally signaling the country's intention to leave the EU. In December it was finally agreed that the UK had made "sufficient progress" on the "divorce" issues to allow the talks to move on to the post-Brexit UK-EU relationship and a possible transition period after March 2019.

With the continuing uncertainty and some influential politicians still openly pushing for a "no-deal" outcome, concern is mounting over the effects of Brexit on the UK life sciences sector – and particularly the people who work in it.

The implications of limiting the free movement of people for sectors such as the National Health Service and university research have been a concern since the June 2016 EU referendum. The concerns are shared by those working in both the regulatory arena and the life sciences industry. The continuing uncertainty also seems to be leading many EU citizens to consider their future prospects in the UK.

But of course, in life sciences as in many other sectors, Brexit is an EU as well as a UK problem. Just ask the European Medicines Agency, which as a result of Brexit is having to relocate from London to Amsterdam. Also ask national regulators in the other member states, many of whom are taking on new staff to deal with the expected increase in workload when the UK agency, the MHRA, is no longer part of the network.

While Amsterdam was among the top five cities in a survey of EMA staff earlier this year, it could still be some time before it's clear exactly how many of the staff will choose to relocate there. The survey found that for the five cities in group 1 (those most favoured), retention rates would be 65% or above, while for group 2 it would be between 50% and 65%, and for group 3, 30-49%.

The figures are important because they will determine the extent to which the agency is able to carry out its activities during and after the relocation. For the cities in group 1, which included Amsterdam, the agency said that core activities such as new drug approvals and safety monitoring would largely be maintained, albeit with possible delays. However, its ability to carry out strategic activities in areas like antimicrobial resistance, collaboration with HTA bodies, and medicines availability would be significantly affected.

The EMA has already suspended some operations under its business continuity plan, which was published in full on Oct. 13 and set out two scenarios in the face of what the agency calls "this unprecedented situation." These are ensuring a "business as usual" scenario as far as possible during the relocation or, failing that, invoking a range of compensatory measures in the plan such as prioritizing its activities and re-allocating freed-up resources.

INDUSTRY WORRIED

The continuing uncertainty over the Brexit outcome now appears to be starting to cause recruitment problems within the UK pharmaceutical industry. This would be a major headache given that companies operating in the UK rely heavily on talent from across the EU.

Confirmation of this trend came in October when Mene Pangalos, an executive vice president at Anglo-Swedish giant AstraZeneca PLC, told a House of Lords Science and Technology Committee hearing that "I had my first conversations where I started to become worried about the impact of Brexit on our employees" – both UK employees in Sweden and elsewhere in Europe, and EU employees working for the company in the UK.

"They are worried about the uncertainty, and obviously we are being as positive as we can be, in terms of saying 'we will look after you', but the fact that we have no idea what is going to happen is a real, real problem, and we are starting to see people turn us down now in the UK because they don't know what the outcome will be in terms of future employment," Pangalos said. "Even though we tell them we have no doubt that great talent is going to be accepted down the road, they haven't got that certainty and so they are saying until we've got it we'd rather go and work somewhere else."

These concerns were echoed by Dave Allen, a senior vice president at GlaxoSmithKline PLC, who told the committee it was important to think hard about the effects of Brexit on the science base and the UK's ability to attract talent. "With a population of 65 million, we cannot expect to have all the talent we need all of the time," Allen said. Companies are asking people to come to the UK to become part of the life science infrastructure "and we need to make it simple for them to do that." The skills they bring are critical, Allen said, and without them "we are not going to compete with countries that are prepared to make it much easier for people to move and thrive in those countries."

FUTURE OF REGULATION

As for the future of the UK and EU regulatory system itself, companies and regulators alike have made it clear that their preferred option is some kind of collaboration agreement that preserves the current alignment of UK and EU regulations over time – and preferably allows the UK to continue its input into the EMA.

In July industry was encouraged by a letter to the *Financial Times* in July from two senior ministers who said the UK "would like to find a way to continue to collaborate with the EU, in the interests of public health and safety." In a return letter, a number of top pharmaceutical company executives said that "patient safety and public health throughout Europe rely on the current pan-European regulations and standards applying to the research, development, manufacture and supply of medicines."

