

# SCRIP 100

2016



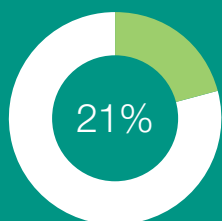


# ICONIK

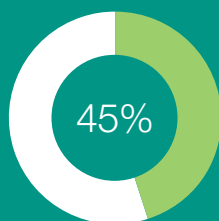
Informatics Hub

From research  
to real world

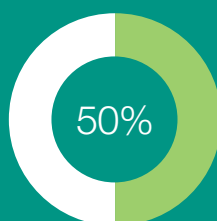
ICONIK Informatics Hub is reducing time and cost in clinical development:



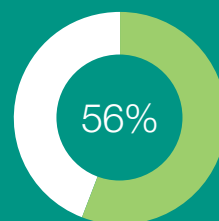
Potential Saving in  
Monitoring Costs



Reduction in  
Data Queries



Reduction in  
Protocol Deviations



Increase in  
Screening Rates

## Combining Optimised Processes with Advanced Technology to Deliver Value

The ICONIK Informatics Hub is ICON's technology platform to analyse the operational, clinical and real world data that we collect during clinical development. This enables us to combine industry leading technologies with best practice processes to deliver real impact in clinical development and provide value to our clients.

The Informatics Hub has 4 key components which combined together provide an integrated advanced technology approach to clinical development.

### ICONIK Design

Uses data to enhance protocol design, match patients to trials and develop model scenarios to assess the impact on timing and cost.

- **Patient Identification:** ICON is working with IBM and using Watson's cognitive computing power to help automate the cumbersome process of identifying patients who meet the criteria for a clinical trial, and to analyse protocols to assess trial feasibility.
- **Adaptive Design Trials:** We are the only CRO that offers the knowledge, technology and global footprint to make adaptive trials a reality. ICON's ADDPLAN® combines the features of sequentially planned clinical trials within a user-friendly interface. Adaptive Design Trials have the potential to save between 30-50% on trial costs.

### ICONIK Delivery

Collects real-time data during the trial process to enable better decision making and the successful implementation of strategies that significantly improve efficiency in clinical trials.

- **Patient Centric Monitoring:** Proactive early detection and mitigation of risk, based on ICONIK data analysis, enables more effective resource deployment with the potential to reduce monitoring costs by up to 21%.
- **Study Start-Up:** Optimised processes and the introduction of industry leading technology assists ICON to accelerate site activation timelines by up to 25%.
- **Patient Randomisation and Clinical Supply Management:** ICON's FLEX ADVANTAGE is a next-generation Interactive Response Technology (IRT) platform that offers enhanced randomisation, clinical supply management capabilities and supports the complex logistics in the execution of adaptive trials.

### ICONIK Engagement

Data and evidence based research is used to develop solutions that engage investigators and patients more effectively to improve patient recruitment and retention.

- **Investigator Communication and Training:** The FIRECREST Investigator Portal is a single sign-on portal to a suite of tools that enhance communication and site training. FIRECREST's award winning dynamic multimedia and Visit-by-Visit Guide are impacting time and quality in clinical trials including 50% lower protocol deviations, 56% improvement in median screening rates for studies and 45% reduction in total data queries.
- **Patient Recruitment and Engagement:** FIRECREST eConsent is a next-generation electronic informed consent solution that incorporates key recommendations from the FDA's recent draft guidance on informed consent. The eConsent solution employs videos and visual aids to assist in the explanation of complex scientific concepts and medical terms found in trial protocols.

### ICONIK Commercialisation

Real word data analysis from multiple sources to enable deeper insights into the safety and value of new treatments to develop commercialisation strategies and provide effective engagement plans for payers, prescribers and regulators.

- **Value-Based Healthcare:** ICON is working with partners to use its powerful data management capabilities and expertise in securely managing and analysing large clinical and real-world datasets which has the potential to improve value-based healthcare.



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**SCRIP**  
Intelligence

*“The Pink Sheet”*



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## Putting Patients At The Center Of Clinical Research

The CRO ICON is making waves in the clinical trial industry by teaming up with IBM to place the patient at the center of every single study. Chief information Officer **Tom O'Leary** tells *Scrip* how technology is influencing patient response and engagement.

It is a problem that continues to plague the pharmaceutical industry - how to ensure that the right patients are recruited for clinical trials and speed up the studies that will bring innovative therapies to the market.

While the number of drug approvals on both sides of the Atlantic went up in 2015, the costs of getting there are soaring. Drugmakers, and particularly their finance chiefs, are increasingly concerned about their return on R&D investment.

It is a problem that ICON plc, one of the world's leading clinical research organizations (CRO), and its chief information officer Tom O'Leary are tackling head on. In an interview with *Scrip*, he said that "the challenge we face as an industry is evolving our approach to put the patient at the center of drug development. The approach we have taken in finding the right ones to participate in studies is the same one the industry has been using for the past 40 years."

That would often involve looking back at the sites used before in studies and doing trials that were very similar to those they have conducted over the years. However, this approach "is not that scientific,"

Mr O'Leary notes, and can result in getting patients who would subsequently be found not to be the ideal match for a study.

Now of course, technology has advanced to a stage where there is a greater availability of health and medical information, thanks to the rise of computing powers that have "extended our ability to interrogate large amounts of data in an anonymized way," he says. But how can the industry make use of all this data?

One of ICON's responses to this dilemma has been to team up with technology giant IBM and its cutting-edge Watson cognitive computing capability, delivered through the cloud. As part of the collaboration, initially ICON is applying Watson Clinical Trial Matching to its breast, lung, colon and rectal cancer trials, enabling the firm to advise sponsors how many patients match their trial criteria, where they are located and how they will recruit them.

When the deal was announced in September, ICON noted that more than \$1.3bn is spent on recruitment of participants by drug developers each year and yet fewer than 5% of cancer patients take part



in a clinical trial. It also typically takes six to 12 months to start up a global Phase III drug trial and another year to enroll the required number of patients.

### Data Delivers Right Patients For Right Trials

Mr O'Leary explains that IBM's Watson Health Cloud includes 100 million patient records including the data set from Explorys, which IBM acquired in April last year. With this "massive amount of unidentified patient live data, we can find where the patients are who meet specific criteria for a particular indication."

He adds that "very scientifically, we have the opportunity to identify patients that meet the required criteria in a specific state, country or region. We can then go to the physicians and hospital sites and say you have these patients and ask them to discuss participation in a study."

Mr O'Leary adds that combined with ICON's own extensive data, "we can provide much more targeted selection," reducing waste of time and resources to get the right patients who can complete a study and help deliver more innovative drugs."

The IBM Watson cloud makes sense from a business point of view but ICON is also determined to make sure that patients are actively involved in its research projects, not just making up the numbers.

The Ireland-headquartered company believes that patients should be partners in drug development, not just the subject of studies, and has a string of initiatives in place to make sure this happens in the real world, starting with enrolment.

Mr O'Leary told *Script* about ICON's Firecrest Patient Portal and eConsent, an innovative approach to explaining complex scientific concepts and medical terms found in trial protocols direct to patients.

### Using Video To Get More Informed Consent

Through the portal, ICON is using animated video so that patients can view the details in their own time and be prepared for a discussion with their doctor. "Research has shown that patients prefer to learn about the trial through the more accessible medium of video," he says, and the information provided in this format is more easily understood as it transcends language barriers and provides consistency across sites.

This approach has been shown to produce better data and the patients understand the protocols better than those at sites that do not use the Firecrest Patient Portal, Mr O'Leary says, adding that eConsent does not simply improve trial efficiency, but perhaps most importantly, it facilitates a trusted relationship with the investigator.

The project substantially improves recruitment, retention and compliance rates and "patients become better equipped to ask their doctor the right questions, so we are getting much more informed consent," he adds. ICON is also sponsoring a series of research projects by Carnegie Mellon University to find new ways to improve information comprehension and retention by clinical trial participants.

Mr O'Leary said that "we are going through a generational shift," where younger people are often far more willing to share their medical information, through social media for example, and are not as concerned about privacy as previous generations. They use technol-



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ogy to self-diagnose, "not using the single source of the physician," and take control of their condition, either through prevention or modifying lifestyle.

However, while people may be more willing to share their data, they insist on getting something back for it. Most people are happy to offer their medical information if it helps others with their condition, Mr O'Leary says, but they also want to see how they themselves are progressing.

### Putting Wearables To The Test

To illustrate how ICON is doing this, he highlights a unique research project the company ran which "put wearables to the test." It sponsored two riders, both with type 1 diabetes, as they cycled the 1,500km mHealth Grand Tour from Brussels to Geneva.

The rise of wearables is undoubted, but how meaningful the data being produced actually is, is still unclear. With this cycling project, however, ICON says it had the opportunity "to engage with the empowered patient who was using wearables and other technological advancements to monitor and manage their own health in a way that was not conceived of previously."

The company wants to learn more about the value and practical use of wearables from its patients, says Mr O'Leary. He also notes that in working with the two riders, it has become clear that they are not only interested in managing their diabetes *per se* with the help of technology, but finding out more about co-morbidities of the disease and they mentioned one in particular: dementia.

They are concerned about a future where maybe one day they will not remember to administer insulin and this project can tap into a whole range of areas associated with the disease, not just measuring blood glucose levels. Mr O'Leary says that this type of project helps ICON face up to the technical, medical and regulatory challenges that are facing the development of mobile health solutions but he returns to the subject of what is in it for the patient.

The riders were provided with detailed feedback, putting them at the heart, in a real sense, of their own healthcare by using the latest technologies in a practical way. This, and all the other initiatives that ICON is working on, are getting patients to fully participate in the clinical trials process, keeping them informed and keeping them engaged.

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**John Hodgson**  
Data Editor,  
Scrip Intelligence

# What It Takes To Sell \$724bn-Worth Of Drugs

The Scrip 100 data set this year is a tale of big pharma dominance at the top and getting financed at the bottom.

**John Hodgson** crunches the numbers.

The Scrip 100 is a story of fallers and risers and a changing helicopter view of the pharmaceutical industry. Data alone cannot predict individual transactions or the fates of particular pharmaceutical products. However, they do paint a clear picture of the nature of the industry and the commercial environment that companies face.

This review starts with some highlights and low-lights from the various league tables that make up the Scrip 100. Originally, the Scrip 100 was a ranking of the 100 biggest companies in the pharmaceutical industry by drug sales. That list has now grown to over 500 companies, but the numbers are still dominated by the top 150.

Between them the top 150 firms account for 93% of drug sales across the industry, 87% of the research and development expenditure, and 91% of the employees (Exhibit 1). They hold 89% of the assets. They also account for more than 100% of the operating profits and net profits, since many of the firms lower down the list are running on investors' money or burning loans. We'll take a look at those development-stage money burners later in this article (see Companies That Sell No Drugs).

Emphasizing the top-heavy nature of pharma, over three-quarters of the industry's \$724bn drug sales in 2014 were made by a top tier of just 30 firms, each of which had drug sales of more than \$5bn. The same exclusive coterie was responsible for 98% of the indus-

try's \$127bn net profit, 76% of its R&D spending and 74% of its assets.

At the top of the tree for FY2014 was Novartis AG, its \$46.6bn in combined drug sales from its pharma division, Sandoz and ophthalmic drugs from Alcon enough to take over the number one slot from Pfizer, Inc. (see The world's top 100 pharma companies). While Novartis' sales only increased 0.5% from the previous year, Pfizer's fell for the fourth year in a row, this time by 5% to \$45.5bn.

Pfizer's somewhat forgettable fiscal 2014 has now, of course, been eclipsed by the events of calendar 2015. Whether it was corporate pride or fiduciary duty that propelled Pfizer to seek solace in the white hot fire of tax inversion we may never know. Unperturbed by its unrequited dalliance with AstraZeneca PLC in the first half 2014, as the leaves began to fall in 2015 Pfizer turned its attentions to Allergan PLC as the true shape of Brent Saunders' frenzied 18 months of asset assembly and reassortment began to emerge. The rest, as they say, is Teva Pharmaceutical Industries – just a reminder that Allergan's generics division is already being sold to Teva for \$40.5bn. Teva sits in 10th place in the Scrip 100 table with \$20.3bn worth of drug sales: the acquisition adds another \$6.5bn (pro forma) to that total.

In October 2014, a company called Actavis (formerly and recently known as Watson Pharmaceuticals and/or Forest Laboratories and Actavis) bought a company

## EXHIBIT 1: TOP-HEAVY PHARMA: 75% OF EVERYTHING IS DOWN TO JUST 30 COMPANIES

	TOP 150 IN 2014	TOP 30 IN 2014	INDUSTRY 2014	INDUSTRY 2013
Pharma Sales	93.2%	76.7%	\$724bn	\$701bn
R&D Spending	86.8%	76.3%	\$136bn	\$129bn
Pharma Operating Profit	104.4%	92.5%	\$149bn	\$162bn
Net Profit	109.5%	97.8%	\$127bn	\$137bn
Pharma Assets	89.2%	74.0%	\$1,384bn	\$1,325bn
Employees	90.7%	66.3%	2.09m	NA

Source: Scrip 100

# A Structured Approach To Enhancing Bioavailability For Early Development Phase Molecules

In the global pharmaceutical pipeline today, 90% of NMEs are poorly water soluble<sup>1</sup>, poorly cell permeable, or both. According to a recent drug delivery landscape survey<sup>2</sup> by the Catalent Applied Drug Delivery Institute, beyond bioavailability, stability, safety and therapeutic efficacy are also considered as key challenges faced by pharmaceutical R&D. Availability of only a minimal amount of materials is especially common in early phase programs. A number of drug delivery technologies are available to overcome these challenges, including lipid based formulation, solid dispersion, particle size reduction and salt conversion. As shown in Table 1, bioavailability enhancing technologies have brought more than 100 drug products to market. However, no single approach can overcome these challenges in all drugs. Bioavailability has to be addressed on a case-by-case basis depending on the unique physicochemical and biopharmaceutical properties of the molecule. The scientists have to weigh the many drug delivery technologies available and decide upon an appropriate technology for that particular molecule.

Under significant time pressure, scientists need to rapidly identify the most suitable formulation to advance the molecule to animal PK studies, and further to phase I human studies as quickly as possible. However, sometimes a formulation technology may be chosen too rapidly without a full evaluation of the other options available including, for example, manufacturability and scalability at later stages, and that may eventually lead to the failure at a later stage of development. It is helpful then to have a structured approach for parallel screening of available formulation technologies in early development phases. Such an approach will enable formulation scientists to fast screen formulations and find those with optimal bioavailability that are not

only good for animal studies, but also enable future development including dose escalation studies in phase I.

Catalent Pharma Solutions has long been recognized as a global leader in development solutions and drug delivery technologies. Combining 80+ years of drug development knowledge, expertise, and a comprehensive scientific toolkit, OptiForm® Solution Suite, a newly launched integrated formulation screening and development service, helps developers find the most suitable formulations for early phase molecules and advance their molecule to animal PK study within 12 weeks, through a three-step approach: ASSESS, ENHANCE and DELIVER.

The ASSESS stage is to fully understand the complexity of the molecule and evaluate for its development potential and risks. The new molecule is fully characterized by high throughput screening tools and its physicochemical properties are thoroughly studied. The salt, crystal-form and co-crystal screening is also applied. Complete pre-formulation data is collected for formulation ranking and risk assessment modeling. Using the Solubility Limited Absorbable Dose model in this early stage is vital to build an early formulation screening scenario in order to reach the necessary drug exposure and ensure the ability to escalate the dose. The molecule is then ranked according to the Developability Classification System (DCS), which is an effective way of differentiating new molecules based on their developability characteristics such as solubility to dose relationship, permeability and stability risks and processing risks with selected dose form.

Equipped with a good understanding of the molecule and its potential risks that may limit drug exposure, the second stage, ENHANCE, considers more specific formulations and solutions through the parallel screening of several delivery technologies. If the molecule belongs to DCS IIa with dissolution rate limited issues, the particle size reduction and salt form approaches are examined closely; if the molecule is DCS IIb with intrinsic solubility issues, lipid formulation and solution dispersion or solution need to be heavily considered. Feasibility studies and rapid prototyping of all available technologies are used to check for effects on drug exposure and the potential for dose escalation. Preliminary stability studies are conducted to assess viability of the selected formulations for future development.

The DELIVER phase provides animal PK study materials, a risk ranking of formulation approaches, and a recommended path to first-in-man studies to reach exposure and dose escalation. After this integrated 12-week formulation screening and development program, the outcome reflects the true potential of the new molecules in terms of developability; and the resulting easier and faster further development shows the value of early formulation optimization.

The structured and integrated formulation screening process is essential for selecting suitable formulations and decreasing the risks associated with new molecules at early phases, and therefore optimizing the development pathway to bring the molecule to market faster.

## REFERENCES

1. R. Lipp; The Innovator Pipeline: Bioavailability Challenges and Advanced Oral Drug Delivery Opportunities, Am. Pharm. Rev., 2013
2. The 3rd annual drug delivery landscape survey was sponsored by Catalent Applied Drug Delivery Institute. For more information, visit [www.drugdeliveryinstitute.com](http://www.drugdeliveryinstitute.com)

**Table 1: Number of NME approvals by Decade**

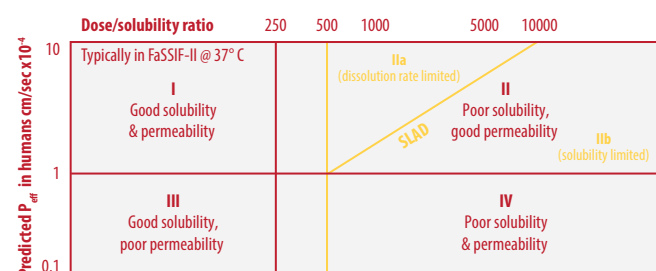
	Oral NMEs <sup>1</sup>	% of NMEs Using Bioavailability Enhancing Technologies
<b>1970s</b>	54	8%
<b>1980s</b>	80	13%
<b>1990s</b>	148	22%
<b>2000s</b>	71	31%
<b>2010s<sup>2</sup></b>	92	34%

<sup>1</sup>NME first approved by FDA CDER, for oral administration

<sup>2</sup>Through September 30, 2015

Source: EvaluatePharma, PharmaCircle, ADIS R&D Insight, Catalent Analysis

**Figure 1: DCS Plot with Human Jejunal Permeability & Aqueous Dose Solubility Ratio**





## THE WORLD'S TOP 100 PHARMA COMPANIES BY DRUG SALES

RANK 2014 (2013)	COMPANY	2014	2013	CHANGE FROM 2013	RANK 2014 (2013)	COMPANY	2014	2013	CHANGE FROM 2013
1 (2)	<b>Novartis AG<sup>1</sup></b>	46,564.0	44,473.0	5%	26 (25)	<b>Mylan NV</b>	7,646.5	6,856.6	12%
2 (1)	<b>Pfizer Inc.</b>	45,708.0	47,878.0	-5%	27 (26)	<b>Celgene Corp.</b>	7,563.8	6,362.3	19%
3 (3)	<b>Sanofi</b>	42,126.6	41,137.2	2%	28 (23)	<b>Baxter International Inc.<sup>11</sup></b>	6,100.0	9,064.0	-33%
4 (4)	<b>Roche</b>	39,476.6	39,186.4	1%	29 (31)	<b>Allergan Inc.<sup>12</sup></b>	6,012.1	5,339.0	13%
5 (5)	<b>Merck &amp; Co. Inc.<sup>2</sup></b>	36,042.0	37,437.0	-4%	30 (33)	<b>Shire PLC<sup>13</sup></b>	5,830.4	4,757.0	23%
6 (7)	<b>Johnson &amp; Johnson</b>	32,313.0	28,125.0	15%	31 (29)	<b>Servier SA</b>	5,579.5	5,579.5	0%
7 (6)	<b>GlaxoSmithKline PLC</b>	30,762.6	33,357.7	-8%	32 (32)	<b>CSL Ltd.</b>	5,335.0	4,791.2	11%
8 (8)	<b>AstraZeneca PLC</b>	26,095.0	25,711.0	1%	33 (27)	<b>Eisai Inc.<sup>14</sup></b>	5,195.6	6,162.1	-16%
9 (21)	<b>Gilead Sciences Inc.<sup>3</sup></b>	24,890.0	10,803.7	130%	34 (42)	<b>Sun Pharmaceutical Industries Ltd.<sup>15</sup></b>	4,474.1	2,643.2	69%
10 (9)	<b>Teva Pharmaceutical Industries</b>	20,272.0	20,314.0	0%	35 (34)	<b>Menarini Group</b>	4,468.7	4,370.0	2%
11 (11)	<b>AbbVie Inc.</b>	19,960.0	18,790.0	6%	36 (36)	<b>UCB Group</b>	3,905.0	4,050.5	-4%
12 (12)	<b>Amgen Inc.</b>	19,327.0	18,192.0	6%	37 (37)	<b>Sumitomo Dainippon Pharma Co. Ltd.<sup>16</sup></b>	3,518.0	3,549.4	-1%
13 (10)	<b>Eli Lilly &amp; Co.<sup>4</sup></b>	16,480.6	20,254.1	-19%	38 (35)	<b>Mitsubishi Tanabe Pharma Corp.<sup>17</sup></b>	3,445.9	4,235.7	-19%
14 (17)	<b>Bayer AG</b>	16,005.0	14,344.8	12%	39 (39)	<b>Abbott Laboratories Inc.<sup>18</sup></b>	3,118.0	2,862.0	9%
15 (13)	<b>Bristol-Myers Squibb Co.</b>	15,879.0	16,385.0	-3%	40 (40)	<b>Hospira Inc.<sup>19</sup></b>	3,035.0	2,759.4	10%
16 (15)	<b>Novo Nordisk AS</b>	15,414.0	14,882.6	4%	41 (41)	<b>Stada Arzneimittel AG</b>	2,682.0	2,676.1	0%
17 (14)	<b>Takeda Pharmaceutical Co. Ltd.</b>	15,294.2	15,694.4	-3%	42 (38)	<b>Shionogi &amp; Co. Ltd.</b>	2,595.5	2,973.7	-13%
18 (16)	<b>Boehringer Ingelheim GMBH</b>	14,091.8	14,468.3	-3%	43 (43)	<b>H. Lundbeck AS<sup>20</sup></b>	2,396.0	2,452.9	-2%
19 (18)	<b>Actavis<sup>5</sup></b>	13,062.3	8,306.0	57%	44 (46)	<b>Aspen Holdings</b>	2,307.5	1,886.5	22%
20 (19)	<b>Astellas Pharma Inc.<sup>6</sup></b>	11,815.3	11,700.0	1%	45 (44)	<b>Galderma SA</b>	2,259.0	2,196.0	3%
21 (30)	<b>Biogen Inc.<sup>7</sup></b>	9,398.8	5,542.3	70%	46 (53)	<b>Alexion Pharmaceuticals Inc.<sup>21</sup></b>	2,233.7	1,551.3	44%
22 (20)	<b>Daiichi Sankyo Inc.<sup>8</sup></b>	8,709.2	10,989.6	-21%	47 (45)	<b>Actelion Ltd.</b>	2,140.4	1,927.8	11%
23 (22)	<b>Otsuka Pharmaceutical Co. Ltd.<sup>9</sup></b>	8,369.4	10,624.1	-21%	48 (47)	<b>Ferring Pharmaceuticals AS</b>	1,990.0	1,859.8	7%
24 (28)	<b>Valeant Pharmaceuticals International<sup>10</sup></b>	8,103.6	5,640.3	44%	49 (48)	<b>Dr Reddy's Laboratories<sup>22</sup></b>	1,976.8	1,805.1	10%
25 (24)	<b>Merck KGAA</b>	7,687.2	7,557.0	2%	50 (49)	<b>Lupin Ltd.<sup>23</sup></b>	1,870.2	1,712.7	9%

<sup>1</sup>Pharma sales include pharma division, Sandoz and ophthalmic drug sales from Alcon<sup>2</sup>Does not include Cubist<sup>3</sup>Growth driven by new launches of antivirals Sovaldi and Harvoni<sup>4</sup>Expected impact of patent expiry<sup>5</sup>Growth mostly from acquisition of Forest Laboratories<sup>6</sup>Figures adversely affected by yen depreciation<sup>7</sup>\$2bn sales increase for Tecfidera over 2013; \$430m growth in Tysabri sales over 2013<sup>8</sup>Sale of Ranbaxy to Sun reduces pharma sales by approximately \$1.5bn<sup>9</sup>Nine months results only, after financial year change from March to December<sup>10</sup>Acquisition of Bausch & Lomb<sup>11</sup>Not like-for-like comparison: 2014 data represent estimates of Baxalta sales, 2013 sales include 'drips' business<sup>12</sup>Company before acquisition by Actavis<sup>13</sup>Rare diseases business unit sales grew by 46%, incorporating \$540m through ViroPharma acquisition<sup>14</sup>Sales flat in yen; exchange rate shift reduces dollar sales 8.4%<sup>15</sup>Acquired Ranbaxy from Daiichi Sankyo<sup>16</sup>Sales flat in yen; exchange rate shift reduces dollar sales 8.4%<sup>17</sup>Exchange rate shift reduces dollar sales 8.4%<sup>18</sup>Total sales: FY ending June 2014<sup>19</sup>Pharma sales is "Established Pharmaceuticals" division: developed markets part sold to Mylan in early 2015<sup>20</sup>Revenue down 5% in Danish kroner: 2013 revenue figure encompassed €1.1bn in downpayments and milestone payments<sup>21</sup>Soliris sales increase 44% to \$2.23bn<sup>22</sup>Pharma sales includes Global Generics only, excludes Pharmaceutical Services and Active Ingredients<sup>23</sup>Pharma sales included US, Japanese and ROW generics and Indian domestic formulations. Excludes 'Finished dosage' and APIs



RANK 2014 (2013)	COMPANY	2014	2013	CHANGE FROM 2013
51 (50)	<b>Cipla Ltd.</b>	1,784.4	1,673.6	7%
52 (51)	<b>Chiesi Farmaceutici SPA</b>	1,783.3	1,642.0	9%
53 (52)	<b>Ipsen</b>	1,673.4	1,627.1	3%
54 (77)	<b>Zhejiang Hisun Pharmaceutical Co. Ltd.</b>	1,619.7	1,037.2	56%
55 (66)	<b>Mallinckrodt PLC<sup>24</sup></b>	1,612.9	1,217.6	32%
56 (58)	<b>Meda AB</b>	1,536.0	1,401.0	10%
57 (70)	<b>Grunenthal GMBH</b>	1,534.4	1,196.9	28%
58 (62)	<b>Hikma Pharmaceuticals PLC</b>	1,489.0	1,365.0	9%
59 (54)	<b>Hisamitsu Pharmaceutical Co. Inc.</b>	1,484.8	1,546.1	-4%
60 (59)	<b>Leo Pharma AS</b>	1,421.5	1,396.5	2%
61 (60)	<b>Meiji Holdings Co. Ltd.<sup>25</sup></b>	1,338.9	1,386.7	-3%
62 (64)	<b>Merz Pharma Group</b>	1,321.2	1,302.2	1%
63 (63)	<b>KRKA, d.d.</b>	1,316.2	1,303.1	1%
64 (61)	<b>Gedeon Richter Ltd.</b>	1,314.9	1,365.8	-4%
65 (57)	<b>Teijin Pharma Ltd.<sup>26</sup></b>	1,314.8	1,420.5	-7%
66 (55)	<b>Santen Pharmaceutical Co. Ltd.</b>	1,289.3	1,525.9	-16%
67 (56)	<b>Ono Pharmaceutical Co. Ltd.<sup>27</sup></b>	1,286.2	1,470.3	-13%
68 (75)	<b>United Therapeutics Corp.</b>	1,279.5	1,106.9	16%
69 (65)	<b>Orion Pharma</b>	1,278.7	1,266.0	1%
70 (68)	<b>Recordati SpA</b>	1,267.6	1,208.8	5%
71 (69)	<b>Pierre Fabre Group</b>	1,216.0	1,208.1	1%
72 (86)	<b>Jazz Pharmaceuticals PLC<sup>28</sup></b>	1,162.7	865.4	34%
73 (74)	<b>Cadila Healthcare Ltd.</b>	1,156.1	1,133.1	2%
74 (81)	<b>Salix Pharmaceuticals Ltd.<sup>29</sup></b>	1,133.5	933.8	21%
75 (67)	<b>Indivior PLC<sup>30</sup></b>	1,115.0	1,215.8	-8%

<sup>24</sup>Acquisitions increased the Specialty Pharmaceuticals segment operating income from 25.3%

<sup>25</sup>Exchange rate shift reduces dollar sales 8.4%

<sup>26</sup>Exchange rate shift reduces dollar sales 8.4%; Pharma sales include other Healthcare Division sales such as devices

<sup>27</sup>Sales flat in yen; exchange rate shift reduces dollar sales 8.4%

<sup>28</sup>Increase driven primarily by sales of Xyrem (sodium oxybate) oral solution, Erwinaze/Erwinase (asparaginase *Erwinia chrysanthemi*) and Defitelio® (defibrotide)

<sup>29</sup>Acquired by Valeant 1 April 2015

<sup>30</sup>Indivior is pharma spin off from Reckitt Benckiser

RANK 2014 (2013)	COMPANY	2014	2013	CHANGE FROM 2013
76 (76)	<b>Esteve</b>	1,113.8	1,076.1	4%
77 (71)	<b>Taisho Pharmaceutical Co. Ltd.<sup>31</sup></b>	1,081.8	1,172.1	-8%
78 (79)	<b>Glenmark Pharmaceuticals Ltd.</b>	1,081.4	1,020.9	6%
79 (94)	<b>Perrigo Co. PLC<sup>32</sup></b>	1,073.8	709.5	51%
80 (73)	<b>Kyorin Pharmaceutical Co. Ltd.<sup>33</sup></b>	1,071.6	1,143.4	-6%
81 (83)	<b>Almirall SA</b>	1,045.3	920.5	14%
82 (82)	<b>Sawai Pharmaceutical Co. Ltd.</b>	999.0	921.9	8%
83 (87)	<b>Yuhan Pharmaceutical</b>	966.6	862.5	12%
84 (90)	<b>Green Cross Corp.</b>	926.6	811.8	14%
85 (85)	<b>Kaken Pharmaceutical Co. Ltd.</b>	889.4	912.9	-3%
86 (92)	<b>China Pharmaceutical Group Ltd.<sup>34</sup></b>	866.1	749.9	15%
87 (95)	<b>Shanghai Pharmaceuticals Holding Co. Ltd.</b>	827.7	696.4	19%
88 (80)	<b>Mochida Pharmaceutical Co. Ltd.<sup>35</sup></b>	826.5	964.3	-14%
89 (78)	<b>Cubist Pharmaceuticals Inc.<sup>36</sup></b>	797.6	1,032.4	-23%
90 (93)	<b>Torrent Pharmaceuticals Ltd.</b>	763.0	713.4	7%
91 (72)	<b>Pharmstandard OJS<sup>37</sup></b>	741.9	1,170.1	-37%
92 (110)	<b>BioMarin Pharmaceutical Inc.</b>	738.4	538.4	37%
93 (89)	<b>Wockhardt Ltd.<sup>38</sup></b>	734.7	829.1	-11%
94 (96)	<b>Medical Yachiyoda Co. Ltd.</b>	724.4	687.9	5%
95 (97)	<b>Hanmi Pharmaceutical Co. Ltd.</b>	723.2	667.3	8%
96 (105)	<b>Daewoong Pharmaceutical Co. Ltd.</b>	699.1	616.8	13%
97 (104)	<b>Zambon Pharma<sup>39</sup></b>	695.2	472.9	47%
98 (106)	<b>Towa Pharmaceutical Co. Ltd.</b>	677.0	629.7	8%
99 (113)	<b>Italfarmaco SpA</b>	664.6	600.0	11%
100 (102)	<b>Biotest AG</b>	656.6	513.1	28%

<sup>31</sup>Exchange rate shift reduces dollar sales 8.4%

<sup>32</sup>Pharma sales from Rx plus Specialty division: \$147m from Tysabri sales

<sup>33</sup>Exchange rate shift reduces dollar sales 8.4%; R&D spend calculated from R&D as 11.4% of Sales

<sup>34</sup>Pharma sales equate to 'Finished drugs' segment

<sup>35</sup>Sales flat in yen; exchange rate shift reduces dollar sales 8.4%

<sup>36</sup>Figures for 9 months to September, prior to acquisition by Merck in December 2014

<sup>37</sup>Pharma sales includes prescription products and third-party products; excludes OTC, equipment, contract manufacturing, APIs

<sup>38</sup>US business halved by continued regulatory alerts

<sup>39</sup>Pharma sales includes some services revenue

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called Allergan. Back then, biotech and pharma stocks were thought to be highly valued, some even said over-valued. The market valuation of the Actavis that included Forest (#19 Scrip 100, Drug sales: \$13bn) in October 2014 was around \$65bn: that of the independent Allergan (#29 Scrip 100, Drug sales: \$6.0bn) around \$51bn. The merger with Pfizer and the disposal of the generic division to Teva makes that combination now worth \$200.5bn. The composite index of pharma stocks is at about the same level as it was in October 2014.

\$65bn + \$51bn + Time = \$200.5bn: Does all that additional value come from inversion?

Speaking of Actavis, look out for Alvogen, Inc., a company steered by former Actavis CEO Robert Wessman. After blazing the acquisition trail in Asia over the past five years and amassing drug sales estimated at around \$750m for 2015, the company has passed into private equity hands (as Actavis did): CVC and the Singaporean fund Temasek took a majority holding in the company in June 2015. In 2014, Alvogen upped its drug sales by 81% to \$580m taking it to 107th place in the Scrip 100 league table.

The biggest mover in the top tier of the Scrip 100 2014 was Gilead (#9 Scrip 100, Drug sales: \$24.9bn) which burst into the top 10 from 21st place in 2013 as its hepatitis C compounds *Sovaldi* (sofosbuvir) and *Harvoni* (ledipasvir and sofosbuvir) increased the company's drug sales 130%. Harvoni is the biggest selling drug of 2015, having taken the number one slot in Q3 from long-standing chart topper, AbbVie's *Humira* (adalimumab).

Gilead also shot to second place in the Scrip 100 league table for pharma operating profit (behind Roche) and took second place behind Johnson & Johnson in terms of net profit, a remarkable feat given the relative size of the two companies: J&J has 126,500 employees; Gilead, 7,000.

Valeant Pharmaceuticals International, which had bid unsuccessfully for Allergan earlier in 2014 before Actavis stepped in, relied on M&A to help move it up the pharma league table. It bought eye-care specialist firm Bausch & Lomb in 2013, giving it \$8.1bn in drug sales, up 44% from 2013 and moving the Canadian firm from 28th to 24th in the Scrip 100 table.

Biogen Inc. moved from 30th position to 21st in the league with drug sales up 70% to \$9.4bn thanks to an additional \$2bn of sales of *Tecfidera* (dimethyl fumarate) and an extra \$430m in sales of *Tysabri* (natalizumab), both important parts of the company's multiple sclerosis franchise. Perrigo Co. PLC, which bought Elan Corporation and therefore also benefits from royalties on Tysabri, became a member of the \$1bn club in 2014, increasing its specialty Rx sales 51% to \$1.07bn in 2014 and moving up the Scrip 100 league table from 94th to 78th place.

Indian companies, too, are on the move. Sun Pharmaceutical Industries' acquisition of the Ranbaxy generics division of Daiichi Sankyo took it from

41st place to 34th, with sales of \$4.5bn in 2014, up 69% from 2013. Three other Indian firms occupied positions 48, 49 and 50: Dr Reddy's Laboratories, Lupin Ltd. and Cipla Ltd. each delivered strong organic growth – 10%, 9% and 7%, respectively – despite a 4.5% fall in the value of the rupee.

Meanwhile, Alexion Pharmaceuticals Inc. takes the top slot (#46) for a company with just one commercial drug, as sales of *Soliris* (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria increased 44% in 2014 to \$2.23bn.

Another acquisitive and tax-inverted company, Mallinckrodt PLC, acquired both Cadence Pharmaceuticals and Questcor in 2014, building its specialty pharmaceuticals segment and increasing its overall drug sales 32% to \$1.6bn, putting Mallinckrodt just outside the top 50.

A few new names were added to the club of top 100 drug-sellers: Indivior PLC at #75 is the pharma division of Reckitt Benckiser, now spun off as an independent firm; rare disease specialist BioMarin Pharmaceutical Inc. is in at #92 with sales up 37% to \$738m; and Korean firm Daewoong Pharmaceutical Co. Ltd. comes in at #96, managing to grow sales 13% to nearly \$700m despite the headwind of a drifting won.

The figures for a number of the major Japanese drug companies continued to be affected by the weakening of the yen against the US dollar. While their results reported domestically in yen look fine, they do not come out well in the Scrip 100 exercise which reports in dollars. Exchange rate drifts take around 8.5% off the value of yen sales.

Thus Takeda Pharmaceutical Co. Ltd. dropped to 17th place from 14th with a 3% decrease in dollar sales to \$15.3bn (a 5% increase in yen).

Astellas Pharma managed a 1% rise in dollar sales (to \$11.8bn) in 2014 but still dropped one place to 20th. Daiichi Sankyo Inc. dropped two places to 22nd, losing \$2.2bn in dollar sales. However, around \$1.5bn of that was its divestment of Ranbaxy to Sun; the residual fall can be attributed to adverse exchange rate effects on flat yen sales.

Drug sales at Eisai Inc. were down 16% to \$5.2bn; at Mitsubishi Tanabe Pharma Corp. they were down 19% to \$3.4bn; Shionogi & Co. fell 13% to \$2.6bn; Ono Pharmaceutical Co. Ltd. also fell 13%, taking sales to just below \$1.3bn; Santen Pharmaceutical dropped down 16% to \$1.3bn and Mochida Pharmaceutical Co. Ltd. was down 14% to \$826m. Kissei Pharmaceutical Co. Ltd. dropped sales 6% to \$625m and dropped out of the top 100 companies.

