RESHAPING POSSIBILITIES TO BRING NEW DIMENSION TO DRUG DEVELOPMENT.

Advancing an entire industry takes bold moves, unique perspectives and scientific expertise. Today’s Covance is folding in new solutions for patient recruitment, therapeutic expertise and risk-based monitoring. From bench to commercialization, we evolve drug development approaches to fit your program’s specific objectives. With exceptional data accuracy and agile communication, you’ll experience higher value and a partner who puts your needs first. Come find out more about how our game-changing solutions are preparing the industry for a transformation.

CALL TO LEARN MORE
The Americas +1.888.COVANCE | Europe/Africa +00.800.2682.2682
Asia Pacific +800.6568.3000 | Or go to covance.com

Covance Inc., headquartered in Princeton, NJ, USA, is the drug development business of Laboratory Corporation of America Holdings (LabCorp). COVANCE is a registered trademark and the marketing name for Covance Inc. and its subsidiaries around the world. © Copyright 2016. Covance Inc.
### Contents

| SCRIP 100 | 4 |
| BUSINES | 14 |
| LEADERSHIP | 22 |
| R&D | 28 |
| CLINICAL TRIALS | 40 |
| EMERGING MARKETS | 50 |
| POLICY | 56 |
| MANUFACTURING | 62 |
| DIGITAL | 68 |
| FUTUROLOGY | 74 |

### SCRIP 100 EDITOR
Joanne Shorthouse  @ScripJo
joanne.shorthouse@informa.com

### EDITORIAL
Eleanor Malone  @ScripEleanor
eleanor.malone@informa.com
Alexandra Shimmings  @ScripAlexS
alex.shimmings@informa.com
Sukaina Virji  @scripsuki
sukaina.virji@informa.com
Anju Ghangurde  @scripanjug
anju.ghangurde@informa.com
Mandy Jackson  @ScripMandy
mandy.jackson@informausa.com
Francesca Bruce  @ScripFrancesca
francesca.bruce@informa.com
Sten Stovall  @stenstoffall
sten.stovall@informa.com
Ilan Schofield  @ScriplanS
ian.schofield@informa.com
Ashley Yeo  @ashleypyeo
ashley.yeo@informa.com
Mary Jo Laffier
maryjo.laffier@informa.com
Lucie Ellis  @ScripLucie
lucie.ellis@informa.com
Lubna Ahmed  @ScripLubna
lubna.ahmed@informa.com
John Hodgson  @ScripJohn
john.hodgson@informa.com
Mike Ward  @ScripMikeWard
mike.ward@informa.com
Peter Charlish  @petercharlish
peter.charlish@informa.com
John Davis  @john023davis
john.davis@informa.com
Emily Hayes  @EmilyKateHayes
emily.hayes@informa.com
Jessica Merrill  @JessicaMerrill
jessica.merrill@informa.com
Joseph Haas
joseph.haas@informa.com
Ian Haydock
ian.haydock@informa.com
Ying Huang
ying.huang@informa.com
Jung-Won Shin
jungwon.shin@informa.com
Brian Yang
brian.yang@informa.com

### DESIGN SUPERVISOR
Gayle Rembold Furbert
gayle.furbert@informa.com

### CONTRIBUTORS
Doro Shin
Andy Smith
Melanie Senior
Roland Foxcroft
Deborah Jeanfavre
Natasha Boliter
Ahmet Sevindik
M. Nielsen Hobbs

---

All stock images in this publication courtesy of www.shutterstock.com unless otherwise stated.

### Customer Services
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: Subscriptions@informa.com
To subscribe, visit scrip.pharmamedtechbi.com
To advertise, contact christopher.keeling@informa.com

Scrip is published by Informa UK Limited.
©Informa UK Ltd 2016: All rights reserved.
ISSN 0143 7690
Immunotherapy drugs have caused huge waves of excitement, not to mention headlines, about the way in which cancer can be fought. Here, Covance notes the vital considerations for clinical success.

With its measurable impact on patient survival, there’s no denying that immunotherapy is already causing momentum in ways that cancer is treated. Drug researchers and developers are identifying new candidates in their growing pipelines and exploring combinations of immunotherapies, while regulatory agencies are providing expedited review and approval of these therapies for new indications at an unprecedented rate.

With checkpoint inhibitors from Yervoy (ipilimumab) to Opdivo (nivolumab) to Keytruda (pembrolizumab) to the most recently approved Tecentriq (atezolizumab), each breakthrough has provided new insights on how the immune system can be activated and manipulated to fight a variety of cancers.

NEWLY RELEASED RESEARCH
Ongoing research strives to understand the longer-term potential of these therapies. For example, pembrolizumab, which may be prescribed when the disease relapses or fails to respond to ipilimumab, has recently been shown to outperform ipilimumab as a first-line therapy. A third of patients treated with pembrolizumab showed an overall response when treated for melanoma; 73% of those respondents had an ongoing response lasting as least two years.

Response durations ranged from >1.3 to >38.8 months, suggesting that the immune system retained its cancer-fighting abilities in those patients, and provided a durable response. Furthermore, in a separate, direct comparison to ipilimumab as a first-line monotherapy, two-year overall survival of metastatic melanoma patients increased from 43% to 55% on pembrolizumab.

Bristol-Myers Squibb also released the results of its two-year overall survival data comparing nivolumab to docetaxel in previously treated metastatic non-small cell lung cancer (NSCLC) patients, demonstrating improved overall survival: 29% vs. 16% for non-squamous NSCLC and 23% vs. 8% for squamous NSCLC.

More clinical research is needed to determine how the duration of treatment affects a patient’s response. It’s unknown if periodic treatments are needed long term after the tumor completely shrinks or if the immune system will naturally retain its anticancer activity, although some patients in earlier studies have remained cancer-free without further therapy for more than five years¹.

EXPANDING THE SCOPE
The FDA has approved many new or expanded indications for immunotherapies, such as nivolumab, for the treatment of patients with classical Hodgkin’s lymphoma (cHL) who have relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and post-transplantation brentuximab vedotin.

Beyond a better understanding and expansion of current therapies, potential opportunities exist for re-examining treatment strategies. While the approval of ipilimumab, nivolumab, pembrolizumab and atezolizumab for various indications validates immunotherapies as a treatment approach, different strategies in the administration of these drugs should now be considered.

For example, adjusting the timing of a treatment from advanced to earlier stages of the disease may attack a tumor more effectively. Treatments could also be expanded beyond their focus and current indications, to see if similar results may be seen in different tumor types.

Combinations of multiple immunotherapies are also being evaluated to see if they may provide greater efficacy potential, as has been noted in melanoma with the combination of ipilimumab and nivolumab, which increases the two-year overall survival in melanoma from 54% to 64% compared to ipilimumab alone. However, combinations will need to be carefully evaluated not only for efficacy, but also for adverse events, because of the potential for increased toxicity.

Other immunotherapies approaching cancer from a different angle than checkpoint inhibitors include cancer vaccines, oncolytic viruses and adoptive cell transfer. In the latter, rather than trying to stimulate the T cells in the body through the use of checkpoint inhibitors, a patient’s own T cells can be manipulated to seek specific antigens on the patient’s tumor cells and kill them. This process involves isolating the patient’s own T cells from the blood and then genetically engineering a chimeric antigen receptor (CAR) into the cells.

After those T cells are multiplied, they are re-infused into the patient where they become directed at and destroy the tumor cells. Initial results have shown the potential of this approach for adults with certain advanced blood cancers, including pediatric acute lymphoblastic leukemia, when other treatments are no longer an option.
FOCUSING ON RESPONDERS
Regardless of the immunotherapy target or approach, autoimmune adverse events remain a concern when the immune system may also attack healthy cells. Obtaining preclinical data and combining it with clinical data might allow for a better understanding of specific mechanisms of action causing autoimmune response. This perspective may then be valuable in establishing strategies to prevent or reduce these adverse events, and help guide the design and effective monitoring of a clinical trial. Despite these side effects, physicians have become adept at recognizing and treating them early in the course of therapy.

Biomarkers could also be used to better target patients more likely to respond and thus increase the therapeutic window by stratifying and treating patients according to their biomarker profile. This would potentially improve treatment response by treating only patients with the best chances to respond. Currently, the PD-L1 biomarker has been used in such evaluations, and while correlated with potential response in a number of tumor types, it is not the only relevant biomarker for immune-based therapies. Other promising immunotherapy biomarkers include genomic markers, such as the determination of mutational burden and production of neo-antigens, along with blood-based biomarkers of the immune response.

Retrospective and prospective analyses in clinical trials will hopefully lead to further novel biomarker discoveries and applications, and enable earlier phase screening of patients. However, much more work is required to define the most predictive biomarker or combination of biomarkers for immunotherapies.

CONSIDERATIONS FOR CLINICAL SUCCESS
With more drug candidates, possible targets, approaches and mechanisms to explore, the immuno-oncology field holds great promise for the industry and patients, yet has distinct development needs quite unlike any other oncology treatment.

Drug developers must consider strategies for identifying patients in an increasingly competitive trial landscape, training and supporting investigators, providing adequate site and patient monitoring and bioinformatic needs to better support the increasing complexity of biomarker studies. Suitable site selection also factors into the equation, in that a site must be able to handle the unique volume, complexity and timeline requirements of an immunotherapy trial.

Past performance in previous trials and relevant oncology experience are key factors to bear in mind when considering suitable sites. With a proprietary knowledge base that has visibility on more than 40% of the world’s trials, Covance can apply its Xcellerate® Informatics Suite to identify the best sites and investigators for performing these specialized trials. Finding patients is also optimized with access to 75 million de-identified patient test results in the LabCorp database to get these trials optimally designed and placed closer to relevant patient populations.

At the most granular level, it’s important to note the unique staffing requirements for an immunotherapy trial. Investigators and clinical research associates must understand how immune-related response criteria differ from those of other oncology treatments. The therapy may take more time to generate a response or the tumor may swell (“pseudo” disease progression) before it shrinks.

To ensure trial compliance, a well-documented plan should outline when to continue or end treatment based on specific response patterns. And from the safety perspective, site staff should be well versed in recognizing, reporting and treating any immune-related adverse events (iRAEs) that appear during the study.

A strong clinical strategy is only one part of the complex equation. With new indications, combination therapies, alternative treatment approaches as well as the response criteria defined by biomarkers, our field has great capacity for discovery and improvement of immunotheapies and their administration. These very unique characteristics pose an immense and imminent challenge, yet it is these same attributes that offer tremendous potential to transform cancer therapy and improve patient survival outcomes.


Shutterstock: HerrBullermann
The Architecture Of A Top-Heavy Industry

No matter where you looked, pharmaceutical sales in dollar terms were down nearly 3% from 2014 to 2015; across the 350 drug-selling companies within the Scrip 100, sales fell 2.7% from $738bn in 2014 to $719bn in 2015; within the top 20 biggest firms sales fell 3.3%. There was a 3% fall in sales, too, among the top 100 drug companies, a set that accounts for 95% of all drug sales.

That universal fall reflected the impotence of the pharma industry against the weakening reporting currencies like the euro, yen and pound sterling. Averaged over the year, the euro was worth just 84% of its average value in 2014: the yen 87% and the pound, 92%. Even the Swiss franc weakened in 2015 to 95% of its 2014 value.

These currency movements, however, disguise fairly healthy underlying growth in pharmaceutical sales. If underlying sales had been flat and, making the reasonable assumption that the North American market accounts for 40-50% of drug sales, Europe 25-30%, and Asia 20-35%, then currency movements alone would reduce drug sales around 9-10% between 2014 and 2015.

So a fall of just 3% in drug dollar sales translates into underlying sales growth across the industry of around 6-7% between 2014 and 2015.

There is no ‘average’ company

For the Scrip 100 study, we have gathered financial data on 620 companies with activity either in drug sales or pharma-oriented R&D. Taken together, those companies generated $719bn in drug sales in 2015 (out of $1.1tn in total revenue) and spent $145bn (20.1% of sales) on pharmaceutical R&D. The collective set generates $146bn in net profits, boasts $1tn in net assets and employs over two million people.

From these numbers, an average company in the Scrip 100 universe would consist of 3,600 people working in an enterprise that sells $1.1bn worth of drugs, and spends $230m annually on R&D. It would turn an operating profit of around $270m into a net profit of $235m and sit on $3.6bn worth of assets while carrying $1.9bn of liabilities.

No real company’s metrics match this Scrip 100 average. Galenica Pharmaceuticals Inc. and Horizon Pharma PLC come close in terms of assets, liabilities and drug sales but they spend much less on R&D than the ‘average’ ($85m and $42m, respectively) and have far fewer employees (1,800 and 750, respectively). Vertex Pharmaceuticals Inc. has $1bn in pharma sales but spent nearly $995m on R&D and consequently made a loss in excess of $550m. South Korea’s Hanmi Pharmaceutical Co. Ltd. sells just under $1bn worth of drugs and spends around $165m on R&D, and makes a profit, but its asset base is under half that of the ‘average’ Scrip 100 firm.

Pharma is very top heavy

There is no ‘average’ company, at least in part because the pharmaceutical industry is extremely top heavy. Half of the dollar value of drug sales for 2015 was generated by just 11 out of 620 companies: Pfizer Inc., Novartis AG, Roche, Sanofi, Merck & Co. Inc., Gilead Sciences Inc., Johnson & Johnson, GlaxoSmithKline PLC, AstraZeneca PLC, Abbott Inc. and Amgen Inc. Half of the R&D spending occurs in an overlapping set of just 12 companies (those just mentioned plus Eli Lilly & Co. and Bristol-Myers Squibb Co. minus Gilead Sciences Inc.). Just nine companies – Pfizer, Allergan PLC, Sanofi, Amgen, AstraZeneca, Novartis, Teva Pharmaceutical Industries, Abbott and Gilead – contribute half of all the pharmaceutical assets within the set.

The 20 companies that sell most drugs accounted for around 69% of drug sales in 2015, 65% of R&D expenditure, and 65% of the assets.

A broader set of 100 companies accounts for 95% of all drug sales, 87% of R&D spending and 89% of assets.

That leaves around 5% of drugs sales, 13% of R&D spending and 11% of the assets in the hands of the other 500 or so companies in the list.

Clocking the Pharma industry

To capture the essence of the distribution of pharmaceutical activity among companies, imagine $719bn in drug sales spread evenly across a single day.

Starting at 12 midnight, it takes until after 01.31 to finish Pfizer. It’s four minutes quicker to get through Novartis,
and just one hour 17 minutes for Roche and thereafter each company goes faster than the last. It takes until 11.20 to get through the top 10 companies, ending with AbbVie.

The top 20 is not completed until more than two-thirds of the day is gone, at 4.50 in the afternoon and just as your junior colleagues may be think about leaving the office. Each company’s sales at this point is represented by 20 or so minutes.

Things then start to happen much faster. By 9.00 pm, the end of the top 50 has been reached and companies like Lupin Pharmaceuticals Inc., Chiesi Farmaceutici SPA and Ipsen are flying by in less than four minutes each.

Whereas getting through the top 50 took 21 hours, the second 50 takes less than two hours. That leaves a good hour and ten minutes to get through the rest of the 170 companies that have some drug sales.

And with the first dong of midnight, the drug sales of 350 companies that don’t sell drugs yet flash by instantaneously.

IT’LL BEGIN WITH TIERS

In terms of pharma sales, the drug industry can also be divided neatly in tiers.

To quite an accurate approximation, getting into the top 100 means that a company must sell over $750m worth of drugs. For the top 50, the bar sits at $2bn. Top 30 companies need $5bn in drug sales, and to make the top 20, sales should exceed $10bn. The top 10 elite companies made sales of over $20bn in 2015 (as did Amgen at #11).

Even though this tiered description of the pharmaceutical industry is somewhat artificial (in that the tiers are overlays on a continuum of sales performance), it does generate a context for the difficulty of any company moving up from one level to another.

In the past three years, only Gilead and Actavis have infiltrated the top 20, one on the back of developing a cure for hepatitis C infections and the other fuelled by serial M&A.

Actavis’ continuing merger-lust meant, of course, that there was a new name in the top 20 for 2015 – rebranded as Allergan, the company appears at #17 with drug sales of $15.1bn. On the basis of pharma sales made in 2015, Allergan should have been at #12 but its accountants placed its generics division’s approximately $6bn worth of sales in a separate pot, marked for divestment to Teva. On a pro forma basis, the combination of Allergan’s two corporate components, legacy Allergan and Actavis, generated sales of just over $19bn in 2014.

WHO IS KNOCKING AT THE DOOR?

The bar for entry into the top 20 of the Scrip 100 lies at around $10bn in drug sales. Merger and acquisition is one route in, but the scale of the task is immense. Consider, for instance, the May 2015 merger that occurred between two of the historically important Italian pharmaceutical companies with roughly equal sales in excess of $500m each per year, Alfa Wassermann SPA and Sigma-Tau Pharmaceuticals Inc.

Its $1.01bn pharmaceutical annual turnover only moves the newly created AlfaSigma to #77 in the league table. Merging AlfaSigma with all of the significant Italian pharma companies - Menarini Group, Chiesi, Bracco SPA, Recordati Industria Chimica & Farmaceutica SPA, Italfarmaco SPA, and Zambon Co. SPA – would only create a company with pro forma drug sales of around $8.5bn, putting it at #24 or #25 in the Scrip 100 league table.

Mergers within a larger and more internationalized industry such as India could produce a contender for the top 20.

A more likely source of new top 20 entrants are those companies currently knocking at the door.

<table>
<thead>
<tr>
<th>TIER</th>
<th>BAR (DRUG SALES)</th>
<th>SALES O’CLOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top 10</td>
<td>$20bn</td>
<td>11.30</td>
</tr>
<tr>
<td>Top 20</td>
<td>$10bn</td>
<td>17.00</td>
</tr>
<tr>
<td>Top 30</td>
<td>$5bn</td>
<td>19.00</td>
</tr>
<tr>
<td>Top 50</td>
<td>$2bn</td>
<td>21.00</td>
</tr>
<tr>
<td>Top 100</td>
<td>$750m</td>
<td>22.50</td>
</tr>
<tr>
<td>The Rest (170, with sales)</td>
<td>&gt;0</td>
<td>00.00</td>
</tr>
<tr>
<td>The Rest (350, no sales yet)</td>
<td>0</td>
<td>00.00</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Pfizer</td>
<td>1 (1)</td>
<td>45,456.0</td>
</tr>
<tr>
<td>Novartis</td>
<td>2 (2)</td>
<td>43,415.0</td>
</tr>
<tr>
<td>Roche</td>
<td>3 (4)</td>
<td>38,791.0</td>
</tr>
<tr>
<td>Sanofi</td>
<td>4 (3)</td>
<td>38,335.1</td>
</tr>
<tr>
<td>Merck &amp; Co</td>
<td>5 (5)</td>
<td>36,171.0</td>
</tr>
<tr>
<td>Gilead Sciences</td>
<td>6 (9)</td>
<td>32,151.0</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>7 (6)</td>
<td>31,430.0</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>8 (7)</td>
<td>27,269.0</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>9 (8)</td>
<td>23,641.0</td>
</tr>
<tr>
<td>AbbVie</td>
<td>10 (10)</td>
<td>22,859.0</td>
</tr>
<tr>
<td>Amgen</td>
<td>11 (12)</td>
<td>20,944.0</td>
</tr>
<tr>
<td>Teva Pharmaceutical Industries</td>
<td>12 (11)</td>
<td>19,652.0</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>13 (17)</td>
<td>16,057.8</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>14 (14)</td>
<td>15,969.6</td>
</tr>
<tr>
<td>Bayer</td>
<td>15 (15)</td>
<td>15,254.3</td>
</tr>
<tr>
<td>Allergan</td>
<td>16 (13)</td>
<td>15,071.0</td>
</tr>
<tr>
<td>Takeda</td>
<td>17 (18)</td>
<td>14,931.0</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>18 (16)</td>
<td>14,045.0</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>19 (19)</td>
<td>12,431.0</td>
</tr>
<tr>
<td>Astellas</td>
<td>20 (20)</td>
<td>11,340.3</td>
</tr>
<tr>
<td>Mylan</td>
<td>21 (26)</td>
<td>9,362.6</td>
</tr>
<tr>
<td>Biogen Idec</td>
<td>22 (21)</td>
<td>9,188.5</td>
</tr>
<tr>
<td>Celgene</td>
<td>23 (27)</td>
<td>9,161.0</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>24 (23)</td>
<td>8,148.9</td>
</tr>
<tr>
<td>Otsuka Pharmaceutical</td>
<td>25 (24)</td>
<td>8,028.0</td>
</tr>
</tbody>
</table>

1 Pfizer’s acquisition of Hospira raised it to #1 in 2014
2 HCV franchise growth
3 Excludes generics division divested to Teva
4 Acquired Abbott Lab’s developed markets branded generics business
5 17% fall in euro/$ exchange rate
6 Excludes API (5%)
7 Specialty and generics
8 Fresenius Kabi division
9 17% fall in euro/$ exchange rate
10 Excludes Biochemicals segment
11 Integrated Pharmacy Solutions; divestment of Baxalta
12 Not API
13 Global Generics
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupin</td>
<td>51 (49)</td>
<td>1,793.5</td>
<td>1,870.2</td>
<td>-4.1%</td>
</tr>
<tr>
<td>Chiesi</td>
<td>52 (52)</td>
<td>1,628.3</td>
<td>1,783.3</td>
<td>-8.7%</td>
</tr>
<tr>
<td>Ipsen</td>
<td>53 (53)</td>
<td>1,602.5</td>
<td>1,673.4</td>
<td>-4.2%</td>
</tr>
<tr>
<td>Shionogi</td>
<td>54 (50)</td>
<td>1,584.5</td>
<td>1,810.3</td>
<td>-12.5%</td>
</tr>
<tr>
<td>Apotex</td>
<td>55 (58)</td>
<td>1,565.2</td>
<td>1,520.0</td>
<td>3.0%</td>
</tr>
<tr>
<td>Santen Pharmaceuticals</td>
<td>56 (68)</td>
<td>1,499.0</td>
<td>1,289.3</td>
<td>16.3%</td>
</tr>
<tr>
<td>United Therapeutics</td>
<td>57 (70)</td>
<td>1,465.8</td>
<td>1,279.5</td>
<td>14.6%</td>
</tr>
<tr>
<td>Hikma Pharmaceuticals</td>
<td>58 (59)</td>
<td>1,440.0</td>
<td>1,489.0</td>
<td>-3.3%</td>
</tr>
<tr>
<td>Ono Pharmaceutical</td>
<td>59 (69)</td>
<td>1,431.1</td>
<td>1,286.2</td>
<td>11.3%</td>
</tr>
<tr>
<td>Zhejiang Hisun Pharma</td>
<td>60 (54)</td>
<td>1,408.2</td>
<td>1,619.7</td>
<td>-13.1%</td>
</tr>
<tr>
<td>Meda</td>
<td>61 (56)</td>
<td>1,397.9</td>
<td>1,536.0</td>
<td>-9.0%</td>
</tr>
<tr>
<td>Meiji Holdings</td>
<td>62 (62)</td>
<td>1,359.3</td>
<td>1,338.9</td>
<td>1.5%</td>
</tr>
<tr>
<td>Gruenenthal</td>
<td>63 (57)</td>
<td>1,345.1</td>
<td>1,534.4</td>
<td>-12.3%</td>
</tr>
<tr>
<td>Jazz Pharmaceuticals</td>
<td>64 (74)</td>
<td>1,314.8</td>
<td>1,162.7</td>
<td>13.1%</td>
</tr>
<tr>
<td>Merz</td>
<td>65 (63)</td>
<td>1,284.1</td>
<td>1,321.2</td>
<td>-2.8%</td>
</tr>
<tr>
<td>Leo Pharma</td>
<td>66 (61)</td>
<td>1,258.3</td>
<td>1,421.5</td>
<td>-11.5%</td>
</tr>
<tr>
<td>Cadila</td>
<td>67 (75)</td>
<td>1,245.3</td>
<td>1,156.1</td>
<td>7.7%</td>
</tr>
<tr>
<td>Teijin Pharma</td>
<td>68 (66)</td>
<td>1,218.5</td>
<td>1,314.8</td>
<td>-7.3%</td>
</tr>
<tr>
<td>Kowa Pharmaceutical</td>
<td>69 (67)</td>
<td>1,200.0</td>
<td>1,294.0</td>
<td>-7.3%</td>
</tr>
<tr>
<td>Nichi-Iko Pharmaceutical</td>
<td>70 (73)</td>
<td>1,185.6</td>
<td>1,203.3</td>
<td>-1.5%</td>
</tr>
<tr>
<td>Glenmark Pharmaceuticals</td>
<td>71 (78)</td>
<td>1,183.9</td>
<td>1,081.4</td>
<td>9.5%</td>
</tr>
<tr>
<td>Aurobindo</td>
<td>72 (83)</td>
<td>1,113.3</td>
<td>1,024.2</td>
<td>8.7%</td>
</tr>
<tr>
<td>Gedeon Richter</td>
<td>73 (65)</td>
<td>1,106.3</td>
<td>1,314.9</td>
<td>-15.9%</td>
</tr>
<tr>
<td>KRKA</td>
<td>74 (64)</td>
<td>1,078.2</td>
<td>1,316.2</td>
<td>-18.1%</td>
</tr>
<tr>
<td>Sawai Pharmaceutical</td>
<td>75 (84)</td>
<td>1,020.2</td>
<td>999.0</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

1Generics, 91% of business
2Prescription drugs, excludes OTC
3Branded division (40% of sales, generics and injectables)
460% of Meda sales are Rx
5Pharma 13% of total sales
6Formulations businesses
7Formulations, 80% of sales
8Sales 20% down, falls in Eastern Europe
9Alfa Wasserman merged with Sigma Tau
10Finished drug Business
11Prescription Pharma and Specialty Sciences (Tysabri)
12Increase in Kalydeco sales; launch of Orkambi
13Includes API and intermediates

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Indivior</td>
<td>76 (77)</td>
<td>1,014.0</td>
<td>1,115.0</td>
<td>-9.1%</td>
</tr>
<tr>
<td>AlfaSigma</td>
<td>77 (81)</td>
<td>1,009.9</td>
<td>1,053.9</td>
<td>-4.2%</td>
</tr>
<tr>
<td>China Pharmaceutical Group</td>
<td>78 (89)</td>
<td>1,005.4</td>
<td>866.1</td>
<td>16.1%</td>
</tr>
<tr>
<td>Perrigo</td>
<td>79 (87)</td>
<td>1,001.1</td>
<td>927.1</td>
<td>8.0%</td>
</tr>
<tr>
<td>Vertex Pharmaceuticals</td>
<td>80 (120)</td>
<td>1,000.3</td>
<td>487.8</td>
<td>105.1%</td>
</tr>
<tr>
<td>Pierre Fabre</td>
<td>81 (72)</td>
<td>997.7</td>
<td>1,216.0</td>
<td>-18.0%</td>
</tr>
<tr>
<td>Yuhan Pharmaceutical</td>
<td>82 (86)</td>
<td>990.3</td>
<td>966.6</td>
<td>2.5%</td>
</tr>
<tr>
<td>Hanmi Pharm</td>
<td>83 (100)</td>
<td>983.5</td>
<td>723.2</td>
<td>36.0%</td>
</tr>
<tr>
<td>Hisamitsu</td>
<td>84 (60)</td>
<td>968.2</td>
<td>1,484.8</td>
<td>-34.8%</td>
</tr>
<tr>
<td>Recordati</td>
<td>85 (71)</td>
<td>966.2</td>
<td>1,267.6</td>
<td>-23.8%</td>
</tr>
<tr>
<td>Esteve</td>
<td>86 (80)</td>
<td>965.5</td>
<td>1,070.0</td>
<td>-9.8%</td>
</tr>
<tr>
<td>Torrent Pharmaceuticals</td>
<td>87 (94)</td>
<td>947.8</td>
<td>763.0</td>
<td>24.2%</td>
</tr>
<tr>
<td>Kyorin</td>
<td>88 (79)</td>
<td>939.6</td>
<td>1,071.6</td>
<td>-12.3%</td>
</tr>
<tr>
<td>Orion Pharma</td>
<td>89 (76)</td>
<td>939.3</td>
<td>1,139.8</td>
<td>-17.6%</td>
</tr>
<tr>
<td>Green Cross</td>
<td>90 (88)</td>
<td>925.7</td>
<td>926.6</td>
<td>-0.1%</td>
</tr>
<tr>
<td>Akorn</td>
<td>91 (115)</td>
<td>924.5</td>
<td>542.8</td>
<td>70.3%</td>
</tr>
<tr>
<td>Shanghai Pharmaceutical</td>
<td>92 (91)</td>
<td>921.7</td>
<td>827.7</td>
<td>11.4%</td>
</tr>
<tr>
<td>Taisho Pharmaceutical</td>
<td>93 (85)</td>
<td>885.6</td>
<td>970.8</td>
<td>-8.8%</td>
</tr>
<tr>
<td>BioMarin Pharmaceutical</td>
<td>94 (96)</td>
<td>884.5</td>
<td>738.4</td>
<td>19.8%</td>
</tr>
<tr>
<td>Galenica AG</td>
<td>95 (113)</td>
<td>878.0</td>
<td>550.0</td>
<td>59.6%</td>
</tr>
<tr>
<td>Amneal Pharmaceuticals</td>
<td>96 (97)</td>
<td>875.0</td>
<td>735.0</td>
<td>19.0%</td>
</tr>
<tr>
<td>Impax Laboratories</td>
<td>97 (108)</td>
<td>860.5</td>
<td>594.7</td>
<td>44.7%</td>
</tr>
<tr>
<td>Intas Pharmaceuticals</td>
<td>98 (90)</td>
<td>844.0</td>
<td>844.1</td>
<td>0.0%</td>
</tr>
<tr>
<td>Alvogen Pharmaceuticals</td>
<td>99 (110)</td>
<td>800.0</td>
<td>580.0</td>
<td>37.9%</td>
</tr>
<tr>
<td>Almirall</td>
<td>100 (82)</td>
<td>760.2</td>
<td>1,045.3</td>
<td>-27.3%</td>
</tr>
</tbody>
</table>

27Hanmi (not Beijing Hanmi)
28Includes Rx segment and Noven
29Not OTC
30Excludes others/CRAMs
31Excludes diagnostics, animal health and contract manufacturing
32Acquisitions of Betimol, Zioptan, Hi-Tech, VersaPharm, Xopenex, Lloyd Products
33Biologicals and chemical drugs (not TCM)
34Ethical drugs segment
35Vifor Pharma division; excludes OTC
36Impax Generics and Impax Specialty Pharma
37FY 2014 data; no FY 2015-16
38Company sources
The 2016 Scrip 100 universe covers the fortunes of 620 companies over financial year 2015. Pharma sales, R&D spending, employee statistics and operating profit all contribute to the overall industry portrait as it faces uncertain times ahead.