But the ministers also said that if the "desired relationship" with the EU failed to materialize, the UK would have to establish its own regulatory system. Pretty much everything therefore hangs on the final outcome of the Brexit process.

In the event of a "soft" exit – for example, continued membership of the EU single market and customs union, if only for a transitional period – the UK could probably carry on playing a part in the EU regulatory system in some form or other. But if the outcome is "no-deal" and the UK simply crashes out of the EU, the situation would be entirely different. EU centralized drug approvals would no longer be valid in the UK, and the country would have to revamp its regulator, the Medicines and Healthcare Regulatory products Agency, to act as an independent body carrying out its own new drug assessments, with all the resource implications this would entail.

There are risks too for the UK's attractiveness as a location for clinical research. At present the country is routinely included in multinational trials in the EU, but this could change once the UK is no longer a member state. It may also not be able to benefit from the new EU Clinical Trial Regulation, which will streamline the system by offering companies a single submission portal and a central clinical trials database.

As reported in October, the UK is planning to adopt a "Withdrawl Bill" that will transpose all pre-Brexit EU legislation onto the domestic statute books and repeal the European Communities Act of 1972, which gives EU law supremacy over UK domestic law. But because of delays with the portal/database system, the provisions of the CTR will not now apply until the second half of 2019, i.e., after the formal Brexit date of March 29, 2019. According to the Department for Exiting the EU, this means the CTR will not be included in the bill, which would effectively exclude the UK from the proposed system, unless some other regulatory arrangements could be reached.

> "With a population of 65 million, we cannot expect to have all the talent all of the time"

COMPANIES, BE PREPARED

The longer the negotiations take to move on from the so-called "divorce settlement" that the UK will have to pay as part of Brexit to the nature of the future relationship, the more likely it is that life science companies will need to prepare for a "no-deal" scenario in which the UK abruptly leaves the EU and automatically falls under World Trade Organization rules.

If no reciprocal regulatory arrangements have been agreed, companies in the UK with marketing authorizations or orphan designations for centrally approved drugs will need to transfer them to a license holder established in the EU if they want to carry on marketing them there. Similar transfers of responsibility will be required in the case of the Qualified Person for Pharmacovigilance, and the UK will become a third party as far as exports of APIs and finished products to the EU are concerned.

To help companies plan for these and other eventualities, the EMA has produced a Brexit Q&A document, which was complemented in November with new practical guidance on how to go about transferring their MAs and other functions.

But time is running out, and while the biopharmaceutical industry has called on the negotiators to agree a transitional period after Brexit, companies have been advised to take action now rather than gamble on such a period being agreed. As the EMA's Agnès Saint-Raymond told companies at a Drug Information Association meeting in October: "You will have to decide whether to implement some changes now."

But when is now? Virginia Acha of the UK Association of the British Pharmaceutical Industry pointed out at a TOPRA symposium that same month: "Negotiators have until 2019. We don't… so at what point do we say 'you just passed my no-go'?"

Companies that fail to make their own preparations risk being left behind in the mayhem that a chaotic Brexit could bring.

The nightmare scenario on what's being called "Day 1" is potential drug shortages for patients if drugs are stuck at borders, allowed neither into the UK from the EU or into the EU from the UK. Nobody wants that.

William Looney
Executive Editor,
Pharma, US

Future-Proofing Human Capital: Does Biopharma Have The Right Stuff?

Biopharma's future depends entirely on the application of human ingenuity to complex problems with no easy solutions. In a survey conducted by *In Vivo* and EBD Academy, industry decision-makers in the US and Europe give recommendations on how to attract talent, boost employee engagement, foster diversity and maintain the product innovation that patients demand and society expects.

In an industry with financial margins so high they induce nosebleeds in consumers and policy-makers alike, it's surprising how little attention is paid to biopharma's equally vast reserves of human capital. By nearly every indication, the industry and its fellow travelers in the life sciences possess the most productive, knowledge-intensive, highly educated and well-compensated workforce in the world. Nevertheless, this disconnect deserves its own question: can we affirm that all is well in this most comfortable of career destinations?