However, although Otsuka Pharmaceutical's reported figures were also significantly down, it actually had a very good year. The company changed its financial year-end and its 21% decrease in sales from \$10.6bn to \$8.3bn occurred because it reported only nine months' results: pro rata, its sales were up 5% even in dollars.

The biggest fallers of 2014 included Eli Lilly & Co. with a 19% drop in drug sales to \$16.5bn as loss of exclusivity hit home. Wockhardt's sales fell 11% to \$735m, beset by regulatory alerts that halved its US business. And Vertex Pharmaceuticals' revenues fell 42% to \$488m as Gilead's success took the bottom out of much of the rest of the anti-HCV market.

### COMPANIES THAT SELL NO DRUGS

The top heavy nature of the industry means that it is necessary to strip away the top strata in order to examine the underlying corporate geology.

The huge influx of capital in late 2013 and through 2014 from the public markets into pharma-oriented biotechnology firms moved some financial needles significantly. In 2013, companies outside the top 150 firms contributed \$6.8bn in operating losses and \$8.1bn in net losses; in 2014, with more public money available to throw around, those operating and net losses rose to \$11bn and \$16bn, respectively. The asset base of companies outside the top 150 drug-sellers R&D spending rose over \$14.5bn, with cash-like assets rising \$11.5bn, as might be expected.

There is a contrast in the resourcing of early-stage public companies in the US and Europe. Exhibit 2 examines the average performance of a set of 260 companies in the US and Europe that made no drug sales in 2014 but spent at least \$1m on R&D. These companies represent just over half the companies covered in the broader Scrip 100 database of biopharma firms.

The first and most noticeable difference is that 222 of these companies are in the US and only 38 in Europe (Exhibit 2). This reflects the availability of public market finances in the two locations.

Almost as striking is the difference in annual R&D spending and in revenues: mean R&D spending per company is nearly 80% higher for US companies while revenues – most of which come from collaborative R&D, license fees, milestones and royalties – are 55% higher on average for US companies (Exhibit 2). Taken at face value, these data suggest that development stage companies in the US are spending a lot more on R&D and, perhaps as a consequence, have assets that attract greater revenues from collaborators or licensees. Alternatively, the additional licensing or collaborative income may mean they can spend more on asset development. Either way, they seem to be getting to the pharmaceutical end-game faster.

However, this conclusion overlooks the fact that most of the mean difference between US and European companies is due to just a few big US firms, just 5% of those in the US sample; Agios Pharmaceuticals, Celldex Therapeutics, FibroGen Inc., ImmunoGen, Infinity Pharmaceuticals, Mannkind, Medivation, Merrimack Pharmaceuticals, Portola Pharmaceuticals, Receptos, Isis Pharmaceuticals, Juno Therapeutics, Inc. and Alnylam Pharmaceuticals.

### EXHIBIT 2: MEAN PERFORMANCES OF US AND EUROPEAN NO-SALES, DEVELOPMENT-STAGE FIRMS

PARAMETER	MEAN US	MEAN EU	TOTAL US	TOTAL EU
Pharma R&D (\$m)	32	18	7,153	675
Total current assets (\$m)	98	74	21,857	2,825
Total revenues (\$m)	17	11	3,788	398
Number of companies	-	-	222	38

Source: Scrip 100

### EXHIBIT 3: MEAN PERFORMANCES OF US AND EUROPEAN NO-SALES, DEVELOPMENT-STAGE FIRMS SPLIT BY R&D SPENDING

PARAMETER	R&D EXPENDITURE			
	UNDER \$100M		OVER \$100M	
	US	EU	US	EU
Pharma R&D (\$m)	24.1	17.8	163	-
Total current assets (\$m)	78.3	74.40	422	-
Total revenues (\$m)	10.7	10.50	119	-
Number of firms	209	38	13	0

Source: Scrip 100

Each of these 13 firms spent over \$100m in 2014 on R&D. Collectively they account for around one-quarter of the R&D spend and assets in the group, and attract 37% of the licensing and collaboration revenue (Exhibit 3). Companies with that scale of resourcing in the absence of drug sales simply do not exist outside the US.

Take those companies out of the equation, and it is only in R&D expenditure that there is anything to choose between the mean performance of the majority of US and European development-stage firms.

There is a European-US dichotomy in the nature of what can be thought of as pharma's greenhouse. However, it does not stem from the superiority of any "average" performance criterion associated with US firms. It comes, firstly, from the scale of the overall investment enterprise, that the number of hopeful firms with no sales is much larger in the US than in Europe (222 versus 38); and from the possibility that a few of those US firms can attract enough finance to fund substantial development programs.



**John Hodgson**  
Data Editor,  
Scrip Intelligence

# Oceans Apart: Transatlantic Gender Odds And How To Beat Them

Using Scrip 100 data, **John Hodgson** unearths the rules that women must play by if they want to join the upper echelons of the pharmaceutical industry.

## FAST FACTS ON GENDER IMBALANCE

**18%** of senior executives are women; Israel has four times the frequency of Germany.

**1 in 7** directors are women; it's 1 in 5 in Europe but only 1 in 15 in Canada.

**6.5%** of biopharma firms have a female CEO.

**1 in 3** companies have men-only senior management; 1 in 6 have men-only management and men-only boards.

*Scrip's* latest survey of gender balance, updated in November 2015, covered 417 firms industry-wide in North America and Europe. It encompasses most of the pharma and biotech companies with operational bases in the US, Canada and Europe (which includes Israel and Eastern Europe). Three times as many North American firms (311) were surveyed as European (106). Data from companies based in Asia and the Rest of the World are not yet available.

The survey deployed an advanced biological analysis system to interpret visual and linguistic data (we looked at photographs on company websites and sifted potted biographies for gender-specific pronouns and possessives).

How representative is the survey? It reached from multinational firms such as Merck & Co, AstraZeneca PLC, and Novartis AG to the companies that surfed the IPO-wave of 2014. Between them, the 417 firms represent just fewer than 1,640,000 employees, over \$600bn in annual drug sales and \$120bn in annual R&D spending.

The more data *Scrip* gathers, the harder it is becoming to sustain the view that there is no gender bias in pharma and biotechnology. The ideal analysis needs a baseline of gender representation across the industry at all levels of employment, just in case the fact that only 19% or so of senior industry executives are women is a reflection of women only being 19% of the employees across the whole industry.

That seems very unlikely since, where gender data are available for total employment rosters, near equality is the norm. Fully 50% of employees at AbbVie Inc., for instance, are women; Johnson & Johnson employees are 45% female worldwide; the number is 52% at Biogen Inc. Around 47% of Novartis' employees were female, according to its 2014 Corporate Social Responsibility report. Around 60% of Medivir AB's employees were women, as were 41% of Circassia Pharmaceuticals PLC's, 52% of Skyepharma PLC's and around 70% of Oxford Biomedica PLC's. The proportion varies from firm to firm, but the available data suggest that the pharma/biotech sector in North America and Europe is at least an equal opportunity employer, even if

equality in rates of pay is currently a matter of some dispute at certain firms.

It does not seem to be, however, an equal opportunity promoter. Relative to their proportions across companies and the industry, far too few women make it to senior management teams in pharma/biotech.

Thus, across the 417 companies surveyed, only 548 senior executives out of 2,894 (18.9%) are women. The difference between European companies (19.4% of management team members are women) and North American firms (18.8%) is negligible.

However, there is some considerable regional variation in the proportion of female senior executives within Europe (Exhibit 1). Leading the way are Israeli companies (Israel falls within *Scrip's* song-contest defined Europe) where around 31% of management members are women, followed by the Nordic nations (Finland, Sweden, Denmark, Iceland and Norway) with 23% and France where one in five biopharma execs (20.6%) is a woman. At the lower end of the scale, only one in nine senior managers is a woman in Swiss (11.1%) or Southern European firms (10.5%: Spain, Portugal, Italy, Greece) while in Germany, the number is one in 12 (8.5%).

The situation for women is even worse when it comes to representation on company boards of directors or supervisory boards. Whereas just fewer than one in five senior biopharma executives is a woman across all the companies, fewer than one in seven (13.9%) directors/board members are. Most of the difference can be attributed to firms in North America where only 11.6% of company board members are women.

Canadian companies are by far the worst offenders in this regard: only one in every 15 directors at a Canadian firm is a woman. The cold is clearly not the explanation because more than one in four directors at Nordic European companies is female (27.5%).

The low level of female directorship in North America may reflect the dominance of relatively small companies in the biopharma industry there. Exhibit 2 shows that while a majority of large and mid-sized companies (more than 1,000 employees) have two or more female directors, the majority of small firms (under 100 em-

ployees) have no women board members. One plausible explanation for this could be that younger, smaller companies that are more dependent on external investment may have a higher proportion of directors from finance houses, institutions not perhaps best known for their gender balance (one estimate suggests that fewer than 5% of venture capitalists are women; even in life sciences, that figure is only 10%). *Scrip's* survey cannot substantiate this explanation.

So companies in Israel and Northern Europe are top of the leagues when it comes to the appointment of senior women executives or board members, respectively. Yet even the best performing groups of companies are still a long way from equality or from reflecting the gender make-up of their wider workforce.

No matter how the situation is analyzed, the statistics pose some challenging questions to a sector that would prefer to think of itself as gender-neutral: If the biopharma industry is gender-neutral, how come 40% of firms have no female directors or supervisory board members? How can women in the workforce believe they stand as good a chance as men of promotion to the most senior ranks when one third of the companies (145/417) have men-only management teams? What message does it send to bright young women thinking of biopharma as a career choice when less than one in a thousand people currently in the industry can see equal numbers of women and men in their management teams (just 22 firms in this survey with 1,500 employees between them in total have senior teams, in which half or more are women; 395 firms with 1,640,000 employees in total do not)? What about a lower threshold of gender balance, far from equality, such as achieving one in four women in a management team? Only 10% of biopharma employees work in companies like that.

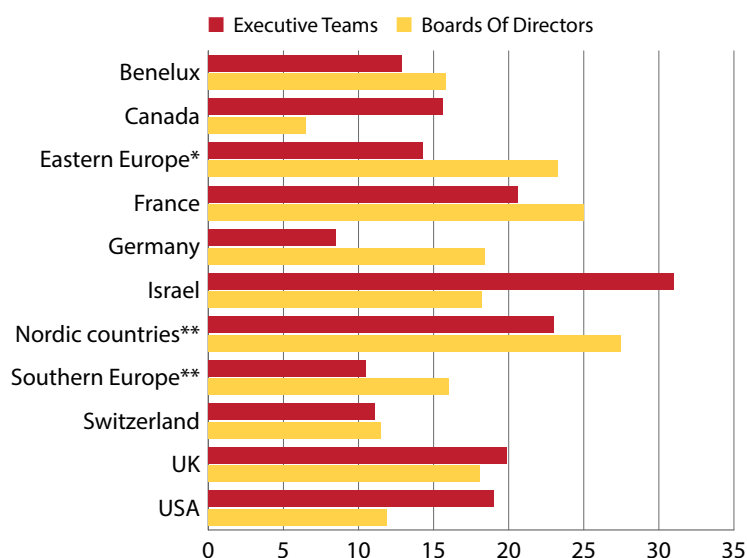
Numerical equality may not be a realistic target for a biopharma industry that, right now, clearly has not come to terms with the sheer waste of talent and resource implicit in its approach to advancement.

So does *Scrip's* survey of the industry's gender balance in 2015 provide anything positive for women in biopharma, or for the managers of women in biopharma concerning their prospects for progression to the top?

Perhaps. There is one small statistical glimmer that might play tactically in women's career choices, or strategically should companies try to address the gender imbalance issues they face: a correlation between the presence of women on a company's board of directors and women on the management team.

It appears that companies that have more women directors tend to have more female senior executives. In companies with no women directors (Exhibit 3, column 1), 44% have no women in the executive team and only 27% have two or more female executives. Put one woman on the board (Exhibit 3, column 2) and the proportion of male-only management teams falls while multi-women teams rise. In companies with

### EXHIBIT 1: REGIONAL VARIATION IN FEMALE EXECUTIVES AND DIRECTORS



\* Russia, Latvia, Hungary: \*\*Denmark, Finland, Iceland, Norway, Sweden: \*\*\*Greece, Italy, Portugal, Spain

### EXHIBIT 2: MOST SMALL AMERICAN COMPANIES HAVE NO FEMALE DIRECTORS

EMPLOYEE LEVEL	AMERICAS			EU		
	0 WOMEN	1 WOMAN	>2 WOMEN	0 WOMEN	1 WOMAN	>2 WOMEN
0-99	116	69	28	14	16	14
100-999	24	21	23	6	5	8
1000+		8	18	5	11	22

### EXHIBIT 3: A CORRELATION BETWEEN BOARD AND EXECUTIVE TEAM COMPOSITION

PROPORTION OF COMPANIES WITH:	NUMBER OF FEMALE BOARD MEMBERS		
	0	1	>2
0 woman	44%	38%	17%
1 woman	30%	25%	28%
2 or more women	27%	36%	55%

Source for Exhibit 1-3: *Scrip*

more than one woman director (Exhibit 3, column 3), the majority of leadership groups have more than one woman, too, while the proportion of executive teams without women falls below 20%.

This is, it should be stressed, just a correlation between two variables that might not be independent of each other. Both might have a causal connection with some other variable: the proportion of women employees in a company, for instance, or advanced corporate wisdom that recognizes the existence of more than one gender in the human race.

# Pharma & Biotech In Numbers



## Financials

**\$725bn**

DRUG SALES IN 2014



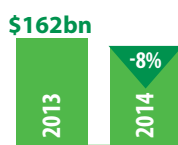
**\$138bn**

ANNUAL R&D SPENDING IN 2014



**\$153bn**

COLLECTED 2014 OPERATING PROFIT



GLOBAL PHARMACEUTICAL  
ASSET BASE

**\$1.8 trillion**

OPERATING MARGIN TOP 20 PHARMA



**81**

COMPANIES BROKE THE

**\$1bn**

DRUG SALES BARRIER



## Europe vs Americas



### AMERICAS

### EUROPE

DRUG SALES

**\$293bn**

**\$319bn**

EMPLOYEES

**710,000**

**960,000**

BIOTECH BURN

Loss-making firms

**214**

**44**

Average cash

**\$95m**

**\$64m**

Average annual R&D spend

**\$32m**

**\$16m**

PHARMA OPERATING  
PROFIT MARGIN

**29.1%**

**24.9%**







R&amp;D

61

RECORD NUMBER OF NEW ACTIVE SUBSTANCES  
LAUNCHED IN THEIR FIRST MARKETS IN 2014

Previous Years	2013	2012	2011	2010
New Active Substances Launched	48	41	27	43

## OF THE NEW ACTIVE SUBSTANCES LAUNCHED



12

were first in  
class products

22

were orphan  
drugs

525

industry-sponsored  
registration trials are  
currently ongoing<sup>1</sup>

4,131

novel drugs  
are in clinical  
development<sup>2</sup>

## Deals



432

pharma R&D alliances  
signed in 2014<sup>3</sup>

480

companies signing  
alliances in 2014<sup>4</sup>

## People

2,130,000

PHARMA/BIOTECH EMPLOYEES WORLDWIDE

710,000

Americas: 33%

960,000

Europe: 45%

460,000

Other: 22%



## JOB CREATION

LOSS MAKING BIOTECHS HAVE

\$20.3bn TO BURN

&amp;

EMPLOY 15,000 PEOPLE

(\$1.3m PER JOB)

Footnotes: Americas includes the US, Canada and Chile. Europe includes the whole of Europe plus Israel and Russia.

Sources: Scrip data except where footnoted. <sup>1</sup>Citeline's Trialtrove; <sup>2</sup>Citeline's Pharmaprojects, Nov 2015; <sup>3</sup>Strategic Transactions;<sup>4</sup>Strategic Transactions



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- Adaptive Design
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Clara Tan

Research Analyst,  
BioMedTracker

# US Biosimilars In 2016: Partnering And Payers

**Clara Tan** looks at how biosimilar producers can prepare for the US market in 2016, despite uncertainty within the reimbursement and approvals landscape.

With little precedence in the industry, biosimilar development is wrought with unknowns. At five years post-launch of the FDA Biosimilar 351(k) pathway, the US has only approved one biosimilar, Sandoz's *Zarxio* (filgrastim-sndz), a relatively simple biologic expressed in bacterial cells. However, regardless of this uncertainty, biosimilar developers can still prepare for this changing market by carefully establishing key partnerships and fully characterizing the reimbursement space.

## PARTNER, AND PARTNER EARLY

A primary observation of 72 US biosimilars in development showed that partnerships for US biosimilars were predominantly initiated during US preclinical development (56%), which confirms the advantage of early partnerships. This is not to mention the 19% of partnerships that were initiated prior to the start of development in the US (Exhibit 1).

By partnering at the discovery phase, large cap companies focus their resources on clinical trials and marketing, while small cap and foreign companies focus on the discovery of biosimilars, thereby leveraging each company's individual strengths. To cite a common example, Baxter International formed a global partnership with small cap Momenta Pharmaceuticals in December 2011 to develop a range of follow-on biologics. Momenta's self-proclaimed strength in biosimilar and reference product characterization may have proven useful to Baxter, who has had little to no prior involvement in biosimilar development. Baxter is therefore able to participate in the biosimilar market without diverting resources to biosimilar discovery. In parallel, Momenta gains the financial

backing of a large cap company to carry its compounds through clinical trials.

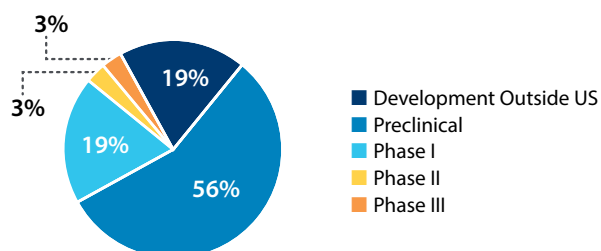
Focusing on core competencies has also become a common theme with foreign partnerships. In its 2013 partnership with South Korea-based Samsung Bioepis, Merck & Co. Inc. purely sought the commercialization rights of biosimilars. With the exception of MK-1293, a Merck compound, Samsung Bioepis is responsible for preclinical and clinical development, process development and manufacturing, clinical trials and regulatory registration. Merck's partnership with Samsung Bioepis makes strategic sense because the Korean biosimilar pathway precedes that of the US. In this partnership, Merck relinquishes all developmental aspects to Samsung Bioepis, a more experienced biosimilar developer. Samsung Bioepis is likely familiar with the nuances of discovery, manufacturing, clinical trial designs, etc. This partnership puts Merck ahead of the curve in the newly established US biosimilars market, and as a whole, these foreign partnerships have proven to be successful.

Of the seven biosimilars partnerships that began prior to US development, all have progressed to Phase III or an approval filing to the FDA. Not only can ex-US data build a stronger case for approval, but US companies can also utilize the experience of emerging market companies that are more familiar with biosimilar development.

The rate of partnerships during Phase III development (3%) is consistent with the rate of 8% for traditional biologics. Late stage partnerships are often priced at a premium since it is a lower risk investment. This result reaffirms the incentive to partner for early phase biosimilars, which is when one receives the greatest value for one's investment.

Another implication to be drawn from these early partnerships is that companies are confident in the approval of biosimilars. After all, biosimilars are not truly novel like blockbuster biologics, and patient populations are well defined by the brand. To reiterate, 56% of biosimilar partnerships began during preclinical development. This compares to a rate of 42% for traditional biologics. The difference demonstrates that standard biologics are a riskier investment (or less likely to be approved) because a greater proportion of partnerships occur during later phases of development. For standard biologics, additional data from later Phase I

EXHIBIT 1: DEAL EVENT PHASE OF US BIOSIMILARS



Source: BioMedTracker

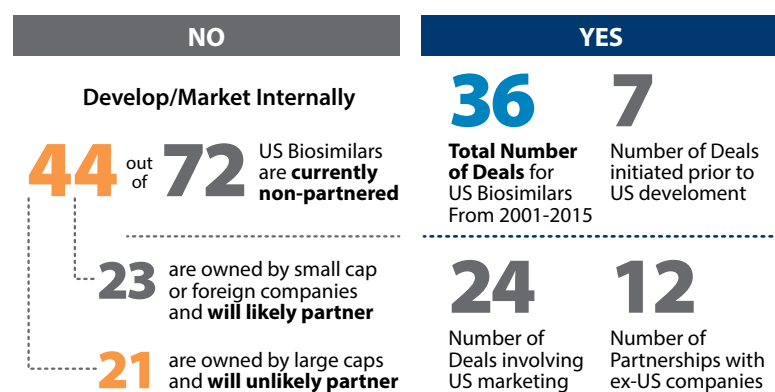


or Phase II clinical trials are necessary to signal the success of the drug to potential partners. In contrast, biosimilar partnerships occur in early phases of development, even when little information is available.

In summary, regardless of one's experience with biosimilar development, companies seeking a stake in the biosimilar market can do so through partnering. We anticipate a growing demand for these types of partnerships for big pharma. In concert with this belief is the continuing emergence of pure-play biosimilar developers like Momenta and Samsung Bioepis.

Presented below are the partnering statistics facing companies entering the biosimilar market.

### Will You Partner?



### REIMBURSEMENT CONSIDERATIONS

On the payer side, one-on-one interviews with reimbursement experts and industry research have revealed that payers are highly receptive to the introduction of biosimilars. The question that remains is: Which biologic product will payers reimburse?

Payers anticipate price and rebate discussions from the biosimilar developer for formulary inclusion and from the brand to maintain formulary access. A drug formulary consists of a list of medications that the payer is willing to reimburse. The use of closed formularies, or limited lists, has been especially effective in shifting market share to generics. By completely removing the branded drug from drug formularies, payers were able to control access to expensive branded drugs at the prescribing level. Providers had no choice but to prescribe generics because patients would otherwise have to pay full price for a branded drug. The present situation differs in that biosimilar products are not as competitive on price.

Due to its higher price, payers do not have a clear incentive to restrict use of the brand as they have done in the past. The branded biologic is presently expected to remain on formulary with the possible inclusion of a biosimilar. Keep in mind that payers may choose to entirely exclude a biosimilar with closed formularies if it does not present ideal price discounts. Changes to a formulary, like the inclusion of a biosimilar, still trans-

lates to disruption for patients. However, as prescribing biosimilars becomes more commonplace, we expect payers to use more aggressive measures like taking the brand off formulary. This would of course vary by indication, especially in disease areas where patients are more reliant on public insurance. Per a reimbursement Key Opinion Leader (KOL), the current breakdown of closed formularies is roughly 70% for public and 30% for private payers.

In addition to competing on price at face value, biosimilar producers must also factor in brand rebates. Rebates are typically a percentage of the drug price that is returned to the payer for maintaining that

drug on formulary. Rebates essentially add a second layer of price competition between the biosimilar and the brand. In order for a biosimilar to be considered for reimbursement, or formulary addition, it must also offer competitive rebates or be priced low enough to dip below brand rebates. One KOL interview suggested that a price reduction of at least 20%, including rebates, would be required to make the formulary disruption worthwhile.

Upon agreement, payers are prepared to use formulary management tools like tiering, step-therapy, and prior authorization to encourage the uptake of biosimilars. Though there is an emphasis on price, major players like pharmacy benefit managers will still be conducting internal analyses on the efficacy and safety of the biosimilar versus the brand. FDA approval does not necessarily ensure payer confidence in biosimilar substitution of the tried and true brand.

Payers are looking to biosimilars as an answer to the rising cost of rare disease treatments, and their limited access. According to a KOL interviewee: "Within the world of specialty pharmacy and orphan, the cost of [specialty] products are \$2,000 to \$5,000 a month. In orphan disease, these costs are \$15,000 to \$100,000. These patients need lots of hands-on services, lots of education, so those are the type of things we are discussing right now, how do we make sure that these patients are well taken care of."

Though the biosimilar market is still at its early stages, it's clear in its direction to bring down the rising costs of drugs. What payers also see in its intention is that the introduction of biosimilars will greatly increase patient access to medication that is currently being distributed by only a handful of suppliers.

*This article is just a small section of BioMedTracker's Biosimilars Special Report. For more information and data please contact [ctan@sagientresearch.com](mailto:ctan@sagientresearch.com).*

Compared to biosimilars, standard biologics are anticipated to spend an additional 3.37 years in Phase I to Phase III development.





**Lisa LaMotta**  
Senior Writer,  
Scrip Intelligence &  
"The Pink Sheet"

# The Secrets Behind GSK's Strategic Sauce

**Lisa LaMotta** goes behind the corporate walls of the big pharma to discover its current investment strategy which, she finds, is just as much about R&D as it is BD.

Brian McVeigh says that GlaxoSmithKline PLC is in a unique position amongst its pharma peers; instead of scrambling to fill its late-stage pipeline, it is working to build the pipeline after that, and the pipeline after that.

McVeigh should know; he's been with the British pharma for 23 years and has spent the last 13 years building the company's pipelines. McVeigh is VP of worldwide business development transactions and investment management at GSK.

"One of the decisions that was made after the merger was to co-locate the business development team within the R&D organization, so you weren't getting this thing where this group over here was doing deals and then throwing it into the pipeline. We were trying to drive more alignment of strategy," he explains, referring to the merger that brought together SmithKline Beecham with Glaxo Wellcome

in 2000, creating the company we know today. This merger moved the dealmaking group out of the corporate function of the company and into the development side, giving McVeigh and his team a closer link to the science.

McVeigh admits that he spent much of the time after the big merger doing deals that would fill the company's late-stage pipeline and help it get over the patent cliff that plagued the industry in the earlier part of the century. Yet, GSK has made a strategic shift in its business development efforts in recent years – opting to make earlier deals and plan for the future. This business model is in sharp contrast to the dealmaking behavior of many of GSK's big pharma brethren, which have focused on collecting some more de-risked assets.

The company pipeline, as of March 2015, is already weighted in favor of earlier stage assets. There are currently 26 Phase III candidates, 39 drugs being tested in Phase II and another 30 in Phase I indications (some drugs are in multiple phases due to testing in multiple indications).

McVeigh seems proud of the late-stage pipeline the company has built and is now focused on finding the drugs that will fill the pipeline as this current wave of products advances – a task that means working closely with venture capitalists and academics alike. In the last five years, GSK has worked to bring all its business development (BD) teams together and McVeigh says this allows them to do more cohesive deals at any stage in development.

## AN EARLY PUSH

Part of this movement to partner earlier is GSK's push to work with academia, including its Discovery Fast Track Challenge – part of its Discovery Partnerships with Academia (DPAC) program. The Fast Track Challenge is a contest the big pharma created to bring the scientific talent and ideas to it after the scouting teams realized they just couldn't find all the great science on their own. Pearl Huang, the global head of DPAC, told sister publication *IN VIVO* in 2014.

GSK announced in late September that the first of these Challenge winners has made the grade and officially been signed as a DPAC collaborator – hopefully



**Brian McVeigh**





resulting in a marketable drug for iron overload at some point in the not-too-distant future.

The British pharma has also invested in other interesting partnering schemes, including a partnership with venture capital firm Avalon Ventures that has promised to provide the seed funding for 10 early-stage life sciences companies. This is just one example of the many investments it has made in this way. This out-of-the-box collaboration was meant to be another means to bridge the gap between big pharma and academia, but also gives GSK a front row seat to any new technology or drugs that could be entering the arena. "These investments don't give us any hard rights in the assets or technology, but they give us a lot more visibility into the new and exciting science that is emerging. If you think about where venture fits, it's before us and after academia and they have a finger on the pulse of what's happening."

McVeigh notes that these kinds of deals are really more research funding and often give the smaller companies or the institutions access to some of the assets that GSK can provide, like screening tools and scientific expertise. In these early stages, McVeigh admits that it's more of an "open collaboration and as things progress we tend to move in to the more formal deal stages."

## MUTUALLY BENEFICIAL

The time is right for these types of acquisitions – all of the players in the biopharma ecosystem are looking for something the others have. McVeigh admits that it's a perfect storm with several factors contributing: funding from the National Institutes of Health (NIH) has been waning in recent years; IPOs are no longer seen as an exit for biotech investors, despite the wide-open window; and big pharma is looking outside its own development engines for innovation. Without enough money coming in from an IPO and even less coming from government sources, biotechs have been left in constant search of further funding.

"Labs are having to come up with other ways of funding their research and we are seeing much more of a commercial flavor to the dialogue we are having with them," says McVeigh. "They realize that they need to spin out companies into startups with venture companies. They realize they need to find more sponsored research opportunities with big pharma and they realize they need to be more creative in the deal structure that they will be willing to use."

McVeigh admits that GSK isn't in the market to make acquisitions and prefers to make licensing deals. He sees the entire 10,000-person strong R&D group as potential "scouts" for any new opportunities. "We've built a culture within GSK that all of our R&D scientists are focused just as much externally, as internally. So when they're out there interacting with their peers and colleagues they are keeping an ear to the ground,"

he says, while admitting it creates a lot of noise that needs to be filtered through the official BD team.

While GSK's approach to business development may not sound radically different, McVeigh explains that it provides a much higher level of de-risking for an asset even when something is still preclinical or in very early stages. For most companies, licensing an asset involves a team of BD guys descending on the small company and conducting weeks to months of due diligence – a proverbial kicking of the tires. This process can often be even more truncated when the situation is competitive.

"What if instead, you happen to be around this company from its inception? You got to see it grow and get a better sense for its culture," says McVeigh. He also pointed out that this can be a beneficial relationship for a biotech as well, with the added bonus of being able to ask questions to its big pharma brethren and structure its clinical development program in a way that would be appealing to the aforementioned big pharma – its potential customer or acquirer.

"We're trying to spend a lot more time with a company before we do the deal," he says. "It's early days with these, but we're really seeing a lot of positive relationships develop."

After these relationships develop, the talk of deals starts. McVeigh explains that his team doesn't come to the table with a blank sheet of paper, but instead, has a few types of deal structures that have served the company well and often work as a starting point in negotiations.

"The one structure that has the most frequent utility as a starting point for us is the option-based license deal, whereby we will typically put an upfront payment down and then we'll structure a series of milestone payments as the early-stage risk gets discharged, leading up to an option point at clinical proof of concept. These deals are usually Phase I or earlier and have lots of backup compounds in the mix," says McVeigh.

"Up until we option it, we like to let the company drive this and take the lead, which is a change from how we used to operate. The other component of these is that we usually take an equity stake in the company," he adds.

McVeigh says the BD team always checks out the company itself to see if it's worth taking an equity stake. GSK typically takes about a 20% share of the biotech so that it has a vested interest in its success. He admits that not every company wants that, but the British pharma has seen some success so far.

For GSK, its strategy of focusing on earlier compounds is coming into stark focus as analysts and investors begin to take a more granular look at the company's immuno-oncology pipeline, which holds particular promise, but is well behind some competitors.

For data on GSK's recent deals and financings head to [www.scrip100.com](http://www.scrip100.com)



**Andy Smith**  
Chief Investment  
Officer,  
Mann Bioinvest



Copyright: Khakimullin Aleksandr

## The Investor's Path To 2016

The road to 2016 and beyond is not without bumps for the biopharma investor, as **Andy Smith** looks into the financial future for the sector.

As the Borg often stated in Star Trek's Next Generation, resistance (to a falling stock market, in this case) is futile. So, with the backdrop of a prolonged recent sell-off in pharmaceutical and biotechnology stocks that started in mid-July and which may have paused or temporarily stabilized at the time of writing, I thought that it would be instructive to explore where the sector could end up in 2016. Surprisingly, it is not all bad news.

History, as usual, is a great teacher, and those of us who have been through more than one cycle of biotech boom and bust can remember what it felt like to be a biotech investor when no one was interested in the sector. I remember marketing my fund to small cap institutional investors in London in the early part of this century when the word 'biotech' would bring growls of 'British Biotech' and 'Vernalis' as if they were lingering evil spirits whose losses still had to be either made up, or fully exorcized from their memories and portfolios. There are still London and NASDAQ IPOs and secondary offerings that are above their IPO price, but some that are underwater. The underwater offerings by number will probably end up winning.

As we move towards next year, institutional fund managers will be window-dressing their portfolios to make it look like they never held their recently poorly-performing investments, but held the good ones all through the year. That is why biotech (and Valeant Pharmaceuticals International, Inc. in particular) will

continue to show share price weakness through to 2016 and will then result in the less fleet-of-foot investors giving up on the sector by divesting their positions that are either *de minimis* or are still above water enough in order for them to book some profit.

On the way to 2016, we can already see that next year will be different to recent years. On a cooling of the sector, IPOs initially tend to raise less and less money because appetites are depressed. Next come IPOs with drastic price cuts and then those that are cancelled. At the time of writing at the start of November, we have had both of the latter two but if investors thought that shutting the IPO window was next, they would be missing the penultimate step. This is where VCs have to buy most of the shares in an IPO just to enable the 'exit' of their portfolio company into the public markets. This is of course not a real exit since the public markets will be either falling or lackluster while the investors remain under a six month lock-up during which unrealized multiples on invested capital can contract further. The highest profile indicator of sentiment will occur at the JP Morgan Healthcare conferences of either January 2016 or 2017. Last year the corridors were seriously congested as thousands of investors tried to move *en mass* from one room to another between presentations. After the mid-year and subsequent pull-backs, we are unlikely to see more attendees at the conference in 2016, but the diehards



will probably have to wait until January 2017 to be accompanied in echoing corridors by the tumbleweeds before the final Thursday morning of the conference.

The first real knock-on effect that will be much more obvious next year is therefore the winter of fundraising. Falls in the public markets represent a drastically reduced appetite for the sector. Demand for cash by loss-making companies is, however, a constant and as the IPO and secondary market dries up, companies will be forced to do the what the private Ark Therapeutics, PLC did having missed its first IPO window and go into suspended animation. The move to dormancy by public biotech companies is more visible than for private companies and because of their number, has more implications. In the private market, valuations lag those in the public markets by between 12 and 18 months so 2016 will likely see the re-emergence of the 'down round' as private life science companies who are down to their last few months of cash burn are forced to accept money from value-orientated investors demanding a large part of the company at a low valuation. Dilution is inevitable, as the Borg would say.

Private companies will look wistfully back from 2016 to the dizzy valuation heights of the previous summer that may not be re-visited in years. This valuation attrition will not be confined to smaller public and private companies. As companies go into hibernation, clinical trials will be either postponed or cancelled and clinical trial manufacturers and research organizations will see a big impact on their bottom lines. The evidence is already there for this in the lower sales figures in the third-quarter financial results of PAREXEL International, Corp., ICON PLC and Quintiles Transnational Holdings, Inc.

I have already seen one piece of research from JMP Securities that ranks public companies by the ratio of their cash to market capitalization since falling stock markets raise this ratio. Soon we will have tables that rank companies by number of years of cash remaining and although this list currently would include companies who have presided over drastic clinical failures, like Sunesis Pharmaceuticals, Inc. and Xenoport Inc., as we move into next year many recent IPOs who may not yet have failed will join this less-than aspirational club.

As the dust settles on 2015, a year that was very different for life sciences than the ones that preceded it, we will see an overall reduction in company announcements since companies in hibernation don't have a lot to shout about. Before that, we will see the kitchen sink period where all the bad news comes out at once and stock market historians associate with the phrase 'capitulation'. This is where many investors finally throw in the towel on the sector. Clinical trials with interim analyses may fail early, and those where no end of cutting the data into smaller and smaller sub-groups in search of significance will save the money of these analyses and fail early. At the time of writing in November 2015, we have not seen this yet, but those

investors who are looking forward to Circassia PLC's positive Phase III trial announcement in the second quarter of 2016, after the platform failed soon after the IPO in mid-2015, are likely to have a rude awakening in store. Kitchen-sinking also applies to companies that report earnings and if there is nothing in it for companies to hit the ball out of the park in their fourth-quarter 2015 or first-quarter 2016 earnings announcements, they may choose to save good news for later in 2016 when it might be better appreciated.

One development that I have already noticed in the last month or so is that we see many recent US IPOs coming to London to see UK investors. The cynics would suggest that this is just the management Christmas shopping, but I would venture that it is broader than that. Supposedly European non-deal roadshows by companies that never before needed the support of European investors means either that their existing investors want them to find a market for their shares, or that they are getting close to that dreaded one year of cash burn. Neither is a good reason for a European investor to throw caution to the wind and invest in a company that did not know or care of their existence in the heydays of the last biotech bubble.

Sometime after all this carnage next year, we would have reached a bottom in biotech sector valuations. At that point in the cycle, I have made the most money for my investors. Loss-making biotech companies with late-stage commercially viable products and cheap valuations are a magnet for the business development departments of big pharmaceuticals. In contrast, this last third-quarter earnings season has been typified by the senior managers of Roche, Pfizer, Inc. and Gilead Sciences, Inc. all suggesting that the unrealistic expectations of their potential targets has precluded M&A. In the same way, and as a value-orientated investor, companies we had liked but turned down only on valuation grounds will get a second chance to see us diluting down their early investors in 2016.

In a broad-based market sell-off like the one life-science investors are currently going through, to paraphrase von Clausewitz, biotechnology becomes the antipathy of risk by any other means. Once we are through this rocky period and closer to 2017 however, opportunities will abound.

The Magna Biopharma Income fund holdings include Roche, Gilead and Pfizer.

*Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager's view on public life science companies. He has been lead fund manager for four life science-specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007.*

Private companies will look wistfully back from 2016 to the dizzy valuation heights of the previous summer that may not be re-visited in years.