**Companies: Who Gets In?**

- **$1m**
  The figure companies need to make on drug sales, or spend on R&D, to get into the Scrip 100

- **2.3m**
  The number of employees working within the Scrip 100 universe

- **$1.63tn**
  in pharma-related assets turned $145bn spent on R&D into

- **$156bn**
  Net profit generated by the pharmaceutical industry in 2015

- **$719bn**
  worth of drugs

**The Pharmaceutical Industry Is Incredibly Top Heavy**

- **394**
  The number of companies that suffered a loss in FY 2015

- **Generated $20.18bn in losses**

- **202**
  The number of companies that made a profit in FY 2015

- **Generated $177bn in profits**

*because many of the other 520 companies made a loss*
**What changed in 2015?**

3% The percentage decrease in drug sales across the industry from 2014 to 2015. R&D spending was the same.

22 The number of companies that made losses in 2014 then became profitable in 2015.

**What did you make last year?**

Drug sales you need to make the Top Tiers (IRO!)

- **TOP 10**
  - $20bn
- **TOP 20**
  - $10bn
- **TOP 30**
  - $5bn
- **TOP 50**
  - $2bn
- **TOP 100**
  - $750m

$727bn the pharma industry’s current assets are now worth more than its 2015 drug sales ($719bn).

In 2015, pharma’s collective net asset balance (assets minus liabilities) exceeded $1,000,000,000,000 for the first time ($1.04tr).

**Of the 258 companies with sales in both 2014 and 2015**

- Drug sales remained the same in 2015
  - 47
- Decreased drug sales in 2015
  - 127
- Increased drug sales in 2015
  - 84

**From 2014 to 2015:**

- **Increased R&D spending**
  - 59%
- **Reduced R&D spending**
  - 33%

Source: Scrip 100
Company Overview

Covance, the drug development business of Laboratory Corporation of America Holdings (LabCorp), is the world’s most comprehensive drug development company, dedicated to advancing healthcare and delivering Solutions Made Real® by providing high-quality nonclinical, clinical and commercialization services to pharmaceutical and biotechnology companies to help reduce the time and costs associated with drug development. Because of our broad experience and specialized expertise, we’re in a unique position to supply insights that go above and beyond testing – We have helped pharmaceutical and biotech companies develop each of the top 50 prescription drugs in the marketplace today.

We also offer laboratory testing services to the chemical, agrochemical and food industries and are a market leader in toxicology services, central laboratory services, discovery services, and a top global provider of Phase III clinical trial management services.

Drug Development Services

▶ Research
  – Research Models

▶ Lead Optimization
  – Lead Optimization
  – Non-GLP Toxicology
  – In Vivo Pharmacology
  – Nonclinical Imaging
  – Nonclinical Pathology Services
  – PK / TK Analysis and Reporting
  – Immunology

▶ Analysis Services
  – Bioanalytical Services
  – Drug Metabolism and Pharmacokinetic Services
  – Radiosynthesis Services

▶ Safety Assessment
  – General Toxicology Studies
  – Genetic Toxicology
  – Immunotoxicology

▶ Clinical Development
  – Early Clinical / Phase Ia
  – Phase Ib / III Services
  – Drug Life Cycle Management
  – Clinical Data Analysis and Reporting
  – Regulatory Services

▶ Consulting
  – Alliance Management
  – Early Phase Development Solutions

▶ Clinical Testing
  – Central Laboratory Services
  – Translational Biomarker & Diagnostics

▶ Commercialization
  – Patient and Provider Services
  – Market Access Consulting

▶ Manufacturing Support
  – Biopharm CMC Solutions

▶ Informatics
  – Xcellerate® - Clinical Trial Optimization®

▶ Companion Diagnostics
  – Genomic Solutions
  – Expanded Laboratory Management Solutions
  – Vaccine and Novel Immunotherapeutics

Covance has offices throughout the US, Canada, Europe, Asia/Pacific, South America and Africa.

TOGETHER WITH OUR CLIENTS, WE CREATE SOLUTIONS THAT TRANSFORM POTENTIAL INTO REALITY.

TO LEARN MORE CALL
The Americas +1.888.COVANCE | Europe/Africa +00.800.2682.2682
Asia Pacific +800.6568.3000 | Or go to covance.com
© Copyright 2015 Covance Inc.
FINDING THE NEEDLE IN THE HAYSTACK JUST GOT EASIER.

Your search ends here. Patient recruitment remains a key challenge in drug development and a critical hurdle for rare and orphan approaches. Now, Covance’s unique recruitment solutions make finding clinical trial patients faster and easier. Only Covance has access to LabCorp’s patient database with de-identified information from over 70 million records used to identify potential areas of patient depth, plus thousands of patients who have agreed to be contacted for future trials through the LabCorp Beacon® patient portal. So when you place clinical work with Covance, we can help pinpoint the right candidates for your study with active programs to opt-in potential patients and reach out to their treating physicians. And our Xcellerate® knowledgebase matches patients with investigators and sites more likely to perform. There’s no need to go searching in the haystack. Call us today to find out more about our clinical solutions and unique patient recruitment approaches.

CALL TO LEARN MORE
The Americas +1.888.COVANCE | Europe/Africa +00.800.2682.2682
Asia Pacific +800.6568.3000 | Or go to covance.com

Covance Inc., headquartered in Princeton, NJ, USA, is the drug development business of Laboratory Corporation of America Holdings (LabCorp). COVANCE is a registered trademark and the marketing name for Covance Inc. and its subsidiaries around the world. © Copyright 2016. Covance Inc.
Who Wins In Pharma’s Externalization Journey?

Sales from drugs acquired via M&A tripled from 2005 to 2014. Amgen, Novartis and Lilly are expected to benefit from external R&D going forward, while Pfizer and BMS will garner a smaller share from this trend.

With external R&D becoming a bigger portion of the biopharma business, a new report lends support to the strategy of looking outside for innovation – showing that over time, externally sourced drugs yielded higher growth than internally developed drugs.

Datamonitor Healthcare’s report *Pharma Externalization Strategies 2016: Externalization Is Critical to Pharma Revenue* notes that co-developed and acquired drugs are driving growth across all biopharma peer sets – big pharma, mid-sized pharma and Japanese pharma.

**A TREND SPANNING BIOPHARMA**

Between 2005 and 2014 revenue from drugs obtained via the M&A process increased from an aggregate of $65bn to $178bn, with a compound annual growth rate (CAGR) of 12%. Meanwhile, co-developed drugs saw sales increase from $16bn to $40bn over that decade, with a 10% growth rate. Overall, externally sourced drugs grew with a 7% CAGR from 2005 to 2014, compared with 3% for drugs resulting from internal R&D.


The report anticipates that these trends will change significantly, however, during the decade spanning 2015 to 2024. The overall percentage of internally developed drugs across all industry segments is expected to drop to 51% in the next decade. Co-developed products will remain a good bet, with a CAGR of 6% over that period, while drugs brought in through M&A are expected to have virtually no growth.

“Revenue of acquired products is forecasted to increase at a CAGR of 3%; this indicates that pharma companies may have had more success with single-product acquisitions, as opposed to portfolios from whole-company acquisitions,” states report author Amanda Micklus.

The biggest decline is expected to be for in-licensed drugs, which have had slower growth than other categories. From 2005-2014, in-licensed drugs increased at a CAGR of 1%, compared to 3% for internally developed drugs. For the forecast period of 2015-2024, in-licensed product sales are expected to have a -3% CAGR, while internally developed drugs are expected to grow “at a slower rate of 1%,” according to the report.

**WHICH COMPANIES REAP MOST BENEFIT FROM EXTERNAL R&D?**

The external R&D trend has not been, nor is projected to be, consistent across all the firms comprising big pharma. In terms of sales, externally sourced drugs accounted for 47% of big pharma revenue during 2005-2014; that percentage is projected to increase to 49% during the 2015-2024 period.

Amgen Inc., Novartis AG and Eli Lilly & Co. are expected to experience the most significant increases in externally sourced product sales, while such revenue is expected to decline sharply at Bristol-Myers Squibb Co., Bayer AG, Merck & Co. Inc. and Pfizer Inc.

Among the 16 companies categorized as big pharma, half are projected to increase the proportion of revenue they derive from externally sourced products during the 2015-2024 period: see Exhibit 2.

In some cases, such as with Bristol and Pfizer, the projected decline is due less to ongoing deal-making and
more to the impact of patent expiration for an externally sourced blockbuster. For example, BMS is projected to see its share of revenue drop from 65% of total earnings during 2005-2014 to 48% during the ongoing decade, partly due to the impact of generic competition on anti-platelet agent Plavix (clopidogrel), which went off-patent in the US in 2012.

This is predicted to occur despite the consistent pace of deal-making the pharma maintained under its “string of pearls” strategy during the past decade. Bristol markets Plavix under a longstanding agreement with Sanofi.

Similarly, the loss of patent coverage in late 2011 for Pfizer’s blockbuster statin Lipitor (atorvastatin) is expected to decrease the share of its sales from external assets from 59% during the earlier decade to 42% in the next 10 years. Pfizer acquired Lipitor through the 2000 buyout of Warner-Lambert Co.

The analysis preceded Pfizer’s recently completed acquisition of Medivation Inc., outbidding Sanofi with a $14bn offer. The move brought in the prostate cancer blockbuster Xtandi (enzalutamide), which “should now have a big impact on Pfizer’s external sales,” Micklus told Scrip. “But it’s also worth noting,” she added, that “Astellas Pharma Inc. and Medivation have a profit split on Xtandi, so Astellas will continue to share in some of that.”

As to whether an M&A prone company like Pfizer could dramatically shift its trends, Micklus said: “For any deals to have an impact on future projections, they would have to include near-term drug candidates, close to commercialization, or drugs, like Xtandi, that are already on the market and are forecasted to have strong future sales. So it is possible that Pfizer will do such deals and balance that with its earlier-stage collaborations.”

By contrast, Novartis is expected to more than double the percentage of sales derived from externally sourced products over the 2015-2024 period, from 20% to 42%, the report says. Products acquired through its buyout of ophthalmology firm Alcon Inc., along with its co-development of the multiple sclerosis therapy Gilenya (fingolimod) and allergy drug Xolair (omalizumab) are expected to drive this change.

**JAPANESE PHARMA EXTERNALIZATION TO INCREASE**

Major Japanese pharma companies historically have relied on internally developed drugs for close to two-thirds of their total revenues, but this is set to fall for most companies in the group over the next few years as they increasingly tap into alliances and M&A, the report predicts.

Compared to the average of 60% for the 2005-14 period, the proportion of revenues deriving from in-house drugs is set to decrease to around 53% over the 2015-24 timeframe, with sales of products sourced from external partners rising in parallel.

**EXHIBIT 2: SHARE OF EXTERNALLY SOURCED REVENUE BY COMPANY**

While Japanese pharma’s revenues from internal drugs grew at a constant annual growth rate of 4% from 2005-14, they are forecast to decrease by 1% over 2015-24 in line with this shift. The comparable figures for external revenues are 6% and 2% respectively.

While there is some variation, the external sourcing of pipeline assets is increasing generally within global big pharma firms, with a clear overall trend towards external sources of innovation.

Globally, in-licensed drugs were also found by the report to bring more growth than those developed in-house. For the Japanese pharma peer set there was strong sales growth in the 2007-12 period, but “there was a shift in 2009, when external R&D began increasing in proportion to internal R&D,” Micklus notes.

“Japan Pharma also goes against the trend of the other (global) peer sets in that the averages for per-drug revenue for internally developed products are slightly higher than those for externally derived drugs,” she adds.

Japanese pharma has had a sharper decrease in its share of partnered drugs (from 50% in 2011 to 39% in 2016), while unpartnered products have increased in share.

The biggest jump is expected at Takeda Pharmaceutical Co. Ltd., which over 2005-14 realized just 27% of its revenue from externally derived products, a figure Datamonitor expects to jump to 48% in 2015-24. A couple of factors have influenced this shift: firstly, the loss of exclusivity for blockbuster Actos (pioglitazone) starting in 2011; and secondly the rising contribution of acquired products.

Among other Japanese firms, Sumitomo Dainippon Pharma Co. Ltd. is expected to see the biggest decrease in its proportion of externally derived product sales, which in 2005-14 were 66% but are forecast to drop to 24% in 2015-24, due to generic erosion of in-licensed and acquired drugs including Amlodin (amlodipine). Novartis is expected to more than double the percentage of sales derived from externally sourced products over the 2015-2024 period.
Biosimilars: The Unlikely Hero Of Specialty Pharma?

In the patent cliff musical chairs game, the music has stopped and generic companies like Mylan and Teva are looking for the next growth driver. While this seems to be biosimilars, it appears that innovator companies that are used to developing biologics are already occupying the seats.

At the J.P. Morgan Healthcare Conference in January 2013, I was struck by how well generic pharmaceutical companies were preparing themselves for their own patent cliff. The end of the lucrative period based on the 180-day generic exclusivity grants on large numbers of blockbuster from big pharmaceutical companies was in sight and plan Bs were being prepared by the companies that were at the time Mylan Pharmaceuticals Inc. and Watson Pharma Inc.

It is testament to the success of those plans – that included US and international consolidation and the development of branded products – that neither of these aforementioned companies exists as they did in 2013. The US generic pharmaceutical sector took on a much more global and specialty bias. That transformation has now largely run its course and for the resulting larger generic pharmaceutical companies with significant branded businesses other challenges have reared their heads. Not the least of these is where to find growth in a deflationary generic drug pricing environment – and that needs a plan C. That plan is likely to be the development and manufacture of biosimilar drugs.

Biosimilar drugs have not had the best of commercial starts and as such, seem an unlikely savior for the specialty pharmaceutical sector. The first biosimilar drug was approved in Europe in 2007 and was one of seven versions referenced to Amgen Inc’s Epogen (epoetin alfa) that were approved that year. There then followed a period where I would listen to Amgen’s quarterly calls describing the muted impact of biosimilar Epogen on its business, which was in any event transitioning away to longer-acting versions still under patent protection.

Nearly 10 years later there are around 20 biosimilar products approved in Europe and that longer-acting Epogen is already facing competition in the US and the EU from Roche’s Mircera (methoxy polyethylene glycol-epoetin beta) which admittedly was approved in the US as a new biologic rather than a biosimilar. The 10-year history of biosimilars in Europe does suggest that their success cannot be guaranteed by just being cheaper than the reference product, despite cost-containment pressures in the EU. This is probably because biosimilars are only similar to the reference molecule and those differences (real or imagined)
have given a new generation of marketing managers something to stress in their messages.

The other reason why biosimilars may appear to be an unlikely savior of specialty pharmaceutical companies is that to be successful, some entity other than the company developing them has to make money. That has only recently started to be appreciated by dialysis clinics where capitated budgets offer an opportunity for profit by substituting a biosimilar for a reference product. Pharmacy benefit managers have also recently started to exclude reference products from their formularies in favor of biosimilars and retain that portion of the profit that is not passed on to their insurance company clients. Add to this profit imperative to what is likely to be a continued focus on drug pricing after the US election, and there are opportunities there for someone.

Generic pharmaceutical companies have been more than dipping their toes into biosimilars. At the thin end of the biosimilar wedge, Novartis AG through its Sandoz subsidiary and partner Momenta Pharmaceuticals Inc.’s generic Lovanox (enoxaparin sodium) has been an example of a complex product that should have been a generic finally succumbing to a biosimilar approach. Multiple generic versions have, however, kept Momenta loss-making. Mylan also has a biosimilar collaboration with Momenta and after holding out the longest while acknowledging its appetite for biosimilars, Teva Pharmaceutical Industries Ltd.’s recent collaboration with Celltrion Inc. on biosimilar monoclonal antibodies finally allowed Teva a seat at the biosimilar table.

The power in this rush for biosimilars by generic pharmaceutical companies does not seem to be with the smaller biosimilar upstarts: despite product approvals, Momenta still seems to be struggling for attention by investors, Coherus BioSciences Inc. has had the odd hiccup with pharmacokinetics and Celltrion had to wait until it had visibility on its transatlantic filings for two biosimilar monoclonal antibodies before Teva jumped on board.

A key issue with biosimilars is that while their profitability is attractive to generic pharmaceutical companies, those best placed to develop a biosimilar may not be small molecule generic companies or the new upstarts but those that have already proven biologic, regulatory and GMP manufacturing competency with regulators and the market. Yes, the best chances for biosimilar success would be found by those big biotechnology and big branded pharmaceutical companies that already produce the reference molecules. What is it called when your nemesis becomes your next growth driver?

In a sense, Novartis was among the first branded pharmaceutical company to invest in biosimilars with its collaborations with Momenta on generic Lovanox and Copaxone (glatiramer acetate) but a better example is probably Amgen. Amgen could have just bleded on to judges and juries in cases covering the exclusivity for its own biologic products (and will continue to do so) but if you have the ability and capacity to produce and market a biosimilar blockbuster like Humira (adalimumab) why wouldn’t you? This is exactly what Amgen, Pfizer Inc. and Biogen Inc. have done but it leaves companies like AbbVie Inc. and Johnson & Johnson (J&J) on the other side of this stance – with just referenced products and no biosimilars – woefully exposed to their traditional growth drivers.

Biosimilar drugs have not had the best of commercial starts and seem an unlikely savior for the specialty pharmaceutical sector.

The potential for biosimilars is starting to be recognized as Momenta’s deal with Mylan on a generic Orencia (abatacept), among others, threatens to do to Bristol-Myers Squibb Co. what Amgen and Pfizer would like to do to AbbVie and J&J. Other biosimilar collaborations are still at an early stage. Nevertheless, their value is also obvious since Pfizer’s acquisition of Hospira Inc. On the day that Shire PLC returned biosimilar versions of Enbrel (etanercept) and Humira to Coherus and Momenta respectively, the share prices of both recipients rose.

While biosimilars are starting to look like the next growth driver for specialty and branded pharmaceutical companies alike, ironically the pressures for their development seem to have been recognized a little late for some innovator companies. The biggest insulin-producing companies, Novo Nordisk AS and Sanofi, have already experienced the sharp end of PBM cost-containment measures that demand the lower prices in order for formulary access. Another strategy in their armory could have been to launch authorized generic insulins not only to secure formulary status, but to head off biosimilar insulin. Unfortunately, Eli Lilly & Co. and Boehringer Ingelheim GMBH’s generic insulin launch and inclusion in UnitedHealth Group Co’s formulary means that the first of those ships has already sailed.
Pharma companies with drugs ranked in the top 10 by global sales in 2015 will need to find an extra $26bn in revenues just to make up for the anticipated loss in sales through to 2020. Of the ten best selling drugs of 2015, only Celgene’s Revlimid, according to Informa’s Datamonitor Healthcare, is expected to see an increase in revenues in 2020.

$26bn The amount of money lost by drugs currently topping the charts is forecast to slip by 2020.

The number of drugs currently in the top ten that will still be there in 2020.

The year Avastin will be relegated from the top ten selling drugs on the market.

Cumulative sales of the TEN TOP selling drugs.

Humira (adalimumab) Inflammatory Abbvie

$14,012

Harvoni (ledipasvir/sofosbuvir) Hepatitis C Gilead Sciences

$13,864

Enbrel (etanercept) Inflammatory Amgen/Pfizer

$8,697

Remicade (infliximab) Inflammatory J&J/MSD

$8,355

Mabthera/Rituxan (rituximab) Cancer Roche

$7,115

Lantus (insulin glargine) Diabetes Sanofi

$7,029

Avastin (bevacizumab) Cancer Roche

$6,751

Herceptin (trastuzumab) Cancer Roche

$6,603

Revlimid (lenalidomide) Blood related disorders Celgene

$5,801

Sovaldi (sofosbuvir) Hepatitis C Gilead Sciences

$5,276

Humira will retain top spot as best-selling drug in 2020.

Harvoni will lose its runner up position, replaced by Gilead Sciences’ follow-up hepatitis C drug with forecast revenues of $12.1bn (2020) and $11.5bn (2023).
How long will it take your sales team to reach 42,000 senior decision makers in pharma companies globally?

Let us demonstrate how we can do this and show you ROI now!

MATT DIAS • HEAD OF ADVERTISING
Phone: +44 (0) 20 701 74188
Email: Matt.Dias@informa.com
Curb Your Enthusiasm:
Chinese Pharmas Going Global Hit Speed Bumps

Ambitious and confident Chinese pharmaceutical buyers have begun to enter a new brave world of foreign M&A. However, this scenario can be littered with internal challenges and increasingly external scrutiny, less solid pre-deal asset identification and poor post-deal execution, all of which can damage their barely gained credibility, creating hurdles for future deals.

They come with big ambitions, and a deep pocket, only to be met by potential acquisition targets who have concerns and second thoughts. The trend is nevertheless evident – the outbound investment from China is going up, year after year.

China’s foreign direct investment (FDI) increased by 18.3%, reaching a record high of $145.6bn in 2015, which puts the country after only the US in the world, according to an annual FDI report released Sept. 22 by China Ministry of Commerce, National Statistics Bureau and State Administration for Foreign Exchange (SAFE).

This is the 13th consecutive year of Chinese FDI growth. By the end of 2015, China Inc. had a total of $4.37tn in capital outside China, according to the official report.

The healthcare sector, for one, has seen a steady increase in deals in which Chinese companies acquire or invest in overseas assets.

In 2016 alone, several such high-profile deals were inked, including Luye Pharma Group Ltd’s acquisition of Swiss Acino Holding AG’s transdermal business for roughly $267m, and Fosun International Ltd’s $1.26bn purchase of Indian Gland Pharma Ltd.

Other less prominent ones include Shenzhen Hepalink Pharmaceutical Co. Ltd’s acquisition of US biotechnological contract manufacturer Cytovance Biologics Inc. for $205m.

M&A aside, overseas expansion is rising rapidly. Jiangsu Hengrui Medicine Co. Ltd. subsidiary Hengrui Therapeutics Inc. completed what is believed to be its Series A round from HR Bio Holdings, a joint venture created by Hengrui and an undisclosed US blue chip investment firm.

The ultimate goal for the Chinese pharmacos is a global presence, and an eventual place among the world’s top 100 pharma companies.

The new crop of outbound M&A transactions from China is aimed to “access new profit pools, capture new markets, and tap the skills of globally competitive leaders. Acquirers also view outbound M&A as a way to obtain cutting-edge technology as well as brand and management experience in overseas markets,” noted analysts at Boston Consulting Group in its report on the subject.

However, the pathway is much more complex, requiring more expertise beyond Chinese pharma’s ambitions and newly gained confidence, experts cautioned.

The challenges come from three fronts: pre-deal asset identification, deal-closing process and post-deal execution.

By the end of 2015, China Inc. had a total of $4.37tn in capital outside China

Buyers’ Burden

When it comes to asset identification, a gap exists between Chinese acquirers and foreign sellers.

Chinese companies are more likely to look for single assets, usually in areas considered to be hot, and work with companies that are already known.

Luye’s acquisition of Acino, for one, is aimed to acquire a new system combining the latter’s transdermal technology with its own new reformulations, said the company VP for international M&A and investor relations, Sammy Jiang.