To find out, *In Vivo*, together with Informa's life sciences learning business, EBD Academy, conducted a comprehensive survey during the months of April and May 2017, involving 300 leading decision-makers in the life sciences sector in the US and Europe. The survey, *Future-Proofing Human Capital In Global Life Sciences*, examined the key drivers affecting workplace culture, skills training, management practices and leadership styles for a cross-section of this diverse industry – today and tomorrow.

COMPANY RESPONDENTS

- two thirds are globally engaged, with operations in multiple regions and countries
- roughly two thirds are active in the R&D-based pharma, biotech and generics businesses, with the remainder in medical devices and the CRO space
- the survey group spans the range, from the big and mid-size pharma players with annual revenues of more than $1bn (20%) to biotech start-ups with no revenue (15%)
- on an individual basis, more than 70% of those polled are age 50 or under
- about half the workforce asked has been at their current job from one to five years

REGULATORY REQUIREMENTS ARE TOP PRIORITY

Asked to prioritize among 15 challenges to the viability of their business, respondents put tougher regulatory requirements at the top, followed by increased complexity in the conduct of R&D and manufacturing and, in third place, retaining a high-skills workforce. This proved true across the board, from age to gender, experience and job function. Trailing at the bottom was cybersecurity; experts have highlighted that biopharma has been slow to grasp the strategic implications of computer crime. *(Also see "Hack Attack: Biopharma Cyber Chiefs Fight Back" - In Vivo, 25 Jun, 2017.)*

Looking ahead to the years beyond 2020, the survey group highlighted a series of unknowns that, taken together, indicate the need for a much more prioritized and systematic approach to identifying company exposure to risk. The biggest unknown is the effect of technology change. Addressing it demands big, all-out investments in IT systems management and data assessment capabilities – the standard IT "patch" solution is not enough. Close behind technology is erosion of the industry's market autonomy, including the freedom to price new medicines and expand market access.

One finding from the survey is the growing interest in a new functional capability in life sciences: risk intelligence. This tied with building human capital for third place in the list of issues CEOs must confront after 2020. "The risk conversation is becoming institutionalized as part of the C-suite decision matrix," says Terry Hisey, Deloitte Consulting's US principal for life sciences. "Uncertainty in the markets reinforces the need to make the analysis of risk factors integral to strategy and execution rather than delegating it to compliance or approaching it ad hoc, in reaction to a crisis. There is an added benefit of increasing internal transparency when the risk conversation becomes part of the normal process of governance. In fact, we see

risk intelligence as a separate function, deserving of its own designated position in the C-suite, and many of our biggest life science clients are following suit."

Despite the challenges to the business model, there is a clear consensus on what life sciences companies must do to maintain growth and profitability. By a two-thirds majority, respondents pointed to more product innovation, led by the timely launch of new medicines, vaccines and medical devices to address unmet medical needs (*see Exhibit 1*). Other top-listed strategies included expansion into new geographies or business segments such as biosimilars as well as a focus on internal commitments, from efficiency initiatives like cost controls to more investment in workplace training programs and a higher profile for M&A, licensing and partnering activities. Those in the group with less than two years at their company differed from the rest in choosing new business segments as their number one strategy for growth.

In terms of the most promising regions for future growth, China accompanied by the rest of Asia took the top spot overall, followed closely by the US and Canada.

LOOKING AHEAD AT LEADERSHIP

The survey numbers show that the top three "must have" skills today are stipulated for success beyond 2020 as well. These are execution capabilities – taking initiative, solving problems, motivating teams and managing for results; followed by a cross-functional orientation; and, third, specific technical expertise. Below that, there is a common thread around the value of scientific literacy as therapeutic options widen and the process of drug development grows more complex.

Recent CEO transitions in the biopharma space do appear to highlight the attributes from working with the research community. "The explosion in scientific knowledge over the past decade has reinforced the desire of boards of directors to recruit industry insiders for top management posts," John Hawkins, vice-chair and director of executive recruiting firm Odgers Berndtson LLC, said. "Companies are looking for CEO candidates that combine knowledge of medicine with deep understanding of how it translates to commerce."