**Mandy Jackson**  
West Coast Editor,  
*Scrip Intelligence*.

# Will M&A Pressure Mount After 2015's Mega Merger?

Large biotechnology companies are poised to become major players in mergers and acquisitions due to fast-growing cash stockpiles, but the \$160bn merger of Pfizer and Allergan may put pressure on other big pharma firms to make some major M&A moves. **Mandy Jackson** reports.

Investors increasingly want to know how pharma and biotech companies plan to deploy their capital to boost shareholder returns over the near and long term, so Pfizer Inc.'s move to merge with Allergan PLC and create the world's largest health care company could make investors even more curious about the potential for additional mega-deals among biopharma firms. The blockbuster deal also flips M&A in the industry on its head with big pharma back to its dominant position after specialty pharma ruled the dealmaking market in 2014, see Exhibit 1.

## MORE MEGA-MERGERS?

Even before the Pfizer-Allergan merger announcement in November, Ernst & Young's global transaction

leader for life sciences Jeff Greene said in an interview with *Scrip* that, "Compared to other industries, this industry is still pretty fragmented. There's potential for even more mega-mergers." The Pfizer-Allergan transaction's \$160bn value dwarfs this year's \$151.3bn in biopharma M&A deals as of the end of September, according to the Informa's *Strategic Transactions* database. The fourth quarter alone will more than double the M&A total for first three quarters of 2015.

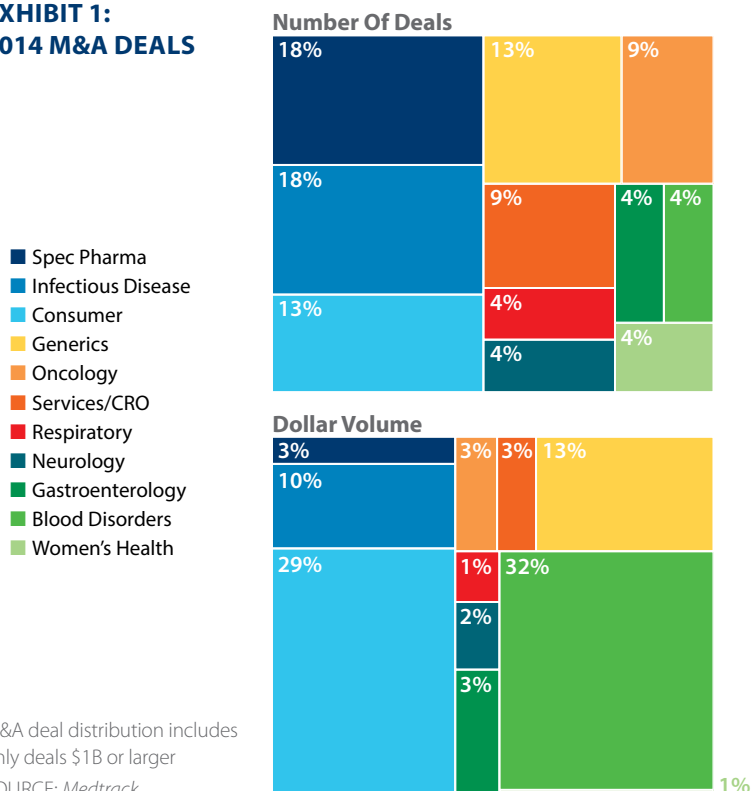
By EY's calculations, biopharma M&A jumped from \$75bn in 2013 to \$220bn in 2014 with specialty pharma responsible for \$130bn in deals and big pharma completing \$90bn in transactions. When EY reported the figures earlier this year, the firm predicted that large biotech companies would begin to use some of their considerable "firepower" – their capacity to do M&A based on market capitalization, cash balance and debt capacity – to buy companies.

And in 2015, biotech companies put money to work in multibillion-dollar M&A deals: Alexion Pharmaceuticals Inc. paid \$8.4bn for Synageva BioPharma Corp., Celgene Corp. spent \$7.3bn on Receptos Inc., Amgen committed up to \$1.25bn for Dezima Pharma BV, and Amicus Therapeutics agreed to pay as much as \$947m for Scioderm Inc.

"Biotech companies, as they grow from a teenager to an adult, realize the same issues as bigger companies. Even though they don't have pipeline issues with products coming off patent, they need to add things to their pipeline or else investors will realize this is no longer a high-growth company," says Dimitri Drone, the global pharmaceutical and life sciences leader at PricewaterhouseCoopers (PwC). "Layered on top of that, biotech companies have a lot of capacity that they haven't fully used yet, because they're not making 100 products, they're making five products. I think that they are going to feel some of those same pressures to do M&A as some of the more mature life science companies."

The pressure to do M&A is still intense for big pharma, which has a \$100bn growth gap (the amount of

**EXHIBIT 1:  
2014 M&A DEALS**





revenue that the world's biggest pharma companies are expected to generate relative to the amount of total pharma sales through 2017), according to EY.

### PRESSURE CONTINUES TO MOUNT

Until 2015, big pharma has not been as active in the M&A market during the past few years as specialty pharma companies, because they've had to absorb major transactions, EY's Greene notes, such as Pfizer's \$90bn Warner-Lambert Co. acquisition in 2000 and its \$68bn Wyeth purchase in 2009. But with cash from product sales and divestitures of non-core assets on their balance sheets, and with mounting pressure from investors to do deals, big pharma has fresh capital and incentives to pursue transactions.

"In 2016, it's hard to see that there wouldn't be a big M&A market, absent a big global economic issue, like a sharp rise in interest rates, which is not likely to happen," Greene says. Johnson & Johnson executives made sure to note during the company's third quarter earnings conference call that it will have plenty of cash for M&A – large-scale as well as smaller deals – despite a plan to repurchase \$10bn worth of outstanding J&J shares and a decline in pharma product sales.

Similarly, while Biogen has been accused of being too slow to act on M&A even though the company has plenty of cash and faces challenges for some of its marketed medicines, executives have tried to appease investors by saying that Biogen will be more aggressive about acquisitions going forward.

PwC's Drone says that large biotech companies may have an upper hand in deal negotiations with small or medium-sized biopharma targets, which may see major biotech firms as like-minded peers. Transactions between large and small biotech companies often begin as licensing deals that may include an option for the bigger entity to buy the smaller firm if their collaboration is successful.

But while more biotechs may be seen as potential buyout targets due to recent fluctuations in smaller companies' stock values, and because an initial public offering could cease to be a funding option for many private firms that hope to become public, Drone expects acquisition pricing to hold steady.

In other words, just because biotech stock prices may fall further and the IPO market may disappear, that doesn't mean big biotech or pharma companies will be able to do deals at a discount.

### BIG MONEY FOR THE RIGHT ASSETS

"Back in '07, '08 and '09 when markets were halted, M&A was down about 50% in some sectors, but the values of deals in that time were never greater, driven by certain transactions," says Drone, such as Merck & Co. Inc.'s \$41bn acquisition of Schering-Plough Corp., Roche's \$46.8bn purchase of Genentech Inc., and the Pfizer-Wyeth transaction.

"Is it possible that the market has turbulence? Yes, but just because there's turbulence it doesn't slow down the need to acquire assets," Drone says. "With certain assets experiencing lower values, it's a better time to buy. But if there are assets that are seen as very valuable, [companies believe that] if they're valuable to me then they're valuable to someone else, and people are not afraid to pay."

Some companies may "take their foot off the pedal in terms of the value of certain deals," but "there may be some deals soon that are the biggest we've ever seen," he noted before the Pfizer-Allergan deal was announced.

BDO partner and life science practice leader Ryan Starkes agreed, noting that biopharma M&A activity is based on the need of bigger companies to grow, especially in terms of novel science. "In this industry, the assets the company has is the overlying reason for the M&A. The market value will always come into play, but ultimately companies are acquired for the science and the drugs they possess," Starkes says.

Based on the need to buy assets in core therapeutic areas and to pursue novel science, he's not convinced that M&A activity will decline anytime soon. "We continue to see a lot of interesting technology being developed and that will continue to mean a lot of transactions will occur" he says.

### THE WILD CARD: DRUG PRICING PRESSURE

However, EY's Greene said it's hard to predict exactly what biopharma M&A activity will look like in 2016 given recent uncertainty caused by recent political commentary on drug pricing in the US. But while mounting pressure on prescription pharmaceuticals could dampen acquisition prospects, he said those concerns are unlikely to have a large impact on dealmaking activity in the industry given recent business leader opinions.

EY surveys C-suite executives from around the world across various industries every six months to gauge their views on economic issues and to identify business trends. The most recent survey of 863 executives included 102 pharma, biotech and medical technology leaders. Among the executives queried in August and September, 83% said the global economy is strongly or modestly improving and 83% said the M&A market is improving. Biotech, pharma and medtech executives were a little more optimistic than the general C-suite population with 85% noting an improved M&A market.

Likewise, 60% of biopharma and medtech executives said they are likely to close M&A deals within the next 12 months compared with 57% of the general C-suite survey respondents. Also, 84% of biopharma and medtech leaders said the quality of M&A deals was high versus 76% of all the surveyed executives. Six months earlier, only 43% of biopharma and medtech CEOs thought they'd close an M&A deal within the next year and just 72% were positive about the quality of potential transactions. "It seems like people are still expecting 2016 to be a pretty strong year for M&A," says Greene.

What could you buy for \$160bn? Head to [www.scripintelligence.com](http://www.scripintelligence.com) for some ideas.





PATENT EXPIRIES IN 2016			
PATENT EXPIRATION DATE	COMPANY	DRUG	INDICATION
01/01/2016-12/31/2016	Merck & Co	Zostavax	Chickenpox and Shingles - Vaccines and Treatments
02/1/2016	Novartis	Gleevec	Gastrointestinal stromal tumor (GIST)
02/1/2016	Novartis	Gleevec	Acute Lymphocytic Leukemia (ALL)
02/1/2016	Novartis	Gleevec	Hypereosinophilic syndrome (HES)
02/1/2016	Novartis	Gleevec	Mastocytosis
02/1/2016	Novartis	Gleevec	Dermatofibrosarcoma protuberans (DFSP)
02/1/2016	Novartis	Gleevec	Myelodysplastic Syndrome (MDS)
02/1/2016	Novartis	Gleevec	Myeloproliferative Disorders (MPD)
02/1/2016	Novartis	Gleevec	Chronic Myelogenous Leukemia (CML)
02/1/2016	Valeant Pharmaceuticals	Glumetza	Diabetes Mellitus, Type II
02/12/2016	Eli Lilly	Erbitux	Colorectal Cancer (CRC)
02/19/2016	Spectrum Pharmaceuticals	Zevalin	Indolent Non-Hodgkin's Lymphoma - NHL
02/23/2016-08/23/2016	Astellas	AmBisome	Fungal Infections - Systemic
02/23/2016	GlaxoSmithKline	Serevent	Asthma
02/23/2016	GlaxoSmithKline	Serevent	Chronic Obstructive Pulmonary Disease (COPD)
04/9/2016	Pfizer	Tygacil	Skin and Skin-Structure Infections (Antibacterial)
04/9/2016	Pfizer	Tygacil	Intra-Abdominal Infections (Antibacterial)
04/20/2016	Allergan	Lastacaft	Allergic Conjunctivitis (Ophthalmology)
04/25/2016	Daiichi Sankyo	Azor	Hypertension (Systemic)
04/25/2016	Daiichi Sankyo	Benicar	Hypertension (Systemic)
04/25/2016	Daiichi Sankyo	Benicar HCT	Hypertension (Systemic)
05/2/2016	AstraZeneca	Crestor	Dyslipidemia / Hypercholesterolemia
06/1/2016	Johnson & Johnson	Prezista	HIV / AIDS
06/01/2016-06/30/2016	Teva	Nuvigil	Narcolepsy
06/01/2016-06/30/2016	Teva	Nuvigil	Sleep Apnea
06/01/2016-06/30/2016	Teva	Nuvigil	Shift Work Sleep Disorder (SWSD)
06/15/2016	Merck & Co	Cubicin	Septicemia or Bacteremia (Antibacterial, including Endocarditis)





PATENT EXPIRATION DATE	COMPANY	DRUG	INDICATION
06/15/2016	Merck & Co	Cubicin	Skin and Skin-Structure Infections (Antibacterial)
06/19/2016	Takeda Pharmaceutical	ACTOplus met XR	Diabetes Mellitus, Type II
06/30/2016	AbbVie	Kaletra	HIV / AIDS
07/3/2016	Sanofi	Nasacort AQ	Allergic Rhinitis
07/19/2016	Astellas Pharma	Astagraf XL	Kidney Transplant Rejection
07/19/2016	Veloxis Pharmaceuticals	Envarsus XR	Kidney Transplant Rejection
07/24/2016	Novartis	Zelnorm	Irritable Bowel Syndrome (IBS)
07/24/2016	Novartis	Zelnorm	Chronic Idiopathic Constipation
08/2/2016	Roche Holding	Tamiflu	Influenza therapeutics (excluding vaccines)
08/28/2016	Allergan	Aerobid	Asthma
08/28/2016	Meda	Aerospan	Asthma
09/11/2016	Allergan	Aczone	Acne
10/14/2016	Vansen Pharma	Spectracef	Community Acquired Pneumonia (CAP) (Antibacterial)
10/14/2016	Vansen Pharma	Spectracef	Respiratory Tract Infections (Excluding Pneumonia) (Antibacterial)
10/14/2016	Vansen Pharma	Spectracef	Skin and Skin-Structure Infections (Antibacterial)
11/1/2016	AstraZeneca	Seroquel XR	Schizophrenia
11/1/2016	AstraZeneca	Seroquel XR	Major Depressive Disorder (MDD)
11/1/2016	AstraZeneca	Seroquel XR	Bipolar Disorder
11/1/2016	Celgene	Refludan	Heparin-Induced Thrombocytopenia (HIT)
12/01/2016-12/31/2016	AbbVie	Humira	Psoriatic Arthritis (PA)
12/01/2016-12/31/2016	AbbVie	Humira	Ankylosing Spondylitis
12/01/2016-12/31/2016	AbbVie	Humira	Rheumatoid Arthritis (RA)
12/12/2016	Merck & Co	Zetia	Dyslipidemia / Hypercholesterolemia
12/14/2016	Amgen	Sensipar	Hyperparathyroidism (Secondary)
12/15/2016	Sanofi	Lantus	Diabetes Mellitus, Type II
12/15/2016	Sanofi	Lantus	Diabetes Mellitus, Type I
12/26/2016	AbbVie	Norvir	HIV / AIDS
12/26/2016	Pfizer	Relpax	Migraine and Other Headaches

Source: BioMedTracker



**Jo Shorthouse,**  
Features Editor,  
Scrip Intelligence

# Bayer's Innovator In Chief

**Jo Shorthouse** talks to the man that has been providing the energy behind Bayer's innovation experience.

Dr Kemal Malik likes change. The new and novel, which coincidentally is also Malik's definition of innovation, are the momentum that keeps his role as head of innovation at Bayer AG interesting and fun.

It is imperative to remember, he says, that innovation has to have value for the customer. Someone has to see value in new ideas, and be willing to pay for them. Given the classic perception of Bayer, of a company that is research-heavy and creativity-light, one of Malik's challenges so far has been to encourage employees of the big pharma that an idea may not be solely research-driven. It could, for example, be a new way to open packaging for a rheumatoid arthritis sufferer. This is the kind of idea that a patient would directly value.

"It's not a classical description of innovation as far as our researchers are concerned, which would be some clever pathway or new molecule, but it's probably more meaningful to the patients to be able to take their medicines easier on a daily basis rather than some great new discovery from research

which may never see the light of day," he enthusiastically explains.

Enthusiasm is something that Malik is certainly not lacking. During our conversation it is easy to see why Malik, who is a member of Bayer's board of directors, was given the chief innovation officer title just over two years ago. His passion for change is currently being used to full advantage to help change the culture at the German corporation. He laughingly describes himself as "terribly scary" when asked about how approachable he is to the 100,000 employees within Bayer. That is the 100,000 people he would like to bring him revolutionary ideas.

And it isn't just internal encouragement that is needed, he says. Bayer needs to find a way of capturing innovation from around the world. The company is much more open to collaboration than it has been before, and although it employs 100,000 "very smart people," Malik explains, tongue in cheek, that the company might just be interested in the ideas of the six billion people on the planet.

To alter the culture of an entire organization is a huge challenge. However, Dr Malik knows that it is a change that needs to happen; at Bayer the need to experiment has now overtaken the fear of failure. "We don't reward and celebrate mistakes. No organization, however insane, would do that. Yet, we should acknowledge that failure happens," he says. "You shouldn't be penalized, in fact you can learn from it. There should be the acknowledgment that occasionally things fail, and the real heart is how you can learn from that failure and apply it to the next thing that you do."

The steadiness of a company such as Bayer is probably why it is still going from strength to strength after 150 years in business. And after more than a century in business you would expect to see a culture of responsibility and efficiency ingrained within the walls of Bayer. But that does not mean the company is blinkered in its approach to modern ways of working. "We need to continually work on experimentation, not having a fear of failure, customer focus and creativity. Are we perfect at it? No. Are we really bad at it? No. We've brought a lot of innovation forward but we need to continually work on those things while retaining our core values of responsibility, being scientific, efficient and professional," Malik explains.

Despite the enormity of the task ahead, Malik's approach to innovation and culture change is full steam



**Dr Kemal Malik**



ahead. Describing his role as “the best in the company” he says the most important elements to cultivating an atmosphere of innovation is leadership and creativity. “Innovation isn’t something weird that you have to be Einstein or Newton to make happen, it’s a process that can be developed. The biggest thing that leadership can do is provide a culture and an environment where people’s natural desire to innovate is fostered and can flourish.”

## LEARNING FROM LIPOBAY

Born in the UK, Dr Kemal Malik studied medicine in London before spending several years in clinical medicine at the Northwick Park Clinical Research Centre and at Hammersmith Hospital, London. He left the profession as a “miserable” consultant’s life didn’t appeal. He joined the pharma industry after being introduced to it by a friend, and subsequently held various positions of increasing responsibility in medical affairs and clinical development at Bristol-Myers Squibb Co.

He joined Bayer in 1995 as head of metabolism and oncology in the then Pharmaceuticals Business Group, and has had a journeyman’s existence at the German major ever since. In his first promotion within the company he served as head of global medical development before being appointed head of global development. He has also been chief medical officer in the Pharmaceuticals division. Today, his role isn’t just innovation-driven; he is also responsible for the North American and Latin American regions.

Malik describes life as Bayer’s chief innovation officer as “jolly enough.” However, in retrospect he relished his first leadership role in Bayer because of the steep learning curve. Having been promoted to the role of European medical director in his late 30s, Malik – a gastroenterologist by training – realized that the end result of his endeavours wasn’t based solely on his own capabilities and efforts, but really working with and through other people to realize his goals. Malik admits that he made mistakes in this role, but learnt from them.

Shying away from challenge is not Malik’s style. When he took on the head of development role, which he says “all happened very quickly” it was at a time when Bayer was “massively retrenching” after the withdrawal of its cholesterol-lowering statin *Lipobay* (cerivastatin), from the market in August 2001 because of fatal rhabdomyolysis.

“The challenge was, in essence, to downsize the organization. But we also had to provide a vision for the future. It was a very interesting time because you’re having to ‘right size’ the organization but also make sure there is something going through development because our R&D was the only thing that was going to influence the future.” Talking to

## WHICH DRUG DO YOU WISH HAD COME OUT OF THE BAYER LABS?

*Plavix* (clopidogrel), I worked on it when I was at BMS, it’s the world’s second largest drug after *Lipitor* (atorvastatin) and I guess I wish Bayer had come up it. We had Aspirin, which is the most amazing drug there is, it helps with joint pain, headaches, God knows it may even help with cancer. But I guess it would have been cool if *Plavix* had come out of Bayer.

Malik, you have a sense that he rather enjoys the thrill of crisis management and thinking laterally to resolve problems. The ability to achieve a lot in a short space of time is a skill he admires in his former Bayer Healthcare bosses Joerg Reinhardt and Arthur Higgins.

“I learnt an awful lot from people I worked for, because you learn a lot from people you interact with but the most from people you work for, both positively and negatively. Some of the people I have worked for have been profoundly useless and some of them have been absolutely amazing,” he says.

Malik’s ability for straight talking arguably comes from his plain-speaking father. The son of first generation immigrants, Malik grew up within a “humble background” with his father, a printer, and his mother who sewed clothes for a living. He recalls a conversation he had with his father when he was 15. He was told he was clever enough to achieve any dream in life, as long as that ambition was to be a doctor, a lawyer or a chartered accountant.

“For them it was really important that you follow a profession, they saw education as a way of stepping out from where they were in life. If everything was equal I probably would have studied English and History and become a lawyer, but my parents were really pretty desperate for me to become a doctor. I think they rather liked the idea of introducing their son, the doctor,” he explains.

Talking to Malik about the people he admires and the things that he has achieved throughout his career in big pharma, it is apparent that his future, post-Bayer, may lie where he started, treating patients on a direct level. He misses the contact with patients, he says, and mulls the idea of one day working for an NGO or a charity. He has no desire to be the CEO or chairman of a large pharma company, but is keen to put the skills he has learned at Bayer, and before that at Bristol-Myers Squibb, to good use, and to use for good. He recites the words his father said to him on graduation from university, he said simply: “Make a difference.”

“Innovation isn’t something weird that you have to be Einstein or Newton to make happen, it’s a process that can be developed.”



**Sukaina Virji**  
News Editor,  
Scrip Intelligence.

# The Biosimilar Brain

**Sukaina Virji** caught up with Celltrion Healthcare's president and CEO Dr Stanley Hong to discuss biosimilar uptake in Europe, his expectations for the US market, and what he believes the biosimilar space will look like in 2016.

South Korean firm Celltrion Healthcare is a pioneer in the biosimilar space, having launched the world's first monoclonal antibody biosimilar, *Remsima* (infliximab). The product was rolled out across Europe earlier this year and is currently under review by the US FDA.

**Sukaina Virji:** *Zarxio* has been launched in the US, the first US biosimilar. How are biosimilars being received in the US? And would the arrival of *Remsima* be a significant milestone for the US biosimilar space?

**Stanley Hong:** A biosimilar has been approved in the US, but *Remsima* – if approved – would be the first monoclonal antibody biosimilar in the US, so it will be a meaningful milestone. My understanding is that physicians, payers and patients, are interested in this monoclonal antibody biosimilar because it is cheaper [than the reference product] and the cost savings will be huge. The US is 55% of the global market.

My prediction is that market uptake in the US [of *Remsima*] is going to be faster than any other territory. US patients are lucky. Assuming our product gets approved some time in 2016 or early 2017, and we launch a few months after that, by that time we will have collected all the necessary data over four years to confirm safety and efficacy of this product.

**SV:** The US FDA's review of the *Remicade* biosimilar *Remsima* was originally scheduled for March 2015. The meeting was postponed in February 'due to information requests pending with the sponsor of the application'. This was later revealed to be a request for more statistical analysis data. What is the current status of the *Remsima* filing in the US?

**SH:** The FDA is still reviewing the BLA. I don't know how much longer it will take, but we are working continuously with the agency. They will need to announce a new date for the advisory committee meeting, that's a necessary step, but we don't have the date yet. This type of postponement is not unusual. It's not a negative or positive symptom.

**SV:** From your experiences in Europe, are there any interesting features that might come into play in the US?

**SH:** I found many interesting things in Europe, as I travel a lot. Interestingly, in western European the government pays for everything. This means patients, physicians and hospitals are not that motivated to use biosimilars. They don't feel any different using reference product or biosimilars. But the payers' position is different. They can save huge amounts of money. Payers have to gain share,

meaning they have to share the costs that have been saved by using biosimilars, since payers are getting the most benefit out of biosimilars in western Europe. They need to share out these cost savings to the healthcare budget with stakeholders like physicians.

Another characteristic is that in eastern European countries, the government does not pay, so patients have to pay by themselves. In this case, accessibility is limited, but market uptake is faster.

So each country has different situations. We've spent such an interesting period of time getting an understanding about each country's market landscape dynamics, and it's going to be helpful for us going into these countries with our second and third biosimilars in the future.

**SV:** What else can you do to encourage biosimilar uptake and engage with payers and clinicians?

**SH:** The most important thing we can do is generate data. Extrapolation data and switching data is important to improve market uptake.

Extrapolation data is the additional clinical data that support extrapolation to other indications, and also data from the intensive mechanism of action studies. These make physicians confident in the indications that the biosimilar developer hasn't done clinical trials in. For example, for our product we did clinical trials for rheumatoid arthritis and ankylosing spondylitis but we didn't do the clinic trials for IBD indications. But we can generate an intensive data set, including a mechanism of action study, a quality study, for those other indications like IBD. Then regulatory authorities are happy to approve all the indications. That is extrapolation.

Switching is when existing patients who are getting reference product are then prescribed the biosimilar. That's switching. We have to secure that data. The clinical trial is done with a biosimilar arm and a reference arm. After a period of time, you maintain the biosimilar arm but switch the reference arm to the biosimilar, and then compare these two arms. We have done this; it's called an extension switching study.

The other switching data is from real life experience from the hospital. Already many physicians prescribe our drug for existing patients who are getting reference products – switching – so we must try and collect all of this data. This kind of data generation is the basis for increasing market uptake, and then to communicate this data across to physicians and pharmacists.



The other way to increase market uptake is by educating stakeholders in the medical community. Some people say you should not switch because of immunogenicity issues, or unclear long term effects. They say that we don't know exactly what might happen [when a biosimilar is used instead of a reference product]. It's kind of unreasonable, unjustifiable scare mongering.

We generate and collect data to support switching. We have one year, two years and three years switching data, which means that after switching we observe the patient's status for one year, two years and three years. There has been no difference in the efficacy or the side effect profile [between the reference product and the biosimilar]. So we collect all that information, and provide it to the physicians, and present it in conferences, and submitted it to the regulatory authorities to support our filings.

**SV: What's the biggest obstacle to biosimilar uptake?**

**SH:** Originator companies, innovators, who say physicians should not switch. To them I say, 'Why? We have data.' They respond, 'Patients should not be switched because there are too many unclear things.'

No! There are no unclear things! We are quite clear, we have data. I ask, 'How many years' data you want to see before switching?' They say, 'One year, two years.' But I have two years of data. Someone else says, 'I need to see three years data.' And I have three years data. Then I ask them, 'How many patients' data you want to see? 500 patients? We have 600 patients here, and much more than that from real life experiences.

All of these discussions must be data driven. Otherwise it's a useless, endless discussion. The two points to increase market uptake are data and education.

**SV: How responsive are physicians to your data argument?**

**SH:** Physicians already have lots of information about biosimilars and they are discussing it with each other. European doctors, US doctors, Australian doctors, Japanese doctors, they communicate in conferences, but they are still debating. Some physicians are more conservative than others. It's not a matter of generation. It's a matter of experience and insurance systems, the market dynamics and landscape, in each country, that influences physicians.

**SV: What has brought you to this exciting stage in the company's history?**

**SH:** We started development of monoclonal biosimilars in 2007. In the beginning we thought that biosimilar development is going to be much easier than innovative product development because the target was proven, and the chance of success was going to be much higher. But it turns out to be that while it is easier than innovative product development, there are still lots of challenging issues and obstacles that we have to overcome.

Originally we thought it is going to take about three or four years to get approval [of a biosimilar]. But it took six years or so in the first country. There was a certain degree of trial and error. Biosimilar development is not so easy!

**SV: Are you a pioneer?**

**SH:** Yes, we are pioneers. We are the front runner. There is no doubt about that. We got the first monoclonal antibody approval from the EMA, from the Japanese PMDA, and many other regulatory authorities. We are closely communicating with the US FDA on Remsima. So definitely we are in a leading position in the monoclonal biosimilar space.

We are also developing seven other monoclonal antibody biosimilars. We want to keep our leading position into the future.



Dr Stanley Hong

**SV: What can we expect in the biosimilar space in 2016?**

**SH:** Several other major companies are developing biosimilars: Pfizer, Amgen, Samsung Biologics, Biogen, Boehringer Ingelheim. I don't know about their products. I don't know what stage their product development is in. But Samsung Biologics has submitted a dossier to the EMA.

But in 2016, the picture of the development stages of these biosimilars from these companies will become clearer.

We will have a better idea of what the other companies' status is going to be, what are going to be their product development preferences going forward. But we are ahead of the pack for a few products and being first to launch is important. It gives you a head start against the competition in the future.

When Celltrion started monoclonal antibody biosimilar development, there were no guidelines available but we took a risk, and we started development in 2007. That's how our company got to be in the leading position in monoclonal antibodies for such a young company. Our company is only 14 years old.

We want to keep this leading position. We are a dedicated biosimilars company. We are 'all in', and we have the necessary infrastructure for biosimilar development. Estimates have put the cost savings from biosimilars at \$55bn by 2020, and some have said the EU community can cut the healthcare budget by 25%, because monoclonal antibodies are very expensive drugs. So keep watching this space!

Celltrion is developing seven other blockbuster biosimilars candidates





**Jo Shorthouse,**  
Features Editor,  
Scrip Intelligence

# MedImmune's Modern Innovator

**Jo Shorthouse** talks with Bahija Jallal, head of AstraZeneca's biologics research and development arm MedImmune, about risks, role models and Eleanor Roosevelt.

When Dr Bahija Jallal stepped out of a conference room full of scientists she knew that her life had changed forever. She had just witnessed a patient personally thanking every person that had worked on a drug she had taken as part of a Phase I trial. Needless to say the trial, and the drug, had worked and the patient was overjoyed. "I remember vividly coming out of that room and thinking that was exactly what I want to do for the rest of my life," she recalls. "That was the beginning of a journey for me. I feel it's a privilege to do this work."

The beginning of Jallal's path to drug development deal maker, VP of AstraZeneca PLC and head of MedImmune, may have started in that room brimming with researchers but it was in Morocco, encouraged by her determined mother and surrounded by her family, which included five sisters and two brothers, that she embarked on her path to education and success. She was in the first generation of women to go to college, she explains, and her mother had always instilled in her daughters the belief that they could go as far in life as they wanted. All this from a woman that hadn't gone to school herself is extraordinary, says Jallal. "She was an inspiration, and still is."

Now it is Jallal's turn to hand that baton on to the future women of science. She serves as president-elect for the Association of Women in Science and an advisory board member of the Healthcare Business

Women's Association. She was named one of *Fierce-Biotech's* "Women in Biotech" and one of the "Women Who Mean Business" by the *Washington Business Journal*. A mother to two daughters, she is very passionate about educating girls early in their school years that the sciences are a realistic and exciting place to have a career. "It's just a matter of making them believe that they can do anything if they put their minds to it," she says, echoing her mother's sentiments. And it is not just looking forward without a nod to those who have gone before her. One of the women Jallal admires the most of Eleanor Roosevelt, first lady of the United States and a humanitarian firebrand in her own right.

To encourage as many women to work in science as possible can only be a good thing, whether or not this allows the gender balance barometer to swing toward a change in diversity is yet to be seen. But it is needed, she insists. "I think it's really important to remember what business we're in. You need those different perspectives. It just so happens that women and men think differently and act differently, and that's a good thing. It's not better or worse, just different. I believe that. And we have to equate that [difference] with creativity and innovation," she explains.

As a young woman, Jallal knew early on that she wanted to work in the sciences. She received a master's degree in biology from the Université de Paris VII in France, and her doctorate in physiology from the University of Pierre & Marie Curie in Paris. She conducted her postdoctoral research at the Max-Planck Institute of Biochemistry in Germany. Armed with her passion for science she moved to America with the idea of pursuing a career in academia and research. However, that fateful day when she saw firsthand the impact that medicines, even at the experimental trial stage, can have on patients, changed the course of her career.

Jallal describes herself as entrepreneurial and a natural risk taker. In fact, it was these two traits that she saw mirrored in MedImmune's company culture when she joined as head of translational research in 2006. Prior to joining MedImmune, Dr Jallal worked with Chiron Corporation where she served as vice-president of drug assessment and development, and successfully established the company's translational medicine group. Before this she worked at Sugen, Inc. where she held positions of increasing responsibility leading to senior director, research.



**Bahija Jallal**



"When I was called about the role at MedImmune, I was in California, and I said 'I'll get back to you' because I'd never heard of the company! So I looked on the website to learn a little bit more about them and two things really stood out to me. First, the product they had at the time, *Synagis* (palivizumab), was the first product in that therapy area that was a prophylaxis and not a vaccine, which had never been done before in the infectious diseases area. Second, it was the only monoclonal antibody (mAb) to be approved in the area for premature babies and is still the only mAb in infectious disease. So I did some research and discovered that it was very innovative. And I thought that this must be a company that allows for innovation but isn't afraid to try something completely unprecedented. Those were two characteristics that, for me, being entrepreneurial, really attracted me."

MedImmune started life as Molecular Vaccines, Inc in 1988 but changed the name to the much catchier MedImmune just a year later. Since joining the company in 2006, Jallal has guided MedImmune through an unprecedented expansion of its pipeline, from 40 drugs to more than 120, and entered into many and varied licensing and collaboration relationships with other companies. She laughs when asked how the pipeline has gone through such a steep growth trajectory. "Maybe it is naive, but we take risks," she says. "You can't be in this job if you can't take risks. If you don't take risks you aren't being innovative."

It is this innovative pipeline that triggered AstraZeneca's interest, and caused it to pay \$15.2bn for the company just a year after Jallal joined. AstraZeneca then merged MedImmune with Cambridge Antibody Technology, which it had acquired in 2006.

When the company was bought by AstraZeneca, biologics made up just 5% of the parent company's pipeline, today that figure is 50%, and Jallal is understandably proud of this. "In 2007 there were really two ways to look at it [the acquisition by AstraZeneca]: one was to give up and say 'ok, this is not going to be the same,' and look at it as a negative. But we chose to take it as an opportunity. We had to show our value to the new company, and we believe there is value in this company. And the only way we could do that was by putting forward a bold vision – one BLA a year by 2016. Then we really drilled that through our organization. All our scientists liked the challenge. But this was not just me, this was a team effort with great scientists and we continue to be on that journey together."

Challenge is something Jallal certainly does not shy away from; she enjoys being challenged and challenging others. She exclaims that this is inherent in a scientist's mind-set, to never accept something as a given. Creativity in drug development is also something Jallal is evangelical about. Transforming the process of drug development and commercialization with creativity and inter-company collaboration is essential if

## QUICK FIRE QUESTIONS

### Who is your most honest critic?

My children definitely keep me grounded. They inspire me every day to be a good role model. At work, I'm known for not wanting to surround myself with people who are just going to agree with me, I can't have that.

### What is the best advice you've ever been given?

Follow your heart; you can't go wrong when you do that.

### Who do you admire most in, and outside of the industry?

The scientists, our unsung heroes. They are so passionate and dedicated; this is not an easy area to be in but they inspire me every single day. They are relentless and they're passionate; my hat goes off to all of them.

### What is the one myth about the industry that you would like to set straight?

A few years ago there were a lot of headlines about the pharma industry disappearing because there was a crisis of innovation. I think that is absolutely not true, in fact it's the opposite. In 2014, the FDA approved 44 new drugs, an all-time high. Now, with the excitement surrounding immunotherapies in oncology it goes to show that the industry can innovate.

### If you could change one thing about the pharma industry what would it be?

We need to collaborate more and work smarter. We need to gain more efficiency and come up with more creative solutions.

the pharma industry is to gain efficiency. She cites the "transformative" deal done with Celgene Corporation as an example of the type of deal which helps to bring medicines to patients faster. This past April, AstraZeneca entered into an exclusive agreement with Celgene for the development and commercialization of durvalumab (MEDI4736) across a range of blood cancers including non-Hodgkin's lymphoma, myelodysplastic syndromes and multiple myeloma.

Durvalumab is an investigational immune checkpoint inhibitor, directed against programmed cell death ligand 1 (PD-L1). Signals from PD-L1 help tumors avoid detection by the immune system. Durvalumab blocks these signals, countering the tumor's immune-evading tactics. Within the collaboration, durvalumab is being assessed both as monotherapy and in combination with other AstraZeneca and Celgene potential and existing cancer medicines. Over time, the collaboration could expand to include other assets.

Celgene is just one example of collaborators for MedImmune; others include Immunocore Ltd, Igenica Biotherapeutics Inc, Innate Pharma SA, and ADC Therapeutics. This step-forward approach to drug development is Jallal's calling card, and her positivity and energy when discussing the possibilities that can be achieved through science is inspiring. She talks frequently of her faith in human beings and her faith in science. "I think that anything is possible. I think drug development is hard enough, you have to be positive, and you have to believe that you can achieve something."



**John Davis**  
European Editor,  
"The Pink Sheet"

# New Allergy Therapies To Come Of Age In 2016

**John Davis** looks at the global allergies pipeline that may provide a soothing balm for sufferers.

The itchy runny nose and red, gritty eyes of allergy sufferers make their lives a misery, and the pharma industry has come up with a broad range of palliative and moderately successful treatments, including antihistamines, steroids, and subcutaneous immunotherapies (SCIT) and sublingual immunotherapies (SLIT).

However, better and more convenient therapies are sorely needed for patients who don't respond to, or don't like, current treatment regimens, particularly those with moderate-to-severe symptoms. "The big impact allergies have on people's lives is often underestimated, they very often affect the way people live their lives," says Steve Harris, CEO of Circassia Pharmaceuticals PLC, a UK biotech with a potential cat allergy vaccine in Phase III studies.

The unmet need for new therapies is perhaps greatest for individuals with peanut or other food allergies, who fear triggering a life-threatening anaphylactic shock through an unfortunate choice of snack or beverage, and where the effects of preventative therapies are uncertain. Ridding patients of the allergy or reducing its effects would likely be preferred over any number of emergency kits and adrenaline injections.