Despite the promises, a more seasoned approach expanding from single assets to long-term cooperation
is likely to yield more results, noted Jin Wang, venture capital partner at Shanghai-based Jianxin Capital.

“Not limiting to single product and its profits, and examining the subject company’s fundamentals and prospect, will likely to deliver more surprising benefits via capital investment cooperation,” Wang wrote in a March article.

The role of middleman is also necessary and needs developing for Chinese buyers. A good middleman allows buyers to proactively scout potential assets, going beyond what they already know or are familiar with.

Jiang said Luye had been getting to know Acino since 2012, and the familiarity helped to seal the deal. Such ability to “name the names” of desirable companies shows that buyers need to have clear strategic targets, she added.

Additionally, a blessing from the boss is usually enough to get it done in China, particularly for private companies. However, it takes considerably more to persuade many in Western companies, not only CEOs but chairman, board directors, etc. How to deal with individuals and how to get it done right requires reckoning, experts pointed out.

That puts the burden on the buyer’s shoulders to do more, and a pursuit of latest technologies also bring more pressure on due diligence.

Chinese companies will have to do more, beyond just the top. They also need to seek out professional advice – not necessarily the cheapest – and put value into the equation, suggested experts.

**BIG AND DIFFICULT**

While Chinese buyers come armed with cash and a strong desire, the high rate of deals failing to go through because of funding or regulatory issues can increase skepticism from foreign sellers, leading to a cost premium and second thoughts.

“In the US, bankers’ perception of buyers from China is now very skeptical, which is fair, they appear to be aggressive [in the beginning] but [deals] fail to go through,” noted a local investment bank’s director of M&A.

The biggest challenge is therefore to differentiate credible buyers from the rest, he noted, adding that for overseas buyers who are more sensitive to bad news, Chinese buyers are perceived to pay top dollars and are welcomed into the process, but sellers have second thoughts.

The reason lies not only in a high uncertainty in China given regulatory challenges, but is also financially-driven: how do the foreign bankers know if the funding for the deal is actually there, he pointed out.

To them, China is big but difficult, the expert said. To that end, the buyers are usually disadvantaged, having to pay 20-30% premium over others.

Wang at Jianxin Capital also emphasized a need to hire professional advisors and a middleman, as well as increasing exposure to deal-making negotiations.

“Chinese drug makers have a relatively short history doing cross-border transactions, and they lack experience and talents. They need to have good lawyers, advisers, and middlemen, an expanding horizon for assets selection and collaboration opportunities.”

Despite this, they may have to manage expectations on timeframe and deal structure. After the first deal is done and reputation established, subsequent deals will follow.

The differentiation of being a credible buyer also involves looking for what a seller wants out of a deal and preparing accordingly. However, both the buyers and sellers need to compromise. While Chinese drug makers need to do their homework, overseas sellers also need to spend time in China and get to know it better. “It needs both sides to make concessions; otherwise the cost of communications will be too high,” Wang said. “After accumulating experiences, they will get better.”

If pre-deal preparation and during-deal execution are time-consuming, post-deal integration is where most fail.

The post-deal challenge is to make sure buyers get what they desire the day following the transaction, said Luye’s Jiang, who added that a three-year plan should be in place to ensure the development is on track.

Although a business transaction may proceed according to plan, the cultural gap is hard to overcome in a short time. Having a Chinese owner is still new and several domestic frontrunners have failed to successfully manage foreign workers after a merger, leading, ultimately, to an M&A battleground.
Christophe Weber became president and CEO of Japan’s Takeda Pharmaceutical on April 1, 2015, in the process becoming both the first non-Japanese and first corporate outsider to hold the position at the more than 230-year old company. He has since initiated a ground-up refocusing and restructuring that will alter the fundamental shape of the company while aiming to retain its core identity.

Q What made you decide to accept the offer from Takeda, and what did you see as the main challenges for the company at the time you took over?

I was really attracted by the history and strong reputation of the company inside and outside Japan, but at the same time it had not completely globalized and had lost some ranking, like many Japanese companies. So it was a very exciting challenge to make Takeda more competitive.

Q Once you became CEO, how did you go about getting to know the company and its people and communicating your vision?

From day one I was really accountable for the whole company…and that was a very powerful way as I didn’t have to think about “Step 1, Step 2, Step 3.” I spent the first few months [from April to July 2015] after joining just understanding the company, the culture, the employees inside and outside Japan, because something that is misunderstood [about Takeda] is that 70% of our employees are outside Japan.

I had a very significant listening period and I held a huge number of workshops to get a good feel about what is working well, what we could improve.

Q Did you feel Takeda had an appropriately balanced business both geographically and by scale at that time?

It depended on the area. Takeda has been an extremely diversified company, there were no real global brands, so every country, every region was generating its own strategy independently from the others, because of the historical set up.

What we decided was to globalize some areas, for example R&D, and reset ambitions here to define what innovation means. We confirmed we want to be an R&D-driven company with an R&D engine serving the world with products with global potential. We also globalized manufacturing which was in three organizations and lacking a lot of potential synergies.

What was more uncommon was that we also globalized the values of the company, which were very strong. We defined that internally as “patient, trust, reputation, business.”

Every manager around the world who joins the company spends one week in Japan now to understand the company. Some areas we wanted to keep more local – the [country] general managers are really key to deliver the right service to the market and we believe that every country is very different…we wanted to keep this agility and customer-centricity.

Q What were the main factors behind the decision to focus on selected therapeutic areas and why do you see these as providing attractive opportunities?

It’s a very strategic and long-term decision. We stepped back and asked what is the environment asking – and that is significant innovation. The winner will be the company able to deliver truly innovative medicines.

We looked at our strengths and weaknesses by therapy area because Takeda was doing screening in the traditional way and developing hit molecules across therapy areas. But the risk is that there is no real innovation and you may not be the first.

Our approach now is to focus on a few areas where we believe we can be the leading company, or one of the leaders. We start from the disease and the biology and then design a molecule against this, finding partners if we cannot do this ourselves.

So it’s a big change and it took a while to narrow down to three areas [oncology, CNS and gastrointestinal] plus vaccines. Takeda has been active in diabetes and cardiovascular for a long time, with some significant products, and we will not drop these.

We also looked at our financial resources and how much we could commit to R&D [about $3.3bn annually at present] and we found a balance with this.

Q Was it the market potential or unmet medical needs in those focus areas that were most attractive?

For sure, also internal capabilities and our market understanding and competition intensity. For example, oncology is already big for Takeda and was a “no-brainer” even though it is highly competitive. But we will not go everywhere in oncology.

In CNS we don’t have a large portfolio but we have invested for many years and we feel the unmet need is very
Within these areas can you talk about why you see Entyvio and Ninlaro becoming so successful?

In 2014 it became clear that Entyvio [vedolizumab, for ulcerative colitis and Crohn's disease] was a major innovation and had potential for a global launch so we are launching as quickly as possible everywhere.

It is a new agenda for Takeda and we are repeating a global launch with Ninlaro [ixazomib, for multiple myeloma] and so I think it has been a huge transformation as historically we were a primary care company and we have become more of a specialty care company, and it has been a huge shift in medical and sales capability for example, but I am very pleased it has been very successful so far.

Entyvio is really delivering well everywhere, including emerging markets, where we have reconfirmed our commitment in our strategic refocus. We want to be present in many countries but not everywhere. We are still much more diverse [in products] than many companies but Entyvio is now our biggest product.

What led to the huge decision to fundamentally restructure R&D – were fixed costs and infrastructure inappropriate? How do you see outsourcing working in practice?

This is linked to our therapy area focus, we have to real-just it’s capacity. It’s more a quality-based process. We believe its good to concentrate our sites to become more efficient because if you have project teams across five sites, it’s very difficult.

So we will concentrate discovery and R&D in Japan and Boston, Japan mostly on CNS and Boston on oncology and GI. The other big change is the partnership with PRA Health Sciences, which will allow us to resource flexibly depending on the pipeline, we don’t want to be constrained by fixed costs and want these to be adjusted according to the pipeline.

It’s not a traditional CRO relationship, it’s a very integrated partnership and we will share pipeline developments with PRA in advance. Takeda was actually outsourcing a lot already.

Another thing is that we want to avoid developing sub-optimal assets just because we have the [internal] capability – we want to put the bar very high for innovation. In a way it will free up our ability to decide which assets to take forward.

Do you have any other internal programs to support women in major executive roles?

Very much, it is part of these moves. We have significant global diversity programs. In Japan we have created a network of women managers who meet a few times a year, but also we have actively looked at HR practices for promotion, work style, and flex-time, so we are trying to help women in their daily life.

We are also progressively moving away from age-based promotions, which tended to work against women who might have missed out at that particular time in their life due to family commitments.

Progress is steady but slow. On the board we have a Japanese woman living in San Francisco [outside director Emiko Higashi]. I know it’s still not a lot.

Takeda is also pretty much unique in its board setup in that we now have many more external directors than internal…it’s very diverse.

Can you describe your vision for the shape of Takeda in five or 10 years?

I would focus on 10 years as this is the type of horizon I have in mind, and my ambition for us is to be a company with a great reputation in society, in Japan and outside. To bring value through innovation and access to innovation – I am very sensitive to the pharma industry’s reputation.

In 10 years we will have an R&D engine among the best in terms of productivity and output in the field of oncology, GI and CNS.

We will be a globally competitive in the top 20 in terms of market capitalization, growth, margin, so financially we will be very competitive, back where Takeda was some time ago.
LeaderShip

FROM Y/Z TO GOODBYE:
Lechleiter’s Lilly Legacy

Outgoing Eli Lilly CEO and president John Lechleiter looks back over his biggest strategic decisions while at the helm of the pharma major and pinpoints some of the key navigational markers for the next phase in Lilly’s lifespan.

When John Lechleiter took the reins of Eli Lilly & Co. back in 2008, the outlook was not very rosy for the Indianapolis-based company. Tasked with leading the company’s 41,000 employees through what he terms the “Y/Z period” (the years 2011-2014 where patent losses punctuated the big pharma’s financial performance), he had to create solid strategies that would guide the company back to its glory days.

Lechleiter had already worked for Lilly since 1979, beginning his career as an organic chemist before winding his way around various company functions including project management, regulatory affairs, product development, and pharma operations. In 2005, he was named president and chief operating officer and joined the board of directors. He jokingly explains that when he became CEO, he had to deal with the challenges that he had helped to create as part of the senior leadership team. At the time, Lilly faced the loss of patent exclusivity on four of its biggest products: the anticancer Gemzar (gemcitabine) in 2010; the antipsychotic Zyprexa (olanzapine) in 2011; the antidepressant Cymbalta (duloxetine) in 2013; and the anti-osteoporotic Evista (raloxifene) in 2014. The board knew the company would need a strategist that could unwaveringly stick to the message: R&D investment will get us out of this.

“We had to have a strategy for navigating through a difficult period, so we put a lot of emphasis on advancing the pipeline. We began to think about opportunities to look outside our walls for innovative molecules,” he recalls. The first evidence of this would be the $6.5bn purchase of ImClone Systems Inc. in October 2008 for reasons centered solely on the pipeline. The pipeline in question, at that time, had four molecules that were in clinical stage development: Cyramza (ramucirumab), which is cleared for first-line squamous NSCLC, and cixutumumab, which ultimately fell by the wayside. The soft tissue sarcoma drug Lartruvo (olaratumab) was recently granted conditional marketing authorization in Europe.

In hindsight, it seems as though Lechleiter’s first big move as CEO has worked in Lilly’s favor. At the time, the company was at one of its darkest hours and Lechleiter knew he wasn’t going to have it easy. “I’d been on the senior management team and so this [patent loss] was not unexpected, and in this industry it’s really hard to avoid: you can’t arrange your products like pieces on a playing board. When patents go, patents go,” he states.

“I think we had a fair degree of confidence in early 2008 that we had a pipeline that would enable us to begin to replace some of the lost revenue and then grow from there. What we didn’t count on was the number of pipeline failures. That, to some degree, surprised us, several of them occurring in Phase III, obviously. I think that increased the challenge – or the degree of difficulty of the challenge – that we faced,” he says.

It was the board’s decision, led by a resolute Lechleiter, to continue the company’s heavy investment in R&D, and to increase this investment every year up to 2014, when it fell to “reflect the maturation” of the company’s Phase III pipeline. Lechleiter acknowledges that R&D spending was cut also because of the huge revenue hit caused by the patent losses on Evista and Cymbalta but he simply describes this as “playing the hand you’re dealt”.

“I knew what my tenure would likely encompass, this whole Y/Z challenge, I’d been here through what we called Year X, which was when we lost the Prozac (fluoxetine) patent in 2001, so the nature of the challenge wasn’t new, but obviously the magnitude was much greater this time,” he recalls.

Restructure

Hit by high-profile Phase III failures and bracing itself for the upcoming tide of patent losses, Lilly’s restructure and downsizing were inevitable. In September 2009 the company was reorganized into business areas to allow it to focus on core therapeutic sectors including diabetes, oncology and what it called Bio-Medicines. Lechleiter says he knew at the time that this was the right move for the company, calling it a “wonderfully helpful decision”. Staff embraced it and it made an immediate difference to the company’s competitiveness in its Y/Z period, he says.

While the company reshuffled it also announced the elimination of 5,000 positions. Lechleiter recalls this as
his most difficult decision but one that was necessary to “keep the company off the skids. That impacts people, it impacts families, it’s not something that I think any CEO could ever not lose sleep over. At the same time the decision was necessary to make sure that ultimately the enterprise succeeded and of course we have so much more there at risk, 35,000 or 38,000 jobs, so you do these things because you have to, and must, in certain situations,” he explains.

**LILLY’S NEXT PHASE**

As one would expect, Lechleiter is Lilly’s biggest cheerleader. His steadying influence and stoic focus when keeping to the company’s strategy has worked in the past when a firm hand was required on the rudder. “I’ve said publicly I think Lilly’s best days are ahead and when I look back at the challenges of the work that we had to do between 2008 and today, I think the good news out of that is that Lilly is well placed and well positioned today to be successful in the future based on what we have been able to put in place.”

In May, the company made clear its ambitions to launch 20 new drugs in the decade between 2014 and 2023. It has launched six already, and two are under regulatory review. Overseeing this next period of potential growth will be David Ricks, Lilly’s current president of Lilly Bio-Medicines since 2012, having previously led Lilly’s business operations in Canada, China and the US.

During the press briefing to announce the CEO succession, Lechleiter said that Ricks “has significant experience in aspects of our business the board believes is essential to success: the development of new products, sales and marketing, and public policy, both in Europe and the US and globally.”

Revenues in Q3 of 2016 were up by 5% from the comparable period of 2015, led by sales of diabetes drugs Trulicity (dulaglutide), Jardiance (empagliflozin), Cyramza and psoriasis drug Taltz (ixekizumab). Lilly has a stated goal of generating at least 5% average annual revenue growth rate from 2015 to 2020, even without its Alzheimer’s disease candidate solanezumab which only recently failed its third Phase III trial in a row, casting a shadow over the AD pipeline portfolio. “If I was going to look at Lilly in 10 years my hope is that we have a substantial neurodegeneration presence. I believe we will continue to be able to build a leading diabetes business with today, in essence a molecule or a drug in most of the key classes or categories there,” he says.

Lechleiter points to Lilly’s four core therapy areas: diabetes, oncology, neurodegeneration and immunology. He also highlights two “very interesting” Phase III molecules in pain; tanezumab, a nerve growth factor (NGF) antibody partnered with Pfizer to treat cancer pain, chronic lower back pain and pain related to osteoarthritis, and galcanezumab, a calcitonin gene-related peptide (CGRP) receptor antagonist in development for cluster headaches and both chronic and episodic migraine. “That’s an area where we really, really need new treatments, we need alternatives to opioid therapies,” he stresses.

**FINAL THOUGHTS**

Pride, he says, is the overall feeling that will accompany him when he retires on Dec. 31. He is notably proud of Lilly’s place as the last non-merged major pharma company, a position of independence that has been earned, he says, by winning the approval of shareholders with its plans for the future. “I think that where we are currently compared to where we were only a few years ago is clear evidence that we are back in favor with shareholders, we can make a claim for that independence.”

Despite Lechleiter’s tumultuous presidency at the company, he is very upbeat about the future of the industry as a whole. Despite the challenges brought on by “navigating through an ever more complex world from a payer perspective”, the good news is, he says, that there is going to be a “tremendous demand” for the products that the industry generates. “The scientific substrate has never been more robust. This has to be the golden age of pharmaceutical science when you look at what we’re able to learn, to use and to capitalize on more quickly to come up with decent drug candidates and to get those into human testing.”

He is realistic about his fortunes and performance as a CEO, and about Lilly as a company, stating that you have to aim high and expect some failures along the way, especially when the stakes are as high as they are in drug development. “No organization is perfect, the path is never straight and there have been many challenges over the years. We’ve made mistakes, but we’ve had some brilliant success.”

---

*John Lechleiter*
Growing Grünenthal

As he leaves after 23 years at the firm, outgoing CEO Eric-Paul Pâques talks about Grünenthal’s growth and strategic priorities under his leadership, while its new head, Gabriel Baertschi, brings his own brand of energy.

Q Has your leadership style changed over the time you’ve been with Grünenthal?

My style changed over time simply because I was getting older. I started in an executive position when I was 40; you learn a lot in 30 years and you adapt your behaviors and beliefs. You can be very dogmatic as a young guy and then life teaches you a thing or two and you change. But something of my style which remains is an emphasis on credibility and authenticity.

I believe if we are not credible as leaders, if we are not authentic we will not endure. I ask everybody to be anti-dogmatic. People follow the mainstream so easily and I say, “We have a brain and a gut, and we need to use our brain as far as possible, but when we come at the end of what we can do with our brain then we need to trust our gut.”

Q What’s been the biggest impact you’ve made on the company in the last three years as CEO?

What I’m very proud of is that we have a very unified executive board and that is a catalyst to boost the company. We moved the company from revenues of €930m up to €1.4bn that we are going to achieve in 2016, in three years. We were losing money when I took over and we are going to generate significant profit this year and that’s all because we are all very much aligned. It’s all about implementation of strategy, and that starts with the board speaking with one voice and delivering on promises.

Once you commit to something you need to deliver. We have been very tough on that and I think the numbers speak for themselves.

Q Grünenthal has sharpened its strategy with regards to R&D, can you explain what has changed?

Currently 60% of our revenues are generated by products we have discovered and/or developed at Grünenthal. We have been working with partners in the US, we had a very long partnership with Johnson & Johnson and then we moved to Depomed, which is now selling our major product in the US and Canadian markets, tapentadol.

That being said we have decided to move Grünenthal in a direction where, due to our size, we concentrate our action on focused label products. We are not going to go in large broad label indications in moderate to severe pain anymore. These days in Europe, you don’t get a decent reimbursement for that, so that’s why we sharpened our strategy. We are going to focus on small indications in pain, for example Complex Regional Pain Syndrome (CRPS), which has an orphan status with an extremely high medical need.

We want to remain a pain company worldwide while focusing on the non-addressed pain status. And there is a huge need. Look at non-responders: can you imagine that almost half of the patients receiving pain analgesics are poor or non-responders? That’s the kind of things we want to address.

The future of a company like Grünenthal is based on innovation. We are not a generic company; we do not want to be a generic company. Since we are a midsize company we can only innovate in very focused areas. We have decided to double our investment in R&D for next year, just to demonstrate that we are highly committed to innovation.

I used to say research is a promise where we very rarely deliver, it’s the nature of R&D in pharma. But despite that,
“Grünenthal will lose the exclusivity for some core products within the next 10 years, starting with INTAC and ending with Palexia (tapentadol). To compensate this, we must seek to develop a sustainable, risk-diversified innovation portfolio. Grünenthal will keep building up in pain and beyond and close gaps in the pipeline by pursuing external growth. To go beyond pain means to develop additional therapeutic fields and Grünenthal is currently evaluating inflammation, late stage Parkinson’s and several technology platforms. It is essential to keep reaching out to biotech companies, universities and industrial partners. The cooperation with a reliable partner network is crucial if we want to enrich our innovation portfolio.

Business-wise, Grünenthal will strengthen engagement in Latin America. Recently we integrated the Laboratorios Andromaco in Chile and the Almirall portfolio in Mexico. That has given us an even stronger basis in this region and it is our aim to make as much revenue in Latin America as in Europe.

Last, but not least, I want to foster our commercial partnering for the US business and have a closer look at our geographical footprint.

I strive to guide the company through these processes and enable the development of game changing innovation in catastrophic diseases. Grünenthal already achieved to be a more than €1bn company in terms of revenues. It is my goal to work together with my team and all employees to make it a €2bn company.”

the commitment to invest is extremely high because that’s the only avenue we see for our company.

Q What achievement are you most proud of at Grünenthal?

Among other achievements, I’m very proud about having identified the need for abuse deterrent technology in the US. One day I was in New York and in the New York Times there was a big article on misuse of opiates. I returned to Germany and said that we needed to find a solution, and today we cover something like 80-85% of the slow release opiate market in the US with our technology, INTAC.

I’m also very proud about how we have developed our Latin American markets. A few years ago LatAm was one tenth of our sales and now LatAm really is exploding, number-wise. These days we are roughly at €500m in terms of revenues and we are moving to bring LatAm at the same level as Europe in terms of top line and bottom line. We want to partner with big pharma in Latin America. A few years ago LatAm was one tenth of our sales and now LatAm really is exploding, number-wise. These days we are roughly at €500m in terms of revenues and we are moving to bring LatAm at the same level as Europe in terms of top line and bottom line. We want to partner with big pharma in Latin America. We are in many countries which are not of interest for big pharma, and Grünenthal is reliable company there.

Q What’s your biggest frustration at working within Europe or European healthcare systems?

My frustration is with the [European healthcare] authorities. The European Medicines Agency (EMA) has evolved rapidly in a good direction, I’m very pleased about that. Now what’s frustrating all of us is the pricing authorities. Each single country has a different pricing authority and different metrics. What is good in Germany is bad for the French authority, and so on and so forth. It’s frustrating for companies and it’s not good for the patients. If you look at the main drug we have put onto the market in the last three years; Tramal (tramadol), we have been fighting with the authorities in France for four years to get a reimbursement.

Q How involved were you in looking for your replacement and what was the executive board looking for in a new CEO?

I met with Gabriel [Baertschi] and I am very much impressed, not only by his international experience, but also by his energy. We are just starting the implementation of the science base of our strategy and I think it’s time to have a change of generation. We need somebody in the company who will be there in 10 years from now and will make sure that we consistently implement the strategy. We need somebody who will learn the positive and the negative side of each implementation. So I think that now is a really good time to do it, it needs to be done by a young, very dynamic person and I think that’s what we have with Gabriel.

Q What are your hopes and dreams for the company as it goes off without your influence?

There are three dimensions. Firstly; I’d like it to keep the pace of the last three years. We have been growing by 15% and we need to keep that going. Secondly; if we do keep growing, then we can invest in R&D as much as we need. In the foreseeable future we should be able to invest at least €400m in R&D. And thirdly; we need to continue to sharpen our R&D effort on focused label indication. We are not big pharma, we cannot go for big indications and there’s plenty of space and plenty of needs which are underserved. That’s where Grünenthal should focus on.

Q What would you like your Grünenthal legacy to be?

I would like to be remembered as somebody very committed. This company has been somehow my life, I have been fighting a lot for this company and I want to be recognized as loyal servant.
In your view, how does the R&D paradigm need to change to deliver more drugs to market?

Drivers such as the patent cliff and the cost of R&D are forcing the industry to think differently. Many companies still operate in silos. There may be experts in various developmental phases, and they all want the gold standard for their specific area, rather than thinking about what is phase appropriate, and what is appropriate for drug development in absolute value terms.

There is a slow change, companies are bundling phases a little more now, and integrating some the value chain vertically. The next big drive is going to be how to align CMC (chemistry, manufacturing and control) with regulatory preclinical, and discovery in an integrated manner. There is still a huge amount of white space between each business segment. We see large numbers of interesting compounds from customers reaching the end of medicinal chemistry phase that are not formulated in a phase appropriate manner. This regularly causes delays before you proceed into formal preclinical. While some steps of the developmental processes have been integrated, the cross-silo challenges still need to be addressed.

Has translational research delivered what it promised?

I think it has but it’s worked in the ‘easier’ therapeutic areas. If you look at oncology, safety and efficacy are typically very clear and you can use classical translational approaches. I believe there is still naivety around the translational models being utilized, with historical precedence driving people to use a certain model. Using COPD as an example, people are still using the same challenge models they’ve used for the last 30 years. People are using other technologies and endpoints around it, but there is still precedence to use old approaches.

Do you think that big pharma has been too slow to evolve the R&D model?

There is a power game going on within the pharma industry. You have the scientists still with the view that they know better, which they theoretically do in terms of making a drug. Then you have the financial driver on the other side. There should be healthy friction between the two and sometimes it doesn’t work the way it should. Take outsourcing as an example, initially scientists chose which CRO to use, then it became procurement-driven where CROs were selected down to three favored providers or even a sole provider. There was a focus on quantity and price rather than actual value created in the asset.

The new generation of strategic procurement experts and a lot of CPOs now understand that ‘time is money’, and you look at the quantitative value of your asset in terms of how it progresses through the pipeline. Looking at Asian CROs versus US or EU CROs on a cost basis, it is clearly cheaper to do the work in Asia. I wouldn’t argue against that, and providing you are very directive, that’s probably very good value. But if you are looking for value which is created as a joint solution from using the technology and knowledge within the CRO industry, that’s a different argument. The value is different.

How has this evolving R&D model been affecting the CRO industry?

It’s changed a lot. The CRO industry used to be seen as a service that you could just buy when required, if you look at the clinical market, that’s changed dramatically. Companies like QuintilesIMC, INC Research, PPD, and ICON have changed that model and people now see integrated clinical development as a single solution. Regulatory non-clinical is getting there, with companies such as Charles River Laboratories, Envigo and Covance, they understand that space. But again, I don’t think they’ve got that early stage piece sorted out yet. It’s still not adding true value to the customer.
The industry has changed for the better, years ago people used to look down on CROs. Now, because of what’s happened in the industry, people transferring from CROs to pharma and vice versa, it’s changed the human dynamics. So, if you work in a pre-clinical CRO, you’re probably seeing 50 or 60 candidates a year, whereas if you are in a pharma company, you’ve probably seen one or two. Even the term CRO is dated because people see that as vaguely subservient. We like to use Partner Research Organization or Innovation Research Organization, so even the language is becoming more collaborative.

Q What are the key hurdles ahead for early stage research?

There are still areas which are untouchable, the undruggable space is still there. Non-enzymatic protein-protein interactions and understanding that 3D chemistry has always been a challenge. The other big one is translational research. The focus at the moment is on choosing the perfect candidate. I think drug discovery has been very efficient in creating more candidates going through the developmental process; but the chemical diversity issue is still key. I think as an industry we’ve been very successful in the drug metabolism and toxicology pace of de-risking but there is still a gap in efficacy and that’s the part I think we’ve got to really push on.