Technical expertise is still a prized commodity, especially as technology helps companies understand their customers and markets through ubiquitous information. Mastery of the complex global regulatory process is most critical, but new areas are looming large: systems biology and other advanced discovery platforms; bioinformatics; precision medicine and diagnostics; health and behavioral economics; and building external partnerships are considered important as well.

Peter Honig, Pfizer Inc.'s senior vice-president for worldwide regulatory and safety, said, "Regulatory and safety has to be an essential function going forward because it is arguably the only core activity that has full line of sight all along the drug life cycle, from discovery to registration, post-market approval and access, right through to product senescence. It's a major responsibility to provide that continuity of support."

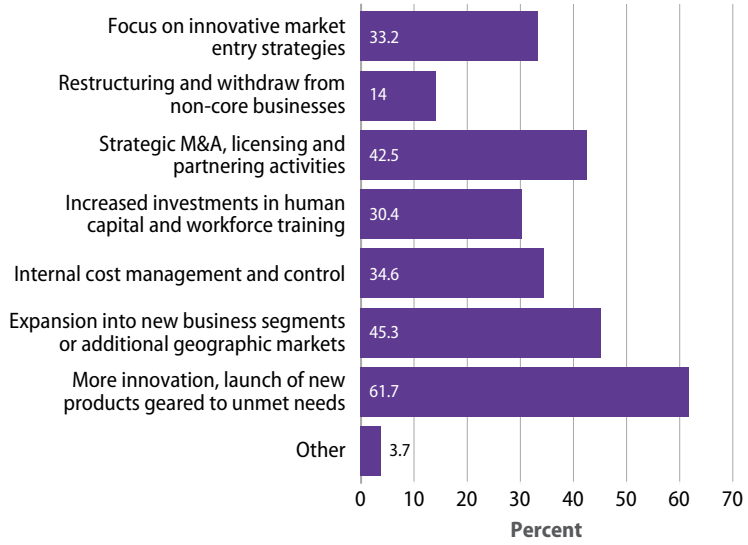
Nearly half of respondents chose the HR division as mission-critical, followed closely by the Strategic Planning and Market Access functions (*see Exhibit 2*). Further down – but still important – are IP, Risk Management and Intelligence, Bioinformatics, and Data Security.

ORGANIZATIONAL DYSFUNCTION RISKS

Significantly, organization and colleague behaviors were tagged as drivers behind the productivity lag in biopharma R&D as well as the slowness in responding to competitive inroads from tech firms, retailers and others outside the industry. The biggest drag is internal bureaucracy, exemplified by multiple layers of management not focused on science, followed closely by a siloed business unit (BU) structure that discourages cross-disciplinary interactions. Respondents highlighted high rates of professional staff turnover as the key manifestation of organizational dysfunction – some 30% of the group noted this as a problem endemic to their own employer.

In fact, the survey indicates that staff turnover is likely to increase if dismantling these internal barriers fails to attract the attention of senior management. Regardless of age, gender or experience, respondents rated the opportunity for professional growth as the principal reason for taking their current job. The sole outlier here is among colleagues over age 55, who chose their company's reputation as the reason, by a narrow margin. Employment that fosters opportunity and continuous learning also highlights the importance of a strong commitment from Human Resources to advanced skills training, 360-degree management performance reviews and leadership behaviors.

EXHIBIT 1: KEY STRATEGIES TO ACHIEVE GROWTH TARGETS OVER NEXT FIVE YEARS



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PD-1 Predictions And Commercialization Challenges

What's next for the PD-1 market, a cancer therapy area that exploded in 2017 as recently launched products secured even more approvals? Maria Whitman, managing principal at sales and marketing firm ZS Associates, talks about challenges facing the booming immuno-oncology market and shares her predictions for 2018.

Whitman, leader of ZS's specialty therapeutics and oncology practice, expects immuno-oncology developers to focus heavily on their drug combination strategies in 2018, using more biomarker studies and tests to find the right patients to treat with the right combinations of novel cancer drugs. Following this trend, Whitman also expects to see more data in the coming years from smaller companies that are developing their own programmed cell death protein 1 (PD-1) inhibitors to use as backbone therapies in combinations.