Not only that, allergies of all types seem to be on the increase, and nobody knows why. Researchers at Anergis SA, a Swiss biotech with a short-course birch pollen vaccine in early clinical studies, believe allergies are the "fastest growing chronic condition in the industrialized world," rapidly adding to the 500 million allergic patients worldwide. Currently marketed SCIT and SLIT therapies involve gradually increasing exposure to an allergen to induce immune tolerance, but they can require giving 50 injections or more over three to five years, and compliance to such regimens can be poor. Such therapies are also sometimes associated with adverse effects including irritation and swelling in the mouth and gastrointestinal intolerance.

Complicating the marketplace is the fact that allergists in some countries like the US make up their own "allergy shots" and don't yet favor regulator-approved medicines. Stallergenes Greer, and Denmark's ALK Abello with partner Merck & Co, launched grass allergy SLIT products in the US in 2014 following FDA approval, but have struggled to gain market share.

ALK-Abello CFO Flemming Pedersen told analysts in November that although Merck was driving good patient awareness of their allergy products, Grastek

and Ragwitek, in the US, this was unfortunately "not turning into a significant number of prescriptions." This may change when ALK's new house dust mite allergy vaccine, Acarizax, reaches the market, possibly in 2017, Pedersen added.

Regulation of the allergy market is changing. Regulators in countries like Germany, a large market for allergy therapies where allergenic extracts are usually available on a named-patient basis, are phasing in a new regulatory process, the Therapieallergene Verordnung (TAV), with first approvals expected in four to five years.

And some allergy companies, like ALK Abello, are already developing products that can pass the scrutiny of regulators. Its new house dust mite vaccine Acarizax sublingual tablet was approved for marketing for allergic rhinitis and allergic asthma through the EU's decentralized procedure in 11 European countries in the middle of 2015, and first launches are expected in 2016. Further approvals are being sought in other countries, including Spain and the Benelux countries, and Merck is preparing a BLA to submit to the US FDA, Pedersen said.

Even the UK is a "country of interest" for the potential marketing of Acarizax, despite the UK medical establishment not being in favor of using allergen extracts, after they were associated with several cases of anaphylactic reaction a number of years ago.

Another European allergy company, the UK-based Allergy Therapeutics PLC is planning to shake up the US allergy market with its "ultra-short-course" Pollinex Quattro grass allergy vaccine, expecting it be one of the first "subcutaneous products for a subcutaneous market". The company announced in June 2015 it was resuming US development of the product, having raised \$31m in a stock market placing, and is planning a pivotal Phase III study.

The US development of Pollinex Quattro, already widely available in Europe, was halted in 2007 because of side-effect concerns, but the clinical hold was lifted in 2012. Pollinex Quattro is administered as three subcutaneous injections given over three weeks, much fewer than other SCIT therapies. The product is aluminum-free and contains a novel adjuvant, MPL, licensed from GlaxoSmithKline PLC, and microcrystalline tyrosine that facilitates the vaccine's depot action. Analysts at UK brokers and investment company Stifel believe



Allergy Therapeutics' product portfolio could achieve sales of \$800m-\$1bn at its peak.

The company's CEO Manuel Llobet has indicated he wants to grow through M&A, having bought the Spanish allergy company Alerpharma in June 2015, and he is not alone. Following the merger of France's Stallergenes and America's Greer Laboratories, completed in September 2015, the new UK-headquartered but Euronext Paris-quoted company Stallergenes Greer PLC became the world's leading allergy company, with 32% of the allergy market. In comparison, ALK Abello has 28%, Allergopharma has 10%, Leti has 6%, HAL Allergy has 5% and Allergy Therapeutics has 5% of the market. The new company has annual sales of around \$344m and just fewer than 1,500 employees.

But this breakdown of the market may not last for long. Stallergenes Greer, whose major shareholder is the Bertarelli family-backed investment firm Ares Life Sciences, is not resting on its laurels, and is hoping to shake up the market. "We are looking for accretive and bolt-on acquisitions, and will focus on the US and EU markets and products in adjacent markets like dermatology, ophthalmology and diagnostic," chairman and CEO Fereydoon Firouz told the market in November.

### MULTI-BILLION DOLLAR MARKET POTENTIAL

Analysts at the investment firm Hardman & Co estimate allergy vaccines had sales of \$1.2bn in 2014, with 55% of the market accounted for by subcutaneous injections. "We see the market rising from an estimated \$1.4bn in 2020 to \$5bn in 2025. The driver of these numbers is the sheer size of the potential US market, which is inadequately serviced today," the analysts said.

Public and private investors have responded to the excitement in the allergy community by backing companies wanting to develop new approaches to allergy. More than \$1bn was raised during 2015, see Exhibit 1.

### ULTRA-FAST-ACTING INJECTIONS

So who is developing novel allergy therapies? Three companies developing fast-acting SCIT products include Circassia, Allergy Therapeutics and Anergis SA.

The results of a Phase III study of its Circassia's lead cat allergy product Cat-SPIRE are expected in the second quarter of 2016, and if positive will bring the high-profile biotech within touching distance of launching its first ToleroMune product.

Circassia's approach involves using a microneedle to inject intradermally a number of short peptides from sequenced allergens that stimulate T-cells to differentiate into regulatory T-cells, inhibiting allergic responses and inducing tolerance. A short course of four or eight injections over 12 weeks gives a strong treatment effect more than two years later, and similar long-lasting effects have been seen with a potential

grass allergy vaccines and house dust mite vaccines. Phase IIb studies have been completed with Ragweed-SPIRE for ragweed allergies, Grass-SPIRE for grass allergies and HDM-SPIRE for house dust mite allergies. Others allergens of interest include birch pollen, Alternaria (a mould) and Japanese Cedar pollen.

A long-lasting effect is also claimed by Allergy Therapeutics for its Pollinex Quattro products that contain novel adjuvants and excipients. It is given as three injections at 7-14 day intervals and it can last for at least a year. Allergy Therapeutics has agreed clinical trial protocols with EU and US regulators and a US Phase III efficacy chamber study is expected to start in the third quarter of 2016, after two smaller safety and dose selection studies.

Anergis's lead product AllerT for birch pollen allergies is given as five injections over two months, and has shown a long-lasting effect in field-based Phase II studies. The company uses Contiguous Overlapping Peptide (COP) technology to produce its allergy vaccines, that each contain several long-chain synthetic peptides that taken together have the complete amino acid sequence of an allergen. Because they do not cross-react with IgE, it is hoped they can be given at relatively high doses to induce desensitization over two months rather than three years.

There is good reason to believe better and more permanent solutions to allergic reactions will be introduced over the next few years, driven by breakthroughs in understanding of the allergic immune process, and the design of novel anti-allergy strategies. Circassia's Steve Harris believes this to be a "very exciting time to be involved in allergy vaccine development."

For more on the pipeline for peanut allergies visit [www.scrip100.com](http://www.scrip100.com)

### EXHIBIT 1: PRIVATE AND PUBLIC CAPITAL RAISED IN 2015 BY ALLERGY COMPANIES

COMPANY	FUNDING RAISED	DATE OF CAPITAL RAISE
<b>Patara Pharma</b>	\$33m series A	Oct
<b>Tunitas Therapeutics</b>	\$10m Series A	Sept
<b>Aimmune Therapeutics</b>	\$168m IPO on Nasdaq	Aug
<b>DBV Technologies</b>	\$281.5m offering on Nasdaq	July
<b>AnaptysBio</b>	\$40m series D	July
<b>Circassia Pharmaceuticals PLC</b>	£275m (\$419m) private placement	June
<b>Aimmune Therapeutics</b>	\$80m series B	March
<b>Allergy Therapeutics</b>	\$30m institutional placement	March

Source: Strategic Transactions





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# Alzheimer's Disease: Remembering The Past To Prepare The Future

**Lubna Ahmed** and **Lucie Ellis** look through the drug failure archives to hunt for clues that may lead the industry to a new Alzheimer's disease drug.

Alzheimer's disease is the most common cause of dementia among the elderly, accounting for between 60% and 80% of cases in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK). Despite decades of heavy investment in research, there are still few effective treatments for this cognitive disease and AD has become a graveyard for a lot of promising drugs and billions of R&D dollars.

No approved treatment has been able to halt the underlying disease processes in the brain in AD patients, and no new treatment has been approved at all in the last decade in this field. R&D of new therapies has been hit by a large number of late-stage, high-profile failures in recent years and a vast number of asset suspensions in the earlier stages of development too.

According to data held by BioMedTracker (BMT), the AD pipeline in the US includes 47 Phase I products that have been suspended or placed on a program hold. Of these 47 drugs, AD was the lead indication for 24 of them. In Phase II (including one Phase IIb program) the picture is similar, as BMT has 55 AD products listed as suspended.

However, in Phase III, where product failures tend to cause more disruption to wider company strategies, root more financial loss, as well as create higher disappointment to patient populations, BMT has recorded 13 drug suspensions or program holds (see Exhibit 1). There is also one record for a drug being withdrawn from the market, Pfizer Inc.'s *Cognex* (tacrine), which was stopped following usage limits on the product because of side effects.

Tommy Dolan vice-president and head of Pfizer Inc.'s Sandwich site, UK, commented to *Scrip*, "Neuroscience research is one of the most challenging areas of science not least because, unlike other organ systems, we do not have direct access to the brain – a highly complex organ. We are therefore continually applying learnings from our own research, as well as through important collaborations with industry, academia, advocates and government."

However, lessons are being learnt and the future for the treatment of Alzheimer's disease isn't as bleak as historical failures might make it seem. The risks and

obstacles for companies working in AD are vast, but so too, potentially, are the rewards. According to *Scrip 100's* sister product Datamonitor Healthcare, the global market for AD drugs was worth a combined \$4.1bn in 2014, although there are a large number of patients at the earliest stages of disease, before the onset of dementia, currently undiagnosed and untreated. As drug development shifts toward these prodromal AD patients, likely with premium-priced biologic therapies, the market will expand considerably.

But who could reap the rewards of this open-market of opportunity? "The number of candidates in development for AD is at its highest ever level, despite the pipeline's collective inability to produce a new chemical entity since *Namenda* (memantine) in 2002," notes Daniel Chancellor, lead analyst at Datamonitor Healthcare.

According to BMT, this breaks down into 51 candidates in Phase I or I/II clinical trials for the treatment of AD. Of these early stage clinical programs, 29 of the products are targeting AD as their lead indication. In Phase II, II/III or IIb there are 43 drugs being developed for the disease, of these 28 have AD listed as their primary indication. Later down the pipeline there are 15 drugs in Phase III clinical studies, eight of which have AD as the lead indication (see Exhibit 2).

This pipeline overview shows that despite some investors' loss of appetite for AD in light of its difficulties and high risk factor, there is still an important amount of drug development action ongoing. This summary also doesn't include the 10-plus investigator initiated studies at various stages of clinical development recorded by BMT.

However, the jump down from 43 opportunities in Phase II to only 15 in Phase III highlights the problem of getting new treatments in AD over the final hurdles to market. Gary Landreth, professor of neurosciences at Case Western Reserve University, told *Scrip*: "The main problem with developing drugs for AD is our profound ignorance of its biology. This can only be fixed with a concerted basic science effort. The narrow focus of pharma's drug development effort remains problematic and their risk aversion has prevented innovative approaches to therapy."





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## RESEARCH & DEVELOPMENT

Despite decades of heavy investment in research, there are still few effective treatments for this cognitive disease and AD has become a graveyard for a lot of promising drugs and billions of R&D dollars.

Still, Chancellor predicts that the next five years “may herald much needed breakthroughs” in AD. As such, *Scrip* has selected four promising Phase III AD drugs with different modes-of-action that could make it to the finish line that is market approval in the next few years.

### POTENTIAL IN THE PIPELINE

Eli Lilly & Co is expected to start giving analysts and investors some color on its AD program for solanezumab (LY2062430), an antibody against beta-amyloid, by the end of 2016 – and the results are highly anticipated by experts in the field. While Lilly’s overall CNS portfolio is

in decline, high hopes are held for its AD drug which is currently leading the race to be the first disease-modifying drug available to treat AD patients.

After two Phase III failures already, solanezumab has not been immune to the perils of AD drug development. However, Lilly is conducting a third trial of solanezumab in mild AD, known as EXPEDITION3, having finally identified the most appropriate patients for its drug. Its developmental hurdles mean that any regulatory approval will be delayed until at least 2018 for the product.

Lilly’s drug would represent the first disease-modifying AD therapy that could theoretically find wide-

### EXHIBIT 1: LATE-STAGE ALZHEIMER’S DISEASE FAILURES

DRUG NAME	LEAD COMPANY	LEAD INDICATION	CURRENT DEVELOPMENT STAGE	MOLECULE	TARGET	DRUG CLASSIFICATION	DEVELOPMENT PHASE WHEN SUSPENDED	ROUTE OF ADMINISTRATION
<b>ABT-126</b>	AbbVie Inc.	N	Suspended	Small Molecule	Nicotinic Acetylcholine Receptor	NME	Phase IIb	Oral
<b>Acrescent</b>	H. Lundbeck A/S	N	Suspended	Small Molecule	Serotonin 5-HT3 receptor	Non-NME	Phase III	Oral
<b>Avandia</b>	GlaxoSmithKline plc	N	Suspended	Small Molecule	PPAR gamma	NME	Phase III	Oral
<b>Bapineuzumab (IV and SQ)</b>	Johnson & Johnson	Y	Suspended	Monoclonal Antibody	Amyloid Beta/ Amyloid Plaques	Biologic	Phase III	Intravenous, Subcutaneous
<b>Bifeprunox</b>	AbbVie Inc.	N	Suspended	Small Molecule	Serotonin 5-HT1 receptor	NME	Phase III	Oral
<b>Dimebon</b>	Medivation, Inc.	Y	Suspended	Small Molecule	Mitochondria	NME	Phase III	Oral (PO)
<b>Flurizan</b>	Myrex, Inc.	N	Suspended	Small Molecule	Gamma-secretase	NME	Phase III	Oral
<b>Gammagard</b>	Baxalta Incorporated	N	Suspended	Protein	Amyloid Beta/ Amyloid Plaques	Biologic	Phase III	Intravenous
<b>Lipitor</b>	Pfizer Inc.	N	Suspended	Small Molecule	HMG CoA Reductase	NME	Phase III	Oral
<b>Memryte</b>	Voyager Pharmaceutical Corp.	Y	Suspended	Peptide	Gonadotropin-Releasing Hormone Receptor	Non-NME	Phase III	Subcutaneous
<b>Phenserine</b>	QR Pharma, Inc.	Y	Suspended	Small Molecule	Acetylcholine	NME	Phase III	N/A
<b>Risperdal</b>	Johnson & Johnson	N	Suspended	Small Molecule	Serotonin 5-HT2A receptor	NME	Phase III	Oral
<b>Semagacestat</b>	Eli Lilly & Company	Y	Suspended	Small Molecule	Gamma-secretase	NME	Phase III	Oral
<b>Xaliproden</b>	Sanofi	N	Suspended	Small Molecule	Serotonin 5-HT1a receptor	NME	Phase III	Oral
<b>Cognex</b>	Pfizer Inc.	Y	withdrawn from Market	Small Molecule	Cholinesterases	NME	Withdrawn from market	Oral

Source: BioMedTracker



## EXHIBIT 2: THE ALZHEIMER'S DISEASE PIPELINE

DRUG NAME	LEAD COMPANY	TARGET	CURRENT PHASE	LEAD INDICATION	LIKELIHOOD OF APPROVAL	MOLECULE
<b>Gantenerumab</b>	Roche Holding AG	Amyloid Beta/Amyloid Plaques	II/III	Y	9% (43% Below Avg.)	Monoclonal Antibody
<b>Albutein + Flebogamma DIF</b>	Grifols, S.A.	Amyloid Beta/Amyloid Plaques	II/III	Y	52% (Same As Avg.)	Protein
<b>AZD3293</b>	AstraZeneca PLC	Beta-secretase (BACE)	II/III	Y	52% (Same As Avg.)	Small Molecule
<b>BAN2401</b>	Eisai Co., Ltd.	Amyloid Beta/Amyloid Plaques	I Ib	Y	16% (1% Below Avg.)	Monoclonal Antibody
<b>NICS-15</b>	Humanetics Corporation	Gamma-secretase	I Ib	Y	17% (Same As Avg.)	Small Molecule
<b>Sembragiline</b>	Evotec AG	Monoamine oxidase B (MAO-B)	I Ib	Y	7% (10% Below Avg.)	Small Molecule
<b>Aducanumab</b>	Biogen, Inc.	Amyloid Beta/Amyloid Plaques	III	Y	53% (1% Above Avg.)	Monoclonal Antibody
<b>ALZT-OP 1</b>	AZTherapies, Inc.	Amyloid Beta/Amyloid Plaques	III	Y	52% (Same As Avg.)	Small Molecule
<b>Crenezumab</b>	Roche Holding AG	Amyloid Beta/Amyloid Plaques	III	Y	45% (7% Below Avg.)	Monoclonal Antibody
<b>Solanezumab</b>	Eli Lilly & Company	Amyloid Beta/Amyloid Plaques	III	Y	16% (36% Below Avg.)	Monoclonal Antibody
<b>MK-8931</b>	Merck & Co., Inc.	Beta-secretase (BACE)	III	Y	53% (1% Above Avg.)	Small Molecule
<b>Masitinib</b>	AB Science S.A.	Fibroblast Growth Factor Receptor (FGFR) ^ KIT/c-KIT ^ Platelet-derived growth factor receptor (PDGFR)	III	N	52% (Same As Avg.)	Small Molecule
<b>Encenidine</b>	FORUM Pharmaceuticals, Inc.	Nicotinic Acetylcholine Receptor - α7 subtype &lt;br>(α7 nAChR)	III	N	51% (1% Below Avg.)	Small Molecule
<b>AVP-786</b>	Otsuka Holdings Co., Ltd.	NMDA Glutamate Receptor	III	N	52% (Same As Avg.)	Small Molecule
<b>Actos</b>	Takeda Pharmaceutical Company Ltd	PPAR gamma	III	N	52% (Same As Avg.)	Small Molecule
<b>Azeliragon</b>	vTv Therapeutics Inc.	Receptor for Advanced Glycation End Products (RAGE)	III	Y	52% (Same As Avg.)	Small Molecule
<b>Rexulti</b>	Otsuka Holdings Co., Ltd.	Serotonin 5-HT <sub>2A</sub> receptor	III	N	52% (Same As Avg.)	Small Molecule
<b>Idalopirdine</b>	H. Lundbeck A/S	Serotonin 5-HT <sub>6</sub> receptor	III	N	56% (4% Above Avg.)	Small Molecule
<b>RVT-101</b>	Axovant Sciences, Inc.	Serotonin 5-HT <sub>6</sub> receptor	III	Y	55% (3% Above Avg.)	Small Molecule
<b>LMTX</b>	TauRx Therapeutics Ltd.	Tau proteins	III	N	49% (3% Below Avg.)	Small Molecule
<b>AC-1204</b>	Accera, Inc.	Tricarboxylic Acid (TCA) Cycle/Citric Acid Cycle (CAC)	III	Y	52% (Same As Avg.)	Small Molecule

Source: BioMedTracker

spread use and change the treatment landscape. A disease-modifying drug could be used to alter the rate of cognitive and functional decline. It would be used as an adjunct to the existing cholinesterase inhibitors, which are actually able to improve the symptoms of patients, albeit over a finite time period. Taken together, this approach could provide short-term symptomatic benefits and slow the progression of the underlying disease, with the ultimate goal of delaying the time until hospitalization and extending life expectancy.

#### LUNDBECK'S IDALOPIRDINE VS. AXOVANT'S RVT-101

H. Lundbeck's AD candidate idalopirdine (Lu AE58054) is the leader of a new class of AD drugs, 5-HT<sub>6</sub> receptor antagonists. A number of pharma companies have managed to get their 5-HT<sub>6</sub> targeting products into large, late-stage clinical trials. Lundbeck's offering and Axovant Sciences's product in the same class, RVT-101, are both in Phase III trials. Meanwhile, Pfizer Inc. and Suven Life Sciences also have 5-HT<sub>6</sub> receptors in



The global market for Alzheimer's disease drugs was worth a combined \$4.1bn in 2014

Phase II for the treatment of AD. AbbVie is a bit further behind with a Phase I candidate.

Axovant and Lundbeck will be battling it out to gain the all-important first-to-market status for this class of AD drugs. They will both also be fighting against Lilly's slightly delayed drug to be the first AD therapy to reach the market in over a decade.

Axovant, a wholly owned subsidiary of Roivant Sciences, picked up RVT-101 from GlaxoSmithKline PLC for just \$5m via a licensing agreement in December 2014. At the time, some saw this as GSK losing faith in the product, which in July 2011 reported poor results in two failed six-month trials. Both of these trials missed primary endpoints of significant improvement in cognition. GSK determined the product didn't warrant the R&D spend required to take it to market. However, others believed the drug was just a victim of cost-cutting. Axovant has since touted statistically significant analyses from the existing Phase II program, taking forward the drug into Phase III testing on the back of its \$315m initial public offering.

According to the paper *5-HT<sub>6</sub> receptors and Alzheimer's Disease* by Maria Javier Ramirez, published on the US National Library of Medicine (Part of the National Institutes of Health) in April 2013, the 5-HT<sub>6</sub> receptor, a member of the 5-HT receptor superfamily, is involved in affective disorders, anxiety and depression, epilepsy, and obesity. Initially, interest in the 5-HT<sub>6</sub> receptors was triggered by evidence showing that certain antipsychotics are able to bind to these receptors.

Ramirez says, "Overall, several 5-HT<sub>6</sub>-targeted compounds can reasonably be regarded as powerful drug candidates for the treatment of Alzheimer's disease." However, Ramirez pointed to the failure of Pfizer and Medivation's *Dimebon* (dimebolin) as a warning that as with all areas of AD research and drug development, there are still issues. Dimebon showed a good affinity for 5-HT<sub>6</sub> receptors in earlier clinical studies but in a multinational Phase III study known as CONCERT it produced no improvements in AD patients. Pfizer and Medivation disbanded their partnership following the failure of the CONCERT trial.

She says, "The crucial point regarding compounds acting on 5-HT<sub>6</sub> receptors is the intracellular pathways activated after the interaction of the compound with the receptor. Therefore, perhaps it is a question not only of developing an agonist or antagonist with good affinity but also of developing compounds able to activate the necessary mechanisms for the pro-cognitive effects."

#### MERCK'S VERUBECESTAT

Merck & Co's verubecestat, formerly known as MK-8931, a beta amyloid precursor protein site-cleaving enzyme (BACE) inhibitor, is being developed for the treatment of mild cognitive impairment (MCI) due to AD and mild to moderate AD. Datamonitor Healthcare notes that BACE inhibition involves the modulation of

amyloid precursor protein (APP) cleavage, reducing the formation of all beta amyloid species. "This distinguishes BACE inhibitors from the unsuccessful gamma secretase inhibitors, which do not lower total amyloid but rather shift its production in favor of shorter, less neurotoxic proteins," notes Chancellor.

While this mode of action is aimed at preemptive treatment, as Merck is positioning verubecestat as a treatment option to slow or stop the conversion into dementia, the company is also researching the drug in patients with mild to moderate AD. The company believes that drug treatment may be viable to improve or slow the decline of symptoms of patients already suffering from dementia. Should verubecestat achieve market approval in both settings Merck would be positioned strongly against competitors that might also get to market in the next five years.

Verubecestat now represents the most advanced BACE inhibitor in the AD pipeline. BMT has given the product a 53% likelihood of approval rating, a modest 1% above the average for a similar product at the same stage of development.

#### THE ROAD AHEAD

While the last 15 years of Alzheimer's R&D have failed to produce a new drug candidate, this investment has not been wholly lost. Arguably it is advances in diagnostics that will facilitate the first disease-modifying drug, as companies such as Biogen, Lilly, and Roche Holding AG can now confirm AD pathology in participants in their clinical trials before dosing drugs specifically designed to target the amyloid pathway. Previously, it had been estimated that up to 20% of patients enrolled in trials actually did not have any AD pathology and that their dementia was due to other causes. This seriously jeopardized the likelihood of clinical trials meeting primary endpoints.

Furthermore, data accumulated by Lilly in its technically failed Phase III EXPEDITION program of solanezumab have forced companies to reconsider the appropriate target patient group. There is now a large amount of evidence suggesting that the pathology of moderate AD is too far progressed for a disease-modifying drug to work, and that it is early AD, including patients before the onset of dementia, that is the right target. There are even preventative trials in progress, whereby amyloid-targeting drugs are being tested in healthy individuals with a genetic predisposition toward AD.

As these latest clinical trials read out in the second half of this decade, the AD research community will finally be able to either celebrate a desperately needed therapeutic breakthrough, or finally lay the amyloid hypothesis to rest. Irrespective of how this unfolds, there can also be hope that Lundbeck's development of idalopirdine will produce a new treatment that offers additional symptomatic benefit on top of the current standard of care.

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## Covance Improves Patient Safety with Xcellerate Data Monitoring Platform

Innovation in clinical trials is coming not only from academic and scientific quarters, but from service providers also. Here, Covance explains how its expertise and experience have catalyzed the creation of its monitoring tools.

The combination of Covance's<sup>1</sup> drug development leadership and LabCorp's medical testing expertise is creating a market leader and partner of unmatched scale, expertise and scientific depth in the healthcare services industry. The company is using its consolidated strengths, from clinical trial expertise to sophisticated analytics capabilities, to help transform the way clinical trials are conducted.

A prime example of new service offerings from Covance is the company's Xcellerate® Monitoring, part of the Xcellerate® Clinical Trial Optimization® platform, a suite of proprietary, technology-enabled solutions designed and proven to help biopharmaceutical companies meaningfully reduce the cost, time, complexity and risk associated with clinical trials. By leveraging consistent processes and practices under a single, world-class technology platform, Xcellerate Monitoring centralizes and consolidates clinical trial data, enhances patient safety, improves trial efficiency and proactively enables clients to identify and mitigate potential risks.

"As an industry leader in creating technology-enabled solutions to accelerate drug development, Covance is committed to building scalable, replicable platforms such as Xcellerate Monitoring to help biotechnology and pharmaceutical companies bring innovative new medicines to patients," said Deborah Keller, Covance Drug Development's chief executive officer.

Covance recently announced that it had received a multi-year award from a leading pharmaceutical company to use its Xcellerate Monitoring platform as an exclusive central monitoring solution for its worldwide clinical trials portfolio.

Referring to that award, Keller noted that "this is an exciting opportunity, in collaboration with a long-standing client, to leverage the unique power of Xcellerate Monitoring to help our client make more informed decisions, lower risks and drive faster results across its global clinical trial portfolio."

Xcellerate® Monitoring uses data integration, analytic and visualization capabilities to ensure patient safety and data quality throughout the clinical development process. The risk-based monitoring (RBM) platform provides unprecedented access to all clinical trial and operational data and enables the comprehensive assessment and mitigation of risk at the study, site and patient level. The platform also enables companies to centralize the monitoring of all of their clinical trials as an integrated portfolio.

"This innovative platform enables users to make informed decisions by making data easily accessible, understandable and actionable through a powerful but highly intuitive user interface," says Keller. "It allows our clients to strategically target the appropriate resources and significantly increase the quality and efficiency of their clinical trials."

### Building A Better Solution – From The Bottom Up

Covance developed its centralized quality and RBM approach over the past several years in response to the substantial increase in the time and cost associated with bringing new medicines to market. "The industry was spending an enormous amount of energy — time, money and technology — reviewing all of the data from every study, without weighing what was most important," said Jill Johnston, Covance's global vice president for Site Activation, Informatics and Optimization, Clinical Development and Commercialization Services.

In August 2013, the US Food and Drug Administration (FDA) released new guidelines for interpreting clinical trial data, focusing on areas of high risk from a patient and quality perspective. Covance anticipated this shift in focus, and began its journey long before the new guidelines were released. "We were already applying several risk-based approaches in our trials years ago," said Johnston. The move by Covance to a more formalized process was a natural continuation, but creating the underlying technology solution was a huge undertaking.

A dedicated project team comprising senior leaders was formed to develop a new framework to monitor clinical trials using a risk-based approach. Finding a complete absence of existing technology in the marketplace that could meet Covance's well-defined set of requirements, the company chose to build a brand new infrastructure.

"Starting with a clean slate allowed us to build an RBM system to our exacting standards," says Johnston. "The solution we created represents the core of our new informatics capability, and serves as a major differentiator for Covance in the marketplace."

### Unprecedented Access To, And Assessment Of, Clinical Trial Data

The Xcellerate Monitoring platform provides unprecedented access to all clinical trial data and enables comprehensive assessment and mitigation of risk at the study, site, and patient level. Its powerful but intuitive user interfaces allow central monitoring staff to maintain site monitoring plans, identify and mitigate potential risks in the conduct of a clinical trial, and efficiently direct site monitors to the right locations with the right frequency to assure patient safety and data quality - all with greater insight, speed, and efficiency than ever before.

The underlying platform methodology is fully aligned with FDA and European Medicines Agency (EMA) guidance and the TransCelerate principles, and is based on the three cornerstones of risk-based monitoring: quality by design, central monitoring, and triggered adaptive on-site and remote monitoring. The solution consists of a clinical data integration layer, a set of proprietary algorithms and workflows, a set of intuitive, responsive, and

elegant web-based user interfaces, application hosting on a secure private cloud environment, and comprehensive user, application, and business support delivered through a SaaS (software-as-a-service) model.

### **Advances In Risk-Based Monitoring Benefit Clients And Patients**

Historically, trial monitoring has involved checking the accuracy of data entered into a patient's medical chart against data collected in a clinical trial through electronic data capture (EDC), and ensuring the two sets of data matched. If EDC was asking for a patient's height, the monitor would check the patient's chart for consistency. Trial monitors would physically visit investigator sites about every six to eight weeks to access the data and to "box check" the data.

Today's RBM model is substantially more sophisticated. It weighs the importance of the multitude of data being collected in the context of a trial, placing much greater emphasis on the safety and efficacy of a drug as opposed to a patient's height or other such demographics. Placing critical data at the forefront allows trial monitors to prioritize their areas of focus, and to effectively mitigate risk much more quickly.

Furthermore, with Xcellerate Monitoring all of the data is entered into a centralized monitoring system—one that has the

ability to compute more complex information, take into account numerous variables and thoroughly examine statistical metrics. The system allows accessibility to data via desktop anytime from anywhere, and is designed to proactively call attention to any potential concerns. For example, if there is a high level of patient dropout at a particular site, the monitoring system will send an alert, prompting careful examination and possibly an earlier site visit from a trial monitor.

### **Too Important To Fail**

Our clients make huge investments of time, energy and money in clinical trials, and failure is not an option. "They cannot redo trials or afford to start slow," said Johnston. "The Xcellerate Monitoring approach allows us anticipate potential points of failure, and to put a preventative strategy or contingency plan in place. We can take immediate action when the unexpected happens."

[www.covance.com](http://www.covance.com)

### **REFERENCES**

1. Covance Inc., headquartered in Princeton, NJ, is the drug development business of Laboratory Corporation of America Holdings (LabCorp). Covance is the marketing name for Covance Inc. and its subsidiaries around the world.



Xcellerate Monitoring  
centralizes and consolidates  
data which proactively  
enables clients to identify and  
mitigate potential risks.



**Michael Liu**  
Research Analyst,  
BioMedTracker

# The Future Looks Bright For Orphan Drugs

The financial incentives of extended exclusivity and regulatory assistance from the US FDA are two driving forces for therapeutic development in orphan indications. **Michael Liu** looks at the pipeline for orphan drugs in oncology to assess their future.

Designed to encourage clinical development in medical diseases that affect fewer than 200,000 people in the US, an orphan drug designation provides assistance in the drug development process, tax credits for clinical costs, exemptions from certain FDA fees and seven years of marketing exclusivity. In the expansive field of oncology, several orphan indications have shown promise in attaining regulatory approval. In solid tumors, niraparib, ruxolitinib (Jakafi), tarextumab, and algenpantucel-L have all demonstrated encouraging trial results. And in hematology, CPX-351 (Vyxeos), JCAR015, and selinexor are several therapies that have also announced promising clinical results. The data seen thus far have affected each drug's likelihood of approval (LOA), as determined by BioMedTracker. To fully secure regulatory approval, these drugs need to demonstrate further efficacy in their respective orphan indications. Thus, all of the listed drugs' sponsors expect additional data readouts in 2016.

Among the few therapies in advanced clinical studies for the treatment of ovarian cancer, niraparib has shown good progress in this highly unmet indication. Niraparib is a poly ADP-ribose polymerase (PARP) inhibitor and its sponsor Tesaro, Inc. expects Phase II top-line results from two studies, QUADRA and NOVA, in the second quarter of 2016. In context to the anticipated readouts, niraparib has already demonstrated, in a Phase I study, a 75% and 50% RECIST (Response Evaluation Criteria in Solid Tumors) response in platinum-sensitive serious high-grade ovarian cancer and platinum-sensitive, germline BRCA-positive mutation ovarian cancer patients, respectively.

However, niraparib has competition amongst the newly developed PARP inhibitors. Hoping to follow in the footsteps of the freshly approved Lynparza (olaparib) in ovarian cancer, Clovis Oncology's rucaparib has shown similar efficacy with a reported RECIST response of 69% in BRCA-positive patients (Phase II ARIEL 2 study). Additionally, rucaparib has secured the advantage of a breakthrough therapy designation. But with such comparable RECIST responses, it's difficult to distinguish a clear front-runner between the two candidates. **BioMedTracker lists**

**niraparib's LOA as 2% above average and rucaparib's at 6% above average.**

In the orphan indication of pancreatic cancer where there is less than a handful of approved therapies, one of the most advanced drugs in clinical development is ruxolitinib phosphate, a Janus-associated kinase (JAK) inhibitor. Sponsored by Incyte Corporation, ruxolitinib currently expects top-line results for its Phase III JANUS 1 study, as a second-line treatment for metastatic pancreatic cancer, in 2016. Thus far, the forecast of ruxolitinib looks somewhat encouraging from the results seen in the Phase II RECAP study in recurrent or treatment refractory metastatic pancreatic cancer. While ruxolitinib in combination with capecitabine failed to reach the study's primary overall survival endpoint in the ITT population (HR = 0.79, one sided p=0.25), the study did show a strong six-month overall survival (HR = 0.47, one sided p=0.01) in patients with a median of  $\geq 13$  mg/L CRP (C-Reactive Protein) at study entry. This paints a concerning backdrop for the expected JANUS 1 study results because the JANUS 1 study defines its inclusion criteria at a lower CRP level, effectively increasing the population of patients who may not benefit from the treatment. However, despite this setback, the outlook remains positive in this subgroup and the Phase III JANUS 1 top-line results in 2016 can hopefully prove ruxolitinib's efficacy in pancreatic cancer. **BioMedTracker currently lists its LOA at 2% above average.**

Not too far behind in development for pancreatic cancer is a novel therapy named tarextumab. As the first therapy in pancreatic cancer to target notch receptors, tarextumab has early promise as a combination therapy with nab-paclitaxel and gemcitabine in advanced pancreatic cancer. Following up these interim results, OncoMed Pharmaceuticals, the drug's sponsor, now expects to release final results for its Phase Ib/II ALPINE study in patients with previously untreated stage IV pancreatic cancer in the second half of 2016.

The interim results reported in January 2014 stated that tarextumab, in combination with gemcitabine and Abraxane, exhibited an overall disease control rate of 77%. This is positive considering the approved Abrax-



ane (sponsored by Celgene Corp.) reported a disease control rate of 68%, when taken with gemcitabine, during its Phase I/II - CA040 study. Nevertheless, because further conclusive data have yet to be reported, the final results in 2016 may shed important light on whether tarextumab can remain a competitor in this orphan indication. Additionally, as one of the most advanced drugs in OncoMed's pipeline, a positive readout may be a pivotal moment for the company because it has yet to garner a single approved therapy. ***BioMedTracker places the LOA at 1% above average based on the positive data seen in the Phase Ib/II ALPINE Study.***

Finally, NewLink Genetics is currently evaluating its most advanced therapy, algenpantucel-L, for the treatment of pancreatic cancer. The company expects to report top-line results from the pivotal Phase III IMPRESS study in surgically resected pancreatic cancer in 2016. In June 2013, NewLink reported that while the company's Phase II study in subjects with surgically resected pancreatic cancer yielded a positive 62% disease free survival at one year (primary endpoint), there was a large efficacy difference in patients with elevated and non-elevated anti-mesothelin antibody levels. Patients with elevated levels of anti-mesothelin antibodies resulted in a median OS of 42 months compared to 20 months in patients without elevated anti-mesothelin antibodies. This is concerning because the Phase III IMPRESS study does not stratify for that biomarker; potentially decreasing the primary endpoint of overall survival. ***Given the Phase II results, BioMedTracker places the LOA at 2% below average.*** But despite this setback, NewLink announced that the company is encouraged with the results and will continue the IMPRESS study without any modification.

In hematological orphan therapies, Celator Pharmaceuticals' CPX-351 currently expects to announce overall survival data from its Phase III 301 study, in acute myelogenous leukemia (AML), in the first quarter of 2016. CPX-351 is an intravenous liposomal formulation of a synergistic 5:1 molar ratio of cytarabine and daunorubicin. Celator has already provided encouraging results from a Phase IIb trial (the 204 study) with CPX-351 demonstrating a complete response rate (CR + CRI) of 66.7% compared to 51.2% ( $p=0.07$ ) in the conventional 7:3 molar ratio of cytarabine and daunorubicin (commonly referred to as 7+3). Similarly, in secondary AML patients, CPX-351 reported a complete response rate of 57.6% compared to 31.6% ( $p=0.06$ ) in 7+3.