The other thing being missed is sharing of information, so every company is doing their own fundamental research but the information transfer is not there. Having innovation groups and partnerships makes a huge difference and you can now see some of the academic groups solving these problems by actually working with pharma but, again, the information needs to be opened up a little bit further. It’s back to intellectual property, who owns the IP?

Also, there has been a change of customer. You get charitable organizations or pseudo-governmental organizations or universities driving a lot of R&D. I wonder where this is going to go. There are certain therapy areas pharma companies won’t pay for, so it’s going to be done by pseudo-governmental organizations or even healthcare agencies. Who’s going to pay for these really tricky areas? A good example of this is the antibiotic space. Who is paying for them? At the moment, it’s governmental grants paying to give companies cash to play with. The product itself is so short term, the value back on the asset is just not worth doing so it has to be government supported. In this process, either patent law has to change so people get more money back out of the drugs, which I don’t think will ever happen, or you’ve got to reward slightly differently.

Q Can you point to any creative solutions that we might be see over the next couple of years?

I think a lot more research is now done at cost in the CRO industry. Innovation is driving the work rather than just profit. Because CROs have that knowledge internally, we look at the asset earlier and add value to take it forward. One of the phrases I quite like is ‘wooden dollars’, a joint innovation fund. If you have a customer you work for on a regular basis, you both put into a research pot to innovate in that area or a similar area – a joint R&D fund, that’s one way of looking at it.

Q What disruptions do you see going forward in R&D?

Digital health is a key part. That is going to deliver better drugs, more targeted to the patient than ever before. That’s got to be good for the industry as a whole. There will be some losers in it but I think, from a population point of view, it’s the right way to go. Another disruptor is that venture capitalists, rather than just sponsoring a company, are creating companies. They see some interesting research in a university and then create the biotech into the asset. All decisions are centered on creating value for that asset or portfolio going forward. If it isn’t creating value, they kill it because their money is more important.
Scrup 100: The R&D Paths Of Top 50 Pharma

How has R&D spending in the pharmaceutical industry changed over the last decade? While the R&D collective picture for Big Pharma may not have changed much, individual company stories differ markedly.

Over the last decade the drug sales from the current Scrip 100 top 50 pharmaceutical companies have risen over 30%. And the amount of money those companies spend on R&D has risen by a commensurate amount (slightly more in fact, see Table 1). All of which means that, taken collectively, the largest pharmaceutical companies are investing about the same proportion of current revenues into the development of future products.

In order to look at the dynamics that underlie that seemingly static aggregate picture, this analysis will chart by company the rates of change of two key R&D parameters – R&D expenditure and the R&D quotient (the ratio of R&D spending to drug sales). For each company 10 years of data is condensed into just two coordinates shown in Figure 1: on the X axis, the rate of change of R&D spending (in millions of dollars per year) and on the Y axis, the rate of change in the R&D quotient.

Figure 1 shows the data plotted for 49 of the 50 companies (Regeneron Pharmaceuticals Inc. is missing because the past decade saw it move into generating drug revenue and therefore its R&D quotient is off the chart).

Figure 1 distinguishes three groups of companies: Big Pharma (companies that generated more than $10bn in drug sales in 2015); Mid-Pharma (companies generating less than $10bn in drug sales in 2015); and Generics (companies where R&D spending is less than 9% of sales).

However, even without breaking the separate groups, a couple of observations are clear.

Firstly, there is a huge disparity between companies within the top 50. The range of drug revenue extends from approaching $50bn (for Pfizer Inc. and Novartis AG) to around $1.4bn (for Stada Arzneimittel AG). The R&D spending numbers are as widespread, too. In 2015, the R&D quotients varied from 3.1% (Endo International PLC) to 60% (Regeneron Pharmaceuticals Inc.).

Secondly, despite these disparities, most companies have increased R&D spending over the past 10 years (their data lies to the right of the Y axis) even though many companies have reduced their R&D quotients (their data lies below the X axis).

### BIG PHARMA

Most of the Big Pharma companies have increased dollar-denominated R&D. Only at Merck & Co. Inc., Sanofi, GlaxoSmithKline PLC and Pfizer, notably, has R&D spending declined.

For Sanofi and GSK, that may be partially due to the downward drift of the euro and the pound against the dollar since 2006. Both currencies have come down approximately 20% reducing the relative cost of R&D operations with a European center of gravity.

But for Merck and Pfizer, the declines in R&D spending are real and indicate evolution and economies at the companies. To be clear, R&D spending and pharma sales figures for 2006-2008 are drawn from the combined contributions of companies that merged to form the present day Merck and Pfizer. For Merck this principally means Merck and Schering-Plough Corp. with a recent contribution from Cubist Pharmaceuticals Inc.;

<table>
<thead>
<tr>
<th>YEAR</th>
<th>PHARMA SALES ($BN)</th>
<th>PHARMA R&amp;D ($BN)</th>
<th>PERCENTAGE OF SALES SPENT ON R&amp;D</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>458</td>
<td>82</td>
<td>18.0%</td>
</tr>
<tr>
<td>2007</td>
<td>513</td>
<td>95</td>
<td>18.4%</td>
</tr>
<tr>
<td>2008</td>
<td>563</td>
<td>105</td>
<td>18.7%</td>
</tr>
<tr>
<td>2009</td>
<td>560</td>
<td>102</td>
<td>18.2%</td>
</tr>
<tr>
<td>2010</td>
<td>593</td>
<td>110</td>
<td>18.5%</td>
</tr>
<tr>
<td>2011</td>
<td>629</td>
<td>110</td>
<td>17.4%</td>
</tr>
<tr>
<td>2012</td>
<td>616</td>
<td>111</td>
<td>18.0%</td>
</tr>
<tr>
<td>2013</td>
<td>620</td>
<td>112</td>
<td>18.0%</td>
</tr>
<tr>
<td>2014</td>
<td>649</td>
<td>118</td>
<td>18.2%</td>
</tr>
<tr>
<td>2015</td>
<td>629</td>
<td>120</td>
<td>19.0%</td>
</tr>
</tbody>
</table>

Source: Scrip 100
for Pfizer it is largely Pfizer plus Hospira Inc. plus King Pharmaceuticals Inc. plus Wyeth.

The bottom line is that Merck in 2015 spent $6.7bn on R&D, just 79% of the $8.5bn it spent in 2010 and 2011 after its merger with Schering-Plough. Back in 2010 Merck spent around 22% of its drug revenues on R&D, one of the highest proportions among Big Pharma; that figure dropped to around 20.5% for the rest of the current decade and then fell again in 2015 to 18.5%.

In Pfizer’s case, its R&D expenditure has declined from $9.4bn in 2010 to $7.7bn in 2015 (82%); going further back, the combined R&D spending of Pfizer and its various acquisition was around $11bn throughout 2006-2008. Its 2015 spending was just 70% of that.

The other noteworthy aspect of Figure 1 is that the R&D quotient has changed greatly for many companies. Circles above the X axis represent companies where the R&D quotient has increased over the past decade, and vice versa.

In the Big Pharma peer set sits a group of companies that could be characterized as the Big Seller: their R&D spending has increased but it hasn’t kept up with their increased sales. The largest decline in R&D quotient occurred at Gilead Sciences Inc. Gilead spent over $3bn on R&D in 2015, nearly three times its spending in 2010 but its drug sales have increased over 4.5 times since then. Consequently, Gilead’s R&D quotient is only 9.4%, the lowest among Big Pharma companies and closer to that of generics firm like Sun Pharmaceutical Industries Ltd. (8.8%) or Teva Pharmaceutical Industries Ltd. (7.4%).

At Allergan PLC, Amgen Inc., Novo Nordisk AS, and Astellas Pharma Inc. the declines in R&D quotient reflect the fact that growth in sales is outstripping growth in R&D spending, albeit on a smaller scale than at Gilead.

The R&D quotients for AstraZeneca PLC, Boehringer Ingelheim GmbH, Eli Lilly & Co. and Bristol-Myers Squibb Co. tell another story. They are the Recovering R&D Investors. They have spent more on R&D relative to their drug sales in the past few years, but it’s declining sales rather than increasing R&D spending that has contributed more to this shift.

AstraZeneca’s and Lilly’s drug sales for 2015 were around 70% of their 2011 peak whereas their R&D spending remains at essentially the same level.

For BMS, the picture is slightly more complicated: its sales in 2015 declined to 66% of its peak (partially due to divestments) but the company has also increased R&D substantially. In trying to maintain its lead in immuno-oncology, BMS has increased its R&D spending by $2bn in just two years, from $3.7bn in 2013 to $5.9bn in 2015. For 2015, BMS’s R&D spending was over 40% of its pharma revenue, more than any other company in the top 50 (Figure 2) apart from Regeneron and Lundbeck Inc. (which attributed a one-time massive impairment to its R&D spending line in 2015).

For Boehringer, the 33% decline in the euro against the dollar between 2008 and 2015 has eroded the dollar value of its sales. In euros, BI’s R&D spend has doubled over the past decade while its pharma sales have been flat.

Seven of the 20 Big Pharma companies have stuck rigidly to a fairly constant R&D quotient. Thus for Johnson & Johnson, Roche, Novartis, Bayer, and Abb’Vie Inc., as sales have increased, R&D spending has increased roughly in proportion. And for GSK and Pfizer, falls in sales have been matched by falls in R&D spending.

MID-PHARMA

The patterns seen in Big Pharma are reflected in the Mid-Pharma group of companies, 16 firms that sell between $2bn and $10bn worth of drugs in 2015 with R&D spending above 9% of drug sales. These are largely European and Japanese companies plus Biogen Inc., Celgene Corp. and two relatively recent US arrivals, Alexion Pharmaceuticals Inc. and Regeneron.

Seven of the Mid-Pharma group have a fairly constant R&D quotient. Only one of these has cut back on R&D spending. Loss of exclusivity on Aricept (donepezil) back in 2010 has meant that Eisai Inc.’s dollar-quoted drug sales have fallen to 55% of their 2009 peak value although half of that fall can be attributed to a weakening yen (sales quoted in yen have fallen 75%). And Eisai has cut its R&D budget commensurately.

Sumitomo Dainippon Pharma Co. Ltd., Mitsubishi Corp., Actelion Pharmaceuticals Ltd., Daiichi San...
kyo Co. Ltd., Merck KGAA, Otsuka Pharmaceutical Co. Ltd. and Celgene have all increased R&D spending in step with an increasing sales trend. Celgene is not only clearly expanding far faster than its rivals, but it also spends a far higher proportion (40%) of revenue on R&D. For Otsuka, loss of exclusivity on Abilify (aripiprazole) may test its commitment to current levels of R&D spending.

Baxter Corp., Servier SA and Lundbeck are the Recovering R&D Investors among the Mid-Pharma set. In Servier's and Lundbeck's cases, the weakening of European currencies against the dollar has exacerbated a falling sales picture, while in Baxter's case the divestment of Baxalta left the company with some residual drug sales but proportionally more pharma R&D.

Also striking are the positions of the specialist medicines companies Fresenius Kabi AG, Shire PLC and Biogen. These are Mid-Pharma's Big Sellers. In 2015, Biogen's sales were over 2.5 times its sales in 2010 but its R&D spending increased only 60%. What Biogen achieved through pure franchise expansion, Shire and Kabi attained through acquisition and expansion.

**Generics**

Perhaps the first thing that needs to be said about the Generics set is that because they have been defined using an R&D-based parameter, it contains some companies that are not traditionally thought of as generics companies.

CSL Behring, for instance, sells protein products based largely on plasma extraction. These are clearly not generic drugs nor are they biosimilars by any of the artificial legal definitions. However, they are traditional products requiring a relatively low level of R&D support. Nevertheless, CSL has been increasing both its R&D spending and its R&D quotient over the past 10 years.

Menarini Group would probably also not characterize itself as a generics company. However, its dependence on the Italian market may encourage strategies focused on local market dominance rather than breaking down global barriers through aggressive R&D.

These provisos aside, generics companies fall into two main categories. There are those (the majority) which maintain or increase R&D spending albeit with some fall in R&D quotient and those like Endo International and Valeant Pharmaceuticals International Inc. where the R&D quotient has fallen significantly accompanied by a fall in R&D spending.

The mechanism for these two different dynamics is clear. Generics companies typically grow by channeling acquisition of new product lines or entire companies into their existing marketing and distributions structures.

In generics companies that have increased R&D spending, elements of the acquired R&D machine are retained so that both sales and R&D spending increase.

In the cases of Endo and Valeant, the deployment of acquired assets has been more stringent.
The R&D Year In NUMBERS
A snapshot of the industry's research and development activity in 2015/16.

Products In Active Development By Therapy Area

- Alimentary/Metabolic
- Blood & Clotting
- Cardiovascular
- Dermatological
- Genitourinary
- Hormonal
- Immunological
- Anti-infective
- Anticancer
- Musculoskeletal
- Neurological
- Antiparasitic
- Respiratory
- Sensory

Number of New Active Substances Launched in Their First Markets


R&D Spend and Pharma Sales

<table>
<thead>
<tr>
<th>Company</th>
<th>2014 (in $m)</th>
<th>2015 (in $m)</th>
<th>change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>8181</td>
<td>8738</td>
<td>6.8%</td>
</tr>
<tr>
<td>Roche</td>
<td>8959</td>
<td>8694</td>
<td>-3.0%</td>
</tr>
<tr>
<td>Pfizer</td>
<td>8393</td>
<td>7690</td>
<td>-12.0%</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>6213</td>
<td>6821</td>
<td>9.8%</td>
</tr>
<tr>
<td>Merck &amp; Co</td>
<td>7471</td>
<td>6704</td>
<td>-10.3%</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>5579</td>
<td>5997</td>
<td>6.6%</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>4534</td>
<td>5920</td>
<td>30.6%</td>
</tr>
<tr>
<td>Sanofi</td>
<td>6203</td>
<td>5836</td>
<td>-5.9%</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>5684</td>
<td>5447</td>
<td>-4.2%</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>4733</td>
<td>4796</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Footnotes: *Either discontinued or re-classified as “No Development Reported” by Pharmaprojects during 2016 until Oct. 25 **For the Scrip 100 dataset of pharma and biotech companies with at least $1m R&D spend and/or sales of at least $10m (620 companies)

Sources: 1Pharmaprojects (Oct 25, 2016) 2 Pharmaprojects 3 Scrip 4 Scrip 5 Citeline 6 Scrip
A Bird’s Eye View Of The Rare Disease R&D Landscape

The number of drugs in development for rare diseases have increased by 56%, with the number of rare diseases on the development map also increasing by 23% in just three years, demonstrating ongoing interest and seemingly increased enthusiasm for research within these areas of high unmet needs.

Rare diseases truly give meaning to the notion of unmet medical need as 95% of rare diseases do not have any drug treatments approved by the FDA. While individual rare diseases may only affect a small pool of patients, rare disease patients as a whole number an estimated 350 million people worldwide.

Perhaps most troubling is the fact that about half of these patients are children, 30% of whom will not live to see their fifth birthday according to Global Genes, a rare disease patient advocacy group. Various regulations and initiatives have been, and continue to be, implemented to both facilitate and incentivize rare disease R&D, and the pharma industry appears to be responding accordingly.

The focus of this analysis is limited to the 499 Pharmaprojects indications considered to be a rare disease, as defined by the FDA and EMA. Specifically, these are the conditions that affect 200,000 people or less in the US (FDA) or ones with a prevalence of 1 in 2,000 people, which is the equivalent of fewer than 250,000 people in the EU (EMA). Pharmaprojects last assessed the rare disease landscape in November 2013, and found that 2,907 drugs were in active development for at least one of 364 rare diseases. As of October 2016, a total of 4,549 drugs are now in development for at least one of 447 rare diseases. This is an increased drug count of 56% and 23% more rare diseases after nearly three years, demonstrating ongoing interest and seemingly increased enthusiasm for research within these areas of high unmet needs.

With regard to the breakdown by disease status, or the highest phase of development a drug has reached for a particular disease, preclinical and early-to-mid stage clinical research continues to be the most active. In addition to the large proportion of early stage development, a total of 1,387 launches have taken place. (Exhibit 1) Since drugs in development for more than one rare disease are counted for each individual indication, the same drug can be counted both across and within the same development phase. As such, this total of 1,387 launches represents 950 unique drugs that have been launched across 232 different rare diseases.

Consistent with the 2013 analysis, Cancer and Infectious Disease (ID) continue to be the industry’s focus within active drug development and both areas are the most prolific in terms of drug count. This is true for both the total number of ‘drugs’ per Therapy Area (TA), which includes a count for each indication when drugs are developed for more than one rare disease within the TA, and when drugs targeting multiple rare diseases within the TA are only counted once (the number of unique drugs per TA). The vast majority of anticancer drugs pursue multiple rare oncology indications, which is evident by the large difference between total and unique number of drugs. In general, most TAs do have drugs that pursue multiple indications, but not to the same dramatic extent as anticancer therapies.

ID also has the largest number of rare diseases with drugs in development, followed closely by Alimentary/ Metabolic, however, both TAs also have the most desig-
nated rare diseases. Currently, drug development is active in 87% of rare infectious diseases and 92% of rare alimentary and metabolic conditions. Blood and Clotting, Genitourinary, and Hormonal all have R&D activity in each of their designated rare diseases, while the largest gap is observed in Dermatological and Cardiovascular, where 24% and 21% of their rare diseases, respectively, remain unaddressed by active drugs.

Although there appears to be some diversity given the number of diseases with active drugs, the top five rare diseases per TA by drug count indicate a skewed distribution of R&D activity. For most areas, the sum drug count for the top five indications within a TA tends to comprise the majority of the total drug count. The exceptions are Alimentary/Metabolic (106/386; 27%), ID (471/1404; 34%), and Neurological (251/599; 42%), which are also the three largest TAs with respect to number of rare diseases. Cancer is right on the edge and the sum of active drugs for the top five rare cancers represent 50% of the efforts within this area (1624/3235).

The largest rare indications by number of drugs are the top five cancers of pancreatic, ovarian, acute myelogenous leukemia, liver, and myeloma. Not only do these cancers lead the rare disease R&D overall, but the drug counts for a single cancer outnumber the total drug counts for some of the TAs. For instance, myeloma’s 255 drugs outnumber the total efforts for Sensory, Cardiovascular, Dermatological, Hormonal, and Genitourinary. The 417 drugs for the largest rare cancer, pancreatic, outpace all non-cancer TAs except for ID, Neurological, and Blood and Clotting. Outside of cancer, myelodysplastic syndrome, which can be triggered by cancer treatments, has the largest number of drugs, followed by tetanus prophylaxis.

RARE DISEASE LEADERS

Exhibit 2 provides a view of the leaders within rare disease R&D, limiting drug counts to those originally discovered/synthesized by the company or group. Development is led by the trio of Sanofi, GlaxoSmithKline PLC (GSK), and Novartis AG, who all originated over 90 unique drugs each.

While Sanofi does top the list of key originators, they only have a small lead ahead of GSK and Novartis. After the top three, drug counts start dropping markedly. Nearly all originators are within the Top 20 Pharma peer set, based on the company’s revenue, with Eisai Inc. and the Medicines for Malaria Venture as the exceptions. The Medicines for Malaria Venture is truly an exception as it is the only non-profit foundation among the Top 15 rare disease drug originators, beating numerous pharma and biotech companies, in addition to the fact that the foundation focuses on a single rare disease.

Considering the vast majority of originators are also Big Pharma companies, the higher number of rare disease drugs could be a reflection of their large portfolios rather than their commitment toward combatting rare diseases. As such, Exhibit 2 also includes the number of non-rare disease drugs to indicate the proportion of their portfolio dedicated to rare diseases. Besides the Medicines for Malaria Venture, whose sole focus is malaria, the non-Top 20 company Eisai becomes the leader with the largest percentage of rare disease drugs (43%), followed by Amgen Inc. (38%). Interestingly, Sanofi, GSK and Novartis are still key players with a three-way tie as rare disease drugs comprise 31% of each of their originated drug portfolios.

Despite the additional challenges of developing drugs for rare diseases, it does not appear that this landscape will fade anytime soon. Sanofi, GSK, and Novartis lead the way with the largest number of drugs, as well as Eisai and Amgen who have dedicated a large percentage of their smaller portfolios to rare diseases. The pursuit of potentially life transforming treatments and preventative measures to avoid certain diseases continues, with a strong focus from the industry on ID and Cancer.
PHILANTHROPIC GIVING: Upsetting The Apple Cart Or Plugging The Pipeline?

Facebook inventor Mark Zuckerberg grabbed headlines across the globe this year when he and wife Priscilla Chan announced a $3bn initiative with one momentous goal: to cure all disease. The initiative has released few details, but the pledge of $3bn from a technology business owner into disease research has sparked curiosity and concern.

The top 100 pharma and biotech companies spent $127bn on R&D in 2015 alone – with 15 companies spending more than $3bn each on research last year, which begs the question: is $3bn enough to cure or prevent all disease? And if the R&D model is working, why does the industry need philanthropy?

Mark Zuckerberg says in an introductory video about the Chan Zuckerberg Initiative's scientific arm (CZI Science) that “the goal is to help the scientific community cure, prevent or manage all diseases within our children's lifetime.” The group aims to do this by using its “world class engineering team,” in partnership with academia and other groups, to create tools for the whole scientific community to use. “Two of the things Chan Zuckerberg is doing is bringing scientists and engineers together and giving them resources to create tools to empower the rest of the scientific community,” he says.

CZI Science has created a Biohub in partnership with University of California, San Francisco, Stanford University and University of California, Berkeley, that will “give access to software engineering and a level of expertise in computer science that most academics have never had access to before,” CZI Science Biohub’s Joe DeRisi says. “If the tool doesn’t exist you’re going to build it, if the software doesn’t exist you’re going to write it.”

CZI is certainly not the first philanthropic group to be formed by a technology mogul. The Bill & Melinda Gates Foundation was set up by the Microsoft founder and his wife Melinda in 2000; the Michael and Susan Dell Foundation was created by the founder and CEO of Dell Inc., and his wife Susan in 1999; and then there’s the eBay creators Pierre and Pam Omidyar who have donated over $1bn to a wide range of causes.

TECH DOES IT BETTER

Biohubs, like the partnership being launched by CZI Science, already exist yet there are still unmet needs and diseases without treatments globally. It will be the technology born from groups like CZI Science that will provide the real proof as to whether tech can do it better than pharma.

Nigel Blackburn, director of drug development at Cancer Research UK, tells Scrip that although the use of technology in drug development has snowballed, he is uncertain how a tech-driven group might use its engineering expertise to speed up and improve drug discovery. “I just don’t know yet how modern technology firms fit in. But if technology groups can apply their engineering expertise to existing methodologies to speed things up that’s a great benefit.”

Recently a number of non-traditional companies entering the pharma and life sciences space, such as: Apple Inc., which has an ongoing partnership with Sanofi's Alcon unit; Alphabet (Google's parent group) with its Verily Life Sciences business; Samsung, which founded Samsung BioLogics in 2011; and Nestlé, which also opened Nestle Health Science SA in 2011, that aims to create a whole new hybrid industry between food and pharmaceuticals. CRUK’s Blackburn, who joined the charity from a career in the pharma industry, says that although pharma will be cautiously optimistic about organizations like Apple and Google moving into the life sciences space, “they will see these businesses as competition but competition is healthy.”

Dr Anthony Martin, chair of Peptinnovate Ltd. and a fellow of the Royal Society of Medicine, tells Scrip that the pharma industry is “in a new ‘scientific paradigm’ with knowledge being created at a rate where we can’t take full advantage of its availability.” New initiatives, he says, which capture, share and utilize this knowledge to create and develop new therapies, new medical devices, simpler and more accurate diagnoses, are needed.

However, Martin points out that one of the biggest challenges for these new initiatives is the lack of encouragement for innovation. “We need to be less bureaucratic and take more risks in our funding of early stage companies aiming to develop new therapies. In particular, we need to look at regulatory structures to ensure they work safely, but do not delay or hinder those therapies or preventive measures that can genuinely help,” he explains.
PHILANTHROPIC GIVING BELITTLES PHARMA R&D

Blackburn tells Scrip that one of his concerns with philanthropic gestures is that they can be harmful to research by “trivializing the real cost of research and drug development.” In 2015, Novartis AG was the top spender on R&D, pouring $8.7bn last year into its research activities. CRUK spends around $400m annually on research specifically for cancer, with the majority being used to fund projects in the UK. Over the last seven or eight years CRUK has spent the equivalent of CZI’s $3bn pledge on research for just cancer indications.

“$3bn sounds like a huge amount of money but in this research space it is not. Action like the CZI’s pledge to cure all disease grab the headlines and divert attention away from the ongoing, year after year investments other groups make in bringing small benefits over time to try and prevent diseases like cancer,” Blackburn says. “The other concern is that people may stop giving to charities; they think Zuckerberg has got it covered.”

Peptinnovate’s Martin notes that more funding is always needed for disease research; however, he cautions that philanthropic donations still need focus. “Executive management must be available to lead companies receiving [this type of funding] to make sure the cash is directed wisely on projects that serve a clear market/disease need, and that reimbursement can be achieved for the indication in question. Strong intellectual property protection, clear clinical endpoints and manufacturability are all crucial; however, navigating a path through the payment structures in each country is becoming more and more significant for success,” Martin states that technology-born philanthropic groups are still needed because they disrupt the traditional pharma R&D model by not only giving larger sums of money to finance early-stage companies, but also by putting together scientists and expertise from “different walks of life” to solve the problem.

However, pharma’s built-in, competitive and defensive culture might make the industry resistant to groups like Google’s Verily. “Pharma should endorse and support these initiatives. However, I suspect that their culture, built over many years, and their overall responsibility to shareholders, may make them wary of technology companies investing in their industry,” Martin laments. Adding that novel collaborations between tech groups and pharma need willing to be shown on both sides: “It is important that the CZI group works with individuals and organizations that have helped build drug development companies and consequently have hands-on operational experience and up-to-date knowledge and awareness of technologies and disease trends in the market,” he says.

CZI’s appointment of Dr Cori Bargmann is a good start. Bargmann, a neuroscientist who heads the Lulu and Anthony Wang Laboratory of Neural Circuits and Behavior at The Rockefeller University, was appointed president of science at CZI in October 2016. Bargmann specializes in the relationships between genes, experience, the nervous system, and behavior.

Donations and funding from wealthy individuals or crowdsourcing is still vital for early drug development, Martin notes, echoing Blackburn’s sentiments. “We need such initiatives because big pharma and biotech primarily invest at later stages of the drug development process (e.g. after Phase II trials), which means early-stage and innovative therapies are not financed. These small, early-stage companies often struggle for investment and rely on wealthy family trusts or crowdfunding sources for capital.” While nobody wants to belittle philanthropic giving towards ridding the world of disease, the same cannot be said for public response to activities by the pharmaceutical industry – at the root of it all one of those groups is seeking a return on investment for helping prevent illness and the other is not.

However, as pharma and biotech commentator Andy Smith told Scrip, “The world would be a worse place without the Gates Foundation and Chan Zuckerberg interventions.” Smith, lead fund manager for four life science-specific funds, says: “In some respects groups like CZI are trying to work in areas that will take a long time for us to know if they are successful. What they need to encourage them and others would be one (not necessarily big) success.”