PD-1 and programmed death-ligand 1 (PD-L1) drugs have bombarded the IO market in the last couple of years, with five products entering the space and gaining numerous approvals between them for indications covering non-small cell lung cancer, head and neck cancer, bladder cancer, colorectal cancer, gastric cancer, melanoma and Hodgkin's lymphoma.

There are also several other PD-1/PD-L1 inhibitors in clinical development and the number of combination trials for IO compounds together with either investigational or approved PD-1/PD-L1 drugs has skyrocketed.

Despite their success, PD-1 therapies have also seen setbacks in the clinic in 2017. In July this year, Merck & Co. Inc.'s PD-1 inhibitor *Keytruda* (pembrolizumab) failed to show a survival benefit in the KEYNOTE-040 study of head and neck cancer. This trial was meant to produce confirmatory data for Keytruda, which had already received accelerated approval for head and neck cancer in the US. Despite the endpoint miss in KEYNOTE-040, Merck does not expect a label change for Keytruda in the US because median overall survival (OS) for the anti-PD-1 drug in the study of recurrent or metastatic head and neck cancer was still better than investigator's choice of chemotherapy.

Roche's *Tecentriq* (atezolizumab) stumbled in May when the company's confirmatory Phase III IMvigor211 study in second-line bladder cancer did not meet its primary endpoint. The drug failed to show failed a survival benefit in patients with previously-treated metastatic urothelial cancer when compared with chemotherapy.

And in April this year, Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab) did not significantly improve overall survival versus Roche/Genentech Inc.'s VEGF inhibitor Avastin (bevacizumab) in the Phase III CheckMate-143 study in glioblastoma multiforme (GBM) – one of the hardest to treat cancers.

THREE THOUGHTS FOR PD-1S IN 2018

With 2017 successes and setbacks for marketed PD-1/PD-L1 therapies in mind, Whitman highlighted three things she believes are critical for the market as we move into the New Year.

Firstly, she spotlighted the extremely high level of investment in the PD-1 space; ZS expects the IO market, which is driven by PD-1/PD-L1 drugs, to be worth around £30bn by 2022. "There's so much more investment in the immunotherapy market than in many other places within oncology," she said.

As of Oct. 2017, there were more than 480 clinical trials enrolling or progressing for drugs targeting PD-1. However, the scale and scope of what's happening in this research area, in terms of clinical trials, is creating challenges for those who are investing. "Obviously, showing differentiation over time will be a contest," Whitman said, "but another challenge is that with so many trials and combinations, accreditation is going to get tougher and tougher."

Secondly, Whitman thinks PD-1/PD-L1 drug developers must improve their use of biomarkers to survive the tough competition in this market. PD-1 tests for the marketed products are not interchangeable and there's a strong growing belief that PD-1 expression may not be enough as a predictor for how well these drugs will work in patients. The market is starting to see genome type biomarkers by mutation burden being studied to evaluate the associational first response to PD-1. Still, looking ahead, Whitman expects more activity in this space.

"This is going to be a big deal, not only from a clinical perspective – looking at where PD-1s fit versus targeted therapy in the regimes – but also from a budget perspective in many countries," she said. "Payers, of course, will be looking to predict which patients these therapies work best in and we also don't want patients on therapies that aren't ultimately the right sequence for them."

Finally, Whitman said controlled combination strategies will be critical for success in the PD-1 space. "There are combinations with chemotherapy, with CTL-4s and the with just about everything else. But there are still a lot of questions around combination strategies," she said.

When speaking of PD-1/PD-L1 combination data seen in 2017, Whitman highlighted examples of objective partnerships like Merck and Incyte Corp.'s Keytruda plus epacadostat as one combination that has generated significant excitement.