Furthermore, Celator strengthened the outlook of CPX-351 when the company announced that the Phase III 301 study of CPX-351 resulted in a 47.7% complete remission rate, compared to 33.3% with

7+3. Because CPX-351 is an advancement over 7+3 in terms of pharmacology and dosing convenience (it does not require continuous cytarabine infusion), and given the patient population and lack of effective treatments beyond 7+3 for AML, the outlook for CPX-351 remains positive. ***Given these preliminary results, BioMedTracker lists the LOA for CPX-351 at 4% above average.***

In the orphan indication of acute lymphocytic leukemia (ALL), Juno Therapeutics is developing JCAR015, an autologous cell product using chimeric antigen receptor (CAR) modified T cells, and expects to report top-line data from the Phase II ROCKET study in late 2016. At the 2014 American Society of Hematology meeting, JCAR015 exhibited a complete response of 89% and an overall survival of 8.5 months in adults with relapsed or refractory ALL. Although positive, these results are too early and thus Juno hasn't clearly differentiated its efficacy as compared to other CAR-T treatments where many programs have also demonstrated varying levels of success in adult ALL patients. ***JCAR015 is currently 3% above average on BioMedTracker.*** As a result, the larger Phase II study can hopefully garner more promising numerical results that will clarify whether JCAR015 is a competitive and efficacious therapy in ALL.

In diffuse large B-cell lymphoma (DLBCL), Karyopharm Therapeutics expects top-line results from the Phase IIb study of its lead drug, selinexor. In a Phase I clinical study in patients with advanced hematologic malignancies, selinexor demonstrated a 43% overall response rate and 71% disease control rate in evaluable heavily pretreated DLBCL patients. In all patient cohorts, the therapy demonstrated a 31% overall response and a 51% disease control rate. Most notably, this promising activity was observed in the difficult-to-treat double hit DLBCL patients (with dual BCL2 + cMyc translocations). Thus, due to these preliminary results, selinexor could potentially be targeted for development in this subgroup. Nevertheless, selinexor's Phase II top-line results in 2016 will further designate whether this therapy can be a treatment option in the orphan indication of DLBCL. ***Based on the early results, BioMedTracker lists the LOA for selinexor at 2% above average.***

With promising therapies on the horizon, the developmental outlook in these orphan oncology indications look bright. It has become clear that the FDA's orphan designation incentive have bolstered growth and development in these indications which may have otherwise been left underdeveloped. Consequently, 2016 will hopefully be a fruitful year for data announcements for the many therapies in solid tumors and hematology.

In the expansive field of oncology, several orphan indications have shown promise in attaining regulatory approval.





**Laura Runkel**  
Associate Director,  
TrialTrove

# Steps On The Long Road To Therapies for Uncontrolled Asthma

Asthma is one of the most common respiratory diseases worldwide, and its prevalence is projected to increase over the coming decades, particularly in the US as the population continues to grow. **Laura Runkel** looks at the current treatments in development for asthma.

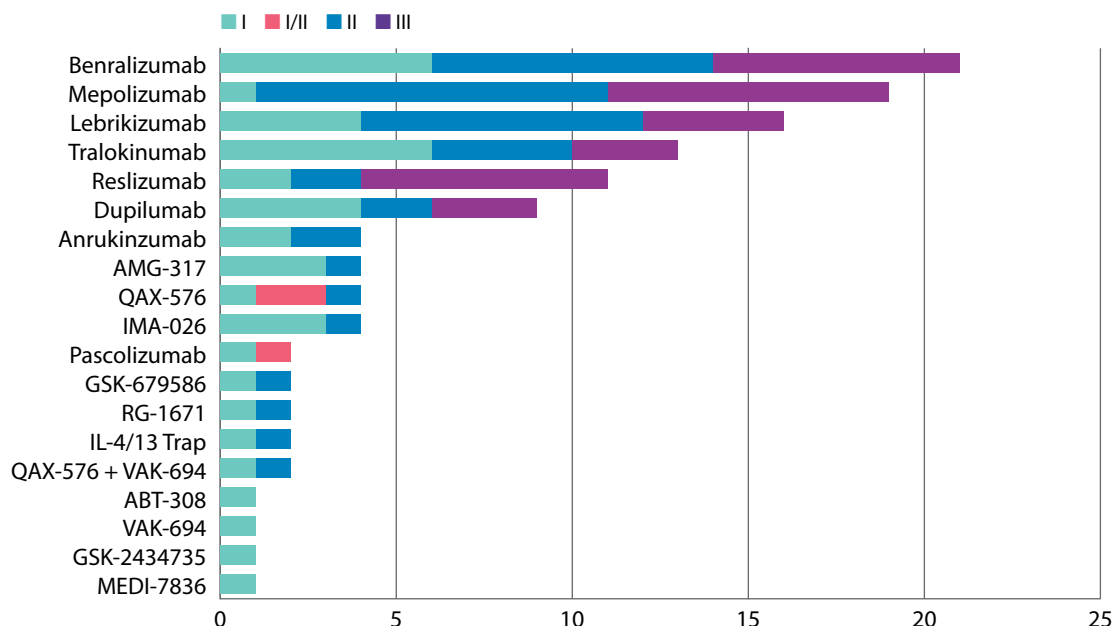
Asthma management utilizes a stepwise approach to control symptoms while minimizing risks. Inhaled corticosteroids (ICS) remain the standard of care for mild asthma, while more severe cases are treated with combination therapies of ICS plus a long-acting beta agonist (LABA) and may require a third, add-on controller medication for the most severe asthma population. However, symptoms for an estimated 5-10% of asthma sufferers remain uncontrolled by available treatment options.

In recent years, uncontrolled asthma has emerged as an area of high unmet need, and has also been recognized to be a heterogeneous syndrome with different underlying pathophysiological features. Efforts to define key drivers for asthma “phenotypes” have focused on the role of eosinophilic inflammation and Th2 type immunological pathways, and led to the clinical development of biologics that antagonize IL-5, IL-4

and IL-13 pathways. After many years of research, the first two novel biologics have been filed for approval for uncontrolled, eosinophilic asthma treatment. Will the hope for truly targeted therapies for uncontrolled asthma now be realized?

Of the 19 clinical asthma programs in TrialTrove, approximately half (10) were discontinued as of September 2015. The programs span approximately 18 years, with GlaxoSmithKline PLC, Regeneron Pharmaceuticals Inc., AstraZeneca PLC, and Roche showing an enduring commitment to development of biologics for at least one of these targets. Several drugs, including Teva Pharmaceutical Co Ltd’s reslizumab and GSK’s mepolizumab, were acquired and have experienced substantial gaps in clinical progression in the process. Novartis AG’s current commitment to these targets, while active, is small. The pattern of discontinuations

**EXHIBIT 1. PHASE I-III TARGETED BIOLOGICS IN ASTHMA TRIALS BY PHASE**



Source: Citeline’s TrialTrove, September 2015





for specific targets points to particular challenges for the IL-4 and IL-13 pathway antagonists, while all three of the IL-5 antagonists remain active. Indeed, reslizumab and mepolizumab were filed for approval in several major markets, and GSK announced a positive CHMP opinion for mepolizumab on September 24, 2015.

### PROGRAM TRIALS AND STATUS FOR IL-5 AND TH2 PATHWAY ANTAGONISTS

A granular view of the trial counts per phase (Exhibit 1) and by trial status (Exhibit 2) provides an overview of these clinical programs from Trialrove. The active programs at the Phase III status include both ongoing pivotal asthma trials for benralizumab (4), lebrikizumab (2), tralokinumab (2), and dupilumab (2), and supporting studies. The newest program in the arena is AstraZeneca's Phase I candidate MEDI-7836, an anti-IL-13 mAb-YTE a potential tralokinumab follow-on that may have a longer half-life. Novartis' single active trial is a slow-moving Phase II trial for the fixed-dose combination of QAX-576 + VAK-694. Development of VAK-694 (anti-IL-4) as a standalone drug was discontinued after Phase I and QAX-576 (anti-IL-13) trials are all completed, or terminated. Many of the discontinued programs only progressed to Phase II, or were abandoned after Phase I.

Three of the six active programs terminated a Phase II (tralokinumab) or III (reslizumab, benralizumab) study in the course of development. These terminated trials appear to reflect a strategic shift in business plans, rather than concerns about efficacy or safety. In addition, Roche's lebrikizumab clinical program experienced delays, disclosed in Q4 2012. The LUTE and VERSE trials were originally designated as pivotal Phase III studies,

but were changed to smaller scale Phase IIb trials, due to undisclosed issues with the clinical trial material. Clearly, there have been some challenges to development for biologics for many of these targets in the asthma field.

### TRIAL OUTCOMES FOR EFFICACY TRIALS OF TARGETED BIOLOGICS IN ASTHMA

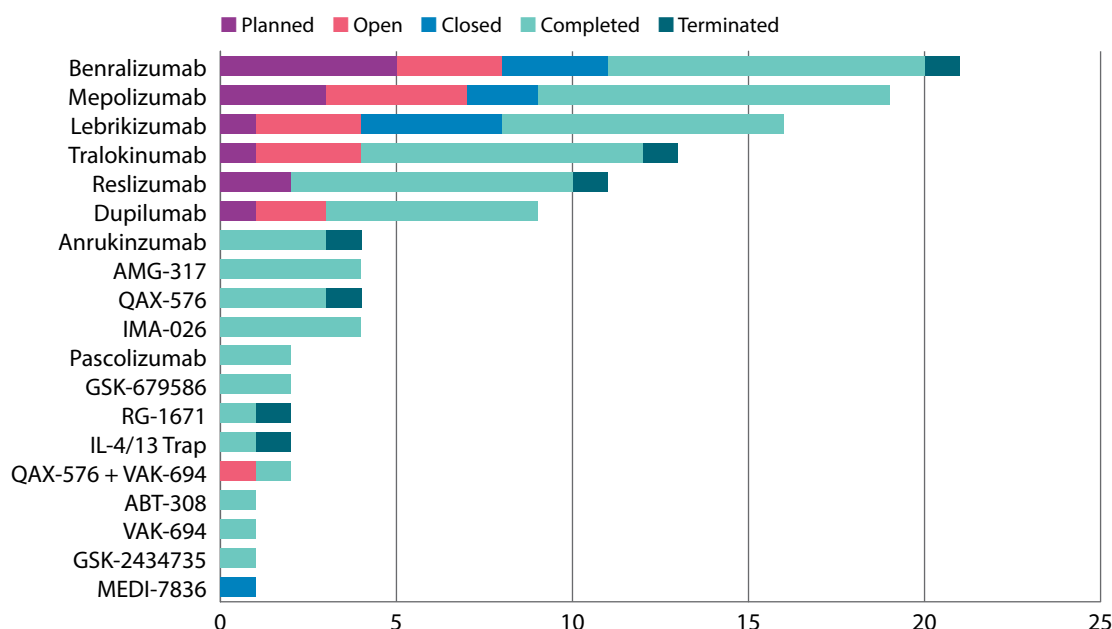
The available trial outcomes for Phase I/II to III efficacy trials (completed or terminated due to lack of efficacy) are profiled in Exhibit 3 to gain insights into which study design attributes potentially played a role in the success or failure of the trials. The most successful programs are defined as ones that returned positive outcomes and/or the primary endpoint(s) of the trial were met. Each of the biologics targeting the IL-5 pathway returned primarily positive outcomes.

The correlation between study design attributes and trial outcomes (positive or negative) is summarized in Exhibit 4. The IL-5 antagonist trials enroll(ed) only uncontrolled asthma subjects, utilize eosinophil levels as biomarkers to further define the target population, and evaluate a common primary endpoint, exacerbation rates over one year. These trials, as well as a biomarker trial that evaluated impact on eosinophil levels in less severe asthma types, all returned positive outcomes. The trial outcomes for the panel of biologics targeting the Th2 pathways are far more mixed. The discontinued programs of GSK-679586, anrukinzumab, and AMG-317 did not meet primary endpoints (ACQ and PEF) in trials enrolling moderate-to-severe or atopic asthma patients.

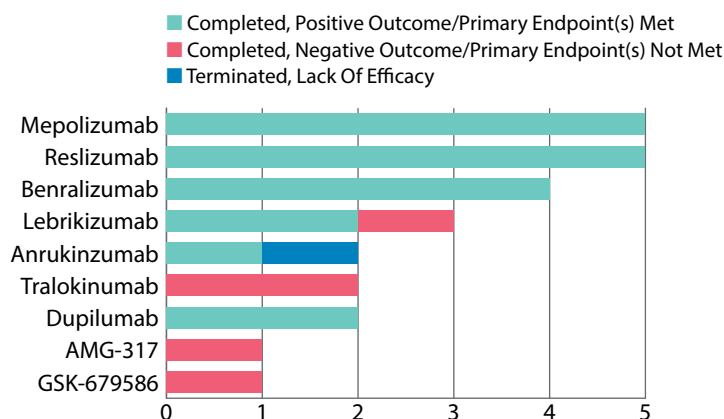
Pfizer Inc.'s anrukinzumab program terminated a Phase II trial in moderate-to-severe asthma due to futility analysis and the program discontinued. Trials

After many years of research, the first two novel biologics have been filed for approval for uncontrolled, eosinophilic asthma treatment. Will the hope for truly targeted therapies for uncontrolled asthma now be realized?

### EXHIBIT 2. PHASE I-III TARGETED BIOLOGICS IN ASTHMA TRIALS BY TRIAL STATUS



Source: Citeline's Trialrove, September 2015

**EXHIBIT 3. TRIAL OUTCOMES IN ASTHMA STUDIES FOR TARGETED BIOLOGICS**

Source: Citeline's Trialtrove, September 2015

**EXHIBIT 4: SUMMARY OF STUDY DESIGN ATTRIBUTES VERSUS TRIAL OUTCOMES FOR COMPLETED EFFICACY TRIALS IN ASTHMA**

■ Positive Trial Outcomes ■ Negative Trial Outcomes

TARGET	PATIENT POPULATION	PRIMARY EFFICACY OUTCOME
IL-5 (IL-5R, alpha)	Eosinophilic, uncontrolled	Exacerbations
	Eosinophilic, uncontrolled	Steroid Use
	Eosinophilic, uncontrolled	ACQ
	Eosinophilic, uncontrolled	FEV1
	Mild, Moderate, or Atopic	Eosinophil levels
anti-IL-13	Stable (no steroids)	FEV1
	Uncontrolled	FEV1
	Uncontrolled	Exacerbations
	Moderate-to-severe	PEF rate
	Moderate-to-severe	ACQ
	Atopic	Late asthmatic response
	Atopic	Eosinophil levels
	Atopic or Uncontrolled	ACQ
IL-4Ra	Atopic	ACQ
	Uncontrolled	Exacerbations
	Eosinophilic, uncontrolled	FEV1

**Endpoint Abbreviations:****ACQ** (Asthma Control Questionnaire)**PEF** (Peak Expiratory Flow)**FEV1** (Forced Expired Volume At 1 Second)**LAR** (Late Asthmatic Response)

Source: Citeline's Trialtrove, September 2015

that returned negative results evaluated FEV1 in asthma subjects who did not receive steroid treatment. However, another Phase II trial returned positive FEV1 results in uncontrolled asthma patients, suggesting this endpoint is attainable in the correct target population. Two other Phase II trials (VERSE and LUTE) completed in 2013 but have yet to report results. Two tralokinumab trials that enrolled uncontrolled asthma patients returned negative results for primary outcomes of ACQ and reduction of acute exacerbations. However, *post hoc*, pooled analyses from these Phase II studies identified a dose-responsiveness for secondary outcomes (FEV1) and an optimal dosing for Phase III studies.

The dupilumab program is an outlier as the only biologic targeting the common IL-4/IL-13 receptor chain (IL-4Ra), and is the most recent Th2 pathway antagonist to initiate pivotal trials in uncontrolled asthma patients, with exacerbations and FEV1 evaluated as primary endpoints. This program has evaluated multiple biomarkers, and reported positive outcomes for uncontrolled asthma subject, both with high and low eosinophil levels. However, a specific diagnostic, beyond eosinophil levels, has not been discussed publically for this program.

The lessons learned in both late-stage anti-IL-13 programs have encouraged refinements that are reflected in the ongoing pivotal trials, both of which enroll uncontrolled asthma patients, are guided by companion diagnostics, and utilize exacerbation rates at one year as the primary endpoint.

Clinical development programs that span nearly 20 years for targeted biologics in asthma provide a useful data set to evaluate reasons for successes and failures. This analysis points to recent progress in IL-5, IL-4 and IL-13 antagonist programs that occurred when more precise definitions of "uncontrolled" asthma were available, biomarkers to identify potentially responsive subsets of the heterogeneous population were proven, and the right primary endpoints were found. Not all molecular targets were equally successful; IL-5 and Th2 pathways antagonists have progressed at different paces.

Clearly, the matching up of the most responsive asthma patients with the right drug, and clear definition of therapeutic outcomes, has worked best for IL-5 antagonists. The complex IL-4 and IL-13 pathways have proven more challenging targets. Pivotal trials for all three active Th2 pathway antagonists are underway, and review of study design details (vs. outcomes from completed studies) points to a focus on stratification of the uncontrolled asthma population by specific biomarker levels as the best bet to reduce exacerbation rates. There may also be FEV1 improvements shown by Th2 antagonist treatments in an uncontrolled asthma population that is distinct from the eosinophilic phenotype. It has been a long development road to find effective targeted biologics for the uncontrolled asthma population, but current advances in clinical research are now coming to fruition.

enrolling atopic asthma subjects have only returned positive results for mechanistic trials evaluating LAR and eosinophil levels. The trial outcomes for lebrikizumab and tralokinumab studies also show a mixture of positive and negative results. The lebrikizumab Phase II trial



# PCSK9 Inhibitors: What Does The Future Hold For This Controversial New Class?



**Natasha Boliter**  
Drug Analyst,  
Citeline

**Natasha Boliter** looks at the current approaches to PCSK9 inhibitors.

With the recent launch of Regeneron Pharmaceuticals Inc./Sanofi's Praluent and Amgen Inc's Repatha, which are both fully human anti-PCSK9 monoclonal antibodies, it is interesting to consider the other molecular approaches being pursued in the burgeoning PCSK9 inhibitor arena.

There are currently eight preclinical drugs and a total of seven in clinical trials with the associated mechanism of action (MOA) of 'PCSK9 inhibitor' in Pharmaprojects as of October 2015. The majority are at Phase I, while there are solitary compounds at both Phases II and III: Eli Lilly & Co's monoclonal antibody candidate and Pfizer Inc's bococizumab, respectively (Exhibit 1).

A total of 13 companies are involved in PCSK9 inhibitors research at preclinical and clinical trial stages. Most drugs are under development as solo endeavors; however, one compound is a collaboration between Pfizer and Halozyme Therapeutics, Inc., while Alnylam Pharmaceuticals is working on another candidate with Arbutus Biopharma and The Medicines Company. Affris AG has the largest number of compounds in the pipeline with four candidates, while Pfizer comes in a close second with three.

Pfizer, Eli Lilly and Alder Biopharmaceuticals each have humanized monoclonal antibodies in various stages of research. As aforementioned, Pfizer's bococizumab, which is being developed collaboratively with Halozyme, is furthest ahead at Phase III. Eli Lilly's humanized mAb started Phase II trials in July of this year while Alder Biopharmaceuticals' compound currently remains in preclinical development. Meanwhile Abeome's chimeric, monoclonal antibody candidate is also preclinical. These humanized and chimeric mAbs approaches differ from the fully human compounds of Praluent and Repatha and therefore could incur some issues related to safety and efficacy.

In contrast to the existing monoclonal antibody approach, Affris is developing four vaccine candidates that could have an advantage in terms of longer term protection and perhaps increased compliance due to the lower frequency of dosing. Two of these vaccine candidates, ATH-04 and ATH-06, entered Phase I trials this year while a combination vaccine is currently preclinical. Another preclinical PCSK9 vaccine candidate comes from Pfizer.

Pfizer also has an oral, small molecule compound in addition to a vaccine candidate. Betagenon, too, is developing its own oral small molecule, which has an additional

MOA of AMPK activator. Small-molecule approaches offer lower manufacturing cost advantages and in general, orally available tablet or capsule forms are preferred over injectables by patients. This preference for oral capsules and tablets can also lead to an overall increase in patient compliance, another advantage the small-molecule approach would have over the rest of the PCSK9 inhibitor treatments which are to be administered as injections.

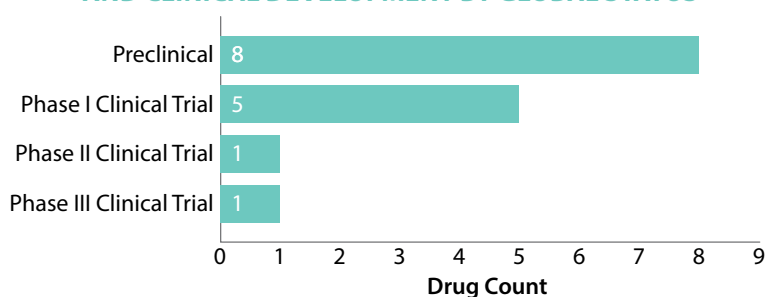
Looking at Pfizer's PCSK9 pipeline in particular, which includes a monoclonal antibody in the form of bococizumab, a vaccine and a small molecule candidate, makes it the most varied company portfolio in this space. If the PCSK9 target proves to be as efficacious as anticipated, having three different compound types in this area could be a very lucrative investment for the company.

A further alternative to monoclonal antibodies, small molecules and vaccines targeting PCSK9 comes from Alnylam in collaboration with The Medicines Company and Arbutus Biopharma. ALN-PCS is an RNA interference molecule, currently at Phase I, which disrupts PCSK9 production via the RNA mechanism rather than inhibiting the PCSK9 protein itself. This variation in the molecular types of the candidates is summarized in the biological versus chemical origins of the candidates.

There is a slightly larger number of chemical synthetic molecules currently in the development pipeline, which potentially means that the PCSK9 inhibitor class may not always be dominated by monoclonal antibodies. With plenty of alternatives to the antibody approach in the pipeline, there certainly looks like there is a lot more to come from the new PCSK9 inhibitor class.

For more data on  
PCSK9 inhibitors head  
to [www.scrip100.com](http://www.scrip100.com)

## EXHIBIT 1: PCSK9 INHIBITOR TREATMENTS IN PRECLINICAL AND CLINICAL DEVELOPMENT BY GLOBAL STATUS



Source: Citeline's Pharmaprojects, October 2015



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**Brian Yang**  
Editor,  
PharmAsia News

# China Health Insurance Sector Entering Fast Track

A complex mix of factors is shaping the development of China's private and public health insurance markets, with global firms now looking to tap into some of the opportunities. But with health schemes still in their infancy, there is a long way to go. **Brian Yang** reports.

What health issue is keeping company managers in China up at night? According to surveys conducted among middle management, the health issue of most concern is cancer. Employees want to know how to better protect themselves and their loved ones from getting the disease or being crushed by large treatment bills.

While expanding national health insurance schemes are providing some protection against illness, it is in this environment that private healthcare insurance is burgeoning in China, although the sector still accounted for only around 3% of the country's total insurance market in 2014.

Late last year, China's cabinet, the State Council, issued a policy to stimulate private insurance schemes to help meet increasing demand, with the coverage to include illness prevention, physical checkups, and specialty drug, device and diagnostic services. The policy also encourages companies to provide health maintenance, chronic disease management and consulting services.

Encouraged by such government policies and incentives, the market is expected to grow, and major global reinsurer Munich Re has now launched a program to help local insurance firms in China offer cancer insurance in the country.

The program, started last year, is sold to individuals and groups and is offered as a standalone product or co-sold with other policies, says William Bossany, general manager of Munich Re Health China. "We observe that the government is more actively promoting health insurance development, and the regulatory environment is now more mature for insurance companies to get into the health insurance business," he said.

## GROWING PAINS

Several traditional life insurance companies in China including Ping An and ChinaLife have also started offering health coverage, while existing players such as Taikang and Kunlun are expanding their product offerings.

But despite the promise, companies are struggling to make a profit and the policies largely target high-income earners, points out Lilly Han, VP of investment at Sunshine Insurance Group, another domestic insurer.

"Due to a relatively short history for private health insurance, Chinese mostly rely on the government

and social insurance for healthcare coverage," Han notes. Although a market-oriented economy has been developing for the past three decades, it takes longer for people to switch from relying on the public safety net to private coverage, she added.

Indeed, three years ago the government started encouraging commercial insurers to cover critical chronic health conditions including cancer, type 1 diabetes and congenital heart disease. The goal, however, was to share the fiscal burden as a social security shortfall starts to emerge, Han says.

Despite the profitability concerns, many health insurers are now testing the water and nurturing the market in the hope that more beneficial policies will help turn the corner, Han says. In addition, at the moment the China Insurance Regulatory Commission requires insurers to apply for separate licenses to supply life, property and health insurance schemes, which adds a further burden.

## EMERGING TRENDS

Low penetration aside, there are other challenges as well. There is a general lack of experience and knowledge in health management, even for major insurance players, and their health subsidiaries don't have the expertise, Munich Re's Bossany says. That's where the company sees a major role to play, and the key to succeed is to explore the main trends in China, he noted.

There are three major trends: one is a high desire to develop insurance products that are relevant to the local population, another is that people are health-conscious, and the third is that people are becoming more conscious of the environment and its relationship to health. For instance, due to a lack of actuaries and disease management data, Chinese insurers use a lump sum system for critical disease coverage.

Unlike in the US, where a coding system is widely used to quantify costs for disease diagnosis and treatment, China doesn't use any such approach. And the bulk of disease data are tightly controlled by large public hospitals, which are reluctant to share them for fear of potential scrutiny.

But prescription benefit management firms are now emerging in China to help select the most



effective treatment, Bossany said. Both multinational and local insurance companies are entering the area and work with local hospitals to help select the appropriate drugs. For individuals, they aid in choosing the right coverage.

### DATA SHORTFALLS

"Munich Health serves as a connection," the executive says. "The goal is to help choose the most effective treatment and contain the cost, but more information and data are needed from the market."

China has also seen a rapid increase in lifestyle- and environment-related diseases such as diabetes, cancer and chronic obstructive pulmonary disease (COPD). The discussion of COPD is especially notable as it was rarely discussed eight years ago when Bossany first came to the country.

Against this backdrop, there is still a lack of epidemiology data which are not captured in China. Health insurers thus issue policies without a clear picture illustrated by data, which in turn has deterred them from offering more customized products.

The situation is slowly changing, partially due to relaxed rules allowing physicians to practice in multiple sites, potentially offering the chance to gather more widespread data. Local insurer Ping An has set up its "Ping An Haoyisheng" service that is signing up such physicians offering medical services.

Mobile apps for insurance in general are also growing particularly fast in China, but the education is lacking, he adds. "The key points are access to physicians and drugs, and the internet is providing the solutions. More educational information on insurance will be required," Bossany predicts.

### MORE SERVICES COMING

In addition to issuing policies, health insurance companies are starting to offer health management services in China, with the more specialized firms further along in this process. Calling it another emerging trend, Bossany says that mobile health tools can help reduce costs and keep people healthy by reminding them to comply with treatment. Other such health management tools include systems to monitor blood pressure, measure glucose levels and weight changes.

Meanwhile, Munich Re is also working with local governments via partners to capture the momentum as authorities build out the nation's basic insurance to cover critical illnesses. Shanghai has plans to build an international medical center in the Hongqiao District, as part of which, in a bid to attract high-caliber talent, it is working to develop its medical insurance sector. The eastern cities of Hangzhou and Qingdao have also allocated funds to reimburse high-cost cancer and immunology treatments. Hangzhou in September released a list that includes 15 drugs under the city's critical condition reimbursement plan. Beijing is also taking some steps, such

as offering the elderly free blood pressure checks across community clinics in the capital.

As the government deepens public hospital reforms, state-run insurance offerings are also expected to expand to cover drug adverse effects, study subjects, long-term care and physician practice liabilities. In addition, China has plans to develop disability insurance to compensate workers who are injured or suffer accident damage while at work. Pilot schemes for long-term care insurance will also start, the government has said.

### POSITIVE FACTORS

Capitalizing on e-commerce opportunities, some health insurers have also started offering insurance products online. However, the products have to be simple, pointed out Bossany, and high-end insurance policies still have to be provided offline. As mid- and high-income earners start shopping around for more options and quality services, the health insurance market is expected to gain further traction, he notes.

The government's policy to reduce tax on health insurance premiums has provided another needed break for the development of the sector, noted Wang Yanping,

Unlike in the US, where a coding system is widely used to quantify costs for disease diagnosis and treatment, China doesn't use any such approach.



head of health insurance at Taikang Insurance Co. in an August forum held in Beijing. Under the change, corporate schemes will have a 5% tax reduction while individuals will be exempted from tax if the annual health policy premiums fall under CNY2,400 (\$378).

Some pharma firms are also tapping into the changing insurance environment. Another global reinsurer, Swiss Re, has collaborated with Roche and multiple domestic insurers such as China Pacific Insurance to market insurance coverage for cancer patients. Under the partnership, Swiss Re provides technical support on product design and pricing, and reinsurance support to Chinese insurers, while Roche provides training and expertise on cancer treatment plans. So far, the practice has been well received and 31 million policies have been sold, noted Roche Pharmaceuticals COO Daniel O'Day in September.



**Jung Won Shin**  
Korea Reporter,  
PharmAsia News

# Line Up: The Runners And Riders In Korea's Licensing Pack

Years of R&D effort seem to be paying off as South Korea's drugs gain stronger global recognition. With various novel therapies undergoing overseas clinical trials, the industry could pleasantly surprise many in the coming years. PharmAsia News' **Jung Won Shin** takes a look at the candidates.

The year 2015 will be remembered for many things, but for the South Korean pharma industry it will be the year that the potential of its domestic firms' R&D pipeline was realized through licensing deals.

The front runner was Hanmi Pharmaceutical Co. Ltd. which has inked a series of record licensing deals with multinational pharma. Hanmi's license and collaboration agreement, worth up to \$690m with Eli Lilly & Co. in March for the South Korean firm's Bruton's tyrosine kinase (BTK) inhibitor, HM71224 has surprised many skeptics and proven that it made the right decision by aggressively investing in R&D over the past decade.

In July, it inked an even larger licensing deal, worth up to \$730m with Boehringer Ingelheim, for the development and global commercialization rights, excluding South Korea, China and Hong Kong, to HM61713, a novel non-small cell lung cancer (NSCLC) therapy developed by the South Korean firm.

As more South Korean pharma and bioventures are looking to progress their pipelines to late stage clinical development through licensing deals and partnerships to fund costs and reduce risks, the industry is likely to see numerous additional deals.

"R&D expectations are still intact. Multinational pharma still need new innovative drugs," said Bora Chung, an analyst at the mid-size South Korean brokerage firm Dongbu Securities. "Domestic R&D projects still have a large potential to be licensed out and in fact, multinational pharma are believed to be quite interested in South Korean therapies."

One of the most anticipated licensing prospects is Hanmi's Quantum Project - epeglenatide (HM11260C, long-acting Exendin-4 analog), LAPS Insulin 115 (HM12470, long-acting insulin analog) and LAPS Insulin Combo (long-acting Insulin 115/Exendin-4 combination). As the three therapies are all in the leading group in development, they have a great potential to be licensed out, Chung said.

"We are seeking a license deal but there is no concrete development on the deal yet," said a company spokesperson in early June. According to Seung-Woo Kim, an analyst at the leading domestic brokerage firm Samsung Securities, a potential licensing deal for Hanmi's LAPS diabetes pipeline is set to exceed the value of the Hanmi-Boehringer contract.

Kim believes Sanofi is the best marketing partner for Hanmi's diabetes therapies as the French pharma giant can best assess its LAPS diabetes pipeline and most successfully commercialize the therapies. He estimated the licensing out value of the LAPS diabetes pipeline as \$1bn, a conservative figure considering its recent deal for HM61713.

"Sanofi is the second biggest player in the diabetes space, but has a relatively weak pipeline to prepare for the future. In other words, it will be able to use its strong diabetes marketing capacity in LAPS diabetes pipeline," Kim said.

Sanofi has launched *Toujeo* (insulin glargine) to cope with the patent expiration of *Lantus* and threats from biosimilars. But *Toujeo* has to compete with Novo Nordisk's already marketed *Tresiba* (degludec). Moreover, *Toujeo* and *Tresiba*'s attractiveness could diminish once Eli Lilly and Samsung Bioepis/Merck launch biosimilars of *Lantus*. As a result, Hanmi's once-weekly formulation LAPS Insulin 115 could come as an attractive target for Sanofi.

Hanmi is known to be seeking a package deal to license out the LAPS diabetes pipeline as it will be easier in terms of marketing to have both long-acting basal insulin and GLP-1 agonist.





Samsung's Kim also picked Dong-A ST's DA-9801, a herbal-derived diabetic neuropathy drug, as a promising candidate to be licensed out. For DA-9801, Dong-A is first trying to get US FDA guidance and seek investors for the program, Byoung-Ok Ahn, executive director of Dong-A ST's development headquarters told *PharmAsia News* in an interview in July.

"To do a clinical trial on pain is not an easy task and making investment by ourselves, especially in botanical drugs, involves too much risk. So we are looking for partners and are talking to some companies at the moment," Ahn said. "We are aiming to hold the FDA guidance meeting early next year, while in case of partnering, the earlier the better. We could reach a deal this year, but normally, it takes longer to reach a partnership."

In April, Dong-A ST said it had successfully completed a Phase II clinical study with DA-9801 in the US. The 12-week trial was conducted in 128 type 1 and 2 diabetes patients with neuropathic pain for at least three months prior to the study across 14 sites including Johns Hopkins University, and marked the first time for a South Korean herbal medicine to complete such a study after US FDA approval.

Analysts also noted a substantial commercialization potential for Chong Kun Dang Pharmaceutical Corp.'s R&D pipeline, particularly inhibitors of histone deacetylase 6 (HDAC6) CKD-504 and CKD-506, which are in preclinical stages, as well as cholesteryl ester transfer protein (CETP) inhibitor CKD-519 and beloranib, therapy for Prader-Willi Syndrome.

KDB Daewoo Securities's Hyun-Tae Kim expects the company to discuss global partnerships for CKD-504, therapy for Huntington's disease, and CKD-506, first-in-class therapy candidate for rheumatoid arthritis, once its toxicity data are available.

For CKD-506, preclinical results in Japan will be released in February next year, so the company is likely to seek a licensing deal with a global pharma based on the result. Its dyslipidemia therapy candidate CKD-519 is set to complete the Phase I study in Korea by 2016, so there is also a potential for a licensing deal for this therapy from the second half of 2016, Kim said.

A spokesperson at Chong Kun Dang said the company is reviewing the matter from various angles including licensing deals.

In the gene therapy field, Kyobo Securities's Kwang-Shik Park picked Kolon Life Science Inc. and ViroMed Co. Ltd. as the most feasible global licensing out prospects as they have marketable therapies in the Phase III clinical stages and are undergoing clinical trials in the US and South Korea at the same time.

Kolon is aiming to find global partners for its osteoarthritis therapy *Innova* (also known as TissueGene-C or TG-C) before it launches the drug in the domestic market.

The affiliate of Kolon Group is negotiating with five multinationals including Chinese and Japanese firms, and aims to submit its new drug application to the Ministry of Food and Drug Safety in December or early next year, said Gun-Young Lee, general manager of Kolon's strategy and planning team during a recent investors relations meeting in Seoul.

The company is also slated to begin a Phase III clinical study for *Innova* in the US early next year after receiving an approval from the FDA in May this year.

Unlike existing therapies, TissueGene-C just requires a single injection and has a relatively low production cost, so the company can more flexibly price the therapy in line with market conditions. So it is believed to be more competitive versus the existing cell therapies, said Dongbu's Chung.

ViroMed's VM202, a proprietary DNA based biopharmaceutical to treat ischemic cardiovascular diseases via therapeutic angiogenesis, is another prospective licensing candidate. A company spokesperson said ViroMed is now talking with a number of potential partners for VM202, without elaborating.

In April, ViroMed said it is moving ahead with plans to conduct a Phase III double-blind US study with its therapy, VM202-DPN, in a total of 477 painful diabetic neuropathy patients, following the recent approval for the study from the US FDA.

The company has also recently received approval from the US FDA to launch a pivotal Phase III clinical trial for its gene therapy VM202-PAD for chronic non-healing ischemic diabetic foot ulcers.

According to Kyobo Securities' Sung-Hwan Choi, the company's DPN therapy has an outstanding effect in terms of pain reduction and safety versus rival product *Lyrica* (pregabalin) and can treat the fundamental cause of the disease. DPN and PAD therapies have a potential to become blockbuster therapies with estimated global markets of \$6-6.9bn (KRW7-8tn) and \$3.5-4.4bn (KRW4-5tn), respectively.

Genexine Inc.'s GX-188E, DNA therapeutic vaccine for cervical intraepithelial neoplasia, is also worth taking a look at, said Kyobo's Park. At present, the company is proceeding with the Phase II study in South Korea and it has received approval to proceed with Phase II studies in four European countries.

Genexine's clinical development stages lag those of Versatis and Inovio, but its therapies are said to be superior in terms of treatment effects. Inovio's treatment vaccine for cervical intraepithelial neoplasia had a cure rate of 49% when its Phase II was completed, but Genexine's therapy has shown a 78% cure rate in the Phase I study, Park said.

GX-188E can also expand its indications to vulvar intraepithelial neoplasia, anal intraepithelial neoplasia and head and neck cancer, so the therapy could draw strong interest from global pharma firms, he added.

Kolon is aiming to find global partners for its osteoarthritis therapy *Innova* before it launches the drug in the domestic market.