While any tools and technologies created to help speed up, improve and increase the world’s ability to create treatments for diseases are likely to be welcomed by pharma and biotech with open arms, rash statements like ‘granting $3bn out of my own pocket to rid the world of disease’ might appear a little egotistical – but would we expect any less from the student who changed the way the world communicates from his university dorm room?
Aptuit provides a broad range of integrated capabilities to pharmaceutical and biotech companies of every size and on a global scale, which includes:

- Drug Design & Discovery;
- API Development and Manufacture;
- Chemistry, Manufacturing and Controls;
- Preclinical and IND enabling GLP/GMP programs.

Services are offered as integrated solutions as well as stand-alone service work. Our customers that adopt our integrated approach benefit from accelerated cycle times and the resulting time and cost savings. This is achieved during the iterative stages of the drug discovery and development process, thanks to fully integrated research units and co-localization of all scientific contributing disciplines.

Aptuit’s services include due diligence and consultancy services and INDiGO®, a program to accelerate early drug candidates into the clinic by reducing time from candidate nomination to regulatory submission. Accelerated development is achieved by tightly integrating traditional drug silos into a single project managed “under one roof”. The program has been proven to reduce time and cost while achieving a quality data package for CTA/IND level regulatory filings.

Aptuit currently employs a staff of approximately 700 people, distributed in UK, Italy, Switzerland and US. Its drug discovery and development professionals are experienced scientists in multidisciplinary areas and possess proven experience in neuroscience, antibacterial, oncology, cardiovascular and other key therapeutic areas. They share a legacy of success, having advanced a large number of molecules efficiently, expeditiously and economically, from early discovery through clinical development, with low attrition rates.

The company has a major center for integrated drug discovery and development in Verona (Italy), which was a Medicines Research Centre of GlaxoSmithKline until 2010, a site in Oxford, UK, for the development and manufacturing of Active Pharmaceutical Ingredients (API), pre-formulation testing, preclinical dose-vehicle screening and formulation development, and a site in Reinach (Switzerland) dedicated to Hit profiling and high throughput screening services.

The headquarters site is in Greenwich, Connecticut (USA).

The global turnover in 2015 was $78.3m.

Aptuit is a privately held company, partnered with Welsh, Carson, Anderson & Stowe, one of the world’s leading private equity investors. It was formed in 2004 and started its activity in 2005.

Aptuit is pursuing a growth strategy through the expansion of its capabilities and investments, which includes acquisitions and strategic alliances. In 2016, it has invested $16m in facility upgrades and equipment to enhance integrated discovery and development capabilities, and it has hired more than 90 scientists between UK and Italy.

We believe Aptuit’s integrated solutions are unique in the marketplace and that our people are our greatest asset. We are focused on helping our customers discover, develop and produce drugs with very high quality, whilst minimizing operational risks. Since 2004, we have built a wealth of knowledge and expertise across the entire spectrum of drug development solutions, from discovery through to commercialization.
Integrated Drug Discovery and Development

- Drug Design and Discovery
- IND Enabling Programs
- Integrated CMC

aptuit.com
Cyndi Verst, president of clinical operations for QuintilesIMS, invites you to imagine a different kind of clinical trial, where there are limited unknowns and precision and predictability is within reach.

Imagine a new type of clinical trial. One where you start with a clear picture of the relevant patients, physicians, unmet needs, and treatment approaches. Know how many patients with a specific condition exist and where to find them. You see what improvements are needed to matter to patients, physicians, regulators and payers. This precision and predictability is within reach – and arriving at a crucial time for a biopharmaceutical industry facing a tipping point.

The current challenges are well-known. The cost to develop a new drug now exceeds $2.5bn, and two-thirds of drugs launched fail to meet pre-launch expectations their first year in the market. Almost 80% of trials are delayed, mainly due to slow enrollment, and a month’s delay can result in potential lost sales in the millions of dollars. And the demand for patients and trial sites is increasing as the number of global trials grows.
As a partner to life science companies, we have been working with our clients to develop solutions to address these challenges. However, in order to truly transform clinical development, a different approach is required.

This new approach requires reframing how we think about evidence development. It starts with a foundation of real-world data to understand the unknowns that often derail clinical trial efficiency. By successfully integrating this data with detailed, fit-for-purpose analytics, technology, and scientific and therapeutic expertise, researchers can address these unknowns as they emerge during development. Biopharmaceutical companies can then better predict and position a product from discovery to commercialization.

CONVERTING DATA TO INSIGHTS TO ENABLE SMARTER DECISIONS

This clinical development transformation is not about ‘big data’ but instead ‘smart data’ resulting in meaningful insights. QuintilesIMS distinctly creates those data linkages and relationships to help our clients make the right decisions for their research program. We leverage and integrate disparate sources of data with our deep therapeutic and scientific expertise, proprietary technology tools and more than 30 years of clinical trial experience to help our clients advance their clinical outcomes and commercial performance.

We start by working with our clients to determine what evidence can best inform their decision-making and whether data are available or need to be created. To truly understand what is happening to patients across care settings, clients often need insights that require thoughtful integration of information from multiple sources, including prospective studies.

We can analyze data from numerous types of data across the healthcare continuum including patient registries, clinical outcomes assessments, pharmacy and medical claims, hospital data, prospective studies, consumer data, social media and wearable devices. By looking at broad cohorts of patients or selected patient groups or settings, clients have both a macro perspective of trends complemented by micro-level detail to make more informed decisions. And the applications are broad. Optimize protocol design. Select sites with eligible patients. Recruit targeted patients quickly.

When these disparate data assets are brought together to support clinical development and commercialization, a new construct for more precise and predictable development becomes clearer. Most, if not all, of the tools and data exist. When used effectively they can provide greater predictability, accelerate timelines and speed drugs to market to maximize the value of the treatment asset.

CASE STUDY: FINDING THE RIGHT SITES WITH THE RIGHT PATIENTS

According to a recent Tufts CSDD report, about 50% of sites miss recruitment targets and many fail to recruit a single patient. If the goal is to reduce these failure rates in clinical trials, how should biopharma companies proceed? By harnessing a range of clinical and real-world data sources as well as using predictive analytics and machine learning to analyze trends. Leveraging these data sources and capabilities will allow companies to proactively identify the sites and locations that are most likely to succeed in their recruiting efforts, based on past performance and patient access.

We recently helped a client improve their recruitment rates by building an investigator “heat map,” using prescription and diagnosis data as well as detailed analytics that uncovered research naïve physicians. We then deployed clinical research associates to work with the investigators to engage these research naïve physicians through the use of referral networks. Creating this map of investigators and referral networks helped our client take advantage of untapped patient populations and clinical experts in a crowded and competitive research marketplace.

"We start by working with our clients to determine what evidence can best inform their decision-making and whether needed data are available or need to be created."
Industry Sponsored Trials Fall Sharply In Challenging Indian Environment

A rise in bureaucracy and increased liability for clinical trial sponsors have impacted the popularity of India as a location for pharmaceutical companies’ clinical studies. Trialtrove’s Deborah Jeanfavre examines the data, which show a continuing decrease in new industry-sponsored trials starting in India over the past five years.

The rosy view of India as a location for relatively low-cost clinical trials with a readily available, treatment-naïve patient population became shaded over the past five years by an untenable time to approval. With the prolonged online review process, combined with increased liability for sponsors and other trial-related restrictions by the Indian government, it is not surprising that India became a less attractive clinical trial location to pharma. Taking a look in Trialtrove, we examined industry-sponsored study starts in India in the aftermath of these regulations, drilling down to explore the effect across major therapeutic areas, sponsors and diseases.

HAVE NEW REGULATIONS IMPACTED INDIAN TRIAL ACTIVITY?
Multiple factors have contributed to an increased approval time in India during the last five years. The country transitioned to a mandatory, online filing process in 2009, extending review completion to as long as nine months by 2012. In 2013, the Indian government also shifted greater responsibility to sponsors for the liability in the running of trials and implemented restrictions regarding ongoing trial numbers for each investigator and the site size required for trials. Repercussions due to the overall changes were evident in
2013 when the NIH stopped as many as 40 ongoing trials in India. It was then speculated that pharma might follow suit. Trialtrove data for trials in all phases support this supposition, showing a marked decline, by 50%, in the number of industry-sponsored trial starts between 2012 and 2013.

INDIA ALONE EXPERIENCED DECREASED TRIAL STARTS ACROSS APAC

With growing interest in Asia Pacific countries (APAC) as emerging markets and recognition as important locations for clinical trials, we looked into whether India’s policies might set it apart from other countries in the region. Data indicates that most of the nine other major APAC countries maintained, or even increased, the number of trial starts in the same period. There was an increase between 2010 and 2013 across Japan, South Korea, China and Turkey. Although a few of these countries may have benefited from India’s lost trials, the data does not highlight a clear migration of trial activity to specific members of APAC.

To dig a bit deeper into this trend, the percentage of trial starts in India (per therapeutic area), was queried for this period (Figure 1). Clearly, the decreased trial initiations can be observed across all areas. The largest changes were observed in CNS and Infectious Diseases, followed by Metabolic/Endocrinology, Cardiovascular and Oncology, all of which exhibit a greater than 50% decrease from 2010 to 2015. The Autoimmune/Inflammation diseases exhibited a smaller, but sustained, decrease by approximately 30% during this period.

The collective drop in trial starts observed during this period, might be attributed to specific sponsors choosing to avoid India’s approval delays and increased regulations. However, it can be seen that the top 10 industry sponsors in 2010 all decreased their trial starts in India by 2013, and most dropped even further in 2015. Interestingly, seven of these 10 companies, still dominated the top positions in 2015, indicating that many of the 2010 primary players chose to stay active in India, but at a lower level.

Since most of the top sponsors did not change, the disease focus of study starts in India might have been expected to also show little change. However, Trialtrove data indicates that the overall diversity of diseases dropped from 92 to 55 diseases, a decrease of about 40% (data not shown). While the top 10 diseases in India varied widely across these five years, the disease with the most starts in 2010, Type 2 diabetes, remained at the top, but with an 80% decrease in new trial starts between 2010 and 2015.

WILL 2016 SEE A REBOUND?

This analysis demonstrated how a dramatic decrease in Indian trial initiations followed the introduction of more arduous registration and approval processes there several years ago. Through 2015, this trend has continued, but there is an expectation that recent changes to more moderate Indian regulations for clinical trials, implemented early in 2016, may revive the country’s attractiveness for industry sponsored trial activity. It is still too early to tell if this year will see a rebound in study starts.
The development of a plethora of new medicines for multiple sclerosis over the past 10 years is truly remarkable. As well as the dozen or so agents now available to treat relapsing MS, the first potential product for the poorly treated condition, primary progressive MS, is nearing the market.

If you question neuroscientists, they will tell you we are nearing a time when it might be possible to reverse neuronal damage and promote the regrowth of myelin sheaths around nerve axons, perhaps stopping the underlying cause of multiple sclerosis in its tracks.

The insulating sheaths of neurons are critical to their function, and if they are damaged, communication between nerves slows down and leads to cognitive impairment, depression and pain, all hallmarks of MS.

The current resurgence in MS-related neuroscience R&D means that progress could also lead to improvements in other neurodegenerative diseases like Parkinson’s disease, Huntington’s or Alzheimer’s.

Before such neuroscience research comes to fruition, MS physicians are now finding themselves in a better position to ask questions that go to the very heart of their clinical practice: Should physicians use newer, potent, therapies for ‘induction’ early in the course of therapy, or ‘escalate’ the potency of MS therapy over time as symptoms develop? Are there drugs that are not associated with the side effect monitoring burden on clinical practice? And, finally, will treating relapsing MS patients with a combination of more than one therapy improve patient outcomes?

Preliminary answers are now found to these questions, because of the increasing availability of new MS therapies.

IS INDUCTION POSSIBLE?

The goal of induction therapy is to increase the proportion of patients having a complete remission, in an attempt to reduce the loss of nerve axons that starts quite early in MS, with potent agents such as Sanofi’s Lemtrada (alemtuzumab), and the generically available chemotherapeutic mitoxantrone being suggested in this role.

Starting therapy with these, or with marketed oral disease modifying treatments (DMT) like Novartis AG’s Gilenya (fingolimod), Biogen’s Tecfidera (dimethyl fumarate) or Sanofi’s Aubagio (teriflunomide), seems logical because of their high level of efficacy. But, equally, there are good reasons to initiate therapy with a ‘platform’ therapy, like beta-interferon or glatiramer acetate, that have fewer side effects, and to ‘escalate’ therapy when patients develop a more aggressive disease.

Emmanuelle Waubant, professor of neurology at the University of California, San Francisco, noted during a presentation at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2016 meeting that nearly 70% of MS patients don’t progress while on beta-interferon therapy. And ECTRIMS president Xavier Montalban pointed out that, as MS is a complex and heterogeneous disease with large individual variability, treatment has to be tailored to individual patients.

Other therapy areas have coped with complex treatment choices by developing treatment guidelines, and MS is no exception. ECTRIMS and the European Academy of Neurology (EAN) have joined together to develop the first European treatment guidelines for MS, the final version of which is expected in 2017.

Susan Otero-Romano of the Catalonia MS Center, Spain, outlined at ECTRIMS some of the provisional recommendations drawn up by the joint committee. They include considering beta-interferon or glatiramer acetate (Teva’s Copaxone or generics) for patients with a first episode of vision abnormalities associated with clinically isolated syndrome (CIS) and an abnormal MRI scan.

The recommendations will also point that there are a number of effective drugs for MS but few comparative studies, and clinicians should discuss possible treatment and drug safety profiles with patients. Physicians should conduct MRI scans six or 12 months after the start of therapy, with patients switched to another DMT if they do not respond.

DRAWBACKS

But there are drawbacks to the MS drug bounty. Gavin Giovannoni, professor of neurology at St. Barts and the Royal London Hospital, London, was concerned about the burden of monitoring patients for the potential side effects of the newer MS agents, that can include liver function, blood counts and other clinical tests. His MS team is becoming a “pharmacovigilance unit,” he remarked. More should be done to think about this monitoring challenge, and simplifying MS clinical practice should be one of the aims of new drugs in development, he added.

When asked what industry could do to lighten this burden, the head of biopharma R&D at Merck KGAA, a
There are a lot of ideas “cooking in the kitchen”, in biotech, pharma and academia, and there should be progress in this area very soon.

company focused on MS research, Luciano Rossetti, told Scrip that companies should try to facilitate monitoring, and should evaluate the appropriate timing and sequencing of treatment.

More tools should be made available to MS patients and physicians, and the better characterization of patients should guide treatment choices, he said. But there are still major gaps in the treatment of patients in MS, he added.

Merck KGAA has submitted a new potential MS product, cladribine, for approval in Europe, and it could reach the market in the second half of 2017 – it has the advantage of being dosed over two weeks initially, and associated with sustained therapeutic benefits three and four years later.

“A recent investigators’ meeting indicated there was enthusiasm for its use as induction therapy,” Rossetti noted. Cladribine was initially filed and then withdrawn from the regulatory process in 2010, amid safety concerns, but the risk/benefit profile is now much better characterized, with more than 10,000 patients being treated, he noted.

Another major step forward in MS therapy could come near the end of 2016, with the late-December PDUFA date of Roche’s CD20-targeted, B-cell depleting therapy Ocrevus (ocrelizumab). Additional post-hoc analyses of clinical data presented at ECTRIMS found the MAb significantly increased the proportion of primary progressive MS patients with no evidence of progression at week 120 after treatment, compared with placebo. And compared with beta-interferon in patients with relapsing MS, ocrelizumab significantly increased the proportion of patients reaching another endpoint, no evidence of disease activity.

Novartis, has shown that a Phase III MS therapy, siponimod, has promise in the similarly difficult-to-treat condition, secondary progressive MS. Patients can develop this after suffering relapsing MS for a number of years, and siponimod’s potential has been underlined by regulator agreement being sought by Novartis for marketing submissions to be made in 2017.

If those developments were not enough, the MS therapeutic landscape could become even more complicated. Europe’s largest biotech Actelion announced Oct. 20 it was to study its investigational oral Phase III MS drug ponesimod in combination with the marketed therapy, Tecfidera. Actelion’s POINT study will be the first late-stage clinical trial to combine two oral MS therapies, with the primary endpoint being a reduction in the annualized relapse rate.

NEUROSCIENCE RESEARCH BLOSSOMING

Early-stage neuroscience research is undergoing a renaissance. There are a lot of ideas “cooking in the kitchen”, in biotech, pharma and academia, and there should be progress in this area very soon, according to Rita Balice-Gordon, Sanofi’s recently appointed head of the neuroscience research therapeutic area.

Balice-Gordon has spent the past several months sifting through Sanofi’s early-research portfolio, selecting promising lines of research that could one day lead to advances in the treatment of neurodegenerative and rare diseases. The R&D executive notes there has been major advances in recent years regarding task-related imaging, better EEGs and behavioral profiling that has, in part, fueled a resurgence of interest in neuroscience drug discovery. But what is holding back MS research is the need for better tools to determine when neuronal damage is being repaired, that could be used in clinical trials to identify and characterize potential new therapies.

ECTRIMS’ president Montalban concluded the meeting by saying that “what we want to do now is to move from treating a disease to treating the patient.” A prospect that is getting closer in MS.
Gene Therapies: Waiting To Emerge From The Bottle

Slowly but surely, gene therapy projects are winning back confidence from the industry and as investment increases, so increase the reports on progress in this area; from sensational claims of restoring sight, to slightly more spurious claims of reversing the aging process.

Gene therapy has been heralded as the ‘Next Big Thing’, not once, but twice. Since its dramatic fall from grace following extreme clinical trial mortalities at the end of the 1990s, investment in the area was widely reported as drying up, but as Figure 1 shows, gene therapy research never really went away.

The number of gene therapies in active development is at an all-time high, according to the historical ‘Trends’ data tracking tool in Pharmaprojects.

Slowly but surely, gene therapy projects are winning back confidence from the industry and as investment increases, so increase the reports on progress in this area from sensational claims of restoring sight, to slightly more spurious claims of reversing the aging process. Following slight pipeline shrinkages between 2009 and 2011, and again between 2012 and 2013 the most significant increase in the number of compounds in active development has occurred in the last two years, with a 37% increase in the number of compounds in active development between 2014 and 2015 and 47% between 2015 and 2016.

However, this is still a high-risk area, as seen recently in the example of Juno Therapeutics Inc’s CAR-T-cell gene therapy candidate, which saw three Phase II trial fatalities and had its development temporarily suspended for a brief period. Another recent example was seen in Adaptimmune Therapeutics PLC’s partial clinical hold placed on its planned pivotal study of NY-ESO SPEAR T-cell therapy in myxoid round cell liposarcoma, but which was reported as not being due to safety concerns.

Figure 2 shows the total number of gene therapy compounds which have entered preclinical and clinical development to date. Currently there are 501 compounds in active development, with the majority in preclinical development; fewer in Phase I than Phase II, and a sharper decrease in Phase III. Within many areas of drug development, a large majority of compounds don’t progress further than the preclinical stage. In the case of gene therapies only 33% of compounds are still in active stages of development while 66% of projects have been either suspended or discontinued after being investigated, or have had no further information to suggest they are ongoing.

**HOW DO THEY WORK?**

The basic concept of gene therapy sounds relatively simple: manipulate defective DNA expression by either introducing a correctly functioning gene or blocking expression of a faulty one.

These two different approaches for targeting gene expression mean that if the fundamental technology of gene therapy could be harnessed, the range and efficacy of therapeutic possibilities could be huge.

*In vivo* approaches could encompass not only the rare, genetic diseases via the insertion of correctly functioning genes, but also the biggest disease area, cancer, by the introduction of ‘anticancer’ genes, which can work by encoding for tumor supressing proteins. Cancer therapies can also be approached *ex vivo*, by extracting tumor cells, modifying them to express a new gene, and reintroducing into a patient to stimulate the immune system rejection of the tumor cells.

The benefit of a corrective gene therapy for patients with a rare, genetic defect disease is that in some cases only a one-off treatment is needed vs a long continuous prescription of more widely-used medicines. For cancer patients, gene therapies may provide a longer term solution to slow down the progression of the disease.

The number of rare diseases and cancers being targeted by gene therapies far surpass any other disease groups. The total for cancer is currently at 693 compounds, which includes both active and inactive compounds in this area. This is an interesting pattern as it ranges from the smallest and most niche disease areas to cancer, the largest and arguably most important disease area for the pharmaceutical industry. Many of the gene therapies in development for rare diseases have also been granted Orphan Drug Designation, in indications as diverse as; mucopolysaccharidosis, Crigler-Najjar syndrome, achromatopsia, retinitis pigmentosa, myotubular myopathy, and Batten’s disease, to name but a few.

However, the majority of disease areas have been targeted by at least some gene therapy approaches, with an increasing number of advances being made in neurological areas of extreme unmet need such as Alzheimer’s, Parkinson’s and Huntington’s diseases. Old favorites such
as heart failure have also been a research focus, while even infectious diseases such as HIV/AIDS also get a look in.

RECENT RESURGENCE IN GENE THERAPY RESEARCH

The renewal in enthusiasm in this therapeutic area follows six drug therapies having been brought to market. The first two were launched in China for head and neck cancer: Gendicine (adenovirus expressing wild-type p53), which was developed and launched by Shenzhen SiBiono GeneTech Co. in 2004, and Oncorine (recombinant human adenovirus type 5 injection), launched by Shanghai Sunway Biotech in 2005.

Third came Rexin-G, which was developed by Epeius also as a cancer gene therapy, and was launched in the Philippines in 2007. Next to reach the market was Neovasculigen, a VEGF 165 gene therapy, developed by Human Stem Cells and launched onto the Russian market in September 2012 for use in the indications of PVD and Limb ischaemia.

2015 saw two further gene therapy launches - Imlygic for melanoma and the highly-publicized Glybera (alipogene tiparvovec), which was launched for lipoprotein lipase deficiency and was the first launch onto the European market. However, it has experienced disappointing financial results, with only one reported prescription, because of its extremely high price.

INDUSTRY PLAYERS LEADING NON-CANCER GENE THERAPY DEVELOPMENT

The current frontrunner in the non-cancer gene therapy space is GlaxoSmithKline PLC, which is the only company within this cohort with an approved product. GSK has a stem cell gene therapy to treat adenosine deaminase deficiency now approved in the EU, and two Phase II candidates – one for the lysosomal storage disease metachromatic leukodystrophy, and the second for Wiskott-Aldrich syndrome, an immune system dysfunction disease.

Spark Therapeutics Inc has the largest number of candidates in the pipeline, with four candidates in total. It currently has three Phase II and one Phase III gene therapies under development for a mix of rare eye diseases and Haemophilia B.

Bluebird bio Inc has the largest number of gene therapies in Phase III, one of which is the widely-hyped LentiGlobin for thalassemia, which has shown very positive trial results in beta-thalassemia patients and has the added benefit of allowing multiple months between treatments, in contrast to the standard practice of monthly blood transfusions.

Genethon’s candidate for Leber’s hereditary optic neuropathy has recently reported promising results from a Phase II/III trial.

A number of Phase III candidates have received fast track and/or breakthrough statuses from the FDA, recognizing the promise of gene therapies to meet unmet medical needs or provide substantial improvements over existing therapy options. CardioNovo received Fast Track designation for the treatment of myocardial ischaemia back in 2007, followed by Collategene who received Fast Track designation for critical limb ischaemia in 2010.

With recent approvals and launches of gene therapy compounds occurring in the last few years, it won’t be long until investment from the larger pharmaceutical companies matches that of the smaller industry players. And, although there has been some significant progress in this therapy area, researchers are still struggling to totally eliminate all the problems experienced of the previous research. But if these issues can be overcome there is huge potential for this new therapeutic class.
QuintilesIMS (NYSE:Q) is a leading integrated information and technology-enabled healthcare service provider worldwide, dedicated to helping its clients improve their clinical, scientific and commercial results.

Formed through the merger of Quintiles Transnational and IMS Health, QuintilesIMS’s approximately 50,000 employees conduct operations in more than 100 countries. Companies seeking to improve real-world patient outcomes through treatment innovations, care provision and access can leverage QuintilesIMS’s broad range of healthcare information, technology and service solutions to drive new insights and approaches. QuintilesIMS provides solutions that span clinical to commercial, bringing customers a unique opportunity to realize the full potential of innovations and advanced healthcare outcomes.

As a global leader in protecting individual patient privacy, QuintilesIMS uses healthcare data to deliver critical, real-world disease and treatment insights. Through a wide variety of privacy-enhancing technologies and safeguards, QuintilesIMS protects individual privacy while managing information to drive healthcare forward. These insights and execution capabilities help biotech, medical device and pharmaceutical companies, medical researchers, government agencies, payers and other healthcare stakeholders in the development and approval of new therapies, and to identify unmet treatment needs and understand the safety, effectiveness and value of pharmaceutical products in improving overall health outcomes.

To learn more, visit www.QuintilesIMS.com.
Creating solutions for you to drive healthcare forward

At QuintilesIMS, we are here to help you:

- Transform clinical development
- Create commercial value
- Lead with real-world insights
- Innovate with technology

Learn more today.

Contact us at www.quintilesims.com
**THE BRIC/MIST PLAYBOOK:**
Flexibility And Sticking It Out

Innovator firms will need more than just sharp business strategies to tap into the high potential but fluid pharmaceutical markets in the BRIC/MIST countries. Flexibility well beyond pricing and the ability to wait it out till the rewards creep in are vital in these markets.

The BRIC/MIST countries (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey), worth an aggregate of around $200bn and growing at double-digit rates, represent an attractive growth opportunity.

Unlocking that potential in these predominantly out-of-pocket (OOP) markets with large underserved patient populations, though, will require more than just tailored business strategies and navigating the evolving regulatory maze.

“Flexibility will be vital to navigate healthcare systems and regulatory frameworks that are less clearly defined than those in developed markets and that are prone to sudden, less explicitly signalled change. Patience will also be essential for originators attempting to unlock the huge untapped potential that exists in most BRIC/MIST markets,” says a report by Informa’s Datamonitor Healthcare.

And then be ready to play a “longer game” in which rewards may be slow to materialize but the potential scale of eventual returns will be worth it. “Maintaining levels of commitment will be particularly important through the remainder of this decade, during which time the challenges faced by multinationals in some BRIC/MIST markets may outweigh new opportunities,” says report author Tim Wesley.

Healthcare financing issues are, often, at the heart of the challenges faced in most of these self-pay BRIC/MIST markets and this could mean the imposition of pricing, reimbursement, and prescribing regulations aimed at keeping the lid on pharmaceutical spending.

OOP payments range from between 44% and 47% of national health expenditure in Indonesia, Russia, and Mexico, and 36% in South Korea; India leads the BRIC/MIST pack in terms of OOP contributions to national health spending – OOP payments account for 89% of all private spending in India, where patients foot more than 62% of the country’s entire healthcare bill.