However, she also noted that Roche has historically done more in-house; the company's combinations for *Tecentriq* (atezolizumab) – or more information about the Swiss pharma's combination strategy – might come to light as the drug secures approvals in other cancer indications. Tecentriq, an anti-PD-L1 therapy, is currently approved for NSCLC and bladder cancer but Roche has Phase III trials ongoing in small cell lung cancer (SCLC), prostate cancer, melanoma, breast cancer, RCC, colorectal cancer and ovarian cancer.

Still, Whitman said, "Irrespective of what partnering strategy they're taking, the biggest challenge that these PD-1 marketers are going to face is how to differentiate; especially if we're not seeing biomarker cut-offs yet that prove true effectiveness."

A NEW KIND OF BLOCKBUSTER

PD-1s have spurred companies to use new commercialization strategies, "I've been defining them as a new kind of blockbuster," Whitman said.

Pharma used to see a lot of single indication oncology products that could reach £1bn in sales and the sector still has a few drugs like this here and there when there are significant improvements in a disease. But newer cancer drugs like the PD-1s are (or soon will be) launching multiple indications in a very short scope of time, all of which will amount to a blockbuster status.

"This is a very different composition commercially for organizations who are used to launching much bigger single indications," Whitman said. Having multiple indications so close together affects everything from investment in marketing to how companies approach doctors because not all indications require the same level of commercialization activity. "It's a challenge for these companies to get the right balance for marketing PD-1s in separate indications." Companies commercializing PD-1s in several indications at once will need to get more creative, she said.

WHERE NEXT FOR IO?

There are more than 20 investigational PD-1 inhibitors in the clinic, alongside the five marketed products. While these drugs are in numerous clinical trials and preclinical studies across various indications, Whitman believes the next hot area for IO therapies will be hematology.

According to *clinicaltrials.gov*, there are around 41 active or planned trials for PD-1 and PD-L1 drugs targeting hematological diseases.

It is "difficult to predict" what will be the next leading and competitive indication for IO drug developers which until now have focused on solid tumors, Whitman noted. But real-world data, as well as clinical trial results, will help to steer the industry as it pursues other indications with IO treatments, particularly PD-1/PD-L1 drugs.

SOLO COMBOS

Another important trend in IO development, according to Whitman, is that smaller companies are developing their own PD-1 products to act as backbone therapies in future combination therapies. Whitman said that because of challenges and complexities of commercializing PD-1 therapies, partnerships are tricky and complicated. "There are a lot of emerging players that don't want to partner," she said. "They want to develop their own PD-1/PDL-1s to combine with the novel assets, with different MOAs, that they have in their own pipelines."

This could result in the creation of two markets: companies promoting branded PD-1s, such as BMS and Merck; and then a series of players making PD-1/PDL-1s for the express purpose of combination.

Whitman's concern with this trend is that the sheer number of PD-1 drugs will dilute the value of the branded products. "This is another reason why the big PD-1 companies are actively searching and partnering with companies that have assets and data for compounds targeting things like OX40 and IDO," she added.

While this isn't an entirely new phenomenon – cancer combinations have grown in popularity over the last few years – action by smaller and emerging companies to go it alone has not been as direct in the past. "Some of the early combinations were done more at the institutional level," Whitman noted. "This emerging company concept is different; it's due to how difficult it can be to commercialize with partners. Many of these businesses want to make a run at it in terms of bringing their company to market and/or securing a buyout. In either case, it's useful for these businesses to have a complete asset."

Approved PD-1/ PD-L1 Drugs:

- Merck & Co.'s Keytruda
- BMS's Opdivo
- Roche's Tecentriq
- Merck KGaA/Pfizer's Bavencio
- AstraZeneca's Imfinzi

CLICK

For a list of PD-1/PD-L1 drugs in clinical development: bit.ly/PD1PredictionsS100

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Are Mega Mergers A Thing Of The Past?

Bolt-ons or big-ticket buys? As another year passes without a big pharma mega merger despite industry giants sitting on cash piles, we consider where M&A will be most likely to take place in 2018.