Anju Ghangurde  
South East Asia  
Editor, *Scrip*  
Intelligence

# Pharma's Experiment With India's Borrow And Treat Model

**Anju Ghangurde** investigates the healthcare financing models gathered pace and popularity in India.

When a 52-year old Indian cart-seller of plastic toys was hospitalized due to a cardiac condition the first time, his family decided against going through with the treatment. They simply could not afford the costs involved.

But the second time round, when he was back in hospital, Arogya Finance, which offers medical loans to the "traditionally un-bankable" in India, ensured that he could not only go through with the required procedure but also need not be plunged into poverty after paying for his treatment. The vendor could repay Arogya in small monthly instalments.

Pharmaceutical companies are closely monitoring examples such as these as they link up with firms like Arogya to experiment with unique financing schemes both in the drugs and devices segment in India. Importantly, the trend appears set to spread to other Asian markets and potentially pockets of the developed world too.

Typically, under such financing schemes, patients can stagger payment of the actual therapy cost over a specified period via equal monthly instalments (EMIs), along the lines of similar schemes for consumer durables.

The chief of a US drug firm in India explained that there is a difference between the "ability" and "willingness" to pay for novel therapies and that more and more firms have begun to recognize the nuances.

"EMI schemes define the ability to pay much better and willingness to pay is about whether you are really convinced about the therapy. If you combine both well you get much better results. People have begun to understand this and you'll probably see more of such efforts," he told *Scrip*.

Optimal reach of such finance schemes for specialty products in a large and diverse market like India, some experts say, would require the involvement of large banks as well as non-banking financial companies.

Ajit Dangi, president and CEO of Danssen Consulting and a former director general of the Organization of Pharmaceutical Producers of India, told *Scrip* that while India has a large under-banked population (only 40% of the population hold bank accounts, he notes referring to a Reserve Bank of India report) things have significantly improved recently after the Government's efforts to incentivize the rural population to open bank accounts.

In addition, India's massive postal network, the

largest in the world, should be roped in for medicine and healthcare financing, he adds.

## EARLY MOVERS

MSD (as Merck & Co. Inc. is known outside the US and Canada) was perhaps among the first drug firms to ensure that its hepatitis C therapy, interferon alfa 2b, can be accessed in India at "cash flow" levels that a patient, typically with average means, may possibly be comfortable with, though the arrival of sofosbuvir is believed to have seen a scale back of the initiative.

Others, like Roche and Boehringer Ingelheim, are keen on financing models for their oncology products in India, while Medtronic offers financial assistance for its heart devices.

Roche says that with 80% of Indians paying out-of-pocket for healthcare, and cancer being the third-highest cause of mortality among non-communicable diseases, it recognizes that one of the key hurdles in access to optimal standard of care for cancer patients is the availability of funds.

It expects to launch a pilot program with a leading financial institution in India to create a financing option for *Herclon* (trastuzumab) as a part of its "The Blue Tree" patient support initiative.

"The aim is to reduce the monthly cash outflow and increase flexibility as much as possible for the applicant. We hope that such an offering will greatly increase access to treatment," Roche told *Scrip*.

More recently Dr Reddy's Laboratories linked up with Arogya to roll out a financing initiative for its hepatitis C therapy, *Resof* (sofosbuvir). Arogya finances up to 100% of the drug cost in this case and the maximum tenure allowed is 36 months, with the maximum loan up to INR200,000 (\$3,009). *Resof* is priced at INR 20,000 for a 28 pack.

Jose Peter, co-founder and CEO of Arogya Finance, a unique social healthcare venture, said that most of the expensive treatments reach only 10-20% of patients who could benefit, mainly due to challenges in awareness, availability and affordability.

"While all these issues need to be addressed, affordability is the single most important aspect in the decision-making process of the patient and the doctor/





care giver," Peter, a former CFO of the retail finance firm, Tata Motor Finance, told *Scrip*.

Arogya also noted how millions of Indians are unable to pay out-of-pocket for medical emergencies and often money is borrowed at high interest rates or organized by selling personal assets or simply ignoring much needed medical attention. This, it estimates, leads to 40 million people falling into poverty every year.

Arogya says it bridges this gap by offering loans at reasonable terms to those who lack formal income proof, in the process creating a "lifeline" for people pushed into poverty due to unexpected health shocks. It uses innovative risk assessment tools that allow it to finance people outside the formal banking system and its business model is structured in a way that it directly pays the medical bills of an individual to the hospital or the healthcare service provider.

Close to 800 patients across four regions and 10 Indian states have so far used Arogya's services. Such financing alternatives also trump the much publicized tiered pricing model, according to Peter. The latter he argues is "very good on paper" and starts off very well, but has not really been able to penetrate and scale. "It ends up with everyone getting the lowest price in the market."

## RELIABLE PEOPLE

Peter also highlighted some interesting trends that the Arogya model has seen. Critically, payback is almost certain in the case of such medical loans. "Our limited experience shows us that these are a very reliable people, although many people feel and think otherwise. About 90% of collections happen automatically, without our intervention; maybe a little telephonic intervention. I see no reason why this cannot scale.... it's just that somebody needs to be successful first."

The Arogya model, he said, is also moving beyond Indian shores. Financing efforts under Medtronic's successful 'Healthy Heart for All' initiative is now available in a "limited manner" in the South East Asian region.

"In the Philippines we ran a pilot in Manila; there are conversations going on about a similar one in Malaysia. They are talking about doing something in the US," Peter said.

Launched in 2010 in India, the Healthy Heart for All initiative provides financial assistance to implant heart devices such as stents, pacemakers and heart valves by partnering with hospitals. More than 100 Indian hospitals are part of Medtronic's access initiative that includes screening camps and patient counselling, besides financial assistance.

The initiative is said to have screened more than 100,000 patients, treating over 14,000 and disbursing in excess of 500 loans.

## GILEAD MODEL

Some experts, however, believe that a hybrid approach, including the "Gilead model", is the way forward to improve access to breakthrough, pricey therapies in the

developing world and point to the limited impact micro-finance firms can have in moving the access needle.

Last year Gilead Sciences Inc. entered into licensing deals with several India-based firms including Cipla Ltd., Zydus Cadila, Hetero Drugs Ltd., Strides Arcolab Ltd, Ranbaxy Laboratories Ltd. and Mylan Labs to develop sofosbuvir and the single tablet regimen of ledipasvir/sofosbuvir for distribution in 91 developing countries.

Dilip Shah, secretary general of the Indian Pharmaceutical Alliance, which represents leading domestic firms, says that a combination of both government financing and the "Gilead model" is the way forward in India.

"For the rich, one can add co-payment as the third element for access to expensive medicines," he told *Scrip*. He does not favor debt-financing for breakthrough pharmaceutical products and believes that it would leave patients at the "mercy" of the patent holder. "How can a government abdicate its responsibility to a private commercial entity?"

Micro finance companies can help, Shah says, but adds that that it does not resolve the issue of access and affordability, given their limited reach.

Others note how naysayers accuse pharma of profiteering and appeal to it for "compassion and understanding" while doing "precious little" to control spiraling costs across the spectrum of health care.

They underscore that medicine prices are a small subset of, and directly proportional to, the overall healthcare costs and that multinationals in India are caught between "a rock and a hard place" because this rationale makes little sense in an out-of-pocket market.

"That is why financing schemes were deemed as a clever way to encourage caregivers to buy these medicines whose prices cannot be reduced due to a variety of reasons such as reference pricing and parallel trade," an industry pundit with a foreign firm told *Scrip*.

He referred to how Gilead is probably the first company to break this paradigm with Sovaldi and hoped that many others follow its lead and that financing schemes "do not end up becoming the way forward" in India.

The industry pundit also believes that debt-financing schemes for breakthrough drugs are not a win-win for stakeholders and merely address the "symptoms" and does nothing about the "malaise." He had some radical suggestions to "build" access by reducing the cost of medicines including pressurizing governments around the world to deregulate and liberalize the health sector, reducing patent life and devising new ways to incentivize pharma R&D.

"The more the sector is opened up to market forces, the quicker we will see prices fall and service improve. Until then, we can only hope to come up with cleverer financing options for prices that are, in the long run, unsustainable," he maintained.

Only 40% of India's population have bank accounts.



**Donna Young**  
Washington Editor,  
Scrip Intelligence

# Could Washington's 2016 Actions Mean Upheaval For Biopharma?

**Donna Young** looks ahead to a potential merry-go-round of senior figures, continued biosimilar legal opaqueness and the modernization of the biomedical enterprise.

Over the next year, some big changes in Washington – the outcome of the 2016 presidential election; continued implementation and legal interpretation of the biosimilars law; the launch of the precision medicine initiative's one-million participant cohort study; and Congress' attempt to overhaul the US biomedical enterprise – could have major impacts on the American biopharmaceutical market, which could mean some upheavals, but also significant advances, for the industry.

With the US poised to elect a new president on Nov. 8, 2016, chances are Barack Obama's predecessor will replace most, if not all, federal chiefs, meaning there's bound to be some changes at the FDA, National Institutes of Health (NIH), Centers for Medicare & Medicaid Services (CMS), the US Patent & Trademarks Office (US PTO) and other agencies that have jurisdiction over, or interact with, biopharmaceutical makers.

Indeed, new FDA, NIH, CMS and US PTO leaders are likely to bring new ideologies and philosophies about the direction those agencies should take – especially if the White House changes political hands from a Democrat to a Republican, whose party has fought to end the *Affordable Care Act*, although most Capitol Hill watchers don't think the law could completely be dismantled, given many of its provisions are well underway.

It's a pretty sure bet, however, Health and Human Services Secretary Sylvia Mathews Burwell would be

replaced, given it has been the tradition for most newly elected presidents to bring in new cabinet-level leaders. It's highly likely Francis Collins would depart the NIH, given he's been the director since 2009 and at the agency itself for more than two decades – coming on board in 1993 to take over the Human Genome Project from James Watson, one of the 1953 co-discoverers of the molecular structure of DNA. Collins has said that after eight years, he thinks he would be ready to leave the NIH by 2017 – declaring it would be a good thing for the agency to get some fresh perspective from a new director, although he's also said he's uncertain what he would do if asked to stay on.

For the FDA, a new president could mean Robert Califf – the incoming commissioner – may have only a short stay at the agency, unless the new president, whether Democrat or Republican, decides to keep the former Duke University professor on for another year or two, or even longer, given the push in Washington to impose a six-year term for the food and drug regulatory chief.

Andy Slavitt, who has been acting as CMS administrator since March 2015 after the departure of Marilyn Tavenner, and Michelle Lee, who took over the US PTO in January 2014 as acting director, but was sworn in to the job in March 2015, are other agency heads whose time could be relatively short with the changeover of US presidents in January 2017.

It remains to be seen whether a new administration will take actions to rein in drug prices – a topic that's been a mainstay on the campaign trail for some of the presidential candidates, although most of the rhetoric has been coming from Democratic White House contenders former Secretary of State Hillary Clinton and Sen. Bernie Sanders (I-VT), with Sen. Marco Rubio (FL) about the only Republican making some noise about it.

While there's still a chance some actions aimed at tackling high drug costs could come out of the current administration before Obama leaves the White House – given some of the questions officials raised at a Nov. 20, 2015 invitation-only forum – a





new president could sign an executive order, if she or he chose to do so, to reverse any rules or regulations imposed before January 2017.

Once ratified, it's unlikely a new administration could change the course of the Trans-Pacific Partnership the US has negotiated with Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore and Vietnam, although that hasn't stopped some of the presidential candidates from insisting they would quash some of the free-trade agreement's provisions.

With Justice Ruth Bader Ginsburg in her 80s and two other Supreme Court justices not far behind, most in Washington anticipate the next president has a very good chance in their first four-year term of nominating at least one, if not more, candidates to sit on the high court – meaning there's the potential for significant ideological shifts in patent laws and other legal measures that could have broad implications for biopharmaceutical makers.

## BIOSIMILARS

With the March 6, 2015 FDA approval and Sept. 3, 2015 launch of Sandoz Inc.'s *Zarxio* (filgrastim-sndz), which is referenced on Amgen Inc.'s human granulocyte colony-stimulating factor *Neupogen* (filgrastim), the US biosimilars market officially got underway – five years after the American agency gained the clear authority from Congress to approve the products.

While Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, said she anticipated it would be an "incremental" process to achieve a robust biosimilars market in the US, she said she also expected a steady increase in other products joining *Zarxio* over the next several years.

Since March 2010, the FDA has been working to implement the provisions of the *Biologics Price Competition and Innovation Act* (BPCIA), including issuing proposed rules and guidance documents. Some in the biosimilars industry have contended that a controversial rule finalized in late October by the Centers for Medicare & Medicaid Services, in which all products referenced on the same innovator biologic will be lumped into the same Medicare Part B reimbursement rate, could have an impact on the future viability of the biosimilars marketplace. But what is expected to have some of the greatest influence over the future direction biosimilars take in the US is the interpretations of the BPCIA that come out of the US court system – with the Supreme Court anticipated to chart the ultimate path of the law.

In *Amgen v. Sandoz*, the US Court of Appeals for the Federal Circuit already has declared the "patent dance's" disclosure and negotiation procedure requirements are optional. But it also said that in a case where the biosimilar applicant does not dance, it must give the reference product sponsor notice 180

days before the first date of commercial marketing of the biosimilar, which can only be given after FDA has licensed the biosimilar product. Three other lawsuits are working their way through the court system – *Janssen Biotech Inc. v. Celltrion Inc.*, which was filed at the US District Court for the District of Massachusetts; *Amgen v. Apotex Inc.*, which was brought at the US District Court for the Southern District of Florida; and *Amgen v. Hospira Inc.*, which is being fought at the US District Court for the District of Delaware. The three cases are expected to eventually end up at the Federal Circuit, with the Supreme Court potentially deciding those battles' ultimate fate.

## PRECISION MEDICINE

The NIH is set to start the enrollment in 2016 for its precision medicine initiative (PMI) cohort study, and while the agency's goal is one million Americans, Collins has acknowledged that given the positive response from the public, there's the "potentially serious possibility" the ultimate number of participants could far-surpass that figure.

The purpose of the PMI cohort is to generate knowledge that can be applied to a whole range of health issues and diseases, according to NIH officials.

Unlike other large cohort studies, the data gleaned from the PMI cohort, which is intended to be a longitudinal project lasting over several years, will be broadly accessible to investigators across the country. For the biopharmaceutical industry, the data could be used to provide critical information about new drug targets for developing compounds and cures. But some have worried that the precision medicine efforts will all be for naught if payers don't catch up with the science – leaving patients without access to the therapies that are produced as a result of the NIH's and drug makers' work.

## BIOMEDICAL ENTERPRISE OVERHAUL

The Senate in 2016 is expected to act on a bill aimed at modernizing the US biomedical enterprise, with the intent of keeping the nation competitive and overhauling FDA regulations and NIH practices – legislation the House already has adopted under the so-called *21st Century Cures Act*. The trick, however, will be in reconciling the House and the Senate bills and coming up with the funding to pay for all of the provisions lawmakers put into the final legislation – something that is bound to be difficult in an election year.

The timing of the legislation also is colliding with the negotiations for the sixth round of the *Prescription Drug User Fee Act*. The FDA's greatest fears with both pieces of legislation, however, is being left with more unfunded mandates to handle, making it even more difficult to carry out its essential mission of approving new therapies and ensuring their safety.

For more Washington news, insight and interviews, the Capital Capsule can be found at [www.scripintelligence.com](http://www.scripintelligence.com)



**Ian Schofield**  
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# I Want You Back: Putting The Patient Into Policy

The European Medicines Agency has gone a long way towards involving patients in the regulatory procedures underlying new drug development and approvals, and patients now play a major role in contributing to scientific advice procedures and benefit-risk discussions. **Ian Schofield** reports.

There was a time when the patient barely got a look in where drug development was concerned. Pharma firms would identify a new substance with therapeutic potential in a disease like breast cancer or hypertension, develop a drug and get it approved. Patients were at the receiving end and had little or no say in how the drug was conceived, developed and evaluated. The regulators themselves had little idea of the impact their decisions and policies had on patients' everyday lives.

That's something of an oversimplification, of course, but as Sir Kent Woods, chair of the European Medicines Agency's management board told the European Commission's conference on 50 years of the EU pharmaceutical legislation in Brussels in September: "In the early days of drug regulation, the industry/regulator relationship was a private dialogue with either a marketing authorization decision or not at the end."

Things have been changing for some time though and an observer from the early 1990s would be astonished by the prominence of the patient role in today's regulatory landscape. Patients and consumers now contribute widely to regulatory discussions on new drugs through their membership of working groups and scientific committees at the EMA, and also have a say in how clinical trials are being designed. Sir Kent went as far as to say: "Now the patient is increasingly seen as the focus of decision making, and ultimately makes the decisions."

The EMA says that this greater interaction allows patients to discuss matters that affect them and helps shape the agency's decision-making process by illustrating the real-life implications of regulatory decisions.

A formal framework for interaction with patients/consumer representatives was established in 2005, and a permanent "Patients and Consumers Working Party" (PCWP) was set up in 2006. Patients and consumers also now have a place at scientific advisory group (SAG) meetings, where they can share their real-life perspective with the group and the pharmaceutical company concerned.

They can contribute to scientific advice meetings requested by companies to discuss matters such as the best way of designing clinical trials, they are formal members of the committees on advanced therapies, orphan drugs, pediatric medicines and pharmacovigilance, and they have representation on the agency's management board. And patients can review drug information prepared by the EMA, such as summaries of European assessment reports, to help ensure the information is clear and understandable.

So what has been the result of all this activity? According to Isabelle Moulon, head of the Patients and Healthcare Professionals Department in the EMA's Stakeholders and Communication Division, it has led to much greater transparency in the regulatory process, and has given those who work on drug evaluation at the agency a much better idea of the issues that patients face in their daily lives. "I hope it also brings trust in the work that we do," she said in an interview with *Scrip Intelligence*.

A significant step was taken late in 2014 when the EMA launched a pilot project to give patients a greater role in the activities of its scientific committee, the CHMP. Patients don't have a seat on this committee, but they do have input via the scientific advice, protocol assistance and other processes. And now, under the pilot, they can, on a case-by-case basis, contribute to oral explanations on benefit-risk aspects at CHMP meeting – for example where the committee wants to assess the impact of a new drug for an unmet medical need on the relevant patient population.

They don't have any decision-making powers, but their participation in these discussions is highly valued for bringing the patient perspective, says Moulon, who is also co-chair of the PCWP. Patients have been invited to these key sessions on three occasions to date: for Clinuvel's phototoxicity drug *Scenesse* (afamelanotide), Shire Pharmaceuticals' *Intuniv* (guanfacine) for ADHD, and Biogen Inc's *Tecfidera* (dimethyl fumarate) for multiple sclerosis. The discussion on Intuniv involved a young patient and a carer (a mother of a child with ADHD) and was a "very fruitful experience," Moulon says.



Moulon is quick to explain that while three cases may not seem a lot, the pilot is intended to be used only where the committee feels it needs direct feedback on the likely impact of its recommendations, and that the contribution that patients make through the SAGs is usually sufficient for the CHMP's purposes.

This all sounds very positive, but what about the patient's perspective? After all, pressure from civil society bodies has played a large part in getting patients' voices heard at the regulatory level over the past 20 years or more. François Houyez, treatment information and access director/health policy advisor at the rare disease organization Eurordis, says a great deal of ground has been covered since the EMA was established in 1995 and began talking to patients about issues like endpoints and surrogate markers for AIDS treatments. This, he says, created the basis for the agency to reflect on how to interact with other patient bodies in order to get their views and feedback.

He welcomes the pilot on greater patient participation, describing it as, in effect, the extension of an experiment that started in 2003 when the CHMP began soliciting the views of patients via written procedures and then videoconferences and meetings. The idea of the pilot, he said, is to invite patients to contribute in specific circumstances – for example, when the experts have doubts about the product in question, the scientific discussion is not straightforward, or the committee needs to know whether there are aspects of importance to patients that it has not considered.

Is it daunting for some patients to appear before the members of the EMA's inner sanctum? Not at all, says Moulon, explaining that there is a substantial support framework in place. "Patients are quite happy to take part. Of course we don't just put them in front of the committee. We explain the issues at stake, they are given documentation and the chance to discuss with the staff in charge of the procedure, and we have a lot of videos and training material on our website, as well as feedback from other patients."

Patients attending the meeting can also have a mentor who is a patient representative on the PCWP. Houyez, who has himself acted as a mentor, says: "After each meeting we have a debrief, talk about how it went, and whether the procedure needs to be adapted."

The decision has now been taken to extend the pilot, and to look at further ways in which patients can play a part. Other situations where it could apply, Houyez suggests, include conditional marketing authorizations (CMAs) where the CHMP has to decide whether to renew the CMA or recommend its conversion into a full approval, or where a request has been made to the CHMP for a compassionate-use opinion. The EMA will also draw up an interim report on the impact of patient involvement in these three cases to date.

Meanwhile, the drive to extend patient contribution in other ways is continuing, guided by the EMA-patient interaction framework, which was revised at the end of 2014 with the aim of building more transparency and trust into the system, notably by "capturing patient values and preferences" along the development pathway.

This, says Moulon, means "weighing in different ways the different benefits and different risks, so that you are better able to judge what you are prepared to accept in terms of risks versus benefits." This in turn will require new methodologies for obtaining information from patients, such as patient-reported outcomes and meaningful endpoints, and some of these are now being explored.

### EARLIER INVOLVEMENT

Efforts are also under way to get patients involved even earlier, for example through the scientific advice procedure, where questions like trial endpoints, the relevant patient population, trial design and so on are discussed, as well as via newer initiatives such as the EMA's adaptive pathways pilot and the PRIME (priority medicines) scheme for early identification of candidates for accelerated approval, which is expected to be launched in the first quarter of 2016.

"The earlier patients are involved the better," says Moulon. "This will ensure all stakeholders are working on the same basis. This early exchange also happens with health technology bodies, so we really need to ensure that all stakeholders involved in drug development and evaluation are discussing the same thing and are clear about what they expect."

Houyez agrees that more needs to be done. "Today there is a consensus that there should be a more systematic patient-expert dialogue, from the very beginning when a company proposes to develop a drug for a disease. The patient should be there, taking part in scientific advice and at all stages where decisions are made, and after the marketing authorization as well."

As part of this effort the EMA is planning to set up a "patient pool" from which the EMA can select the most appropriate patients to take part in a particular procedure. Usually patients have to be found at short notice – sometimes as little as two days – and this is not always easy.

"Of course we go through our list of eligible organizations but sometimes we have gaps and patients are not involved because we couldn't find any. The pool would allow us to have direct access to patients where we are short of time and don't find them through our lists," Moulon observes. The EMA is now looking at the technical aspects of setting up such a pool, as well as questions such as protection of private data. A call for expressions of interest will be launched, possibly in 2016.

For more on how regulators are using social media to involve the patient go to [www.scrip100.com](http://www.scrip100.com).





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# Can EU Member States Solve the Affordability Crisis Together?

New ways of working together may be necessary within the EU if drugs are to keep getting to the patients that need them the most. MEP Philippe de Backer talks to **Francesca Bruce** about the possibilities.

Prices for orphan and specialty drugs continue to spiral even though Europe's payers aren't getting any richer. But greater collaboration on pricing and reimbursement, like joint pricing negotiations or sharing services, could be the answer, argues Philippe de Backer, a Belgian member of the European Parliament belonging to the Alliance of Liberals and Democrats for Europe.

The fragmentation in Europe, he says, is making the affordability problem worse. This is especially true for smaller countries whose lack of negotiating clout can lead to "jacked up prices" or which can be ignored completely by pharmaceutical companies that don't see the value of bringing their drugs to a small patient population. De Backer acknowledges

that member states are keen to hold on to their sovereignty but thinks they need to start sharing practices and devising innovative ways to tackle the affordability crisis together.

On first glance, the idea of encouraging joint action on pricing and reimbursement from member states may seem unpalatable for companies, but de Backer is quick to point out that his vision is one that includes "buy in" for industry. "We have to make a distinction between those who are blaming pharma and biotech and accusing them of extorting government with their prices. This is about saying ok, let's make it easier for you to bring it to the market."

De Backer points to the Benelux joint pricing negotiations initiative. Belgium, The Netherlands and Luxemburg are developing a pilot that will see the three countries, and possibly others, join together to get better prices for orphan drugs. It is still early days, and the finer details of the pilot have not been worked out, but it will go beyond pricing talks. The countries involved will share data and analyze it together and set up joint registries to generate more information between them on how the drug works in real life.

The three countries will also look at coordinating "assessment methodologies" and will examine which innovative drugs will come to the market in the next few years. De Backer argues that the initiative is positive for companies. "They are trying to create a win-win situation for all stakeholders," he says. The member states get lower prices while companies get to reach a bigger patient population without having to go through the process three or more times. It is important to distinguish between the Benelux pilot and the initiative between Romania and Bulgaria to start purchasing high cost drugs together, says de Backer. The latter is simply about joint procurement with no buy in for companies.

However, de Backer wants to go further and is proposing the establishment of a Europe-wide fund for rare diseases. This would streamline health technology appraisals into one European process, which would



Philippe de Backer



provide the basis for European level talks on a differential price. The price each member state would pay could be calculated according to factors such as patient population, purchasing power or GDP to ensure that the lower income states like Romania and richer countries like Germany don't end up paying the same.

There are numerous benefits for companies, says de Backer. Firstly, the streamlined process would get the drug to a much bigger market a lot quicker and the firm would not have to go through multiple health technology appraisals and pricing talks. Designing and executing clinical trials could also get easier as companies only have to please one HTA authority, not 28 agencies with differing requirements. Other supporting measures that might be set up, like European registries to gather data, could also benefit companies.

De Backer thinks firms will "buy in when they understand the whole system." During discussions, he says, companies initially saw the proposal as a new form of joint procurement, but became more open to the idea when they saw the opportunities for earlier, faster and bigger market access. Member states, however, could be more difficult to convince. For example, Germany, like other countries, does not want to compromise its autonomy. Nor does it want to risk the quality of its HTA system. De Backer counters this saying that the quality of a joint HTA system should be equal to that of the best in Europe. He points out that reluctant member states could be convinced if the Benelux pilot is a success. Indeed, the Benelux pilot has attracted attention from other member states and a number are exploring whether they might join it.

The cross-border healthcare directive could provide member states with another opportunity to work together. It sets out a number of public health areas where member states can potentially co-operate, including the right for patients to buy treatment or services elsewhere in the EU and apply for reimbursement. De Backer says the implementation of this provision is very restricted and that a more flexible interpretation could allow member states to better share healthcare costs by "trading expertise." For example, patients from different EU states with a rare disease could receive treatment at a specialized center in France that is able to deliver care more cheaply while other countries could offer other services. "By really trading, centers of excellence patients may be treated elsewhere, the chain of care could be much better organized. It's not just about taking a pill, it's also about the side treatments and follow ups. These things can be shared between member states, but now they are duplicating the whole system and this is very expensive. We should take a pragmatic look at how we organize these things."

It is early days but de Becker believes member states will have to come round to the idea of working together on a European level as new waves of expensive new innovative drugs are coming. "All these member states are now confronted with patients on their doorstep asking why they aren't paying for new life-saving products. They face this criticism and the only way out is to think how this can be dealt with on a European level. Minds are changing; the Benelux initiative is one example of that."

On first glance, the idea of encouraging joint action on pricing and reimbursement from member states may seem unpalatable for companies.

## SPECIAL REPORT

# REIMBURSEMENT UNRAVELLED

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## How To Optimize Your Product's Path To Market

The many and varied European approaches to granting marketing approval for drugs can make the region a very complicated place for those seeking approval. NDA Group's **Thomas Lönngren** talks to *Scrip* 100 about how the company is helping those in the US to find the right path through Europe.

After years of research, and millions of dollars invested in developing a product, companies often find they are ill-equipped to hurdle the regulatory barriers on both sides of the Atlantic to actually get those products onto the market.

It is a daunting landscape and one that few know better than Thomas Lönngren, strategic advisor to NDA Group, Europe's leading regulatory drug development, pharmacovigilance and health technology-assessment (HTA) consultancy. Having worked for Sweden's health regulators, he is best known as a former executive director of the European Medicines Agency (EMA), where he was at the helm for 10 years.

In an interview with *Scrip*, he acknowledged that there are huge differences in Europe among individual member states and their stances when it comes to pricing and reimbursement. "Some are focused on cost containment, while others have developed sophisticated algorithms," Dr Lönngren noted, citing the quality adjusted life year (QALY) measure used by England and Wales' National Institute for Health and Care Excellence (NICE) and Germany's IQWiG, which evaluates the therapeutic benefits of new treatments, rather than looking at cost.

He also mentions the Swedish approach which emphasizes the importance of not only the medical effects of different treatments, but also the prevalence of the disease, current practices in the country and economic, social and ethical aspects – all very different approaches and a headache for companies looking to launch in Europe.

### More Similarities Than Differences

However, Dr Lönngren notes that "when it comes to the evidence that you need to generate from a scientific point of view there is more commonality when you have to demonstrate value. There are more similarities than differences – the differences being procedural and in the scope of assessment".

NDA, which has over 100 employed consultants, is very well-placed to help with how to assess a product's value and navigate in the procedural jungle. More than 25% are ex-European Union regulators and the Group, which has offices in the UK, Sweden, Germany and Switzerland, as well as the USA, can boast an advisory board made up not just of regulatory but also specific HTA experts.

The board includes some of the biggest hitters in the sector, from academia and the pharmaceutical industry, as well as several former members of the Committee for Medicinal Products for Human Use (CHMP), the panel responsible for preparing EMA opinions. Figures such as Ken Paterson, who was instrumental in setting up the Scottish Medicines Consortium, renowned health economist and NICE veteran Martin Buxton are included on the board.

It also includes Mira Pavlovic-Ganascia, former vice-chair of the EMA Scientific Advice Working Party and more recently deputy director at Haute Autorité de Santé (HAS), the French HTA authority. She was also coordinator of EUnetHTA's framework for relative effectiveness assessment and early scientific advice.

These experts provide strategic advice to help clients "with all areas of the regulatory lifecycle", Dr Lönngren states, be it in terms of scientific advice, during review of a marketing authorization application or at any stage post-authorization and market access. Those clients do include big pharma but NDA is finding that its services are very much in demand especially among smaller biotechnology firms on both sides of the Atlantic.

Dr Lönngren reveals that NDA now has over 150 clients in the USA and set up its office in Boston to be at the heart of the biotechnology sector where start-ups are pouring out from the likes of Massachusetts Institute of Technology and Harvard. Many of these smaller biotechs have concentrated their efforts on getting to grips with the regulatory processes of the US Food and Drug Adminis-



Thomas Lönngren

tration (FDA) and so have little knowledge of Europe and in some cases shown little interest.

He adds that much depends on where the management of these companies come from. If they are solely from the USA, "it is harder to explain the intricacies of European states where they have to deal with reimbursement," while if they also have foreign leadership, "they are more aware of the importance of payers."

### **US Firms Need Transatlantic Strategy**

Dr Lönngren is sympathetic to the plight of companies unaware of the pitfalls of doing business in Europe, noting that NDA also have over 30 members of staff who have FDA submissions and meetings experience. However, he believes that those who adopt a "transatlantic strategy" at an early stage, incorporating both FDA and EMA requirements at the outset, are the firms that are most likely to succeed.

He points out that the European system for market access and reimbursement is much more complex than the situation in the USA (in the EU, there are more than 90 different bodies at different regional levels making decisions on what drugs will be supported) and engaging early with these agencies is vital. Timely EMA input into a development program will also increase the chances of overcoming regulatory hurdles, Dr Lönngren stressed.

The USA is also increasingly becoming more important to NDA's business as more companies emerge from the Boston/Cambridge cluster and other significant American research clusters, boosted by the relative ease they have in raising funds compared to their European counterparts, he added.

As for the overall regulatory environment, Dr Lönngren notes that Europe is still some way behind its US counterpart when it comes to time to market, noting the FDA's various expedited pathways - priority review, breakthrough therapy, accelerated approval and fast track. These mechanisms have been employed to speed up the approval of around 60% of drugs submitted to the agency, compared to around 6% in Europe.

On this side of the pond, these expedited reviews do not really exist so the process of getting approval takes longer. However, he is encouraged by pilot schemes such as the EMA's adaptive pathways approach, which applies primarily to treatments in areas of high medical need where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine.



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### **Patients Playing A Bigger Role**

As for patients, Dr Lönngren believes that they are going to be playing a much more influential role when it comes to the regulatory lifecycle. He notes that patients in Europe are already heavily involved and the added value of their input to benefit/risk evaluations has enriched the quality of opinions given by the EMA's scientific committees.

He added that the views of patients are becoming more important at the initial stages of clinical development and are helping to shape new clinical endpoints, especially in the field of orphan diseases. Furthermore, "patient-reported outcomes have been getting more attention in the last three-four years," Dr Lönngren added, and that will continue, a fact small biotechs preparing to file need to keep in mind.

2015 was a bumper year for approvals with 45 new medicines given the green light by the FDA, representing a 19-year high. Some 93 therapies were recommended for approval in 2015 by European regulators, 11 more than in the prior year and Dr Lönngren expects this trend to continue.

"Thanks to our connections, we have very good insight into the pipelines of a number of biotechs," he said, and many are offering targeted therapies, which again require knowledge about regulatory systems that many companies do not have. Dr Lönngren is also hoping to see more research and products in areas where the pipeline has been pretty dry, notably CNS (especially Alzheimer's disease) and anti-infectives.

He predicts many more applications to be made in the coming years and feels NDA, with its vast expertise, is well-equipped to help them. NDA supported more than 38% of the new medicinal products that were approved in the EU in 2014 and feels that by providing its services as a gateway to Europe for US biotechnology firms, that figure may well rise.

[www.ndareg.com](http://www.ndareg.com)





**Francesca Bruce**  
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# How England Might Just Solve The Cancer Drugs Problem

**Francesca Bruce** takes a look at how the new English reimbursement system might address some of the problems with patient access to cancer drugs and how it may stack up against solutions elsewhere in Europe.

A sustainable way for oncology drug manufacturers to get their treatments to patients in England could finally be a reality soon. NHS England and HTA body the National Institute for Health and Care Excellence (NICE) have put forward their provisional plans for conditional reimbursement, which could help promising but “data lite” drugs that would have come unstuck under the old system.

A better system for reviewing whether cancer drugs should be funded on the National Health Service is overdue. A 2010 report by the then National cancer director for the Department of Health, Sir Mike Richards, found that the UK came tenth out of 14 high-income countries in terms of overall cancer drug uptake and 12th when comparing uptake of cancer drugs older than five years. The Conservative Party’s short-term solution, when it won a majority in the new coalition government in 2010, was a new Cancer Drugs Fund (CDF). This would run from 2011 to 2014 with a £200m a year budget (plus £50m for October 2010 to March 2011 ) and would provide access to drugs that were rejected by NICE, or awaiting or undergoing an assessment. A new value-based pricing system for innovative new drugs, to be ready for 2014, was supposed to make the fund redundant. But VBP never materialized and the fund will stagger on until 1 April 2016. Its total budget, set initially at £650m, will reach £1.27bn by the end of the fund’s life span.

The fund did improve access, says the National Audit Office’s (NAO) Investigation into the Cancer Drugs Fund. “The Fund has become part of mainstream cancer services – in 2014-15, it supported almost one in five of the patients starting a new chemotherapy treatment ... Between 2009 and 2013, use of new cancer drugs (those launched in the previous 5 years) increased in the UK relative to the average in other comparable countries,” said the report. But it did nothing to address the failings in the system, and the overspend prompted NHS England to slash numerous drugs from the list of funded treatments. Critics claim the CDF was a colossal waste of time and money. “It was never

sensible and did what everyone thought it would do; be shambolic and overspend. England has wasted five years not putting in place a sensible and sustainable policy,” said Eric Lowe, chief executive of Myeloma UK.

One of the big failings of the current NICE system is that it has difficulty recommending drugs for rare or end-of life cancers. Certainly, NICE has been less disposed to say yes to oncology drugs. According to the NAO’s investigation, NICE recommended or partially recommended 47 of the 102 cancer drugs it appraised. “This positive recommendation rate, 46%, was lower than the rate for other drugs, 81%,” it says. However, drugs rejected by NICE are routinely available elsewhere in Europe and without the help of a dedicated fund. For example NICE said no to Roche’s *Avastin* (bevacizumab) for several types of cancer, but Roche says it is widely reimbursed in Europe. It is funded in 26 out of 28 European countries for metastatic colorectal cancer and in 20 countries for metastatic breast cancer.

One issue that has lead NICE to say no is uncertainty as drugs for rare diseases and end-of-life conditions seldom come with the full data packages that HTA bodies would like to see. NICE decides whether a drug is cost-effective based a drug’s cost per QALY (quality adjusted life year) and treatments costing more than £20,000-£30,000 per QALY are not generally considered cost-effective, although NICE can use limited flexibility for end-of-life drugs to boost this up to £50,000 per QALY. The system works well to secure value for money for chronic disease treatments but uncertainty drives up the cost per QALY for drugs for end-of life or rare diseases so that they do not appear cost-effective.

The details for the new scheme are still out for consultation as *Scrip 100* goes to press and as yet are sketchy, but they do give NICE the opportunity to deal with uncertainty. It will be able to publish one of three initial recommendations around the time of marketing authorization: “recommended for routine use”; “not recommended for routine use”; and crucially “recommended for use within the Cancer Drugs Fund”.





The latter means that NICE will not have to reject outright promising drugs backed by data that is too weak to secure a positive recommendation. Instead, the company has up to 24 months to collect a pre-determined data set (which the company has to finance), during which time the drug is to be financed by an interim “managed access fund.” When the evidence is in, NICE will review the product again and consider the impact of the new data on cost-effectiveness. It will then decide whether to recommend it for routine funding. Cost-effectiveness thresholds look set to stay the same as the cost per QALY for these drugs financed by the interim fund “must have the potential to lie within the current thresholds specified by NICE.”