Financing gaps are clearly high on industry’s watchlist. For instance, at the 50th annual general meeting of the Organization of Pharmaceutical Producers of India (OPPI), Dr Shailesh Ayyangar, managing director (India) and vice president (South Asia) at Sanofi, invoked the lyrics of Beatles founder John Lennon’s ‘Imagine’ and called for an India where nobody gets denied healthcare because of their socio-economic status.

The Sanofi executive said that while the India story has witnessed significant milestones, and the country was at the “edge of transformation,” it had yet to fix healthcare financing issues, so that the disease burden doesn’t impoverish the nation. OPPI essentially represents foreign firms in India.

But then top industry executives maintain that experience suggests as economic parameters become stronger, healthcare tends to usually be a beneficiary.

Wesley says that the return to stronger economic growth will also drive up patient spending on medicines, rendering original brands more affordable to a larger proportion of BRIC/MIST populations. Most BRIC/MIST economies have slowed appreciably, while those in Brazil and Russia contracted sharply in 2015.

“With patients still footing a substantial proportion of national drug spending bills in most of the eight BRIC/MIST markets, this will act as a significant driver of demand for originator products. Rising incomes will also drive up demand for private health insurance, as well as out-of-pocket spending on treatment in private clinics and hospitals.”
IPR, REGULATORY REFORM

Despite the diverse nature of the BRIC/MIST pack, a host of common trends fuel a generally optimistic tenor around these markets for pharma. Improvements in levels of intellectual property (IP) protection and in the efficiency of drug development and registration procedures are some of the anticipated pluses.

Wesley says that pricing and reimbursement trends are less positive while the ability of foreign companies to service some BRIC/MIST markets effectively through imports is “under threat.” Though investment in local manufacturing capabilities could eliminate that problem, outstanding IP protection issues mean multinationals are still reluctant to go down the local manufacturing route,” he explains.

The report refers to World Trade Organization commitments and pressure exerted unilaterally by major trading partners (notably the US) that are driving gradual improvements in the IP protection sector. Significantly, China, India, Russia and Indonesia all figure on the USTR’s “priority watch list,” while Brazil, Mexico and Turkey are on the “watch list” as per the USTR’s 2016 Special 301 List. The annual Special 301 report discusses the adequacy and effectiveness of US trading partners’ protection and enforcement of intellectual property rights (IPR).

Key sticking points for innovator firms include the weak enforcement of existing patent regulations, the absence of effective patent linkage mechanisms and poor data protection.

Ineffective IP protection may result in original brands being exposed to competition from generic copies at a very early stage, with patent holders struggling to rid the market of infringing copies.

There have also been compulsory licenses for the generic supply of patented drugs issued by governments in both India and Indonesia, and the status of other patents is potentially at risk, Wesley says.

Several BRIC/MIST countries have also initiated reform in the area of clinical trial regulations as well as drug registration. Steps to expedite clinical trial approval procedures and a relaxation in trial requirements for orphan drugs and, in some countries, other new products targeting serious, life-threatening diseases have been made in certain markets.

In the area of product registrations, drug approval procedures have been overhauled or are being improved in several BRIC/MIST countries as part of a broader move by regulators to address existing drug lag times. Staffing increases and shorter review timelines are other important changes.

Wesley says that Mexico, where regulators now recognize marketing authorizations issued in the US, EU, and several other developed markets, has witnessed the most dramatic improvement in average drug approval times.

“Significant changes are also afoot in China, although some key measures there appear designed to favor local manufacturers,” he adds.

Pricing

Drug pricing, an increasingly debated issue in developed markets, has always been thorny in most BRIC/MIST markets.

The report notes how drug prices in the private sector remain free from regulatory control in Mexico and Indonesia, but that more interventionist approaches are being pursued in most other BRIC/MIST markets; institutional market prices are under much greater pressure.

The report expects major changes to ensue in China with the recent overhaul of pricing regulations.

“These will see patent-expired brands forced to compete directly on price with locally manufactured generics, while patented drug prices will be established through negotiations conducted at national level,” Wesley explains.

Earlier this year public complaints over rising medicine costs led to a renewed investigation by Chinese authorities of drug firms.

Cross-country referencing as a tool to control new drug launch prices is also widespread and can be restrictive in low-income countries. Brazil, Russia, and Turkey have all set maximum launch prices for innovative new drugs via reference to ex-manufacturer prices prevailing in a basket of overseas markets. Similar benchmarks are applied by regulators in Turkey, and in Russia, the list of reference countries has recently been updated to include the comparatively lower-priced European markets of Hungary and Croatia, while excluding Germany and Switzerland from the list.

The report also notes how pooled purchasing and increasingly aggressive tendering procedures are being used to drive down procurement costs in most BRIC/MIST countries, while institutional purchases in Brazil and Turkey are subject to compulsory discounts. Provincial procurement policies have hurt prices in China and originators hope that prices negotiated for patented brands at the national level will eliminate pressure exerted at the provincial and hospital level.

Physician prescribing freedom in many BRIC/MIST markets continues to be significant, in part, since government-subsidized drugs have been largely restricted to the public hospital setting; where regulations do exist enforcement has been lax.

But physicians are clearly under growing scrutiny, especially in markets where government-backed reimbursement has been made available more widely – monitoring and control systems are tightest in South Korea. Graft charges against companies like GlaxoSmithKline PLC in China where the government has embarked on a broad-based anti-corruption drive has led to new rules that regulate the conduct of both suppliers and providers.

Clearly, success in emerging markets will require a deft mix of strategy, flexibility and effective and innovative engagement with a broad range of stakeholders. Innovator firms will also need to stock up on patience and stay vested for the long haul.
Boehringer Ingelheim GMBH’s decision to cull its lung cancer partnership with Hanmi Pharmaceutical Co. Ltd. seems to have dampened high hopes for the success of the South Korean drug development industry, and skimmed off some of bubbles in the sector in general.

Although the cancellation of licensing deals and clinical trial failures are commonly seen in the global pharma space, the South Korean biopharma industry, which is burgeoning in terms of innovation, hasn’t experienced such a cycle yet, so the news has come as a bigger shock and raised worries that this could weaken R&D activities by the domestic industry.

In July 2015, Boehringer and Hanmi inked an exclusive license and collaboration agreement for the development and global commercialization rights, except South Korea, China and Hong Kong, for olmutinib, a novel third generation EGFR-targeted therapy for the treatment of EGFR mutation-positive lung cancer.

Boehringer will not conduct new clinical trials and Hanmi will retain the upfront and milestone payments of $65m received so far. The German group decided to return the rights taking into consideration a reassessment of all clinical data for olmutinib, recent trends for innovative lung cancer therapies, and Boehringer’s own vision for the sector, according to Hanmi’s disclosure to the stock market.

This announcement on Sept. 30, plus the news that an investigation had been launched by South Korean prosecutors over suspicions that Hanmi may have leaked undisclosed information, have soured investor sentiment in biotechs and pharmas seeking novel drug development, with their stock prices falling substantially.

Hanmi has reiterated that there has not been any “intentional, company-wide leakage of internal information or delay in disclosure,” adding that “we expect the investigation will clarify the parts that have caused misunderstanding”.

Meanwhile, South Korea’s Ministry of Food and Drug Safety has distributed safety letters to inform domestic medical professionals, patients and consumer groups about the occurrence of the serious adverse skin reactions during clinical trials with olmutinib.

SOUTH KOREA CONFIDENCE
While the Hanmi news may have disappointed many who have been counting on the success of the pharma, which has been at the forefront of the country’s innovation move, it is part of the inevitable growing pains when developing drugs and this shouldn’t hurt the entire industry’s ongoing innovation efforts.

GtreeBNT Co. Ltd’s president and CEO Won S. Yang brushed off concerns over Hanmi, saying such failures after reaching licensing deals can always happen, that: “Even if two out of five early-stage projects that you have licensed out fail, I still believe it is a success.”

According to a report by Informa Pharma Intelligence’s Biomedtracker database on clinical development success rates 2006-2015, the Phase II transition success rate (30.7%) was substantially lower than Phase I (63.2%), and the lowest of the four phases studied. The second-lowest phase transition success rate was found in Phase III (58.1%).

“South Korea’s novel drug R&D capability isn’t weak and the country’s entire R&D activities aren’t swayed by the success or failure of a company’s project. It is true that Hanmi has recently been leading the country’s new drug development, but the country’s new drug R&D isn’t all about Hanmi,” said James Jungkue Lee, CEO of Bridge Biotherapeutics.

He noted that the recent Hanmi events have also provided a “good learning opportunity” for the domestic pharma industry and investors, and a chance to look more seriously at the biopharma sector.

PROMISING SIGNS
Olmutinib was approved in South Korea in May and launched for the first time globally earlier this year as Olita. It is used in late-stage non-small cell lung cancer patients who cannot be treated with existing EGFR-targeting drugs due to resistance and have no other treatment options.

In fact, there seem to be plenty of positive signs South Korean firms are making good progress with their novel drug development, excluding Hanmi’s achievement of clinching major licensing deals with multinational pharmas.

One of the indicators that suggest a promising outlook
for the country’s biopharma sector is rising fund inflows into listed and unlisted biopharmas and bioventures.

According to Mirae Asset Daewoo, capital increase by listed pharmas/biotechs more than doubled to KRW1.37tn ($1.21bn) last year and recorded KRW707.2bn in the first half of this year.

Among them, ViroMed Co. Ltd. announced a plan in July to launch a major new rights offering worth KRW182.6bn, mainly to fund the late-phase clinical development of its lead project VM202, which is being developed as the first gene therapy globally for painful diabetic peripheral neuropathy (DPN) and peripheral artery disease (PAD).

Also in July, Genexine Inc. announced a plan to raise a total of KRW80bn in bond and share issues to enable progression of global clinical trials for its core pipeline projects, including a promising HPV vaccine, and pursuing expanded indications.

Kolon Life Science Inc. has unveiled a rights offering plan worth KRW130bn in April, as part of a long-term investment plan to expand its novel biologics business. The funds will be invested over the next three years in building facilities for mass production of Invossa, the world’s first cell-mediated gene therapy for osteoarthritis as well as in its R&D pipeline.

Sizable funds are estimated to have flowed into unlisted bioventures as well. According to Korean Venture Capital Association, venture capitals have invested KRW317bn in the biotech sector alone in 2015, marking the highest amount invested in the sector since 2002. During the first half of this year, the amount totaled KRW194.5bn.

In parallel with the government support, venture capital firms have begun to sharply increase investment in the biotech and health care sector from 2014, as unlisted bioventures began to more actively progress their R&D pipelines and enter global markets.

By sector, the industry had drawn the biggest investment from venture capital firms in the year to May, a marked shift from 2011 when investors were focusing more on the ICT (information and communications technology), manufacturing, mobile phones and visual display sectors.

“In novel drug development, technology innovation and liquidity increase are referred to as the chicken and egg situation in terms of order,” said Mirae Asset Daewoo, adding that the brokerage believes liquidity increase should come first.

Moreover, R&D spending by South Korean pharmas/biotechs is on the rise. The brokerage estimates the spending by 22 listed pharmas and biotechs has risen 12.3% in the first half of this year to KRW559.2bn, potentially topping KRW1tn in 2016 as well as in 2015. However, about 74% of the investment was made by top nine pharmas in 2015.

Another encouraging sign is increased global clinical trials of novel drug development by South Korean firms, reflecting their strong appetite for innovations and ambitions to enter global markets.

Table 1, shows some novel clinical stage South Korean drug candidates in development for global markets. The majority of these companies are seeking global partnerships to further progress their clinical development or commercialization.

**GOVERNMENT SUPPORT**

Meanwhile, the government continues to come up with new measures to support innovation and R&D activities to fulfill the country’s goal of turning into a major bio-pharma nation in the coming years.

Among the latest steps, the MFDS plans to enact a new law that would realign and expand the current conditional approval system for new drugs to increase treatment options for patients with late-stage cancer or other life-threatening diseases, and to deal promptly with public health crises.

The MFDS noted the planned breakthrough system will be similar to the US FDA’s breakthrough designation, Japan’s “Sakigake” scheme and the European Medicine Agency’s priority medicine program.

“We will create the environment and basis to promote development of breakthrough therapies so that even bioventures can develop novel drugs,” Mungi Sohn, Minister of Food and Drug Safety, said in a statement.

---

**TABLE 1: NOVEL STAGE CLINICAL STAGE CANDIDATES DEVELOPED BY SOUTH KOREAN FIRMS**

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>DRUG</th>
<th>PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GtreeBNT</td>
<td>RGN-259 (thymosin beta 4)</td>
<td>Second Phase III study in US for dry eye syndrome</td>
</tr>
<tr>
<td>PharmAbcine</td>
<td>tanibirumab</td>
<td>Phase IIa study in Australia</td>
</tr>
<tr>
<td>Oscotec</td>
<td>Spleen kinase inhibitor (SKI-O-703)</td>
<td>Phase I trial in US</td>
</tr>
<tr>
<td>ViroMed</td>
<td>VM202 (proprietary gene therapy targeting DPN, PAD, CAD, ALS)</td>
<td>Late stage clinical trials in US</td>
</tr>
<tr>
<td>Genexine</td>
<td>GX-188E (HPV therapeutic DNA vaccine)</td>
<td>Phase II in South Korea, Europe</td>
</tr>
<tr>
<td>SillaJen</td>
<td>Pexa-Vec (oncolytic virus-based immunotherapy)</td>
<td>Global Phase III trial</td>
</tr>
<tr>
<td>Kolon Life Science</td>
<td>Invossa (allogeneic cell therapy)</td>
<td>To begin Phase III in US</td>
</tr>
<tr>
<td>SK Biopharmaceuticals</td>
<td>YKP3089 (novel compound with broad-spectrum anticonvulsant activity)</td>
<td>Completes Phase II in multiple sites, gains US FDA approval to skip Phase III efficacy trial</td>
</tr>
</tbody>
</table>
How A New Healthcare Dialogue Is Driving Market Access In Mexico

Companies stand a better chance of securing public reimbursement in Mexico for innovative medicines if they understand changing approaches to healthcare. The shift means the emergence of managed entry agreements and a focus on economic impact, explains AMIIF, Mexico’s research-based pharmaceutical industry association.

Getting new innovative medicines to patients in Mexico, one of Latin America's biggest markets, is not easy. But the idea that healthcare, including medicines, can create a more productive workforce and drive economic growth means more doors are opening. Cristobal Thompson, executive director of AMIIF, Mexico’s research-based pharmaceutical industry association, explains how this shift in thinking should translate into market access strategies and what else companies need to think about to succeed.

Mexico is attractive for pharmaceutical companies and is viewed as a gateway to other markets in the region. Worth Ps209bn ($11.4bn), Mexico is Latin America’s second biggest market and is growing at 6.6% in value and 4.9% in units. This growth compares well to traditional markets and has driven a growth in the private segment and improved access to generic medicines, say industry commentators. However, according to Thompson, access to innovation has been more limited. “Most of this business is through the government, and the government has had big budget constraints,” he explains. Economic troubles like falling oil prices mean there is less to spend. By early October 2016, social security plans had approved just 11 new molecules for their formularies, including biologics, says Thompson.

NEW DIALOGUE

Although getting innovation to the market can be difficult, there have been some helpful developments for companies. The first hurdle – regulatory approval – is now easier to clear. COFERPRIS, Mexico’s medicines regulator, is doing its job much more efficiently and approval now takes around a year, which is a big improvement, says Thompson. Some years ago there was a big backlog of drugs awaiting approval or renewal and the process was more complex. Second, says Thompson, comes listing on the General Healthcare Council (the CSG), which is responsible for evaluating cost/benefit. According to Thompson, this body has also worked hard to improve its timelines.

And next companies have to list their drugs on the government funded social security institutes: IMSS, ISSSTE and Seguro Popular. However, this can be a more complicated process because of the big emphasis on cost containment, and to succeed companies must have the right access plan that responds to a changing approach to medicines and healthcare. Thompson explains that AMIIF has been pushing a new dialogue around healthcare, emphasizing that investing in a healthy population will mean greater competitiveness and productivity, which will in turn drive economic growth and...
development. This has garnered a lot of attention and is also something that AMIIF has been discussing with Mexico’s biggest employer, to help them understand that a healthy workforce is a productive workforce.

To make its point, the association has been looking into studies that examine the economic implications of poor health. Thompson points to a US Chamber of Commerce report. This looked at the impact of employee health on economic growth in various countries and showed that in Mexico, absenteeism, presenteeism, and early retirement due to ill health cost the country 5.34% of GDP. Presenteeism is defined in the report as when an employee is “present at work but not working at full capacity due to illness.” AMIIF wanted to do something similar and looked at the impact of poor health on a car industry cluster in Guanajuato, where the automotive industry has a big presence. “AMIIF found that the cluster could improve around 7.3% of its aggregate value. That means if we invest better in health, we could increase and maximize the value of the industry. It is a first step to really start debating the impact of health on value,” explains Thompson.

Next, the association is collaborating with Frank Lichtenberg from the Colombia Business School on a study looking at the impact of early access to innovation and its impact on longevity in Mexico and AMIIF hopes to present the findings next year. Lichtenberg has already conducted similar studies looking at various countries.

MANAGED ENTRY AGREEMENTS COME TO MEXICO
One nascent example of this shift in action that companies must pay attention to is the emergence of managed innovative managed entry agreements. AMIIF has been promoting this strategy with IMSS and ISSSTE as a possible way to fund innovative and high value new medicines and a number of discussions between the institutions and companies began this year. These agreements include risk sharing models or outcomes based models that have proved successful elsewhere in the world for the companies involved, says Thompson. He hopes that more companies will enter into talks with the institutions and that they will result in more medicines for patients as of next year. “It is early days, but I am encouraged that both sides are open to discussion. I see good will from the government to sit down and discuss models to bring in better innovation that will benefit patients early on and have a bigger impact in bringing patients back to work sooner for a healthier and productive society.”

Thompson says companies that want to launch a new drug in Mexico need to think about possibilities for agreements from the off. “You have to come in with your models for from day one. Understand that this is something that is being discussed right now.” He advises companies to review what might have worked well in other markets. Now, more than ever before companies have to think about their value proposition and understand exactly where the product fits in, he says. “Show that instead of spending a month at home, this person can go back to his job after a week and add to the economy. You have to use economic information, not only medical data, which helps economic development. This is the new kind of dialogue and the people you hire have to understand this new mind-set.”

One other key piece of advice that Thompson offers to companies starting up in Mexico is to work hard with physicians, payers and regulators to “build their story” as soon as possible. All the big companies have been in Mexico for over 60 years and have good relations with authorities and doctors, explains Thompson. “You have to work on this so when your field force start working, everyone knows who you are and what your global history is … there is a lot to do to build a company brand and gain a heritage,” he says.

THE FUTURE
Despite the economic challenges the country faces, Thompson is optimistic about the future. There is still a great deal of unmet need in Mexico in terms of access to medicines and one big opportunity could be a more robust and efficient universal healthcare system that ensures much wider coverage. Discussions on how the government can improve state-funded healthcare schemes have been ongoing for some time, but Thompson believes that the matter will become the priority of the government that comes to power following the 2018 general election. “We still have to work on understanding the impact of health but if we can continue working and create this dialogue and really take stronger steps we can reduce gaps in care, there is no doubt that the potential of Mexico is huge.”
Optimize clinical trial design with Trialtrove’s new Standard of Care service

Minimize Risk:
• Quickly access Standard of Care disease treatments by patient segment and country.
• View Standards of Care by treatment regimen or individual drug views.

Data is sourced directly from Datamonitor Healthcare’s expert and robust primary resource analyses.

Covering a variety of disease areas in US, Spain, France, Japan, UK, Germany and Italy.

Request a demo!
citeline.com/products/trialtrove/
Joe Jimenez, CEO of Novartis and EFPIA president talks about why the acceleration towards an outcomes-based healthcare system is so important to Europe, and to the reputation of the pharmaceutical industry.

It is "very frustrating for my industry to see all of the incredible innovation that is coming to market and not reach European patients, or patients in general where healthcare systems are under pressure," says Joe Jimenez, talking exclusively to Scrip at the European Federation of Pharmaceutical Industries and Associations' (EFPIA) annual conference.

EFPIA's outcomes-driven message is centered on the idea of improving health in a holistic and evidence-based way by evolving healthcare systems in Europe to systematically allocate resources towards interventions that are often less expensive in the long term, and more sustainable than the current "transaction-oriented approach to healthcare."

According to data from EFPIA, over the next decade the global population is predicted to increase by one billion people, with half a billion more people over the age of 50. European healthcare systems have to face up to the perfect storm of more patients with chronic disease and an aging population that will, together, put a huge demand on current ways of treating disease, and could double spending.

"[There] are these wonderful new drugs that can extend life, or can improve quality of life substantially. They're either not being reimbursed or they're being delayed to market in some way. We feel a huge sense of urgency to help these systems move to an outcomes-based [system] where they can look not just at the pharmaceutical outcome but at the entire chain of inputs that go into delivering quality of care and get rid of the waste will make more room for innovation," says the Novartis AG CEO and EFPIA president.

Removing waste from the system to allow investment in innovation is a key driver for the industry, he says. "We [the pharmaceutical industry] invest billions in research and development and we must be able to get our innovations to patients for that innovation cycle to continue, because we reinvest what we earn from the new innovations for the next wave of innovations. So it's very important for us."

Changing to an outcomes-led healthcare system has significant technical and structural barriers that the pharmaceutical industry must work hand-in-hand with healthcare systems to overcome. "To be able to deliver positive outcomes, and be able to measure them, you have to have data, really good data. And today we don't," says Jimenez. "We don't have good in-market data, and you would think that with single-payer systems in Europe, where you have control over that data, you would."

The second type of barrier is a structural barrier, in that sometimes the payer doesn't have the incentive to look for a positive outcome. "We saw that with some of the hepatitis C drugs where the upfront cost is what they were concerned about," he explains. "If they had just looked at the long-term savings that those drugs were going to create, you would see that you have to look at those drugs as an investment, not as a cost, because they actually save the healthcare system money. It's a good health economic outcome."

INDUSTRY REPUTATION

The reputation of the pharmaceutical industry has been battered and bruised of late, with the increasingly politicized debate around pricing in the US and certain personalities within the market adding to the a decreasing level of trust. The drive towards an outcomes-based system can also address these concerns, says Jimenez. "I think there is a high level of frustration around these new medicines coming to market and the ability of the healthcare systems to be able to manage through all the demands that are on their system. So you have that frustration which leads to a reputation that is not as positive, I think, as it could be."

Joe Jimenez
The Competition Begins To Host The Post-Brexit EMA

Denmark, France, Ireland, Italy, Spain and Sweden have all have expressed a keen interest in hosting the European Medicines Agency once the UK leaves the EU. Bids are expected to be made sometime early next year, probably once the UK government triggers Article 50. There is at present no formal process for allocating an agency to a particular EU country, as this tends to be done via a process of political wrangling, so each prospective candidate will need to garner as much support for their bid as possible from the other member states.

Key factors to be taken into account when deciding who should host the EMA include the existing life sciences network in the country, the role and size of the national regulatory body, factors like language and accessibility from other EU countries, and whether there is already an EU agency established in the country. Having an existing agency could militate against a country getting another, although some argue that there could be synergies if the existing agency worked in an overlapping area such as food or the environment.

2017 EMA Host Choices

**Denmark**
- **Life sciences:** Denmark is home to a number of major pharmaceutical and biotech companies including Novo Nordisk, LEO Pharma and Lundbeck. The country is also part of the Medicon Valley life science alliance with Sweden, which includes 12 universities and 32 hospitals.
- **Regulatory agency:** The Danish Medicines Agency has some 400 employees and is based in Copenhagen. Its director general Thomas Senderovitz said in September that the agency was strengthening its leadership and setting up a new medical evaluation and biostatistics division to create a “Danish Medicines Agency in the European top class.”
- **Travel and language:** Good transport links to other European capitals: one hour by air to Berlin, two hours to London and Paris, a bit longer to Barcelona and Milan. Copenhagen has the largest airport in Scandinavia. Official language Danish, but English widely spoken.
- **Other agencies:** European Environment Agency (Copenhagen).

**France**
- **Life sciences:** France has a strong R&D-based pharmaceutical industry. Its life science network includes Paris Biotech Santé (a bioincubator for medicines and medical devices start ups), the Genopole biocluster, and the biotech, health and environment cluster, Biocitech (all in Paris) as well as regional hubs like the Lyon Bio Pole and the Eurasante health and biotechnology park in Lille.
- **Regulator:** ANSM is a high-profile and proactive regulator and has a strong representation at the EMA.
- **Travel and language:** France is at the heart of the EU both geographically and politically, and Paris has good links transport to other European cities. Lille and Lyon are also contenders to host the EMA because of the regional life science hubs there. Language: French, English widely spoken.
- **Other agencies:** European Securities and Markets Authority (Paris), EU Institute for Security Studies (Paris), Community Plant Variety Office (Angers), European Railway Agency (Valenciennes and Lille).
To Host The Post-Brexit EMA

The Competition Begins

Overlapping area such as food or the existing agency worked in another, although some argue to a particular EU country, factors like language and security studies (Paris), Community Plant Variety Office (Angers), European Railway Agency (Valenciennes and Lille).

Key factors to be taken into consideration at the EMA are also contenders to host the EMA because of the regional life science hubs there. France is at the heart of the EU both geographically and politically, and biotechnology park in Lille.

Travel and language:

Regulator: The Medical Products Agency (MPA) will be the largest national medicines agency in the EU once the UK leaves, and that it would collaborate well with the EMA.

Travel and language:

Regulator: The government's life science advisor has said that Stockholm is a "little bit further away" and there are not as many flights as to London. Language is Swedish, but English is widely used.

Other agencies: European Centre for Disease Prevention and Control (Stockholm). This might count against Sweden as a location for the EMA, but on the other hand there could be synergies between the two.

Other agencies: Eurofound (Dublin), which provides information and advice in the area of social and work-related policies, particularly living and working conditions and industrial relations.

Key factors to be taken into consideration:

Having an existing agency could be a key advantage. Other factors include good transport links to other European capitals, access to qualified workforce, and the cultural and language environment.

Ref: Commons debate on EMA https://www.theyworkforyou.com/whall/?id=2016-10-12a.115.0&s=speaker%3A25386
The Outcomes-Based Reimbursement Experiment

US payers and drug companies are showing interest in outcomes-based contracts and even implementing some, but whether they will become the reimbursement arrangements of the future remains highly uncertain.

Value-based reimbursement contracts between pharmaceutical manufacturers and US payers appear to be gaining momentum, with several such contracts signed in the last year. But while tying the cost of a drug to the value it delivers appeals to both payers and drug manufacturers, regulatory roadblocks and execution challenges will limit their adoption in the near term. Their viability long-term will probably depend on the savings they deliver to the US healthcare system.

The shift towards outcomes-based reimbursement is in some ways a middle ground for insurers and drug companies. The insurer is looking to save money when a drug is not working the way it is supposed to, but drug makers get the benefit of retaining value when it does.