Will 2018 bring the return of the marquee mega-merger? Rumors of Pfizer Inc. prowling for a large acquisition, with Bristol-Myers Squibb Co. and (again) AstraZeneca PLC among the presumed targets, continue to circulate, along with questions about how Pfizer sees its future involvement in immuno-oncology and whether it is fully satisfied by its arrangement with Merck KGAA in that space. The coming year will bring further data for all of the IO front-runners and therefore more clarity on the positioning of *Bavencio* (avelumab), Merck and Pfizer's programmed death-ligand 1 (PD-L1) inhibitor that is playing catch-up to programmed cell death protein 1(PD-1)/PD-L1 inhibitors from BMS, Merck & Co. Inc., Roche and AstraZeneca.

Nevertheless, the IO field is fluid and the plurality of emerging data on different agents, in different combinations, in patients with different cancers, at different stages and with different mutations makes it difficult to envisage any one of the big pharma businesses currently at the forefront of IO emerging in the near term as unassailably dominant, or conversely any of the contenders imminently being driven right out of the space. With so much data yet to read out, would BMS or AstraZeneca's shareholders really be ready to hand over to Pfizer?

Pfizer aside, large-scale big pharma consolidation looks unlikely in 2018, despite the fact that most big companies harbor sizeable cash piles. The tax inversion impetus that drove big-ticket deals in pharma and medtech as well as other industries, leading up to the high-profile failed mergers of Pfizer/AstraZeneca and AbbVie Inc./Shire PLC in 2014 and Pfizer/Allergan PLC in 2016, is no longer there. The Obama administration's actions to restrict tax inversion deals, and then the anticipation of business-friendly tax reform under Trump's leadership, have jointly laid that to rest.

Improving operations through greater efficiency is still something pharma needs to work on, but whereas in the past mergers followed by synergies and organizational rationalization were the strategy of choice, the industry's challenge now is to better embrace the data revolution, rethink its processes and effectively exploit the myriad information it gathers or has access to. That may require substantial investments and partnerships with non-traditional players in the healthcare market, but merging with a fellow big pharma behemoth is unlikely these days to help an industry leader get smarter in R&D, manufacturing or sales and marketing.

Nevertheless, one area where pharma does look likely to be involved in big business M&A is in the consumer arena. Major consumer health businesses look set to continue changing hands in 2018. Still, if pure consumer businesses like Nestle SA or Reckitt Benckiser Group PLC have their way, there will actually be a net reduction in big pharma groups' activities in the space.

CONSUMER HEALTH M&A EXPECTED

Pfizer recently decided once again that it will divest its consumer business, while earlier in 2017 Merck KGaA announced it would follow compatriot Boehringer Ingelheim GMBH out of the space. Meanwhile, March 2018 will bring the expiration of Novartis AG's put option on its 36.5% stake in its consumer joint venture with GlaxoSmithKline PLC, set up in 2014 as part of a complex asset swap. GSK's CEO Emma Walmsley appears keen on the opportunity to double down in consumer, while Novartis's interest lies less in strategic involvement in OTC, and more in managing the stake as a financial asset. Will the impending deadline force a decision to sell by Novartis's incoming CEO Vas Narasimhan, who unlike current head Joe Jimenez has a medical rather than a consumer background?

BOLT-ON DEAL MAKING

Fortunately, the broader biopharma ecosystem is looking more fruitful than ever, with the rapid pace of technological breakthrough continuing to be amply irrigated by both private and public money markets. As the industry continues to lean towards increasingly expensive, specialized and targeted therapies rather than high-volume small molecule drug sales, the likelihood is that big pharma's acquisition activity will mostly be around small and mid-sized biotechs that can help them leapfrog rivals to claim territory in expanding treatment areas.

Target company valuations remain high, but gone are the times when big pharma had any hope of relying on internal engines to keep pipelines sufficiently well stocked to sustain their top lines. Expect platform technology and product-focused M&A to dominate over mega-deals once again in 2018.

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17th Regulatory and Scientific Affairs Conference
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25 APRIL 2018

14th Legal Affairs Conference
24th April - Networking dinner with legal experts (separate registration)
LONDON #LAC18

26-27 APRIL 2018

16th Biosimilar Medicines Conference
LONDON #BIOS18

13-15 JUNE 2018

Joint 24th Medicines for Europe and 21st IGBA Annual Conference
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