More flexibility to deal with uncertainty has improved access to the same medicines in other countries where authorities ask companies to gather more evidence, perhaps in the form of a new trial, observational data, or a registry. For example, NICE rejected Celgene Corp’s *Imnovid* (pomalidomide) for multiple myeloma, citing substantial uncertainty regarding its relative effectiveness. But according to Celgene, other countries found a way to deal with this uncertainty. The firm highlights a pilot “pay for benefit scheme” in the Netherlands that gathers evidence involving a “value-based price.” These types of agreements appear across Europe. Italy agrees to fund expensive cancer drugs on the condition that a registry is set up to accumulate more data, says Mondher Toumi, director of the European Market Access University Diploma at the University of Lyon, France. And in Germany, the G-BA, the body in charge of HTA assessments, can issue a “time limited resolution”, which means the decision is valid for a set period until more data is generated. In France a company and a payer agree a price and when there is uncertainty they set another higher price with the difference held in a bank account. If the company comes back with enough additional evidence to justify the better price, that extra money account goes to the firm. If not, it goes back to the health service. Toumi believes that something like this could complement a new conditional reimbursement system in England.

A lack of flexibility in dealing with uncertainty in England has been disappointing for firms and companies will likely be pleased at the chance to remedy this. The patient access schemes approved by the department of health to help companies improve cost-effectiveness for NICE could in theory include evidence generation to support a higher price later on. But by November 2015, 43 out of the 61 patient access schemes accompanying NICE recommended drugs involved simple discounts with other types of scheme seemingly being phased out. Wim Souverijns, general manager of Celgene UK and Ireland, says that the company would welcome the chance to commit to outcomes in relationship to prices and revenue generated by the products in question. “But feedback from

the department of health [has been] ‘don’t come back with any complex schemes, stick with the rebates and we are happy.’ It’s sad because we could do so many things together to measure impact and outcomes and to educate the system.” Souverijns believes a fantastic opportunity has so far been missed.

Another issue impacting the availability of cancer drugs is price. Industry’s critics claim it has been slow to adapt to a changing market that can no longer afford to pay whatever companies ask. Myeloma UK’s Lowe is unimpressed with the prices companies charge for end-of-life drugs. “They don’t listen to the market or to their customers. Up until now we’ve just accepted that we pay premiums for drugs that bring side-effects, marginal benefit and poor data... In no other industry does this happen.” But whether reasonable or exorbitant, UK prices are similar, if not lower than elsewhere in Europe. Roche’s UK prices have come under heavy fire. Nevertheless, they are not much different from what the firm charges in other countries, says Tina Bachelor the firm’s head of communications. “The difference is that other European markets don’t demand a big discount ... only in England because of financial pressures.” Roche had to give two discounts to make sure *Kadcyla* (trastuzumab emtansine), rejected by NICE and reimbursed in 15 other European countries, stayed on the Cancer Drug Fund’s list.

Other countries have other ways of reigning in spending if treatment could be costly. Common in Italy and France are volume caps, which see companies repay the health service if they sell beyond fixed quotas. In France, which Toumi describes as a low-price high-volume market, the more a company exceeds the quota, the bigger the rebate it gives, which can equate to a 50-60% discount on the drug. Another interesting idea, says Toumi, is that companies operate within a fixed budget based on assumptions about the money available and how many patients need treatment. The price is then set according to those assumptions and companies must repay any money if they exceed that budget. Under England’s new system, companies will have to come up with a “managed access agreement” based on what the drug will cost the NHS and the data collection agreement. But this is only for drugs entering the interim fund, and the impact on pricing strategies for drugs entering routine funding is unclear.

Meanwhile, big prices may be less palatable for England because it spends less overall on medicines than other comparable markets. The UK spends around \$400 per capita on pharmaceuticals, which is lower than spending in Spain, Italy, France and Germany, says Toumi. Germany and France spend around \$600 per capita, he adds. In 2011 the UK spent less on medicines as a percentage of GDP than Japan, the US, France, Spain, Italy and Germany, says the Office of Health Economics. The new system is unlikely to have any effect on the UK’s drug budget.

“England has wasted five years not putting in place a sensible and sustainable policy.”



**Cathy Kelly**  
Senior Writer,  
"The Pink Sheet"

# A Closer Look At The US Pricing Pushback

Critics of high prescription drug prices are making headlines in the US, and politicians on the presidential campaign trail and on Capitol Hill are talking about government-imposed price controls. But the real news may be unfolding behind the scenes in the private health insurance market, as **Cathy Kelly** finds out.

The financial challenges posed by the launch of expensive but highly effective specialty drugs over the past two years may have finally tipped the scales toward a more serious pursuit of innovative performance-based risk sharing contracts between manufacturers and payers.

Under such contracts, drug pricing is tied to pre-specified outcomes demonstrating the value of treatment. Agreements may also include guarantees that drug utilization will be limited to certain types of patients to control payer costs. In return, payers provide preferred coverage and may also offer assistance with other access challenges, such as medication adherence.

Although they've been talked about for years, performance-based risk sharing arrangements have not moved very far beyond the pilot stage in the US. One challenge to widespread adoption has been the lack of detailed information on how effective they are. Other obstacles have included defining outcomes, determining who would measure outcomes and agreeing on how they would be measured.

Nevertheless, as manufacturers face serious resistance from payers concerned with the prospect of covering highly priced drugs that could be prescribed very broadly the incentives are there to slog through some of the difficulties and execute these kinds of arrangements.

It's worth taking a closer look at what's been going on in that area. The introduction of Gilead Sciences Inc's hepatitis C drug *Sovaldi* (sofosbuvir) in early 2014 at a list price of \$84,000 per treatment regimen galvanized payer demands for value-based contracts. *Sovaldi*'s launch was followed in October 2014 by the introduction of Gilead's follow-on hepatitis C drug, *Harvoni* (sofosbuvir/ledipasvir), at a comparable cost.

It wasn't until competition to *Harvoni* and *Sovaldi* came out in December of 2014, in the form of AbbVie Inc's *Viekira Pak* (ombitasvir/paritaprevir/ritonavir plus dasabuvir), that payers were equipped with better leverage to negotiate innovative deals with the manufacturers.

Although the most highly publicized aspect of those contracts have been big discounts in pricing – Gilead estimates average discounts to *Harvoni* approached

50% in 2015 – they also involve assurances that patients achieve a sustained virologic response (SVR), the accepted surrogate for a cure.

For example, national insurer Cigna Corp. announced a performance-based contract in early 2015 that provides exclusive formulary coverage to *Harvoni* for hepatitis C patients with genotype 1 premised on patients achieving SVR. Cigna has been one of the more proactive payers pursuing outcomes-based agreements.

Although innovative payment arrangements are accelerating among commercial payers, performance-based contracts have not taken hold in one of the largest markets for hepatitis C drugs, Medicaid, due to manufacturer concerns they don't fit the traditional drug rebating model in that program.

The current approach to Medicaid rebating is based on per-unit pricing, which is a model that performance-based contracts attempt to move away from. Manufacturers are required to pay a rebate to Medicaid programs that is the greater of either 23.1% of the average manufacturer price for brand drugs, or the difference between AMP and the best price offered to any purchaser of the drug.

In the hopes of encouraging outcomes-based contracts in Medicaid, the Centers for Medicare and Medicaid Services recently took the unusual step of contacting manufacturers of hepatitis C drugs to better understand their concerns. The goal is for CMS to develop guidance on how such contracts could square with the rules regarding Medicaid rebates.

## PCSK9 INHIBITORS AND HARVARD PILGRIM

If the challenges of covering the costly hepatitis C drugs constituted a wake-up call for payers and providers, the advent of the super cholesterol-reducing PCSK9 inhibitors have further heightened concerns. As a result, performance-based contracts for the PCSK9s are already coming to light.

Harvard Pilgrim Health Care announced in November that it had reached a "first in the nation" type of contract with Amgen Inc. for its *Repatha* (evolocumab). Under the arrangement, Amgen will provide pricing discounts to the insurer if patients taking the cholesterol-lowering



drug fail to reach certain outcomes measures or its utilization exceeds predetermined levels.

The payer described the deal as containing “a pay for performance guarantee through which Amgen is taking financial risk by providing the health plan with an enhanced discount if the reduction in LDL levels for Harvard Pilgrim members is less than what was observed during clinical trials.” Patients will also need to reach the acceptable level of cholesterol reduction within six months of use.

The firms declined to divulge the utilization levels that would trigger an additional discount, as well as the amount of the discounts. However, Harvard Pilgrim will have responsibility for collecting and analyzing outcomes and utilization data.

In return, Repatha will get a “preferred formulary position” at the health care system relative to competing PCSK9, *Praluent* (alirocumab), which is marketed by Sanofi and Regeneron Pharmaceuticals Inc. The contract may be followed by others like it for Repatha. Amgen said it continues to “engage constructively with other payers to enable patients to have access” to the drug.

Harvard Pilgrim’s announcement about the contract follows Amgen’s public declarations about its interest in negotiating performance-based contracts. In a late-August release on the approval of Repatha, Amgen suggested it would respond to payer concerns about the drug’s \$14,100 annual list price by pursuing contracts that tie Repatha’s net cost (after rebates) to its value in the relatively narrow population it is indicated for.

Amgen’s comments were noteworthy because they signaled a new level of support in the industry for such contracts. In another example, Novartis AG invited innovative coverage arrangements for its heart failure treatment, *Entresto* (sacubitril/valsartan), around the time the drug was approved in July.

Like the PCSK9s, *Entresto* would be a chronic-use drug, possibly taken for life, and payers worry it could be prescribed more widely than its current labeled indications. However, its annual list price of \$4,560 is considerably lower than the \$14,100 and \$14,600 prices for Repatha and *Praluent*, which has kept it out of the news as another example of egregious pricing by the biopharma industry.

Novartis has said it is interested in pursuing outcomes-based reimbursement models for *Entresto* that are similar to a pilot coverage program underway for its multiple sclerosis therapy *Gilenya* (fingolimod). Such an approach might involve a lower wholesale acquisition cost, company executives said, but Novartis would receive additional payment if a certain cost-reduction threshold is met.

No performance-based contracts for *Entresto* have been announced to date. However, a technology assessment of the drug by the independent Institute for Clinical and Economic Review modeled the potential savings that might result from a performance-based contract.

In the risk-sharing arrangement envisioned for *Entresto*, payers would not have to pay for the drug for six months if a congestive heart failure hospitalization occurs following initiation of treatment. If a patient on the drug dies of cardiovascular disease, any payments made in the previous six months would be refunded.

Express Scripts Holding Co. expressed support for a performance-based payment approach for *Entresto* during a recent public meeting. The PBM’s chief medical officer, Steve Miller, commented during the National Cancer Comprehensive Network Policy Summit held in September that: “Novartis is very interested in doing a pretty simple approach to outcomes-based [contracting] for heart failure, especially because these patients end up in the emergency room so often. This is truly a remarkable drug, so we’re excited about entering into something like that.”

However, he noted that defining patient endpoints is a key part of any risk sharing arrangement and that many outcomes-based contracts in the past have failed because of disagreements between manufacturers and payers over measuring endpoints. “The reality is that every single one of these experiments has collapsed under its own weight because the administrative overhead ate up the potential savings.”

Further complicating such a contract with a stand-alone PBM like Express Scripts is the fact that it would not have in-house access to medical claims and would have to make arrangements with its payer clients to track outcomes like hospitalization rates.

## POLICIES TO PROMOTE OUTCOMES-BASED CONTRACTS

The US Pharmaceutical Research and Manufacturers of America (PhRMA) is advocating regulatory changes that might facilitate innovative contracting, such as relaxing FDA restrictions around communications between biopharma manufacturers and payers about the value of treatment.

It is promoting the idea that manufacturers should be able to provide more information to payers and other health care professionals before a drug is approved, to allow them to better prepare for the expense of a new treatment. After a drug is approved, manufacturers should be able to proactively go to payers and discuss outcomes that are not necessarily part of the approved label, such as a reduction in hospital stays, according to the organization.

PhRMA also advocates the establishment of a safe harbor from federal anti-kickback penalties for manufacturer-run medication adherence programs. Such programs are being discussed more frequently as part of outcomes-based contracts. The changes being sought can be accomplished administratively and without legislation, PhRMA believes, which may improve prospects for achieving them.

Although they’ve been talked about for years, performance-based risk sharing arrangements have not moved very far beyond the pilot stage in the US.



**Francesca Bruce**  
Senior Reporter,  
Scrip Intelligence

# How To Get Ahead In Canada's Private Market

**Francesca Bruce** looks at what companies need to know about the Canadian product listing agreements to get ahead in the market.

Canada's private pharmaceutical market is a big and growing opportunity for companies, but taking a piece of the pie is not as easy as it used to be, says Arvind Mani, director of market access and policy research at PDCI Market Access (PDCI), a Canadian pricing and reimbursement consultancy. Private insurers are starting to worry about cost containment and according to PDCI, product listing agreements could become a prerequisite for companies selling expensive specialty drugs.

Canada was the world's 10th biggest pharmaceutical market in 2014. The private sector generated nearly 60% of drug spending, or \$CDN16.7bn. Private insurers took \$CDN10.3bn, with the rest generated by out-of-pocket spending. But insurers are no longer the "free ride" for companies that they used to be, says Mani. Traditionally they have been reluctant to apply the kind of cost savings seen in the public sector, but they are now starting to voice concerns about the cost of some drugs. Specialty drugs account for 2% of claims, but 26% of drug spending, according to the 2014 Drug Trend Report from Express Scripts, Canada's second biggest PBM (pharmacy benefit manager, which adjudicates claims).

One big insurer, Manulife, says it is concerned about the increasing number of high priced drugs entering the market, and it wants to start a debate about whether "more expensive drugs generate sufficient additional health outcomes to justify the higher cost." It cites as an example Amgen's anti-cholesterol PCSK9 inhibitor Repatha (evolocumab), which it says can cost up to \$CDN7,300 per patient per year. "That's 80 times the cost of the generic version of the cholesterol drug Crestor. When you consider that about 40% of all Canadians between the ages of 40 and 59 have unhealthy levels of cholesterol, the scope of the financial impact grows," it says.

One way insurers are taking on big prices is with product listing agreements. Manulife looks set to roll some out – it recently announced its DrugWatch program, under which it will place very expensive drugs "on watch" and gauge their value using information made public by the Canadian Agency for Drugs and Technologies in Health (CADTH), Canada's HTA body. It will then "work with companies" to find the best possible price. The program signals a dramatic shift ahead in the way private insurers operate, says Mani. "If you are a specialty drug maker the world is going to be just a bit more challenging in Canada. If you are non-spe-

cialty it is status quo for time being." However, he adds that private insurers are also addressing the chronic diseases that affect drug spending and productivity, which may open the door to new collaborations on disease management.

Previously these agreements were largely limited to the public sector, and were negotiated between companies and the pan-Canadian Pharmaceutical Alliance (pCPA), Canada's key public reimbursement body. However, PDCI's Private Payer PLA Survey, available at no cost, and to which 19 companies and eight payers responded, suggests that 2015 has so far been a big year for these agreements. Mani believes that the agreements will only become more important in the near future.

There are two types of agreement: non-outcomes-based deals and outcomes-based deals. The former include volume agreements, price rebates and caps on expenditure, while the latter depend on some sort of clinical measure and are similar to the risk sharing deals or coverage with evidence development deals seen in Europe.

Companies responding to the survey flagged up two outcomes based deals, which PDCI found surprising, says Mani. These certainly won't be the norm, he predicts. In the short-term, or over the next two or three years, the bulk of deals are likely to be non-outcomes focused. This is because private insurers, aside from the three biggest providers, lack the systems to keep track of the outcomes that outcomes-based deals inevitably require. "From a payer perspective, the simpler the better, they don't want to put a lot of systems in place. If you look at the agreements in the public sector, they are simply a rebate cheque that the manufacturers provide to the drug plans on a quarterly basis." However, it isn't clear what might happen over the longer term, especially where specialty drugs are concerned. As Mani points out, all payers will want to ensure that some measures are in place to show the product has a meaningful impact.

## HOW TO STRIKE THE BEST DEAL

So how can companies prepare for the deals? According to Mani, many will already have experience through negotiating deals with public payers in Europe and private insurers in the US. However, he warns that insurers are likely to come up to speed very quickly when they see potential in the agreements.



## EIGHT NEED-TO-KNOWS ABOUT CANADA'S MARKET ACCESS SECRET

The pan-Canadian Pharmaceutical Alliance (pCPA) has become a formidable market access force in Canada since its inception in 2010. Its decisions are make or break for pharmaceutical companies targeting the market, and changes on the horizon mean its importance is set to increase. So, if you are not yet up to speed on what the pCPA is and what it does, now is the time to brush up.

### 1. What is the pCPA?

The pCPA is a pricing negotiation body for brand name drugs and generics comprised of all of Canada's provincial public drug plans. It sits alongside Canada's health technology appraisal bodies and negotiates a price for drugs with manufacturers based on the drug's success at HTA level.

It was created in 2010 as a way for all of Canada's provinces to pool their negotiating power and thereby improve overall market access in the country. By 2013, the system was working so well from the point of view of the provinces that they committed to reviewing and negotiating every product which was assessed by the national HTA bodies.

### 2. How does it work?

Once a drug has been through HTA assessment, it is usually reviewed by the pCPA within a month. The pCPA first decides whether or not it is going to negotiate – depending on the HTA outcome, the alliance sometimes decides it is not worth negotiating at all, and sometimes negotiations are still left to individual provinces. The alliance will then decide which province is going to lead the negotiation. The lead province and pharma company thrash out a price, and once the price is agreed a letter of intent is signed, and the rest of the provinces make a final decision on whether or not to fund the drug.

### 3. Why is it important?

Incredibly for such a young body, PDCI's Mani describes the pCPA as "the most important step in obtaining public funding for branded prescription drugs." This is especially true for manufacturers who make drugs aimed at anyone over 65, those who are covered by Canada's public drugs plan.

### 4. What are the benefits/risks to pharma?

Pricing negotiations in Canada have been simplified. Before, pharma companies would have to carry out separate negotiations for each individual province, now it is all done in one go. However, industry has

raised several concerns, these include: no obligation for provinces to accept negotiated deal, a lack of transparency, lack of consistency, and no mechanism for pharma to challenge the system.

### 5. What can pharma do to ensure success?

Pharma must secure a positive HTA outcome. Those who receive one of the top two recommendations from the CDR have a much quicker, easier negotiating process with the pCPA than those whose clinical and cost-effectiveness is in doubt. Those who get the worst HTA outcome are unlikely to be allowed to negotiate at all.

Proposals need to be clear, concise, and straightforward to implement. If more innovative pricing strategies are suggested companies need to ensure that they are practicable. Companies should not quibble with the pCPA about any points they were unhappy with from the HTA process. As far as the pCPA is concerned, that part of the system has been concluded and its job is to negotiate on the terms laid out by the HTA.

### 6. How does it compare with other global systems?

For anyone who is more familiar with Germany's AMNOG system, this is probably one of the closest global comparisons. In the German system, IQWiG (Germany's HTA body) reviews a drug giving it a rating of additional benefit; this is then either confirmed or changed by the G-BA (which has the final say in the early benefit assessment). Once a rating is confirmed, the manufacturer then negotiates a price with the GKV-Spitzenverband, the body which represents Germany's statutory health insurers. In theory, as in Canada, the better your IQWiG/G-BA outcome, the better price you can negotiate.

### 7. Who has been through the pCPA process successfully?

Some of the first products to go through the pCPA included: Boehringer Ingelheim's blood thinner *Pradaxa* (dabigatran), Bristol-Myers Squibb's melanoma drug *Yervoy* (ipilimumab), Alexion Pharmaceuticals Inc.'s orphan drug product *Soliris* (eculizumab), and Novartis AG's COPD drug *Onbrez* (indacaterol).

### 8. Who are the pCPA losers?

Two negotiations that have ultimately been unsuccessful were both for type 2 diabetes: AstraZeneca PLC's *Byetta* (exenatide) and Novo Nordisk A/S's *Victoza* (liraglutide). All the pCPA's documents say is that the negotiations were closed because agreements could not be reached.

Because a deal will likely lead to lower end prices further down the line, Mani advises companies to make sure they win the best possible entry price, which is regulated by the Patented Medicine Prices Review Board (PMPRB), Canada's patented drug pricing regulatory body. In the past this was the price that private insurers generally paid while the public payers negotiated it down. However, these deals mean that private insurers will also regard it as a starting price, particularly for specialty drugs.

Firms should also be prepared that the final price may not remain confidential. In the public sector, both government and companies remain tight-lipped and are bound by confidentiality agreements. However, in the private sector there are more stakeholders, including pharmacy benefit managers and consultants, involved in talks, which means that it is harder to make sure everybody keeps quiet, especially if there are potential conflicts of interest. In addition, there may be a need for more transparency in

the private sector to ensure that the insurer passes on the savings to the patient.

Although the bulk of PLAs will likely be negotiated for costly specialty drugs, Mani says other drugs stand to benefit too. They could help firms secure a competitive advantage over rivals by negotiating preferential sequencing in the treatment pathway.

Mani also advises companies to tailor their approaches according to the insurer. For example, smaller carriers don't have the capacity to negotiate more complex deals. Meanwhile, the three biggest insurers, which account for 60% of the market, have much more expertise and impact.

It is also likely that the industry trade group, Canadian Life and Health Insurance Association, will continue to push for a single national price for each drug, and for closer ties with both the provincial pCPA and the federal PMPRB. "If or when those alliances are established, the Canadian reimbursement landscape will become a lot more interesting for all new products," says Mani.





# Guiding you all the way



NDA supported **over 38%** of the new medicinal products that were **approved in Europe in 2014**

With 100 experts and a unique Advisory Board covering every therapeutic area, NDA can support small as well as large, multi-national pharmaceutical companies with strategic advice and operational support to get their medicines to market and keep them there.

NDA's support spans right across a development program, from early development to lifecycle management of a medicinal product, incorporating regulatory affairs, health technology assessment, pharmacovigilance and quality assurance.

**NDA - Let's bring medicines to the world**

Regulatory  
Affairs

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# An Overview of NDA

***NDA contributed to over 38% of the new products that were approved in Europe in 2014***

## Our company

NDA Group is a leading global drug development consultancy providing small as well as large, multi-national pharmaceutical companies with strategic advice and operational support to get good medicines to market and keep them there. Based in Boston, London, Munich, Stockholm and Zurich, NDA offers a range of professional drug development consulting services that spans from early development phase to lifecycle management of a medicinal product. These services incorporate regulatory affairs, health technology assessment, pharmacovigilance and quality assurance. Clients are supported by a team of over 100 consultants and a unique Advisory Board comprising industry experts, many of whom are ex- European Agency and FDA staff.

## Our heritage

NDA was born from the idea that there must be a way to minimize the unnecessary delays suffered by good medicines because of poor communication and understanding between industry and regulators. In 1997, Dr Lars-Helge Strömquist, then a well-established and experienced industry veteran, saw the challenges pharmaceutical companies faced in getting their drugs to the market, and keeping them there. He recognized that companies, large and small, face similar issues in understanding the regulatory requirements, and that they lacked experienced hands-on support to make it happen. There are many complexities, from creating the right data generation strategies required to prove a drug's efficacy, safety and quality through the way that data should be presented to the regulators, right up to the challenges of getting pricing and reimbursement agreed in each country.

Dr Strömquist brought together a team of experts from across the industry in Europe, and today, current CEO Johan Strömquist, continues building on this first class team to best support clients.

## Our team

The NDA team is divided into two areas designed to support a diversity of client needs:

### Expert consultants

NDA has a team of more than 100 employed consultants who actively advise and provide day-to-day support to a broad range of pharmaceutical companies, across therapeutic areas, at various stages of drug development. The consultants have all been selected for their in-depth knowledge of regulatory affairs, pharmacovigilance or health technology assessment, their excellent client skills, and their ability to deliver first class projects.

### NDA Advisory Board

The consultancy team is supported by the NDA Advisory Board, and consists of a mix of some of the biggest names in the industry, many of whom have been involved in designing the regulatory and HTA systems in place today. The Advisory Board provides strategic advice and unbiased second opinions to pharmaceutical clients during part of, or the complete end-to-end drug development life cycle.

For more information: [info@ndareg.com](mailto:info@ndareg.com)

## The value we bring

NDA offers independent and objective advice and support across the complete lifecycle of a drug to ensure optimal regulatory outcomes in Europe and the US, as well as achieving the right price in key markets.

In Europe NDA has successfully supported clients since 1997 contributing to over 38% of the products that were approved in 2014. Our services fall into three main categories:

### Development

NDA can support with any strategic advice and planning required to get your drug ready for application and your team ready for regulatory and pricing and reimbursement discussions

### Application

NDA has the skills and expertise to provide both strategic and operational support to get a drug ready for approval with the US as well as European Agencies

### Post authorization

Once your drug has gained regulatory approval, NDA can provide support and advice to make sure your

## Xellia Sees USA As Land Of Opportunity With Bedford Buy

The Danish anti-infectives manufacturer Xellia Pharmaceutical has recently expanded in the US with the acquisition of a former Ben Venue Laboratories site. CEO **Carl-Åke Carlsson** talks to Scrip 100 about the prospects for this new facility.

It is fair to say that eyebrows were raised by the news that Xellia Pharmaceuticals had agreed to acquire the former Ben Venue Laboratories manufacturing site in Bedford, Ohio, USA. The plant has been in the headlines for all the wrong reasons and been closed for two years, but industry observers believe that the Denmark-headquartered group is the ideal company to bring Bedford back to life.

Xellia is buying the plant from Hikma Pharmaceuticals which acquired the Bedford site from Boehringer Ingelheim last May, for \$225m upfront. The German company decided to cut its losses on its troubled US generic injectables business, having closed Ben Venue in December 2013 following a series of compliance problems.

Hikma never resumed operations at the plant but Xellia, one of the world's leading manufacturers of anti-infectives, plans to begin commercial production at the site within just 24 months. Speaking to Scrip 100, chief executive Carl-Åke Carlsson believes the Copenhagen-based firm has the expertise and focus needed

to meet this demanding target.

Xellia certainly has the pedigree with over 100 years of pharmaceutical industry expertise and Carlsson notes that it has been fermenting antibiotics since the early 1950s. The company was a highly successful active pharmaceutical ingredient (API) manufacturer and since it was spun-out from Alpharma in 2008, it has become a specialty pharmaceutical company focused on anti-infective products.

The transformation from being a provider of bulk API to producing therapies for multi-drug resistant infections and becoming a world-leading supplier of vancomycin and colistimethate sodium (CMS) has been boosted by its \$700 million acquisition by Novo Nordisk in May 2013. Carlsson says that getting such a prestigious industrial powerhouse as the new owner of Xellia, and one with a long-term outlook, meant that the group could start to look at expanding its global manufacturing footprint in addition to its facilities in Denmark, Croatia, Norway, Hungary and China.





Carlsson eyed the USA as the place to be, a logical step given that Xellia works with all the major pharmaceutical companies there and “it makes sense to be closer to our customers.” The first step was the purchase of Fresenius Kabi’s lyophilised (freeze-dried) vial manufacturing facility in Raleigh, North Carolina in July 2014 but Xellia needed a bigger plant to meet the growing demand from customers.

The search for additional manufacturing capacity led to Bedford. Under the terms of the agreement, the financial details of which have not been disclosed Xellia has acquired substantial parts of the site including several new manufacturing units for sterile injectables. It intends to recruit around 170 new employees across a range of departments including manufacturing, supply chain, distribution, quality, engineering, human resources and finance at the Bedford site over the next couple of years.

In January 2013, having stopped production in 2011, Boehringer entered into a consent decree with the FDA, allowing it to manufacture critical cancer drugs that were in short supply.

Carlsson notes that while there are four pharmaceutical manufacturing buildings on the site, Xellia’s strategy is to focus on the two newest ones. In terms of the consent decree, he added that the company has been working closely with the FDA regarding Xellia’s future plans for the facility which involve the production initially of just one product - vancomycin. “This is a smart way to do it,” he notes.

Furthermore, the response from Xellia’s partners (and there are over 500 of them in over 70 countries) has been very positive. “While some thought we were slightly crazy, most think it is a great move,” Carlsson said. He stressed that the USA “is a very important market for us, and as a region with a strong manufacturing heritage and a uniquely skilled and specialized workforce, Bedford, Ohio is an ideal location to expand our manufacturing capabilities.”

Together with the production site in Bedford and new US headquarters in Raleigh, “Xellia is in a great place to help make critical anti-infectives available to the patients that need them,” Carlsson claims. He also noted that at a time when the world is contemplating a post-antibiotic era, with policy makers looking at the best way to tackle antimicrobial resistance, Xellia is becoming an increasingly important player, and not just in providing product.

From being a company that only produced bulk API just five years ago, “we are changing focus,” Carlsson told *Scrip 100*. This includes developing new finished dosage forms using Xellia’s APIs, and if required, APIs sourced from its wide network of suppliers.

To complement the company’s dry powder fill and freeze-dried vials for injectable delivery, it is also developing innovative proprietary delivery systems and formulations for topical, inhaled or injectable administration either in-house or through partnerships.



Xellia also offers contract manufacturing services and custom synthesis for clinical trial material supply.

“We are also looking for new compounds to bring to the party,” Carlsson adds, noting that Xellia is actively seeking to acquire additional parenteral anti-infectives to expand the portfolio as well as developing novel antibiotics effective against MDR Gram-negative bacteria. The latter is a development project with SINTEF Materials and Chemistry in Trondheim and the Statens Serum Institut in Copenhagen, supported by a grant from the Research Council of Norway.

Xellia has been operating in a tough market, and Carlsson acknowledges that “it is hard to be western-based manufacturer” that has to battle for market share with the low-price producers in the likes of China and India. However, the company’s constant emphasis on quality through every stage of its anti-infectives development, from manufacturing to distribution, makes it stand out from the competition.

“We have an excellent reputation among our partners who see the additional security that we offer,” he says. All of Xellia’s production sites are subject to continuous approval by the FDA and local authorities and in the past five years, the firm’s facilities have been inspected 20 times - all inspections were passed.

Technical excellence is also married to sound business ethics and the company, which employs over 1,200 people, states that “we value integrity and openness, and are committed to a high level of compliance in all aspects of our work. As a global business with international customers it is vital that we have a uniform set of standards that can be applied to our business regardless of the country in which we operate.”

There are interesting times ahead at Xellia as it builds what Carlsson calls “a stronger, more connected US operation” and aims to get more life-saving medicines to its customers and patients. The next two years promise to be fascinating for customer, industry observers and the wider industry.

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# Indian CMOs Hit Their Stride

Is the general uptrend in India's contract manufacturing segment sustainable, despite some sentiment-dampening run-ins with regulators over compliance concerns? **Anju Ghangurde** takes a look.



**Anju Ghangurde**  
South Asia Editor,  
Scrip Intelligence

CARE Ratings, an Indian credit rating agency, earlier this year said that it expects the Indian contract manufacturing segment to grow at a compound annual growth rate (CAGR) of around 17-18% till 2018.

Navroz Mahudawala, managing director of Candle Partners, a boutique investment banking firm, told *Scrip* that the current growth rates are "definitely sustainable" for the next four-five years as they are still on a low base.

He maintained that Indian firms in the space such as Dishman Pharmaceuticals and Chemicals, Syngene International and Piramal Enterprises are still generally small compared with their global counterparts and the low base effect will make the growth sustainable.

Others, like SV Veeramani, president of the Indian Drug Manufacturers' Association, believe that the growing contract manufacturing industry could also provide a burgeoning opportunity for small and medium enterprises.

This comes as the Indian government is considering incentivizing firms that are compliant with Schedule M [which specifies good manufacturing practice (GMP) requirements in India] to upgrade to WHO GMP compliance levels with the help of soft loans. India's department of pharmaceuticals has previously indicated that it hopes to cover around 500 medium scale pharmaceutical enterprises through soft loans of up to INR40m per unit at a concessional rate of 5% per annum under the Pharmaceutical Technology Upgradation Assistance Scheme. The latest on this could not immediately be ascertained, though.

CARE Ratings also noted that drugs worth about \$85bn in potential annual sales in the US are expected to go off patent during 2014-20, forcing a shift in focus to price competitiveness and cost effective manufacture. This is likely to boost the prospects of Indian contract manufacturing firms.

Besides, with the Indian Contract Research and Manufacturing Services (CRAMS) industry gradually moving up the value chain and players investing in better technology and higher capacities, manufacture of value-added products for biotech and specialty therapy areas may also be outsourced to India.

Piramal's pharma solutions division, a key player in contract development and manufacturing, recently said that it hopes to become the market leader in the development and manufacturing of antibody drug conjugates (ADCs) over the next five years. To this end, it is making focused investments at its current site in Grangemouth, UK and has acquired a specialized ADC fill/finish site in Kentucky, US.

It also noted that despite the increase in development targets for ADCs, the global contract manufacturing sector was still "significantly under resourced" with just a handful of players with experience and even fewer with the "required regulatory accreditations."

## INTEGRATED SERVICES

Experts like Mahudawala believe that integrated service models that follow clients' molecules across discovery, development and manufacturing could be critical to success, though there may not be too many examples of that happening as yet in the Indian context.

"The upside of this model is when the EBITDA [earnings before interest, taxes, depreciation and amortization] margins can move towards 30-40%+. Except Divi's [Laboratories] frankly there is no Indian player who has yet managed to demonstrate sustainably these margins as yet," he said.

One such firm offering integrated services, Syngene, said that it has evolved from essentially being a pre-commercial manufacturing service provider to an integrated provider of end-to-end discovery, development and commercial manufacturing service for NMEs.

"We believe this wide scope of activities is the primary distinguisher for us. In addition, our business model allows multiple entry points for a client to engage with us across the discovery, development and manufacturing continuum and enables forward integration opportunities," Syngene's CEO, Peter Bains, said.

## SENTIMENT

But despite the upbeat tenor, experts admit that the recent run-ins with the FDA by a few Indian firms had affected client sentiment for Indian contract manufacturing.

Mahudawala, though, says that there have been fewer cases of issues with API units – the bulk of the run-ins have been with formulation units and those using sites for their own captive businesses.

Bains believes the larger issue is that the quality standards that Indian contract manufacturing companies follow have not been "rightfully projected" to the global audience.

"There are many Indian companies, including Syngene, who have consistently cleared the FDA inspections without any 483s. However, these do not get reported thereby creating an imbalance in the quality projection of Indian companies," he said.



**Bowman Cox**  
Editor,  
"The Gold Sheet"

# A Day Of Reckoning For Aging Facilities: Is It Time To Invest In Change?

With its acquisition of Hospira, Pfizer joins those struggling to eke out a profit from aging sterile injectables facilities without shutting them down for badly needed upgrades. Meanwhile, flexible, modular next-generation facilities are looming. **Bowman Cox** looks at the possibilities for the industry's golden oldies.

The quality troubles that Pfizer Inc. acquired with Hospira Inc. are symptoms of an aging, shortage-prone sterile injectables infrastructure that the pharmaceutical industry is preparing to resolve with new, more agile manufacturing facilities. Pfizer is piloting a modular oral solids manufacturing system that could be adapted for sterile injectables, even as other manufacturers work to resolve the challenges of the aging sterile injectable facilities they recently acquired.

Meanwhile, Amgen has taken a modular approach using single-use systems with a new biologics manufacturing facility in Singapore. For its part, Hospira has been finding ways to upgrade its facilities without incurring downtime as it races against shortages.

## CAUGHT IN A SQUEEZE

Pressured by price-cutting healthcare providers and generic competitors and by the profit demands of their own shareholders, generic injectables manufacturers have been cutting the cost of goods to the point of triggering shortages. Maik Jornitz, president of G-CON Manufacturing Inc., explained in April at the Parenteral Drug Association's 2015 annual meeting.

As facilities age, they fall prey to increased risk of quality issues, unit operations breakdowns, supply problems and yield losses, he explained. Periodic upgrades of these facilities, often spurred by regulators, require extensive downtime and high remediation costs, but only provide temporary relief. Also, because older facilities are less automated, their quality can be highly dependent upon the retention of experienced personnel, he noted.

PDA's task force is exploring solutions that would involve retrofitting such operations with quicker, more flexible closed systems that are less risky and that rely on advanced process analytical technologies. It's also looking into encouraging regulatory authorities to reduce their scrutiny of such changes so as not to inadvertently prevent them. But for these retrofits to proceed, manufacturers will need to justify their expense, given the low margins of generic injectable drug products.

Pfizer said it expects the Hospira acquisition will deliver \$800m in annual cost synergies by 2018, with a significant portion expected from manufacturing. How Pfizer expects to achieve those manufacturing savings while modernizing the infrastructure is a question the company has not yet answered.

Now that drug shortages have precluded the type of extended shutdowns the industry has historically used to repair its aging infrastructure, Hospira has adapted by cleverly interweaving bite-size upgrades into its plant operations.

## LIVING ON BORROWED TIME

With a nearly 50% US market share of specialty injectables like morphine, lidocaine, meropenem and propofol, Hospira has to approach facilities modernization with great care, global engineering VP Craig Johnson told PDA's post-conference Aging Facilities Workshop. "It doesn't give us many freedoms to potentially take a facility down for an extended period of time because the impact of that could be rather significant," he said.

If you're a sole supplier of a product on drug shortage, "at the end of the day, you're probably running your manufacturing operation at 100% utilization just to keep up with demand or just to try to keep the product off the drug shortage list. So guess what? That makes very little time for an engineering guy to come in and say, 'I've got \$20m approved. Let's go and take this line out of service for six months and do this great modernization project.'" However, he added, "With some very careful planning, modernizing aging facilities can be done and done well without impacting drug supply."