The proposition sounds straightforward yet it is quickly confounded by complexities around defining value, the outcome to measure, the time horizon for measuring a benefit and data collection. Many wonder if it isn’t just simpler for drug makers to lower the price of a drug and make it more affordable.

But with drug rebates already having grown substantially in the last few years and eating increasingly into the bottom line, some drug makers view standing behind their drug through outcomes-based contracts as one of the few ways to retain some value. Companies in the competitive diabetes space, like Novo Nordisk AS, Sanofi and AstraZeneca PLC, for example, spent nearly 50% of gross US pharma sales on rebates in 2014.

“For the end game is going to be telling,” said Sean Karbowicz, the founder of a new drug report card startup called MedSavvy that looks to provide clinical and cost evaluations on drugs to physicians and patients. Karbowicz has experience making value-based determinations for insurance plans, having previously worked as the drug policy director at the pharmacy benefit manager OmedaRx. “Is the net benefit to consumers there,” he asked. “That remains to be seen, and I think that is going to be the yardstick that these deals ultimately need to be held to. How are these helping patients and healthcare overall? Does it actually lower costs or make costs sustainable if not lower?”

FOR EARLY ADOPTERS, EXPERIENCE EQUALS KNOWLEDGE

For now, the emphasis by early adopters is largely on gaining experience in the area. Payers in particular have a big learning curve when it comes to adopting value-based reimbursement because the burden of collecting data on drug usage and outcomes to determine rebates generally falls to them. Putting the appropriate systems in place to manage the program requires some significant investment, as Cigna Corp. senior VP of integrated clinical and specialty drug solutions Christopher Bradbury said in an interview earlier this year.

Aetna Inc.’s former national medical director, pharmacy policy & strategy, Edmund Pezalla, acknowledged during a panel at Informa’s Pharmaceutical Strategy Conference in September that the benefit of value-based reimbursement contracts at this stage is as much about the collaboration as savings.

United Health Group Co. is also looking to gain experience in the area. Pharmacy Management Strategies VP Lida Etemad said during the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) annual meeting in May that the insurance company had made a strategic decision to invest behind more value-based contracts for drugs this year, with the hope of signing about three to five agreements as pilot programs for the purpose of experience.
She said the insurer favored traditional rebate contracts historically because they were able to get a better financial return, in part because of the administrative costs required to set up outcomes-based reimbursement. The company’s renewed interest in the area was ignited partly by growing acceptance that the use of higher-priced medicines can help to reduce medical expenses, she said.

Insurers typically silo drug spending from medical spending so the potential benefit of a drug on the medical side of the business isn’t always as clear as industry believes it should be.

**INTEREST IN USING VBR CONTRACTS IN CV/METABOLIC**

Humana is considered the most active large private payer engaged in outcomes-based risk sharing contracts. The national insurer has about 15 contracts currently in place, covering 20 drugs, Humana Pharmacy Solution president William Fleming said in a recent interview. But the company like many other insurers, has chosen not to announce the contracts, so its activities have not garnered widespread public attention.

On the other hand, Aetna, Cigna and Harvard Pilgrim Health have been among the more proactive insurers when it comes to announcing value-based reimbursement contracts. Cigna confirmed that it has six such contracts in place for medicines for high cholesterol heart failure, diabetes, multiple sclerosis and hepatitis C. This year, the insurer has signed three deals, one with Novartis AG for the heart failure drug Entresto (sacubitril/valsartan) and two separate agreements around the cholesterol-lowering PCSK9 inhibitors. Aetna signed deals with Amgen Inc’s Repatha (evolocumab) and Regeneron Pharmaceuticals Inc./Sanofi’s Praluent (alirocumab).

Much of the focus for outcomes-based reimbursement contracts recently has been on drugs in the cardiovascular/metabolic space, partly because the therapy areas are competitive, which gives payers more leverage in negotiations. There have also been several new launches of high-priced drugs in potentially large therapeutic categories, which have raised alarms with payers about the budget impact.

In the case of the PCSK9 inhibitors, which were the basis for several outcomes-based contracts with a variety of payers, the drugs are expensive biologics moving into highly a competitive market dominated by cheap generics, and with the potential long-term to be used in a broad patient population though their current indications are relatively niche.

Diabetes is another area that has seen activity. Aetna and Merck & Co. Inc. announced a value-based reimbursement agreement for the DPP-4 inhibitor Januvia (sitagliptin) and the combination pill Janumet (sitagliptin/metformin) for the treatment of type 2 diabetes in October. Harvard Pilgrim Health and Eli Lilly & Co. announced an agreement for the GLP-1 agonist Trulicity (dulaglutide) in July.

The two agreements are quite different. In the Trulicity agreement Lilly agreed to pay a higher rebate if fewer of Harvard Pilgrim’s members taking the drug reach hemoglobin A1C of less than 8% compared to those taking other GLP-1s. In Aetna/Merck agreement on Januvia, the rebate Merck will pay is linked to intensification of treatment rather than a health outcome like reduction in HbA1C, so Merck would pay larger rebates for Januvia and Janumet if patients need to add another therapy to reach their HbA1C goals after starting the drugs.

In an interview, Merck’s VP of strategy and commercial model innovation, Lisa French, suggested that intensification of treatment as a value measure might be more straightforward to track versus monitoring patients’ reductions in HbA1C. Most outcomes-based agreements in diabetes tend to use HbA1C as a measure, and Aetna said it was unaware of any other agreements based on intensification of treatment.

Tracking patients’ HbA1C has proved challenging in other cases. Takeda Pharmaceutical Co. Ltd. VP of managed markets and government affairs, Richard Ascroft, talked about the Japanese pharma’s disappointing experience with a sliding-rebate contract with several large payers on a diabetes drug that relied on HbA1C as a value measure.

“The rebate was higher if the drug didn’t perform as well as we thought it would and the rebate was lower if it did,” he said. But, Takeda was unable to calculate the rebates and complete the project because the payers were unable to collect the HbA1C data.

Because of the complexities, Ascroft predicted the contracts will remain limited in the near-term and focused on the most expensive new drugs with unclear efficacy.

“Operationalizing risk-based deals has been really challenging,” agreed Pratap Khedhar, managing principal at the consulting firm ZS Associates. “I think it will be the pharma companies and payers who are fairly sophisticated (that will sign them).”

One change, Khedhar has noticed, is that newer contracts have shifted from being patient-based to population-based to simplify the execution, so that if 80% of the population, for example, hits the agreed upon threshold than the two parties agree to accept the outcome. The more straightforward the arrangement the more successful it might be, he indicated.

“The focus is going to be on those areas that are relatively high level of spend and where there is a high level of uncertainty because it’s not clear how the drug is going to perform,” MedSavvy’s Karbowicz said.

“Given the resource requirements involved on both sides, if we are going to spend this much time and person-resources figuring out those arrangements, why not just lower the price or increase the rebate,” he said. “That might just be the simpler way of doing it.”

Industry would certainly have a counter argument against steeper discounts. So the value-based reimbursement experiment continues – for now.
Turkey Jostles For Slice Of Biologics Manufacturing Pie

Many local pharma companies in Turkey have been launching capital investments in new production facilities for biologics and biosimilars in the hope of attracting new foreign partners and have already met with some success, but a number of obstacles remain.

Although Turkey is an attractive market for the global pharma industry, its government’s policy of keeping drug prices low along with the country’s continuing political instability – which has already cast a significant shadow over the economy through moves including company seizures – is making inward investment decisions by foreign firms increasingly difficult.

At present, simply importing and marketing products, rather than manufacturing these locally, is the less risky route for global companies, as long as end product prices in Turkey remain basically economically viable.

In the meantime, and helped by government incentives, domestic pharmaceutical companies of all sizes have been announcing new capital investments in production capacity over the past couple of years as they seek to advance their own capabilities and also to become attractive potential partners for foreign firms.

Abdi Ibrahim Ilac Sanayi ve Tic AS, Turkey’s leading pharma firm, has unveiled a $100m investment in AbdiBio, a production facility for biotech drugs that aims to be operational in 2017 and will conduct biotech R&D and manufacture drugs against multiple sclerosis, cancer, diabetes, CNS disorders and rheumatism.

Kocak Farma, a mid-sized company that has been attracting interest as a potential acquisition target, has invested over $150m since 2013 to establish one of Turkey’s most advanced production facilities to produce biosimilars products in oncology.

TR-Pharm, another upcoming local company, also disclosed plans last year for an investment of €100m ($112m) over six years to complete a plant to produce anticancers, while Onko Kocsel last year opened a new €100m plant in Gebze near Istanbul to manufacture generic cancer drugs and biologics not currently
produced in Turkey or only in limited volumes.

Nobel İlaç Sanayii ve Ticaret AS, another prominent Turkish firm, has launched a joint project with the Marmara Research Center of TÜBİTAK (The Scientific and Technological Research Council of Turkey) to produce biosimilars against metastatic colorectal and head and neck cancer.

There are other examples and the broad push into biologics is an obvious trend.

**ARE INCENTIVES, PRICES SUFFICIENT?**

As they increase their technological infrastructure and improve production quality in terms of compliance with global GMP standards, the hope is that these investments will make local companies more attractive for joint investments. The government has also made it clear that it wants to create viable local partners for multinationals looking to invest in Turkey.

The Health Industries Guiding Committee (SEYK), established by the government to encourage and coordinate pharmaceutical investments, has been negotiating with some multinationals and is offering incentives including purchasing guarantees for the output from local manufacture. However, the condition is that at least 60% of investment in any joint project must come from local sources and partnerships with local companies are being strongly encouraged.

While purchasing guarantees are important, their incentive value is limited as tenders for Health Ministry hospitals comprise less than 20% of the national drug market. Product pricing is more important and the government’s low price policy appears to be dissuading companies from even importing certain products, let alone producing them in Turkey.

But there is no sign yet that the government is ready to award higher prices to locally produced biologics to encourage investment. The impression by the industry is that the government’s motivation is mostly to meet domestic demand for advanced products with costs kept as low as possible.

Although government spokespeople often underline the potential for pharma exports from Turkey to surrounding regional markets, in reality – and to some extent naturally – meeting the needs of domestic patients is their priority.

The AIFD (Association of Research Based Pharmaceutical Companies) for one is objecting to that approach and wants the government to focus more on the export dimension of manufacturing investments. It points out that the conditions of local majority investment and the low price policies are not helping attract foreign capital.

Another problem is the vagueness of Turkey’s legal regulations in terms of biological products and biosimilars, as even the draft new patent law doesn’t have a specific category governing intellectual property rights for such products.

**ASIAN POTENTIAL?**

Industry analysts point out that Turkey could try to tap globalizing generic and biosimilar companies, particularly from India, China or South Korea, that may be more aggressive and willing to take risks than their innovative rivals in order to use Turkey’s developing infrastructure to gain a strong foothold in the region. Using Turkey as a base, they could become more competitive in nearby regional markets like the Middle East, North Africa, the Caucuses and even Europe.

There have already been a few deals suggesting this strategy is gaining momentum. In June 2016, Eczacıbaşı entered a partnership with India’s Zydus Cadila to market a number of biologic/biosimilar products in Turkey, with a focus on oncology.

But there is no sign yet that the government is ready to award higher prices to locally produced biologics to encourage investment.

Another example is the strategic collaboration between Dr. Reddy’s Laboratories Ltd. and TR-Pharm for three biosimilars from the Indian firm, which will be registered and subsequently commercialized in Turkey by TR-Pharm under the deal.

TR-Pharm has also entered a distribution deal with Sigma-Tau Pharmaceuticals Inc. for an orphan product, as part of which TR-Pharm will seek regulatory approval and provide named patient supplies for a currently untreated indication.

Eczacıbaşı also founded a joint company with Baxter International Inc., which subsequently worked with the US firm’s spin out Baxalta Inc. and is now collaborating with Shire PLC following its Baxalta merger. Merck & Co. Inc. has signed a strategic cooperation deal with Turgut İlaç, a local company, to develop biotech infrastructure and produce biosimilars in Turkey.

Sanofi meanwhile has announced that it is assessing the local production in Turkey of a biotech insulin product (probably Lantus (insulin glargine)) in cooperation with an unnamed local company, for which negotiations are continuing.

These types of deals generally include options for the local production of products over the mid- or long-term but whether these will actually be taken up remains far from certain.
Boehringer Ingelheim’s head of BioXcellence, its contract manufacturing business, talks about best practice when forming a long-term relationship with an outsourcing services provider.

Boehringer Ingelheim GMBH has operated its biopharmaceutical contract manufacturing business for more than 20 years, during which time it has brought 26 molecules to market together with its customers. In 2012, it launched BioXcellence, its biopharmaceutical contract manufacturing brand.

Over the past two years there has been a flurry of investment in its manufacturing capacity by the German major; a new facility in Shanghai has been handed over with operations due to start in the beginning of 2017, a €500m investment planned for a new cell culture manufacturing facility in Vienna, and agreements with several companies, including Sanofi, to manufacture therapeutic monoclonal antibodies.

Uwe Buecheler heads up BioXcellence. A molecular biologist by training, he is responsible for the global biopharmaceutical operations network and in particular for the contract manufacturing business.

What are the most common pain points when working with new clients?

With a new relationship you have not had the chance to deliver and to show that you are living up to your promise, but you have to establish a relationship. Each company has a different philosophy, culture and business processes. What each new relationship requires is an interface that works for both companies. And this interface requires collaboration on both sides.

Typically, we have a tiered approach; we have working project teams, technical and business steering and as a CMO we generally try to mirror our customer organization from working level up to joint executive steering teams.

What is one of the most common misconceptions about working with a CMO?

Companies expect that the CMO exactly mirror their quality system or their supply system, which is not feasible from a CMO perspective, because we have to run our network in a consistent manner. Over the different sites, we manage and steer the network and we cannot mirror the quality system of more than 10 other companies. That’s a perception which is challenging.

The pharma sponsor has to accept that there is a system in place with a CMO who has been around for more than 20 years, who has successfully brought more than 25 products to the market, or supported sponsors to bring them on the market.

What is the long-term growth strategy for BioXcellence?

We think our biopharmaceuticals manufacturing expertise as a technology to generate new therapeutic principles will be very important for the entire pharma industry for the future. Most pharma pipelines have really shifted towards the new biological entities. And this is the opportunity for a contract manufacturer being specialized in this technology. I think a major driver for our contract manufacturing growth is very likely a successful therapeutic pipeline for new biologic entities.

There are two areas that are very important. One is that you provide the necessary capacities to manufacture at the locations needed. And the second is that you run the state-of-art technology that is needed to most effectively and efficiently manufacture product according to global quality standards. Technology that is very important for that business and the growing biological entity pipeline worldwide.
India Mandates Formal Certification Of Personnel In Manufacturing

The Indian drugs regulator has mandated specific formal certification for personnel in the manufacturing space effective 2018, amid an ambitious ongoing initiative to improve skills across functional areas and levels in the life sciences sector.

India’s Central Drugs Standard Control Organization has stipulated that in order to bring about “substantial improvement” in the quality of pharmaceutical products it has become “imperative” that “all personnel” employed in pharmaceutical manufacturing units should undergo certification programs developed by the Life Science Sector Skill Development Council.

“With effect from Jan. 1, 2018, no person shall be employed in any pharmaceuticals/bio pharmaceutical manufacturing units unless he has obtained a formal diploma or degree in the relevant area or has been certified by the LSSSDC or equivalent organization in the area in which he has been deployed,” said Dr GN Singh, Drugs Controller General of India.

The LSSSDC is a not-for-profit organization, backed by the government and industry, among other stakeholders, and essentially aims to address skill shortfalls, both qualitative and quantitative, in the rapidly advancing and growing life sciences sector in India. It is chaired by Satish Reddy, chairman of Dr. Reddy’s Laboratories Ltd., while its governing body includes representatives from industry, government and academia.

Asked whether the government notice would generally apply to all personnel at Indian sites including those in quality control and quality assurance, Dilip Shah, member of the LSSSDC’s governing body, said: “In principle, yes. In practice, it may take time as the skilling is of thousands of employees - a challenge both for the industry and the LSSSDC.”

Shah maintained that the initiative to improve skills is not a consequence of the spate of compliance deviations flagged at Indian sites but an independent initiative with the government.

“This is not just related to quality. This effort covers all jobs in the industry,” he said when asked if the plan has the support of foreign regulators like the US Food and Drug Administration and the UK healthcare products agency, the MHRA.

The LSSSDC, over a 10-year timeframe, aims to map all job roles in the sector, enlist over 300 training organizations, train over 39,000 trainers and certify around 3.4 million skilled workers. Initial funding is through a combination of grants through the National Skill Development Corporation, a public private partnership under India’s Ministry of Skill Development and Entrepreneurship, and contributions from industry, though the council is expected to become self-sustaining subsequently.

These sectoral efforts are part of the government’s broader “Skill India” initiative that hopes to empower the youth of the country with skill sets that make them more employable and productive in their work environment.

Anju Ghangurde
Deputy Editor,
Pharma, APAC
Bachem is the leading independent supplier of peptidic active pharmaceutical ingredients (APIs) for the human and veterinary pharmaceutical market. Since its foundation in 1971, Bachem’s concepts and technologies pioneered the industrial peptide manufacturing. Our history of firsts drive us to continue developing innovations and we offer a full range of integrated services to bring our partner’s breakthroughs to market.

RESEARCH
Bachem offers the world’s largest collection of amino acid derivatives which are used by customers interested in manufacturing peptides. Also solid phase supports for peptide synthesis are available. Other essential product lines are bioactive peptides, enzyme substrates and inhibitors as well as some organic molecules. New products are added to maintain an innovative touch. Strong emphasis is placed on quality.

PRECLINICAL DEVELOPMENT
During preclinical development, lead finding and lead optimization require large panels of peptides. These are generated as custom synthesized molecules for customers around the world. Frequent consultation with Bachem experts allows further refining of target compounds. As such, a clear partnering aspect is required to come up with pioneering concepts and molecules to bring into clinical development.

CLINICAL DEVELOPMENT
When clients have selected their lead compound, they commence clinical trials. It is a decade-long process to approval of the drug. During this time, there is a close collaboration to learn more about the product. Each production step is scrutinized and manufacturing reproducibility is strived for. Scale-up and full control of the process is targeted. Validation and control of the process is the end result of an intense partnership.

PEPTIDE DRUGS
The responsibility to manufacture sufficient drug substance rests on the shoulders of the Contract Manufacturing Organization. This can only be done by being extremely reliable and also by coordinating activities closely with our partners. Forecasting the quantity needed is extremely difficult, especially for new drugs where the commercial success has not been proven. Hence, responsiveness to customer needs becomes paramount.

MARKETING & SALES CONTACT
Europe, Africa, Middle East and Asia Pacific
Bachem AG
Tel. +41 58 595 2020
sales.ch@bachem.com

Americas
Bachem Americas, Inc.,
Tel. +1 888 422 2436 (toll free in USA & Canada), +1 310 539 4171
sales.us@bachem.com
TOGETHER WE WRITE HISTORY WITH PEPTIDES

BUILDING ON OUR HERITAGE, WE PIONEER INNOVATIONS TO DELIVER THE BEST QUALITY FOR EVERY PEPTIDE NEED.

- MORE THAN 40 YEARS EXPERIENCE IN PEPTIDE CHEMISTRY
- PROCESS DEVELOPMENT AND CUSTOM MANUFACTURING
- COMPREHENSIVE TECHNICAL AND REGULATORY SUPPORT
- A LARGE NUMBER OF GENERIC APIs
- MULTI-KG SCALE cGMP MANUFACTURING FACILITIES IN USA AND EUROPE

WWW.BACHEM.COM
WEARABLES: A World Of Pharma Partnership And Potential

Pharma does not need to make wearables. Instead, it needs to figure out how best to use the data these technologies can provide, how to integrate wearables into product offerings and how to persuade payers to foot the bill.

As the commercial and scientific potential of wearable devices in medicine becomes clearer, not least to slow the competition-driven price slide typically seen in consumer tech, both established technology giants and start-ups are vying for some of the action. This presents pharma firms with new potential partners — and potential competitors — in the likes of Google, Apple and Samsung, as well as in smaller specialists like Empatica and AliveCor.

Pharma does not need to make wearables. Instead, it needs to figure out how best to use the data that these technologies can provide and how to integrate wearables into product offerings. “Our energy is spent more on making meaning out of the data that wearables are able to generate [rather than on building the tools themselves],” says Pfizer Inc’s head of clinical innovation Craig Lipset.

Since most wearable devices are freely available on the consumer market, “whatever we see out there, we buy and try it. We have a cupboard full of wearables. Sometimes I have four or five on together, to test them,” says Kristian Hart-Hansen, CEO of LEO Innovation Lab. “We’re looking at how to incorporate them into our solutions and thinking, but I don’t think we’ll be the people developing them.”

A handful of pharma firms have acquired technology partners, preventing competitors from tapping the same technology or approach. In 2015, Teva Pharmaceuticals Inc. bought smart inhaler firm Gecko Health Innovations, for example, following a similar move by diversified healthcare group OPKO Health Inc. Also, AstraZeneca PLC made a small investment in New Zealand-based smart inhaler company Adherium Ltd during 2015, having shortly before announced a long-term commercialization agreement.

Indeed, partnerships are for now the most popular arrangement between biopharma companies and technology firms. Partnerships offer both sides flexibility and ensure technological innovation can continue freely; in the case of larger tech groups, acquisition is generally not an option in any case.

Hence partnerships are proliferating as the potential of mobile and wearable technologies to transform therapeutic development and healthcare delivery becomes clear, and as both sides seek the other’s expertise to make that happen. Biogen has tied up with Google’s Verily Life Sciences; Novartis AG has deals with Microsoft and Qualcomm; and Pfizer has joined forces with IBM to use remote monitoring devices to investigate Parkinson’s disease.

DIGITAL HEALTH INVESTMENTS

Pharma’s foray into wearable technologies is happening as part of its broader drive to embrace digital technologies and patient-centricity. Most have brought on technology expertise to help both R&D and commercial teams understand and exploit new opportunities.

GlaxoSmithKline PLC recently formalized a multi-disciplinary innovation unit whose mission is to modernize clinical trials using digital technologies; the Clinical Innovation and Digital Platforms group has a dedicated team and budget to ensure that initiatives move beyond experimental pilots toward more widespread applications.

Jessica Federer, Bayer AG’s digital development head was appointed in July 2014 to take the entire organization digital, across all its divisions, thereby helping foster closer integration between the various segments.

Novartis has set up a digital medicines team to think about how to use beyond-the-pill technologies to improve outcomes and has a digital development group within the team to look specifically at how to bring new technologies into the R&D organization. Many in the team are technologists with high scientific aptitude, often from the venture capitalist community. “We’re looking at how to absorb these technologies into regular operations and to scale them up,” explains Vas Narasimhan, global head of drug development and chief medical officer at Novartis. “That’s how they can substantially improve the efficiency of the whole process.” He’s referring to technologies across the board, including software linking to searchable electronic health records to help identify trial patients,
e-consent systems, and data entry, as well as telemedicine and wearables to allow virtual trials.

Integrating wearables systematically across an R&D organization requires not just testing the wearables themselves, but an entire infrastructure of people, process and technology. “Over the last 2–3 years, we’ve made specific investments...to use these novel data capture instruments in a more consistent manner,” explains Pfizer’s Lipset. That includes making sure that they are understood by, and accessible to, all study teams, that they generate meaningful data that impact development and that the data interfaces are optimized for the patient experience. It means ensuring compliant usage and an understanding of patient preferences. It also means changing the approach to running trials and generating data. “It’s not just about strapping wearables on patients in [an] existing study setup. You need a different approach,” insists Lipset.

Neither Lipset nor Narasimhan, like most of their counterparts at other pharma companies, will quantify how much they are investing in digital technologies and related expertise. But Novartis’s Narasimhan is clear on the timeframe for returns. “We’ve bet ourselves that within five years we’ll see a step change in R&D efficacy,” he says, “though we’re still trying to dimensionize it.” As the technologies scale up, he expects quality to improve first, with efficiency and cost gains coming later.

It is still too early to identify a common investment approach. Bayer’s Federer says only that the group’s digital transformation should not cost a lot of money, but instead take advantage of existing expertise.

Footing the Bill
The hope among most drug developers and makers of wearables is that, ultimately, payers will fund wearables, either as part of a therapeutic solution or as a solution in themselves – assuming they are proven to improve outcomes and/or lower the costs of unnecessary treatment and poor adherence. “We’ve bet ourselves that within five years we’ll see a step change in R&D efficacy,” he says, “though we’re still trying to dimensionize it.” As the technologies scale up, he expects quality to improve first, with efficiency and cost gains coming later.

It is still too early to identify a common investment approach. Bayer’s Federer says only that the group’s digital transformation should not cost a lot of money, but instead take advantage of existing expertise.

RETURN ON INVESTMENT FROM WEARABLES MAY BE REALIZED BY SUPPORTING HIGHER REIMBURSEMENT

FOOTING THE BILL
The hope among most drug developers and makers of wearables is that, ultimately, payers will fund wearables, either as part of a therapeutic solution or as a solution in themselves – assuming they are proven to improve outcomes and/or lower the costs of unnecessary treatment and poor adherence. “We’ve bet ourselves that within five years we’ll see a step change in R&D efficacy,” he says, “though we’re still trying to dimensionize it.” As the technologies scale up, he expects quality to improve first, with efficiency and cost gains coming later.

It is still too early to identify a common investment approach. Bayer’s Federer says only that the group’s digital transformation should not cost a lot of money, but instead take advantage of existing expertise.

BETTER OUTCOMES FROM A MORE TARGETED TREATMENT PACKAGE
In any case, it will have to be supported by data.

Wearable technologies are not expensive relative to the costs of many drugs and of hospital care; furthermore, their cost is likely to fall, not rise. But sponsors cannot assume that wearables costs will simply be absorbed within existing payer structures. Device developers and their pharmaceutical partners will have to bear the costs of establishing evidence and evidence standards around wearables and their enabling more cost-effective outcomes. Most pharma companies are not expecting short-term profits as they experiment with wearables and digital health technologies more broadly, but understand that ultimately these will have to be paid for.

Importantly, wearables are likely to themselves enable outcomes data collection, thus supporting results-based reimbursement deals between payers and pharma firms that could, ultimately, mean higher reimbursement for pharma companies. This could pay back their investment in the technology and justify their supporting its costs in the early stages. Over time, as certain technologies and data types become better recognized and trusted, pharma may be able to include technology costs within its overall product pricing.

In the longer term, patients may have to take more responsibility for their health, as the counterpart to being more informed and engaged. LEO Innovation Lab’s CEO Hart-Hansen believes that, ultimately, health insurance premiums will be linked to treatment adherence and other healthy behaviors. “We’re not there yet. But in the long run, insurance companies have to start looking at how to incentivize people to live a better life. If not, it will ruin us [as a society],” he says.
Philips Plugs Into Patient Connectivity

Philips is working towards making personal pathways for every patient, with a vision of connecting healthcare providers with each individual to create a rounded continuum of care as the norm. It’s a passion project for Jeroen Tas, the company’s head of connected care and health informatics.