Johnson, who came to Hospira in 2012 after a career at Merck & Co, GlaxoSmithKline PLC and Novartis AG, acknowledged that he would be the first to say, based on prior experience, that there is no time for upgrades during annual maintenance shutdowns.

On the surface, it doesn't seem ideal to add a modernization project when the plant is racing 24 hours a day to complete preventive maintenance activities, he



said. At Hospira, the risk is particularly severe. “Most of our manufacturing facilities are running flat out, so our shutdown windows are very narrow and we’re under a tremendous amount of pressure to get back up and running right away.”

The company has nevertheless found some creative ways to slip architectural upgrades into those shutdowns, Johnson said, “and I’ll tell you, it’s some of the biggest bang for the buck ... and if you can stagger them every six months through shutdowns, it’s a great move.”

Another strategy common in the industry is to build up inventories before going offline for upgrades. But this can be difficult if there is a shortage, because the line probably is already operating continuously, he said. And if a competitor goes off market or stops operating and a shortage begins, “then you’re running flat out immediately, no questions asked.”

If there is room in the manufacturing area, Hospira will install new equipment while the old equipment is operating, then during a shutdown connect it to the manufacturing line. But because there’s not a lot of space in its plants, Hospira often resorts to building an expansion area for the new equipment.

The company stages these modernization changes to give each at least a short window to work through any “hiccups.” Start too many at once, and any little issue could very quickly impact drug supply. While obtaining funding for upgrades takes work, Johnson said that, “for me, getting capital approved is not the secret to modernizing facilities.” The bigger challenges are around scheduling the projects and their regulatory approval processes.

It would be a lot simpler to just build new facilities, whether at a green field site or as an expansion of an existing facility, Johnson said. “However,” he added, “it’s typically more expensive and typically takes much longer.”

Johnson was asked if Hospira had already missed its best opportunity to improve production, which the questioner suggested would have involved investing in upgrades before exceeding a 70% utilization threshold. “It’s common across the whole industry that you would tend to push some of the manufacturing areas toward the higher end of that utilization, higher than they should, and as you know, that leaves very little time for modernization,” he replied.

“If you’re looking across the manufacturing facility, and across every single line you’re at 99% utilization, you’re living on borrowed time ... and that’s a lesson that I think has been learned by a lot of companies across the industry,” he added.

### PFIZER TRIES AGILE APPROACH

Pfizer in March piloted a more agile approach to building facilities for manufacturing oral solid dosage forms, and that also could apply to sterile injectables, Pfizer technology and innovation VP Michael O’Brien told the PDA annual meeting.

The idea is to truck or ship manufacturing pods and small-footprint continuous manufacturing equipment for installation in warehouses where they could quickly begin producing development, clinical and commercial product.

Pfizer’s Portable, Continuous, Miniature and Modular, or PCM&M, model provides the flexibility needed to produce to demand rather than to forecast, O’Brien said. Because it does this, Pfizer endures significant expiry consequences, he said. “We burn probably \$500m to \$1bn a year of inventory. Why? Because we’re trying to meet the demand, but we have to go to forecasts and when demand falls short of forecast, we’re in trouble.”

Pfizer could rapidly deploy pod farms around the world to develop, manufacture and distribute pharmaceuticals regionally, O’Brien suggested. And those farms could include pods from multiple manufacturers, he suggested. “It’s an industry journey, not a Pfizer journey by any stretch of the imagination.” The more companies that use them, the lower their cost will be, he noted.

For the oral solid dosage prototype facility, G-Con built the pods, GEA built the continuous manufacturing equipment and they assembled everything in a warehouse at Pfizer’s Groton, Conn., site. He told attendees it cost \$15m for the prototype, including detailed design, fabrication and assembly. With wider usage, the cost could drop toward that sweet spot where it would be affordable for manufacturers while still profitable for the vendors, he said.

Moving pods from one site to another is feasible, though the estimated expense of \$300,000 to \$500,000 “is not trivial,” he said.

### THE NEED FOR SPEED

George Wiker, VP with M+W US Inc., the US unit of the high technology engineering and construction company M+W Group, described some strategies for saving money and time by acquiring aging facilities for expansion projects, rather than building in greenfield locations.

He gave examples where firms accelerated their schedules by repurposing a former biotech facility, a former cathode ray tube television assembly plant and an old warehouse. His main point was to move quickly by scoring the sites on a scale of one to 10 based on preset defined criteria. And rather than performing detailed assessments of existing equipment like pumps and boilers, he said to just keep anything less than five years old and replace anything more than 10 years old. The key is to focus rigorously on net present value, he said.

Wiker said he’s a big believer in the type of modular approach that Pfizer prototyped. Manufacturers can build the pods while they’re preparing the building. By taking the brownfield approach he described rather than the typical greenfield strategy and relying on modules, manufacturers can reduce project time from the 24 to 28 months traditionally required to just nine to 14 months, he said.

With some very careful planning, modernizing aging facilities can be done and done well without impacting drug supply.



**Bowman Cox**  
Editor,  
"The Gold Sheet"

# Data Integrity Inspections Go Global

As FDA and other regulatory authorities learn how to conduct the type of inspections that have put a spotlight on data integrity failures in India, they warn that no manufacturer, no matter where they're located, is immune from this potentially devastating issue. **Bowman Cox** reports.

Data integrity inspections that have disrupted pharmaceutical exports from India to the US and Europe are spreading to exporters in China and other countries, as well as to US and European manufacturers that may be unprepared for them.

Even as US FDA authorities warn global manufacturers against complacency, there are indications that they remain vulnerable to the type of inspections that have troubled manufacturers based in India.

Consultants are doing a brisk business advising pharmaceutical companies on how to ensure data integrity in their manufacturing operations, which starts with recognizing that they are no longer functioning in a paper-based environment.

Those who fail on data integrity can remedy the situation, but the process of restoring the faith of FDA, other regulatory agencies and business partners is difficult and fraught with uncertainty.

## NO TIME FOR COMPLACENCY

FDA remains focused on the data integrity issue, Tom Cosgrove, director of the Office of Manufacturing Quality in FDA's Center for Drug Evaluation and Research compliance office, told the Parenteral Drug Association's PDA/FDA conference.

Cosgrove said that nine of the 13 warning letters his office had issued so far this year raised data integrity issues. He added that more than half the firms the agency placed on import alert through August of this year for failure to meet drug GMP requirements had data integrity issues.

The percentage of firms placed on drug GMP import alert that have data integrity issues has steadily risen from zero to 56% over the past five years.

Cosgrove warned the audience against complacency. "There is a line of thinking in many places, both sometimes in the agency and certainly within industry, that these kind of data integrity violations are other peoples' problems and they are reflective only of the developing markets, that there are a certain kind of firm that you see data integrity and certain kind of firm that you don't, and for well-established, large pharma companies, this is something we don't have to worry about."

"Well let me just say from experience, and recent experience, this is not true. And the biggest pharma company and the most sophisticated company out there needs to be really thinking hard about this and doing deep-dive audits," he warned.

Without giving specifics, he said data integrity issues are threatening major firms' new drug applications, including for breakthrough therapies. "This is frustrating and disappointing. And we're working hard to help the firms work through the problems, and it is yet to be seen whether it is successful or not. So do not walk away from this topic thinking this is someone else's problem."

## NO INDICTMENT OF ANY ONE REGION

The rash of recent FDA data integrity inspection findings concentrated in India is a function of inspectors' backgrounds, not an indictment of the region's ethical standards. Speaking at the PDA conference, Rebeca Rodriguez, a national drug expert investigator in FDA's Office of Regulatory Affairs, suggested two factors may be at play. One is the agency's establishment of foreign posts, which "provided a tool that we previously did not have of having access to the facilities in a more efficient way."

The other is the increased involvement of FDA investigators who have backgrounds in chemistry, the pharmaceutical industry and information technology. "You may have investigators that were previously chemists and some of them may have worked in industry, so they are more aware of these practices or how to find them because that's their background. If you are a chemist, or you're a computer person, you know how to look into these things."

### EXHIBIT 1: PERCENTAGE OF FIRMS PLACED ON DRUG GMP IMPORT ALERT THAT HAVE DATA INTEGRITY ISSUES

2011	2012	2013	2014	2015*
0%	24%	33%	41%	56%
* Through to end of August				

Source: FDA



FDA's Brooke Higgins, a senior policy advisor in the office Cosgrove directs, agreed that people who have the best training and the best background for identifying data integrity issues "might be stationed in a specific post overseas. ... So it's hard to say, well, it's this country that has the most data integrity issues. It's probably more related to the investigator going out and focusing on those areas."

Pressed to ascribe data integrity observations to local quality culture, Rodriguez demurred. "We want to be careful about what kind of conclusions we draw from inspection trends, because I don't really think that you can make that kind of correlation, to say it's the culture of a particular country."

She noted that when she started at FDA, one of her first big cases concerned data integrity issues that came to light in the wake of the US generic drug scandal. "Being a chemist, I knew how to look into this data," she said. "It was an advantage."

Mathew Thomas, director of FDA's India office, told the Drug Information Association annual meeting in June that "one of the questions that we get frequently asked is: why are we doing so many inspections in India? And of course the other question is: are you singling out India?"

He made the agency's position clear: "We do the inspections across the world and in the US using the same standards. There is no need to single out any country." The reason why FDA is inspecting more in India is simple, he said: India is exporting more products to the US. But there are other reasons why the agency has found more data integrity violations there.

Because data integrity failures are not a function of the regions where they've been found in the past, they're likely to be found anywhere in the future, warned FDA's top official in China.

Asked about the type of data integrity issues that have arisen primarily in India, Leigh Verbois, director of FDA's China office, told the DIA meeting that FDA is looking to inform not just local industry but also the regulatory authorities in China about the importance of ensuring data integrity.

She emphasized that FDA has begun staffing up its office in Beijing now that agency employees can obtain swift approval to work there. "Our visas have been getting issued relatively quickly compared to what had happened before," she said. FDA staff members are receiving visas within two weeks of applying for them. Previously, it took two years. "We're able to not only hire people that we feel are really good investigators and staff, but also get them on the ground in China much quicker."

## INDUSTRY GUIDANCE DRAFTED

Inspectorates have now begun publishing industry guidance on data integrity. MHRA provided guidance early this year, and FDA has updated its question-and-answer guidance, which dates back to 2004, with three

data integrity questions and answers. FDA's Cosgrove told the PDA/FDA conference the most important answer "explains in relative detail why trial injections are really disfavored and should essentially never be done."

Meanwhile, the World Health Organization has published for comment a 35-page draft guidance document on good data and record management practices. MHRA expert inspector Ian Thrussell led a team that won approval from a WHO expert committee in October 2014 to draft the guidance "in view of the increasing number of observations made during inspections regarding data management practices," the draft guidance says.

## INDUSTRY'S TRAINING JUST BEGINNING

As regulatory authorities hammered on data integrity in inspections over the past several years, industry consultants have grown increasingly busy training the global pharmaceutical industry on data integrity. Consultants like Monica Cahilly are jetting around the world to put an end to the industry's data integrity crisis. But when she and other consultants speak on data integrity, the feedback they are getting from their audiences suggests that pharmaceutical manufacturers have a long way to go to achieve compliance.

When Cahilly asked attendees at the PDA/FDA conference and at a Product Quality Research Institute conference the following week for a show of hands, very few indicated that they had established data integrity programs at their companies.

When Crystal Mersh, president of Quality Executive Partners, Inc., surveyed attendees of the international GMP conference, they expressed confidence in data integrity for their paper-based processes, but not for their electronic processes.

This is a point that Cahilly emphasized in her remarks at the PDA/FDA meeting: It's just human nature for control strategies to lag behind, she said. So it's no surprise people cling to paper-based methods long after they've switched to computerized systems, printing out reports rather than running queries through audit trail information or metadata.

"When you walk into a company in 2015 and they say to you very proudly, 'we are a paper-based company,' and you look around that company and you're hoping to just see abacuses and slide rules, and instead you see computers, now you know you have a big risk. That is a high risk company, because that company is using technology that they haven't really figured out how to properly use, and they're probably not, they're definitely not reviewing those original electronic records from a scientific perspective to see what's happening as it relates to patient safety and product quality."

When inspectors from FDA, MHRA and the growing ranks of international inspectorates that know how to check the integrity of electronic systems arrive at such companies, they may be in for a rude awakening.

The percentage of firms placed on drug GMP import alert that have data integrity issues has steadily risen from zero to 56% over the past five years.





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in the U.S., allowing it to meet the growing demand for sterile injectable products locally, as well as address drug shortages of critical life-saving antibiotics globally.

Building off Xellia's stronghold in the anti-infective market and high quality manufacturing platform, the company is committed to developing its product portfolio beyond generic injectables, actively seeking to acquire additional parenteral anti-infectives and focusing R&D investments within inhalable and injectable product technologies, which not only improve patients' quality of life, but crucially save lives.



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# 2016: A Big Year For Tackling Drug Resistance

**Lord Jim O'Neill** explains why he believes the opportunity to fight antimicrobial resistance in 2016 must not be wasted.



**Lord Jim O'Neill,**  
Chairman, Review  
on Antimicrobial  
Resistance

In the summer of 2014, entirely out of the blue, I received a call from the British Prime Minister's office asking me to lead a Review into Antimicrobial Resistance (AMR) – an issue that I then knew little about, and which seemed superficially unrelated to my background in economics and finance. The ambitious task set of me – to recommend and build support for a global package of action to tackle AMR by the summer of 2016 – has meant that the 18 months since, spent immersed in this difficult topic, have been a steep but very fulfilling learning curve.

On one hand, the solutions to the problems of AMR now seem increasingly clear to me, and the progress made by the global community during 2015 in coming together around the issue appears truly remarkable. On the other hand, there are still huge challenges to overcome, and a long way still to go in crafting workable, meaningful solutions to the main elements of the drug resistance problem.

As you might expect of an economist, I have come to view the complex problems of AMR through a simplified lens of supply and demand: the need to ensure that we have an adequate supply of new antibiotics for the future, and to cut back on excessive and unnecessary demand for them.

On the supply side, it is vitally important that we make progress towards new market models that are capable of sustaining investment and innovation in the antibiotics space. Last May, I set out my proposals for how this might be done, in *Securing New Drugs for Future Generations*. This suggested a three-pronged approach to stimulating R&D in this field: an innovation fund endowed with \$2bn over five years; action by global regulators to remove barriers to market wherever possible; and an international system of 'market entry rewards' – lump-sum payments of \$1bn or more to developers of the most-needed new antibiotics.

The last of these would certainly be the most challenging to implement, requiring global coordination and financial commitments on a grand scale. However, I believe strongly that it is achievable, and indeed crucial, if we are to support a sustainable antibiotics pipeline for the future. I hear many arguments that there are better or 'easier' ways to support drug development – usually using the familiar policy levers of higher prices and more generous market exclusivity or

patent protection. We continue to listen to these arguments, and see scope for these tools to play a role in righting the market for some very specific types of products, but I firmly believe that there remain other areas of the antibiotics market where there is a critical need for bolder and more innovative solutions.

While further developing our proposals for supporting a sustainable supply of antibiotics, equally important is the need to address the demand for them, and the way they are prescribed and consumed. Fundamental global changes are needed in how we use antibiotics, so as to curb our excessive and often wasteful usage.

In October 2015, our report on rapid diagnostics explained our belief in the transformative power of a new generation of technology to move from a paradigm where antibiotic use is overwhelmingly guided by empirical judgment, to one where a precision diagnosis is the norm. I find it extraordinary that whereas diagnostic technologies in so many other fields of health-care have been transformed beyond all recognition in recent decades, we have seen no such revolution in how we guide the use of antibiotics. A change is long overdue, and new rapid diagnostic tests that are either already on the market or only a few years away present enormous potential to dramatically reduce unnecessary and inappropriate prescribing.

As with antibiotics themselves, interventions are needed to give this new diagnostic technology a leg up to ensure that its path to market is as clear as possible and that it will be widely adopted when it gets there. Our proposals for a series of diagnostic market stimulus 'pots', and our recommendations for greater collaboration between industry, the medical profession, and regulators, are intended to deliver precisely this.

The complexity of AMR, and the wide range of fronts on which it needs to be tackled, mean that none of these recommendations will be straightforward to implement. But exceptional progress has been made over the past 12 months in building global political support for action, including from the G7 and G20. We therefore have a unique opportunity in 2016 to take action that can transform the world's handling of drug resistance: we must not let this go to waste.

*More information about the Review's work is available at [www.amr-review.org](http://www.amr-review.org)*





**M. Nielsen Hobbs**  
Editor,  
"The Pink Sheet"

# A Trump Presidency: Would It Make The Rx Industry Great Again?

The Republican front-runner presents a unique set of challenges for pharmaceutical companies – or could he just restore the industry to its primary care heyday? **M. Nielsen Hobbs** follows the Trump trail to assess the pros and cons.

Among the most noteworthy aspect of Donald Trump's presidential campaign is how an outsized figure could be so underrated by so many. Given that, it probably makes sense for the Rx industry to start preparing for the possibility of a Trump presidency even before the first nominating contest begins.

Before Trump formally announced his bid, many people thought he wouldn't actually run. Speaking about his appearance alongside many declared candidates at an Iowa forum in January 2015, comedian John Stewart said, "It can't get more entertaining and less electable than Trump."

But after the real estate mogul and reality TV star formally entered the race in June, no one was laughing. Trump's announcement speech was widely criticized for its comments about Mexican immigrants, but he shot to the top of the polls. Only recently has neurosurgeon Ben Carson nudged him out in some of the rankings, but Trump's standing remains solid, especially impressive for a campaign without a real field operation and whose major expenses, until a radio ad in November, had included hats and T-shirts.

So for pharma companies then, it's fair to ask the question of what unique challenges Trump might present to industry if he ends up taking up residency in the White House. It's probably the most destabilizing scenario for drugs firms of the potential election outcomes – and not just because of Trump's personality.

If a Democrat wins the 2016 presidential election, pharma companies should expect more of the status quo. The House will definitely stay in Republican hands and the Senate almost certainly will. That means that significant legislative reform would be off the table, and must-pass bills like renewal of FDA user fee programs would be tempered lest they risk becoming stuck in partisan battlefields.

That would leave a Democratic president with administrative avenues to pursue policy reforms, and though any changes at FDA and CMS will be meaningful to industry, those dials can only be turned so far, even in the unlikely event that the more left-lean-

ing Bernie Sanders wins the nomination and then the general election.

## REPEALING OBAMACARE ISN'T NECESSARILY WHAT PHARMA WANTS

If a Republican is elected president, however, things get more interesting. And to paraphrase John Stewart, it can't get more interesting than Trump. Republican control of both legislative chambers and the White House provides not just a mandate, but an avenue for larger healthcare reforms, even without a 60-vote super majority in the Senate.

Mandates aren't guarantees of change, of course. George W. Bush won reelection in 2004 after campaigning for Social Security reform. Nothing ever passed, despite solid Republican majorities in the House and Senate.

The biggest perceived mandate a Republican-dominated federal government would have in 2017 would be repealing the *Affordable Care Act* and replacing it with a different set of health insurance reforms. What the new structure might look like isn't entirely clear; neither Trump nor his competitors for the nomination have fleshed out their plans for a post-Obamacare landscape, and plans are of course subject to change.

Repealing Obamacare isn't necessarily what pharmaceutical companies want. Industry brought chips to the table when the law was being drafted in 2009 and achieved a complete tactical victory, including phase-out of the Medicare Part D donut hole. In contrast, the broad outlines of establishment Republican policy proposals tend to run towards scaling back regulations on insurance companies and moving towards vouchers for Medicare and Medicaid to boost competition.

Pharma firms, in all honesty, would probably prefer *more* regulation of insurers when it comes to formulary inclusion and copays. And while government health programs have meaningful pitfalls for industry, reimbursement from Medicare and Medicaid is in many ways more predictable than from private payers. That





doesn't mean that an American healthcare landscape with beefed up private insurance plans would be bad for pharma, but the prospect of that kind of change could cause gyrations in the stock market and fretfulness in lobbyists. There aren't even any products in the pipeline that can treat those conditions.

Trump, of course, isn't in the Republican mainstream, and those policies may not resemble what his proposals end up being. But the tax plan that he detailed is much closer to traditional Republican precepts than his stump speeches have been, so any healthcare reform proposals might be as well.

Trump distinguishes himself from other presidential candidates not just with platform differences, but with the force of his personality. And that could be a problem for pharma if the industry attracts public ire as it has with the recent pricing controversies. He's called Turing's CEO a "spoiled brat" and emphasized that his superior negotiating skills could resolve whatever healthcare policy dilemmas might arise.

In general, Trump's nativist, populist campaign would seem a bad fit for a global, highly profitable industry.

### COULD PHARMA GO BACK TO ITS PRIMARY CARE SALAD DAYS?

But what if firms could stop worrying and learn to love Trump's rhetoric? What if pharma believed that it could be "great again," as Trump says that he will make America? Like all political slogans, Trump's message is inspiring, not specific; it's not entirely clear when America stopped being great or what's been lost since the end of greatness. And for groups in society that feel like their standing has never been better, the slogan could even be worrisome.

Nevertheless, imagine if Trump could make the pharmaceutical industry great again. It would probably be a return to the primary care salad days, when herds of sales reps roamed the land and prescriptions ran like mighty rivers.

Price complaints have always dogged pharmaceuticals, and likely always will until money ceases to be a medium of exchange (or pharmaceuticals cease to exist; whichever comes first). But many of the regulatory and social critiques that big pharma firms faced during the height of their prowess in the '90s and the '00s revolved around worries stemming from too many people taking their products – and those were good problems to have.

From the REMS drug safety initiative designed to ensure only the right people got a script, to complaints that direct-to-consumer advertising was leading people to ask their doctor if something they had never heard of was right for them, many of the policy fights of that era focused on efforts to cap demand, not cap prices. And wouldn't it be nice to go back to a time when drug shortages really were driven by excess demand?

Restoring the pharmaceutical industry to mass market glory isn't a Trump campaign plank, but if it were, the official spokes-product might be AstraZeneca PLC's proton pump inhibitor *Nexium* (esomeprazole).

It's a great example of what made pharma so fearsome back in the day and the product even resembles The Donald's appearance: those gold bands on the pills resemble Trump's golden mane, or maybe just the gold-plated belt buckles on his private jet.

One could even imagine Trump promoting Nexium: "A very classy product. The best. HUGE seller."

And much like the feelings that Trump has inspired in the Republican establishment and many media observers, Nexium was a product that only its patients loved. Nearly everyone else thought it didn't deserve to be there, that it didn't really earn its prescriptions.

A blockbuster enantiomer to the blockbuster *Prilosec*, Nexium wasn't a profound advancement in the treatment of gastroesophageal reflux disease, but it eliminates the cost and expense of surgery, and the label even has some comparative data to other drugs. How many products can say that?

Sadly, AstraZeneca is now reduced to suing generic rivals over who has the right to produce pills that are purple. Nothing innovative about that. But in this fight, one can see parallels to the motivations of a Trump voter – I worked really hard to get where I am, and now I feel like people are trying to take it away from me.

How Trump's candidacy moves forward depends to a large degree on how deeply that kind of message resonates. How the pharmaceutical industry moves forward depends on how little that message is needed.

In general, Trump's nativist, populist campaign would seem a bad fit for a global, highly profitable industry.



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# Technology Dreams Of Its Pharma Future

**Armando Uribe** takes a look at collaboration between technology giants and healthcare providers to assess what benefits these may bring to the patient in years to come.

In January 2015, *Fortune* reported that at \$2.9tn, the state of the US healthcare industry is very strong and continues to grow. Additionally, a *Top Issues* report revealed that 40% of Fortune 50 companies pursued new healthcare partnerships in 2014. Given the rapid growth in the healthcare industry over the last few years, it is no surprise that we are starting to see more non-traditional healthcare partnerships, specifically with big tech companies.

Google, Apple Inc. and other technology companies have pursued collaboration and license opportunities with pharma and research institutions with increasing frequency in the last few years. Healthcare companies are built around biology and science, millions of dollars of investment, and lengthy clinical trials. Technology leaders see this as an opportunity to make data collection and analysis more effective through digitization. Biotech, research institutions, and pharma have the

medical and regulatory knowledge to understand the biology and take a drug through the lengthy approval process. It would seem this collaboration, when efficacious, may be a match made in heaven.

With little information available about long-term goals and intention, we can only speculate about the changes that tech companies could create in the pharmaceutical and biotech industry. Additional investment and a new tech interest in the crossover between these fields could mean the difference between finding a cure for many lifelong diseases, and spending a lifetime treating for one.

Andrew Conrad, chief scientist of the life science team previously under Google[x], the company's research and development facility, has stated that his goal for the division is to be an R&D partner for pharma. Google[x] works on projects that include selfdriving cars, Google



Glass, smart lenses, etc. Since 2014, Google[x] has made collaboration agreements with Novartis AG, Biogen Inc, Sanofi, and Johnson & Johnson. Google Life Sciences also announced that it will be teaming up with the American Heart Association (AHA) in a \$50m research initiative to develop new tools and resources to address heart disease. The division is particularly focused on technology to facilitate data collection, tracking and analysis. This is especially important for people with chronic diseases. Studies that test treatment in chronic diseases can be very long and costly. This collaboration will allow pharma companies running these trials to have larger and more robust datasets. The end result could mean more definitive conclusions on disease progression and effective treatment.

In addition to the six collaboration and research agreements, there are additional in-house Google projects that have been disclosed. The most interesting one to date is the nanoparticle project, announced at a *Wall Street Journal* conference in October 2014. Engineers have been tasked to design nanoparticles less than one-thousandth the width of a red blood cell to 'patrol' the human body for signs of cancer and other diseases. These particles would seek out and attach themselves to cells, proteins or other molecules inside the body. The patient would wear a magnetized device to attract and count the particles and gather all information collected. The magnetic particles would work as an early detection system for a number of diseases. Although industry experts say that the nanoparticle project faces huge challenges, both technical and social, the idea that we may be able to detect a disease before it spreads is truly exciting.

Unfortunately, improving the survival rates is only part of the puzzle. Patients will also need to be able to receive the appropriate treatment. This is where Google's other in-house projects, such as the baseline study, will help to fill this gap. This study is designed to collect anonymous genetic and molecular information from participants to map the human body and identify potential biomarkers to help form new more effective treatments.

The announcement in September 2013 that Google had formed a new company, Calico Life Sciences LLC, and installed Genentech Inc. CEO and Apple chairman Arthur Levinson to head up the new venture came as a surprise to many on both sides of the technology and healthcare seesaw. Initially thought of by some as slightly mysterious, the biotech focuses on age-related illnesses and has formalized collaborations with AbbVie Inc., the University of California San Francisco (UCSF) and other research institutions with the intention of gaining a better understanding of the biology that controls human lifespan. With over seven collaborations to better understand human biology and its mission statement "to devise interventions that enable people to lead longer and healthier lives," Calico is headed for novel drug innovation.

Furthermore, Google's investment arm, Google Ventures, has recently increased its focus on its life sciences

division. Google Ventures began in 2008 and has funded companies like HomeAway, Uber, and 23andMe. It announced in 2014 that the company now has 36% of the fund's assets invested in life sciences, a huge step up from 6% in 2013. In 2014, Google Ventures led an investment round of \$130m in Flatiron Health. Flatiron, which focuses on healthcare technology, is now the firm's largest life sciences backing. To date, the life sciences division of Google Ventures includes 22 companies. Bill Maris, the president and managing partner of Google Ventures, said during an interview with *Bloomberg Markets*, "If you ask me today, is it possible to live to be 500? The answer is yes... We aren't trying to gain a few yards, we are trying to win the game. And part of it is that it is better to live than to die".

The companies that Google Ventures has backed range from insurance coverage to cloud platforms that analyze cancer data, but it isn't only Google that is eyeing a piece of the health tech pie. Apple's collaborations with Epic Systems and IBM Watson Health Cloud have also positioned the company to become a key player in the collection and analysis of medical data. It currently has HealthKit and ResearchKit helping to create a future "ecosystem" around healthcare technologies. HealthKit allows apps that provide health and fitness services to share their data with the new Apple Health app, and with each other. ResearchKit is an open source framework introduced by Apple that enables the iOS app to become a tool for medical research. The first applications made with ResearchKit target Parkinson's disease, diabetes, cardiovascular disease, breast cancer, and asthma. With Epic Systems, which currently handles more than half of the patient and medical data of the US population, and IBM Watson Cloud, data from HealthKit and ResearchKit can be shared, anonymized, and combined efficiently with other existing healthcare datasets.

New technology such as Apple's ResearchKit could help to speed up patient enrolment in future clinical trials. One example of this has already been seen with the iPhone health application: MyHeart Counts. MyHeart Counts is a cardiovascular-focused ResearchKit app which was designed by the Stanford University School of Medicine. Within four days of its release, it was downloaded 52,900 times in the US and Canada, with an additional 22,000 people consenting to participate in the study.

Efficient data collection and the increased 'consumerization' within healthcare, where patients want increased - and easier - ownership of their healthcare information has been driving the rise in collaboration between tech and pharma. Although it is unclear what the playing field for healthcare innovation will look like for many pharma companies in the years to come, we can speculate that tech providers such as Google will be right there every step of the way as both industries capitalize on their strengths to form new partnerships.

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# The Patient Experience

**Jo Shorthouse** talked to PatientsLikeMe CEO Martin Coulter about the industry's new ways of engaging with the patient for the best healthcare outcomes.



**Jo Shorthouse**  
Features Editor,  
Scrip Intelligence

## **Q** What would you like to see change in the way pharma interacts with patient communities?

I think every company has a different tack. You're seeing senior level executives recognizing the need to move from the challenge of selling more drugs to engaging patients right through the process in a way that will enable us to understand them better, understand the journey that they take through the disease, and ultimately be in a position to serve them where they are at the right time with the right drug. What's difficult now is moving that concept from the boardroom, and making it operational.

Pharma is going through the expected adoption curve of patient-centricity, and what we are witnessing and experiencing is appetite, investment and intentionality in experimentation and innovation. It's a very exciting time. We're not just seeing it with pharma companies; we're seeing it with regulators, providers and distributors. This is really a time of 100,000 experiments across healthcare.

A lot of collective learning will come out of this, which will create the guidebooks, best practices and the confidence to start organizing the underlying operation of how these companies do their business in a more patient-centric manner. I think we're just going through that period of trying to find out what works and what doesn't, and then being in a position to start incorporating this notion of patient-centricity into all parts of the process, from R&D through post-launch phases. Our pharma partners, including AstraZeneca PLC and Genentech Inc., are already making great strides. We've helped them connect with members to shape research and clinical trial design, and help patients leverage the power of their own personalized health information.

## **Q** You have recently been working with the FDA in order for them to understand the patient experience more. How important is the role of the regulators in this?

We've just been so encouraged; I'm very optimistic about what I'm seeing out there. I'm seeing CEOs of large companies basically saying that they have to change and organize around the patients. And we're seeing a reflection of that in our work with the FDA. They have as much 'giddy up' as any group that we work with, in terms of wanting to experiment and really wanting to incorporate new thinking, new data sets and new sources of information.

I don't think the regulators want to be the bottleneck to change, and in many ways they have a leadership role in laying out a blueprint, and have been incredibly innovative. At the highest level the FDA has spent a lot of time with us and understanding our data, how we work with patients and how validated and rigorous our measurement systems are. They are very interested in how to pull data sets like ours to help in the ongoing monitoring of how patients are experiencing therapies in real life.

I think they're interested in leveraging our platform, our patients and our data to understand the patient journey and the patient need and how the patient describes his or her symptoms and side-effects. Down the road this will have to be a part of 'in the real world' capturing those patient-reported and patient-generated outcomes as a one component of the approvals process.

It's logical to believe that if industry and regulators aren't working in lockstep, one could bottleneck the other.

## **Q** What is your message to pharma for 2016?

Don't underestimate the degree to which patients individually, and in well-organized groups, are willing, able and motivated to help pharma in all aspects of their work. There is no more motivated party in this whole healthcare system than the patient. Once we, as a system, recognize and leverage this to help the patients help themselves – we, in turn, will help to change the system. With that comes an expectation of a social contract with patients. There is an expectation of responsibility, of transparency, and of reciprocity. We need to see our patients as partners in the process of change, and that does bring a set of responsibilities. What I have seen with the organizations we work with is that executives are being very thoughtful about that, and that's very powerful.

*PatientsLikeMe is a network that allows patients to track their health and connect with others like them. It gathers patient-reported information to help the pharma industry understand the patient experience. [www.patientslikeme.com](http://www.patientslikeme.com)*



**Martin Coulter**





**Eleanor Malone**  
Editor,  
Scrip Intelligence

# I-O Silver Lining For Biopharma In 2016

**Eleanor Malone** looks ahead to next year's potential product approvals, the Pfizer fallout and the excitement that I-O therapies may offer for patients in 2016.

As 2015 nears its end, pharma and biotech stock indices are hovering around the levels at which they started the year. It will be many months, possibly years, before they rise to the values at which they peaked in July and August, to judge from the magnitude of the decline in August and September. But even as the breeze of the bubble gently deflating shakes a few leaves from the biotech trees and sends cash-rich pharma on the hunt for windfalls, the fruits of biotechnology continue to mature.

The flood of money into pharma and biotech in the past couple of years has highlighted how the sector has been able to put the patent cliff behind it and focus on making real commercial strides with new technologies that promise to regenerate the industry at the same time as extending and improving patients' lives. In 2015, chief among those was immuno-oncology.

While Bristol-Myers Squibb Co's *Opdivo* and Merck & Co. Inc.'s *Keytruda*, both PD-1 inhibitors, forged ahead on the market, conquering new indications along the way, there was a tremendous amount of activity as others developed their own immuno-oncology products and prepared for the next wave: I-O combination therapies.

BMS may have been the brightest star in the I-O firmament to date, with Merck & Co adding to the sparkle, but in 2016 others could start to shine.

In particular, oncology stalwart Roche, with its PD-L1 inhibitor atezolizumab, is expected to release important data in 2016, including on new I-O combinations with OX40 agonists and IDO inhibitors as well as with chemotherapies. It could also gain its first approvals, in bladder cancer and notably in non-small cell lung cancer, in 2016.

Other big pharma companies that could move forward in the field in 2016 include partners Merck KGaA and Pfizer Inc. with PD-L1 inhibitor avelumab, and AstraZeneca PLC. The latter might win US approval next year for its CTLA-4 inhibitor tremelimumab in mesothelioma, whereas it has conceded that early approval of its PD-L1 inhibitor durvalumab in NSCLC is looking less likely following approvals in the indication for *Keytruda* and *Opdivo*.

Outside the world of immuno-oncology, significant data read-outs in 2016 will include Eli Lilly & Co's Phase III trial of solanezumab in Alzheimer's disease; Novartis AG's Phase III study of *Serelaxin* in acute heart failure;

and cardiovascular outcomes trials both for the PCSK9 inhibitor *Praluent* and for Novo Nordisk AS's GLP-1 receptor agonist *Victoza*, the results of which are keenly awaited following the demonstration of cardiovascular risk reduction in 2015 with Lilly/Boehringer Ingelheim GMBH's SGLT2 inhibitor *Jardiance*.

Among the exciting new drugs expected to gain approval in 2016 are Roche's ocrelizumab in primary progressive and relapsing multiple sclerosis; Gilead Sciences Inc.'s sofosbuvir+velpatasvir, the first pangenotypic, all-oral hepatitis C combination; AbbVie Inc.'s venetoclax in chronic lymphocytic lymphoma; and both Lilly/Incyte Corp.'s baricitinib and Sanofi/Regeneron's sarilumab for rheumatoid arthritis.

Meanwhile, biosimilars will march onwards in 2016, with the EU approval of biosimilar etanercept (Amgen's *Enbrel*) imminent, data on a number of major monoclonal antibody blockbusters including Roche's *Avastin*, *Rituxan* and *Herceptin*, and insulin products including Lilly's *Humalog* and Sanofi's *Lantus* under threat.

Developing and launching new drugs is only part of what this industry does, though. Unfortunately, sometimes it seems that it is better known to the world at large for elaborate tax avoidance maneuvers, extortionate pricing and dodgy selling practices.

The pursuit of the holy tax inversion grail led to the recent inking of the M&A deal of the century, Pfizer and Allergan's \$160bn merger. 2015 was a fertile year for investment bankers and lawyers looking to harvest fees for deal negotiations, and 2016 will no doubt provide another bumper crop, assuming that the Pfizer/Allergan combination is not derailed by legislative action and closes as expected in the second half. Declining valuations in the biotech sector and the cost of borrowing remaining appetizingly low will help.

The drug pricing debate will also rumble on, fuelled by the political grandstanding in the run-up to the US presidential election in November.

As for scandal, it is futile to hope that there won't be any, not least because of the searchlight shining on the sector following the furores around Turing Pharmaceuticals' huge price increase for the anti-infective pyrimethamine, the use of specialty pharmacies by Valeant Pharmaceuticals International, Inc. and the audacity of Ian Read and Brent Saunders' plans to free Pfizer from the shackles of the US tax regime.

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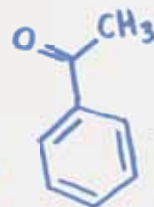
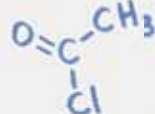
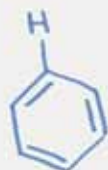
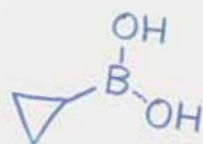
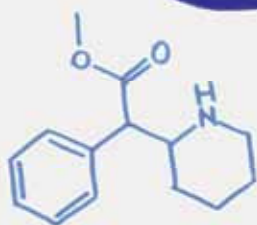
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