Two years ago Royal Philips (Philips) took the decision to sharpen its strategic focus by splitting the company into two very disparate divisions; Lighting and Health-Tech, the latter of which would combine its existing Healthcare and Consumer Lifestyle brands.

On announcing this split in 2014, Philips said in a statement that it would be able to “capitalize on the convergence of professional healthcare and consumer end-markets across the health continuum, from healthy living and prevention, to diagnosis, treatment, recovery and home care.” The rising levels of patients who choose to proactively monitor and manage their health, and the increasing pressures put upon the existing healthcare systems around the world to create new models of care are two reasons why Philips thought this restructure was opportune.

Since the split, Philips’ Connected Care and Health Informatics team, led by Jeroen Tas, has been working with the pharmaceutical industry, payers and patients to find a better way to “support the continuum of healthy living,” Tas tells Scrip, through patient engagement and connecting healthcare providers.

“Clearly, the best way to get better outcomes is to engage the patient better,” he states. “Today, half of the people that are on medication don’t take it on time, or at all. If you’re truly concerned with outcomes, that’s probably one of the first levers that you want to pull, because we spend a lot of money on pharma but if the way that people adhere to their medication is not working that needs to be addressed.”

Empowering the patient clearly enthuses Tas, who speaks at length about the need to ensure that all healthcare providers have some way of linking information, so the best and most individualized clinical decisions are made. He is very vocal about his daughter, Kim, who lives with type 1 diabetes and the burden of daily decisions that someone living with the condition has to make. Connected care is the way forward, he evangelizes. The healthcare industry as a whole has to know more about the patient generally, use that data proactively and exploit modern technology to create “personal pathways” for every patient.
To gauge how ready countries around the world are to meet outcomes-based healthcare through connected technology, Philips conducted a large report, the Future Health Index (FHI). It measures the perceived readiness of 13 key markets, assigning each a score out of 100.

The FHI focuses on the three factors necessary to move towards more future-ready, financially sustainable and patient-centered healthcare systems: access to healthcare, integration of the health system and adoption of connected care technology. Based on a survey of 25,355 patients and 2,659 healthcare professionals across 13 countries it highlights a growing opportunity for digital technology to drive healthcare transformation.

The United Arab Emirates (UAE) leads the index in readiness stakes, followed by the Netherlands and China. Germany, Brazil and Japan received the lowest scores on the index. “Having met with many of the healthcare leaders there [in Dubai], I can see a clear drive towards much more connectivity between patients and the care providers; much more interest also in tele-health solutions,” says Tas. “What didn’t surprise me [about the survey results], is that a lot of the patients said that they have to repeat a lot of the same information to multiple healthcare professionals, 74%, and I can see it with people like my daughter, she says, ‘I am the care coordinator and data aggregator because I have to tell my story over and over again to each of the professionals.’”

GETTING TO KNOW THE PATIENT

“Part of our vision is to get to know the patient,” Tas explains. “This can be both contextual information about how you behave, to really deep information about how you’re wired from your genomic reading. We want to know what can truly impact your health, where are your risks and what is the impact of your DNA in certain diseases.”

As the pharmaceutical industry moves from hunting the next blockbuster to creating precise medical fits for an increasingly engaged patient, Tas wants to not only know about the individual, but impact the way those creating and taking treatments interact with each other. “A radiologist, for example, rarely knows, or rarely finds out how his observations are actually contributing to the outcome of the patient. Similarly, you go to the doctor, they see an issue, they try to resolve the issue. You may come back for a check now and then but there is no continuous feedback loop that helps you to fine tune diagnosis, treatment and adherence to that treatment,” he says.

As the pharmaceutical industry increasingly works with healthcare systems around the world that reimburse based on outcomes- and evidence-based medicine, the way in which pharma creates new therapies is critical, but lifecycle management also plays a pivotal role. “In the world of connected technology there is a huge opportunity for the pharma industry to find new ways to optimize outcomes for patients,” says Tas. “And probably even with their existing portfolios and of course, by precision medicine that can extend their portfolios. Their existing portfolios can be applied way more effectively, if they knew more.”

INTERNET OF THINGS

Philips has created a health infrastructure to connect all its medical devices, Tas terms it a medical “internet of things.” It has a clinical repository for each patient so medical records, imagery and clinical studies can be brought together. Once that information is compiled analytics can be used to create new insights into the data that support patient and physician decisions.

Philips manufactures more than half of all patient monitors used in ICUs in the US. This experience is now allowing the company to “leverage what we learned in being a leader in patient monitoring, and increasingly we are looking at combining that data with the full profile of the patient. We’re increasingly using that information to make better decisions about health,” he explains.

Tas says that this approach to connecting health is reflected in most of the products that Philips brings to market now. All its new propositions are connected to its platform, in addition it is also connecting its patient monitors, imaging systems or homecare propositions to the same platform. This allows the company to support a continuum of care whereby specialists can glean a much richer set of data that’s been cleansed to make sure that it is clean and interoperable.

The overarching course that Philips is taking to create a world of data osmosis and interactivity between software and specialist, and of course the patient, is a path led by Tas’ conviction. Changing attitudes, habits and ways of working to create an all-round interaction between healthcare provider and patient will take time but is undoubtedly required in the brave new world of outcomes-driven healthcare.
Five Principles For Building Successful Digital Partnerships

How should pharma build partnerships with digital leaders to create mobile apps that satisfy all stakeholders? Deloitte’s five-point-plan should help.

Investment in digital health is growing rapidly and has cumulatively reached $15.5bn in the US alone. However, much of this growth has been characterized by fragmentation for pharmaceutical companies. Despite iOS and Android hosting over 165,000 health apps, more than 48% of pharmaceutical company published apps do not have a single user review. It is little wonder, therefore, that a recent study has highlighted that only 13% of pharmaceutical leaders are satisfied with their current digital activities.

Currently, 82% of mobile apps have just one or two functions which only allow them to support one specific part of the pharmaceutical value chain. However, digital technology, when properly deployed, allows us to reuse both data and functionality. Our most digitally mature clients have moved away from building individual mobile and internet solutions with just one or two functions. Instead, they are beginning to link these solutions to create integrated platforms that can be used by different teams throughout the business.

As pharmaceutical companies begin to focus increasingly on linking digital solutions, we are seeing a move away from investing in recreating existing technologies. New forms of partnership between pharma, digital companies and the healthcare system now allow digital leaders to access the very best individual digital solutions where appropriate.

We have identified five principles to help leaders develop these partnerships:

1 Due diligence beyond technology. During the initial partner selection phase, companies often bias their assessment toward a holistic procurement process for technology today, rather than thinking about a partner of the future. A strategic partner should have the ability to balance short term technology delivery with longer term partnership development. Successful alliances are formed by those companies with a broader view of partners’ priorities, leadership skills and cultural compatibility.

2 Strong governance that shares both benefits and risks. Companies often do not invest enough time and resources into developing a governance framework that clearly defines roles and responsibilities beyond immediate delivery plans. This often leads to unresolved cross-organizational tension. Strong alliance frameworks fairly allocate the risks and benefits; reinforce incentives; and provide a collaborative forum for partners to openly address emerging issues.

3 A pan-partner view of compliance. Digital alliances raise complex challenges around pharmacovigilance, ethics, information governance and other regulatory issues and are complicated further due to risk processes that vary across organizations, with many prospective digital partners demonstrating inexperience in the healthcare sector. Early development of pan-partner compliance processes is critical to align expectations, avoid unexpected delays and reduce risk.

4 A networked view of stakeholder engagement. Too often, digital partnerships underemphasize the level of interaction with enabling and blocking stakeholders, largely as a result of placing too much focus on end customers, like physicians or patients. Nevertheless, many delays arise from other stakeholder groups, such as government policy-setting bodies, public health authorities, doctors’ unions and patient advocacy charities. An insider view of the local healthcare system is often essential to avoid costly missteps.

5 Management of value, not insight. In the rush to deliver insights straightaway, partners often deprioritize planning future implementation programs. Successful programs articulate how they link to each partner’s corporate strategy early on and then proactively identify which organizational processes should be modified and what new skills will need to be developed in order for the partnership to reach its full potential. As good digital initiatives deliver benefits to multiple functions in each partner’s organization, managing this change is often more complex.

To make these partnerships successful, digital leaders need new skills in their team – strategy, external relationship management and governance, risk management, communications and change management. In many cases, these skills are not accessible in digital teams and so digital leaders will need to either reshape their teams or else access talent from elsewhere.
The hope for a world-changing drug is the reason you exist. Helping you make that hope a reality is why we exist, providing the architecture to accelerate it.

The Medidata Clinical Cloud®, which supports nearly 800 life sciences companies worldwide, was built to help you navigate the entire clinical trial process—faster, more confidently and with more control than you ever thought possible.

For more information, visit mdsol.com
TRUMP’S RX FOR THE DRUG INDUSTRY: Take Two And Have No Idea What Will Happen In The Morning

To call the incoming US president unpredictable would be an understatement, but that doesn’t mean that industry shouldn’t know what to expect.

Suspension of disbelief is a key element to the success of many dramas, so it seems fitting that even as the results of one of the most dramatic elections in US history became apparent, hardly anyone could believe it. The Coastal Elites can be forgiven for aching like a drug sponsor does when a product is rejected by FDA even after it’s been endorsed by an agency advisory committee. Their data told them it would succeed, and they won a popular vote, but they are still left profoundly disappointed and wondering what to do next. Sometimes life itself can resemble being regulated by FDA.

Now that Donald Trump has been approved for domestic and external use, industry will need to be ready for the benefits and side effects of that prescription. The efficacy is immediate, but the challenges are significant as well. There has never been a president with such open contempt for traditional political mores, and there are those who maintain that combining the power of the presidency with Trump’s volatile personality could produce cataclysmic results. The fate of the world is beyond the scope of our discussion here, but suffice to say that those in the industry who are most worried about a Donald-induced apocalypse are likely no longer thinking about pipeline performance or quarterly sales targets; instead, their focus on medications revolves around deciding what products to stock in their underground shelters.

On the stump, Candidate Trump made numerous statements that went against the Republican mainstream, most notably for pharma firms a suggestion that the government should negotiate drug prices in Medicare. Another pledge, one that was actually on his website for a time, would allow importation of drugs from countries where products are cheaper.

But as has been the case for much of Trump’s populist rhetoric, firebrand campaign speeches have cooled to more doctrinaire policy proposals. To wit, the transition agenda released after the election talks about reforming FDA, not cracking down on Rx prices.

That’s not to say that drug firms have nothing to fear from a Trump administration when it comes to drug prices, even as stocks in the sector went on a giddy rally after the prospect of the Clinton presidency, and its sharp attention to pricing, disappeared.

The idea that drug prices are too high remains one of the few areas of bipartisan agreement among voters, and the bully pulpit of yore is now the bully Twitter account, so it’s not hard to imagine Trump burnishing his populist credentials by excoriating the next example of Rx price gouging. Some within industry think that problem will extend beyond 140 characters and are urging companies to take proactive steps on pricing before they again face the prospect of genuine reform efforts.

REPEAL AND REPLACE

The biggest near-term risk to industry from a Trump presidency appears to be uncertainty created by efforts to repeal and replace the Affordable Care Act (ACA), underscored by the fact that Congressional Republicans are debating whether the undertaking should be legislation that repeals and replaces.

The ACA brought health insurance to tens of millions of Americans, expanding the number of customers for pharmaceutical companies. If repeal and replace results in a lot fewer people with coverage, that could mean a lot less medication dispensed. And while industry is aware of the
risks of government involvement in healthcare purchasing, strengthening the relative hand of insurance companies to set coverage policies, as many replace proposals would do, is not something sponsors want to see either.

It’s too early to see how the health insurance reform debate will play out, but it seems safe to say that the exchanges will have been eliminated in one fashion or another by the mid-term elections. What rises in their place remains hard to say, which means companies will be forced to manage their pipelines and price their products without a clear sense of who their customers are going to be and how they will pay for their prescriptions.

**CHANGES AT FDA**

In the face of all that uncertainly emanating from Capitol Hill and CMS, FDA could end up being seen as a bastion of calm by comparison. Sponsors may not always like what they hear, but the applications move smoothly through. True, the agency is well off last year’s record-setting pace for approvals, but the numerous complete responses letters and other submission dynamics could be setting up a blockbuster 2017.

FDA will of course change in many ways during the Trump administration. Indeed, the sixth iteration of the user fee agreement, if enacted as planned, is already poised to push the agency towards greater use of patient-reported data and post-market evidence. And the 21st Century Cures legislation moving through Congress will give sponsors more flexibility on biomarkers and clinical trial design.

On top of that will be all the changes that Trump appointees will make. FDA has been uncomfortable, to put it mildly, with the idea of allowing sponsors more latitude on off-label communications. One can expect that attitude to change quickly in the new administration, and if regulation and guidance aren’t immediately forthcoming, sponsors themselves will probably still feel like the line has shifted even without a formal declaration.

But the downside of changes like that, and even just an increase in the rhetoric calling for FDA reform, is that the agency staff itself may begin to feel disheartened. Time spent on internal policy fights is time that can’t be spent advising sponsors, and a staff being constantly told it needs to change its approach may not be able to maintain the currently strong review pace, especially if employees become disillusioned and leave.

**THE SIGNATURE ISSUES**

Those are the kind of risks and benefits that industry would be facing under any Republican president. Where companies may face special risks are around Trump’s signature issues of immigration and trade. The pharma industry relies on both, and the incoming president has expressed some deep skepticism about them. Undocumented workers aren’t key to pharma’s business planning, but many of the proposals being developed by the administration would eliminate visas for highly skilled workers, meaning that companies might not be able to recruit, or even just relocate, executives and scientists as needed.

On trade, pharma long ago transitioned much of its product manufacturing overseas, and any successful effort by Trump to Bring Jobs Back through tariffs would be incredibly disruptive. It’s uncertain how much Trump could even accomplish on that front, though, given that his position is an outlier within the Republican party, and building bridges to anti-trade Democrats might make accomplishing other parts of his agenda more complicated.

When it comes to the status of US jobs at risk of moving overseas, pharma should pay careful attention to the situation with the Carrier factory in Indiana. The company announced plans to relocate production to Mexico, and the decision had been a focus of Trump’s campaign. He’s going to be president and the company has changed its mind. It’s unclear what motivated the switch – financial or regulatory concessions from the state, perhaps, or potentially a decision by the defense-contracting parent company to encourage good relations with the incoming head of state. The terms of the arrangement will probably become clear eventually.

Does that mean that pharma firms contemplating moving research or production overseas should try to cut a deal with Trump to keep the jobs in the states? If it would allow the administration the opportunity for a good public relations moment, it could be worth a try.

Any firms undertaking that strategy should realize they are playing with bright, orange fire. For firms that don’t get too close to the flame, however, its basic Republican glow and the fundamentally solid economy the new president will inherit likely means that industry is looking at a great four years.
BREXIT: What Can The Life Sciences Industry Do About It?

With the UK heading towards an exit from the European Union in just two and a half years’ time, restrictions on the free movement of people, products and finance will impact the life science sector as much as, if not more than, many others.

Brexit means that access to research networks and funding could be impaired, and the mobility of scientists, researchers and company staff limited. Moreover, the relocation of the European Medicines Agency will bring its own staffing and recruitment problems, and the possibility of regulatory divergences between the UK and the EU threatens to delay new drug approvals and clinical trials.

While the life science sector is well accustomed to adapting to rapidly changing circumstances, the upheavals and uncertainties brought by Brexit are so fundamental and wide-reaching that it is difficult to know how best to mitigate the effects of these changes and make the most of any opportunities that might arise.

The problem is that no one yet knows what kind of relationship the UK government is planning to negotiate with the EU after Article 50 is triggered, probably in spring 2017, and this makes it very difficult to plan ahead.

Prime minister Theresa May insists she is seeking the “best possible deal” for the UK in its relations with Europe, but if she is adamant about curbing the free movement of EU citizens into the UK, and the EU sticks by its insistence that the “four freedoms” are indivisible, the result is likely to be some sort of “hard Brexit” with all that entails in terms of trade, legislation, regulation and migration.

In the meantime, life science businesses are left wondering: should we invest in the UK, wait or decide now to go somewhere else to avoid the continuing uncertainty?

LIFE SCIENCES STEERING GROUP

To come up with some answers in the wake of the vote, the biopharmaceutical industry and the government set up a “UK EU Life Sciences Transition Programme” led by the UK EU Life Sciences Steering Group, a joint industry-government task force co-headed by Andrew Witty, Pascal Soriot and Neil Mesher, respectively CEOs of GlaxoSmithKline PLC, AstraZeneca PLC and Philips Electronics UK.

On Sept. 6, the group presented a report to ministers outlining the key issues facing the sector as well as a range of options for preserving competitiveness once the UK departs the EU. The report identified four priority areas:

- The ability to trade and move goods and capital across borders.
- Ensuring long-term, predictable funding for scientific research, and continued ability to collaborate at scale.
- Access to the best talent: unrestricted movement of researchers and industry staff would be key to maintaining access to the best scientific talent in the UK.
- The need for a unique cooperation agreement on the regulation of medicines in Europe.

This last point is probably the area of most immediate concern to industry. Brexit means the EMA will have to relocate out of the UK, with all that means for its staff and its experts, not to mention the input from the UK’s Medicines and Healthcare products Regulatory Agency.

Following Brexit, EU drug approvals would no longer be automatically valid in the UK, while EU incentives like regulatory data protection and orphan drug rewards could be lost and co-operation in pharmacovigilance and other areas impaired.

Some fear the country would as a result become a “second priority” launch market that was less attractive to investments in drug development and manufacture, particularly if the UK chose not to implement the provisions of the new EU Clinical Trial Regulation with its streamlined trial approval system, due to come into effect in 2018.

It is clearly in the interests of the life sciences industry to stress the importance of keeping regulations aligned as far as possible, and industry has made much of the need for some sort of regulatory cooperation agreement where the UK could continue to play a part in future EU policy, guidance and legislation.

But the government is sending out mixed messages about how far it is prepared to go to protect the interests of the life sciences sector. The prime minister may have said she considers it of great strategic importance to the country, but it’s not clear how far ministers were impressed by the concerns outlined in the steering group’s report.

In any case, even if the government did support a reg-
ulatory cooperation agreement in principle, this would still have to be negotiated with the rest of the EU, with the outcome far from certain.

So life science firms are understandably uneasy about what the future holds, and there are signs that the uncertainty is already making the UK look less attractive as a place to invest in the longer term.

**HOLDING OFF ON DECISIONS**

Recent research by pharma strategy consultancy Novasecta found that many firms are holding off on key decisions in areas like R&D (particularly clinical research), manufacturing and the supply chain.

Similar concerns were expressed at a round table organized by Scrip and PricewaterhouseCoopers in September. Jo Pisani, partner in the UK pharma and life sciences consulting practice at PwC, said: “Unfortunately, we have seen some foreign direct investment decisions being reversed at the last minute; we’ve seen some collaboration agreements being dismantled, and clinical trials locations changed.”

There is also anxiety over aspects of recruitment to life science firms. Novasecta cited some CEOs as saying that several senior level people had decided not to apply to work in their companies. The “uncertainty and risk of the UK as a potential non-EU country is adding a negative weighting to business cases that involve investing in it,” it commented. “The whole talent pool and system of MHRA, EMA and clinical trials in the UK requires a strong network, close relationships and a hub location. Our research reveals that executives do not view the UK as favorably as they used to.”

Moreover, Brexit is taking up a great deal of companies’ time and resources, and is a huge distraction from the day to day business of building up companies and will remain so for many years, according to Harren Jhoti, CEO of Astex Pharmaceuticals Inc.

“We also need to remind ourselves that we are working in a ferociously competitive sector,” Jhoti said at the round table discussion. “So while the executives running the companies are distracted by this huge issue, they’re not building the company. All our competitors around the world are building their companies. There’s no answer to that, it is what it is, but we all know the EU doesn’t move very fast.”

Of course, Brexit may also give rise to new opportunities, and industry is doing its best not to paint too bleak a picture. As the BioIndustry Association pointed out in a Nov. 21 discussion document, the upsides could include greater freedom to design innovation-friendly regulations in areas such as genetic modification and cell-based therapies, and better targeting of tax incentives to key industry sectors.

And in his autumn statement, Chancellor Philip Hammond announced measures for funding and promoting R&D and innovation, including additional R&D spending via a new National Productivity Investment Fund, a review of the R&D tax credit and a patient capital review intended to tackle obstacles to getting long-term investment into innovative firms. The BIA said it was “fantastic to see this government showing an understanding of what is important to life science companies.”

**WHAT MORE CAN BE DONE?**

But with the cloud of uncertainty still hanging over the sector, what more can the industry do to shore up its future prospects as a non-EU country?

As part of an ongoing process, the life sciences steering group held its second meeting on Nov. 23. Little has been revealed publicly about what was discussed although it seems that industry is taking a two-pronged approach in its talks with ministers.

One is to highlight the specific Brexit-related impacts on the sector – regulatory, trade, people – in an attempt to ensure that the future UK-EU relationship provides a stable environment allowing timely access to innovative medicines in the UK and mobility of staff between the UK and the EU.

The other aim is to build on the financial and R&D support promised by the prime minister and the Chancellor in November as the first steps in a “modern, ambitious Industrial Strategy,” and to ensure that the strategy is conceived in such a way as to strengthen the UK life science sector and make it better able to face the challenges ahead, whatever happens on the Brexit front.

It is understood that the government will release the Industrial Strategy before Christmas, and will then invite the various industry sectors to comment on it before the next Budget, which is expected to take place in March or April 2017 – around the time that the prime minister has said she expects to trigger Article 50 and begin negotiations over the future relationship of the UK and the EU. It looks like spring 2017 will be an interesting time in more ways than one.
Therapeutic Progress Amid Political Turbulence: Could 2017 Be Pharma’s Year?

Delivering clinical advances in areas including immuno-oncology and Alzheimer’s disease data while navigating the stormy seas of global politics could represent an opportunity for pharma to influence change.

At the beginning of 2016, we expected the year in pharma to be dominated by immuno-oncology and M&A, with drug pricing questions, the US corporate taxation debate and fears about a bursting biotech bubble framing the picture.

Sure enough, immuno-oncology provided a constant stream of headlines throughout the year, and that won’t change in 2017. Bristol-Myers Squibb Co’s shock unseating from the IO throne when its PD-1 inhibitor Opdivo (nivolumab) failed a key lung cancer trial has left Merck & Co. Inc. poised to wrench the crown for Keytruda (pembrolizumab). Aside from the moving and shaking in the large and lucrative lung cancer market, among the plethora of IO mono-therapy and combination trial read-outs and subsequent filings anticipated for the coming year, Keytruda is likely to be filed and approved for bladder cancer. This will turn the heat up further on BMS, and on Roche, whose Tecentriq (atezolizumab) became in May 2016 the first US-approved PD-1/L1 inhibitor for bladder cancer.

AstraZeneca PLC is among the IO hopefuls that has yet to win a product approval. Key for the UK company will be the Phase III MYSTIC study of its PD-1/CTLA4 combination of durvalumab and tremelimumab, which should read out in January, enabling it to get a head start on other combinations for first-line non-small cell lung cancer. Other late-stage PD-1/L1 contenders include partners Pfizer Inc. and Merck KGAA; a number of Phase III data read-outs from their broad JAVELIN clinical program for the PD-L1 inhibitor avelumab will be reported in 2017, including in first- and later-line lung cancer.

Alzheimer’s disease R&D was hit by the recent failure of the hotly anticipated Phase III EXPEDITION 3 trial of Eli Lilly & Co’s amyloid-targeting solanezumab. The road to success in Alzheimer’s disease is strewn with failed drugs and the latest setback reinforced the uncertainty about the route and the destination. The amyloid hypothesis in the pathology of Alzheimer’s disease is under renewed scrutiny, and EXPEDITION 3 sheds fresh doubt on its relevance and practical suitability as a target to treat dementia. Companies including Roche and Biogen continue to develop products aimed at addressing the accumulation of amyloid plaques, and now stand at the front line after solanezumab’s failure. Another boost (or blow) to the field will come when Merck & Co unveils results of the Phase III EPOCH trial of BACE1 inhibitor verubecestat in July 2017.

Beyond the clinic, pharma will continue to be rocked by the uncertainties of global politics. So many questions hang over what the US’s maverick new leader will do once he takes office: expect the unexpected. Over in Europe, more than five months after Britons voted for Brexit, there is a notable absence of clarity on what happens next.

While confusion is unsettling, the pharma industry now has an opportunity to push its agenda in the US, EU and UK while governments ponder how to proceed. Pharma’s importance as a driver of both economic growth and improved health should stand it in good stead.

In the US, Donald Trump may well implement a tax holiday, allowing US firms to repatriate the cash they have locked away overseas. If that happens, we can expect to see share buybacks – and M&A. Following a bumper year for corporate acquisitions in 2015, some of us anticipated another busy year in 2016, helped by a deflation of biotech stock prices. An absence of the kind of mega-deals that had been seen previously meant that total deal value fell in 2016. Greater access to cash could reinvigorate the M&A market in 2017, with several companies having expressed an interest in bolt-on acquisitions. Increased competition in M&A following a US tax holiday could make it even harder for non-US big pharma like Novartis AG and AstraZeneca to clinch acquisitions, though.

One company that did manage to pull off a sizeable deal in 2016 was Shire PLC, with the purchase of Baxalta Inc. This was a noteworthy bounce-back after it had failed to become a part of AbbVie Inc, that takeover having been stymied by the US tax inversion crackdown. Shire is now looking to grow its turnover to $20bn by 2020, which would see it leap from being a top-30 pharma company to a top-15 company: not bad for a firm that expects to derive 65% of its sales from drugs for diseases with very few sufferers.
YOU BUILD HOPE WE ACCELERATE IT
A PROVEN PATHWAY TO COMPANION DIAGNOSTIC SUCCESS

Your therapeutic needs a companion; you need a resourceful partner. Whether you pursue development via in vitro diagnostic (IVD) or laboratory-developed test (LDT), Covance’s companion diagnostics (CDx) team is uniquely equipped to support your personalized therapy with proven pathways to success. With more than 80 diagnostics delivered to the market, including 14 of the 21 FDA-approved companion diagnostics, our scientific insight and experience can help you determine the best approach. As your partner, we’ll develop and validate your test, leverage the resources and scale of our market-leading central lab and guide the regulatory submission. Together, we can illuminate your CDx’s unique path from bench to commercialization.

SEE YOUR CDX IN A NEW LIGHT

The Americas +1.888.COVANCE | Europe/Africa +.800.2682.2682
Asia Pacific +800.6568.3000 | Or go to covance.com/cdx

Covance Inc., headquarted in Princeton, NJ, USA, is the drug development business of Laboratory Corporation of America Holdings (LabCorp). COVANCE is a registered trademark and the marketing name for Covance Inc. and its subsidiaries around the world. © Copyright 2016. Covance Inc.